Prognosis after Colorectal Cancer

A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment

PhD dissertation

Rune Erichsen

Health

Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital

Supervisors

Henrik Toft Sørensen, MD, PhD, DMSc, professor (main supervisor)

Department of Clinical Epidemiology

Aarhus University Hospital

Lars Pedersen, MSc, PhD, professor

Department of Clinical Epidemiology

Aarhus University Hospital

Evaluation committee

Anders Ekbom, MD, professor

Department of Epidemiology

Karolinska Institute, Stockholm, Sweden

Finn E. Nielsen, MD, DMSc,

Danish Prison and Probation Service

Copenhagen, Denmark

Mogens Vestergaard, MD, PhD, professor

Department of Public Health – Institute of General Medical Practice

Aarhus University, Denmark

Preface

During the last three years, many friends and family members have asked me about my research. Most of these nice people are not researchers and have mainly been interested in knowing if I had made new discoveries or cured cancer. Legitimate questions, since I have been spending their tax money. I have had to disappoint them every time usually by saying that things are a little more complicated than you would expect. I usually ended up describing detailed methodological problems which at that point in time were troubling me the most, rather than describing the aim of my research. I do not think anybody ever felt that their tax money was well spent. However, concluding my dissertation has forced me to look at the big picture and put things into perspective. Although I have not made discoveries that will completely change our way of thinking or cure cancer, I proudly and with all possible humbleness present this dissertation with the feeling of providing evidence that will benefit people affected by colorectal cancer. And that is what I have been doing over the last three years; fostering evidence that can improve the chances of surviving colorectal cancer. That simple and worth the money, I would think!

In the dissertation, I use the term “we” to emphasize that the research was done in collaboration with many highly skilled people. I want to express my sincere gratefulness to all the wonderful coworkers at the Department of Clinical Epidemiology. Particularly, I want to thank my supervisor and mentor, professor Henrik Toft Sørensen for sharing his endless knowledge, teaching me to do clinical research, and opening the doors to the leading international experts. I want to thank the highly skilled statisticians Lars Pedersen, Erzsébet Horváth-Puhó, and Trine Frøslev for their support and for providing all the data, and thank professor John A. Baron from University of North Carolina for welcoming me at his institute, introducing me to his colleagues, and for helping me with the various projects. Furthermore, I want to thank my girlfriend, friends, and family for their support despite my inability to appropriately share my research.

Finally, I want to thank Aarhus University for financial support over the last three years.

The dissertation is based on the following three papers:

I. Does comorbidity interact with colorectal cancer to increase mortality? A Danish nationwide population-based cohort study, 1995-2010 *(submitted)*

II. Characteristics and survival of interval and sporadic colorectal cancer patients: A nationwide population-based cohort study *(submitted)*

III. Mortality and recurrence after colorectal cancer surgery with preoperative stenting – A Danish nationwide cohort study *(in manuscript)*

Table of contents

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the world.[1] Although survival has improved over the last few decades, the overall five-year survival in Denmark remains below 50%.[2] Despite accumulated evidence related to CRC prognosis, three important issues are not well examined in the literature. First, CRC is diagnosed at a median age of 71 years in Denmark, and patients of this age or older are often burdened by coexisting disease (i.e. comorbidity).[3] However, detailed understanding of the interaction between comorbidity and CRC and the subsequent risk of death is limited. Such evidence is important in light of an aging Danish population in which the number of Danes older than 70 years is expected to increase from 630,000 to 1,000,000 over the next two decades.[4] The number of CRC cases will therefore continue to increase,[5] which may foster additional challenges in handling CRC patients. Second, colonoscopy has proven to be effective in detecting CRC[6,7] and is used for CRC screening in many countries.[8] In Denmark, the examination will be part of the Danish screening program that is being introduced in 2014.[9] Despite the effectiveness of colonoscopy in detecting CRC and its precursors, a substantial number of CRC cases are diagnosed in the years following a colonoscopy,[10] but the prognosis for these cases is unknown. Third, CRC patients presenting with obstruction can be treated with self-expanding metal stents (SEMS) to avoid primary acute resection and facilitate subsequent elective resection.[11] SEMS are under suspicion for causing cancer spread as a result of the mechanical expansion, but evidence of long-term survival and risk of recurrence is sparse.

Therefore, this dissertation aimed to examine these aspects of the prognosis of Danish CRC patients based on three clinical epidemiological studies. Study I examined the interaction between comorbidity and CRC in relation to long term mortality. Study II examined CRC survival in cases occurring relatively soon after a negative colonoscopy (interval CRC), whereas study III examined recurrence and survival after colonic stent treatment. Before going into detail about these prognostic studies, a general introduction to CRC occurrence, diagnostics, and prognosis is warranted.

2. Background

Colorectal cancer (CRC) is the third most common cancer among Danish men after lung and prostate cancer, and the third most common cancer among women after breast and lung cancer (excluding non-melanoma skin cancers).[12] In 2010, an estimated 4,300 new cases of CRC were diagnosed in Denmark with a median age at diagnosis of 71 years.[12] The age-standardized incidence of CRC has increased up to 20% over the last 20 years in Denmark, which contrasts the stable incidence in, for example, the USA over the last few decades.[12] In absolute terms, however, the USA still has the highest CRC incidence worldwide, followed closely by other westernized countries. Thus, the lifetime risk of CRC in the Western world is approximately 5-6%.[1,13] Over the last three decades, the incidence of left-sided CRC (i.e. mid-transverse through rectal) has decreased, whereas the incidence of right-sided (i.e. cecum through mid-transverse) CRC has increased.[14] CRC incidence increases with age with 90% of all CRC diagnoses occurring in individuals older than 50 years.[15]

A substantial number of other risk factors have been identified, including genetics (i.e., familial adenomatous polyposis and Lynch syndrome), family history (first-degree relative diagnosed younger than age 50), other diseases (e.g., diabetes, obesity, and inflammatory bowel disease), sedimentary lifestyle, smoking, high alcohol consumption, and low-fiber/high-fat diet.[16,17] Migration studies have shown that people moving from low-risk areas, such as South East Asia, to high-risk countries, such as Sweden or the USA, adapt the high risk of CRC, suggesting that the Westernized lifestyle as a whole is related to disease development.[18,19] Furthermore, a number of protecting factors have been identified including aspirin, non-steroid anti-inflammatory drugs, and exercise.[20,21]

Survival after CRC diagnosis has increased over the last decade in Denmark but, for unknown reasons, is the lowest in international and Nordic comparisons.[22-24] The overall five-year survival among Danish CRC patients is approximately 40-50%.[2] As discussed in detail later, several factors can potentially affect CRC prognosis. Among the factors that have been suggested to be important for the poor Danish CRC survival

rate are delayed diagnosis leading to more advanced disease at diagnosis, patients' general health (including comorbidities), and insufficient medical treatment.[22,25]

2.1 Development of colorectal cancer: Pathological aspects

When referring to CRC in this dissertation, we consider adenocarcinomas originating from epithelial cells in the colorectal mucosa because more than 90% of all colorectal carcinomas can be categorized as this histological type (among other rare types, e.g., neuroendocrine, squamous cell, spindle cell, and undifferentiated carcinomas).[26] Although details about the histological and molecular characteristics of CRC development are beyond the scope of this dissertation, understanding some of the basic aspects is important, particularly for study II. Most colorectal carcinomas are derived from precursor lesions commonly referred to as polyps, and resection of polyps can arrest cancer development.[27] The process from normal mucosa to precursor lesions and cancer has been characterized relatively well. Approximately 60% of carcinomas are estimated to arise from conventional adenomas via the suppressor (chromosome instability) pathway initiated by a mutation of the APC gene,[28,29] 35% through the serrated pathway leading to CpG island-methylated phenotype carcinoma (CIMP+), and the remaining 5% via the mutator (microsatellite instability) pathway in Lynch syndrome.[29] These pathways can be subdivided according to microsatellite stable/instable carcinomas and by the presence/absence of certain mutations, such as KRAS and BRAF. Detailed knowledge about CRC pathways have led to the understanding that the conventional adenomas that develop into cancer (probably < 10%) require many years to progress (probably >10 years). In contrast, lesions arising in Lynch syndrome appear to progress rapidly to carcinoma.[15,28] However, for the serrate pathway, which was characterized much more recently, controversy still exists about the course from precursor lesion to cancer. The specific histological characteristics of conventional adenomas, including villous structure, high-grade dysplasia, size > 1 cm, and ≥3 lesions, are related to high risk of cancer development.[8,30] Taken together, this knowledge is important for identifying high-risk people and defining intervals for CRC follow-up examinations or screening.

2.2 Colonoscopy and colorectal cancer diagnosis in Denmark

In the diagnosis of CRC or its precursors, endoscopy is pivotal, particularly colonoscopy.[8] In Denmark, a set of national recommendations for diagnosis was introduced by the Danish Centre for Health Technology Assessment in 2001.[31] The recommendations suggest using colonoscopy in defined risk patients and sigmoidoscopy in other symptomatic patients.[32] However, in 2009, a new report based on economic evaluation recommended initial colonoscopy as the preferred strategy for symptomatic patients.[33] Colonoscopy is also an important part of the national screening program for all subjects 50-74 years of age that will be introduced in Denmark in 2014.[9] This program will offer biennial fecal occult blood testing as a first line screen test, and subjects with positive tests will be offered a colonoscopy. The aim of the program is to both decrease CRC incidence by detecting precursor lesions and increase survival by detecting CRC at an early stage. Colonoscopy offers the opportunity to remove precursor lesions, thereby arresting CRC development.[27] Studies have confirmed that CRC incidence is reduced up to 10 years or more after a negative colonoscopy.[6,7,34] However, as study II highlights, polyps might be missed or incompletely resected during examination and CRC occur in the years after the examination.

2.3 Treatment and prognosis

Surgery is the cornerstone treatment in the battle against CRC. However, the effect of surgery is highly dependent on CRC spread.[35] In stage I and II patients, surgery is usually applied as the only treatment, whereas in stage III and IV patients it is combined with adjuvant or palliative chemotherapy.[36] For rectal cancer patients, a combination of chemotherapy and radiation is used for selected patients prior to surgery. Surgery is usually performed with curative intent in most stage I-III CRC, but also sometimes in stage IV patients to whom resection of, for example, liver metastases can be offered.[37] Other treatments used primarily for palliative purposes include radiofrequency ablation of liver metastases, tailored chemotherapeutic agents, and radiation.[36]

Colonoscopy also plays a therapeutic role in the clinical management of CRC. In the event that CRC causes large bowel obstruction, a SEMS can be placed during a colonoscopy procedure to temporarily relieve the obstruction (SEMS can also be placed using sigmoidoscopy and procoscopy).[11] SEMS are used in both the palliative setting, to avoid surgery and stoma, and the potential curative setting, to convert an acute operation associated with high morbidity and mortality to a much more favorable elective surgery that can be performed after thorough optimization of the patient's medical and surgical status (study III).

The fact that treatment choice depends on CRC stage at diagnosis reflects the importance of stage as a determinant for CRC survival. The CRC stage is usually categorized into four stages (UICC) according to the

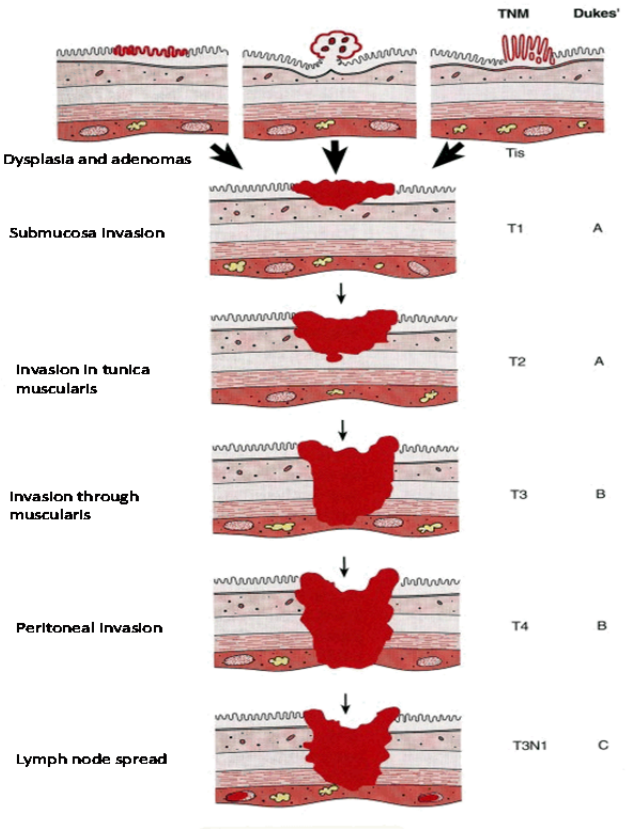

Figure 2.1. Colorectal cancer staging. For completeness, lymph node (N) and distant metastasis (M) must also be defined.

TNM (tumor, node, and metastasis) system. Duke's classification system was used previously and, as shown in Figure 2.1, the systems are comparable. The five-year survival for CRC varies from more than 80% in stage I (T1-2, N0, M0) to less than 20% in stage IV (any T, any N, M1).[35] Another important determinant of CRC survival is radical surgery. Overall and among patients who undergo CRC resections described as radical, five-year survival is 65% compared to 14% among those who undergo non-radical surgery.[35] CRC survival is also dependent on a number of patient characteristics. Most importantly, the age at diagnosis has a substantial effect on CRC survival, with an estimated overall five-year survival of 55-60% for patients aged 65-79 years, and 20-30% for those aged 80 years or more.[2] The presence of coexisting diseases is also important,[3] as described in study I, whereas gender seems to be less important, though women tend to have slightly higher survival rates.[2]

Finally, some of the histological and molecular characteristics of CRC appear to be predictive of prognosis. For example, adenocarcinomas sub-classified as mucinous (>50% composed of extracellular mucin) or signet-cell (>50% showing signet ring features characterized by a prominent mucin vacuole that pushes the nucleus to the periphery) or categorized as high-grade/poorly differentiated (<50% gland formation) have been related to aggressive behavior leading to impaired survival.[26] Microsatellite stable tumors are also generally associated with impaired survival. In addition, the effects of some chemotherapeutics used in CRC treatment depend on the molecular characteristics of the cancer, thereby affecting the prognosis, such as KRAS mutations that predict a non-response of anti-epidermal growth factor receptor antibody therapy in metastatic CRC patients.[38]

2.4 Studying prognosis in colorectal cancer patients

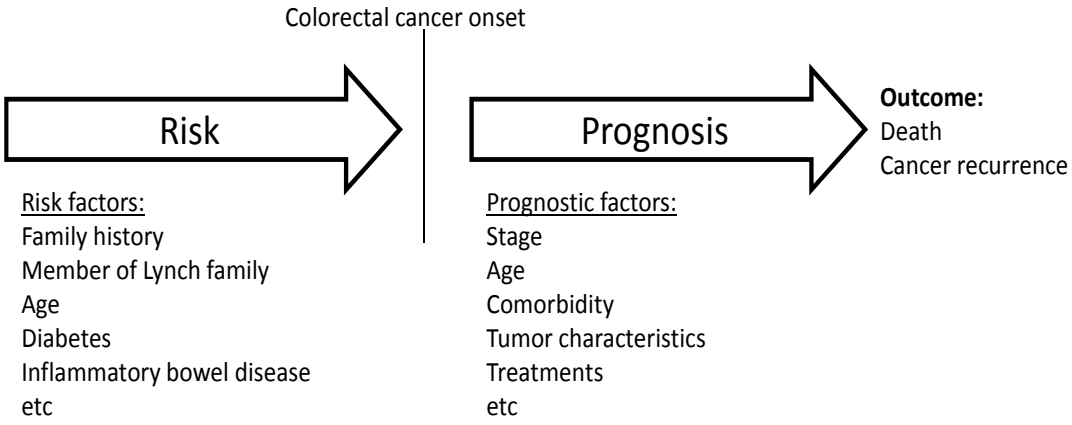

Figure 2.2. Concept of colorectal cancer risk and prognosis

The three studies in this dissertation all focus on prognosis. Prognosis is a prediction of the disease course following its onset and can be described as either a clinical course or natural history.[39] In this dissertation we focus on the clinical course of CRC because it refers to patients that have undergone medical treatment. Natural history refers to prognosis without medical intervention and, thus, describes how patients will fare if nothing is done about their disease.[39] The outcome in studies of prognosis can vary (e.g., complications of treatment, recovery, length of hospitalization, quality of life), but we focus on CRC recurrence and death (i.e. mortality or survival). When studying prognosis, we might not only be interested in describing, for example, time until CRC recurrence or death, but may also identify factors that are associated with improved or impaired prognosis. These factors are usually referred to as prognostic factors and should not be confused with risk factors, as demonstrated in Figure 2.2, although some factors, such as age, might be related to both risk and prognosis. By identifying prognostic factors, patients and physicians can improve prognoses by eliminating or reducing their influence. Therefore, knowledge about prognosis (i.e. the expected course of CRC) and prognostic factors are important to both patients and physicians. Patients are particularly interested in knowing their prognosis (e.g., life expectancy) and how they can improve it. For

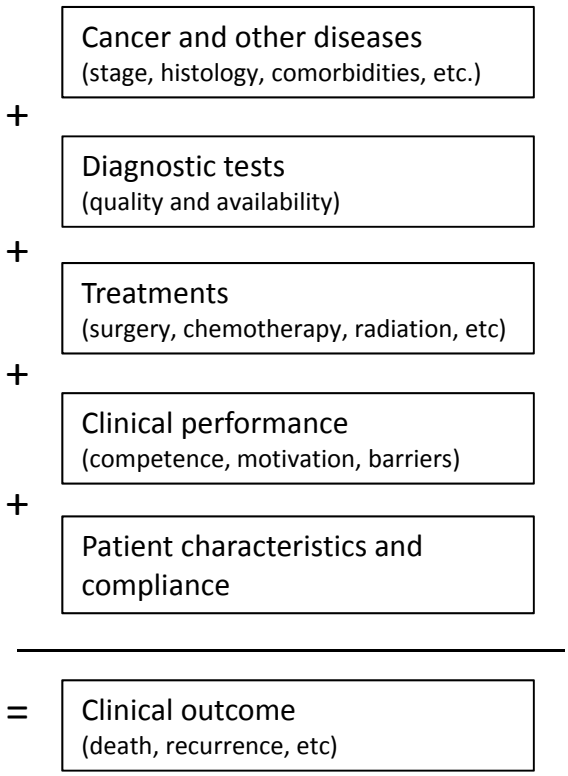

Figure 2.3. Determinants of colorectal cancer outcome

physicians, prognostic knowledge is important to predict, understand, and change the outcome of disease, particularly to delay the time to death. Furthermore, evidence on prognosis is important to decision/policy makers because it can help guide changes in the organization of health care, such as the decision to introduce CRC screening in Denmark from 2014. Figure 2.3 describes the determinants of CRC prognosis.[40]

Another distinction that is important to consider when studying prognosis is the difference between etiology and prediction.[41] The three studies included in this dissertation are etiological studies characterized by a defined hypothesis about a potential causal association between exposure and outcome. When conducted in an observational setting, confounding plays an important role in this association because the exposure is not assigned randomly by the researcher.[42] Thus, patients who are exposed to the factor of interest may differ from the non-exposed patients in other ways that are related to the outcome,

and the association between exposure and outcome can by confused or distorted by the effect of other factors (i.e. confounding). Confounding can be dealt with in both the study design and the statistical analysis. This dissertation demonstrates both methods. When conducting an etiological prognosis study, possible confounding factors that might bias the association under study should be selected *a priori* based on existing evidence of their causal association with the outcome; they should also be related to the exposure and not be a step on the causal pathway between exposure and outcome. Confounding factors should not be selected after evaluating whether they are unequally distributed between exposed and non-exposed patients, or by their effect on changing the estimate in regression analysis.[41] If such an approach is used, the association of interest might be underestimated or overestimated. The regression analysis might fit well with the data if only factors that have a substantial statistical impact are included, but the generalizability will be compromised, which is what should be avoided in etiological studies. A randomized controlled trial is an efficient method of minimizing the effect of confounding factors and the only way to deal with unknown confounding, as it by design randomly assigns people (and confounding factors) to the exposure/treatment or comparison groups.[42] Therefore, this design is considered by many to be the gold standard and the only design that can "prove" causality between exposure and outcome. However, randomized controlled trials are not suited for studying all research questions (e.g., side-effects or long-term outcomes) and have their own inherent problems.[43] For example, randomized trials usually exclude certain patient categories for ethical reasons and offer a setting that is better than the real world setting, thereby losing generalizability. In addition, adherence to treatment might be a problem, resulting in dilution of the results of an association. Moreover, randomized trials are often quite expensive.[43] Eventually, the research question should define the study design, and any potential limitations related to the observational or randomized design should be dealt with as carefully and open-mindedly as possible.

In contrast to etiological studies, the aim of a prediction study is to predict the outcome for future patients based on a number of factors that do not necessarily influence the outcome.[41,44] These factors are usually included based on their ability to help predict the outcome using different statistical approaches. Candidate

factors are selected beforehand, but only included if they have sufficient statistical impact on the result, which is usually defined by a certain significance level. The best statistical model is developed in one setting and tested in another to evaluate its quality at predicting the outcome.[45]

Many studies use methods that can be characterized as a mix of etiological and prediction studies, and along with other studies, the interpretation of the results should reflect the method used.[46]

2.5 Comorbidity and prognosis (study I)

Comorbidity refers to diseases that coexist with the index disease at the time of diagnosis.[47] In this dissertation, the index disease is CRC and comorbidities relate to other diseases diagnosed prior to or at the time of CRC diagnosis. Conditions occurring after CRC diagnosis can be complications of the cancer and are therefore not referred to as comorbidities. These conditions can be intermediate steps between CRC and the outcome and, as mentioned above, should not be thought of as confounders.

Because the median age at CRC diagnosis in Denmark is 71 years,[2,35] many CRC patients are expected to be burdened by comorbidities, with an estimated one-third of Danish CRC patients burdened by severe comorbidities.[3] As previously mentioned, CRC patients are also particularly prone to comorbidity because some diseases are associated with CRC development (i.e. risk factor for CRC). This association may reflect distinct causal mechanisms, similar to insulin resistance and the association between diabetes and CRC, or shared risk factors, such as smoking and the association with chronic pulmonary disease.[17] Of particular interest is the impact of comorbidity on mortality after CRC diagnosis. Comorbidities can affect survival in CRC patients in several ways: they can be independent causes of mortality, delay cancer diagnosis to a more advanced stage,[48,49] lead to more aggressive CRC biology, and impair treatment.[50,51] Comorbidities can be studied as individual diseases, but combining them in an index that summarizes several diseases into a single score is often required in order to study the effect of multimorbidity and generate sufficient statistical power. Charlson's Comorbidity Index (CCI)[52] is a widely used comorbidity index in observational

Table 2.1. Charlson's Comorbidity Index

Disease	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonarydisease	1
Connective tissue disease	1
Ulcerdisease	1
Mild liver disease	1
Diabetes I and II	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ failure	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS	6

studies that include a regression model, thereby controlling for confounding and defining exposure. This index assigns between one and six points to 19 different diseases (Table 2.1), and the sum of these points for each patient can be used to categorize them into different comorbidity groups. The CCI was developed to predict one-year mortality in 559 US medical patients in 1984 but has since been used in many different settings, including cancer research and studies of long-term outcomes.[52] The original data were collected from medical records, but the index has been adapted to administrative databases, facilitating large-scale observational studies.[53] The CCI has been tested against other comorbidity indices in a CRC population and found to be just as useful as the more recently developed indices.[54] In our studies, the CCI was used to define and study individual comorbid diseases, but also on the aggregate level.

2.5.1 Existing literature on comorbidity and prognosis

We searched the existing literature for studies investigating mortality after CRC in patients with different comorbidity levels. The strategy was to include all studies within this area regardless of CRC stage at diagnosis or treatment. However, studies with the primary aim to include comorbidities as covariates rather than investigate the impact of comorbidity (or chronic diseases) on CRC mortality, or in which CRC

could not be differentiated from other cancers, were not included. Studies not available in English were excluded.

To search for studies that potentially included a comparison group from the background population, we used the following query in Medline:

("Colorectal Neoplasms"[Mesh] OR colorectal cancer) AND ("Comorbidity"[Mesh] OR "Chronic disease"[Mesh]) AND ("Mortality"[Mesh] OR "Survival"[Mesh]) AND general population

This query resulted in eight hits, none of which included a comparison group from the general population. Nonetheless, three studies were relevant to our investigation.[55-57]

Next, we expanded the search to identify studies outside the general population as follows:

("Colorectal Neoplasms"[Mesh] OR colorectal cancer) AND ("Comorbidity"[Mesh] OR "Chronic disease"[Mesh]) AND ("Mortality"[Mesh] OR "Survival"[Mesh])

This query resulted in 102 hits. After reading the titles of these publications, the abstracts of 28 papers were collected and reviewed, resulting in a total of 19 relevant studies (two were duplicates from the first search). Of these 19 studies, five were excluded after reviewing the full publication.

Finally, the reference lists of the 14 remaining articles were reviewed, revealing an additional six papers.[50,58-62] Therefore, a total of 20 papers were found to be relevant (Table 2.2).

Table 2.2. Studies of the impact of comorbidity on colorectal cancer survival					
Author/ year	**Journal**	**Design/ country**	**Study population, period, and exposure**	**Outcome of interest**	**Results and comments**
Jørgensen/ 2012[55]	Br J Cancer	Regional case-control and cohort study/ Denmark (Funen)	6,325 cases (≥70 years of age) with cancer (breast, prostate, CRC [n=2,040], lung, or ovary) and 25,299 controls without cancer to study the association with comorbidity (CCI). Cohort of cancer patients to study the impact of comorbidity on survival. 1996-2006	Overall and cancer-specific survival (3 months, 1 year, and 5 years)	Cases with CRC had more comorbid disease than controls, particularly ulcer disease, chronic obstructive pulmonary disease (COPD), vascular disease, renal disease, and diabetes. Overall survival: 5-year HR 1.41 (1.14-1.73) for CCI≥3 compared to CCI=0. The association was 1.00 for cancer-specific mortality. Authors interpret this as CRC patients dying from comorbidities rather than the cancer. No information on stage.
Panis/ 2011[46]	Ann Surg	Nationwide population-based cohort study/ France	All patients who underwent CRC resection (n=84,524) during the 2006-2008 period. Comorbidity was defined as any presently associated diagnosis. The association between the outcome and 13 variables was examined.	30-day postoperative mortality.	Diabetes, vascular, respiratory, and neurological comorbidities were found to be associated with 30-day postoperative mortality in a prediction model. Also showed that laparoscopic surgery is inversely associated with 30-day mortality in a predictive model.
Roxburgh/ 2011[63]	Ann Surg Oncol	Single center cohort study/ UK	302 CRC patients undergoing resection with curative intent, 1997-2005. Comorbidity measured by CCI, Lee Cardiac Risk Index, National Institute on Aging index, and Adult Comorbidity Index (ACE-27). Systemic inflammatory response was measured by a prognosis score (mGPS).	Cancer-specific and overall 5-year mortality.	5-year cancer-specific survival was 77% in CCI=0 compared to 59% for CCI≥4. Corresponding estimates were 62% and 0% for overall 5-year survival. In multivariate analysis, CCI was not significantly associated with mortality, whereas the comorbidity measured by Lee Cardian risk Index was. The systemic inflammatory response also predicted survival, and comorbidity could not fully explain this association.
Sarfati/ 2011[64]	N Z Med J	Cohort study/ New Zealand	11,524 colon cancer patients, 1996-2003. The CCI was used to assess the comorbidity level.	Predictors of comorbidity scores, length of hospital stay, and in-hospital and 5-year survival.	Male gender, advanced age, and unknown extent of disease were associated with high comorbidity levels. Comparing CCI ≥3 to CCI=0, RR of in-hospital mortality was 4.8 (3.5-6.6) and HR after 5 years was 2.0 (1.8-2.3).
Asmis/ 2011[65]	Ann Oncol	Cohort study (based on a RCT comparing cituximab with best supportive care)/ Canada and USA	572 metastatic CRC patients randomly assigned to receive cituximab or best supportive care. Comorbidity measured by the CCI (score 0 vs. ≥ 1).	Overall survival and progression-free survival.	Comorbidity score ≥1 was associated with improved mortality compared to 0 (HR=0.8, 95% CI 0.65-1.00). This association was more pronounced among those treated with cituximab, but was not found among those receiving best supportive care. No association was found between comorbidity and progression-free survival.
Koroukian/ 2010[66]	J Gerontol A Biol Sci Med Sci	Cohort study/ Ohio, USA	CRC patients 65 years of age or older (AUG 1999-NOV 2001). Comorbidity measured by CCI. N=1,009	Likelihood of receiving different treatments. Overall and disease-specific survival.	Comorbidities were associated with increased likelihood of surgery only, but not surgery-chemotherapy. Comorbidity was not associated with overall mortality, but inversely associated with disease-specific mortality (HR 0.78, 95% CI: 0.61-1.00), probably caused by the inclusion of geriatric syndromes and functional disorders in the regression model.
Kleespies/ 2009[67]	Int J Colorectal Dis	Single center cohort study/ Germany	Non-curable stage IV CRC that underwent elective operation (n=156 [colon] and n=77 [rectal]), 1996-2002. Comorbidity measured by individual disease and included as 0-1 and >1 organ.	Postoperative 30-day mortality.	Postoperative 30-day mortality was 5.1% for colon and 3.9% for rectal cancer patients. Comorbidity was not associated with 30-day mortality: HR 0.94, 95% CI 0.69-1.27. Note: Did not use etiological design.
Iversen/ 2009[3]	Dis Colon Rectum	Regional population-based cohort study/ Denmark	CRC patients from 1995-2006 (n=13,190) in the Central and Northern Region of Denmark. Comorbidity according to CCI.	1- and 5- year survival stratified by time periods and surgery types.	One-third had comorbidities. Both colon and rectal cancer patients with moderate and severe comorbidity had increased mortality, 2-fold and 2-3-fold, respectively. Note: No information on stage

Table 2.2. Studies of the impact of comorbidity on colorectal cancer survival					
Author/ year	**Journal**	**Design/ country**	**Study population, period, and exposure**	**Outcome of interest**	**Results and comments**
Sarfati/ 2009[51]	BMC Cancer	Cohort study/ New Zealand	589 colon cancer patients (1996-2003). Data obtained from clinical records. Comorbidity evaluated individually, by counts, and by CCI.	Impact of comorbidity on survival and treatment choice.	CCI ≥3 associated with poorer all-cause mortality (HR 2.63, 96% CI 1.82-3.81) compared to CCI=0. This was also the case for comorbidity counts and individual disease, particularly cardiac disease, vascular disease, diabetes, and renal disease. The results were not as clear for cancer-specific mortality though same patterns were seen. Stage III patients with CCI ≥3 were less likely than CCI=0 patients to be offered chemotherapy (19% vs. 84%) despite the therapy reduced mortality
Janssen-Heijnen/ 2007[58]	Eur J Cancer	Regional cohort study/ Eindhoven Cancer Registry, Netherlands	Lung, breast, and stage I-III colon (n=4,911) and rectal (n=2,674) cancer, 1994-2004. Data extracted from medical records. Modified CCI, but individual diseases were also evaluated	Postoperative complications and mortality. Survival.	For CRC: Postoperative complications were related to cardiovascular disease, reduced pulmonary function, and neurological comorbidity. Comorbidity in general was related to increased mortality (e.g., HR= 1.8 in the presence of 2 or more diseases). In particular, cardiovascular disease, COPD, and diabetes were related to increased mortality.
Gross/ 2006[56]	Ann Intern Med	Cohort study/ USA	SEER-medicare database, 1993-1999, CRC patients 67 years or older. N= 35,755. Comorbidities were identified and grouped according to numbers (0,1-2, ≥3) or individually.	Life expectancy.	Life expectancy was strongly associated with age and the burden of chronic illness, e.g., among men diagnosed with stage I CRC at 67 years of age, life expectancy decreased from 19 years for patients with no comorbidity to 7.6 years for those with ≥3 illnesses. A similar pattern was observed for women and patients with more advanced stages.
Gross/ 2006[68]	J Am Geriatr Soc	Cohort study/ USA	SEER-medicare database, 1993-1999, stage I-III CRC patients 67 years or older. N= 29,733. Chronic conditions selected based on prior publications and clinical judgment.	Adjusted HR for mortality associated with each condition and population attributable risk (PAR).	All chronic conditions were associated with increased mortality (HRs ranging from 1.1 in VTE patients to 1.77 in chronic renal failure patients). 9.4% of deaths were attributable to congestive heart failure, 5.3% to COPD, and 4% to diabetes. Some evidence of the interaction for HR was found between, e.g., CHF and diabetes, but not clearly for other combinations, e.g., diabetes and COPD. Note: This study specifically calls for studies including patients with and without cancer to understand independent effects.
Janssen-Heijnen/ 2005[57]	Crit Rev Oncol Hematol	Population-based cohort study/ Eindhoven Cancer Registry, Netherlands	Included cancers (1995-2002) from several sites, including CRC (n=8,494). Comorbidities were assessed according to a modified CCI.	2- and 5-year survival. The prognostic effect of comorbidity evaluated by Cox regression (etiological model).	The prevalence of comorbidity increased with age from approximately 40% among CRC patients younger than 65 years to around 70% among those older than 80 years 5-year survival: 57% in colon and 62% in rectal patients younger than 70 years and 59% and 51% in those older than 70 years. HRs for CCI=1-2 and ≥3 (compared to CCI=0) were 1.2 (95% C: 1.1-1.3) and 1.4 (95% CI 1.2-1.5) for colon cancer and 1.3 (95% CI 1.1-1.5) and 1.6 (95% CI 1.4-1.9) for rectal cancer, respectively.
Lemmens/ 2005[50]	Br J Surg	Regional cohort study (Eindhoven Cancer Registry)/ Netherlands	6,931 CRC patients >50 years of age, 1995-2001. Comorbidities (adapted CCI) were extracted from medical records.	Rate of treatment and survival according to level or specific comorbidity.	Co-morbidity had no influence on resection rate, but was associated with a lower probability of receiving adjuvant chemotherapy (particularly previous malignancy and COPD, and the combination of diabetes and hypertension in rectal cancer). The stoma rate was not influenced by comorbidity. Mortality increased with increasing comorbidity: HR=1.4 for colon and 1.6 for rectal cancer cases with ≥ 2 comorbidities compared to those without comorbidity. Previous malignancy, cardiovascular disease, COPD, and hypertension (only rectal cancer) were individual factors associated with death. Combination of hypertension and diabetes was also associated with death.

Table 2.2. Studies of the impact of comorbidity on colorectal cancer survival					
Author/ year	**Journal**	**Design/ country**	**Study population, period, and exposure**	**Outcome of interest**	**Results and comments**
Read/ 2004[69]	J Clin Oncol	Single-center (Barnes Jewish Hospital) cohort study/ USA	11,558 cancer patients (breast, lung, CRC [n=1,878], or prostate), 1995-2001. Comorbidity according to ACE-27 index including 27 different ailments.	Prognostic impact of comorbidity on 1-year overall survival.	Among CRC patients, 37% had no comorbidity, and 9.5% had severe comorbidity. Comparing moderate/severe comorbidity cases to non/mild cases, the HR was 2.48 (1.67-3.68) for localized CRC and 1.28 for metastatic disease. The proportion of explained variation was 4.69 in localized CRC and 0.58 in metastatic CRC.
Ouellette/ 2004[59]	SSAT Annual Meeting	Single-center cohort study/ USA	279 CRC patients undergoing laparotomy, 1997-2001. Comorbidity assessed by Charlson-Age-Comorbidity Index: Age included by adding 1 point for each decade after 40 years.	Mortality and morbidity evaluated by different measures.	Median follow-up was 18.5 months. Comparing the lower age-comorbidity index to the higher index by different cut-offs revealed an HR of 3.8-5.6. For each 1 point increase in the Age-Comorbidity index, peri-operative (30 day) mortality increased by 36%.
Munro/ 2004[60]	Eur J Cancer Care	Single center cohort study/ Tayside Scotland	483 CRC patients referred for chemotherapy or radiation (both incident and recurrence), 1997-1999. Comorbidity assessed according to CCI. Socioeconomic deprivation assessed by Carstairs.	Cause-specific survival and overall survival comparing comorbidity scores and deprivation scores.	Comorbidity was present in 48% of patients. 3-year cause-specific survival without comorbidity 54%, 45% with comorbidity (no estimates given for overall survival). Cox regression demonstrated an independent effect of comorbidity on survival, i.e. deprivation did not account for the excess mortality.
Rieker/ 2002[70]	Langenbeck's Arch Surg	Single center cohort study/ Germany	531 operated CRC patients, 1991-1995. Comorbidity was assessed according to the CCI.	Overall survival evaluated by Kaplan-Meier method. Prognostic model with backwards selection used to evaluate different covariates' (including CCI) associations with death.	Survival was 59% among CCI= 0-2 and 32% among CCI≥3 (follow-up time not specified). HR of CCI≥3 vs. 0-2: 1.77 (95% CI 1.29-2.42) for overall survival. CRC patient with CCI≥3 had an almost four-fold increased risk of dying from non-CRC-related causes compared to CCI=0-2.
De Marco/ 2000[61]	Eur J Cancer	Regional cohort study (Eindhoven Cancer Registry)/ Netherlands	3355 CRC patients, 1993-1995. Comorbidities (adapted CCI) were extracted from medical records.	Prevalence of comorbidities by gender and age. Influence of comorbidity on resection rates and short-term mortality.	35% of patients < 70 years of age and 61% of patients ≥ 70 years of age had at least 1 comorbid disease (most frequently cardiovascular disease, previous cancer, and hypertension). Comorbidity was not associated with resection rate, but was negatively associated with short-term mortality (only p-values provided).
Yancik/ 1998[62]	Cancer	Retrospective medical record review from SEER registry/ USA	799 males and 811 female colon cancer patients.	Prevalence of comorbidity and association with 2-year survival.	Hypertension, heart conditions, gastrointestinal "problems", arthritis, and COPD were prevalent in colon cancer patients. 28% died within 2 years, and the number of comorbid diseases was associated with increased mortality (p=0.0007).

In summary, Table 2.2 shows that various publications from many different settings over the last 15 years have investigated the impact of comorbidity on CRC survival. One of the two studies from Denmark demonstrated that CRC was associated with a poor 5-year survival of approximately 40-50%, even in the absence of comorbidities, but in the presence of a high comorbidity burden (defined as CCI ≥3), the 5-year survival was as low as 20%.[3] This pattern was confirmed by most of the studies outlined in Table 2.2. In a study of nearly 30,000 American CRC patients older than 67 years of age at diagnosis, approximately 9% of deaths were attributed to congestive heart failure, >5% to chronic obstructive pulmonary disease (COPD), and nearly 4% to diabetes.[68] This study also confirmed that coexistence of more than one comorbidity is both common and exerts a substantial effect on CRC survival.[68]

2.5.1.1 Limitations of the existing literature

Although numerous studies have shown that CRC patients burdened by comorbidities have increased mortality compared to CRC patients without coexisting disease, no study of CRC mortality has included a cohort free of CRC while accounting for comorbidity. Therefore, whether comorbidity interacts with CRC to increase the mortality rate beyond what can be explained by CRC and comorbidities acting alone is unknown. Such information is needed to improve our biological understanding of the influence of comorbidity on CRC mortality, and clinically to guide treatment and patient information. Therefore, we decided to conduct a nationwide cohort study (study I) addressing these exact limitations.

2.6 Clinical characteristics and survival after interval colorectal cancer (study II)

The concept of interval cancer arises from screening programs and refers to cancers that occur in the interval between screening tests. In the area of CRC, no internationally accepted screening program currently exists, though colonoscopy seems to be the preferred modality,[8] and the term interval CRC has been used in many different settings with different screening modalities, including fecal occult blood test, sigmoidoscopy, and colonoscopy.[8,71,72] The optimal time interval between CRC screening tests is also

controversial, making the concept of interval CRC even more confusing. Some authors have suggested using more specific terms according to the relevant setting (e.g., post-colonoscopy CRC[73]), but this has not yet met broad acceptance. Therefore, we use the term "interval CRC" in this dissertation as most readers familiar with this particular field of research would expect this term. We acknowledge that the term can be confusing, especially in the Danish setting without broad CRC screening. We will use the term "interval CRC" for CRC arising after a colonoscopy during which CRC was not detected, unless we otherwise specify the exact definition. We will not focus on CRC arising after fecal occult blood test or sigmoidoscopy.

As mentioned briefly, colonoscopy has proven to be very effective in the detection of CRC, and endoscopic polypectomy offers the potential of arresting CRC development.[27,74] Thus, colonoscopy is used as a screening test in the USA,[8,75] but also as a diagnostic examination of symptomatic patients. Studies suggest that CRC risk decreased for more than 10 years after a negative colonoscopy.[6,34] Nonetheless, recent reports suggest that 5-8% of all CRC cases are diagnosed in patients who undergo colonoscopies in the 3-5 years preceding diagnosis.[10,76-79]

Although interval CRC can derive from missed lesions or insufficiently resected polyps,[80] some studies have suggested that a subset of interval CRC cases represent rapidly growing and aggressive cancers[28,76,81] associated with poor survival. By comparing survival between interval CRCs and sporadic CRC patients (i.e. CRC cases with no previous colonoscopy), evaluating whether interval CRC has a particularly aggressive course (i.e. specific biology), rather than a course similar to garden-variety CRC, is possible. Specific characteristics, such as advanced stage and mucinous histology at diagnosis, might also reflect aggressive tumor biology as described in section 2.4. Therefore, study II aimed to evaluate clinical characteristics and survival in patients with interval CRC compared to patients with sporadic CRC.

2.6.1 Existing literature on interval colorectal cancer

We searched the existing literature for studies written in English that investigated survival after interval CRC. We also searched for studies that compared clinical characteristics other than survival in patients diagnosed with interval CRC to non-interval CRC. First, we searched Medline using the following query:

(Interval OR post colonoscopy) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer) AND ("Mortality"[Mesh] OR "Survival"[Mesh])

This query resulted in 673 publications, but none were relevant. Next, we searched Medline using the following query:

"Colonoscopy"[Mesh] AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer) AND ("Mortality"[Mesh] OR "Survival"[Mesh])

This query resulted in 265 publications. After reading the titles, six papers were included for abstract review and one was found relevant for describing the characteristics of interval CRC.[77] The same query, but including colonoscopy as a general word and not as a Mesh-term, provided 64 additional hits; none were relevant. We expanded the search in Medline using the following query:

"interval colorectal cancer" OR "interval colorectal cancers" OR "post colonoscopy" OR "colonoscopy screening" OR "complete colonoscopy"

This query resulted in 418 publications. After reading the titles, 33 were selected for abstract review and 20 were selected for full review. Of these 20 reports, seven described survival patterns in interval CRC (one was a duplicate from above[77]), and another two compared the characteristics at diagnosis between interval and non-interval CRC. Finally, we searched Medline using the following query:

"Interval cancer AND colonoscopy"

This query resulted in 921 hits and 35 publications that were relevant, six of which had already been identified. After reading the abstracts we included one additional publication[82] comparing clinical characteristics. Finally, we reviewed the reference lists of the publications that had been identified, but no additional publications were found. Therefore, we ended up with a total of 10 relevant studies (Table 2.3)

Table 2.3. Studies comparing clinical characteristics and/or survival among interval and non-interval colorectal cancer patients

Author/ year	Journal	Design/ country	Study population and exposure	Aim/outcome of interest	Results and comments
Gill/ 2012[71]	Br J Cancer	Population-based cohort study (The Northern Colorectal Cancer Audit group), 2007-2010/UK	Biennial fecal occult blood testing followed by colonoscopy after positive result. Interval CRC defined as CRC occurring between screening rounds	Demographics, tumor characteristics, and survival were compared between controls (diagnosed before first screen invite), screen detected, interval CRC, and non-uptake CRC.	192 (23%) cases were interval CRC. Compared to screen-detected CRC, interval cases were older, more likely to be female, have proximal location, and to be advanced cancer stage, and survival was impaired. Interval CRC was virtually identical in regards to measured characteristics and survival s compared to controls. Note: This paper did not fulfill the criteria set up in the literature search, but was included because the existing literature including survival estimates was sparse.
Brenner/ 2012[82]	Gut	Case-control study, 2003-2007/Germany	Cases=interval CRC (colonoscopy 1-10 years prior to diagnosis). Controls=screen detected CRC *or* non-CRC patients with negative colonoscopy	Compare sociodemographic and tumor characteristics, and colonoscopy characteristics.	Compared to screen detected CRC: Female sex and cecum/ascending location were independently associated with interval CRC. Compared to non-CRC controls: Positive FOBT prior to colonoscopy and incomplete exam were independently associated with interval CRC,
Manser/ 2012[83]	Gastrointest Endosc	Population-based closed cohort study, 2001-2007 /Switzerland	People 50-80 years of age invited for colonoscopy screening. 2,044 of 22,818 signed up (132 excluded from study due to insufficient examination)	Risk of CRC comparing screened and non-screened. Comparison of CRC characteristics.	11 CRC cases were detected at baseline screening and only 1 CRC case occurred during follow-up, preventing any comparison of "interval CRC" and sporadic CRC. Screening colonoscopy was associated with decreased CRC risk.
Shaukat/ 2012 [72]	Dig Dis Sci	Single center cohort study (VA center), 1991-2004/ MN USA Note: Same population as Farrar et al below.	Interval CRC defined as CRC occurring 1-5 years after complete colonoscopy (n=65). Frequency matched to non-interval CRC with no previous colonoscopy (n=131). 98% were men.	Comparison of KRAS mutation, MSI, and survival (5-year follow-up).	Interval vs. non-interval CRC: KRAS mutation: 12.9% vs. 28.9% (p=0.03). OR=0.36 (0.15-0.90) in multivariate analysis. MSI 29% vs. 11% (p=0.004) BRAF mutation 28% vs. 19% ("non-significant") Survival was similar comparing KRAS mutation to non-mutated cases and interval to sporadic cases.
Cooper/ 2012[84]	Cancer	Prevalence study based on the SEER-medicare database, 1994-2005/USA	CRC patient ≥69 years of age. Interval CRC defined by colonoscopy 6-36 months prior to diagnosis. Detected CRC were cases with colonoscopy within 6 months of diagnosis.	Comparison of characteristics between interval and detected CRC. A regression model was used to determine the odds of interval cancer by different variables.	Total of 4,192 interval CRC cases and 53,647 detected CRC cases were included out of 299,260 initially identified patients. Interval cases were older, had higher comorbidity scores, higher diverticular disease prevalence, more early stage tumors, and were more likely to be proximal. In addition, polypectomy was associated with interval CRC, whereas gastroenterologists and physicians with high polypectomy rates and high colonoscopy volume had lower odds of interval CRC.
Singh/ 2010[77]	Am J Gastroenterol	Population-based prevalence and cohort study, 1992-2008/Manitoba, Canada	50-80 years with CRC Early/missed cancer defined as colonoscopy 6-36 months (n=388) prior to diagnosis. Compared to "detected" cancers (n=4,495) with colonoscopy within 6 months of diagnosis.	Patient, endoscopy, colonoscopy, and CRC factors associated with early/missed CRC.	CRC miss rate 7.9%. Women had a higher miss rate than men. Predictors of early/missed CRC were prior colonoscopy (particularly with polypectomy), absence of comorbidity, family physician, recent years, and proximal site of CRC. Survival was identical (hazard ratio adjusted for gender and age was 0.99 (0.84, 1.17)). Stage was similar.

Table 2.3. Studies comparing clinical characteristics and/or survival among interval and non-interval colorectal cancer patients

Author/ year	Journal	Design/ country	Study population and exposure	Aim/outcome of interest	Results and comments
Shaukat/ 2010[85]	Dig Dis Sci	Single center cohort study (VA center), 1991-2004/ MN USA Note: Same population as Farrar et al below.	Interval CRC defined as CRC occurring 1-5 years after complete colonoscopy (n=63). Frequency matched to non-interval CRC with no previous colonoscopy (n=131). 98% were men.	Comparison of BRAF mutation and survival (5-year follow-up).	Interval vs. non-interval CRC: BRAF mutation: 28% vs. 19% (p=0.18). BRAF OR=0.93 (0.15-0.90) in multivariate analysis. Proximal location and MSI were independently associated with interval CRC. Survival was worse comparing BRAF mutation to non-mutated cases, particularly in microsatellite stable patients.
Arain/ 2009[76]	Am J Gastroenterol	Single center cohort study (VA center), 1989-2004/ MN USA Note: Same population as Farrar et al below.	Interval CRC defined as CRC occurring 1-5 years after complete colonoscopy (n=63). Frequency matched to non-interval CRC with no previous colonoscopy (n=131). 98% were men.	Comparison of CIMP status and survival (5-year follow-up).	Interval vs. non-interval CRC: CIMP: 57% vs. 33% (p=0.004). CIMP OR=2.41 (1.2-4.9) in multivariate analysis. Proximal location and MSI were also independently associated with interval CRC. Survival was similar comparing CIMP to non-CIMP cases.
Sawhney/ 2006[86]	Gastroenterol	Single center cohort study (VA center), 1989-2004/ MN USA Note: Same population as Farrar et al below.	Interval CRC defined as CRC occurring 1-5 years after complete colonoscopy (n=51). Frequency matched to non-interval CRC with no previous colonoscopy (n=112). 98% were men.	Comparison of microsatellite instability and survival (5-year follow-up).	Interval vs. non-interval CRC: Microsatellite instability: 30% vs. 10% (p=0.003). OR=3.7 (1.5-9.1) in multivariate analysis. Proximal location and MSI were also independently associated with interval CRC. No difference in tumor stage, histological type or grade, or survival was found.
Farrar/ 2006[81]	Clin Gastroentol Hepatol	Single center cohort study (VA center), 1989-2004/ MN USA	Interval CRC defined as CRC occurring 1-5 years after complete colonoscopy (n=45). Compared to frequency matched non-interval CRC with no previous colonoscopy (n=90). 98% were men.	Inadequate earlier colonoscopy, incomplete polypectomy, or aggressive tumor behavior including survival (5-year follow-up).	Interval vs. non-interval CRC: Right-sided: 51% vs. 29% (p=0.01). Tumor size: 3.5 cm vs. 4.4 cm (p=0.02). No difference in tumor stage, histological type or grade, carcinoembryonic antigen level, or survival (5-year: 36% vs. 46%) was found.

In summary, a total of seven reports compared survival between interval and non-interval CRC, but five of them originated from the same population, and one study defined interval CRC based on previous fecal occult blood tests. The five reports from the same population included comparisons of molecular characteristics, and another three papers compared clinical characteristics between interval and non-interval cases.

2.6.1.1 Limitations of the existing literature

Previous studies did not find any difference in survival between interval CRC cases and cases with no prior colonoscopy.[77,81] These studies were hampered by small sample sizes (between 50 and 400 cases), lack of clinical information (e.g., comorbidity), and an arbitrary choice of the interval between colonoscopy and diagnosis for the definition of interval or missed CRC (e.g., 6-36 months or 1-5 years).[72,76,77,81] In addition, with the exception of one population-based study,[77] other analyses of survival were based on one study population from a single medical center consisting of 98% males.[72,76,81,85,86]

In study II, we conducted a nationwide population-based cohort study of CRC arising after colonoscopy to evaluate demographic, tumor, and comorbidity characteristics and survival.

2.7 Survival and recurrence after pre-operative stenting (study III)

Ideally, CRC surgery is performed in an elective setting, allowing for optimization of patient medical and surgical status, complete oncological staging, and a decreased need for stoma and multi-staged operations.[11] However, obstruction occurs in approximately 10% of CRC cases requiring emergency surgery with/without stoma or endoscopically placed SEMS.[87,88] SEMS are used to avoid palliative stoma surgery in incurable patients and as a bridge to elective surgery with curative intent.[11] By serving as a bridge to surgery, SEMS can convert acute CRC resection associated with 30-day mortality as high as 20% to elective resection with 30-day mortality of approximately 5%.[89] In addition, elective surgery is related to a lower risk

of permanent stoma compared to acute resection, which is substantially important for quality of life among CRC patients.[90] Although SEMS have been used since the early 1990s and numerous studies, including randomized trials, have evaluated their safety, efficacy (results in ideal situations), and effectiveness (results under usual conditions), controversy still exists about their use, especially in the bridge to surgery setting.[91-97] This controversy mainly arises from the conflicting results regarding complications related to the stenting procedure.[98] Observational studies have reported technical and clinical success rates of more than 90% for stent placement. In these observational settings, SEMS placement results in symptom relief and improved short-term morbidity and mortality compared to acute surgery,[91,92] but these findings have not been reproducible in randomized trials.[96-98] Several trials have been terminated prematurely due to high complication rates among SEMS patients that could alert clinicians about their use.[99,100] However, the trials have been criticized for having lower than expected success rates due to inexperienced endoscopists, thereby not providing generalizable results.[101]

Another concern about the use of SEMS that we attempt to address in study III is the possibility of stents inducing tumor dissemination, thereby increasing CRC recurrence and worsening long-term survival. This concern has been emphasized by studies showing high frequency of tumor reappearance or silent perforation among CRC patients undergoing stenting.[100,102] Unfortunately, very little evidence exists for the long-term outcomes after SEMS placement in obstructive CRC patients.

2.7.1 Existing literature on prognosis after pre-operative stenting

We searched the existing literature for studies of long-term mortality and recurrence after stent placement in CRC patients. Publications that were not in English or that only reported short-term mortality defined as either in-hospital or 30-day mortality were excluded. We required that the studies had a comparison group of CRC patients undergoing surgery. We included reviews with meta-analyses if they were related to recurrence or mortality. We used the following query in Medline:

("Stents"[Mesh] OR stent OR endolaparoscopic) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer OR colorectal obstruction) AND ("Mortality"[Mesh] OR mortality OR "Survival"[Mesh] OR survival)

The query resulted in 228 hits, of which we read 114 abstracts. Among these 114 publications, 22 were selected for full review and 16 were relevant. We found one additional relevant publication[100] by reviewing the reference lists of the 16 papers.

Next, we searched the existing literature for studies of CRC recurrence after stent placement using the following query:

("Stents"[Mesh] OR stent OR endolaparoscopic) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer OR colorectal obstruction) AND ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] or recurrence)

This query resulted in 57 hits, of which we reviewed 10 abstracts. None of these 10 studies were relevant to our investigation.

Table 2.4. Studies comparing colorectal cancer mortality or recurrence after stent placement with primary resection					
Author/ year	**Journal**	**Design/ country**	**Study population and exposure**	**Outcome of interest**	**Results and comments**
Kim/ 2012[103]	Int J Colorectal Dis	Single center cohort study/ South Korea (1996-2007)	Left-sided CRC: 25 patients undergoing stent-laparoscopy vs. 70 patients undergoing emergency open lavage (primary anastomosis with resection).	Overall survival and tumor recurrence.	Median follow-up was 51 months. The 5-year overall survival was 67% in stent vs. 62% in primary surgery (p=0.233). The overall recurrence rate in stage II and III patients was 35% in both groups (time to recurrence not specified and competing risk analysis not used).
Knight/ 2012[104]	Int J Colorectal Dis	Single center cohort study/ UK (1998-2008)	Left-sided CRC: 15 SEMS patients with subsequent surgery vs. 88 elective resection patients.	Long-term survival.	5-year survival for SEMS was 60%, 58% for patients with elective resection (p=0.96).
Lee/ 2012[105]	Am J Surg	Single center cohort study/ Korea (2000-2008)	Obstructive colon cancer and unresectable synchronous metastases (stage IV). 88 of 132 patients were included (reason for non-inclusion not provided). 36 had SEMS and 52 had surgery.	Complication/morbidity rates, length of hospital stay, stoma formation, time until starting chemotherapy, survival.	Complication rate was 25% for SEMS compared to 30.6% in surgical patients (p=0.157). Median hospital stay was 7.2 days in SEMS vs. 12.3 days in surgical patients. Stoma formation was 16.7 in SEMS vs. 38.5 in surgical patients (p=0.021). Median time to chemotherapy was 8.1 days in SEMS vs. 21.7 in surgical patients (p=0.001). Median survival was 7.6 months in SEMS vs. 15.9 in surgical patients (p=0.002).
Zhang/ 2012[91]	Surg Endosc	Meta-analysis/ China	8 studies comparing SEMS as a bridge to surgery to emergency surgery; only 4 reported long-term survival (Saida, Pessione, Dastur, and Xu). Two studies reported short-term mortality (Saida and Baik).	Treatment details, short-term adverse events, and long-term outcomes.	No difference in short-term mortality (RR=0.73, 95% CI 0.31-1.71) 1-year mortality (n=309): RR= 1.07, 95% CI 0.87-1.31 2-year mortality (n=390): RR=1.14, 95% CI 0.98-1.34 3-year survival (n=374): RR=1.08, 95% CI 0.90-1.31
Alcántara/ 2011[102]	World J Surg	Single center randomized controlled trial/ Spain (2004-2006)	Obstructive left-sided colonic cancer. Group 1: Stent and surgery (n=15). Group 2: Emergency intra-operative colonic lavage (n=13).	Operation time, complications, hospitalization details (e.g., length), economy, and survival.	The study was suspended upon detecting excess morbidity in group 2. Mean follow-up was 37.6 months with no difference in survival (p=0.843). No estimates provided. 'Tumor reappearance' was more frequent in group 1 (8 cases) compared to group 2 (2 cases) (p=0.055).
Van Hooft/ 2011[99]	Lancet Oncology	Multicenter (n=25) randomized trial/Netherlands (2007-2009)	47 SEMS patients and 51 emergency surgery patients presenting with acute obstruction.	Primary: Mean global health status during 6-month follow-up. Secondary: mortality, morbidity, stoma rate.	Primary: No difference Secondary: 30-day mortality: 5 deaths in each group, 0.92 (0.28-2.98). Overall 9 deaths in each group: 0.92 (0.40-2.12). Study prematurely terminated due to increased morbidity in SEMS group.
Vemulapalli/ 2010[106]	Dig Dis Sci	Single center cohort study/ USA (2002-2008)	Stage IV CRC: 53 SEMS vs. 70 acute surgery.	Overall survival.	Median survival was 24 weeks for SEMS vs. 23 weeks for surgery (p=0.76).
Pirlet/2010[100]	Surg Endosc	Multicenter (n=9), randomized controlled trial/France	60 were randomized to acute surgery or SEMS as a bridge to elective surgery.	Primary: need for stoma Secondary: mortality, morbidity, length of hospital stay.	Stoma: 17 surgery vs. 13 SEMS Mortality: surgery deaths n=1, SEMS deaths n=3. 8/30 SEMS had silent perforations. The study was closed prematurely because of 3 colonic perforations.

Table 2.4. Studies comparing colorectal cancer mortality or recurrence after stent placement with primary resection					
Author/ year	**Journal**	**Design/ country**	**Study population and exposure**	**Outcome of interest**	**Results and comments**
Kim/2009[107]	World J Surg	Single center cohort study/Korea (1999-2007)	35 left-sided colon cancer patients with SEMS: 350 elective non-obstructive left-sided colon-cancers (matched for stage II, III, and IV) Rectal cancer patients and TNM stage I were excluded.	Followed at 3-month intervals for the first 3 years, and 6-month intervals for 4-5 years and annually thereafter for medical history, examination, blood test, X-rays and CT/MRI. Survival was estimated among other things.	Time from SEMS to surgery: 8.6±5.5 days. Mean age 61 years. Overall 5-year survival: 38.4% (SEMS) vs. 65.6% (p=0.025) Disease-free 5-year survival 48.3% (SEMS) vs. 75.5% (p=0.024)
Dastur/ 2008[108]	Tech Coloproctol	Single center/UK (1997-2002)	19 patients with SEMS, 23 patients undergoing emergency surgery.	Short term: 30-day mortality, complications, hospital length, ICD admission, postoperative complications. Overall 3-year survival.	Median delay to surgery was 70 days (1-223) in SEMS patients. 12 SEMS acted as a bridge to surgery. 30-day mortality: 9% SEMS vs. 13% in emergency surgery. 3-year survival: 48% in SEMS vs. 46% in emergency surgery, p=0.54 (similar when restricted to curative resections).
Faragher/ 2007[109]	Colorectal disease	Single center cohort study/ Australia (1998-2006)	Incurable left-sided CRC: 29 had stent treatment (4 went on to surgery) and 26 had primary acute surgery.	Overall survival.	Median survival after stenting was 14 months vs. 11 months after surgery (p=0.89).
Tilney/ 2007[95]	Surg Endosc	Review with meta-analysis/ UK	10 studies comparing SEMS and open surgery in patients with large bowel obstruction were included (451 patients incl. 244 SEMS). Three studies reported long-term survival (Saida, Carne, and Law).	Treatment details, functional recovery, short-term adverse events, and long-term outcomes (stoma and survival).	Short-term adverse events: Significant benefit towards SEMS patients, e.g., post-operative mortality: OR 0.45 (95% CI 0.22-0.91) No difference in long-term mortality: Weighted mean difference 14.7 (95% CI -77 - 107.4). Note: Age and disease stage were not taken into account.
Ptok/ 2006[110]	World J Surg	Single center cohort study/Germany (1999-2005)	Incurable stenosing CRC: 38 treated with SEMS and 38 with surgery.	Median survival	3 patients from the SEMS group underwent subsequent surgery because of complications. Median survival was 9.9 months in SEMS vs. 7.8 months in the surgery group (p=0.506).
Carne/ 2004[111]	Dis Colon Rectum	Single-center comparison/ New Zeeland (1997-2002)	Left-sided CRC stage IV patients: 25 SEMS and 19 open surgery patients.	Median survival	Median survival was 3.9 months for open surgery and 7.5 months for SEMS patients (p=0.2156).
Johnson/ 2004[112]	Ann R Coll Surg Engl	Single center cohort study/ UK (no study period provided)	Obstructive CRC: 18 SEMS patients were matched for disease and sex to 18 stoma controls.	Survival	Median age was 81 years among stent vs. 70 years among stoma patients. Stent patients were more comorbid. Median survival 92 days in stent vs. 121 days in stoma patients (p=0.5).
Law/2003[113]	Br J Surg	Single center comparison/ Hong Kong (1997-2002)	Incurable obstructive CRC distal to the splenic flexure treated with SEMS (n=30) or surgery (n=31) (1997-2002).	Median survival	Median survival in SEMS patients 107 days, 119 days in the surgical group (p=0.088). Note: Subsequent surgery was only performed in 6 SEMS patients.
Saida/2003[114]	Dis Colon Rectum (abstract)	Single center cohort study/Japan (1986-2001)	44 SEMS (1993-2001) and 40 emergency operations (1986-1996).	Postoperative complications and long-term prognosis.	Complications: significantly less frequent 3-year survival: 50% vs. 48% 5-year survival: 44% vs. 40% (no 95% CI)

To summarize, of the 17 relevant publications (Table 2.4) comparing stenting procedures and primary surgery, 15 were single center studies or reviews with meta-analyses of such, two were multicenter investigations, and none were population-based. Three studies were randomized trials including 15 to 47 patients in the stenting arm, and all were prematurely terminated because of high complication rates in either the stenting arm[99,100] or among patients undergoing acute surgery.[102] Of the observational studies, only one reported the risk of recurrence in addition to survival after stent placement and two studies included elective surgery as a comparison group.

2.7.1.1 Limitations of the existing literature

The main limitation of the existing literature is a lack of large population-based investigations facilitating generalizability to the broad population based clinical setting. Much of the existing literature – particularly the observational investigations – is based on highly specialized centers with a high volume of stenting procedures conducted by one or few expert endoscopists. Furthermore, the existing literature includes too few patients to control for confounding by, for example, age, CRC stage or location, or comorbidity in the statistical analysis; therefore, the existing evidence is likely to be biased by these and potentially other factors. As previously mentioned, the randomized trials – which might not face the same confounding issues – have not been able to provide clear answers regarding the use of SEMS in the setting of obstructive CRC and are particularly vulnerable when studying long-term outcomes. Therefore, in study III, we aimed to investigate long-term survival and recurrence in a population-based setting while adjusting for important potential confounders in order to address some of the concerns related to the use SEMS.

3. Aims of the dissertation

The review of the existing literature revealed that, although several studies have shown that CRC patients burdened by comorbidities have increased mortality compared to CRC patients without comorbidity, no study has included a cohort free of CRC while accounting for comorbidity. In addition, the existing literature has evaluated survival after interval CRC to only a very limited extent and used different arbitrary definitions of "interval CRC". Finally, long-term mortality and risk of recurrence after using SEMS as a bridge to surgery in patients with obstructive CRC has been evaluated primarily in small, specialized settings without accounting for important potential confounders and no population-based investigations exist. To address these gaps in the existing evidence, we conducted three studies with the following aims:

Study I: To examine the interaction between comorbidity and CRC and the subsequent risk of death, conducting a nationwide population-based cohort study of all Danish CRC patients compared to a population-based cohort free of CRC.

Study II: To evaluate demographics, comorbidity characteristics, and survival in CRCs arising in the years after colonoscopy and compare to CRC patients with no colonoscopy prior to diagnosis, in a nationwide population-based setting.

Study III: To investigate mortality and recurrence after CRC surgery with pre-operative stenting compared to CRC patients undergoing primary acute or elective surgery, in a nationwide population-based setting.

4. Methods

4.1 Setting

All three studies were conducted within the entire Danish population of approximately 5.5 million people.[115] In Denmark, tax-funded health care is provided equally to all citizens. Essentially, all Danish CRC patients are managed by public hospitals and their outpatient clinics.

4.2 Data sources

The Civil Registration System (CRS) assigns a unique 10-digit identifier (the CPR number) at birth or immigration to all Danish inhabitants, which is used in all contacts with public authorities, including health care contacts, facilitating linkage of information between registries on an individual level.[115,116] The CRS was established in 1968, keeps track of vital status and residential address for all Danish inhabitants, and is updated daily.

The Danish Cancer Registry (DCR) has recorded all incident malignant neoplasms in Denmark since 1943 and is based on notifications from hospital departments, specialists, and autopsy reports.[117,118] Individual-level data in the DCR are linked to histopathological findings in the Danish Pathology Registry (DPR) to secure high data quality. The data include CPR number, month and year of cancer diagnosis, cancer type/site, primary histology, and tumor spread at diagnosis. In 2004, three important administrative changes occurred: (i) reporting to the DCR became electronic and through the Danish National Registry of Patients (DNRP), (ii) the date of diagnosis was defined as date of the first cancer-related admission (until 2004 the diagnosis date was defined as the month of hospitalization), and (iii) the classification system changed from International Classification of Disease (ICD) version 7 to ICD-10.[119] In addition, the recording of cancer stage was changed to the TNM system from the Duke's system for CRC.

The Danish National Registry of Patients (DNRP) has tracked all non-psychiatric hospitalizations in Denmark since 1977 and outpatient hospital contacts since 1995.[120,121] The recording is mandatory and the data are used for administrative purposes and to monitor health care, including costs. For each hospital contact, the DNRP records CPR number, dates of admission and discharge, procedure and surgery codes, selected treatments (e.g., chemotherapy), and up to 20 discharge diagnoses coded by physicians according to the ICD system (8th revision until the end of 1993 and 10th revision thereafter; the 9th edition has never been used in Denmark). Since 1996, surgery codes have been recorded according to the Nordic Medico-Statistical Committee Classification (NOMESCO) of Surgical Procedures.[122] Procedures and treatments are coded according to a Danish classification system.

The Danish Pathology Registry (DPR) has recorded all pathology diagnoses in Denmark according to Systematized Nomenclature of Medicine (SNOMED)[123] codes since 1997, and to some extent since the 1970s. The DPR data also include the CPR number, date of biopsy/resection, and requisition numbers. This registry is based on data transfer from the Danish Pathology Databank, which is a daily updated system used for clinical practice by all Danish pathologists.[124,125]

Paper Medical records: In study II, we included information from 101 CRC patients from the catchment area of Aalborg Hospital to obtain detailed data on colonoscopy indication, completeness, and preparation quality, which is not recorded in the existing registries. In study III, we validated the secondary outcome (CRC recurrence) among 15 patients also from Aalborg Hospital.

4.3 Study design

The three studies were designed as nationwide population-based cohort investigations utilizing information from the Danish data sources mentioned above (i.e. historical or retrospective cohort studies).

4.4 Study populations

Study I included all incident CRC patients recorded in the DCR between 1 January 1995 and 31 December 2010. In this study, we used the DNRP and CRS to match each CRC patient with five persons from the general population who were alive and without a CRC diagnosis at the time of the CRC patient's diagnosis. Matching criteria were age (5-year intervals), gender, and presence of the comorbidity groups included in the CCI, with the addition of atrial fibrillation and obesity.

In studies II and III, we included all incident CRC cases recorded in the DCR between 1 January 2000 and 31 December 2009 and 1 January 2005 and 31 December 2010, respectively. These studies did not include a matched comparison cohort without CRC, but internal comparisons were performed within the CRC cohorts.

4.5 Main exposures

The exposure in study I was CRC and comorbidity in order to examine whether comorbidity interacts with CRC to increase the rate of mortality beyond that explained by CRC and comorbidity acting independently. Based on DNRP records back to 1977, we defined comorbidities according to the diagnoses of conditions in the CCI, excluding CRC. In addition to the original conditions in the CCI, we included a prior diagnosis of atrial fibrillation/flutter and obesity (both assigned a score of 1). The CCI disease groups were considered individually and as the components of a summed, aggregate score that we classified into four groups as follows: 0, ''no comorbidity''; 1, ''low comorbidity''; 2–3, ''moderate comorbidity'', and ≥4, ''high comorbidity''.

In study II, we considered patients with interval CRC as the exposed group. We defined a colonoscopy performed within 90 days before the date of CRC diagnosis as diagnostic, and the latest colonoscopy more than 90 days prior to the CRC diagnosis as the index colonoscopy. For the primary analysis, CRC patients

were categorized as interval cases if an index colonoscopy had been performed 1 to 5 years prior to CRC diagnosis. This definition agreed with those of previous publications.[72,76,81,85,86] For comparison purposes we considered (i) patients with index colonoscopy ≥10 years prior to CRC diagnosis and (ii) sporadic CRC patients without a record of an index colonoscopy as the non-exposed group. We included the group of CRC patients with an index colonoscopy ≥10 years prior to CRC diagnosis based on the assumption that these patients are less likely than sporadic CRC patients to include rapidly growing tumors because the mean time for progression from adenoma to carcinoma is estimated to be at least 10 years.[28,126] Subjects with an index colonoscopy between 3-12 months and 5-10 years prior to CRC diagnosis were excluded from the primary analysis. All CRC patients were included in the secondary analyses, and the time duration between index colonoscopy and CRC date was considered in one-year intervals (1st year [3-12 months], 2nd year, 3rd year, ..., 10th year, and more than 10 years).

In study III, the exposure was CRC patients with SEMS. Thus, we classified our CRC cohort into the following groups based on the first-line surgical procedure after CRC diagnosis: (i) those with an initial SEMS procedure (exposed), (ii) those with primary acute colorectal resection, and (iii) those with primary elective colorectal resection. We defined acute surgery by hospitalization recorded as acute in the DNRP and elective surgery as non-acute hospitalization.[127] In the exposed group with an initial SEMS procedure, we also noted the presence or absence of subsequent colorectal resections. All colorectal resections were classified as *with* or *without* concurrent stoma.

4.6 Outcomes

In all three studies, the primary outcome was all-cause death; for regression analysis we considered time until death. The date of death for each individual was identified in the CRS. In study III we included a secondary outcome of CRC recurrence. This outcome was investigated exclusively for patients undergoing colorectal resection for local or regional spread of CRC. Because CRC recurrence is not directly coded in

Danish medical registries, we defined this outcome using the following criteria: a) any metastasis code in the DNRP >180 days after CRC resection; b) cytostatic therapy code >180 days after resection and >60 days after their last cytostatic therapy code; or c) a biopsy recorded in the DPR>180 days after the resection date and registered as either colorectal malignancy or metastasis. Patients were excluded from this analysis if they were diagnosed with any other primary cancer before recurrence date. The medical record review showed that this definition of recurrence had a positive predictive value of 80%.Both primary and secondary outcomes were evaluated according to specified time periods after the start of follow-up.

4.7 Confounders

As potential confounders, we considered variables that are associated with the outcome but not in the causal pathway between the exposure and outcome, and are likely to be unequally distributed between exposure/reference groups.[42] We used the CRS to obtain information on age and gender. From the DCR we obtained information on CRC date, anatomical site, and stage at diagnosis relevant to studies II and III. In study II, however, stage at diagnosis could be an intermediate variable between the time of diagnosis and death; therefore, we conducted the analysis without stage. From the DNRP we included information on CCI (potential confounders in studies II and III), year of colorectal resection (study III), and surgery type (i.e. *with* or *without* concurrent stoma, study III).

4.8 Statistical analysis

In studies I and II, follow-up started at the date of CRC diagnosis in the DCR. For study III, time since CRC diagnosis was considered as the underlying timescale, but patients were not considered at risk before 30 days after colorectal resection (delayed entry or left truncation).

4.8.1 Characteristics

In all three studies, we calculated the frequency of patients with demographic, tumor, and comorbidity characteristics. In study II, we used multivariate logistic regression to explore the association between characteristics and interval CRC, using as separate comparison groups patients with index colonoscopy ≥10 years prior to CRC diagnosis and sporadic CRC cases.

4.8.2 Mortality rates and absolute risks

In study I, we calculated mortality rates (MRs) by dividing the number of deaths by total follow-up time for the CRC and matched comparison cohorts. To evaluate short-term and long-term mortality separately, we computed MRs between the index date and 365 days and from 366 days to 5 years. The analysis within strata of comorbidity scores and follow-up required that we dissolved the matching because the age and gender distribution differed by comorbidity strata and because the age and gender distribution was different among one-year survivors than among all participants. For all analyses, we standardized the MRs to the age and gender distribution of the CRC inception cohort.

In study II, we calculated Kaplan-Meier estimates for absolute survival after 1 and 5 years of follow-up. The Kaplan-Meier method was also used to evaluate 1 and 5-year survival in study III, but for CRC patients surviving the first 30 days after colorectal resection. To evaluate short-term mortality in study III, we calculated mortality proportions within the first 30 days after resection or stenting. Mortality proportions were calculated as the number of deaths within the first 30 days divided by the total number of CRC patients undergoing surgery and/or stenting.

For the secondary outcome of CRC recurrence in study III, we calculated the absolute recurrence risk after 1 and 5 years treating death as a competing factor.[128]

4.8.3 Interaction contrasts (study I)

In study I, we computed interaction contrasts (ICs) to estimate the excess MR in patients with both CRC and comorbid disease beyond that expected from the independent effects of these diseases.[129] We used

standardized rates for this analysis and the matched subjects without comorbidity from the general population as the reference.[130] This interaction corresponds to the "biological (causal) interaction" and should not be confused with a statistical interaction specific for a given statistical model. Statistical interaction describes an effect dependent on the level of another factor for the outcome of interest.[129] The IC was calculated by subtracting the standardized mortality difference between CRC patients with *e.g.* CCI=4 and CCI=0 from the mortality difference between general population (pop) cohort members with CCI=4 and CCI=0 [*e.g.* $IC_{CCI4} = (MR_{CRC,CCI4}-MR_{CRC,CCI0})-(MR_{pop,CCI4}-MR_{pop,CCI0})$]. Hence, positive ICs describe the excess MR caused by the interaction, whereas a negative IC would indicate a protective role.

4.8.4 Cox proportional hazard regression analysis

We used Cox proportional hazard regression to compute the hazard ratios for death and 95% confidence intervals in all three studies. The hazard ratios were used as estimates of mortality rate ratios (MRRs). In addition, in study III we used Cox regression to estimate the relative risk/incidence rate ratio of CRC recurrence. We used multivariate Cox regression to control for potential confounding factors. The assumption behind the regression models, i.e. that the hazards are proportional, was checked graphically by log(-log) plots and found to be fulfilled.

In study I, we used Cox regression to compare mortality after 1 and 5 years among CRC patients and the age, gender, and comorbidity-matched persons from the population-based comparison cohort, adjusting for age (as a continuous variable), gender, year of index date (5-year intervals), and, in the overall analysis, comorbidity scores.

In study II, we used Cox regression to compare the mortality after 1 and 5 years among interval CRC patients relative to (i) patients with index colonoscopy ≥10 years prior to CRC diagnosis and (ii) sporadic CRC. The MRRs were computed for the first year and years 2 to 5 after diagnosis, and adjusted for age (0-49, 50-69, 70-79, ≥80 years), gender, year of cancer diagnosis (5-year intervals), CCI, CRC stage at diagnosis,

and tumor location. As mentioned previously, we also calculated MRRs without adjusting for CRC stage because stage at diagnosis may be an intermediate variable between the time of diagnosis and death.

We also used Cox regression to compare the mortality in resected CRC patients with pre-operative SEMS to patients who underwent primary acute or elective colorectal resection (study III). For this regression analysis, time since CRC diagnosis was considered as the underlying timescale. As a way to separate short and long-term mortality and to avoid problems with non-proportionality, patients were not considered at risk until 30 days after resection (left truncation). MRRs were adjusted for age, gender, year of surgery, CRC stage, CRC location, surgery type, and CCI. Using similar methodology, we used Cox regression to evaluate the relative risk (or incidence rate ratio) of recurrence comparing resected CRC patients with pre-operative stenting to patients who underwent primary acute and elective resection.

4.8.5 Stratified analysis

All three studies included analyses stratified by certain covariates. These analyses are also referred to as sub-group analyses or sub-analyses and were conducted to evaluate whether the association between exposure and outcome varied by subgroup (i.e. effect-measure modification). In study I, we stratified by CRC stage, gender, and age groups. In study II, we stratified by gender, CRC stage, and location. In study III, we stratified by gender, stage, CRC anatomic site, and surgery type (with and without stoma).

5. Results

5.1 Study I: Comorbidity

5.1.1 Characteristics

We identified 56,963 CRC patients and 271,670 persons from the general population matched by age (median age 72 years), gender (51% men), year of index date, and comorbidity (Table 5.1.1). As we were unable to match five persons from the general population to all CRC patients, small differences were found in the characteristics of the CRC patients and general population cohort.

Table 5.1.1. Characteristics of colorectal cancer patients and the population-based comparison cohort matched by gender, age, year of diagnosis, and comorbidity, Denmark 1995–2010.

	Colorectal cancer cohort		Population-based comparison cohort	
	Number	%	Number	%
Female	27,665	49	132,537	49
Male	29,298	51	139,133	51
Age at diagnosis/index:				
0 -59 years	10,285	18	51,467	19
60-69 years	14,541	26	70,613	26
70-79 years	18,547	33	87,444	32
80+ years	13,590	24	62,146	23
Stage of colorectal cancer:				
Non-metastatic	37,381	66	N/A	-
Metastatic	12,687	22	N/A	-
Unknown	6,895	12	N/A	-
Cancer location:				
Colon	37,859	67	N/A	-
Rectal	19,014	33	N/A	-
Colon and rectal	90	0.2	N/A	-
Charlson's Comorbidity Index score:				
0 (no comorbidity)	34,918	61	172,040	63
1 (low comorbidity)	9,747	17	47,193	17
2-3 (moderate comorbidity)	9,522	17	44,786	17
4+ (high comorbidity)	2,776	4.9	7,705	2.8

5.1.2 One-year mortality

CRC patients had a 0–365 day standardized MR of 400 (95% CI 394-406) per 1,000 person years (PY), compared to 47.5 (95% CI 46.6-48.3) per 1,000 PY in the comparison cohort, confirming overall higher mortality among patients with CRC (adjusted MRR=8.3, 95% CI 8.1-8.5). The 0–365 day standardized MRs increased with higher comorbidity scores, and increased more among CRC patients than among matched subjects from the general population (Table 5.1.2). For example, among CRC patients with a CCI score of 1 the standardized MR was 415 (95% CI 401-430) per 1,000 PY. The interaction between CRC and comorbidity accounted for an excess (i.e., IC) of 39 per 1,000 PY (95% CI 22-55) or 9.3% of the standardized MR. An even greater excess was observed for patients with a CCI score of 2–3, with an IC of 79 per 1,000 PY (95% CI 36-121), accounting for 16% of the total standardized MR. For patients with a CCI score ≥ 4, the IC was 262 per 1,000 PY (95% CI 215-310), accounting for 34% of the MR.

5.1.3 Five-year mortality

CRC remained associated with increased subsequent mortality (overall adjusted 366 day–5 year MRR = 3.0, 95% CI 2.9-3.0), though to a lesser extent than during the first 365 days after diagnosis. The 366 day–5 year standardized MRs increased with higher CCI scores. However, mortality increased more among CRC patients with a CCI score ≥ 4 than among the matched cohort, with the interaction accounting for 14% of the MR (Table 5.1.2).

Table 5.1.2. Mortality, mortality rate ratios (MRRs), and interaction contrasts for colorectal cancer (CRC) patients compared to a matched population-based comparison cohort, overall and by Charlson's Comorbidity Index (CCI) score.

CCI score	Cohort	No. of persons	No. of deaths	Person-years	Standardized mortality rates per 1000 person-years		Adjusted MRRs	Interaction contrast	
0-365 days of follow-up									
All	CRC	56,963	17,089	45,559	400	(394, 406)	8.3 (8.1, 8.5)	N/A	
All	Comparison	271,670	11,962	265,223	48	(47, 48)	Ref.	N/A	
0	CRC	34,918	8,881	29,245	351	(343, 359)	15 (14, 15)	Ref.	
0	Comparison	172,041	3,652	170,008	27	(26, 28)	Ref.	.	
1	CRC	9,747	3,254	7,509	415	(401, 430)	7.4 (7.0, 7.7)	39	(22, 55)
1	Comparison	47,139	2,755	45,723	53	(51, 55)	Ref.	.	
2–3	CRC	9,522	3,548	7,035	489	(447, 530)	5.1 (4.9, 5.3)	79	(36, 121)
2–3	Comparison	44,788	4,234	42,521	86	(83, 89)	Ref.	.	
4+	CRC	2,776	1,406	1,771	761	(715, 80)	3.9 (3.7, 4.3)	262	(215, 310)
4+	Comparison	7,702	1,321	6,971	175	(165, 185)	Ref.		
366 days to 5 years of follow-up									
All	CRC	39,862	14,274	102,813	143	(141, 146)	3.0 (2.9, 3.0)	N/A	
All	Comparison	258,729	40,310	808,019	50	(49, 50)	Ref.	N/A	
0	CRC	26,029	8,606	69,909	131	(128, 134)	4.2 (4.1, 4.3)	Ref	
0	Comparison	167,766	17,549	549,904	36	(36, 37)	Ref.	.	
1	CRC	6,490	2,482	16,193	146	(140, 152)	2.3 (2.2, 2.4)	-9.8	(-17, -3.1)
1	Comparison	44,215	9,585	131,313	61	(60, 62)	Ref.	.	
2–3	CRC	5,973	2,491	13,917	172	(165, 179)	2.0 (1.9, 2.0)	-3.0	(-11, 4.9)
2–3	Comparison	40,390	10,902	111,329	80	(79, 82)	Ref.	.	
4+	CRC	1,370	695	2,793	261	(231, 290)	1.7 (1.6, 1.8)	37	(7.0, 68)
4+	Comparison	6,358	2,274	15,473	129	(123, 134)	Ref.	.	

Numbers in parentheses are 95% confidence intervals

5.1.4 Stratified analyses

We found that CRC mortality during the 0-365 day period after diagnosis interacted with comorbidity in CRC patients with metastatic or non-metastatic disease. For example, among patients with a CCI score ≥ 4, the interaction accounted for 28% of the MR in patients without metastases and 24% in patients with metastatic spread. Consistent with the overall results, the interaction between CRC and comorbidity had less of an impact on mortality among CRC patients with non-metastatic or metastatic disease during the 365 days – 5 years after CRC diagnosis.

The results in patients with non-metastatic CRC who underwent colorectal resection were similar to the overall results (not shown). For mortality within 0–365 days of the index date, the interaction between CRC and comorbidity was particularly important for the younger age groups (0–69 years), and it accounted for 14% of mortality among those with a CCI score of 1, 29% among those with a CCI score of 2–3, and 45% among CRC patients with a CCI score ≥ 4. No material difference was found between men and women in the first 0-365 days; the overall interaction observed for the 366 day-5 year mortality among CRC patients with a CCI score ≥ 4 was mainly found in women (IC=49/1,000 PY, 95% CI 9.4-89), and to a lesser extent in men (IC=27/1,000 PY, 95% CI -19-72).

5.1.5 Individual comorbidities

For CRC patients, nearly all comorbidities included in the CCI (with the addition of atrial fibrillation/flutter and obesity) interacted with CRC to increase mortality during the first 0–365 days following diagnosis. In contrast, the interactions for individual diseases had limited influence on mortality during the subsequent 366 days–5 years.

5.2 Study II: Interval colorectal cancer

5.2.1 Characteristics

We identified 38,064 CRC patients diagnosed during 2000-2009. A total of 982 (3%) patients had interval CRC (colonoscopies between 1 and 5 years prior to diagnosis), 358 (1%) patients were diagnosed with CRC ≥10 years after colonoscopy, and 35,704 (94%) were sporadic patients with no colonoscopy more than 3 months prior to diagnosis. For the primary analysis, we excluded 580 (2%) CRC patients who underwent colonoscopy 3-12 months prior to diagnosis and 440 (1%) CRC patients who underwent colonoscopy 5-10 years prior to diagnosis. Table 5.2.1 describes the characteristics of the CRC patients according to time since index colonoscopy. The median age at CRC diagnosis was 74 years for interval cases, 75 years for cases diagnosed ≥10 years after colonoscopy, and 71 years for sporadic cases.

In general, interval cases were similar to cases diagnosed with CRC ≥10 years after colonoscopy. However, we found differences between the interval and sporadic cases. A higher proportion of interval cases were women. Proximal location and mucinous histology were more prevalent among interval cases, whereas distal location and non-mucinous adenocarcinomas were more common in sporadic cases. Patients with interval CRC had higher levels of comorbidity, particularly IBD and diverticular disease (Table 5.2.1). In multivariate logistic regression analyses with sporadic cases as reference, year of diagnosis, female gender, stage, CRC location, and comorbidities including IBD and diverticular disease were independently associated with interval CRC (Table 5.2.1).

Table 5.2.1. Characteristics of patients with colorectal cancer (CRC), Denmark 2000-2009.

	Interval CRC	Comparison groups			
		CRC diagnosed ≥10 years after colonoscopy, N (%)	*Odds ratios, (95% CI)**	Sporadic CRC, N (%)	*Odds ratios, % (95% CI)* ‡
	(%)				
Total number of patients	982	358		35,704	
Year of colorectal cancer diagnosis					
2000-2004	349 (36)	136 (38)	*1.0 (ref)*	17,043 (48)	*1.0 (ref.)*
2005-2009	633 (64)	222 (62)	*1.0 (0.77, 1.3)*	18,661 (52)	*1.5 (1.3, 1.7)*
Age at colorectal cancer diagnosis					
0-49 years	46 (4.7)	11 (3.1)	*1.0 (ref)*	1,714 (4.8)	*1.0 (ref)*
50-69 years	296 (30)	96 (27)	*0.51 (0.24, 1.1)*	14,124 (40)	*0.94 (0.67, 1.3)*
70-79 years	353 (36)	108 (30)	*0.50 (0.24, 1.1)*	11,425 (32)	*1.1 (0.80, 1.6)*
≥ 80 years	287 (29)	143 (40)	*0.28 (0.13, 0.60)*	8,411 (24)	*0.99 (0.70, 1.4)*
Gender					
Women	453 (46)	155 (43)	*1.0 (ref)*	18,739 (52)	*1.0 (ref)*
Men	529 (54)	203 (57)	*1.1 (0.82, 1.4)*	16,965 (48)	*0.89 (0.78, 1.0)*
Stage of colorectal cancer					
Localized	377 (38)	143 (40)	*1.0 (ref)*	12,995 (36)	*1.0 (ref)*
Regional	193 (20)	86 (24)	*0.82 (0.59, 1.1)*	9,340 (26)	*0.70 (0.59, 0.84)*
Metastatic	221 (23)	70 (20)	*0.93 (0.66, 1.3)*	8,642 (24)	*0.71 (0.59, 0.85)*
Unknown	191 (19)	59 (16)	*1.2 (0.85, 1.8)*	4,727 (13)	*1.1 (0.93, 1.4)*
Location of colorectal cancer					
Right-sided colon	376 (38)	128 (36)	*1.0 (ref)*	7,969 (22)	*1.0 (ref)*
Transverse colon	65 (6.6)	30 (8.4)	*0.79 (0.49, 1.3)*	1,813 (5.1)	*0.78 (0.59, 1.0)*
Left-sided colon	210 (21)	93 (26)	*0.79 (0.57, 1.1)*	10,676 (30)	*0.44 (0.36, 0.52)*
Rectal cancer	223 (23)	91 (25)	*0.85 (0.61, 1.2)*	13,303 (37)	*0.45 (0.37, 0.53)*
Several regions or unknown	108 (11)	16 (4.5)	*2.3 (1.3, 4.0)*	1,943 /5.4)	*1.1 (0.87, 1.4)*
Histology of colorectal cancer					
Adenocarcinoma	682 (69)	263 (73)	*1.0 (ref)*	28,368 (79)	*1.0 (ref)*
Polyp adenocarcinoma	42 (4.3)	12 (3.3)	*1.4 (0.69, 2.7)*	1,106 (3.1)	*1.5 (1.1, 2.1)*
Recorded as "solid carcinoma"	24 (2.4)	8 (2.2)	*1.1 (0.45, 2.5)*	391 (1.1)	*1.7 (1.1, 2.7)*
Neuroendocrine	10 (1.0)	1 (0.3)	*3.0 (0.37, 24)*	161 (0.5)	*2.0 (1.0, 3.91)*
Mucinous carcinoma	89 (9.1)	29 (8.1)	*1.1 (0.69, 1.7)*	2,484 (7.0)	*1.1 (0.88, 1.4)*
Signet ring	14 (1.4)	6 (1.7)	*0.88 (0.32, 2.4)*	377 (1.1)	*1.2 (0.69, 2.1)*
Other histology	35 (3.6)	11 (3.1)	*1.0 (0.49, 2.1)*	895 (2.5)	*1.2 (0.83, 1.7)*
Not histologically verified	86 (8.8)	28 (7.8)	*1.0 (0.62, 1.6)*	1,922 (5.4)	*1.3 (1.0, 1.7)*
Charlson's Comorbidity Index					
0 points: No comorbidity	374(38)	166 (46)	*1.0 (ref)*	19,426 (54)	*1.0 (ref)*
1-2 points: Low comorbidity	332 (34)	128 (36)	*1.2 (0.89, 1.6)*	10,813 (30)	*1.4 (1.2, 1.6)*
3 or more points: High comorbidity	276 (28)	64 (18)	*1.9 (1.4, 2.7)*	5,465 (15)	*2.2 (1.8, 2.6)*
No inflammatory bowel disese	918 (93)	321 (90)	*1.0 (ref)*	35,523	*1.0 (ref)*
Inflammatory bowel disease	64 (6.5)	37 (10)	*0.46 (0.29,0.73)*	181 (0.5)	*14 (10, 20)*
No diverticular disease	792 (81)	289 (81)	*1.0 (ref)*	34,530 (97)	*1.0 (ref)*
Diverticular disease	190 (19)	69 (19)	*1.1 (0.77, 1.5)*	1,174 (3.3)	*6.1 (5.1, 7.3)*

* Odds ratios associating characteristics with interval CRC (reference: CRC patients diagnosed ≥10 years after colonoscopy); ‡ Odds ratios associating characteristics with interval CRC (reference: sporadic CRC).

We reviewed the medical records from 101 CRC patients from one medical center who underwent an index colonoscopy >90 days prior to CRC diagnosis. In six patients, the index exam was either misdated (true date was within 3 months of CRC diagnosis) or miscoded as flexible sigmoidoscopy/rectoscopy, and in five patients the index colonoscopy was suspicious of CRC, but the diagnosis was not recorded until 3 or more months later. For the remaining 90 patients, the cecum was visualized in 69% and the preparation quality fair/excellent in 78%, poor in 13%, and not recorded in 9% of patients. The indications for colonoscopy were symptoms (50%), polyp follow-up (26%), family history of CRC (5.6%), prevalent IBD (8.9%), abnormal X-ray/imaging (1.1%), or not recorded (8.9%). A total of 40 (44%) patients had polyps removed at the index colonoscopy. Thirty five of the 101 patients had index colonoscopy 1-5 years prior to CRC diagnosis. In them, the caecum was visualized in 86%, preparation quality was fair/excellent in 83%, and 57% had polyps removed at that time. Indications for the diagnostic colonoscopy were symptoms (31%), follow-up of polyps (31%), family history (11%), prevalent IBD (11%), abnormal X-ray/imaging (2.9%), or not recorded (11%).

5.2.2 Survival after colorectal cancer

One-year survival was similar among interval CRC patients (68%, 95% CI 65%-71%), patients who underwent colonoscopy ≥10 years prior to CRC diagnosis (72%, 95% CI 66%-76%), and sporadic CRC patients (71%, 95% CI 70%-71%), corresponding to MRRs close to 1.0. Adjustments materially affected only the comparison of interval and sporadic cases, as the MRR changed from 1.1 (95 % CI 1.0-1.3) to 0.92 (95% CI 0.82-1.0). Differences in co-morbidity and cancer location were largely responsible for the change in MRR. After excluding CRC stage from the adjusted analysis, the one-year MRRs were similar to those obtained in the full analyses.

Five years after CRC diagnosis, survival was close to 40% in all CRC groups and 2-5 year MRRs varied around the null with little change in the estimates after adjusting for covariates. Excluding CRC stage from the adjusted model did not change the adjusted 2-5 year MRRs. Analyses stratified by gender, CRC stage, and

location did not materially affect the MRRs for the comparison of interval CRC cases to cases with an index colonoscopy ≥10 years prior to CRC diagnosis or sporadic cases (results not shown).

Table 5.2.2 outlines the results of the secondary analysis categorizing CRC according to each one-year period between diagnosis and index colonoscopy and comparing mortality to sporadic CRC. The 1-year MRRs had point estimates ≤1.0 except cases diagnosed in the fifth year after colonoscopy (1-year adjusted MRR of 1.4, 95% CI 1.1-1.7). The 5-year MRRs all varied around the null.

Table 5.2.2. Survival and adjusted mortality rate ratios (aMRR) after colorectal cancer (CRC) diagnosis according to duration between colonoscopy and date of diagnosis, Denmark 2000-2009.

		1-year			5-year		
	N	No. deaths	Survival, %	aMRR	No. deaths	Survival, %	2-5 year aMRR
Sporadic CRC†	35,704	10,085	0.71 (0.70, 0.71)	Reference	7,208	0.43 (0.42, 0.43)	Reference
Time since colonoscopy							
< 1 year	580	157	0.73 (0.69, 0.76)	0.81 (0.70, 0.96)	117	0.44 (0.39, 0.49)	1.0 (0.83, 1.2)
1- <2 years	381	125	0.66 (0.61, 0.71)	0.98 (0.82, 1.2)	70	0.40 (0.34, 0.45)	1.1 (0.84, 1.3)
2- <3 years	240	63	0.73 (0.67, 0.78)	0.76 (0.59, 0.97)	47	0.47 (0.40, 0.54)	0.96 (0.72, 1.3)
3- <4 years	215	56	0.73 (0.66, 0.78)	0.77 (0.59, 1.0)	41	0.42 (0.33, 0.50)	1.0 (0.73, 1.4)
4- <5 years	146	64	0.55 (0.46, 0.63)	1.4 (1.1, 1.7)	23	0.30 (0.21, 0.40)	1.2 (0.77, 1.8)
5- <6 years	143	44	0.67 (0.59, 0.75)	1.0 (0.76, 1.4)	30	0.35 (0.25, 0.45)	1.3 (0.90, 1.9)
6- <7 years	90	26	0.70 (0.59, 0.78)	1.1 (0.72, 1.5)	12	0.44 (0.29, 0.57)	0.59 (0.33, 1.0)
7- <8 years	84	29	0.64 (0.53, 0.74)	1.0 (0.71, 1.5)	19	0.26 (0.14, 0.39)	1.4 (0.92, 2.3)
8- <9 years	67	20	0.71 (0.58, 0.80)	0.74 (0.47, 1.2)	14	0.45 (0.31, 0.57)	1.2 (0.69, 2.0)
9- <10 years	56	13	0.75 (0.60, 0.85)	0.82 (0.48, 1.4)	9	0.46 (0.29, 0.62)	0.77 (0.40, 1.5)
≥ 10 years	358	100	0.72 (0.66, 0.76)	0.93 (0.76, 1.1)	65	0.40 (0.33, 0.46)	1.2 (0.91, 1.5)

Numbers in parentheses are 95% confidence intervals.

5.3 Study III: Self-expanding metal stents

5.3.1 Characteristics and short-term (30-day) mortality

We identified a total of 17,728 patients who underwent SEMS placement (n=1,118) or primary acute (n=3,333) or elective (n=13,722) resection for CRC (Table 5.3.1). Of the 1,118 SEMS patients, 581 (52%) underwent subsequent surgery after a median 17 days (interquartile range 8-27 days).

Table 5.3.1. Characteristics of the study III cohort, Denmark 2005-2010.

	Self-expanding metal stents				Primary colorectal resection			
	All		*Subsequent surgery*		Acute		Elective	
	n	%	*n*	*%*	n	%	n	%
Total	1,118	100	*581*	*100*	3,333	100	13,277	100
Female	520	46.5	*274*	*47.2*	1,773	53.2	6,048	45.6
Male	598	53.5	*307*	*52.8*	1,560	46.8	7,229	54.4
Age								
0-49	52	4.7	*35*	*6.0*	147	4.4	618	4.7
50-69	377	33.7	*215*	*37.0*	1,079	32.4	5,567	41.9
70-79	349	31.2	*195*	*33.6*	1,057	31.7	4,392	33.1
80+	340	30.4	*136*	*23.4*	1,050	31.5	2,700	20.3
Resection type								
Without stoma	N/A	-	*413*	*71.1*	2,335	70.1	11,807	88.9
With stoma	N/A	-	*168*	*28.9*	998	29.9	1470	11.1
Location of CRC								
Right-sided	31	2.8	*9*	*1.5*	1,296	38.9	3,229	24.3
Transverse	94	8.4	*50*	*8.6*	297	8.9	550	4.1
Left-sided	662	59.2	*415*	*71.4*	1,148	34.4	3,781	28.5
Rectal	284	25.4	*90*	*15.5*	402	12.1	5,329	40.1
Several/unspecific	47	4.2	*17*	*2.9*	190	5.7	388	2.9
Stage of CRC								
Localized	187	16.7	*170*	*29.3*	1,077	32.3	5,548	41.8
Regional	181	16.2	*165*	*28.4*	913	27.4	4,125	31.1
Metastasized	552	49.4	*183*	*31.5*	999	30.0	1,860	14.0
Unknown	198	17.7	*63*	*10.8*	344	10.3	1,744	13.1
Charlson's Comorbidity Index								
Low: 0	566	50.6	*347*	*59.7*	1,775	53.3	7,658	57.7
Medium: 1-2	314	28.1	*161*	*27.7*	1,061	31.8	4,058	30.6
High: 3+	238	21.3	*73*	*12.6*	497	14.9	1,561	11.8

Median age at date of SEMS placement was 72 years, compared to 74 years in patients who underwent acute surgery and 70 years in patients who underwent elective surgery. Characteristics are presented in Table 5.3.1.

The 30-day mortality was 12% (95% CI 9.8%-14%) after SEMS placement, 14% (95% CI 13%-15%) after primary acute surgery, and 3.8% (95% CI 3.5%-4.2%) after elective surgery. Among the 581 SEMS patients who underwent subsequent colorectal resection, the 30-day mortality after resection was 8.1% (95% CI 6.1%-10.6%). The mortality by gender, CRC stage, location, and surgery type did not vary materially, though it was particularly high among patients undergoing resections with stoma, probably indicating the choice of this procedure for severely ill patients.

5.3.2 Long-term mortality

The median follow-up was 2.0 years (range 0-6.5 years) for patients with pre-operative SEMS, 2.0 years (range 0-6.9 years) for patients with acute surgery, and 2.8 years (range 0-6.9 years) for patients undergoing elective surgery. Survival in the years after CRC resection remained higher among patients with pre-operative stenting compared to patients undergoing primary acute resection, but lower compared to patients undergoing elective surgery. The overall 5-year survival was 49% (95% CI 43%-55%) in patients with pre-operative stenting, compared to 40% (95% CI 38%-43%) after acute and 65% (95% CI 64%-66%) after elective resection. Similar patterns were seen within the strata of gender, CRC stage, and location. In patients undergoing resections with stoma, long-term survival was particularly poor, probably reflecting the choice of this procedure for very ill patients.

Comparing mortality in patients with pre-operative stenting to patients with acute resection, we found that the overall and stratified 1 and 5-year adjusted MRRs were close to 1.0 (Table 5.3.2). However, for patients with rectal cancer and resections with stoma, the MRRs were slightly increased. In the comparison of CRC patients with pre-operative stenting and those with primary elective resection, we found increased 1 and 5-year adjusted MRRs within the strata of gender, stage, location, and resection type (Table 5.3.2).

5.3.3 Colorectal cancer recurrence

We restricted the evaluation of CRC recurrence to the 11,469 patients with localized and regional spread of CRC at diagnosis who survived 30 days after colorectal resection. Among the 320 patients with pre-operative stenting, recurrence occurred among 12% (95% CI 8.7%-16%) after 1 year and 40% (95% CI 33%-47%) after 5 years. The corresponding numbers for the 1,796 patients with primary acute surgery were 12% (95% CI 10%-13%) and 30% (95% CI 28%-33%), respectively. Comparing patients with pre-operative stenting to the reference group undergoing primary acute surgery resulted in an adjusted RR after 5 years of 1.12 (95% CI 0.99-1.26) with no material changes based on gender, CRC location, or resection type.

For the 9,353 patients with localized and regional spread of CRC who underwent elective resection, 8.0% (95% CI 7.5%-8.8%) had recurrence after 1 year and 23% (95% CI 22%-24%) after 5 years. Comparing patients with pre-operative stenting to those who underwent elective surgery, the adjusted RR after 5 years was 1.72 (95% CI 1.39-2.13). The RR was particularly high when comparing localized CRC, rectal cancer, and resection without stoma.

Table 5.3.2. Mortality rate ratios (MRRs) after colorectal cancer resection in patients with pre-operative stenting compared to those who underwent primary acute or elective resection, Denmark 2005-2010.

	One-year MRR		Five-year MRR	
	Crude	**Adjusted**	**Crude**	**Adjusted**
Primary acute resection	Reference	Reference	Reference	Reference
Pre-operative stenting, overall	0.77 (0.67, 0.87)	0.91 (0.79, 1.05)	0.88 (0.81, 0.95)	0.99 (0.91, 1.07)
Men	0.78 (0.65, 0.94)	0.89 (0.73, 1.08)	0.89 (0.79, 0.99)	1.00 (0.89, 1.12)
Women	0.76 (0.62, 0.91)	0.95 (0.77, 1.17)	0.87 (0.78, 0.97)	0.98 (0.97, 1.11)
By stage				
Localized	0.61 (0.39, 0.96)	0.85 (0.53, 1.37)	0.85 (0.70, 1.02)	1.00 (0.82, 1.22)
Regional	0.82 (0.64, 1.05)	1.07 (0.82, 1.41)	0.92 (0.80, 1.06)	1.11 (0.95, 1.29)
Metastatic	0.80 (0.67, 0.96)	0.90 (0.74, 1.09)	0.87 (0.77, 0.98)	0.93 (0.82, 1.06)
Unknown	0.53 (0.30, 0.96)	0.68 (0.36, 1.30)	0.78 (0.58, 1.04)	0.99 (0.72, 1.38)
By location				
Right-sided	1.35 (0.76, 2.38)	1.07 (0.60, 1.89)	1.27 (0.82, 1.98)	1.00 (0.64, 1.55)
Transverse	0.93 (0.62, 1.38)	1.02 (0.67, 1.57)	0.91 (0.69, 1.19)	0.97 (0.73, 1.29)
Left-sided	0.80 (0.67, 0.96)	0.85 (0.70, 1.03)	0.89 (0.80, 0.99)	0.96 (0.86, 1.08)
Rectal	1.04 (0.75, 1.44)	1.07 (0.76, 1.51)	1.20 (1.00, 1.44)	1.25 (1.04, 1.51)
Several/unspecified	0.93 (0.52, 1.68)	1.06 (0.57, 1.96)	0.77 (0.49, 1.21)	0.84 (0.53, 1.34)
By resection type				
Resection without stoma	0.61 (0.50, 0.74)	0.77 (0.63, 0.94)	0.79 (0.71, 0.87)	0.89 (0.80, 1.00)
Resection with stoma	1.14 (0.94,1.39)	1.14 (0.93, 1.40)	1.17 (1.03, 1.33)	1.17 (1.02, 1.34)
Primary elective resection	Reference	Reference	Reference	Reference
Pre-operative stenting, overall	1.71 (1.32,2.23)	1.23 (0.93, 1.62)	1.73 (1.49, 2.01)	1.39 (1.19, 1.63)
Men	1.70 (1.18, 2.45)	1.21 (0.83, 1.78)	1.68 (1.36, 2.07)	1.44 (1.16, 1.79)
Women	1.72 (0.18, 2.51)	1.28 (0.86, 1.91)	1.79 (1.44, 2.22)	1.37 (1.09, 1.72)
By stage				
Localized	0.97 (0.40, 2.35)	0.92 (0.37, 2.28)	1.46 (1.02, 2.08)	1.55 (1.08, 2.24)
Regional	1.67 (1.04, 2.70)	1.71 (1.03, 2.84)	1.68 (1.29, 2.19)	1.76 (1.33, 2.32)
Metastatic	1.22 (0.86, 1.73)	1.23 (0.85, 1.79)	1.21 (0.96, 1.52)	1.21 (0.95, 1.55)
Unknown	0.96 (0.30, 3.03)	0.79 (0.24, 2.57)	1.29 (0.74, 2.25)	1.15 (0.65, 2.04)
By location				
Right-sided	5.03 (1.61, 15.7)	1.87 (0.59, 5.90)	3.48 (1.45, 8.39)	1.31 (0.54, 3.17)
Transverse	1.74 (0.79, 3.84)	1.30 (0.57, 2.98)	1.34 (0.78, 2.28)	1.12 (0.65, 1.96)
Left-sided	1.47 (1.03, 2.08)	0.99 (0.69, 1.43)	1.69 (1.39, 2.05)	1.27 (1.04, 1.55)
Rectal	3.26 (1.78, 5.97)	1.88 (1.00, 3.50)	2.87 (2.07, 3.99)	2.20 (1.58, 3.07)
Several/unspecified	2.37 (0.73, 7.74)	2.29 (0.64, 8.12)	1.44 (0.59, 3.54)	1.48 (0.58, 3.76)
By resection type				
Resection without stoma	1.15 (0.79, 1.66)	1.04 (0.71, 1.52)	1.40 (1.15, 1.69)	1.27 (1.04, 1.54)
Resection with stoma	2.33 (1.58, 3.43)	1.56 (1.02, 2.40)	2.15 (1.67, 2.77)	1.64 (1.24, 2.17)

Numbers in parentheses are 95% confidence intervals.

6. Discussion

In summary, we found that comorbidity interacts with CRC to increase mortality, particularly in the first 0–365 days after diagnosis (study I). Within this follow-up period, the interaction accounted for 9% of the total standardized MR in patients with low comorbidity, but as much as 34% in patients with high comorbidity burden. In study II, we found that interval CRC patients were older at diagnosis, more likely to be female, and to have more co-morbidities and right-sided tumors than sporadic CRC patients. Nonetheless, CRC stage and survival were similar between interval and sporadic cancer patients. In study III, we demonstrated that CRC patients with pre-operative stenting had long-term mortality similar to patients undergoing primary acute resection, but this was 39% higher than the mortality of patients undergoing elective resection. In study III, we also showed that pre-operative stenting was associated with a 12% increase in recurrence risk after 5 years compared to acute surgery, and a 72% increased recurrence risk compared to elective resection.

6.1 Methodological considerations

The estimates in our three studies represent the product of the study design, study conduct, and data analysis.[131] Our overall methodological goal is to obtain precise and valid estimates of the associations between exposure and outcome, as well as to obtain estimates that are generalizable to relevant target populations. By precise estimates, we refer to estimates with little random error (or play of chance) that we evaluated statistically by 95% confidence intervals and presented in the results section. The large number of patients in our cohorts, together with the large number of outcomes, yielded statistically precise estimates with narrow confidence intervals; therefore, chance played a minimal role and will not be discussed in more detail.

Valid estimates refer to the absence of systematic errors or biases and, in studies of causation such as the three in this dissertation, it corresponds to accurate measurements of the effects apart from random

variation. Generalizability refers to the validity of inference for the source population, and in nationwide population-based studies like ours, the results are likely to be highly generalizable if internal validity is high. Notably, the results in study II may not be generalizable to a setting in which routine CRC screening is conducted by colonoscopy.

Therefore, going into detail about features affecting the internal validity, i.e. biases, is essential for the methodological discussion of the three studies in this dissertation. Most violations of internal validity can be classified into selection, information, and confounding biases, of which only the latter can be dealt with in statistical analyses.[131]

6.1.1 Selection bias

Selection bias is usually defined as systematic error stemming from the procedures used to select subjects and from factors that influence study participation.[42] This bias arises when the association between exposure and outcome is different for study participants and non-participants. Because the association among non-participants is rarely known, selection bias cannot be observed, but inferred.

Within the different study periods of the three investigations included in this dissertation, we had nearly complete inclusion of all incident CRC patients in Denmark.[117] In addition, we had complete follow-up of all CRC patients, as well as the population-based comparison cohort in study I. The complete follow-up was ensured by the Danish CRS as described previously.[115,116] These features eliminate nearly all selection bias in our studies.

6.1.2 Information bias

Information bias is defined as systematic error that occurs because the information collected for exposure and outcome is erroneous.[42] Information about exposure and outcome in our studies was considered in categories, and information error led to subjects being misclassified into incorrect categories. For both exposure and outcome, this misclassification could be differential or non-differential based on its relation to the presence or absence of its counterpart. Non-differential misclassification of dichotomous variables

bias an association towards unity, whereas differential misclassification biases the association in an unpredictable manner.[42]

In study I, exposure misclassification could have arisen from incorrect coding of the comorbidities included in the CCI with the addition of atrial fibrillation/flutter and obesity. Previous validation studies reported high positive predictive values for these comorbidities, but the completeness (i.e. sensitivity) is not likely as high.[53,132,133] In addition, we may have missed other diseases affecting mortality (e.g. psychiatric diseases). These factors could have led us to underestimate comorbidity burden and to classify patients with comorbidities in the group without comorbidity, resulting in more uniform MRs and MRRs approaching 1.0. However, the impact on ICs is not predictable.

That the CCI was developed in 1984 should be considered when it is used,[52] as well as that the diseases included and weights assigned are not likely to reflect today's setting because the treatment and prognosis of several of the diseases has improved substantially (e.g., AIDS and most cancers). Furthermore, the index does not rank comorbidities by time elapsed before the date of the index disease (i.e. CRC in this setting), which might conceal important differences related to the impact on prognosis. For example, diseases such as diabetes and dementia usually have a progressive course likely to impact the prognosis more with longer duration, whereas myocardial infarction or ulcer disease are likely to have a prognostic impact relatively close to onset. These issues may have caused errors in the categorization of patients into low vs. high comorbidity groups.

In study II, the presence of a colonoscopy more than 90 days prior to CRC diagnosis was considered an exposure. Even though the positive predictive value of coding in the NRP has been shown to be high,[120] our record review suggested that some cases we designated as interval CRC were misclassified, which might have conservatively biased the comparison of interval and sporadic CRC cases.

In study III, the coding of SEMS procedures and acute and elective surgery is likely to be both accurate and complete.[120] The use of the administrative registration of hospitalizations to define surgeries as acute or

elective has been validated in the inflammatory bowel disease setting and found to be 91% sensitive/complete and 100% specific.[127,134]

Finally, with respect to outcome misclassification, death is coded essentially without errors in the CRS,[116] and information bias originating from this source is negligible. However, for the secondary outcome of CRC recurrence in study III, we cannot rule out some misclassification. CRC recurrence was identified using an algorithm that could not differentiate between recurrence and new primary CRC, or capture recurrences that were not diagnosed by biopsy or resulted in chemotherapy or a diagnosis code for metastasis. Our record review indicated the false positive recurrence rate to be 20%. If such measurement error of the outcome variable is independent of the treatment, the bias, however, is typically in the direction of underestimating the treatment effect

6.1.3 Confounding

As described in section 2.4, confounding is a central issue of observational studies, particularly those designed to study etiological/causal questions. Confounding can be thought of as confusion or distortion of the association between exposure and outcome caused by the effect of other factors. To be a confounder, a factor should fulfill the following criteria: 1) An independent cause of the outcome (or a proxy/marker for the cause); 2) imbalanced across exposure categories; and 3) not occurring on the causal pathway between the exposure and outcome.[42] Though bias caused by selection and information bias can only be prevented in the design phase of a study, confounding can be countered in the statistical analysis by adjustment, stratification, and standardization. In the design phase, confounding can be prevented by randomization, restriction, and matching; note that matching a confounder in a case-control design might cause bias rather than prevent it.[135] Randomization has the advantage of potentially preventing unknown confounding, whereas other countermeasures only deal with known confounders.

In study I, we dealt with potential confounding caused by age and gender in the design phase by matching, and in the analysis by standardization, stratification, and adjustment. We also matched for conditions

included in the CCI to balance comorbidities between CRC patients and the population-based cohort. However, the analysis within strata of comorbidity scores required that we dissolved the matching, as the age and gender distribution differed by comorbidity strata and over the follow-up periods. For these analyses, we standardized the MRs to the age and gender distribution of the inception cohort of CRC patients to counter confounding by gender and age. Nonetheless, our results may have been affected by confounding by unmeasured factors, such as alcohol consumption, smoking, and medication use. Despite these limitations and based on the strength of the associations in study I, it is unlikely that these unmeasured factors explain our results completely.

In study II, we dealt with potential confounding by age, gender, year of cancer diagnosis, comorbidity, cancer stage at diagnosis, and tumor location by adjustment and stratification. Although we cannot rule out residual confounding by some of these factors due to incomplete measurement (e.g., of comorbidities), the main limitation was a lack of detailed data on the index colonoscopy in the nationwide data. Whether the indications prompting the index colonoscopy in interval CRC patients could have confounded our results is unclear. However, our restricted analysis comparing interval CRC diagnosed 1-5 years after index colonoscopy to cases diagnosed more than 10 years after colonoscopy, which would likely have similar indications for colonoscopy, supported our overall findings.

Although we adjusted for and stratified by many important potential confounders in study III (i.e. age, gender, year of surgery, CRC stage, CRC location, surgery type, and comorbidity), our results may still be influenced by residual confounding by CRC stage and comorbidities or by unknown confounding. Most importantly, we had no information on the indication for SEMS placement or for performing acute surgery, and our results may be confounded by the indication.[42] SEMS are mainly used for large bowel obstruction, whereas acute surgery is used for perforation and bleeding. Physicians may also be more likely to use SEMS for particular CRC groups, which could affect our finding in an unpredictable way. Thus, we may have

compared patients with different a priori risks of dying or recurrence. These uncertainties could ultimately be overcome only using an experimental design.

6.2 In light of the existing literature

The following three subsections will discuss our findings in light of the existing evidence succinctly outlined in sections 2.5 - 2.7.

6.2.1 Study I (comorbidity)

Although previous studies have been unable to evaluate the independent effects of CRC and comorbidity or their concurrent effect on mortality, they have demonstrated that CRC patients with comorbidities have poorer survival rates than CRC patients without comorbidities, a pattern that was also observed in our study. Impaired survival has been demonstrated over the short-term[46,55,64]and long-term,[3,55,64]and in population-based studies[3,46,57]and single-center studies.[59,69] Impaired survival has also been reported when comorbidities are evaluated using indices, such as the CCI or Adult Comorbidity Index (ACE-27),[3,59,69]and for individual diseases.[50,51,56,58] In addition, impaired survival of CRC patients with comorbidities has been demonstrated regardless of treatment received, anatomical site of CRC, gender, and age.[3,57,59] At least two studies have indicated that comorbidity does not have as important a role in mortality among patients with end-stage CRC. A recent study from North America (exploratory analysis of the CO.17 clinical trial) that included 572 patients with metastatic CRC found that patients with more comorbidity have improved survival compared to patients with fewer comorbidity (HR=0.8, 95% CI 0.65-1.00).[65] A single-center German study of 233 CRC patients with metastatic disease undergoing non-curative elective surgery found no association between comorbidities, as measured by the number of affected organs, and 30-day mortality.[67] These findings suggest that, among patients who are severely ill with CRC, the coexistence of other, often

less aggressive diseases adds little to their high a priori mortality. In our study, however, we found that interactions between comorbidity and CRC still play a substantial role in the mortality of CRC patients with metastatic disease, though only during the first 0–365 days of follow-up and primarily among those with high comorbidity burdens.

Our study thus extends the existing literature by including a population cohort free of CRC, thereby allowing for evaluation of the excess mortality caused by the interaction between comorbidity and CRC. Since successful treatment of the comorbidity would delay death from the comorbidity and the interaction between the comorbidity and the CRC, efforts to enhance clinical management of both CRC and concurrent comorbidity will have substantial effects on improving the prognosis. From a prevention standpoint, the mortality caused by the interaction can be delayed either by treating comorbidity or the CRC, not necessarily both. These findings strongly underscore the need for health care providers to pay particular attention to comorbid diseases while treating CRC patients.

6.2.2 Study II (interval colorectal cancer)

To the best of our knowledge, no prior study has conducted a detailed investigation of survival in patients with interval CRC to evaluate whether these cancers have an aggressive course (see section 2.6). If a subgroup of interval CRC represented particularly aggressive tumors, we would have expected survival to be worse than that of other CRC patients. However, we found that survival was similar among interval and sporadic CRC cases, suggesting that the majority of interval cases were more likely missed lesions. These results are also supported by our findings regarding the distribution of clinical characteristics. Lesions missed by colonoscopy are more frequently located on the right side,[77,82] perhaps because poor bowel preparation prevents complete colonoscopy. Poor bowel preparation is more likely to occur in older individuals with a high degree of comorbidity,[136,137] a pattern that is also consistent with our findings. The high proportion of interval cases with previously resected polyps in the medical records we reviewed may

also indicate that some interval CRC cases develop from prevalent lesions that were incompletely resected, or even missed.[81] Furthermore, the relatively high prevalence of IBD and diverticular disease among interval cases might reflect index colonoscopies that had been technically complicated with an increased risk of overlooking a lesion.[84] Finally, in accordance with our findings, at least two studies confirmed that advanced age and female gender are factors associated with a CRC diagnosis in the period relatively soon after a colonoscopy (i.e. missed cancers).[77,82]

Five reports from a single-center US study of men described the clinical and molecular characteristics of 45-63 interval cases arising 1-5 years after colonoscopy, and twice the number of sporadic cases.[72,76,81,85,86] No major difference was found in overall survival between interval and sporadic cases (5-year survival 36%, 95% CI 18%-55% vs. 46%, 95% CI 36%-60%)[81] or in markers of aggressive tumor behavior, such as histological grade, carcinoembryonic antigen levels, and stage. However, mucinous histology was more prevalent among interval cases, suggesting potential aggressive behavior.[72] Because mucinous cancers are more likely right-sided, which is also the location of most interval cancers, the mucinous histology may simply reflect location, and not aggressive biology, as our results suggest. Similarly, the association of microsatellite instability and CIMP with interval CRC[76,86] may be explained by interval cancers occurring more often on the right side. Of note, sessile serrated adenomas are likely to occur in the right colon and are thought to be precursors of CIMP+ CRCs.[28,138] These lesions are often small and flat, and therefore more likely to be missed.[139] Nonetheless, as the authors of the US reports indicate, microsatellite instability and CIMP seem to be more prevalent in interval cases regardless of CRC localization, and may be in accordance with a subset of interval CRC showing rapid growth, but this was beyond the scope of our investigation.

Two other studies have described survival after interval CRC. A Canadian population-based study (Manitoba region) published in 2010 included 388 CRC patients diagnosed 6-36 months after colonoscopy and compared them to 4495 CRC cases diagnosed 0-6 months after colonoscopy.[77] This study also did not detect any difference in survival, but it only included CRC cases diagnosed up to 3 years after colonoscopy

and may have excluded cases that were most likely to represent *de novo* lesions. Finally, a recent UK study that defined interval CRC (n=192) as CRC diagnosed between biennial screening rounds found that the screen-detected CRC cases (n=322) were more likely to be men, left colon tumors, and have superior survival, whereas a comparison of interval CRC and CRC patients diagnosed before first screen invitation (n=511) revealed no differences.[71] However, because the definition of interval CRC was based on a prior fecal occult blood test and not colonoscopy, the results offer little support to our findings.

6.2.3 Study III (self-expanding metal stents)

The decision to use SEMS for CRC obstruction as a bridge to elective surgery instead of proceeding immediately to primary acute surgery should be made after weighing the pros and cons related to both short- and long-term outcomes. Findings from randomized trials would provide the most solid evidence for such decisions, but trials have so far proven infeasible in the setting of SEMS vs. acute surgery.[99,100,102] Recently, van Hooft et al conducted a trial including patients from 25 centers in the Netherlands[99] that was prematurely terminated after the inclusion of 47 SEMS patients and 51 acute surgery patients because of increased morbidity, particularly perforations, in the SEMS group. The trial reported no difference in mortality after 6 months of follow-up (risk difference -0.02, p=0.84). Other randomized trials have also been prematurely terminated because of morbidity among patients undergoing acute surgery[102] or receiving SEMS.[100] Thus, the trials have provided only limited evidence for the clinical management of patients with obstructive CRC.[96,97]

Therefore, physicians need to refer to evidence from observational research for guidance regarding information given to patients and for clinical decision making, particularly for long-term outcomes, such as recurrence and mortality. To date, only small (<50 SEMS patients) single-center observational studies, primarily from highly specialized centers, have compared stenting with primary acute or elective surgery (Table 2.4), and only one of these studies[103] included CRC recurrence as an outcome. This study included 25

SEMS patients and 70 acute surgery patients, finding no difference in 5-year survival (67% vs. 62%) or recurrence (35% vs. 35%). Most of the other studies comparing SEMS placement with acute surgery found either no difference in survival or favored SEMS.[91,95,106,108,109,111] Furthermore, only one study including stage IV cases found better long-term survival in patients treated with acute surgery.[105] The two studies that included cases undergoing elective surgery as a comparison group found either similar survival[104]or improved survival[107] compared to SEMS patients. Thus, our findings extend the existing literature by providing robust estimates of long-term mortality and recurrence in a population-based setting, and by accounting for differences in age, gender, CRC stage, location, and comorbidity.

7. Conclusions

7.1 Study I (comorbidity)

This population-based matched cohort study showed that comorbidities interact with CRC to increase mortality beyond that explained by CRC and comorbidities acting independently, particularly in the first year after CRC diagnosis. In an effort to improve CRC survival, successful treatment of the comorbidity is pivotal since it would delay death from both the comorbidity and the interaction and health care providers should therefore pay particular attention to comorbid diseases while treating CRC patients.

7.2. Study II (interval colorectal cancer)

In this large population-based study, demographic, tumor, comorbidity characteristics, and survival estimates among interval CRC cases did not suggest aggressive biology, but rather that the majority of interval CRC cases represent missed lesions. Thus, clinicians should focus on optimizing the quality of colonoscopy examinations.

7.3. Study III (self-expanding metal stents)

The use of SEMS as a bridge to surgery was associated with long-term mortality, comparable to that of primary acute surgery but not as low as that observed after elective surgery. The use of SEMS might be related to an increased risk of CRC recurrence.

8. Perspective

The investigations presented in this dissertation add to the existing literature with respect to three important areas of CRC prognosis. First, our findings underscore the important impact of comorbidities on CRC survival. To foster further understanding of this important issue, future investigations should attempt to develop more sensitive measures of comorbidity burden, thereby allowing more detailed understanding of the interaction with CRC. Such measurements should ideally take duration and severity of comorbidity into account which is largely possible using the DNRP and potentially other Danish registries. In addition, future studies should attempt to evaluate intermediate steps between CRC diagnosis and death in order to modify the cause of the disease. Second, our findings from study II are important for CRC screening because they point towards optimizing colonoscopy for avoiding interval CRC. However, research including CRC tissue, and perhaps precursor lesions, should compare molecular characteristics among interval cases to evaluate whether characteristics of rapid growth, such as microsatellite instability, differ with time since colonoscopy. Such investigations would be the optimal method for evaluating the hypothesis underlying the occurrence of interval CRC. If specific biology is responsible for some interval CRC cases, this knowledge may have a substantial impact on the clinical follow-up of certain patient populations. The Danish population-based setting may be ideal for conducting a study using biopsies or resections, as all tissue is stored indefinitely in the archives of Danish pathology institutes and accessible without patient consent through the DPR.[124] Furthermore, recording of more detailed information from colonoscopies such as endoscopist specialty, completeness, and preparation quality are warranted. Third, the findings of study III highlight the need for more evidence for the use of SEMS as a bridge to surgery for obstructive CRC. This information ideally should come from randomized clinical trials, but such trials may prove impossible owing to the relatively few cases, the large difference in clinical skills between endoscopists, and the requirement of a long follow-up to study mortality and recurrence. Therefore, observational studies will need to provide more evidence as data from existing registries accumulate. Of note, specific and complete recording of CRC

recurrence is needed to facilitate studies in this field in addition to more detailed data for SEMS use including indication, technical success, perforation, type of SEMS, and stent migration.

9. Summary

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western world, and though survival has improved over the last few decades, it remains poor. The aim of this dissertation was to contribute to improving survival after CRC through three specific research studies. In study I, we evaluated whether comorbidity interacts with CRC to increase the rate of mortality beyond what can be explained by CRC and comorbidities acting alone. In study II, we compared survival among interval CRC (cases diagnosed in the years after a colonoscopy) and sporadic CRC (cases with no prior colonoscopy) under the hypothesis that some interval cases are caused by aggressive and rapidly growing tumors. In study III, we compared survival and CRC recurrence in patients with pre-operative stenting to those proceeding directly to acute or elective resection. Stenting is under suspicion for causing cancer spread as a results of the mechanical expansion, thereby impairing long-term survival.

All three studies were conducted as nationwide population-based cohort studies utilizing existing Danish registries. We used the unique civil registration number to link individual-level data. The statistical analyses were conducted using time-to-event analysis, including Kaplan-Meier methods and Cox proportional regression. In study I, we also computed interaction contrasts to estimate the excess mortality rate in patients with CRC and comorbid disease beyond that expected from the independent effects of these diseases. We accounted for important confounding factors in all three analyses.

In study I (1995-2010), we included 56,963 CRC patients and five-times as many subjects in a matched comparison group. Depending on the severity of the comorbidity burden, we found that the interaction between CRC and comorbidity accounted for 9%-34% of the total one-year mortality. For 1 to 5-year survival, the interaction accounted for 14% of the mortality in patients with high comorbidity burdens, whereas interaction had no effect in subjects with low burdens. These results underscore the importance of comorbidity in CRC survival.

In study II (2000-2009), we compared clinical characteristics and survival in 982 interval CRC patients who underwent colonoscopy 1-5 years prior to diagnosis to 35,707 sporadic CRC patients with no previous colonoscopy and to CRC patients diagnosed ≥10 years after colonoscopy (approximating a "screened" population). In subsequent analyses we defined interval CRC by one-year categories after colonoscopy. Because characteristics did not support aggressive behavior and survival was similar, our findings suggested that the majority of interval CRC cases represented missed lesions.

In study III (2005-2010), we compared 581 CRC patients who underwent pre-operative stenting to 3,333 patients who underwent acute resection and 13,277 patients who underwent elective resection. Five-year mortality was similar between patients who underwent pre-operative stenting and those who underwent acute resection, but it was 39% higher if compared to elective patients. In addition, pre-operative stenting was associated with a 12% increased 5-year risk of recurrence compared to acute surgery, and a 72% increased recurrence risk compared to elective resections.

The most important methodological considerations are related to the use of the administrative registries and the observational study design. Thus, our finding could have been influenced by selection, information, and confounding bias, with the latter two being the most likely. However, we find it implausible that our findings would be explained solely by the effect of these factors.

10. Dansk resume

Colorectalcancer (CRC) er den næst hyppigste årsag til cancerrelateret død i den vestlige verden og selvom overlevelseschancerne er forberede over de seneste årtier, så er dødeligheden fortsat høj. Formålet med denne ph.d.-afhandling er at bidrage til at forbedre overlevelsen efter CRC ved at undersøge tre udvalgte områder. Studie I undersøger betydningen af interaktionen mellem komorbiditet og CRC for overlevelseschancerne. Studie II undersøger CRC overlevelsen hos patienter diagnosticeret i årene efter en koloskopi, som ikke påviste cancer (kendt som interval CRC). Hypotesen er, at interval CRC kan repræsentere en særligt hurtigt-voksende og aggressiv type. Studie III sammenligner patienter, der har fået anlagt stent inden operation, med patienter, der som første behandling blev akut eller elektivt opereret. Stent-behandlingen er mistænkt for at kunne forårsage spredning af cancerceller ved den mekaniske ekspansion under anlæggelsen og dermed forringe langtidsoverlevelse.

De tre studier er landsdækkende, populations-baserede kohortestudier, som anvender data fra eksisterende danske registre. Alle data er koblet vha. CPR nummeret. De statistiske analyser er lavet efter principperne for "time-to-event", hvor metoder som Kaplan-Meier og Cox regression er anvendt. I studie I er endvidere anvendt en metode til udregning af interaktions-kontraster baseret på standardiserede incidensrater. Der er taget hånd om vigtige confoundere i alle tre studier.

I studie I (1995-2010), som inkluderede 56.963 CRC patienter og fem gange så mange personer i en matchet sammenlignings-kohorte, fandt vi, at interaktion mellem komorbiditet og CRC forklarede mellem 9 % og 34 % af den totale etårs-mortalitet afhængig af komorbiditetens sværhedsgrad. For 1-5 års mortaliteten betød interaktionen mindre, om end den kunne forklare op til 14 % af den totale mortalitet hos CRC patienter med høj komorbiditets-byrde. Disse resultater understeger betydningen af behandlingen af komorbiditet for overlevelseschancerne hos danske CRC patienter.

I studie II (2000-2009) inkluderede vi 982 interval CRC patienter defineret ved tilstedeværelsen af en koloskopi 1-5 år før CRC diagnosen. Overlevelsen hos interval CRC patienter var sammenlignelig med

overlevelsen hos de 35.707 CRC patienter uden en koloskopi før CRC diagnosen, samt sammenlignelig med patienter med en koloskopi ≥10 år før diagnosedatoen for CRC. Derudover fandt vi ikke karakteristika hos interval-CRC patienterne, som er typiske for aggressive cancere. Således tydede resultaterne på, at interval-CRC repræsenterede "normale/sporadiske" CRC'ere, som blev oversete under koloskopien.

I studie III (2005-2010) inkluderede vi 581 CRC patienter, som havde fået anlagt stent før CRC operationen. Vi sammenlignede mortaliteten og recidivrisikoen i denne gruppe med CRC patienter, hvis indledende behandling var enten akut (n=3.333) eller elektiv operation (n=13.277). Overordnet fandt vi, at mortaliteten var ens hos stent-behandlende og akut opererede, men at den var 39 % højere hos de sten-behandlende i forhold til de elektivt opererede. Vi fandt også, at stent-behandlingen var associeret med en 12 % øget risiko for recidiv i forhold til de akut opererede og en 72 % øget recidivrisiko i forhold til de elektivt opererede patienter.

De væsentligste metodemæssige problemer i de tre studier relaterede sig til det observationelle design samt anvendelsen af eksisterende registre. Således kan resultaterne være påvirket af selektion, information og confounding bias, hvoraf de to sidstnævnte er de væsentligste. Vi finder det dog usandsynligt, at disse potentielle metodemæssige problemer kan forklare vores resultater.

11. References

1. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010; 127:2893-2917.

2. Ostenfeld EB, Erichsen R, Iversen LH et al. Survival of patients with colon and rectal cancer in central and northern Denmark, 1998-2009. *Clin Epidemiol.* 2011; 3 Suppl 1:27-34.

3. Iversen LH, Norgaard M, Jacobsen J, Laurberg S, Sorensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006--a population-based cohort study. *Dis Colon Rectum.* 2009; 52:71-78.

4. Statistics Denmark. Statbank Denmark [Internet]. Available from http://www.statistikbanken.dk/. 2012.

5. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009; 27:2758-2765.

6. Brenner H, Haug U, Arndt V et al. Low Risk of Colorectal Cancer and Advanced Adenomas More Than 10 Years After Negative Colonoscopy. *Gastroenterology.* 2010; 138:870-876.

7. Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA.* 2006; 295:2366-2373.

8. Davila RE, Rajan E, Baron TH et al. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc.* 2006; 63:546-557.

9. The Danish National Board of Health. Recommandations for colorectal cancer screening [report in Danish]. 2010.

10. Sanduleanu S, Masclee AM, Meijer GA. Interval cancers after colonoscopy-insights and recommendations. *Nat Rev Gastroenterol Hepatol.* 2012; 9:550-554.

11. Gainant A. Emergency management of acute colonic cancer obstruction. *J Visc Surg.* 2012; 149:e3-e10.

12. Sundhedsstyrelsen. Cancerregisteret 2010, tal og analyse [report in Danish]. 2012.

13. Ingle SB, Limburg P. Colorectal Carcinoma. In: Talley NJ, Locke GR, Saito JA, editors. GI Epidemiology. 1 ed. Blackwell Publishing; 2007. 170-175.

14. Ries LA, Wingo PA, Miller DS et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. *Cancer.* 2000; 88:2398-2424.

15. Giovannucci E, Wu K. Cancers of the Colon and Rectum. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. 3rd ed. Oxford University Press; 2006. 809-829.

16. Kahi CJ, Rex DK, Imperiale TF. Screening, surveillance, and primary prevention for colorectal cancer: a review of the recent literature. *Gastroenterology.* 2008; 135:380-399.

17. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology.* 2010; 138:2029-2043.

18. Mousavi SM, Fallah M, Sundquist K, Hemminki K. Age- and time-dependent changes in cancer incidence among immigrants to Sweden: colorectal, lung, breast and prostate cancers. *Int J Cancer.* 2012; 131:E122-E128.

19. Flood DM, Weiss NS, Cook LS et al. Colorectal cancer incidence in Asian migrants to the United States and their descendants. *Cancer Causes Control.* 2000; 11:403-411.

20. Chan AT, Arber N, Burn J et al. Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res (Phila).* 2012; 5:164-178.

21. Cuzick J, Otto F, Baron JA et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol.* 2009; 10:501-507.

22. 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.

23. 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.

24. Sant M, Allemani C, Santaquilani M et al. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer.* 2009; 45:931-991.

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

26. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol.* 2012; 3:153-173.

27. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med.* 1993; 329:1977-1981.

28. Snover DC. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol.* 2011; 42:1-10.

29. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology.* 2007; 50:113-130.

30. Cotton S, Sharp L, Little J. The adenoma-carcinoma sequence and prospects for the prevention of colorectal neoplasia. *Crit Rev Oncog.* 1996; 7:293-342.

31. Danish Institute of Health Technology Assessment. Colorectal cancer: diagnosis and screening. Danish health technology assessment 2001. Copenhagen: National Board of Health, DIHTA. [report in Danish]. 2001

32. 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.

33. Olsen KR, Bjerregaard NC, Ibfeldt EH, Laurberg S. Sundhedsøkonomisk analyse af diagnostiske strategier ved symptomer på ende- og tyktarmskræft - en medicinsk Teknologivurdering. 11 (1), 1-38. The Dnaish National Board of Health. [report in Danish]. 2009.

34. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. *Clin Gastroenterol Hepatol.* 2008; 6:1117-1121.

35. Danish Colorectal Cancer Group. The Danish Colorectal Cancer Group, yearly report 2010 [Landsdækkende database for kræft i tyktarm og endetarm. Årsrapport 2010]. [report in Danish]. 2010.

36. The Dansih Colorectal Cancer Group, Guidelines 2012 [in Danish]. Available from: http://www.dccg.dk/retningslinjer/indeks.html. 2012.

37. Morris EJ, Forman D, Thomas JD et al. Surgical management and outcomes of colorectal cancer liver metastases. *Br J Surg.* 2010; 97:1110-1118.

38. Lin AY, Buckley NS, Lu AT, Kouzminova NB, Salpeter SR. Effect of KRAS mutational status in advanced colorectal cancer on the outcomes of anti-epidermal growth factor receptor monoclonal antibody therapy: a systematic review and meta-analysis. *Clin Colorectal Cancer.* 2011; 10:63-69.

39. Fletcher R, Fletcher S. Prognosis. In: Sun B, Linkins E, editors. Clinical Epidemiology. 4 ed. Lippincott Williams & Wilkins; 2005. 105-124.

40. Sackett D, Haynes R, Guyatt GH, Tugwell P. Introduction: How to Review Your Own Performance. Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd ed. Little, Brown and Compagny; 1991. 305-333.

41. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ.* 2009; 338:b375.

42. Rothman KJ. Biases in Study Design. Epidemiology: an introduction. 1st ed. Oxford University Press; 2002. 94-112.

43. Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology.* 2006; 44:1075-1082.

44. McMillan DC, McArdle CS, Morrison DS. A clinical risk score to predict 3-, 5- and 10-year survival in patients undergoing surgery for Dukes B colorectal cancer. *Br J Cancer.* 2010; 103:970-974.

45. Lee M, Cronin KA, Gail MH, Feuer EJ. Predicting the absolute risk of dying from colorectal cancer and from other causes using population-based cancer registry data. *Stat Med.* 2012; 31:489-500.

46. Panis Y, Maggiori L, Caranhac G, Bretagnol F, Vicaut E. Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. *Ann Surg.* 2011; 254:738-743.

47. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med.* 2009; 7:357-363.

48. Bjerager M, Palshof T, Dahl R, Vedsted P, Olesen F. Delay in diagnosis of lung cancer in general practice. *Br J Gen Pract.* 2006; 56:863-868.

49. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. *Br J Cancer.* 2008; 98:60-70.

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

51. 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.

52. 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.

53. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol.* 2011; 11:83.

54. 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.

55. Jorgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. *Br J Cancer.* 2012; 106:1353-1360.

56. 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.

57. Janssen-Heijnen ML, Houterman S, Lemmens VE et al. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol.* 2005; 55:231-240.

58. Janssen-Heijnen ML, Maas HA, Houterman S et al. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer.* 2007; 43:2179-2193.

59. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. *J Gastrointest Surg.* 2004; 8:1061-1067.

60. Munro AJ, Bentley AH. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. *Eur J Cancer Care (Engl).* 2004; 13:254-262.

61. 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.

62. 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.

63. Roxburgh CS, Platt JJ, Leitch EF et al. Relationship between preoperative comorbidity, systemic inflammatory response, and survival in patients undergoing curative resection for colorectal cancer. *Ann Surg Oncol.* 2011; 18:997-1005.

64. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. *N Z Med J.* 2011; 124:76-88.

65. Asmis TR, Powell E, Karapetis CS et al. Comorbidity, age and overall survival in cetuximab-treated patients with advanced colorectal cancer (ACRC)--results from NCIC CTG CO.17: a phase III trial of cetuximab versus best supportive care. *Ann Oncol.* 2011; 22:118-126.

66. Koroukian SM, Xu F, Bakaki PM et al. Comorbidities, functional limitations, and geriatric syndromes in relation to treatment and survival patterns among elders with colorectal cancer. *J Gerontol A Biol Sci Med Sci.* 2010; 65:322-329.

67. Kleespies A, Fuessl KE, Seeliger H et al. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. *Int J Colorectal Dis.* 2009; 24:1097-1109.

68. 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.

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

70. Rieker RJ, Hammer E, Eisele R, Schmid E, Hogel J. 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.

71. Gill MD, Bramble MG, Rees CJ et al. Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. *Br J Cancer.* 2012; 107:417-421.

72. Shaukat A, Arain M, Anway R et al. Is KRAS Mutation Associated with Interval Colorectal Cancers? *Dig Dis Sci.* 2011.

73. Baxter NN, Sutradhar R, Forbes SS et al. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. *Gastroenterology.* 2011; 140:65-72.

74. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med.* 2012; 366:687-696.

75. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2012: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2012.

76. Arain MA, Sawhney M, Sheikh S et al. CIMP Status of Interval Colon Cancers: Another Piece to the Puzzle. *Am J Gastroenterol.* 2009.

77. Singh H, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. *Am J Gastroenterol.* 2010; 105:2588-2596.

78. Gorski TF, Rosen L, Riether R, Stasik J, Khubchandani I. Colorectal cancer after surveillance colonoscopy: false-negative examination or fast growth? *Dis Colon Rectum.* 1999; 42:877-880.

79. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer.* 2012; 118:3044-3052.

80. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clin Gastroenterol Hepatol.* 2010; 8:858-864.

81. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol.* 2006; 4:1259-1264.

82. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. *Gut.* 2012; 61:1576-1582.

83. Manser CN, Bachmann LM, Brunner J et al. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. *Gastrointest Endosc.* 2012; 76:110-117.

84. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer.* 2012; 118:3044-3052.

85. Shaukat A, Arain M, Thaygarajan B, Bond JH, Sawhney M. Is BRAF mutation associated with interval colorectal cancers? *Dig Dis Sci.* 2010; 55:2352-2356.

86. Sawhney MS, Farrar WD, Gudiseva S et al. Microsatellite instability in interval colon cancers. *Gastroenterology.* 2006; 131:1700-1705.

87. Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. *Br J Surg.* 1994; 81:1270-1276.

88. Iversen LH, Bulow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. *Br J Surg.* 2008; 95:1012-1019.

89. Osler M, Iversen LH, Borglykke A et al. Hospital variation in 30-day mortality after colorectal cancer surgery in denmark: the contribution of hospital volume and patient characteristics. *Ann Surg.* 2011; 253:733-738.

90. Sprangers MA, Taal BG, Aaronson NK, te VA. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. *Dis Colon Rectum.* 1995; 38:361-369.

91. Zhang Y, Shi J, Shi B et al. Self-expanding metallic stent as a bridge to surgery versus emergency surgery for obstructive colorectal cancer: a meta-analysis. *Surg Endosc.* 2012; 26:110-119.

92. 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.

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

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

95. 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.

96. Sagar J. Colorectal stents for the management of malignant colonic obstructions. *Cochrane Database Syst Rev.* 2011;CD007378.

97. Tan CJ, Dasari BV, Gardiner K. Systematic review and meta-analysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. *Br J Surg.* 2012; 99:469-476.

98. Al SA, McCallum IJ, Kenny L et al. Colorectal stents: do we have enough evidence? *Int J Surg.* 2011; 9:595-599.

99. van Hooft JE, Bemelman WA, Oldenburg B et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol.* 2011; 12:344-352.

100. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. *Surg Endosc.* 2011; 25:1814-1821.

101. Bridoux V, Kianifard B, Moutel G, Herve C, Tuech JJ. Stenting as a bridge to surgery for colorectal cancer. *Lancet Oncol.* 2011; 12:621-622.

102. Alcantara M, Serra-Aracil X, Falco J et al. Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer. *World J Surg.* 2011; 35:1904-1910.

103. Kim HJ, Choi GS, Park JS, Park SY, Jun SH. Higher rate of perineural invasion in stent-laparoscopic approach in comparison to emergent open resection for obstructing left-sided colon cancer. *Int J Colorectal Dis.* 2012.

104. Knight AL, Trompetas V, Saunders MP, Anderson HJ. Does stenting of left-sided colorectal cancer as a "bridge to surgery" adversely affect oncological outcomes? A comparison with non-obstructing elective left-sided colonic resections. *Int J Colorectal Dis.* 2012.

105. Lee WS, Baek JH, Kang JM, Choi S, Kwon KA. The outcome after stent placement or surgery as the initial treatment for obstructive primary tumor in patients with stage IV colon cancer. *Am J Surg.* 2012; 203:715-719.

106. Vemulapalli R, Lara LF, Sreenarasimhaiah J, Harford WV, Siddiqui AA. A comparison of palliative stenting or emergent surgery for obstructing incurable colon cancer. *Dig Dis Sci.* 2010; 55:1732-1737.

107. 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.

108. 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.

109. 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.

110. Ptok H, Marusch F, Steinert R et al. Incurable stenosing colorectal carcinoma: endoscopic stent implantation or palliative surgery? *World J Surg.* 2006; 30:1481-1487.

111. 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.

112. Johnson R, Marsh R, Corson J, Seymour K. A comparison of two methods of palliation of large bowel obstruction due to irremovable colon cancer. *Ann R Coll Surg Engl.* 2004; 86:99-103.

113. Ng KC, Law WL, Lee YM et al. Self-expanding metallic stent as a bridge to surgery versus emergency resection for obstructing left-sided colorectal cancer: a case-matched study. *J Gastrointest Surg.* 2006; 10:798-803.

114. 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.

115. Frank L. Epidemiology. When an entire country is a cohort. *Science.* 2000; 287:2398-2399.

116. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health.* 2011; 39:22-25.

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

118. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health.* 2011; 39:42-45.

119. Helqvist L, Erichsen R, Gammelager H, Johansen MB, Sorensen HT. Quality of ICD-10 colorectal cancer diagnosis codes in the Danish National Registry of Patients. *Eur J Cancer Care (Engl).* 2012; 21:722-727.

120. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull.* 1999; 46:263-268.

121. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health.* 2011; 39:30-33.

122. NOMESCO Classification of Surgical Procedures. 1.15 ed. Copenhagen: Nordic Medico-Statistical Comittee. 2010.

123. College of American Pathologists, Chicago Illinois. Systemized Nomenclature of Medicine (SNOMED). 2nd ed. 1979.

124. Erichsen R, Lash TL, Hamilton-Dutoit SJ et al. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol.* 2010; 2:51-56.

125. Bjerregaard B, Larsen OB. The Danish Pathology Register. *Scand J Public Health.* 2011; 39:72-74.

126. Risio M. The natural history of adenomas. *Best Pract Res Clin Gastroenterol.* 2010; 24:271-280.

127. Tottrup A, Erichsen R, Svaerke C, Laurberg S, Srensen HT. Thirty-day mortality after elective and emergency total colectomy in Danish patients with inflammatory bowel disease: a population-based nationwide cohort study. *BMJ Open.* 2012; 2:e000823.

128. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res.* 2007; 13:559-565.

129. Greenland S, Lash T, Rothman K. Concepts of interaction. Modern Epidemiology. 3rd ed. Lippincott Williams & Wilkins; 2008. 71-83.

130. Lash TL, Johansen MB, Christensen S et al. Hospitalization rates and survival associated with COPD: a nationwide Danish cohort study. *Lung.* 2011; 189:27-35.

131. Rothman KJ, Greenland S, Lash TL. Validity of Epidemiologic Studies. Modern Epidemiology. 3rd ed. Lippincott Williams & Wilkins; 2008. 128-147.

132. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med.* 2004; 164:1993-1998.

133. Rix TA, Riahi S, Overvad K et al. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J.* 2012; 46:149-153.

134. Erichsen R, Sværke C, Tøttrup A. The coding quality of acute total coloectomy in inflammatory bowel disease patients in a nationwide hospital registry. Pharmacoepidemiology and Drug Safety 20[S1], S165. 2011.

135. Rothman KJ, Greenland S, Lash TL. Design Strategies to Improve Study Accuracy. Modern Epidemiology. 3rd ed. Lippincott Williams & Wilkins; 2008. 168-182.

136. Hassan C, Fuccio L, Bruno M et al. A Predictive Model Identifies Patients Most Likely to Have Inadequate Bowel Preparation for Colonoscopy. *Clin Gastroenterol Hepatol.* 2012.

137. van Steenbergen LN, Lemmens VE, Straathof JW et al. Improvable quality of diagnostic assessment of colorectal cancer in southern Netherlands. *Eur J Gastroenterol Hepatol.* 2009; 21:570-575.

138. Brenner H, Hoffmeister M, Arndt V et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst.* 2010; 102:89-95.

139. Heresbach D, Barrioz T, Lapalus MG et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. *Endoscopy.* 2008; 40:284-290.

Study I

Does comorbidity interact with colorectal cancer to increase mortality?

A Danish nationwide population-based cohort study, 1995-2010

Rune Erichsen,[1] MD; Erzsébet Horváth-Puhó,[1] PhD; Lene Hjerrild Iversen,[2] DrMedSci; Timothy L. Lash,[1,3] DSc; Henrik Toft Sørensen,[1] DrMedSci

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, 8200 Aarhus N, Denmark

[2]Department of Surgery P, Aarhus University Hospital, Tage Hansens gade 2, 8000 Aarhus C Denmark

[3]Department of Epidemiology & Prevention, Wake Forest School of Medicine, Medical Center Boulevard, WF22, Winston-Salem, North Carolina, USA

Corresponding Author: Dr. Rune Erichsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Phone +45 87168231, fax: +45 87167215. E-mail: re@dce.au.dk

Financial support: The work was supported by a grant from the Danish Agency for Science Technology and Innovation. The first author was supported by a scholarship from Aarhus University.

Conflict of interest: The authors declare no conflict of interest. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have relation to the present paper.

Word count: 3034 (excluding abstract of 282 words)

Abstract

Introduction: It is unknown if comorbidity interacts with colorectal cancer (CRC) to increase the rate of mortality beyond that explained by the independent effects of CRC and comorbid conditions.

Methods: Using population-based nationwide Danish registries (1995-2010), we conducted a cohort study of all CRC patients (n=56,963) and five times as many persons from the general population (n=271,670) matched by age, gender, and specific comorbidities. To analyze comorbidity, we used the Charlson Comorbidity Index (CCI) scores. We estimated standardized mortality rates per 1,000 person-years (PY) over 0–365 days and 366 days–5 years, and calculated interaction contrasts (ICs) as a measure of the excess mortality rate not explained by the independent effects of CRC or comorbidities.

Results: Among CRC patients with a CCI score = 1, the 0–365 day mortality rate was 415/1,000 PY (95% confidence interval (CI): 401, 430) and interaction accounted for 9·3% of this rate (IC=39/1,000 PY, 95% CI: 22, 55). For patients with CCI scores of 2–3, interaction accounted for 16% of the mortality (IC=79/1,000 PY, 95% CI: 36, 121), and for patients with a CCI score of 4 or more, interaction accounted for 34% of the mortality (IC=262/1,000 PY, 95% CI: 215, 310). Findings were similar within strata of cancer stage, gender, and receipt of surgery. Interaction between CRC and comorbidities seemed particularly important for patients aged ≤69 years. Interaction between CRC and comorbidities had limited influence on mortality 366 days–5 years following diagnosis.

Conclusion: Because mortality caused by the interaction was substantial, successful treatment of the comorbidity is pivotal. From a prevention standpoint, the mortality caused by the interaction can be delayed either by treating comorbidity or the CRC, not necessarily both.

Key words: Biological interaction; Colorectal neoplasm; Epidemiology; Survival; Synergy

Introduction

With a lifetime risk of approximately 5%, colorectal cancer (CRC) is the second most common malignancy in the western world.[1,2] Since the disease primarily occurs in patients over age 65, who are likely to suffer from other chronic diseases, as many as one-third of newly diagnosed CRC patients are burdened by severe coexisting diseases (*i.e.*, comorbidities), some of which are associated with increased CRC risk (*e.g.*, diabetes).[3-5]

Even in the absence of comorbidities, CRC is associated with 5-year survival of only 40%–50%. However, in the presence of a high comorbidity burden, defined for instance as a Charlson Comorbidity Index (CCI) score ≥3, 5-year survival is as low as 20%.[4] In a study of nearly 30,000 American CRC patients over age 67 at diagnosis investigating population attributable risks (and therefore specific for this US population), approximately 9% of deaths were attributable to congestive heart failure, 5% to chronic obstructive pulmonary disease, and nearly 4% to diabetes.[6] The study also confirmed that multimorbidity was common and had a substantial effect on CRC survival.[6] Several other studies have shown that CRC patients burdened by comorbidity have higher mortality than CRC patients without coexisting disease.[4,5,7-17]

To our knowledge, however, no study of CRC mortality has (1) included a comparison cohort free of CRC and (2) accounted for comorbidity. Therefore it is not known if comorbidity interacts with CRC to increase the rate of mortality beyond that explained by CRC and comorbidity acting independently. Such information is needed to improve our biological understanding of the influence of comorbidity on CRC mortality, may be helpful in clinical practice, and would contribute to improving outcomes after CRC. On this basis, we conducted a nationwide cohort study of all Danish CRC patients diagnosed during a recent 16-year period and a matched population-based comparison cohort free of CRC, in order to study the interaction between comorbidity and CRC and subsequent risk of death.

Methods

We conducted this cohort study in the setting of the entire Danish population (accumulated 6·9 million people during the 1995–2010 study period). The Danish healthcare system provides tax-supported healthcare to all Danish residents. The unique civil registration number assigned to all Danes at birth or upon immigration by the Civil Registration System (CRS) allows unambiguous linkage between databases.[18,19] The CRS also tracks vital status and the residence of all Danish citizens and is updated daily.

Colorectal cancer cohort

We used the Danish Cancer Registry (DCR) to identify all patients diagnosed with incident CRC between 1 January 1995 and 31 December 2010.[20] The DCR maintains records on all incident malignant neoplasms diagnosed in Denmark since 1943, including patients' civil registration number, month and year of cancer diagnosis, cancer type according to the *International Classification of Disease* (ICD), 10th revision (ICD-10), and tumour spread at diagnosis. (See Appendix for ICD-10 codes for CRC.)

Population comparison cohort

We used the Danish National Registry of Patients (DNRP) and CRS to match each CRC patient with five persons from the general population who were alive and without a CRC diagnosis as of the CRC patient's diagnosis date (index date). Matching criteria were age (5-year intervals), gender, and history of the comorbid diseases included in the Charlson Comorbidity Index (CCI) (see below and Appendix).[18,21] The DNRP has recorded all non-psychiatric hospitalizations in Denmark since 1977 and hospital outpatient contacts since 1995. Its records contain dates of admission and discharge, treatment and procedure codes, and up to 20 diagnoses coded by physicians according to ICD-8 from 1977–1993 and ICD-10 since 1994. In the event that an individual from the comparison cohort developed CRC during the study period, follow-up time was terminated and the individual joined the CRC cohort.

Comorbidity

Based on DNRP records, we defined comorbidities according to diagnoses of the conditions in the Charlson Comorbidity Index (CCI), excluding CRC. The CCI's scoring system assigns weights between one and six to a range of diseases (see Appendix). In addition to the original conditions in the CCI, we also included a prior diagnosis of atrial fibrillation/flutter and obesity (both assigned a weight of one). The CCI disease groups were considered individually for matching and analysis, but also as the components of a summed, aggregate score that we classified as follows : score of 0 (''no comorbidity''), score of 1 (''low comorbidity''); score of 2–3 (''moderate comorbidity''), and score of 4 or more (''high comorbidity'').[22]

Statistical analysis

We calculated the frequency and proportion of persons in the CRC and the matched comparison cohorts within categories of demographic variables and comorbidities. CRC patients and persons matched to them were followed from the index date to date of death from any cause, emigration, or end of follow-up (31 December 2011), whichever came first. We calculated mortality rates (MRs) by dividing the number of deaths by total follow-up time for the CRC and matched comparison cohorts. To evaluate short-term and long-term mortality separately, we computed MRs between the index date and 365 days and from 366 days to 5 years. The analysis within strata of follow-up period required that we dissolve the matching, as the age and gender distribution was different among one-year survivors than among all participants. For all analyses, we standardized the MRs to the age and gender distribution of the CRC inception cohort. Furthermore, as a measure of mortality rate ratios (MRRs), we calculated hazard ratios using Cox regression analysis comparing CRC patients to matched persons from the general population, adjusting for age (as a continuous variable), gender, year of index date (1995–1999 vs. 2005–2010, 2000–2004 vs. 2005–2010), and, in the overall analysis, comorbidity scores.

We computed interaction contrasts (ICs) to estimate the excess MR in patients with both CRC and comorbid diseases, beyond that expected from the independent effects of these diseases.[23] We used standardized

rates for this analysis, using the persons without comorbidity from the general population as the reference. The IC was calculated by subtracting the standardized mortality difference between CRC patients with *e.g.* CCI=4 and CCI=0 from the mortality difference between general population (pop) cohort members with CCI=4 and CCI=0 [*e.g.* $IC_{CCI4} = (MR_{CRC,CCI4}-MR_{CRC,CCI0})-(MR_{pop,CCI4}-MR_{pop,CCI0})$]. Hence, positive ICs describe the excess MR caused by the interaction, whereas a negative IC would indicate a protective role.

Analyses were stratified by CRC stage (non-metastatic vs. metastatic, see Appendix), age group (0–69, 70–79, and 80+ years), and gender. We also calculated standardized MRs and ICs restricted to CRC patients without metastatic disease undergoing colorectal surgery, as defined by relevant procedure codes (see Appendix), within 60 days before and 180 days after the diagnosis date, and persons matched to them from the general population. Finally, we calculated standardized MRs and ICs for each individual disease included in the CCI (with the reference group of persons free of any comorbidity, as above).

Results

Characteristics

We identified 56,963 CRC patients and 271,670 persons from the general population who were matched by age (median age = 72 years), gender (men = 51%), year of index date, and comorbidity (Table 1). Since we were unable to match five persons from the general population to all CRC patients, small differences occurred between the characteristics of the CRC patients and general population comparison cohort. At the aggregated CCI level, however, it was mainly among CRC patients with a high comorbidity burden that these differences were noticeable (CCI score of 4 or more: 4·9% vs. 2·8%).

Short-term mortality

CRC patients had a 0–365 day standardized MR of 400 (95% CI: 394, 406) per 1,000 person years (PY), compared with 48 (95% CI: 47, 48) per 1,000 PY in the population comparison cohort, confirming overall higher mortality among patients with CRC (adjusted MRR=8·3, 95% CI: 8·1, 8·5). The 0–365 day standardized MRs increased with higher comorbidity scores and increased more among CRC patients than among matched persons from the general population (Table 2). For instance, among CRC patients with a CCI score of 1 the standardized MR was 415 (95% CI: 401, 430) per 1,000 PY. The interaction between CRC and comorbidity accounted for an excess (*i.e.*, IC) of 39/1,000 PY (95% CI: 22, 55) or (39/415=) 9·3% of the standardized MR. An even greater excess was observed for patients with a CCI score of 2–3, with an IC of 79/1,000 PY (95% CI: 36, 121), accounting for 16% of the total standardized MR. For patients with a CCI score of 4+, the IC was 262/1,000 PY (95% CI: 215, 310), accounting for 34% of the MR.

Long-term mortality

Although to a lesser extent than during the first 365 days after diagnosis, CRC remained associated with increased subsequent mortality (overall adjusted 366 day–5 year MRR = 3·0, 95% CI: 2·9, 3·0). The 366 day–5 year standardized MRs increased with higher CCI scores. However, only among CRC patients with a CCI

score of 4+ did mortality increase more than among matched persons in the population comparison cohort, with the interaction accounting for 14% of the MR (Table 2).

Stratified and restricted analyses

Tables 3 and 4 present the standardized MRs and ICs by CRC stage at diagnosis. These results confirm that CRC mortality during the period 0-365 days after diagnosis interacted with comorbidity among CRC patients with both metastatic and non-metastatic disease. For example, among patients with a CCI score of 4+, the interaction accounted for 28% of the MR in patients without metastases and 24% in patients with metastatic spread. Consistent with the overall results, interaction between CRC and comorbidity had less impact on mortality among CRC patients, regardless of non-metastatic and metastatic disease, during the period 366 days –5 years after the CRC diagnosis (Tables 3 and 4).

For mortality within 0–365 days after the index date, the interaction between CRC and comorbidity was particularly important for the younger age groups (0–69 years). For example the IC was 257/1,000 PY (95% CI: 176, 338) for CRC patients with a CCI score of 4+ accounting for 45% of the total standardized MR. The ICs for the older age groups were closer to the overall estimates (Supplementary table 1). For mortality within 366 days–5 years, the interaction between CRC and comorbidity was only evident for the age group 0–69 years with a CCI score of 4+, where it accounted for 30% (IC = 74, 95% CI: 19, 128).

Whereas there was no material difference in interaction for men and women in the first 0–365 days, the overall interaction observed for the 366 day–5 year mortality among CRC patients with a CCI score of 4 or more was mainly found in women (IC=49/1,000 PY, 95% CI: 9·4, 89) and to a lesser extent in men (IC=27/1,000 PY, 95% CI: -19, 72).

In patients with non-metastatic CRC undergoing colorectal resection, interaction accounted for 18% of the mortality among those with a CCI score of 1 (IC = 34/1,000 PY, 95% CI: 20, 48), 8·9% among those with a CCI score of 2–3 (IC = 19/1,000 PY, 95% CI: 4·0, 35), and 26% among those with a CCI score of 4+ (IC = 91/1,000

PY, 95% CI: 48, 134), during 0–365 days of follow-up. For patients who survived the first year after CRC surgery, coexistence of CRC and comorbidity did not lead to MRs higher than that explained by CRC and comorbidity acting independently (results not shown).

Individual comorbidities

Table 5 presents standardized MRs for CRC patients according to the presence of individual comorbidities. For CRC patients, a variety of comorbidities interacted with CRC to increase mortality during the first 0–365 days following diagnosis. In contrast, the interactions had limited influence on mortality during the subsequent 366 days–5 years.

Discussion

In this large nationwide population-based matched cohort study we found that comorbidity interacted with CRC to increase mortality, particularly in the first 0–365 days after diagnosis. The interaction accounted for 9% of the total standardized MR in patients with low comorbidity (CCI score of 1), but as much as 34% in those with high comorbidity burdens (CCI score of 4+). Nearly the same results were found for men and women, both when CRC patients with either non-metastatic or metastatic disease were evaluated, and when the analysis was restricted to CRC patients without metastases who underwent CRC surgery. The interaction seemed particularly important for patients aged 69 years or younger and was evident for a wide variety of comorbidities in CRC patients. Although the interaction between CRC and a high comorbidity burden (CCI score of 4+) accounted for 14% of mortality 366 days–5 years after diagnosis, mortality in this period was not higher than that explained by CRC and comorbidity acting independently.

Our study extends the existing literature by including a population comparison cohort free of CRC, thereby allowing evaluation of the excess mortality caused by the interaction between comorbidity and CRC. Since successful treatment of the comorbidity would delay death from the comorbidity and the interaction between the comorbidity and the CRC, efforts to enhance clinical management of both CRC and concurrent comorbidity will have substantial effects on improving the prognosis. From a prevention standpoint, the mortality caused by the interaction can be delayed either by treating comorbidity or the CRC, not necessarily both. These findings strongly underscore the need for health care providers to pay particular attention to comorbid diseases while treating CRC patients.

No earlier study has evaluated the independent effects of CRC and comorbidity or their synergistic effect on mortality, although they have generally demonstrated that CRC patients with comorbidities have poorer survival than CRC patients without comorbidities; a pattern also observed in our study. Impaired survival has been demonstrated over the short-term[5,8,12] and long-term,[4,5,8] and in population-based studies[4,12,15] and single-center studies.[10,16] Impaired survival also has been found when comorbidities were evaluated

using indices such as Charlson's Comorbidity Index or Adult Comorbidity Index (ACE-27)[4,10,16] and for individual diseases including cardiovascular disease, pulmonary disease, diabetes, previous malignancy, and renal disease.[7,9,13,14] In addition, impaired survival of CRC patients with comorbidities has been demonstrated regardless of treatment received, anatomical site of CRC, gender, and age.[4,15,16] Nonetheless, at least two studies have indicated that comorbidity does not have as important a role in mortality among patients with end-stage CRC. A recent study from North America (exploratory analysis of the CO·17 clinical trial) including 572 patients with metastatic CRC found that patients with more comorbidity had improved survival compared with patients with less (HR=0·8, 95% CI 0·65, 1·00).[24] A single-center German study of 233 CRC patients with metastatic disease undergoing non-curative elective surgery found no association between comorbidities (measured by number of affected organs) and 30-day mortality.[25] These findings suggest that among patients severely ill with CRC, the coexistence of other often less aggressive diseases has little effect on their poor prognosis. In our study, however, we found that interaction between comorbidity and CRC played a substantial role for mortality in CRC patients with metastatic disease, though only during the first 365 days of follow-up and primarily among those with high comorbidity burdens. The same pattern is likely to be observed with increasing age, which our study also confirmed.

Although it was beyond the scope of our study to evaluate underlying reasons for excess mortality among CRC patients with comorbidities, there are several possibilities. First, it has been shown that diseases such as diabetes and inflammatory bowel disease increase CRC risk, and it has been speculated that this association might result in particularly aggressive CRC with poor survival.[26,27] Second, severe comorbidities might impair or delay cancer diagnosis or interfere with diagnostic follow-up, leading to more advanced spread,[28] although some studies have shown decreased delays among comorbid CRC patients.[29] Third, physician behavior and patient compliance may be affected by the presence of other diseases. Finally, treatment and post-treatment care might be suboptimal in the presence of comorbidities.[9,13,30] However, these potential explanations remain speculative and need to be confirmed in future investigations.

The strengths of our study include its population-based cohort design and a setting providing free access to healthcare, which virtually eliminates referral bias. We were able to study a large, well-defined population with complete follow-up owing to computerized nationwide registries, thus making selection biases negligible. Because of the large number of CRC patients and matched persons from the general population without CRC, we were able to estimate the independent effects of cancer and other conditions and how their co-occurrence affects mortality. Earlier research has called for such an investigation.[14]

Our study also had several limitations. Inaccurate coding in the nationwide registries is an important concern in registry based analyses such as ours. Fortunately, the completeness and positive predictive values of diagnoses in the DCR have been found to be 95%–98%.[20] The positive predictive value of the coding of comorbidities also has been shown to be high, while the completeness of coding is likely to be lower.[22] In addition, even though we included comorbidities in the CCI, with the addition of atrial fibrillation/flutter and obesity, we may have missed other diseases affecting mortality. These factors could have led us to underestimate comorbidity burdens and to classify patients with comorbidities in the group without comorbidity, resulting in more uniform mortality rates and MRRs approaching 1·0. Finally, although we attempted to deal with potential confounding caused by age and gender by matching, standardization, and adjustment, our results may have been affected by confounding by unmeasured factors such as alcohol consumption, smoking, and medication use. Nevertheless, given the strength of the associations, we find it unlikely that these unmeasured factors could explain our results completely.

In conclusion, our population-based matched cohort study showed that comorbidities interacted with CRC to increase mortality beyond that explained by CRC and comorbidities acting independently, particularly in the first year after CRC diagnosis. Successful treatment of the comorbidity is pivotal since it would delay death from both the comorbidity and the interaction. From a prevention standpoint, the mortality caused by the interaction can be delayed either by treating comorbidity or the CRC, not necessarily both.

Table 1. Characteristics of colorectal cancer patients and a population-based comparison cohort matched by gender, age, year of diagnosis, and comorbidity, Denmark 1995–2010.

	Colorectal cancer cohort		Population-based comparison cohort*	
	Number	**%**	**Number**	**%**
Sex				
Female	27,665	49	132,537	49
Male	29,298	51	139,133	51
Age at diagnosis/index:				
0 –59 years	10,285	18	51,467	19
60–69 years	14,541	26	70,613	26
70–79 years	18,547	33	87,444	32
80+ years	13,590	24	62,146	23
Year of diagnosis/index date:				
1995–1999	16,230	29	78,136	29
2000–2004	17,359	31	83,088	31
2005–2010	23,374	41	110,446	41
Stage of colorectal cancer:				
Non-metastatic	37,381	66	N/A	-
Metastatic	12,687	22	N/A	-
Unknown	6,895	12	N/A	-
Cancer location:				
Colon	37,859	67	N/A	-
Rectal	19,014	33	N/A	-
Colon and rectal	90	0·2	N/A	-
Comorbidities included in the Charlson Comorbidity Index:				
Myocardial infarction	3,270	5·7	13,825	5·1
Congestive heart failure	2,783	4·9	10,652	3·9
Peripheral vascular disease	2,322	4·1	9,299	3·4
Cerebrovascular disease	5,014	8·8	21,852	8·0
Dementia	594	1·0	2,297	0·8
Chronic pulmonary disease	4,009	7·0	17,061	6·3
Connective tissue disease	1,567	2·8	6,293	2·3
Ulcer disease	3,026	5·3	12,711	4·7
Mild liver disease	478	0·8	1,670	0·6
Diabetes type I and II	3,007	5·3	11,945	4·4
Hemiplegia	100	0·2	252	0·1
Moderate to severe renal disease	811	1·4	2557	0·9
Diabetes with end organ failure	1,384	2·4	4,901	1·8
Any tumor (excluding colorectal cancer)	5,037	8·8	22,517	8·3
Leukemia	158	0·3	494	0·2
Lymphoma	295	0·5	1,010	0·4
Moderate to severe liver disease	113	0·2	311	0·1
Metastatic solid tumor	519	0·9	1,944	0·7
AIDS	10	0·0	25	0·0
Diseases not originally included in the Charlson Comorbidity index:				
Atrial fibrillation/flutter	1,164	2·0	4,213	1·6
Obesity	1,197	2·1	4,320	1·6
Charlson Comorbidity Index scores:†				
0 (no comorbidity)	34,918	61	172,041	63
1 (low comorbidity)	9,747	17	47,139	17
2-3 (moderate comorbidity)	9,522	17	44,788	17
4+ (high comorbidity)	2,776	4·9	7,702	2·8

* Matched on age, gender, year of CRC diagnosis, and presence of individual comorbidities listed in this table.

† The Charlson Comorbidity Index included the 19 diseases from the original Index with the addition of atrial fibrillation /flutter and obesity (both assigned one point).

Table 2. Mortality, mortality rate ratios (MRR), and interaction contrasts for colorectal cancer (CRC) patients compared with persons in a matched population-based comparison cohort, overall and by Charlson Comorbidity Index (CCI) score.

CCI score	Cohort	No. of persons	No. of deaths	Person-years	Standardized mortality rates per 1000 person-years (95% CI)		Adjusted MRRs* (95% CI)	Interaction contrast (95% CI)	
0–365 days of follow-up									
All	CRC	56,963	17,089	45,559	400	(394, 406)	8·3 (8·1, 8·5)	N/A	
All	Comparison	271,670	11,962	265,223	48	(47, 48)	Ref.	N/A	
0	CRC	34,918	8,881	29,245	351	(343, 359)	15 (14, 15)	Ref.	
0	Comparison	172,041	3,652	170,008	27	(26, 28)	Ref.	.	
1	CRC	9,747	3,254	7,509	415	(401, 430)	7·4 (7·0, 7·7)	39	(22, 55)
1	Comparison	47,139	2,755	45,723	53	(51, 55)	Ref.	.	
2–3	CRC	9,522	3,548	7,035	489	(447, 530)	5·1 (4·9, 5·3)	79	(36, 121)
2–3	Comparison	44,788	4,234	42,521	86	(83, 89)	Ref.	.	
4+	CRC	2,776	1,406	1,771	761	(715, 807)	3·9 (3·7, 4·3)	262	(215, 310)
4+	Comparison	7,702	1,321	6,971	175	(165, 185)	Ref.		
366 days to 5 years of follow-up									
All	CRC	39,862	14,274	102,813	143	(141, 146)	3·0 (2·9, 3·0)	N/A	
All	Comparison	258,729	40,310	808,019	50	(49, 50)	Ref.	N/A	
0	CRC	26,029	8,606	69,909	131	(128, 134)	4·2 (4·1, 4·3)	Ref	
0	Comparison	167,766	17,549	549,904	36	(36, 37)	Ref.	.	
1	CRC	6,490	2,482	16,193	146	(140, 152)	2·3 (2·2, 2·4)	-9·8	(-17, -3·1)
1	Comparison	44,215	9,585	131,313	61	(60, 62)	Ref.	.	
2–3	CRC	5,973	2,491	13,917	172	(165, 179)	2·0 (1·9, 2·0)	-3·0	(-11, 4·9)
2–3	Comparison	40,390	10,902	111,329	80	(79, 82)	Ref.	.	
4+	CRC	1,370	695	2,793	261	(231, 290)	1·7 (1·6, 1·8)	37	(7·0, 68)
4+	Comparison	6,358	2,274	15,473	129	(123, 134)	Ref.	.	

* Adjusted for age, gender, and CRC/index year. For the overall analysis we also adjusted for Charlson Comorbidity Index scores.

Table 3. Mortality, mortality rate ratios (MRR), and interaction contrasts for patients with non-metastatic colorectal cancer (CRC) compared with persons in a matched population-based comparison cohort, by Charlson Comorbidity Index (CCI) scores.

CCI score	Cohort	No. of persons	No. of deaths	Person-years	Standardized mortality rates per 1000 person years (95% CI)		Adjusted MRRs* (95% CI)	Interaction contrast (95% CI)	
0–365 days of follow-up									
0	CRC	23,428	3,211	21,405	177	(171, 183)	7·5 (7·1, 7·9)	Ref.	
0	Comparison	115,423	2,382	114,121	26	(25, 27)	Ref.		
1	CRC	6,420	1,407	5,448	241	(228, 254)	4·7 (4·4, 5·1)	40	(26, 55)
1	Comparison	31,049	1,728	30,161	49	(47, 52)	Ref.	.	
2–3	CRC	6,004	1,481	4,983	288	(251, 326)	3·1 (2·9, 3·3)	52	(14, 90)
2–3	Comparison	28,299	2,620	26,892	85	(82, 88)	Ref.	.	
4+	CRC	1,529	551	1,145	441	(401, 481)	2·6 (2·3, 2·9)	125	(83, 168)
4+	Comparison	4,237	700	3,850	164	(151, 177)	Ref.		
366 days to 5 years of follow-up									
0	CRC	20,211	5,487	59,101	101	(98, 104)	3·2 (3·1, 3·3)	Ref.	
0	Comparison	112,638	11,875	376,876	37	(36, 37)	Ref.		
1	CRC	5,012	1,673	13,586	116	(110, 122)	1·9 (1·8, 2·0)	-8·4	(-15, -1·8)
1	Comparison	29,219	6,285	88,895	60	(59, 62)	Ref.	.	
2–3	CRC	4,522	1,667	11,481	139	(132, 146)	1·6 (1·5, 1·7)	-5·3	(-13, 2·7)
2–3	Comparison	25,581	6,807	72,780	80	(78, 82)	Ref.	.	
4+	CRC	978	456	2,190	202	(179, 226)	1·4 (1·3, 1·6)	10	(-14, 35)
4+	Comparison	3,525	1,309	8,708	128	(121, 135)	Ref.		

* Adjusted for age, gender, and CRC/index year.

Table 4. Mortality, mortality rate ratios (MRRs), and interaction contrasts for patients with metastatic colorectal cancer (CRC) compared with persons in a matched population-based comparison cohort, by Charlson Comorbidity Index (CCI) scores.

CCI score	Cohort	No. of persons	No. of deaths	Person-years	Standardized Mortality rates per 1000 person years (95% CI)		Adjusted MRRs* (95% CI)	Interaction contrast (95% CI)	
0–365 days of follow-up									
0	CRC	7,956	4,476	5,138	1,023	(990, 1,055)	53 (49, 58)	Ref.	
0	Comparison	39,232	681	38,819	22	(20, 24)	Ref.		
1	CRC	2,030	1,313	1,148	1,166	(1,102, 1,231)	22 (20, 25)	116	(44, 189)
1	Comparison	9,839	528	9,570	49	(45, 54)	Ref.	.	
2–3	CRC	2,005	1,314	1,093	1,244	(1,062, 1,426)	13 (12, 15)	169	(-16, 354)
2–3	Comparison	9,442	815	9,009	74	(69, 80)	Ref.	.	
4+	CRC	696	515	332	1,548	(1,403, 1,693)	7·9 (6·9, 9·1)	373	(224, 523)
4+	Comparison	2,051	338	1,858	174	(154, 193)	Ref.		
366 days to 5 years of follow-up									
0	CRC	3,479	2,409	5,035	490	(470, 511)	22 (21, 23)	Ref.	
0	Comparison	38,400	3,425	123,082	26	(25, 27)	Ref.		
1	CRC	716	495	1,020	496	(450, 542)	10 (9·2, 11)	-16	(-67, 35)
1	Comparison	9,272	1,792	27,385	48	(45, 50)	Ref.	.	
2–3	CRC	691	478	924	492	(444, 540)	6·3 (5·7, 7·0)	-40	(-92, 13)
2–3	Comparison	8,595	2,241	23,084	67	(63, 70)	Ref.	.	
4+	CRC	181	133	233	590	(449, 730)	4·9 (4·0, 5·9)	15	(-127, 158)
4+	Comparison	1,704	529	4,278	110	(99, 121)	Ref.		

* Adjusted for age, gender, and CRC/index year.

Table 5. Standardized mortality rates (per 1,000 person years) and interaction contrasts for colorectal cancer (CRC) patients compared with persons in a matched population-based comparison cohort, according to the presence of selected comorbid diseases included in the Charlson Comorbidity Index.

	0–365 days of follow-up				366 days–5 years of follow-up			
	standardized mortality rates, CRC cohort (95% CI)		Interaction contrasts (95% CI)		standardized mortality rates, CRC cohort (95% CI)		Interaction contrasts (95% CI)	
Myocardial infarction	470	(439, 500)	73	(40, 105)	155	(142, 169)	-11	(-26, 3·1)
Congestive heart failure	630	(588, 672)	188	(144, 231)	205	(184, 225)	-2·8	(-24, 19)
Peripheral vascular disease	542	(503, 581)	130	(90, 171)	195	(176, 214)	10	(-9·6, 30)
Cerebrovascular disease	512	(487, 537)	105	(78, 131)	160	(149, 171)	-17	(-29, -5·7)
Dementia	1,010	(851, 1,169)	538	(378, 698)	318	(225, 412)	72	(-23, 166)
Chronic pulmonary disease	566	(537, 595)	145	(114, 175)	183	(169, 197)	-7·2	(-22, 7·4)
Connective tissue disease	466	(424, 508)	85	(42, 127)	201	(165, 238)	47	(9·8, 84)
Ulcer disease	490	(461, 520)	94	(63, 125)	160	(144, 177)	-7·5	(-24, 9·4)
Mild liver disease	767	(638, 896)	277	(94, 459)	209	(168, 250)	-0·1	(-45, 44)
Diabetes type I and II	505	(474, 536)	105	(73, 138)	177	(163, 191)	1·3	(-13, 16)
Hemiplegia	997	(571, 1,423)	617	(190, 1,044)	351	(138, 564)	162	(-52, 377)
Moderate to severe renal disease	644	(575, 714)	208	(137, 279)	183	(155, 211)	-4·8	(-34, 25)
Diabetes with end organ failure	546	(495, 597)	134	(81, 187)	185	(164, 206)	-5·6	(-28, 17)
Any tumor (excluding colorectal cancer)	484	(454, 515)	60	(28, 91)	182	(171, 193)	13	(1·1, 25)
Leukemia	778	(490, 1,065)	372	(84, 661)	331	(101, 562)	147	(-84, 378)
Lymphoma	529	(417, 641)	108	(-6·2, 222)	274	(207, 341)	92	(24, 160)
Moderate to severe liver disease	1,266	(656, 1,877)	818	(205, 1,430)	207	(113, 300)	-9·9	(-108, 89)
Metastatic solid tumor	945	(828, 1,062)	358	(237, 478)	625	(4·0, 1,246)	415	(-206, 1,036)
AIDS	3,334	(-3,201, 9,869)	2,998	(-3,537, 9,533)	202	(-143, 548)	98	(-248, 443)
Diseases not originally included in the Charlson index:								
Atrial fibrillation/flutter	450	(405, 494)	53	(6·7, 99)	175	(152, 197)	5·2	(-18, 29)
Obesity	485	(425, 545)	102	(41, 163)	177	(153 , 202)	11	(-16, 37)

Abbreviations: CRC: Colorectal cancer; IC: Interaction contrast;

Supplementary Table 1. Mortality rates and interaction contrasts within 0-365 days of follow-up for patients with colorectal cancer (CRC) compared with persons in a matched population-based comparison cohort, by age and Charlson Comorbidity Index (CCI) scores.

CCI score	Cohort	No. of persons	No. of deaths	Person-years	Standardized Mortality rates per 1000 person years (95% CI)		Interaction contrast (95% CI)	
Age 0–69 years								
0	CRC	18,058	3,150	16,248	197	(190, 204)	Ref.	
0	Comparison	90,206	457	89,872	5·4	(4·9, 5·9)	.	
1	CRC	3,277	702	2,838	240	(221, 258)	34	(14, 53)
1	Comparison	16,156	260	16,019	15	(13, 17)	.	
2–3	CRC	2,751	669	2,328	324	(232, 416)	92	(0·6, 184)
2–3	Comparison	13,329	565	13,026	40	(37, 44)	.	
4+	CRC	740	291	541	569	(489, 648)	257	(176, 338)
4+	Comparison	2,389	288	2,224	120	(106, 135)	.	
Age 70–79 years								
0	CRC	10,337	2,915	8,445	349	(337, 362)	Ref.	
0	Comparison	50,321	1,004	49,754	21	(20, 22)	.	
1	CRC	3,536	1,193	2,726	435	(410, 460)	58	(30, 86)
1	Comparison	17,162	850	16,724	49	(46, 53)	.	
2–3	CRC	3,585	1,288	2,693	477	(451, 503)	64	(35, 93)
2–3	Comparison	16,963	1,388	16,205	85	(80, 89)	.	
4+	CRC	1,089	526	721	723	(661, 785)	198	(133, 264)
4+	Comparison	2,998	539	2,707	196	(179, 213)	.	
Age 80+ years								
0	CRC	6,523	2,816	4,552	635	(612, 659)	Ref.	
0	Comparison	31,514	2,191	30,382	75	(72, 78)	.	
1	CRC	2,934	1,359	1,945	709	(671, 747)	23	(-23, 68)
1	Comparison	13,821	1,645	12,980	126	(120, 132)	.	
2–3	CRC	3,186	1,591	2,014	805	(765, 845)	73	(26, 120)
2–3	Comparison	14,496	2,281	13,290	171	(164, 178)	.	
4+	CRC	947	589	509	1,166	(1,070, 1,261)	360	(259, 461)
4+	Comparison	2,315	494	2,040	245	(223, 267)	.	

Appendix: Codes and definitions used in the present study

Colorectal cancer: Colon: ICD-10: C18

Rectal: ICD-10: C19-20

Surgery codes for colorectal resection: KJFB20-97, KJFH00-33, KJFH96, KJGB00-50, and KJGB96-97

Definition of colorectal cancer stage in the Danish Cancer Registry

	Dukes 1995-2003	**TNM 2004-2010**
Non-metastatic (i.e. localized and regional spread)	A,B, and C	T0-4,x; N0-3; M0 T0-2; N0; Mx T0-1; Nx; M0,x
Metastatic	D	T0-4,x; N1-3; M1,x T0-4,x; N0; M1 T0-4,x; Nx; M1
Unknown		T2-4,x; Nx; M0,x T3-4,x; N0; Mx

Charlson's Comorbidity Index:

	Diseases	ICD-8	ICD-10	Score
1	Myocardial infarction	410	I21;I22;I23	1
2	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430-438	I60-I69; G45; G46	1
5	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0; DB18	1
10	Diabetes type1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1
	Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9	
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes with end-organ damage type1	249.01-249.05; 249.08	E10.2-E10.8	2
	type2	250.01-250.05; 250.08	E11.2-E11.8	
14	Any tumor (except colorectal cancer)	140-194 (excluding 153.xx, 154.09-19)	C00-C75 (excluding C18-C20)	2
15	Leukemia	204-207	C91-C95	2
16	Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumor	195-198; 199	C76-C80	6
19	AIDS	079.83	B21-B24	6
	Additions to the original definition			
	Atrial fibrillation/flutter	427.93	I489	1
	Obesity	277	E66	1

References

1. Ingle SB, Limburg P. Colorectal Carcinoma. In: Talley NJ, Locke GR, Saito JA, editors. GI Epidemiology. 1 ed. Blackwell Publishing; 2007. 170-175.

2. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917.

3. 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.

4. Iversen LH, Norgaard M, Jacobsen J, Laurberg S, Sorensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006--a population-based cohort study. *Dis Colon Rectum* 2009; **52**: 71-78.

5. Jorgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. *Br J Cancer* 2012; **106**: 1353-1360.

6. 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.

7. Janssen-Heijnen ML, Maas HA, Houterman S et al. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer* 2007; **43**: 2179-2193.

8. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. *N Z Med J* 2011; **124**: 76-88.

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

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

11. 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.

12. Panis Y, Maggiori L, Caranhac G, Bretagnol F, Vicaut E. Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. *Ann Surg* 2011; **254**: 738-743.

13. 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.

14. 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.

15. Janssen-Heijnen ML, Houterman S, Lemmens VE et al. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol* 2005; **55**: 231-240.

16. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. *J Gastrointest Surg* 2004; **8**: 1061-1067.

17. Rieker RJ, Hammer E, Eisele R, Schmid E, Hogel J. 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.

18. 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.

19. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000; **287**: 2398-2399.

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

21. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263-268.

22. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; **11**: 83.

23. Greenland S, Lash T, Rothman K. Concepts of interaction. Modern Epidemiology. 3rd ed. Lippincott Williams & Wilkins; 2008. 71-83.

24. Asmis TR, Powell E, Karapetis CS et al. Comorbidity, age and overall survival in cetuximab-treated patients with advanced colorectal cancer (ACRC)--results from NCIC CTG CO.17: a phase III trial of cetuximab versus best supportive care. *Ann Oncol* 2011; **22**: 118-126.

25. Kleespies A, Fuessl KE, Seeliger H et al. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. *Int J Colorectal Dis* 2009; **24**: 1097-1109.

26. Larsen M, Mose H, Gislum M et al. Survival after colorectal cancer in patients with Crohn's disease: A nationwide population-based Danish follow-up study. *Am J Gastroenterol* 2007; **102**: 163-167.

27. Jensen AB, Larsen M, Gislum M et al. Survival after colorectal cancer in patients with ulcerative colitis: a nationwide population-based Danish study. *Am J Gastroenterol* 2006; **101**: 1283-1287.

28. Bjerager M, Palshof T, Dahl R, Vedsted P, Olesen F. Delay in diagnosis of lung cancer in general practice. *Br J Gen Pract* 2006; **56**: 863-868.

29. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. *Br J Cancer* 2008; **98**: 60-70.

30. Koroukian SM, Xu F, Bakaki PM et al. Comorbidities, functional limitations, and geriatric syndromes in relation to treatment and survival patterns among elders with colorectal cancer. *J Gerontol A Biol Sci Med Sci* 2010; **65**: 322-329.

Study II

Characteristics and survival of interval and sporadic colorectal cancer patients: A nationwide population-based cohort study

Rune Erichsen,[1] MD; John A Baron,[1,2] MD; Elena M Stoffel,[3] MD; Søren Laurberg,[4] DMSc; Robert S. Sandler,[2] MD; Henrik Toft Sørensen,[1,2] DMSc

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark

[2]Department of Medicine, Center for Gastrointestinal Biology and Disease, University of North Carolina School of Medicine, Mason Farm Road, Chapel Hill, NC, USA

[3]Department of Medicine, University of Michigan Health System, 1500 E. Medical Center Drive, Ann Arbor, MI, USA

[4]Department of Surgery P, Aarhus University Hospital, Tage-Hansens Gade 2, Aarhus C, Denmark

Corresponding author: Dr. Rune Erichsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. E-mail: re@dce.au.dk. Phone: +45 87168231. Fax: +45 87167215

Financial support: The work was supported by Clinical Epidemiology Research Foundation, Aarhus University. The first author was supported by a scholarship from Aarhus University.

Conflict of interest: The authors declare no conflict of interest. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have relation to the present paper.

Word count: 3,174 (excluding abstract of 257 words)

Abstract

Introduction: Colorectal cancers (CRCs) diagnosed relatively soon after a colonoscopy are referred to as interval CRCs. It is not clear whether interval CRCs arise from prevalent lesions missed at colonoscopy or represent specific aggressive biology leading to poor survival.

Methods: Using Danish population-based medical registries (2000-2009), we investigated patients with "interval" CRC diagnosed within 1-5 years of a colonoscopy, and compared them to cases with colonoscopy ≥10 year prior to diagnosis and to "sporadic" CRCs with no colonoscopy prior to diagnosis. Multivariate logistic regression was used to explore the association between characteristics and interval CRC. We assessed survival using Kaplan Meier methods and mortality rate ratios (MRR) using Cox regression, adjusting for covariates including the Charlson Comorbidity Index (CCI 0, 1-2, 3+).

Results: The comparison of the 982 interval CRCs to the 358 patients with CRC ≥10 years after colonoscopy revealed nearly similar characteristics and mortality. In the comparison to the 35,707 sporadic CRCs, female sex, localized stage at diagnosis, proximal tumor location, and high comorbidity burden were factors independently associated with interval CRC. The 1-year survival was 68% (95% CI: 65%, 71%) in interval and 71% (95% CI: 70%, 71%) in sporadic cases, with an adjusted MRR of 0.92 (95% CI 0.82, 1.0). After 5 years, survival was 41% (95% CI: 37%, 44%) in interval and 43% (95% CI: 42%, 43%) in sporadic cases, and the adjusted 2-5 year MRR was 1.0 (95%CI 0.91, 1.2).

Conclusion: Clinical characteristics and survival among interval CRCs did not suggest aggressive biology, but rather that the majority represented missed lesions.

Keywords: Colonoscopy; Colorectal neoplasm; Mortality; Prognosis

Introduction

Colonoscopy has proven very effective in the detection of colorectal cancer (CRC), and endoscopic polypectomy offers the potential of arresting CRC development (1). Studies suggest that CRC risk is clearly decreased for more than 10 years after a negative colonoscopy (2, 3). Nonetheless, recent reports suggest 5-8% of all CRCs are diagnosed in patients who had undergone colonoscopies in the 3-5 years preceding diagnosis (4-7). These cancers are commonly referred to as interval CRCs because they are diagnosed in the interval relatively soon after colonoscopies (8).

Although interval CRCs could derive from missed lesions or insufficiently resected polyps (9), some studies have suggested that a subset of interval CRCs could represent rapidly growing and aggressive cancers (4, 8, 10) that may be associated with poor survival. However, previous studies have not found any difference in survival between interval CRC cases and those with no prior colonoscopy (5, 8). These studies have been hampered by small sample sizes (between 50 and 400 cases), lack of clinical information (e.g. comorbidity), and an arbitrary choice of the interval between colonoscopy and diagnosis for the definition of interval or missed CRCs (e.g. as 6-36 months or 1-5 years) (4, 5, 8, 11). In addition, with the exception of one population-based study (5) other analyses were based on one study population from a single medical centre consisting of 98% males (4, 8, 11-13).

We therefore conducted a nationwide population-based cohort study of CRCs arising after colonoscopy to evaluate demographic, tumour, and comorbidity characteristics and survival.

Methods

We conducted this cohort study in the setting of the entire Danish population (5.5 million people) using nationwide databases. We linked individual-level data using the civil registration number, a unique 10-digit identifier assigned at birth or emigration to all Danish residents by the Civil Registration System. The system also tracks vital status and residence and is updated daily.

Colorectal cancer patients

We identified all patients with a CRC diagnosis recorded in the Danish Cancer Registry (DCR) from January 1, 2000 through December 31, 2009. The DCR has kept records of all incident malignant neoplasms in Denmark since 1943 (14). Its data include civil registration number, month and year of cancer diagnosis, location of the tumour (proximal [caecum, appendix, ascending colon, and right flexure]; Transverse colon; distal [left flexure, descending colon, and sigmoid]; Rectal [rectal and junction]; and several regions/unspecified), tumour histology, and tumour stage at diagnosis (classified as localised [Duke's A/B and T1-4,N0,M0], regional [Duke's C and Tx,N1-3,M0], metastasised [Duke's D and Tx,Nx,M1], or unknown). Cancers are recorded according to the International Classification of Diseases (ICD) codes, 10th revision (recoded from ICD-7 before 2004, see the Appendix for CRC codes). Tumour histology is recorded according to the morphology codes used by Danish pathologists (15). We considered separately the histological types recorded for more than 1% of either interval or sporadic CRCs and grouped the remaining histologies as "other histology".

We linked CRC patients to the Danish National Registry of Patients (NRP) to obtain information on all colonoscopy exams and hospital diagnoses prior to the CRC diagnosis. The NRP has tracked all non-psychiatric hospitalisations in Denmark since 1977 and outpatient visits (including gastroenterology specialist care) since 1995 (16). The NRP records civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses, coded by physicians according to the ICD- 8 codes until the

end of 1993 and the ICD-10 codes thereafter. Furthermore, surgical procedures (including colonoscopy) are recorded according to Danish classification of surgical procedures from 1977 to 1995 and since 1996 to the NOMESCO (Nordic Medico-Statistical Committee) Classification of surgical Procedures. We defined a colonoscopy procedure performed within 90 days before the date of CRC diagnosis as diagnostic, and the latest colonoscopy more than 90 days prior to the CRC diagnosis as the index colonoscopy (see Appendix for codes).

For the primary analysis, CRC patients were categorized as interval cases if an index colonoscopy had been performed between 1 and 5 years prior to CRC diagnosis. This definition followed conventions used in previous publications (4, 8, 11-13). For comparison purposes, we included (i) patients with index colonoscopy ≥10 years prior to CRC diagnosis and (ii) sporadic CRC patients without record of an index colonoscopy. We included the group of CRC cases with an index colonoscopy ≥10 years prior to CRC diagnosis based on the assumption that this group is less likely than sporadic CRCs to include rapidly growing tumours since the mean time of progression from adenoma to carcinoma is estimated to be at least 10 years (10, 17). Patients with an index colonoscopy between 3-12 months and 5-10 years prior to CRC diagnosis were excluded from the primary analysis. In secondary analyses, all CRC patients were included and the time duration between index colonoscopy and CRC date was considered in one year intervals (1st year [3-12 months], 2nd year, 3rd year, ..., 10th year, and more than 10 years).

Since the detailed indication for the index colonoscopy was not recorded in the NRP, we retrieved and reviewed the colonoscopy reports for all cases with an index colonoscopy at any time more than 90 days prior to CRC diagnosis at Aalborg Hospital (N = 101, approximately 5% of all cases).

Comorbidity

Using electronic records from 1977-2009 in the NRP, we identified information on subjects' comorbid diseases. As a measure of co-morbidity we used the Charlson Co-morbidity Index (18), a scoring system that assigns between one and six points to a range of diseases (see Appendix) as the components of a summed,

aggregate score. Patients were classified in three groups according to their sum of points: 0 points (''no co-morbidity''), 1-2 points (''low co-morbidity''); and 3 or more points (''high co-morbidity''). In addition, we also identified presence of diverticular disease and inflammatory bowel disease (IBD).

Statistical analysis

For the primary analysis, we calculated the proportion of patients within categories of demographic, tumour, and comorbidity characteristics. We used multivariate logistic regression to explore the association between clinical characteristics and interval CRC, using as separate comparison groups patients with index colonoscopy ≥10 years prior to CRC diagnosis and sporadic CRC cases. Furthermore, patients were followed from date of CRC diagnosis until death of all causes, emigration, or end of follow-up (1 January 2010), whichever came first. We calculated Kaplan-Meier estimates for survival after 1 and 5 years of follow-up. We used Cox proportional-hazards regression to compute hazard ratios as an estimate of the mortality rate ratio (MRR) for patients with interval CRC relative to (i) patients with index colonoscopy ≥10 years prior to CRC diagnosis and (ii) sporadic CRCs. The MRRs were computed for the 1st year and years 2-5 after diagnosis, and were adjusted for age (0-49, 50-69, 70-79, ≥80 years), gender, year of cancer diagnosis (5-year intervals), Charlson Co-morbidity Index, cancer stage at diagnosis, and tumour location. We also calculated MRRs without adjusting for CRC stage, since stage at diagnosis could be an intermediate variable between time of diagnosis and death. We stratified MRRs by gender, CRC stage, and location. In sensitivity analyses, data were analysed both including, and excluding, IBD patients. The Cox proportional hazard assumptions were tested graphically using log -log plots and found to be fulfilled.

In the secondary analysis, we used the same methodology as described above to calculate absolute survival and MRRs by one year intervals in the time between index colonoscopy and CRC date, compared to sporadic cases.

Results

Characteristics

We identified 38,064 CRC patients diagnosed during 2000-2009. A total of 982 (3%) were interval CRCs (colonoscopies between 1 and 5 years prior to diagnosis), 358 (1%) patients were diagnosed with CRC ≥10 years after colonoscopy, and 35,704 (94%) were sporadic patients with no colonoscopy more than three months prior to diagnosis. For the primary analysis we excluded 580 (2%) CRC patients with a colonoscopy between 3-12 months prior to diagnosis and 440 (1%) CRC patients with a colonoscopy 5-10 years prior to diagnosis. We compared interval cancers with patients who had a colonoscopy >10 years before diagnosis, and with sporadic cases (Table 1). Median age at CRC diagnosis was 74 years for interval cases, 75 years for cases diagnosed ≥10 years after colonoscopy, and 71 years for sporadic cases.

In general, interval cases were very similar to cases diagnosed with CRC ≥10 years after colonoscopy. However, there were differences between the interval and sporadic cases. A higher proportion of interval cases were women. Proximal location and mucinous histology were more prevalent among interval cases, whereas distal location and non-mucinous adenocarcinomas were more common in sporadic cases. Patients with interval CRC had higher levels of comorbidity, particularly IBD and diverticular disease (Table 1). In multivariate logistic regression analyses with sporadic cases as reference, year of diagnosis, female gender, stage, CRC location, and comorbidities including IBD and diverticular disease were independently associated with interval CRC (Table 1).

In the analysis excluding IBD patients, very similar results were found (data not shown).

We reviewed the medical records from 101 CRC patients at one medical centre with an index colonoscopy >90 days prior to CRC diagnosis. In six patients, the index exam was either misdated (true date was within three months of CRC diagnosis) or miscoded as flexible sigmoidoscopy/ rectoscopy, and in five patients the index colonoscopy was suspicious for CRC, but the diagnosis was not recorded until 3 or more months later.

For the remaining 90 patients, the caecum was visualized in 69% and preparation quality was fair/excellent in 78%, poor in 13%, and not recorded in 9%. The colonoscopy indications were: symptoms (50%), follow-up of polyps (26%), family history of CRC (5.6%), prevalent IBD (8.9%), abnormal X-ray/imaging (1.1%), or not recorded (8.9%). A total of 40 (44%) patients had polyps removed at index colonoscopy. Thirty five of the 101 patients had index colonoscopy 1-5 years prior to CRC diagnosis. In them, the caecum was visualized in 86%, preparation quality was fair/excellent in 83%, and 57% had polyps removed at that time. Indications for the diagnostic colonoscopy were symptoms (31%), follow-up of polyps (31%), family history (11%), prevalent IBD (11%), abnormal X-ray/imaging (2.9%), or not recorded (11%).

Survival after colorectal cancer

One-year survival was very similar among interval CRC patients (68%; 95% CI: 65%, 71%), cases with colonoscopy ≥10 years prior to CRC diagnosis (72%; 95% CI: 66%, 76%), and sporadic CRC patients (71%; 95% CI: 70%, 71%). The corresponding MRRs were close to 1.0 (Table 2). Adjustments materially affected only the comparison of interval to sporadic cases, as the MRR changed from 1.1 (95 % CI: 1.0, 1.3) to 0.92 (95% CI: 0.82, 1.0). Differences in co-morbidity and cancer location were largely responsible for the change in MRR. After excluding CRC stage from the adjusted analysis, the 1-year MRRs were very similar to those from the full analyses.

Five years after CRC diagnosis, survival was close to 40% in all CRC groups (Table 2) and 2-5 year MRRs varied around 1.0 with little change in estimates after adjustment for covariates. Excluding CRC stage from the adjusted model did not change the adjusted 2-5 year MRRs either. Analyses stratified by gender, CRC stage, and location did not materially affect the MRRs for the comparison of interval CRC cases with those having an index colonoscopy ≥10 years prior to CRC diagnosis or with sporadic cases (results not shown).

In the analysis excluding IBD patients, the adjusted 0-1 and 2-5 year MRRs remained virtually unchanged (data not shown).

Table 3 outlines the results for the secondary analysis categorizing CRCs according to each one-year period between diagnosis and index colonoscopy, and comparing mortality with sporadic CRCs. The 1-year MRRs had point estimates below or around 1.0 except cases diagnosed in the fifth year after colonoscopy (1-year adjusted MRR of 1.4, 95% CI 1.1, 1.7). The 5-year MRRs all varied around 1.0.

Discussion

In summary, we found that interval CRC patients were older at diagnosis, more likely to be female, and to have more co-morbidities and proximal tumours as compared to sporadic CRC patients. Furthermore, a large proportion of interval cases had prevalent IBD or diverticular disease and our chart review indicated many had polyps removed at index colonoscopy. CRC stage at diagnosis was similar between the interval and sporadic cancer patients, although advanced stage turned out to be inversely associated with interval CRC in multivariate analysis. In general, the mortality was similar when comparing interval to sporadic CRC patients and this was also the case when categorizing CRCs according to each 1-year period after colonoscopy. We found no noteworthy differences in characteristics or mortality comparing interval CRC patients to those who had undergone colonoscopy 10+ years prior to their CRC diagnosis.

To our knowledge, no prior study has conducted a detailed investigation of survival in patients with interval CRC to evaluate if these cancers tend to have an aggressive course. If a subgroup of interval CRCs represented particularly aggressive tumours, we would have expected the survival to be worse than that for other CRC patients. However, we found that survival was similar among interval and sporadic CRC cases suggesting that the majority of interval cases were more likely missed lesions. These results are further supported by our findings on the distribution of clinical characteristics. Lesions missed by colonoscopy are more frequently located on the right side of the bowel (5, 19, 20), perhaps because poor bowel preparation prevented complete examination. Poor bowel preparation is more likely in older individuals with high degree of comorbidity (21, 22) – a pattern also consistent with our findings. The high proportion of interval cases with previously resected polyps in our medical record review also might indicate that some interval CRCs develop from prevalent lesions that were incompletely resected or even missed (8, 23-25). Furthermore, the relatively high prevalence of IBD and diverticular disease among interval cases might reflect an index colonoscopy that had been technically complicated with increased risk of overlooking a

lesion (7). Finally, in accordance with our findings, a number of studies have confirmed that advanced age and female gender are factors associated with a CRC diagnosis in the period relatively shortly after a colonoscopy (i.e. missed cancers) (5, 20, 24, 26, 27). Nevertheless, the high proportion of women among interval cases could be due to the fact that women live longer than men, although the difference in mortality over 5-10 years is small.

Five reports from a single-centre US study population, exclusively men, described clinical and molecular characteristics of 45-63 interval cases (arising 1-5 years after colonoscopy) and twice the number of sporadic cases (4, 8, 11-13). There were no major differences in overall survival between interval and sporadic cases (5-year survival 36% [95% CI: 18%, 55%] vs. 46% [95% CI: 36%, 60%]) (8) or in markers of aggressive tumour behaviour such as histologic grade, carcinoembryonic antigen levels, and stage. However, mucinous histology was more prevalent among interval cases, suggesting potential aggressive behaviour (11). Because mucinous cancers are more likely right-sided which is also the location of most interval cancers, the mucinous histology may simply reflect location (and not aggressive biology), as our results suggest. Similarly, the association of microsatellite instability (MSI) and CIMP (CpG island methylator phenotype) with interval CRCs (4, 12) may also be explained by the fact that interval cancers are more often right-sided lesions. Of note, sessile serrated adenomas are likely to occur in the right colon and are thought to be precursors for CIMP+ CRCs (10, 20). These lesions are often small and flat and therefore more likely to be missed (28). Nonetheless, as the authors of the US reports outline, MSI and CIMP seemed to be more prevalent in interval cases regardless of CRC localization and may accord with a subset of interval CRCs showing rapid growth, but neither previous reports nor our investigation specifically evaluate tumour growth.

Two other studies have described overall survival after interval CRC. A Canadian population-based study (Manitoba region) published in 2010 included 388 CRC patients diagnosed 6-36 months after colonoscopy and compared them to 4495 CRCs diagnosed 0-6 months after colonoscopy (5). This study also did not

detect any difference in survival, but since it only included CRCs diagnosed up to 3 years after colonoscopy it may have excluded cases most likely to have represented *de novo* lesions. Finally, a recent UK study that defined interval CRCs (n=192) as those diagnosed between biennial screening rounds, found that the screen-detected CRCs (n=322) had a higher proportion of men, left colon tumours, and superior survival whereas the comparison of interval to CRC patients diagnosed before first screen invitation (n=511) revealed no differences (29). However, since the definition of interval CRC was based on prior faecal occult blood test and not colonoscopy, the results are of little relevance to our study.

The strengths of our study include the population-based cohort design, in a setting with free access to healthcare which virtually removes referral bias. We studied a large and well-defined population with complete follow-up owing to the computerized nationwide registries. Because of the large number of interval CRC patients, we were able to detail the analysis of time from colonoscopy to CRC diagnosis and not solely rely on arbitrary definitions.

Our study also has certain limitations, including misclassification caused by inaccurate coding in the large registries. Fortunately, the completeness and positive predictive values of the cancer diagnosis in the DCR has been found to be 95-98% (14). Even though the quality of the procedure coding in the NRP has likewise been shown to be high (16), our record review suggested that some cases we designated as interval were misclassified. This might have conservatively biased the comparison of interval and sporadic cases. Furthermore, the study was conducted in a population in which colonoscopies are not routinely performed for general CRC screening and no specific details of the index colonoscopy exams were recorded in the registries. Therefore, we had data regarding colonoscopy indication, bowel preparation quality, and completeness only from the limited number of patients in our record review. It is unclear whether the indications prompting the index colonoscopy in interval CRC patients could have influenced our results. However, our analysis comparing interval CRCs diagnosed 1-5 years after index colonoscopy to cases diagnosed more than 10 years after colonoscopy, which would more likely have similar colonoscopy

indications, supported our overall findings. We also did not have information on family CRC history or hereditary syndromes and were therefore unable to evaluate their impact on interval CRC. Finally, in the cases we reviewed, the completeness of colonoscopy was lower than the 91% expected from a previous Danish evaluation (30). These findings could imply that our single-centre sample was not representative. However, our colonoscopy sample was enriched with interval cases and a low completeness would be expected if the majority of interval CRCs are missed. Moreover, the comparison of survival between distal interval and distal sporadic CRCs (which would not reflect poor completeness) was virtually identical to the overall findings.

In conclusion, in this large population-based study, demographic, tumour, and comorbidity characteristics together with survival estimates among interval CRCs did not suggest aggressive biology, but rather that the majority of interval CRCs represented missed lesions.

Table 1: Characteristics of patients with colorectal cancer (CRC), Denmark 2000-2009. Odds ratios from multivariate logistic regression analysis explore the independent association between characteristics and interval CRC using the two different comparison groups as reference.

	Interval CRC	Comparison groups			
	(%)*	CRC diagnosed ≥10 years after colonoscopy, N (%)	*Odds ratio, (95% CI)***	Sporadic CRC, N (%)†	*Odds ratio, (95% CI)* ‡
Total number of patients	982	358		35,704	
Year at colorectal cancer diagnosis					
2000-2004	349 (36)	136 (38)	1.0 (ref)	17,043 (48)	1.0 (ref.)
2005-2009	633 (64)	222 (62)	1.0 (0.77, 1.3)	18,661 (52)	1.5 (1.3, 1.7)
Age at colorectal cancer diagnosis					
0-49 years	46 (4.7)	11 (3.1)	1.0 (ref)	1,714 (4.8)	1.0 (ref)
50-69 years	296 (30)	96 (27)	0.51 (0.24, 1.1)	14,124 (40)	0.94 (0.67, 1.3)
70-79 years	353 (36)	108 (30)	0.50 (0.24, 1.1)	11,425 (32)	1.1 (0.80, 1.6)
≥ 80 years	287 (29)	143 (40)	0.28 (0.13, 0.60)	8,411 (24)	0.99 (0.70, 1.4)
Gender					
Women	529 (54)	203 (57)	1.0 (ref)	16,965 (48)	1.0 (ref)
Men	453 (46)	155 (43)	1.1 (0.82, 1.4)	18,739 (52)	0.89 (0.78, 1.0)
Stage of colorectal cancer					
Localised	377 (38)	143 (40)	1.0 (ref)	12,995 (36)	1.0 (ref)
Regional	193 (20)	86 (24)	0.82 (0.59, 1.1)	9,340 (26)	0.70 (0.59, 0.84)
Metastatic	221 (23)	70 (20)	0.93 (0.66, 1.3)	8,642 (24)	0.71 (0.59, 0.85)
Unknown	191 (19)	59 (16)	1.2 (0.85, 1.8)	4,727 (13)	1.1 (0.93, 1.4)
Location of colorectal cancer					
Cecum/ascending colon	376 (38)	128 (36)	1.0 (ref)	7,969 (22)	1.0 (ref)
Transverse colon	65 (6.6)	30 (8.4)	0.79 (0.49, 1.3)	1,813 (5.1)	0.78 (0.59, 1.0)
Descending/sigmoid colon	210 (21)	93 (26)	0.79 (0.57, 1.1)	10,676 (30)	0.44 (0.36, 0.52)
Rectal cancer	223 (23)	91 (25)	0.85 (0.61, 1.2)	13,303 (37)	0.45 (0.37, 0.53)
Several regions or unknown	108 (11)	16 (4.5)	2.3 (1.3, 4.0)	1,943 (5.4)	1.1 (0.87, 1.4)

	Interval CRC	Comparison groups			
	(%)*	CRC diagnosed ≥10 years after colonoscopy, N (%)	*Odds ratio, (95% CI)***	Sporadic CRC, N (%)†	*Odds ratio, (95% CI)* ‡
Histology of colorectal cancer:					
Adenocarcinoma	682 (69)	263 (73)	1.0 (ref)	28,368 (79)	1.0 (ref)
Polyp adenocarcinoma	42 (4.3)	12 (3.3)	1.4 (0.69, 2.7)	1,106 (3.1)	1.5 (1.1, 2.1)
Recorded as "solid carcinoma"	24 (2.4)	8 (2.2)	1.1 (0.45, 2.5)	391 (1.1)	1.7 (1.1, 2.7)
Neuroendocrine	10 (1.0)	1 (0.3)	3.0 (0.37, 24)	161 (0.5)	2.0 (1.0, 3.91)
Mucinous carcinoma	89 (9.1)	29 (8.1)	1.1 (0.69, 1.7)	2,484 (7.0)	1.1 (0.88, 1.4)
Signet ring	14 (1.4)	6 (1.7)	0.88 (0.32, 2.4)	377 (1.1)	1.2 (0.69, 2.1)
Other histology	35 (3.6)	11 (3.1)	1.0 (0.49, 2.1)	895 (2.5)	1.2 (0.83, 1.7)
Not histological verified	86 (8.8)	28 (7.8)	1.0 (0.62, 1.6)	1,922 (5.4)	1.3 (1.0, 1.7)
Charlson Co-morbidity Index					
0 points: No co-morbidity	374(38)	166 (46)	1.0 (ref)	19,426 (54)	1.0 (ref)
1-2 points: Low co-morbidity	332 (34)	128 (36)	1.2 (0.89, 1.6)	10,813 (30)	1.4 (1.2, 1.6)
3 or more points: High co-morbidity	276 (28)	64 (18)	1.9 (1.4, 2.7)	5,465 (15)	2.2 (1.8, 2.6)
No inflammatory bowel disease	918 (93)	321 (90)	1.0 (ref)	35,523 (99)	1.0 (ref)
Inflammatory bowel disease	64 (6.5)	37 (10)	0.46 (0.29, 0.73)	181 (0.5)	14 (10, 20)
No diverticular disease	792 (81)	289 (81)	1.0 (ref)	34,530 (97)	1.0 (ref)
Diverticular disease	190 (19)	69 (19)	1.1 (0.77, 1.5)	1,174 (3.3)	6.1 (5.1, 7.3)

* Interval CRCs were defined as duration of 1-5 years between colonoscopy and cancer diagnosis.

** Odds ratios from multivariate logistic regression testing association of individual characteristics with interval CRC, compared with CRCs diagnosed ≥10 years after colonoscopy as reference.

† Sporadic CRCs are defined as those with no colonoscopy more than 3 months before diagnosis

‡ Odds ratios from multivariate logistic regression testing association of individual characteristics with interval CRC, compared with sporadic CRCs as reference

Note: A total of 580 CRC patients with 3-12 months and 440 patients with 5-10 years between index colonoscopy and cancer diagnosis were excluded.

Table 2: Survival and mortality rate ratios (MRRs) for interval colorectal cancer (CRC) diagnosis, Denmark 2000-2009

	First year after CRC diagnosis (95% confidence intervals)				2-5 years after CRC diagnosis (95% confidence intervals)			
	No of deaths	**1-year survival**	**MRR**	**Adjusted MRR**	**No of deaths**	**5-year survival**	**MRR**	**Adjusted MRR**
CRC cases diagnosed ≥10 years after colonoscopy	100	72% (66%, 76%)	1.0 (reference)	1.0 (reference)	65	40% (33%, 46%)	1.0 (reference)	1.0 (reference)
Sporadic CRC*	10,085	71% (70%, 71%)	1.0 (reference)	1.0 (reference)	7,208	43% (42%, 43%)	1.0 (reference)	1.0 (reference)
Interval CRC†	308	68% (65%, 71%)			181	41% (37%, 44%)		
Reference: CRCs diagnosed ≥10 years after colonoscopy	-	-	1.1 (0.90, 1.4)	1.0 (0.80, 1.3)	-	-	0.97 (0.73, 1.3)	0.89 (0.66, 1.2)
Reference: Sporadic CRC	-	-	1.1 (1.0, 1.3)	0.92 (0.82, 1.0)	-	-	1.0 (0.91, 1.2)	1.0 (0.88, 1.2)

* Sporadic CRCs were defined as those with no colonoscopy more than 3 months before diagnosis.

† Interval colorectal cancers were defined as duration of 1-5 years between colonoscopy and cancer diagnosis.

Adjusted MRRs controlled for age, gender, location, year, and Charlson Comorbidity Index

Table 3: Survival and adjusted mortality rate ratios (aMRR) after colorectal cancer (CRC) diagnosis according to duration between colonoscopy and date of diagnosis, Denmark 2000-2009

		1 year			5 years		
	No	**No of deaths**	**Survival, %**	**aMRR***	**No of deaths**	**Survival, %**	**2-5 year aMRR***
Sporadic CRC†	35 704	10,085	0.71 (0.70, 0.71)	Reference	7,208	0.43 (0.42, 0.43)	Reference
Time since colonoscopy‡							
< 1 year	580	157	0.73 (0.69, 0.76)	0.81 (0.70, 0.96)	117	0.44 (0.39, 0.49)	1.0 (0.83, 1.2)
1- <2 years	381	125	0.66 (0.61, 0.71)	0.98 (0.82, 1.2)	70	0.40 (0.34, 0.45)	1.1 (0.84, 1.3)
2- <3 years	240	63	0.73 (0.67, 0.78)	0.76 (0.59, 0.97)	47	0.47 (0.40, 0.54)	0.96 (0.72, 1.3)
3- <4 years	215	56	0.73 (0.66, 0.78)	0.77 (0.59, 1.0)	41	0.42 (0.33, 0.50)	1.0 (0.73, 1.4)
4- <5 years	146	64	0.55 (0.46, 0.63)	1.4 (1.1, 1.7)	23	0.30 (0.21, 0.40)	1.2 (0.77, 1.8)
5- <6 years	143	44	0.67 (0.59, 0.75)	1.0 (0.76, 1.4)	30	0.35 (0.25, 0.45)	1.3 (0.90, 1.9)
6- <7 years	90	26	0.70 (0.59, 0.78)	1.1 (0.72, 1.5)	12	0.44 (0.29, 0.57)	0.59 (0.33, 1.0)
7- <8 years	84	29	0.64 (0.53, 0.74)	1.0 (0.71, 1.5)	19	0.26 (0.14, 0.39)	1.4 (0.92, 2.3)
8- <9 years	67	20	0.71 (0.58, 0.80)	0.74 (0.47, 1.2)	14	0.45 (0.31, 0.57)	1.2 (0.69, 2.0)
9- <10 years	56	13	0.75 (0.60, 0.85)	0.82 (0.48, 1.4)	9	0.46 (0.29, 0.62)	0.77 (0.40, 1.5)
≥ 10 years	358	100	0.72 (0.66, 0.76)	0.93 (0.76, 1.1)	65	0.40 (0.33, 0.46)	1.2 (0.91, 1.5)

Numbers in parentheses are 95% confidence intervals.

* aMRR: Mortality rate ratios by time intervals between colonoscopy and colorectal cancer diagnosis with sporadic cases as reference, adjusted for gender, age, year, cancer location, stage, and Charlson Comorbidity Index.

† Sporadic colorectal cancers are defined as those with no colonoscopy more than 3 months before diagnosis.

‡ Time between date of colorectal cancer and most recent (index) colonoscopy prior to diagnosis.

Appendix: The international Classification of Disease (ICD) codes, version 8 and 10, and the procedure codes used in the present study.

The Danish Cancer Registry:

Colorectal Cancer: ICD-10: DC18-20

The Danish National Registry of Patients:

Procedure codes for colonoscopy: 1977-1995: 91.070; 1996-2006: KUJF32, KUJF35

Diagnosis codes:

Inflammatory bowel disease:

ICD-8: 563.01, 563.19, 569.04

ICD-10: K50, K510, K511, K512, K513

Diverticular disease:

ICD-8: 562.10- 562.19

ICD-10: K572- K579

The Charlson Co-morbidity Index:

	Diseases	ICD-8	ICD-10	Score
1	Myocardial infarction	410	I21;I22;I23	1
2	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430-438	I60-I69; G45; G46	1
5	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0; B18	1
10	Diabetes type1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1
	Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9	
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes with end organ damage type1	249.01-249.05; 249.08	E10.2-E10.8	2
	type2	250.01-250.05; 250.08	E11.2-E11.8	
14	Any tumour (except colorectal cancer)	140-194 (excluding 153.xx, 154.09-19)	C00-C75 (excluding C18-C20)	2
15	Leukemia	204-207	C91-C95	2
16	Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumour	195-198; 199	C76-C80	6
19	AIDS	079.83	B21-B24	6

References

1. Winawer SJ, Zauber AG, Ho MN *et al*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977–81.

2. Lakoff J, Paszat LF, Saskin R, *et al*. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin Gastroenterol Hepatol 2008; 6: 1117–21.

3. Brenner H, Haug U, Arndt V, et al. Low Risk of Colorectal Cancer and Advanced Adenomas More Than 10 Years After Negative Colonoscopy. Gastroenterology 2010; 138:870–6.

4. Arain MA, Sawhney M, Sheikh S *et al*. CIMP Status of Interval Colon Cancers: Another Piece to the Puzzle. Am J Gastroenterol 2010; 105(5):1189–95.

5. Singh H, Nugent Z, Demers AA, *et al*. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. Am J Gastroenterol 2010; 105:2588–96.

6. Gorski TF, Rosen L, Riether R, *et al*. Colorectal cancer after surveillance colonoscopy: false-negative examination or fast growth? Dis Colon Rectum 1999; 42:877–80.

7. Cooper GS, Xu F, Barnholtz Sloan JS, *et al*. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer 2012; 118:3044–52.

8. Farrar WD, Sawhney MS, Nelson DB, *et al*. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4:1259–64.

9. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol 2010; 8:858–64.

10. Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol 2011; 42:1–10.

11. Shaukat A, Arain M, Anway R, *et al*. Is KRAS Mutation Associated with Interval Colorectal Cancers? Dig Dis Sci 2012; 57(4):913–7.

12. Sawhney MS, Farrar WD, Gudiseva S *et al*. Microsatellite instability in interval colon cancers. Gastroenterology 2006; 131:1700–05.

13. Shaukat A, Arain M, Thaygarajan B, *et al*. Is BRAF mutation associated with interval colorectal cancers? Dig Dis Sci 2010; 55:2352–56.

14. Storm HH, Michelsen EV, Clemmensen IH, *et al*. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997; 44:535–39.

15. Erichsen R, Lash TL, Hamilton-Dutoit SJ, *et al*. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. Clin Epidemiol 2010; 2:51–6.

16. Andersen TF, Madsen M, Jorgensen J, *et al*. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46:263–68.

17. Risio M. The natural history of adenomas. Best Pract Res Clin Gastroenterol 2010; 24:271–80.

18. Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011; 11:83.

19. Singh H, Turner D, Xue L, *et al*. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006; 295:2366–73.

20. Brenner H, Hoffmeister M, Arndt V, *et al*. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010; 102:89–95.

21. Hassan C, Fuccio L, Bruno M *et al*. A Predictive Model Identifies Patients Most Likely to Have Inadequate Bowel Preparation for Colonoscopy. Clin Gastroenterol Hepatol 2012; 10(5):501–6.

22. van Steenbergen LN, Lemmens VE, Straathof JW, *et al*. Improvable quality of diagnostic assessment of colorectal cancer in southern Netherlands. Eur J Gastroenterol Hepatol 2009; 21:570–5.

23. Pabby A, Schoen RE, Weissfeld JL *et al*. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005; 61:385–91.

24. Robertson DJ, Greenberg ER, Beach M *et al*. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005; 129:34–41.

25. Brenner H, Chang-Claude J, Jansen L, *et al*. Role of colonoscopy and polyp characteristics in colorectal cancer after colonoscopic polyp detection: a population-based case-control study. Ann Intern Med 2012; 157:225–32.

26. Bressler B, Paszat LF, Chen Z, *et al*. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007; 132:96–102.

27. Singh H, Nugent Z, Mahmud SM, *et al*. Predictors of Colorectal Cancer After Negative Colonoscopy: A Population-Based Study. Am J Gastroenterol 2010; 105(3):663–73.

28. Heresbach D, Barrioz T, Lapalus MG *et al*. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008; 40:284–90.

29. Gill MD, Bramble MG, Rees CJ, *et al*. Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. Br J Cancer 2012; 107:417–21.

30. Ginnerup PB, Christiansen TE, Bjerregaard NC, *et al*. Colonoscopy and multidetector-array computed-tomographic colonography: detection rates and feasibility. Endoscopy 2003; 35:736–42.

Study III

Mortality and recurrence after colorectal cancer surgery with preoperative stenting – A Danish nationwide cohort study

Rune Erichsen[1], MD; Erzsébet Puho[1], MSc; Tove Nilsson[1], MD, DMSci; John A. Baron[1,2], MD;

Henrik Toft Sørensen[1], MD, PhD, DMSci

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

[2]Department of Medicine, Center for Gastrointestinal Biology and Disease, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Corresponding Author: Dr. Rune Erichsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Phone +45 5716 8231. Fax: +45 8716 7215. E-mail: re@dce.au.dk

Financial support: This research was supported by the Clinical Epidemiology Research Foundation, Aarhus University Hospital, Denmark. The first author was supported by a scholarship from Aarhus University.

Conflict of interest: The authors declare no conflict of interest. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. All authors had access to the data and played a significant role in writing the manuscript.

Word count: 3034 (excluding abstract of 288 words)

Abstract

Introduction: The use of self-expanding metal stents (SEMSs) as a bridge to surgery for obstructive colorectal cancer (CRC) has fallen under suspicion for inducing tumor dissemination and thereby increasing CRC recurrence and long-term mortality. However, there are very little data regarding the long-term clinical outcome of patients treated with SEMSs.

Methods: We used Danish population-based medical registries (2005-2010) to investigate CRC mortality and recurrence in all patients receiving preoperative SEMS (n=581) and compared them with CRC patients undergoing immediate (n=3,333) or elective resection (n=13,722). For CRC patients who survived the first 30 days after resection, we computed the mortality rate ratio (MRR) and the relative risk (RR) of recurrence after 5 years, using Cox regression and adjusting for age, gender, CRC stage, CRC location, surgery type, and comorbidity. Recurrence was defined using information on chemotherapy, presence of distant metastasis, or a positive biopsy >180 days after resection. Recurrence was investigated only for CRC patients whose disease was localized/regional spread.

Results: The 5-year survival was 49% among patients with SEMS, 40% among patients undergoing immediate resection, and 65% among patients with elective resection. For SEMS vs. immediate resection, the adjusted MRR was 0.99 (95% CI: 0.91-1.07) and for SEMS vs. elective resection, it was 1.39 (95% CI: 1.19-1.62). The 5-year risk of recurrence was 40% after SEMS treatment, 30% after immediate resection, and 23% in elective patients. The adjusted RRs were 1.12 (95% CI: 0.99-1.26) for SEMS vs. immediate and 1.72 (95% CI: 1.39-2.13) for SEMS vs. elective.

Conclusion: Long-term mortality associated with use of SEMS as a bridge to surgery was comparable to that of immediate resection, but not as low as that observed following elective resection. SEMS use might be related to increased risk of CRC recurrence.

Key words: Colonoscopy; Colorectal neoplasms; Prognosis; Survival

Introduction

Surgery is the cornerstone in treatment of colorectal cancer (CRC), one of the most common cancers in the western world.[1] CRC surgery ideally is performed in an elective setting, allowing for optimization of patient medical and surgical status, complete oncologic staging, and a decreased need for stoma and multi-staged operations.[2]

However, bowel obstruction occurs in approximately 10% of CRC cases[3], requiring emergency surgery with or without a stoma or an endoscopically placed self-expandable metal stent (SEMS).[2] SEMSs are used to avoid palliative stoma surgery in patients with incurable disease or as a bridge to elective surgery with curative intent.[2] SEMSs have been used since the early 1990s and several studies[4-8], including randomized trials[9,10], have evaluated their safety, effectiveness, and efficacy. Nonetheless, controversy remains about their use. Recently, a multi-center randomized study of preoperative stenting (n=47) vs. emergency surgery (n=51) for malignant colonic obstruction was prematurely terminated because of high perforation rate in the stenting arm.[11]

Of particular interest to our study, preoperative stenting in the bridge-to-surgery setting has fallen under suspicion for inducing tumor dissemination thereby increasing CRC recurrence and worsening long-term survival. This concern was recently underscored by a small Spanish randomized trial reporting a higher frequency of tumor recurrence in the stent group (8 of 15 cases) compared to the emergency surgery group (2 of 13 cases, p=0.055), after mean follow-up of 37.6 months.[12] Another small randomized trial has detected high frequencies (8/30) of silent perforations after SEMS use which could potentially cause cancer spread, but this study did not evaluate long-term outcomes.[13]

Unfortunately, only single-center studies conducted in highly specialized settings have compared long-term mortality in CRC patients receiving SEMS with that in patients undergoing primary surgery. Most of these studies have not shown any significant difference in mortality[8,14,15], although two have favored surgery over

SEMS placement (of which one included elective and not emergency surgery).[16,17] To our knowledge, only one single-center study has evaluated CRC recurrence after SEMS placement, finding it similar to that among patients undergoing immediate surgery.[18] No population-based evidence exists.[4,6,8]

We therefore conducted a nationwide population-based cohort study of SEMS utilizing existing Danish medical registries. Our aims were primarily to investigate mortality and secondarily to investigate recurrence after CRC surgery with preoperative stenting, compared to CRC patients undergoing immediate or elective surgery.

Methods

We conducted this cohort study in the setting of the entire Danish population, which over the study period included 6.2 million people. The Danish National Health Service provides tax-funded medical care for all Danish residents. We used the unique civil registration number assigned to all Danes at birth or upon immigration[19] to link information between registries.[20]

Cohort

We used the Danish Cancer Registry (DCR) to identify all patients with incident CRC between 1 January 2005 and 31 December 2010 (n=24,686). We chose this study period because SEMSs were taken into clinical practice in Denmark in the beginning of the 2000s and coded routinely since 2005 in the Danish National Registry of Patients (DNRP) (see below).[21] The DCR has maintained records on all incident malignant neoplasms diagnosed in Denmark since 1943. Its database includes patients' civil registration number, month and year of cancer diagnosis, cancer type and location, and tumour spread at diagnosis.[22] CRC location is categorized as proximal (appendix, cecum, ascending, and right flexure), transverse, distal (left flexure, descending, and sigmoid), rectal, and unspecified while CRC stage is categorized as localized (Duke's A and B), regional (Duke's C) and metastatic. We linked CRC patients to the DNRP to obtain information on SEMS, colorectal surgery, and medical history. The DNRP covers all non-psychiatric hospitalizations in Denmark since 1977 and hospital outpatient clinic visits and emergency room contacts since 1995. Its records include dates of admission and discharge, type of hospitalization (emergency vs. planned), surgery and procedure codes, treatment codes, and up to 20 diagnoses coded by physicians according to the *International Classification of Diseases* (ICD), 10th revision since 1994.[23] We included only CRC patients for whom the DNRP documented either a SEMS placement procedure or colorectal resection. Patients with a first CRC diagnosis dated more than three months after their first SEMS or colorectal resections were excluded.

We separated our CRC cohort into three groups based on the first surgical procedure occurring at or after CRC diagnosis: (i) those with an initial SEMS procedure, (ii) those with immediate colorectal resection, and (iii) those with a primary elective colorectal resection. Immediate resection was defined as a relevant surgery code recorded during an emergency hospitalization in the DNRP whereas elective resections were defined as codes recorded during a planned hospitalization. For patients in the group with an initial SEMS procedure, we also determined whether subsequent colorectal resections took place. All colorectal resections were classified as performed *with* or *without* concurrent stoma. Finally we linked all our CRC patients to the Danish Pathology Registry (DPR) to obtain information on subsequent biopsies (see below). The DPR has recorded all pathology diagnoses nationwide since 1997 according to the SNOMED classification system.[24] Details on diagnosis, surgery/procedure, and SNOMED codes are provided in the Appendix.

Comorbid diseases

We summarized comorbidity (*i.e.*, diseases coexisting with CRC) in our study population using the Charlson Comorbidity Index (CCI). Its scoring system assigns between one and six points to a range of diseases (see Appendix). Each patient's sum of points (score) is used as a measure of comorbidity burden. Information about patients' histories of comorbid diseases since 1977 was obtained from the DNRP. We classified patients into three CCI groups as follows: score of 0 ("no comorbidity"), score of 1–2 ("low comorbidity)", and a score of 3 or more ("high comorbidity"). [25]

Outcomes

Our primary outcome was time to all-cause mortality. To identify this outcome, we used the Civil Registration System (CRS)[19], which has maintained records on vital status, date of death, and residence of all Danish citizens since 1 April 1968.

Our secondary outcome was CRC recurrence. We investigated this outcome only for patients undergoing colorectal resection for CRC with localized/regional spread. Since CRC recurrence is not separately coded in Danish medical registries, we identified this outcome as any of the following: a) any first metastasis coding in the DNRP >180 days after CRC resection; b) cytostatic therapy code >180 days after resection and >60 days after the last cytostatic therapy code; or c) a biopsy recorded in the DPR >180 days after the resection date, which was coded as either colorectal malignancy or metastasis (see Appendix). The positive predictive value of the algorithm for the secondary outcome was 80%, validated through medical records of 15 cases from one region. Of the three misclassified recurrence cases, one had metastatic disease at diagnosis, one had test for PMS conducted on tissue from the primary tumor seven months after diagnosis, and one had acute myeloid lymphoma.

Statistics

We first calculated frequencies of characteristics of the study cohort and evaluated short-term mortality by computing mortality proportions within 30 days after the date of SEMS, immediate surgery, or elective surgery for CRC. In analyses of 30-day mortality, patients were stratified by gender, CRC location, and stage at diagnosis. We also determined the number of SEMS patients with subsequent colorectal resection and computed their 30-day mortality after resection. To investigate the impact of SEMS placement on long-term survival after colorectal resection, we then followed patients from 30 days after their resection date until death, emigration, or end of follow-up, whichever came first. We used the Kaplan-Meier method to estimate survival after one and five years.

To compare long-term mortality in resected CRC patients who received preoperative SEMS to that in patients with immediate or elective colorectal resection, we used hazard ratios from Cox proportional regression as an estimate of mortality rate ratios (MRRs). Time since CRC diagnosis was considered as the underlying timescale in this analysis. As a way to separate short and long-term mortality and to avoid problems with non-proportionality, patients were not considered at risk until 30 days after resection (left

truncation). MRRs were adjusted for age, gender, year of surgery, CRC stage, CRC location, surgery type, and comorbidity. They were subsequently stratified by gender, CRC stage, location, and surgery type.

To evaluate CRC recurrence, our secondary outcome, we restricted the analysis to CRC patients with localized/regional spread. We followed patients starting 30 days after resection and calculated the recurrence risk after one and five years, treating death as a competing risk.[26] We used hazards ratios from Cox proportional regression to estimate relative risk of recurrence, comparing resected CRC patients with preoperative stenting to those with immediate and elective resection. Again time since CRC diagnosis was considered as timescale and patients were not considered at risk until 30 days after resection.

Results

Characteristics and short-term (30-day) mortality

We identified a total of 17,728 CRC patients during the study period; 1,118 underwent SEMS placement at a median of 1 day after CRC diagnosis (interquartile range [IQR]: 0-12 days), 3,333 had immediate resections (median 2 days after CRC, IQR: 1-10 days), and 13,722 had elective resections (median 13 days after CRC, IQR: 1-32 days) (Table 1). Of the 1,118 SEMS patients, 581 (52%) underwent subsequent colorectal resection after a median of 17 days (IQR: 8-27 days) after SEMS placement. Median age at date of SEMS placement was 72 years, compared to 74 years among patients with immediate surgery, and 70 years among patients with elective surgery.

Resections with stoma were equally common among patients with preoperative SEMS and those undergoing immediate resection, but less frequent after elective resection. SEMSs were most frequently used for distal and rectal lesions (Table 1). Stage at CRC diagnosis was more often localized in patients undergoing elective surgery, while patients with SEMS or immediate surgery were more likely to have metastatic cancers. Comorbidity was more prevalent among SEMS patients, although comorbidity levels among SEMS patients who subsequently underwent surgery were very similar to levels among patients undergoing immediate or elective surgery.

Thirty-day mortality was 12% (95% CI: 9.8%-14%) after SEMS placement, 14% (95% CI: 13%-15%) after immediate surgery, and 3.8% (95% CI: 3.5%-4.2%) after elective surgery (Table 2). Among the 581 SEMS patients who subsequently underwent colorectal resection (median age at resection 71 years), the 30-day mortality post-resection was 8.1% (95% CI: 6.1%-11%). Table 2 further describes mortality by gender, CRC stage, location, and surgery type. Notably, 30-day mortality was particularly high among patients who underwent resections with stoma, probably indicating choice of this procedure for severely ill patients.

Long-term mortality

In Supplementary Table 1, characteristics of the CRC patients who were alive 30 days after their colorectal resection (534 SEMS, 2,883 immediate, and 12,771 elective) are described in detail. Median follow-up from 30 days after resection was 2.0 years for patients with preoperative stenting, 2.0 years for patients undergoing immediate surgery, and 2.8 years for those undergoing elective surgery. Table 3 shows that crude survival in the years after CRC resection remained higher among patients with preoperative stenting than among those undergoing immediate resection, but was lower than survival among patients undergoing elective surgery. For instance, overall five-year survival was 49% (95% CI: 43%-55%) among patients with preoperative stenting, compared to 40% (95% CI: 38%-43%) among patients with immediate resection, and 65% (95% CI: 64%-66%) among patients after elective resection (Table 3). Similar patterns were seen within strata of gender, CRC stage, and location. Among patients undergoing resections with stoma, long-term survival was particularly poor, again probably reflecting the choice of this procedure for very ill patients.

When mortality among patients with preoperative stenting was compared to mortality among patients with immediate resection, we found a one-year adjusted MRR of 0.91 (95% CI: 0.79-1.05) and a five-year adjusted MRR of 0.99 (95% CI: 0.91-1.07). Within strata of gender and CRC stage, the MRRs also were close to 1.0 (Table 4). However, for patients with rectal cancer and for those with resections with stoma, the MRRs were slightly increased.

Comparing CRC patients with preoperative stenting with those with primary elective resection, we found that the overall one-year adjusted MRR was 1.23 (95% CI: 0.93-1.62) and the five-year adjusted MRR was 1.39 (95% CI: 1.19-1.62). The MRRs largely remained increased within strata of gender, CRC stage, location, and resection type (Table 4).

Colorectal cancer recurrence

We restricted the evaluation of CRC recurrence to the 11,469 CRC patients with localized/regional spread at diagnosis who survived 30 days after resection. Among the 320 patients with preoperative SEMS, recurrence occurred among 12% (95% CI: 8.7%-16%) after one year and 40% (95% CI: 33%-47%) after five years. The corresponding percentages for the 1,796 patients with immediate surgery were 12% (95% CI: 10%-13%) after one year and 30% (95% CI: 28%-33%) after five years. Comparing patients with preoperative SEMS to a reference group of those undergoing immediate surgery, we found that the adjusted RR after five years was 1.12 (95% CI: 0.99-1.26), with little difference within strata of gender, CRC location, and resection type (Table 5).

For the 9,353 patients who underwent elective resections and survived the first 30 days, 8.0% (95% CI: 7.5%-8.8%) had a recurrence after one year and 23% (95% CI: 22%-24%) had a recurrence after five years. Comparing patients with preoperative SEMS to those with elective surgery, the adjusted RR after five years was 1.72 (95% CI: 1.39-2.13). Table 5 shows RRs by gender, stage, location, and resection type.

Discussion

In this nationwide population-based cohort study, we found that five-year survival for patients surviving the first 30 days after CRC resection was highest among elective patients followed by those with preoperative SEMS and immediate surgery. However, after adjusting for important covariates, five-year mortality among CRC patients with preoperative SEMS was similar to that of patients undergoing immediate resection, but 39% higher than that of patients undergoing elective resection. Finally, among CRC patients with localized/regional disease, subjects with preoperative SEMS had a 12% higher risk of recurrence within five years following CRC resection as compared with patients undergoing immediate resection, and a 72% increased recurrence risk compared to patients undergoing elective resection.

The decision to use SEMS for CRC obstruction as bridge to elective surgery instead of proceeding immediately to surgery should occur after weighing pros and cons for both short- and long-term outcomes. Findings from randomized trials would provide the most solid evidence for such decisions, but in the setting of SEMS vs. immediate surgery, trials have so far proven infeasible and inconsistent.[11-13] Recently, van Hooft *et al*. initiated a trial including patients from 25 centres in the Netherlands.[11] It was prematurely terminated after inclusion of 47 SEMS and 51 emergency surgery patients because of increased morbidity (particularly perforations) in the SEMS group. The trial reported no difference in mortality after six months of follow-up (risk difference -0.02, p=0.84). Other randomized trials comparing SEMS vs. immediate surgery also have been prematurely terminated either because of excess morbidity among those undergoing immediate surgery[12] or receiving SEMS.[13] Thus they have provided only limited evidence for the clinical management of patients with obstructive CRC.[9,10]

For this reason, physicians also need to refer to evidence from observational research to guide information given to patients and for clinical decision making, particularly for long-term outcomes such as recurrence and mortality.[27] The study by Kim *et al.*[18], which is the only one describing CRC recurrence, of 25 SEMS patients and 70 patients undergoing emergent open resections found no substantial difference in five-year

survival (67% vs. 62%) or recurrence (35% vs. 35%). Most other studies comparing SEMS placement with emergency surgery have found either no difference in survival or favored SEMS. [4,8,14,28-30] Furthermore, only one study including 88 stage IV cases found better long-term survival among patients treated with immediate surgery.[17] The two studies that included patients undergoing elective surgery as the comparison group found either similar survival[31] or improved survival[16], compared with SEMS patients. Hence, our findings extend the existing literature by providing robust estimates of long-term mortality and recurrence in a population-based setting, and by accounting for differences in age, gender, CRC-stage, location, and comorbidity.

Among the strengths of our study are inclusions of a large number of patients from a nationwide population-based setting within a free tax-supported healthcare system. The CRS ensured complete follow-up for mortality of all patients.[20] Furthermore, we identified CRC patients using the high- quality DCR, whose completeness and sensitivity reaches almost 100%.[22] We were able to link to the DNRP, which has high-quality data on surgical procedures.[23] The use of hospital admissions to define immediate colorectal resection has been validated in the inflammatory bowel disease setting and found 91% sensitive and 100% specific.[32] These features reduced the risk of referral, selection, and information bias and permit high generalizability of our findings.

Our study also has limitations. The secondary outcome of CRC recurrence was identified using measures that could not differentiate recurrence from new primary CRC or capture recurrences that were not diagnosed by biopsy or that did not result in chemotherapy or a diagnosis code for metastasis. Our record review indicated the false positive recurrence rate to be 20%. If such measurement error of the outcome variable is independent of the treatment, the bias, however, is typically in the direction of underestimating the treatment effect. Finally, although we controlled for many important covariates, our results could be influenced by residual (e.g. comorbidity) confounding. Most importantly, we had no information on the indication for SEMS placement or for performing immediate surgery and our findings could thus be

confounded by indication. SEMS are mainly used for large bowel obstruction, while immediate surgery is also used for perforation and bleeding. Physicians may be more likely to use SEMS for particular CRC groups, which could affect our findings in an unpredictable way. Thus it is possible that we compared patients with different a priori risks of dying or recurrence. These uncertainties ultimately could only be overcome using a randomized design. We also did not have information on types of SEMS or the use of balloon dilatation and were therefore unable to evaluate these issues.

In conclusion, use of SEMS as a bridge to surgery was associated with long-term mortality comparable to that for immediate surgery, but not as low as that observed after elective surgery. Use of SEMS might be related to increased risk of CRC recurrence.

Table 1. Characteristics of the study cohort comprising colorectal cancer patients with first-line treatment with either self-expandable metal stents (including those with subsequent surgery) or immediate or elective resection, Denmark 2005-2010.

	Self-expanding metal stents				Colorectal resection			
	All		*Subsequent surgery*		Immediately		Electively	
	n	%	*n*	*%*	n	%	n	%
Total	1,118	100	*581*	*100*	3,333	100	13,277	100
Female:	520	46.5	*274*	*47.2*	1,773	53.2	6,048	45.6
Male:	598	53.5	*307*	*52.8*	1,560	46.8	7,229	54.4
Age:								
0-49	52	4.7	*35*	*6.0*	147	4.4	618	4.7
50-69	377	33.7	*215*	*37.0*	1,079	32.4	5,567	41.9
70-79	349	31.2	*195*	*33.6*	1,057	31.7	4,392	33.1
80+	340	30.4	*136*	*23.4*	1,050	31.5	2,700	20.3
Year of CRC surgery:								
2005	54	4.8	*21*	*3.6*	630	18.9	1,922	14.5
2006	165	14.8	*89*	*15.3*	594	17.8	2,245	16.9
2007	199	17.8	*106*	*18.2*	548	16.4	2,166	16.3
2008	226	20.2	*109*	*18.8*	535	16.1	2,237	16.8
2009	208	18.6	*122*	*21.0*	473	14.2	2,227	16.8
2010	249	22.3	*133*	*22.9*	522	15.7	2,245	16.9
2011*	17	1.5	*1*	*0.2*	31	0.9	235	1.8
Resection type								
Without stoma	N/A	-	*413*	*71.1*	2,335	70.1	11,807	88.9
With stoma	N/A	-	*168*	*28.9*	998	29.9	1470	11.1
Location of CRC:								
Proximal:	31	2.8	*9*	*1.5*	1,296	38.9	3,229	24.3
Appendix (C181)	.	.	.	.	40	1.2	97	0.7
Caecum (C180)	3	0.3	*1*	*0.2*	671	20.1	1,390	10.5
Ascending (C182)	14	1.3	*3*	*0.5*	441	13.2	1,337	10.1
Right flexure (C183)	14	1.3	*5*	*0.9*	144	4.3	405	3.1
Transverse (C184)	94	8.4	*50*	*8.6*	297	8.9	550	4.1
Distal:	662	59.2	*415*	*71.4*	1,148	34.4	3,781	28.5
Left flexure (C185)	57	5.1	*45*	*7.7*	115	3.5	183	1.4
Descending (C186)	109	9.7	*74*	*12.7*	116	3.5	302	2.3
Sigmoid (C187)	496	44.4	*296*	*50.9*	917	27.5	3,296	24.8
Rectal:	284	25.4	*90*	*15.5*	402	12.1	5,329	40.1
Junction (C19)	25	2.2	*11*	*1.9*	41	1.2	158	1.2
Rectal (C20)	259	23.2	*79*	*13.6*	361	10.8	5,171	38.9
Several/unspecific:	47	4.2	*17*	*2.9*	190	5.7	388	2.9
Several regions (C188)	7	0.6	*2*	*0.3*	42	1.3	58	0.4
Unspecified (C189)	40	3.6	*15*	*2.6*	148	4.4	330	2.5
Stage of CRC:								
Localized	187	16.7	*170*	*29.3*	1,077	32.3	5,548	41.8
Regional	181	16.2	*165*	*28.4*	913	27.4	4,125	31.1
Metastatic	552	49.4	*183*	*31.5*	999	30.0	1,860	14.0
Unknown	198	17.7	*63*	*10.8*	344	10.3	1,744	13.1
Charlson comorbidity Index								
Low: 0	566	50.6	*347*	*59.7*	1,775	53.3	7,658	57.7
Medium: 1-2	314	28.1	*161*	*27.7*	1,061	31.8	4,058	30.6
High: 3+	238	21.3	*73*	*12.6*	497	14.9	1,561	11.8

* We included CRC patients diagnosed in the 2005-2010 period, some of whom had SEMS or surgery in 2011.

Table 2. Cumulative mortality after 30 days in colorectal cancer patients provided first-line treatment with either self-expanding metal stents (SEMS) or immediate or elective colorectal resection, Denmark 2005-2010.

	Self-expanding metal stents				Colorectal cancer resection			
	Overall		*Resections with preoperative stenting*		Immediately		Electively	
Overall	11.5	(9.8-13.6)	*8.1*	*(6.1-10.6)*	13.7	(12.6-14.9)	3.8	(3.5-4.2)
Women	11.0	(8.6-14.0)	*8.0*	*(5.4-12.0)*	14.3	(12.7-16.0)	3.3	(2.9-3.8)
Men	12.1	(9.7-15.0)	*8.1*	*(5.6-11.8)*	13.0	(11.4-14.8)	4.3	(3.9, 4.8)
By location								
Proximal	9.7	(3.2-27.1)	-	-	13.0	(11.2-14.9)	4.6	(3.9-5.4)
Transverse	8.5	(4.3-16.3)	*8.0*	*(3.1-19.9)*	15.5	(11.8-20.1)	5.3	(3.7-7.5)
Distal	10.1	(8.1-12.7)	*8.0*	*(5.7-11.0)*	15.1	(13.1-17.3)	3.6	(3.1-4.3)
Rectal	15.1	(11.5-19.9)	*10.0*	*(5.3-18.3)*	10.7	(8.0-14.1)	3.1	(2.7-3.6)
Several/unknown	17.0	(8.9-31.2)	*5.9*	*(0.9-35.0)*	13.7	(9.5-19.4)	7.7	(5.5-10.9)
By stage								
Localized	5.9	(3.3-10.4)	*5.9*	*(3.2-10.7)*	11.5	(9.7-13.6)	3.4	(3.0-3.9)
Regional	3.9	(1.9-7.9)	*3.6*	*(1.7-7.9)*	8.0	(6.4-10.0)	3.2	(2.7-3.8)
Metastatic	13.6	(11.0-16.8)	*13.7*	*(9.5-19.6)*	17.4	(15.2-19.9)	5.5	(4.6-6.7)
Unknown	18.2	(13.5-24.3)	*9.5*	*(4.4-20.0)*	24.7	(20.5-29.6)	4.9	(4.0-6.0)
Resection type								
Without stoma	N/A	-	*3.1*	*(1.8-5.4)*	10.8	(9.6-12.1)	3.6	(3.2-3.9)
With stoma	N/A	-	*20.3*	*(14.9-27.2)*	20.4	(18.1-23.1)	6.1	(5.0-7.5)

Note: Numbers in parenthesis are 95% confidence intervals.

Table 3. Absolute survival (Kaplan-Meier estimates) (in percent) one and five years after colorectal cancer (CRC) resection, Denmark 2005-2009

	Resection with preoperative stenting		Colorectal cancer resection			
			Immediately		Electively	
	1 year	5 years	1 year	5 years	1 year	5 years
Overall	85.1 (81.7 - 87.8)	48.7 (42.6 - 54.6)	74.5 (72.9 - 76.1)	40.3 (38.1 - 42.6)	91.0 (90.5 - 91.5)	65.0 (63.9 - 66.0)
Men	85.0 (80.2 - 88.7)	51.1 (43.1 - 58.6)	75.4 (73.0 - 77.6)	40.1 (36.8 - 43.4)	90.9 (90.2 - 91.6)	63.2 (61.7 - 64.6)
Women	85.2 (80.2 - 89.0)	45.8 (36.2 - 54.9)	73.8 (71.5 - 75.9)	40.5 (37.5 - 43.5)	91.1 (90.3 - 91.8)	67.1 (65.5 - 68.6)
Stage of CRC						
Localized	95.7 (91.1 - 97.9)	65.9 (53.5 - 75.7)	87.2 (84.9 - 89.1)	58.2 (54.0 - 62.1)	95.6 (95.0 - 96.1)	76.6 (75.1 - 78.0)
Regional	86.7 (80.4 - 91.1)	49.5 (39.0 - 59.2)	79.3 (76.4 - 81.9)	41.5 (37.3 - 45.6)	91.4 (90.5 - 92.2)	63.7 (61.7 - 65.6)
Metastatic	68.7 (60.6 - 75.4)	23.4 (14.5 - 33.5)	54.6 (51.1 - 57.9)	15.8 (12.8 - 19.0)	75.3 (73.2 - 77.2)	27.9 (25.2 - 30.8)
Unknown	94.7 (84.5 - 98.3)	61.8 (36.2 - 79.6)	76.4 (70.8 - 81.1)	51.3 (43.8 - 58.3)	92.0 (90.6 - 93.2)	69.0 (65.9 - 71.9)
CRC location						
Proximal	50.0 (15.2 - 77.5)	25.0 (3.7 - 55.8)	68.8 (66.0 - 71.4)	37.3 (33.9 - 40.7)	87.8 (86.6 - 88.9)	60.3 (58.0 - 62.4)
Transverse	78.6 (63.9 - 87.9)	54.1 (36.3 - 68.9)	75.4 (69.6 - 80.2)	45.6 (38.1 - 52.8)	87.5 (84.3 - 90.0)	61.0 (55.3 - 66.2)
Distal	87.4 (83.6 - 90.3)	49.9 (41.9 - 57.3)	79.8 (77.1 - 82.2)	42.1 (38.2 - 46.0)	91.9 (91.0 - 92.7)	67.4 (65.5 - 69.3)
Rectal	82.4 (72.1 - 89.2)	39.0 (26.2 - 51.6)	80.3 (75.8 - 84.1)	46.2 (39.3 - 52.9)	92.9 (92.1 - 93.5)	66.7 (65.0 - 68.3)
Several/unsp.	80.0 (50.0 - 93.1)	58.7 (23.4 - 82.2)	68.9 (61.1 - 75.3)	31.5 (22.9 - 40.4)	88.7 (85.0 - 91.6)	61.7 (54.9 - 67.9)
Resection type						
Resection without stoma	91.2 (87.9 - 93.6)	57.4 (50.3 - 63.9)	75.7 (73.8 - 77.5)	42.9 (40.3 - 45.6)	91.8 (91.3 - 92.3)	66.8 (65.6 - 67.8)
Resection with stoma	66.7 (58.0 - 74.1)	21.4 (10.6 - 34.6)	71.6 (68.3 - 74.6)	33.6 (29.5 - 37.8)	84.3 (82.3 - 86.1)	49.7 (46.2 - 53.2)

Note: Only colorectal cancer patients surviving the first 30 days after colorectal resection were included in this analysis. Numbers in parenthesis are 95% confidence intervals.

Table 4. Mortality rate ratios (MRRs) after CRC resection comparing patients with preoperative stenting to those with either immediate or elective resection, Denmark 2005-2010.

	One-year MRR		Five-year MRR	
	Crude	**Adjusted***	**Crude**	**Adjusted***
Immediate resection	Reference	Reference	Reference	Reference
Preoperative stenting, overall	0.77 (0.67 - 0.87)	0.91 (0.79 - 1.05)	0.88 (0.81 - 0.95)	0.99 (0.91 - 1.07)
Men	0.78 (0.65 - 0.94)	0.89 (0.73 - 1.08)	0.89 (0.79 - 0.99)	1.00 (0.89 - 1.12)
Women	0.76 (0.62 - 0.91)	0.95 (0.77 - 1.17)	0.87 (0.78 - 0.97)	0.98 (0.87 - 1.11)
By stage:				
Localized	0.61 (0.39 - 0.96)	0.85 (0.53 - 1.37)	0.85 (0.70 - 1.02)	1.00 (0.82 - 1.22)
Regional	0.82 (0.64 - 1.05)	1.07 (0.82 - 1.41)	0.92 (0.80 - 1.06)	1.11 (0.95 - 1.29)
Metastatic	0.80 (0.67 - 0.96)	0.90 (0.74 - 1.09)	0.87 (0.77 - 0.98)	0.93 (0.82 - 1.06)
Unknown	0.53 (0.30 - 0.96)	0.68 (0.36 - 1.30)	0.78 (0.58 - 1.04)	0.99 (0.72 - 1.38)
By location:				
Proximal	1.35 (0.76 - 2.38)	1.07 (0.60 - 1.89)	1.27 (0.82 - 1.98)	1.00 (0.64 - 1.55)
Transverse	0.93 (0.62 - 1.38)	1.02 (0.67 - 1.57)	0.91 (0.69 - 1.19)	0.97 (0.73 - 1.29)
Distal	0.80 (0.67 - 0.96)	0.85 (0.70 - 1.03)	0.89 (0.80 - 0.99)	0.96 (0.86 - 1.08)
Rectal	1.04 (0.75 - 1.44)	1.07 (0.76 - 1.51)	1.20 (1.00 - 1.44)	1.25 (1.04 - 1.51)
Several/unsp.	0.93 (0.52 - 1.68)	1.06 (0.57 - 1.96)	0.77 (0.49 - 1.21)	0.84 (0.53 - 1.34)
By resection type:				
Resection without stoma	0.61 (0.50 - 0.74)	0.77 (0.63 - 0.94)	0.79 (0.71 - 0.87)	0.89 (0.80 - 1.00)
Resection with stoma	1.14 (0.94 - 1.39)	1.14 (0.93 - 1.40)	1.17 (1.03 - 1.33)	1.17 (1.02 - 1.34)
Elective resection	Reference	Reference	Reference	Reference
Preoperative stenting, overall	1.71 (1.32 - 2.23)	1.23 (0.93 - 1.62)	1.73 (1.49 - 2.01)	1.39 (1.19 - 1.63)
Men	1.70 (1.18 - 2.45)	1.21 (0.83 - 1.78)	1.68 (1.36 - 2.07)	1.44 (1.16 - 1.79)
Women	1.72 (1.18 - 2.51)	1.28 (0.86 - 1.91)	1.79 (1.44 - 2.22)	1.37 (1.09 - 1.72)
By stage:				
Localized	0.97 (0.40 - 2.35)	0.92 (0.37 - 2.28)	1.46 (1.02 - 2.08)	1.55 (1.08 - 2.24)
Regional	1.67 (1.04 - 2.70)	1.71 (1.03 - 2.84)	1.68 (1.29 - 2.19)	1.76 (1.33 - 2.32)
Metastatic	1.22 (0.86 - 1.73)	1.23 (0.85 - 1.79)	1.21 (0.96 - 1.52)	1.21 (0.95 - 1.55)
Unknown	0.96 (0.30 - 3.03)	0.79 (0.24 - 2.57)	1.29 (0.74 - 2.25)	1.15 (0.65 - 2.04)
By location:				
Proximal	5.03 (1.61 - 15.7)	1.87 (0.59 - 5.90)	3.48 (1.45 - 8.39)	1.31 (0.54 - 3.17)
Transverse	1.74 (0.79 - 3.84)	1.30 (0.57 - 2.98)	1.34 (0.78 - 2.28)	1.12 (0.65 - 1.96)
Distal	1.47 (1.03 - 2.08)	0.99 (0.69 - 1.43)	1.69 (1.39 - 2.05)	1.27 (1.04 - 1.55)
Rectal	3.26 (1.78 - 5.97)	1.88 (1.00 - 3.50)	2.87 (2.07 - 3.99)	2.20 (1.58 - 3.07)
Several/unsp.	2.37 (0.73 - 7.74)	2.29 (0.64 - 8.12)	1.44 (0.59 - 3.54)	1.48 (0.58 - 3.76)
By resection type:				
Resection without stoma	1.15 (0.79 - 1.66)	1.04 (0.71 - 1.52)	1.40 (1.15 - 1.69)	1.27 (1.04 - 1.54)
Resection with stoma	2.33 (1.58 - 3.43)	1.56 (1.02 - 2.40)	2.15 (1.67 - 2.77)	1.64 (1.24 - 2.17)

*Adjusted for age, gender, CRC surgery year, stage, location, and Charlson's Comorbidity Index score.
Note: Only colorectal cancer patients surviving the first 30 days after colorectal resection were included in this analysis (delayed entry analysis). Numbers in parenthesis are 95% confidence intervals.

Table 5. Relative risk of colorectal cancer recurrence after surgical resection in patients with localized and regional spread cancer at diagnosis, Denmark 2005-2010.

	One year after resection		Five years after resection	
	Crude	**Adjusted***	**Crude**	**Adjusted***
Immediate resection	Reference	Reference	Reference	Reference
Preoperative stenting, overall	0.98 (0.82 - 1.17)	1.05 (0.87 - 1.28)	1.05 (0.94 - 1.17)	1.12 (0.99 - 1.26)
Localized	0.88 (0.64 - 1.20)	0.94 (0.67 - 1.31)	1.02 (0.84 - 1.23)	1.05 (0.86 - 1.29)
Regional	1.02 (0.83 - 1.26)	1.12 (0.89 - 1.42)	1.05 (0.92 - 1.20)	1.16 (0.99 - 1.35)
By gender:				
Men	0.96 (0.75 - 1.21)	1.11 (0.85 - 1.45)	1.02 (0.87 - 1.19)	1.12 (0.94 - 1.33)
Women	1.00 (0.77 - 1.29)	0.99 (0.75 - 1.32)	1.08 (0.92 - 1.27)	1.13 (0.95 - 1.35)
By location:				
Proximal	2.19 (0.82 - 5.87)	2.14 (0.78 - 5.85)	1.52 (0.57 - 4.06)	1.85 (0.68 - 5.03)
Transverse	0.90 (0.43 - 1.88)	1.00 (0.47 - 2.15)	0.98 (0.61 - 1.57)	1.23 (0.75 - 2.01)
Distal	0.97 (0.78 - 1.22)	0.97 (0.76 - 1.23)	1.07 (0.93 - 1.24)	1.11 (0.95 - 1.29)
Rectal	1.34 (0.87 - 2.06)	1.42 (0.91 - 2.21)	1.27 (0.98 - 1.64)	1.27 (0.97 - 1.66)
Several/unsp.	0.85 (0.31 - 2.38)	1.11 (0.37 - 3.30)	0.70 (0.34 - 1.44)	0.76 (0.36 - 1.58)
By resection type:				
Resection with stoma	0.97 (0.79 - 1.18)	1.02 (0.81 - 1.28)	1.03 (0.91 - 1.17)	1.10 (0.96 - 1.27)
Resection without stoma	1.08 (0.74 - 1.56)	1.14 (0.78 - 1.68)	1.19 (0.94 - 1.51)	1.24 (0.97 - 1.58)
Primary elective surgery	Reference	Reference	Reference	Reference
Preoperative stenting, overall	1.56 (1.12 - 2.17)	1.48 (1.05 - 2.08)	1.77 (1.44 - 2.18)	1.72 (1.39 - 2.13)
Localized	1.45 (0.79 - 2.65)	1.36 (0.73 - 2.52)	1.66 (1.16 - 2.38)	1.72 (1.19 - 2.48)
Regional	1.50 (1.01 - 2.22)	1.57 (1.04 - 2.38)	1.70 (1.32 - 2.19)	1.76 (1.35 - 2.30)
By gender:				
Men	1.48 (0.94 - 2.31)	1.35 (0.85 - 2.16)	1.57 (1.18 - 2.08)	1.52 (1.13 - 2.05)
Women	1.67 (1.03 - 2.72)	1.67 (1.01 - 2.77)	2.06 (1.52 - 2.78)	1.99 (1.46 - 2.72)
By location:				
Proximal	9.40 (1.32 - 67.1)	13.0 (1.78 - 95.1)	4.50 (0.63 - 32.0)	5.43 (0.75 - 39.1)
Transverse	0.93 (0.22 - 3.87)	1.01 (0.24 - 4.26)	1.13 (0.46 - 2.79)	1.26 (0.50 - 3.16)
Distal	1.61 (1.07 - 2.42)	1.39 (0.92 - 2.11)	1.91 (1.48 - 2.47)	1.64 (1.26 - 2.13)
Rectal	2.05 (0.97 - 4.33)	1.80 (0.85 - 3.83)	2.40 (1.52 - 3.78)	2.25 (1.43 - 3.56)
Several/unsp.	1.36 (0.18 - 10.2)	1.18 (0.15 - 9.58)	1.10 (0.27 - 4.57)	1.05 (0.25 - 4.46)
By resection type:				
Resection with stoma	1.52 (1.05 - 2.21)	1.51 (1.03 - 2.22)	1.68 (1.33 - 2.12)	1.71 (1.35 - 2.18)
Resection without stoma	1.49 (0.73 - 3.07)	1.37 (0.63 - 3.01)	1.95 (1.23 - 3.09)	1.63 (0.99 - 2.70)

* Hazards ratios from Cox proportional regression were used as estimates of relative risks. They were adjusted for age, gender, year of colorectal resection, type of resection, Charlson Comorbidity Index score, and colorectal cancer location.
Note: Only colorectal cancer patients surviving the first 30 days after colorectal resection were included in this analysis (delayed entry analysis). Numbers in parenthesis are 95% confidence intervals.

Supplementary Table 1. Characteristics of colorectal cancer patients surviving the first 30 days after resection, Denmark 2005-2010.

	Self-expanding metal stents with Subsequent surgery		Colorectal resection			
			Immediately		Electively	
	n	%	n	%	n	%
Total	534	100	2,883	100.0	12,771	100.0
Female	251	47.0	1,525	52.9	5,854	45.8
Male	283	53.0	1,358	47.1	6,917	54.2
Age:						
0-49	34	6.4	143	5.0	617	4.8
50-69	208	39.0	1,028	35.7	5,485	42.9
70-79	183	34.3	930	32.3	4,199	32.9
80+	109	20.4	782	27.1	2,470	19.3
Year of CRC surgery:						
2005	18	3.4	549	19.0	1,817	14.2
2006	82	15.4	500	17.3	2,149	16.8
2007	96	18.0	481	16.7	2,085	16.3
2008	101	18.9	464	16.1	2,155	16.9
2009	111	20.8	411	14.3	2,153	16.9
2010	125	23.4	452	15.7	2,184	17.1
2011*	1	0.2	26	0.9	228	1.8
Resection type						
Without stoma	400	74.9	2,086	72.4	11,390	89.2
With stoma	134	25.1	797	27.6	1,381	10.8
Location of CRC:						
Proximal:	8	1.5	1,131	39.2	3,083	24.1
Appendix (C181)	.	.	36	1.2	96	0.8
Caecum (C180)	1	0.2	5,814	20.2	1,335	10.5
Ascending (C182)	3	0.6	384	13.3	1,270	9.9
Right flexure (C183)	4	0.7	130	4.5	382	3.0
Transverse (C184)	47	8.8	252	8.7	521	4.1
Distal:	382	71.5	91	3.2	173	1.4
Left flexure (C185)	45	7.7	98	3.4	283	2.2
Descending (C186)	72	13.5	788	27.3	3,188	25.0
Sigmoid (C187)	266	49.8	384	13.3	1,270	9.9
Rectal:	81	15.2	359	12.5	5,165	40.4
Junction (C19)	11	2.1	35	1.2	151	1.2
Rectal (C20)	70	13.1	324	11.2	5,014	39.3
Several/unspecific:	16	3.0	164	5.7	358	2.8
Several regions (C188)	2	0.4	31	1.1	55	0.4
Unspecified (C189)	14	2.6	133	4.6	303	2.4
Stage of CRC:						
Localized	161	30.1	954	33.1	5,359	42.0
Regional	159	29.8	842	29.2	3,994	31.3
Metastatic	157	29.4	828	28.7	1,758	13.8
Unknown	57	10.7	259	9.0	1,660	13.0
Charlson comorbidity Index						
Low: 0	327	61.2	1,643	57.0	7,494	58.7
Medium: 1-2	143	26.8	863	29.9	3,849	30.1
High: 3+	64	12.0	377	13.1	1,428	11.2

* We included CRC patients diagnosed in the 2005-2010 period, some of whom had SEMS or surgery in 2011.

References

1. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010; 127:2893-2917.

2. Gainant A. Emergency management of acute colonic cancer obstruction. *J Visc Surg.* 2012; 149:e3-e10.

3. Iversen LH, Bulow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. *Br J Surg.* 2008; 95:1012-1019.

4. Zhang Y, Shi J, Shi B et al. Self-expanding metallic stent as a bridge to surgery versus emergency surgery for obstructive colorectal cancer: a meta-analysis. *Surg Endosc.* 2012; 26:110-119.

5. 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.

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

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

8. 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.

9. Sagar J. Colorectal stents for the management of malignant colonic obstructions. *Cochrane Database Syst Rev.* 2011;CD007378.

10. Tan CJ, Dasari BV, Gardiner K. Systematic review and meta-analysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. *Br J Surg.* 2012; 99:469-476.

11. van Hooft JE, Bemelman WA, Oldenburg B et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol.* 2011; 12:344-352.

12. Alcantara M, Serra-Aracil X, Falco J et al. Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer. *World J Surg.* 2011; 35:1904-1910.

13. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. *Surg Endosc.* 2011; 25:1814-1821.

14. 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.

15. Martinez-Santos C, Lobato RF, Fradejas JM et al. Self-expandable stent before elective surgery vs. emergency surgery for the treatment of malignant colorectal obstructions: comparison of primary anastomosis and morbidity rates. *Dis Colon Rectum.* 2002; 45:401-406.

16. 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.

17. Lee WS, Baek JH, Kang JM, Choi S, Kwon KA. The outcome after stent placement or surgery as the initial treatment for obstructive primary tumor in patients with stage IV colon cancer. *Am J Surg.* 2012; 203:715-719.

18. Kim HJ, Choi GS, Park JS, Park SY, Jun SH. Higher rate of perineural invasion in stent-laparoscopic approach in comparison to emergent open resection for obstructing left-sided colon cancer. *Int J Colorectal Dis.* 2012.

19. 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.

20. Frank L. Epidemiology. When an entire country is a cohort. *Science.* 2000; 287:2398-2399.

21. Iversen LH, Kratmann M, Boje M, Laurberg S. Self-expanding metallic stents as bridge to surgery in obstructing colorectal cancer. *Br J Surg.* 2011; 98:275-281.

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

23. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull.* 1999; 46:263-268.

24. Erichsen R, Lash TL, Hamilton-Dutoit SJ et al. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol.* 2010; 2:51-56.

25. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol.* 2011; 11:83.

26. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res.* 2007; 13:559-565.

27. Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology.* 2006; 44:1075-1082.

28. Vemulapalli R, Lara LF, Sreenarasimhaiah J, Harford WV, Siddiqui AA. A comparison of palliative stenting or emergent surgery for obstructing incurable colon cancer. *Dig Dis Sci.* 2010; 55:1732-1737.

29. 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.

30. 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.

31. Knight AL, Trompetas V, Saunders MP, Anderson HJ. Does stenting of left-sided colorectal cancer as a "bridge to surgery" adversely affect oncological outcomes? A comparison with non-obstructing elective left-sided colonic resections. *Int J Colorectal Dis.* 2012.

32. Tottrup A, Erichsen R, Svaerke C, Laurberg S, Srensen HT. Thirty-day mortality after elective and emergency total colectomy in Danish patients with inflammatory bowel disease: a population-based nationwide cohort study. *BMJ Open.* 2012; 2:e000823.

Appendix. The *International Classification of Disease* (ICD) codes, versions 8 and 10, and the procedure codes used in the present study.

The Danish Cancer Registry:

Colorectal Cancer: ICD-10: DC18-20

The Danish National Registry of Patients (DNRP) and the Danish Pathology Registry (DPR):

Procedure codes for placement of self-expanding metal stents (the DNRP): KJFA68 and KJGA58A

Procedure codes for colorectal resection (the DNRP):

1. Resection without stoma: KJFB 20-97 (excluding KJFB60-64), KJFH (excluding KJFH10-21 and KJFH33-40), and KJGB (excluding KJGB10-11 and KJGB40) and no concurrent KJFF13-41 code
2. Resection with stoma: KJFB60-64, KJFH10-21, KJFH33-40, KJGB10-11, and KJGB40 *OR* KJFB20-97/KJFH/KJGB with a concurrent KJFF13-41 code.

Algorithm for defining recurrence:

a) Metastasis code (C76–C80) in the DNRP >180 days after surgery.
   OR
b) Cytostatic therapy code in the DNRP >180 days after surgery and 60 or more days after their last cytostatic therapy code. Treatment codes BWHA1–2
   OR
c) The following SNOMED combinations in the DPR recorded >180 days after surgery date:
    a. T67*** or T68*** in combination with M8***X, where X≥3
    b. Any T code in combination with M8***Y, where Y= 4 or 6 or 7

The Charlson Comorbidity Index (codes from the DNRP):

	Diseases	**ICD-8**	**ICD-10**	**Score**
1	Myocardial infarction	410	I21;I22;I23	1
2	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430-438	I60-I69; G45; G46	1
5	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0; B18	1
10	Diabetes type1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1
	Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9	
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes with end organ damage type1	249.01-249.05; 249.08	E10.2-E10.8	2
	type2	250.01-250.05; 250.08	E11.2-E11.8	
14	Any tumour (except colorectal cancer)	140-194 (excluding 153.xx, 154.09-19)	C00-C75 (excluding C18-C20)	2
15	Leukemia	204-207	C91-C95	2
16	Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumour	195-198; 199	C76-C80	6
19	AIDS	079.83	B21-B24	6

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. *2000*.
2. Nana Thrane: Prescription of systemic antibiotics for Danish children. *2000*.
3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. *2001*.
4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. *2001*.
5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. *2001*.
6. Gitte Pedersen. Bacteremia: treatment and prognosis. *2001*.
7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. *2002*.
8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. *2002*.
9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. *2002*.
10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. *2003*.
11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. *2004*.
12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.
14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. *2004*.
15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.
16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.
17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.
18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.
19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. *2006*.
20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. *2006*.
    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.
21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.
22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.
23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.
24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.
25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.
27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. *2007*.
28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. *2007*.
29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. *2007*.
30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. *2007*.
31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.
32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. *2007*.
33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. *2007*.
34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.
35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. *2007*.
36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. *2008*.
37. Use of medical databases in clinical epidemiology. *2008*.
38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.
40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.
41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.
42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.
43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. *2009*.
44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. *2009*.
45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. *2009*.
46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. *2009*.
47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. *2009*.
48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. *2009*.
49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.
50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. *2009*.
51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. *2010*.
52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. *2010*.

53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.
54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.
55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. *2010*.
56. Thomas Patrick Ahern: Estimating the impact of molecular profiles and prescription drugs on breast cancer outcomes. *2010*.
57. Annette Ingeman: Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome. *2010*.
58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.
59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. *2010*.
60. Knoglemetastaser og skeletrelaterede hændelser blandt kvinder med brystkræft i Danmark. Forekomst og prognose 1999-2007. *2010*.
61. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft. Region Midtjylland og Region Nordjylland 1998-2009. *2010*.
62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. *2011*.
63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. *2011*.
64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. *2011*.

65. Gitte Vrelits Sørensen: Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. *2011*.

66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. *2012*.

67. Marie Louise Overgaard Svendsen: Early stroke care: studies on structure, process, and outcome. *2012*.

68. Christian Fynbo Christiansen: Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis. *2012*.

69. Jennie Maria Christin Strid: Hospitalization rate and 30-day mortality of patients with status asthmaticus in Denmark – A 16-year nationwide population-based cohort study. *2012*.

70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. *2012*.

72. Anna Maria Platon: The impact of chronic obstructive pulmonary disease on intensive care unit admission and 30-day mortality in patients undergoing colorectal cancer surgery: a Danish population-based cohort study. *2012*.