Real-world Aspects of Colorectal Cancer Survival in the Netherlands

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ISBN 978-94-6299-886-5

Cover design Mertin Cimen and Amanda Bos
"Life can be a rollercoaster ride" – Thought painting of the past four years inspired by artworks of Joseph Klibansky

Lay-out Nikki Vermeulen - Ridderprint BV

Printing Ridderprint BV - www.ridderprint.nl

Financial support by Netherlands Comprehensive Cancer Organisation (IKNL) and Erasmus University Rotterdam (EUR) is gratefully acknowledged.

Erasmus University Rotterdam

Real-world Aspects of Colorectal Cancer Survival in the Netherlands

Real-world aspecten van colorectaal carcinoom overleving in Nederland

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. H.A.P. Pols

en volgens het besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

16 mei 2018 om 15.30 uur

door
Amanda Catharina Rosemary Kusproborini Bos
geboren te Amsterdam

Erasmus University Rotterdam

Erasmus

PROMOTIECOMMISSIE

Promotoren	Prof. Dr. V.E.P.P. Lemmens
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General introduction

COLORECTAL CANCER

Epidemiology

Colorectal cancer is a major health problem. Colorectal cancer mainly occurs in developed countries.[1] In the Netherlands it is the second most common cancer among males (representing 16% of all cancers), after prostate cancer (20%), and it is the third most frequent cancer among females (13%), after breast cancer (28%) and skin cancer (excluding basal cell carcinoma; 15%).[2] In 2015, the age-standardized incidence rate (World Standardized Population (WSR)) was 44.3 per 100,000 person-years. The absolute number of colorectal cancer patients in the Netherlands has more than doubled in the last 25 years; from 7,100 in 1990 to 15,800 in 2015.[2] The majority of the colorectal cancers (approximately 60%) is located in the colon. As a result of the introduction of the Dutch colorectal cancer screening program and aging of the population, the incidence of colorectal cancer is increasing in the Netherlands.[3, 4]

Risk factors

The risk of developing colorectal cancer increases with advancing age. Colorectal cancer rarely occurs before age 40. Nowadays, mean age at time of colorectal cancer diagnosis is 69 years and approximately 80% of the colorectal cancer patients is aged 60 years or older at diagnosis.[2, 5] With the aging of the population, comorbidity among colorectal cancer patients is common. The proportion of Dutch colorectal cancer patients with two or more concomitant diseases varied from 35% in those aged 65-74 years to 51% in those aged 85 years or older. Common comorbidities among patients aged 75 years or older were hypertension, cardiac and vascular diseases, diabetes mellitus and previous malignancy (Figure 1).

Additionally, several lifestyle- or environmental factors, including obesity, physical activity, high consumption of red and processed meat, alcohol intake, smoking, hormone replacement therapy and non-steroidal anti-inflammatory drugs influence the risk of developing colorectal cancer.[6-8] Other high-risk groups include patients with inflammatory bowel disease like ulcerative colitis and Crohn's disease.[9] Furthermore, individuals can be at increased risk due to their genetic constitution. Approximately 5% of all colorectal cancers are genetically determined. The main hereditary forms are Lynch syndrome (hereditary non-polyposis colorectal cancer), familial colorectal cancer (non-polyposis) and adenomatous polyposis (MYH associated polyposis).[10]

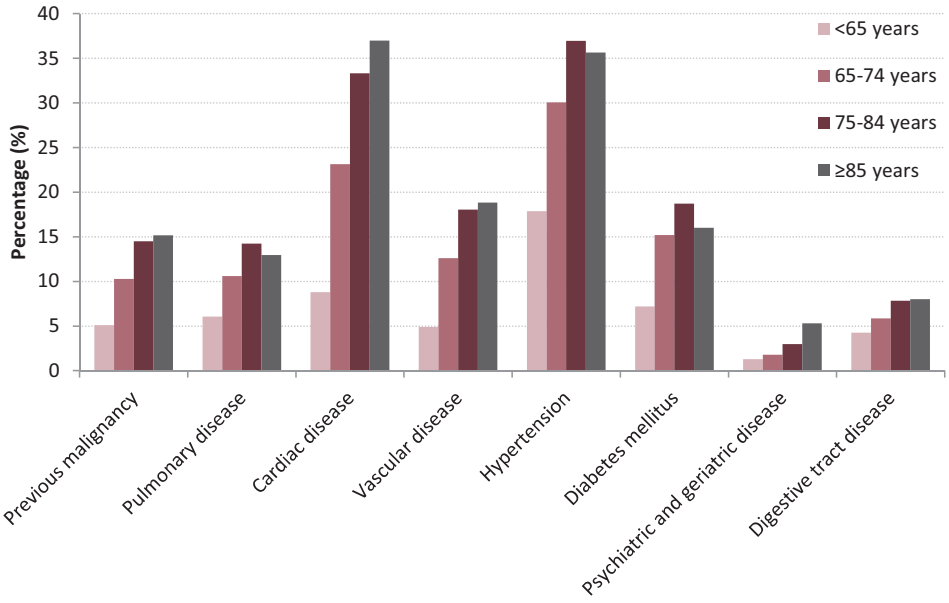

FIGURE 1 Proportion of comorbidities present at diagnosis among colorectal cancer patients diagnosed in the Netherlands between 1994-2014, by age group.
Source: Netherlands Cancer Registry (southeast part)

Stages of the disease

The tumour-node-metastasis (TNM) staging system is most commonly used to classify invasiveness of the disease.[11] The system consists of four stages; stage I to IV. In stage I colorectal cancer, the tumour has grown through several layers of the large bowel, except its muscular wall. Stage II colorectal cancers have grown through the wall, but have not involved the lymph nodes. When the tumour has spread to at least one lymph node in the nearby area, but not to other body parts, the tumour is classified as being stage III. Stage IV is the most advanced stage of the disease; the tumour has reached distant organs or tissues, most commonly the liver, lungs and peritoneal surface.[12, 13]

Treatment modalities

Since 2000, there have been national evidence-based guidelines regarding cancer care in the Netherlands. The most recent guidelines for colorectal cancer, revised in 2014, contain recommendations for diagnosis, treatment and follow-up.[10]

For colon cancer patients, the primary treatment is surgical removal of part of the colon in which the tumour is located, and of regional lymph nodes. The two ends of the colon are reconnected, or sometimes a temporary colostomy may be constructed. Since the introduction of laparoscopic surgery in 1991[14], this minimally invasive approach is

more often performed in colorectal cancer patients compared to the conventional open abdominal resection.[15] Laparoscopic surgery appears to be associated with less postoperative pain, better pulmonary function, reduced occurrence of ileus and shorter hospital stay compared with open surgery, without compromising oncological outcome.[16-19] Adjuvant chemotherapy can be used with the intention to eradicate any residual micrometastatic disease.[20] Several clinical trials[21-24] have shown that adjuvant chemotherapy has a positive effect on disease-free and overall survival in stage III colon cancer patients and is therefore standard treatment since the nineties. Furthermore, since 2005 adjuvant chemotherapy can be considered for high-risk stage II colon cancer patients, defined as patients with perforation or obstruction, T4 tumours, venous invasion, fewer than 10 lymph nodes examined, or poorly differentiated or undifferentiated tumours.[10]

For patients with rectal cancer, the type of surgical resection depends on the localization and size of the tumour. Transanal endoscopic microsurgery is recommended for patients with T1 tumours. An abdominoperineal resection (including a permanent colostomy) is performed when tumours are located in the lower part of the rectum, near the anal sphincter. Patients with tumours in the middle or upper part of the rectum might undergo a low anterior resection, thereby preserving the anal sphincter to prevent a permanent colostomy. The total mesorectal (TME) technique is used for these resections. The TME technique involves radical resection achieved by sharp dissection under direct vision of the rectum with its mesorectum and the visceral pelvic fascia. The introduction of TME in the mid 1990's resulted in a decreased local recurrence rate.[25] The Dutch Colorectal Cancer Group (DCCG) investigated the effects of preoperative radiotherapy in combination with standardized TME. This and several other studies showed the survival benefits of preoperative radiotherapy.[26-28] Since 2001, preoperative radiotherapy became standard practice for all rectal cancer patients with clinical T2-T4 tumours. Additionally, since 2004, based on results of previous studies[29, 30], preoperative chemoradiotherapy became the standard treatment for locally advanced rectal cancer. Nowadays, neoadjuvant radiotherapy is indicated for patients with clinical T1-T2 tumours with positive lymph nodes and for patients with clinical T3 tumours with >5 millimeter (mm) extramural invasion. Neoadjuvant chemoradiotherapy is recommended for patients with clinical T4 tumours, T3 tumours in which the distance to the mesorectal fascia is ≤1 mm and tumours with clinical N2.[10] Neoadjuvant chemoradiotherapy can result in complete disappearance of tumour and involved nodes. Approximately 15% to 20% of the rectal cancer patients who undergo neoadjuvant chemoradiotherapy experience a pathological cmplete response in which no residual tumour is reported at histology after a standard resection.[31] Habr-Gama et al.[32] introduced a so-called "wait-and-see policy" in 2004, in which patients with low rectal cancer who achieved a clinical complete response after neoadjuvant chemoradiotherapy were closely followed and did not undergo surgery. Although the

safety and long-term effect of this approach is currently still under investigation in a wait-and-see trial in the Netherlands, it could potentially save patients from the morbidity of conventional surgery, which may affect their bowel and sexual function.

Metastatic disease is a common manifestation in patients with colorectal cancer. Approximately one fifth of the patients presents with metastasized disease at diagnosis[12, 33, 34] and in another 14-34% of the patients metastases occur during the course of disease.[35, 36] An increasing proportion of stage IV colorectal cancer patients receive surgical treatment of the metastasis with curative intent, however, the majority of the patients are still ineligible for curative treatment modalities and remain dependent on palliative treatment. Over the past decade, the spectrum of systemic treatment in non-resectable metastatic colorectal cancer has widened. Chemotherapeutic regimens combining fluoropyrimidines and oxaliplatin or irinotecan have become available. In the early 21st century a new class of agents, usually referred to as targeted therapy, was introduced including bevacizumab, cetuximab and panitumumab, which have improved the prognosis of patients with stage IV remarkably[37, 38], defining the backbone of current systemic therapy.[39-43] According to the Dutch national treatment guidelines, patients with non-resectable metastatic colorectal cancer should be treated with first-line mono- or combination chemotherapy with the addition of bevacizumab as targeted therapy.[10] Approximately 10% of colorectal cancer patients is diagnosed with peritoneal metastases.[13, 44, 45] Recently, the understanding that peritoneal carcinomatosis results from loco-regional rather than systemic spread, resulted in the development of loco-regional treatment modalities combining cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[46] In the Netherlands, CRS-HIPEC was introduced 20 years ago. The number of hospitals offering CRS-HIPEC has increased gradually, all using a uniform technique.[47, 48]

Mortality and survival

Nine percent of all cancer patients die from colorectal cancer, making it the fourth most common cause of death from cancer worldwide.[1] In the Netherlands, 5,117 patients died of the disease in 2015.[2] Mortality due to colorectal cancer is slowly decreasing from 15.9 per 100,000 person-years (WSR) in 1989 to 12.3 per 100,000 person-years in 2015.[2] In the year 2005, the proportion of postoperative 30-day mortality among colon cancer patients was 5.7% and among rectal cancer patients 2.9%. This proportion decreased in 2014 to 2.4% among colon cancer patients and 1.0% in rectal cancer patients (Figure 2).

Survival rates of colorectal cancer patients in the Netherlands have been improving since the end of the 1980's[12, 49], which has been attributed to major advancements in the diagnostic process[50, 51] and treatment of colorectal cancer. Improved surgical techniques substantially contributed to better perioperative care and a decrease of morbidity by minimally invasive surgery.[52, 53] Furthermore, over time the administration of ((neo)adjuvant)

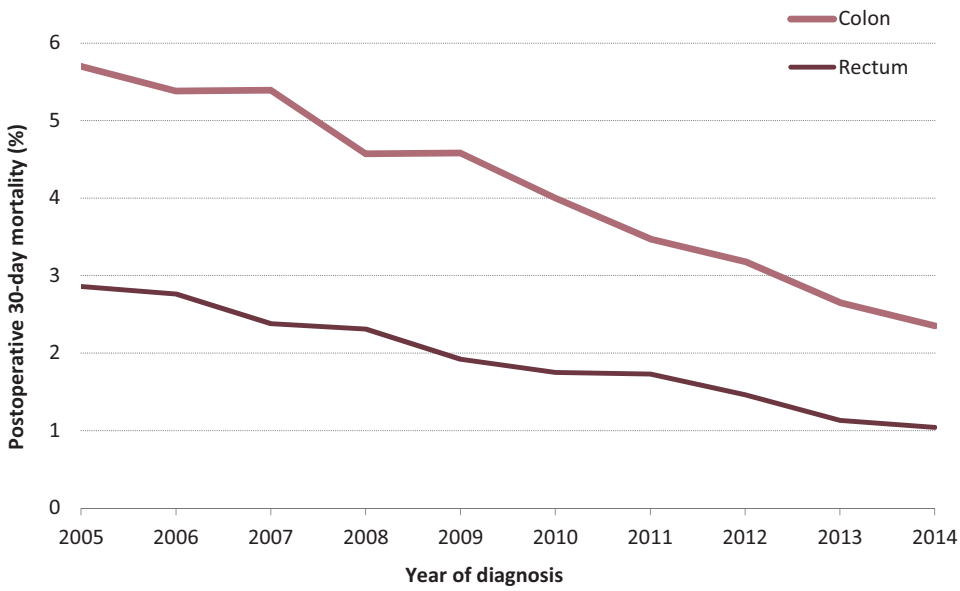

FIGURE 2 Trend in postoperative 30-day mortality of colorectal cancer patients diagnosed in the Netherlands between 2005-2014, by year of diagnosis.
Source: Netherlands Cancer Registry

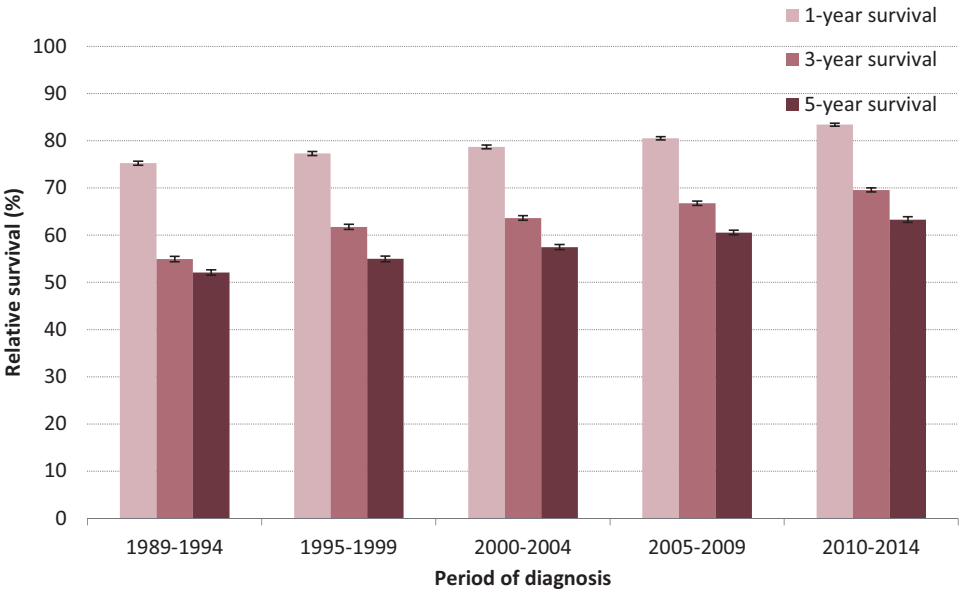

FIGURE 3 Trend in 1-, 3-, and 5-year relative survival of colorectal cancer patients diagnosed in the Netherlands between 1989-2014, by period of diagnosis.
Source: Netherlands Cancer Registry

(chemo)radiotherapy has been used more frequently.[33, 34, 54-58] The 5-year relative survival rate of patients with colorectal cancer in the Netherlands increased from 52% for patients diagnosed in the period 1989-1994 to 63% for patients diagnosed in the period 2010-2014 (Figure 3). Prognosis is better if colorectal cancer is detected at an earlier stage. Five-year relative survival rate was 88% for patients with stage I and 4% for patients with stage IV diagnosed in the period 1989-1994, which increased to 93% for patients with stage I and 13% for patients with stage IV diagnosed in the period 2010-2014. Compared to other European countries, the Netherlands show high survival rates for colorectal cancer.[59, 60]

Prognostic determinants for colorectal cancer survival

Despite considerable improvements in the diagnostic process and treatment, colorectal cancer remains a leading cause of morbidity and mortality in the Netherlands. With an increasing age of the population and the introduction of a screening program, the number of new patients will also rise. Further improvement in survival of colorectal cancer patients could be achieved by better understanding of the factors that influence colorectal cancer care and outcome.

Survival of colorectal cancer is influenced by various determinants. Tumour-related factors including tumour stage and differentiation grade largely influence survival. Patient characteristics like age at diagnosis and comorbidity often influence the choice of oncological treatment, which results in altered survival rates. Furthermore, demographic factors influence patterns of care and survival among colorectal cancer patients. Investigating differences in clinical and demographic determinants affecting patterns of care and survival among colorectal cancer patients, supports to discuss and understand the disparities and helps the medical specialists and hospitals to improve the quality of colorectal cancer care. Population-based studies are needed to provide insight in everyday clinical practice by providing a platform in which all patients within a well-defined area are included irrespective of clinical trial participation.[61]

OUTLINE

The content of this thesis is divided into two parts, with the following main objectives:

- To give an overview of colorectal cancer survival in the Netherlands in a large population-based setting (part I).

- To identify determinants which influence treatment, quality of care and survival among colorectal cancer patients in the Netherlands (part II).

Part I: Colorectal cancer survival: an overall picture

Chapter 2 gives an overview of trends in survival among colorectal cancer patients diagnosed between 1989-2014 in the Netherlands. **Chapter 3** compares survival rates among non-metastastic colorectal cancer patients between different age groups.

Part II: Determinants of survival

Chapter 4 reveals whether second colorectal tumours have an effect on oncological treatment, short- and long-term patient outcomes. **Chapter 5** analyzes whether hospital volume for colorectal cancer is associated with surgical care characteristics and overall survival. In **chapter 6** prediction models for postoperative 90-day mortality and overall survival for colorectal cancer patients are developed and validated. **Chapter 7** investigates which demographic and clinical variables are associated with the timing of adjuvant chemotherapy and how this timing is associated with overall survival.

In **chapter 8**, the main findings and methodological considerations are discussed. Additionally, implications for clinical practice and future research are outlined.

DATA SOURCE

Netherlands Cancer Registry

The studies in this thesis are based on data from the nationwide Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR was established in 1989 and is a population-based registry based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR). Since 1993, the southeast part of the Netherlands registers comorbid conditions present at time of cancer diagnosis.[62, 63] The NCR is used for supporting epidemiological and clinical research, developing and evaluating guidelines, evaluating screening programs, planning health services and improving quality of care.

Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and national level. Anatomical site of the tumour is registered according to the International Classification of Disease – Oncology (ICD-O).[64] The TNM classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[11]

Vital status of all patients is obtained actively on a regular basis by linking the cancer registry database to the Municipal Personal Records Database (GBA).

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PART I

COLORECTAL CANCER SURVIVAL: AN OVERALL PICTURE

2

Survival continuously improves during 25 years of treating colorectal cancer patients
Results from the Dutch Cancer Registry

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Submitted

ABSTRACT

Aim

The aim of this study was to analyze developments in incidence, treatment and survival for patients diagnosed with colorectal cancer between 1989 and 2014 in the Netherlands. These trends are considered to be indicative for first world countries.

Methods

Using data of the nationwide population-based Netherlands Cancer Registry, 267,765 patients diagnosed with colorectal cancer between 1989-2014 were included for analyses on incidence, mortality, stage distribution, treatment and relative survival.

Results

The incidence of both colon and rectal cancer has risen. The use of adjuvant chemotherapy for stage III colon cancer increased, as well as the use of neoadjuvant (chemo)radiotherapy for rectal cancer (14% to 60% and 2% to 66% respectively). The administration of systemic therapy and metastasectomy increased for metastasized disease. The 5-year survival increased significantly (53% to 62% for colon cancer; 51% to 65% for rectal cancer), with the largest improvement in stages II and III, and the most obvious gain in survival within the first 12 months after diagnosis.

Conclusion

The continuous improvement in the survival of colorectal cancer patients should not only be attributed to the ongoing advancements in treatment, but also to improvement in other factors in the care of colorectal cancer patients, particularly in more recent years.

INTRODUCTION

Colorectal cancer is one of the most common cancer types in developed countries, with more than 15,000 patients diagnosed in the Netherlands in 2016.[1, 2] The epidemiology and treatment of colorectal cancer have seen major changes over the years, and are still changing today. The incidence of colorectal cancer in the Dutch population has increased over time and although mortality rates have decreased, colorectal cancer is still the second leading cause of cancer-related death, accounting for over 4,900 deaths in 2014.[1] To further decrease mortality rates, the Dutch government introduced a nationwide screening program for colorectal cancer in 2014.[3]

Besides changes in incidence and mortality, survival rates of colorectal cancer patients in the Netherlands have been improving since the end of the 1980's, which has been attributed to major advancements in the diagnostic process and treatment of colorectal cancer. The successful multimodality management of colorectal cancer requires a multidisciplinary approach, due to the rapidly increasing diagnostic and therapeutic options in these different aspects of colorectal cancer care. CT scanning has become standard for staging with the addition of MRI in rectal cancer patients.[4] Flexible endoscopy has technically evolved with more accurate detection of (pre-)malignant lesions, relevant for surveillance of high risk groups and screening, with increasing possibilities for polypectomy.[5] Improved surgical techniques as well as subspecialization substantially contributed to the quality of oncological treatment, besides reducing morbidity by minimally invasive surgery and better perioperative care.[6-8] Preoperative radiotherapy options have increased with several new schedules combining this modality with systemic treatment as induction, concomitant or consolidation therapy.[9, 10] The use of adjuvant 5-fluorouracil (5-FU) based chemotherapy has become standard treatment in high risk stage II and stage III colon cancer patients.[11, 12] For metastatic colorectal cancer, the use of combination chemotherapy, various new systemic and regional multimodality treatment, metastasectomies and other local treatments are increasingly being performed.[13-16]

Regarding the continuous changes in the diagnostic process and treatment of colorectal cancer, it is important to evaluate both long-term trends as well as trends during the most recent years, which are relevant to give direction for further research and innovations in cancer patient care. Therefore, the aim of this study was to analyze trends in incidence, mortality, stage distribution, treatment and relative survival for patients diagnosed with colorectal cancer between 1989 and 2014 in the Netherlands, which are considered to be indicative for other first world countries.

METHODS

Data collection

Nationwide population-based data on colorectal cancer patients from 1989 onwards were obtained from the Netherlands Cancer Registry (NCR). Since 1989, the NCR registers all newly diagnosed malignancies in the Netherlands. The NCR receives the notification mainly from the pathology departments of hospitals, all taking part in the automated pathology archive (PALGA), and the National Registry of Hospital Discharge Diagnoses (LMR). Following the notification, trained registrars gather patient, tumour and treatment characteristics directly from the medical records.

Anatomical subsite of the tumour is coded according to International Classification of Diseases for Oncology (ICD-O).[17] The TNM (tumour-node-metastasis) classification was used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[18] Pathological TNM took precedence over clinical stage except for unknown pathological stage. In case of a positive cM, stage was always registered as stage IV.

All cases of primary colorectal cancer diagnosed in the period 1989-2014 were selected for this study. The study period was divided into five time periods of five years each (1989-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2014). Patients were stratified by tumour localization: colon (C18) and rectum (rectosigmoid and rectum, C19-C20).

Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database (GBA). Follow-up was completed until January 1st, 2016.

Statistical analyses

For analyses on patient and tumour characteristics, incidence and mortality, data from all patients was included. The χ^2 test was used to analyze differences in TNM stage between the different time periods. The Cochran-Armitage test was performed to analyze trends in the other patient and tumour characteristics. For the analyses on incidence and survival, the criteria of multiple tumours of the International Association of Cancer Registries (IACR) were applied.[17] Annual incidence and mortality were described per 100,000 person-years and standardized according to the European Standard Population (ESR). In addition, analyses of trends in incidence and mortality over different time periods were achieved by performing the average annual percentage of change analysis.

For the analyses on treatment and survival, patients with either 'no histologically confirmed colorectal cancer' or 'unknown TNM stage' were excluded. For metachronous primary tumours, the first diagnosed colorectal cancer was included. In case of synchronous multiple colorectal cancer, the tumour with the most advanced TNM stage was used for these analyses. Treatment characteristics were reported as percentages per age group and

per time period. The Cochran-Armitage test was performed as statistical test for trend.
Relative survival was calculated for the different age groups as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on age, gender and year of the corresponding general population (Pohar Perme method).[19] The relative survival analyses were performed according to tumour localization and stage.
P values below 0.05 were considered statistically significant. Analysis was performed in SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC), STATA (version 13.0, Statcorp LP, College Station, TX) and SPSS Statistics for Windows (version 22.0).

RESULTS

Between 1989 and 2014, 267,765 patients were diagnosed with colorectal cancer in the Netherlands.
Patient and tumour characteristics are presented in Table 1. All analyzed characteristics revealed a significant change over time with a *p* value of <0.0001 for either the χ^2 test or Cochrane-Armitage trend test. There was an increase over time in the proportion of colon tumours compared with rectal tumours. The proportion of males has increased in both colon and rectal cancer. Distribution of histology changed for both colon and rectal cancer, due to a decrease in the number of patients with mucinous adenocarcinoma and an increase in the number of patients with adenocarcinoma not otherwise specified.
The proportional stage distribution in Table 1 showed a decrease in stage II over time, whereas the proportion of stage IV increased. Moreover, a recent trend is the increasing number of rectal cancer patients with a complete pathological response after pre-operative treatment, starting from the period 2005-2009.

Incidence and mortality (European standardized rates)

The incidence of colorectal cancer in the Netherlands increased with 35% in the last 25 years. Figure 1a illustrates that age standardized incidence has increased predominantly for male colon cancer patients. The mortality of both male and female colon cancer patients decreased significantly over time. The incidence of rectal cancer is presented in Figure 1b, showing a stable incidence among females, whereas the incidence among males increased moderately from 21 to 26 per 100,000 person-years. The annual colorectal cancer mortality decreased slightly over time, for both males and females. For all groups, a strong increase in incidence is seen in 2014 following the introduction of the national screening program.

TABLE 1 Tumour site distribution of all patients diagnosed with colorectal cancer, and age, gender, morphology and TNM stage distribution of all patients diagnosed with colon or rectal cancer in the Netherlands between 1989 and 2014, by period of diagnosis (n=267,765).

	Period of diagnosis									
	1989-1994		1995-1999		2000-2004		2005-2009		2010-2014	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
COLORECTAL CANCER										
Colon	30,136	(66)	28,417	(65)	32,486	(65)	40,140	(67)	47,674	(69)
Rectum	15,812	(34)	14,973	(35)	17,114	(35)	19,741	(33)	21,272	(31)
COLON CANCER										
Age at diagnosis										
<50 years	1,885	(6)	1,583	(6)	1,714	(5)	1,826	(5)	2,047	(4)
50-59 years	3,418	(11)	3,432	(12)	4,195	(13)	4,878	(12)	5,008	(11)
60-69 years	7,668	(25)	6,989	(25)	7,793	(24)	10,025	(25)	13,135	(28)
70-79 years	10,330	(34)	9,935	(35)	11,381	(35)	13,467	(34)	16,254	(34)
≥80 years	6,835	(23)	6,478	(23)	7,403	(23)	9,944	(25)	11,230	(24)
Gender										
Male	13,916	(46)	13,720	(48)	15,938	(49)	20,369	(51)	25,054	(53)
Female	16,220	(54)	14,697	(52)	16,548	(51)	19,771	(49)	22,620	(47)
Morphology										
Adenocarcinoma	22,994	(76)	22,195	(78)	25,945	(80)	32,455	(81)	40,015	(84)
Mucinous adenocarcinoma	5,739	(19)	4,908	(17)	5,141	(16)	5,736	(14)	5,305	(11)
Signet ring cell carcinoma	287	(1)	314	(1)	375	(1)	571	(1)	650	(1)
Other	1,116	(4)	1,000	(4)	1,025	(3)	1,378	(3)	1,704	(4)
TNM-stage										
Stage 0	1	(0)	0	(0)	4	(0)	7	(0)	41	(0)
Stage I	4,673	(16)	4,291	(15)	4,768	(15)	6,279	(16)	8,729	(18)
Stage II	11,267	(37)	10,209	(36)	11,311	(35)	12,579	(31)	13,850	(29)
Stage III	6,637	(22)	6,778	(24)	7,895	(24)	10,001	(25)	11,972	(25)
Stage IV	5,833	(19)	5,433	(19)	6,691	(21)	8,861	(22)	11,211	(24)
Stage X	1,725	(6)	1,706	(6)	1,817	(6)	2,413	(6)	1,871	(4)
RECTAL CANCER										
Age at diagnosis										
<50 years	1,173	(7)	1,030	(7)	1,125	(7)	1,274	(6)	1,315	(6)
50-59 years	2,278	(14)	2,425	(16)	3,085	(18)	3,430	(17)	3,319	(16)
60-69 years	4,403	(28)	4,101	(27)	4,838	(28)	5,787	(29)	6,740	(32)
70-79 years	4,974	(31)	4,718	(32)	5,135	(30)	5,906	(30)	6,391	(30)
≥80 years	2,984	(19)	2,699	(18)	2,931	(17)	3,344	(17)	3,507	(16)

TABLE 1 Tumour site distribution of all patients diagnosed with colorectal cancer, and age, gender, morphology and TNM stage distribution of all patients diagnosed with colon or rectal cancer in the Netherlands between 1989 and 2014, by period of diagnosis (n=267,765). *(Continued)*

	Period of diagnosis									
	1989-1994		1995-1999		2000-2004		2005-2009		2010-2014	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender										
Male	8,763	(55)	8,555	(57)	9,970	(58)	11,674	(59)	13,116	(62)
Female	7,049	(45)	6,418	(43)	7,144	(42)	8,067	(41)	8,156	(38)
Morphology										
Adenocarcinoma	13,768	(87)	13,189	(88)	15,115	(88)	17,701	(90)	19,578	(92)
Mucinous adenocarcinoma	1,630	(10)	1,431	(10)	1,550	(9)	1,516	(8)	1,188	(6)
Signet ring cell carcinoma	287	(1)	314	(1)	375	(1)	571	(1)	650	(1)
Other	330	(2)	258	(2)	348	(2)	370	(2)	374	(2)
TNM-stage										
Stage 0	1	(0)	3	(0)	26	(0)	435	(2)	1,017	(5)
Stage I	4,175	(26)	3,845	(26)	4,402	(26)	5,097	(26)	6,076	(29)
Stage II	4,344	(27)	3,837	(26)	4,309	(25)	4,427	(22)	4,106	(19)
Stage III	3,573	(23)	3,614	(24)	4,278	(25)	4,945	(25)	5,214	(25)
Stage IV	2,436	(15)	2,427	(16)	3,078	(18)	3,901	(20)	4,236	(20)
Stage X	1,283	(8)	1,247	(8)	1,021	(6)	936	(5)	623	(3)

Treatment

In Table 2, trends in treatment for colon and rectal cancer are presented. Almost all patients diagnosed with stage I-III colon cancer underwent resection (this includes local excision such as polypectomy). Administration of adjuvant systemic therapy increased in patients with stage III colon cancer. Patients diagnosed with stage IV colon cancer less frequently underwent resection of the primary tumour without systemic therapy. The combination of systemic therapy and resection, the use of only systemic therapy, and the use of metastasectomy increased.

The primary tumour in non-metastasized rectal cancer was almost always resected, similar to colon cancer. The use of adjuvant radiotherapy in patients with rectal cancer decreased significantly, whereas the use of neoadjuvant radiotherapy and chemoradiotherapy increased during the same period. The administration of adjuvant chemotherapy increased until 2005-2009 in patients with stage II/III rectal cancer, but decreased in more recent years. In patients with stage IV rectal cancer, similar trends can be seen as for colon cancer.

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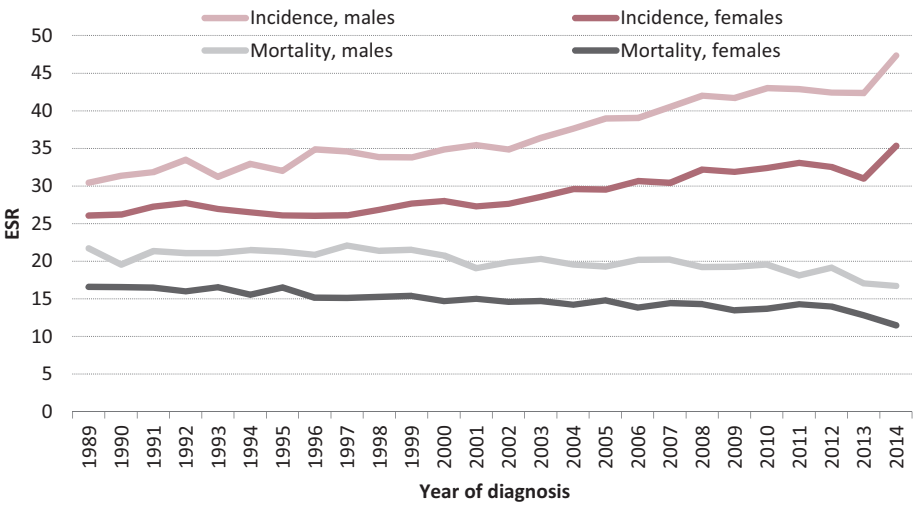

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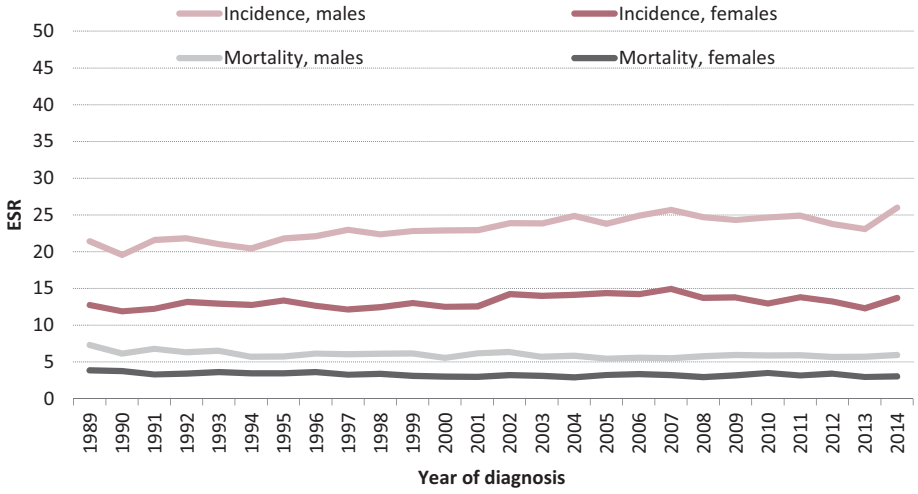

	Annual percentage of change			
	Incidence (95% CI)		Mortality (95% CI)	
COLON CANCER				
Male	1.54	(1.37-1.71)	-0.73	(-0.97--0.49)
Female	1.06	(0.85-1.26)	-1.02	(-1.22--0.82)
RECTAL CANCER				
Male	0.75	(0.54-0.95)	-0.59	(-0.83--0.34)
Female	0.37	(0.09-0.65)	-0.58	(-0.94--0.23)

FIGURE 1 Incidence and mortality rates per 100,000 person-years, for colon cancer (a) and rectal cancer (b), age-standardised to the ESR, according to gender (n=260,774).

TABLE 2 Trends in primary treatment for patients with colon or rectal cancer in the Netherlands, according to postoperative stage (n=247,667).

		Period of diagnosis									
		1989-1994		1995-1999		2000-2004		2005-2009		2010-2014	
	Stage	n	(% of total)	n	(% of total)	n	(% of total)	n	(% of total)	n	(% of total)
COLON CANCER											
Resection	I-III	21,389	(98)	19,952	(99)	22,333	(98)	26,653	(98)	31,693	(98)
Adjuvant chemotherapy	II	251	(2)	297	(3)	438	(4)	877	(7)	1,024	(8)
	III	918	(14)	2,465	(38)	4,019	(53)	5,621	(58)	6,855	(60)
Resection of primary tumour only	IV	3,341	(59)	2,624	(50)	2,295	(35)	2,097	(24)	1,812	(17)
Use of systemic therapy only	IV	299	(5)	384	(7)	889	(14)	1,947	(23)	3,112	(30)
Both resection of the primary tumour and systemic therapy	IV	671	(12)	1,061	(20)	1,841	(28)	2,779	(32)	3,471	(33)
Metastasectomy	IV	104	(2)	264	(5)	391	(6)	915	(11)	1,810	(17)
RECTAL CANCER											
Resection	0-III	11,439	(96)	10,593	(96)	12,141	(95)	13,774	(95)	14,581	(92)
Neoadjuvant radiotherapy	0-III	196	(2)	1,590	(14)	5,634	(44)	6,552	(45)	5,578	(35)
Neoadjuvant chemoradiation	0-III	11	(0)	88	(1)	391	(3)	2,751	(19)	4,964	(31)
Adjuvant radiotherapy	II/III	2,315	(3)	1,218	(17)	478	(6)	225	(2)	163	(2)
Adjuvant chemotherapy	II/III	295	(4)	688	(9)	1,142	(14)	1,495	(16)	899	(10)
Resection of primary tumour only	IV	1,192	(49)	958	(40)	776	(26)	556	(15)	434	(11)
Use of systemic therapy only	IV	149	(6)	226	(9)	593	(20)	1,377	(36)	1,778	(43)
Both resection of the primary tumour and systemic therapy	IV	236	(10)	418	(18)	748	(25)	936	(24)	833	(20)
Metastasectomy	IV	54	(2)	127	(5)	212	(7)	550	(14)	939	(23)

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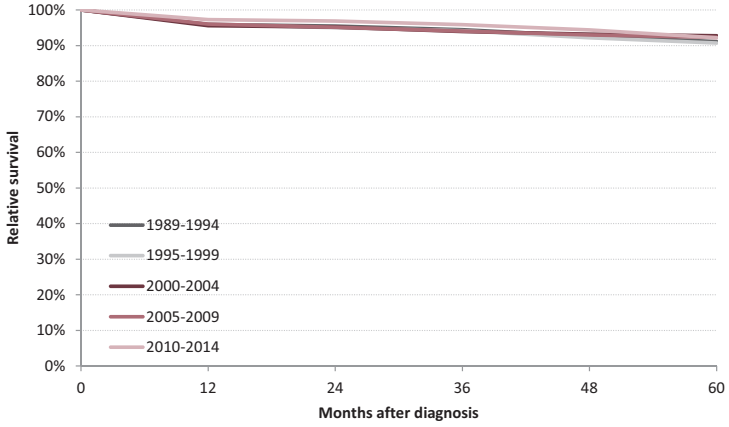
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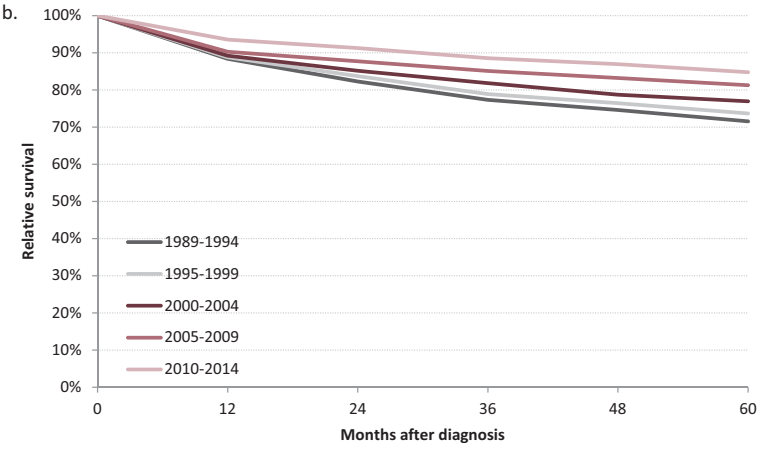
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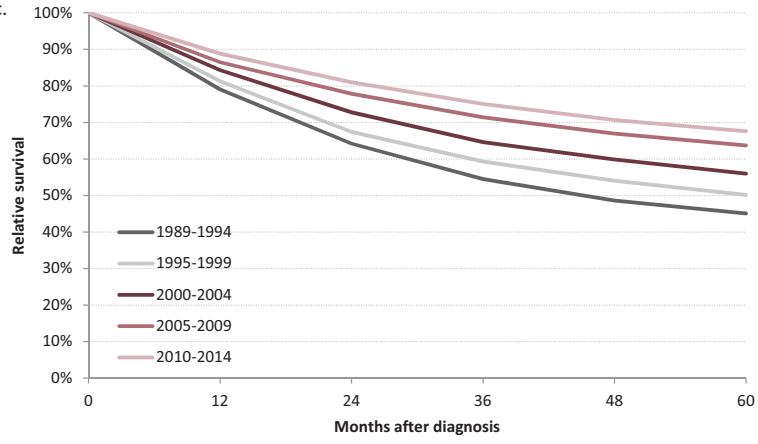
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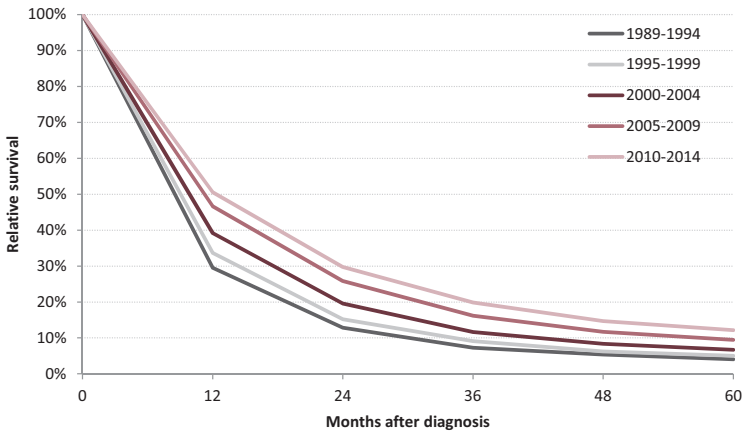
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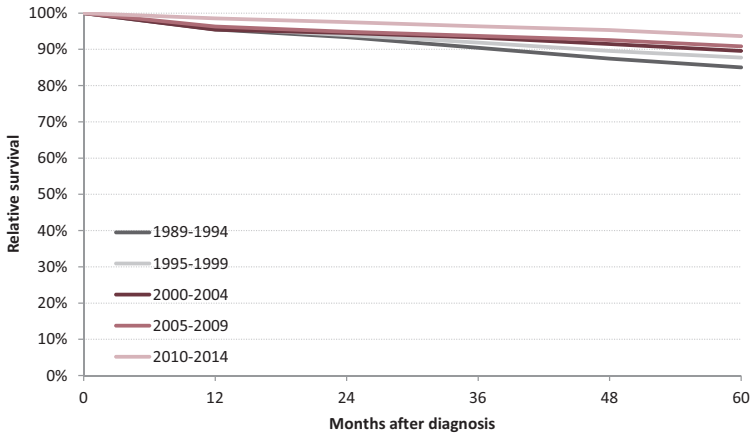
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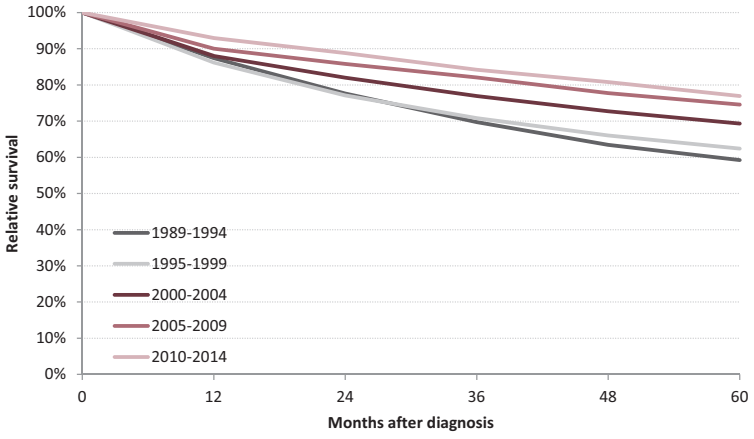
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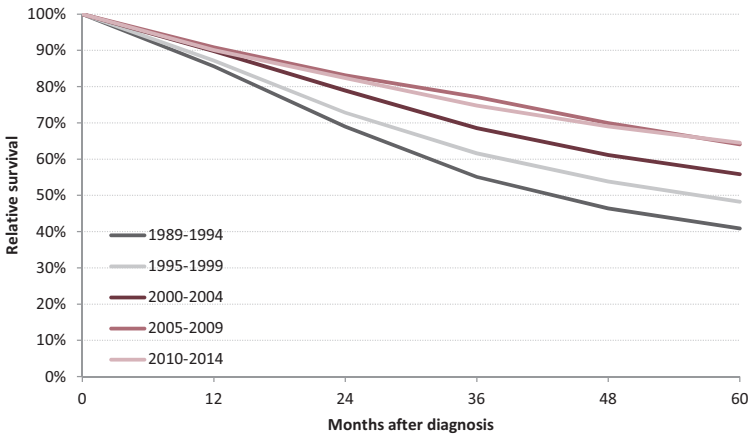
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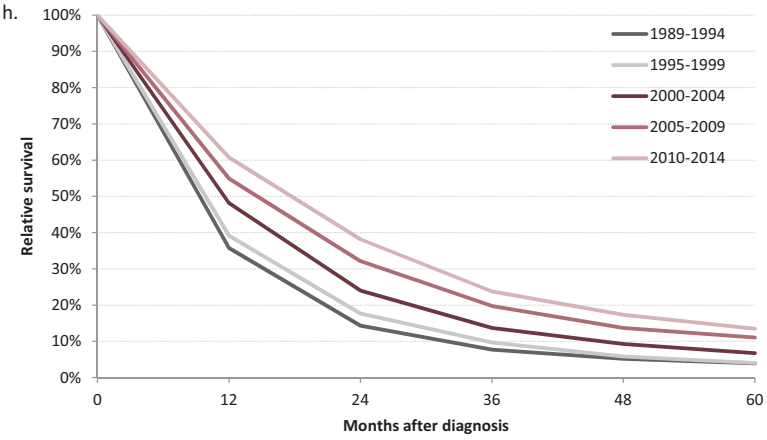
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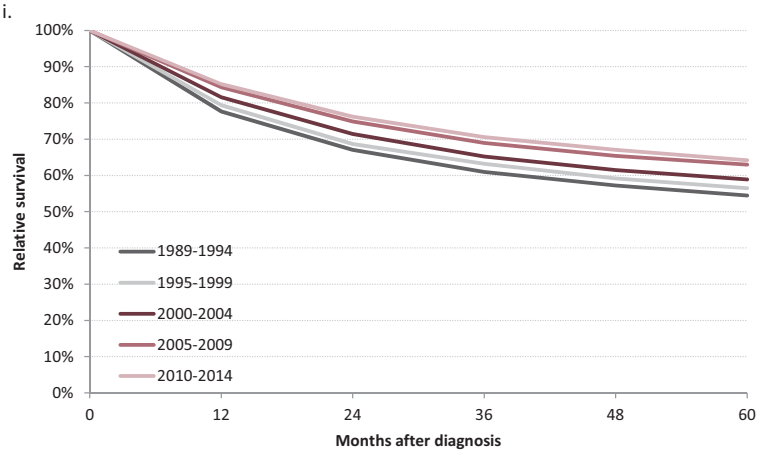
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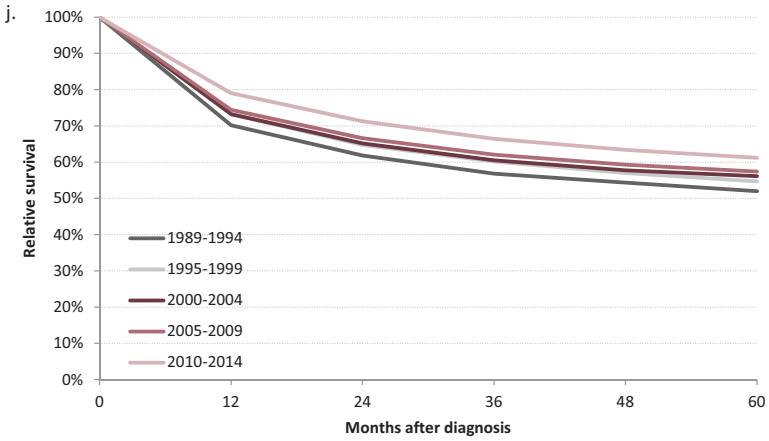

FIGURE 2 Stage-specific relative survival and relative survival for all stages combined for colon and rectal cancer, according to postoperative stage (n=233,522).

(a) Relative survival among patients with postoperative stage I colon cancer (including postoperative stage 0). (b) Relative survival among patients with postoperative stage II colon cancer. (c) Relative survival among patients with postoperative stage III colon cancer. (d) Relative survival among patients with postoperative stage IV colon cancer. (e) Relative survival among patients with postoperative stage I rectal cancer (including postoperative stage 0). (f) Relative survival among patients with postoperative stage II rectal cancer. (g) Relative survival among patients with postoperative stage III rectal cancer. (h) Relative survival among patients with postoperative stage IV rectal cancer. (i) Relative survival among patients with colon cancer, all postoperative stages and ages. (j) Relative survival among patients with rectal cancer, all postoperative stages and ages.

Survival

Relative survival rates are depicted in Figure 2 and have improved over time for both colon and rectal cancer. For patients with stage I colon cancer, the 5-year relative survival remained stable over time, around 92%. For patients with stage II colon cancer, survival improved during all periods. In the most recent periods this was mostly caused by a better survival rate within the first 12 months after diagnosis. The most remarkable increase in survival was seen for patients with stage III colon cancer, with an improvement in 5-year survival from 45% in 1989-1994 to 68% in 2010-2014. The 5-year survival for patients with stage IV colon cancer increased from 4% to 12%.

A gradual improvement in survival is seen in patients with stage I rectal cancer. The most substantial increase in survival for patients with stage II rectal cancer was seen between 1995-1999 and 2000-2004, but also in the following periods survival improved. For patients with stage III rectal cancer, 5-year survival has increased substantially until 2005-2009, whereas no further increase was observed in the most recent period. The improvement in survival for patients with stage IV rectal cancer was equal to the developments in colon cancer. The 5-year survival increased for all colon cancer stages combined from 53% to 62%, and for all rectal cancer stages combined from 51% to 65% between 1989-1994 and 2010-2014.

DISCUSSION

The current large population-based study provides an overview of the remarkable changes in epidemiology, treatment and survival of colorectal cancer in the Netherlands in the period 1989-2014. Changes in treatment were seen next to a significant increase in overall as well as stage-specific survival for both colon and rectal cancer patients. In the last 25 years, stage specific 5-year survival especially continued to improve in stage II and III disease. Furthermore, intensified treatment of metastatic colorectal cancer has also resulted in better outcome for these patients with a poor prognosis.

The incidence of colorectal cancer in the Netherlands increased with 35% in the last 25 years. The most significant increase was seen for colon cancer and males which is in line with trends in other European countries.[20] The implementation of a nationwide bowel screening program in the Netherlands explains the steep increase in the incidence of both colon and rectal cancer in 2014, which is expected to continue for several years, after which it is likely to decrease.[21, 22] The annual colorectal cancer mortality in the Netherlands has decreased modestly over the years. It is to be expected that, ultimately, mortality rates will further decrease because of the screening program, by earlier diagnosis and thereby more curative treatment options.[23]

The increasing incidence and decreasing annual colorectal cancer mortality points towards an improvement in survival of colorectal cancer patients, which has been attributed previously to advancements in treatment.[24] Results from the present study show that formal oncological resection is still the cornerstone in the treatment of non-metastatic colorectal cancer, although the introduction of screening programs will increase the use of less invasive procedures such as polypectomies and local excisions.

Since the 1990's, the use of adjuvant systemic therapy is recommended for stage III colon cancer, and the administration has continued to increase during more recent time periods.[25-27] Considering stage II colon cancer, Dutch, European and American guidelines recommend the use of adjuvant chemotherapy only in high risk patients.[12, 28, 29] Unfortunately, it was not possible to select for high risk stage II in the NCR. However, a previous Dutch study found that only 16% of high-risk stage II patients received adjuvant chemotherapy in 2008-2012.[12] Compared with colon cancer, rectal cancer treatment changed significantly over recent decades. Since 2001, the total mesorectal excision (TME) technique became the standard for rectal cancer surgery in the Netherlands and contributed to improved survival.[7, 30] Simultaneously, preoperative radiotherapy and chemoradiotherapy were implemented in the treatment for stage II/III rectal cancer in the Netherlands, as demonstrated by the trends in this study.[7] The addition of neoadjuvant (chemo)radiotherapy has not demonstrated an overall survival benefit for the whole group of patients in randomized trials, although a more tailored application for high risk groups might impact survival based on subgroup analysis.[31-35] Whether neoadjuvant

chemoradiotherapy should be combined with adjuvant chemotherapy in stage II/III rectal cancer is a subject of controversy due to inconclusive evidence. The current Dutch guidelines discourage the use of adjuvant chemotherapy based on negative studies, but most guidelines in the US and many other countries do recommend its use.[36-38]

The findings for metastasized colorectal cancer show a continuation of the trends in treatment described previously in the Dutch population, with a shift from resection of the primary tumour alone to either chemotherapy alone or in combination with surgery of the primary tumour, and an increase of the use of metastasectomy.[14, 15, 24, 39, 40] However, there is still room for improvement since the proportion of patients undergoing a metastasectomy for liver only disease shows large institutional variation and is described to be around 20% in the Netherlands, which is comparable to data from Great-Britain and France.[14, 41, 42]

Despite the advancements in the treatment of colorectal cancer, the increase in 5-year survival in the more recent periods seems remarkable as there have been no major breakthroughs in treatment and most of the trends in treatment have leveled off, except for the use of metastasectomy. Besides developing treatment strategies, other mechanisms might play a role. Firstly, it is striking that the most obvious gain in survival between the different time periods in this study was made in the first year after diagnosis. This suggests a substantial improvement in the management of factors associated with short term mortality such as emergency surgery, advanced age, comorbidity, and postoperative complications, and by means of better pre- and postoperative care and dedicated surgery.[43, 44] Secondly, the improvements of diagnostic imaging tools may have led to stage migration due to detection of small metastases which would otherwise have been missed. This upstaging is reflected by a slight increase in the proportion of stage IV. These patients are also treated more often with curative intent by metastasectomy, which further improves the stage specific relative survival in stage IV.[15] Thirdly, neoadjuvant chemoradiotherapy in rectal cancer might have shifted stage specific outcome, since postoperative stage has been used in this study. Patients who respond well to neoadjuvant treatment have been downstaged, thereby deteriorating survival rates in the higher stages. However, these downstaged patients started out as clinically higher stages, with worse prognosis, thereby possibly also decreasing survival rates for the lower stages. The stagnation in survival improvement of stage III rectal cancer in 2010-2014 might be explained by this phenomenon. Lastly, the improvement in survival in the more recent years could also be caused by lead-time bias due to earlier diagnosis through various regional screening programs.[45-47] Despite up- or downstaging effects, survival of all stages combined still improved, showing that the increase of survival in our data is not only the result of stage migration. Even though there are persistent differences in relative survival of colorectal cancer across Europe, similar increases in relative survival were observed for both colon and rectal cancer across different regions.

Another interesting finding is that over time, rectal cancer survival has caught up with colon cancer survival and even surpassed the latter in the more recent periods of our study. This has previously been described, and our results show a progression of this trend.[24, 48] A smaller cohort study from Germany describes an equally good outcome for stage II/III colon and rectal cancer.[49] There are several possible explanations. Firstly, there has been more focus in the past decades on rectal cancer treatment than on colon cancer treatment. Colon cancer surgery has been considered to be of less complexity with a slower increase of specialization than for rectal cancer surgery. Secondly, the concept of complete mesocolic excision with optimal specimen quality has only been introduced decades after the introduction of TME.[50] Comorbidity is more frequent among colon cancer patients, and postoperative complications in colon cancer patients have a higher impact on mortality than in rectal cancer patients.[43, 51] This is especially important considering that colon cancer is more often treated in an emergency setting.[52] Lastly, rectal cancer patients have a tendency to be diagnosed at an earlier stage, perhaps due to complaints of rectal bleeding which is more commonly seen with distal tumours.[53, 54]

High quality, long-term nationwide population-based data was used for this study, making it possible to describe trends in recent years in the context of long-term trends. However, there are also some limitations to this study. Comorbidity, socioeconomic status and ethnicity were missing, which might have influenced survival in colorectal cancer patients. Also, we decided to use postoperative stage for our analyses, encountering a dilemma because treatment strategies are based on clinical stage, and downstaging may have occurred after preoperative treatment with (chemo)radiotherapy. However, postoperative staging is the gold standard and clinical staging using CT and MRI is notoriously unreliable, especially regarding lymph node staging, which was also reflected in our data by a large discrepancy between clinical and pathological stage.[55, 56]

In conclusion, this study showed an increase in incidence and an ongoing improvement in survival. This improvement in survival is a continuum, which is partly due to evolving cancer treatment, but presumably also to other factors in the organization of care for colorectal cancer patients, especially in more recent years. It is to be expected that this trend will continue in the coming years, also due to screening and further patient tailored treatment based on better insight into tumour heterogeneity.

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3

Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying

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ABSTRACT

Background

Worse prognosis in elderly colorectal cancer patients may be cancer or treatment related, but also due to death from other causes. This population-based study aimed to compare survival among non-metastatic colorectal cancer patients between age groups and notice time trends in mortality rates.

Methods

Primary stage I-III colorectal cancer patients who underwent resection between 2008-2013 were selected from the Netherlands Cancer Registry. Patients were grouped by age: <65, 65-74, 75-84 and ≥85 years. Overall survival, relative survival and conditional relative survival (condition of surviving 1 year), were calculated by age groups and tumour localization. Furthermore, relative excess risks of death, 30-day, 1-year mortality and 1-year excess mortality were calculated.

Results

52,296 patients were included. Differences in 5-year overall survival were observed between age groups (colon cancer: 82%, 73%, 56% and 35%; rectal cancer: 82%, 74%, 56% and 38%; $p<0.0001$). Age-related differences were less prominent in relative survival and disappeared in conditional relative survival. Thirty-day mortality rates decreased over time (colon cancer: 4.9% to 3.4%; rectal cancer: 3.0% to 1.7%); 1-year mortality rates decreased from 11.9% to 9.6% in colon cancer and from 8.0% to 6.4% in rectal cancer. One-year excess mortality increased with age (17.3% and 12.9% in patients with colon or rectal cancer aged ≥85 years).

Conclusion

One-year mortality rates remain high in elderly patients. However, age-related differences in survival disappeared after adjustment for expected death from other causes and first-year mortality. Beneficial time trends in 1-year mortality rates underline that survival in elderly after colorectal cancer surgery is modifiable.

INTRODUCTION

Nowadays more than 50% of colorectal cancer is being diagnosed in patients over 70 years of age.[1] The incidence of colorectal cancer among elderly people in the Dutch population will increase due to ageing of the population and the introduction of the Dutch colorectal cancer screening program. Also, there is still an increase in incidence in the general population.[2]

Surgery is the cornerstone treatment in stage I-III colorectal cancer patients. Compared to younger patients, in the elderly excess mortality after surgical interventions does not only occur in the first postoperative month but in the first postoperative year. A previous population-based study (period 1991-2005) showed an overall mortality of 20-23% in elderly patients (aged ≥75 years) within the first postoperative year after colorectal surgery. A significant excess mortality one year after surgical resection (16% for colon cancer and 13% for rectal cancer) was found in the oldest age groups.[3] After the first post-operative year, elderly colorectal cancer patients had similar relative survival compared to younger patients.

During the last decade several developments in peri-operative care have been made: surgical techniques have changed, i.e. the introduction of minimally invasive endoscopic surgery.[4-6] Also referral of patients to high-volume centers and differentiation of surgical areas has increased.[7, 8] Furthermore peri-operative care has been improved by introducing enhanced recovery programs, and for frail elderly patients a pre-operative comprehensive geriatric assessment (CGA) has been developed.[9]

The primary aim of this study was to evaluate population-based survival data for young (<65 years), aged (65-74 years), elderly (75-84 years) and the oldest old patients (≥85 years) with stage I-III colorectal cancer who underwent surgery in the period 2008-2013 in the Netherlands. To give insight in time-trends on colorectal cancer survival during the last decade, we compared these new data to previous population-based studies on survival of elderly after surgery for non-metastatic colorectal cancer.[3, 4]

PATIENTS AND METHODS

Data from the nationwide Netherlands Cancer Registry (NCR) were used, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR is a population-based registry based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR).

Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and

national level. Anatomical site of the tumour is registered according to the International Classification of Disease – Oncology (ICD-O).[10] The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[11]

Population-based data from the NCR in the Eindhoven area were used for a sub analysis to provide data on comorbidities for this study. This region records data on all patients newly diagnosed with cancer in the south-eastern part of the Netherlands, an area with 2.4 million inhabitants (~15% of the Dutch population) and no university hospitals. Comorbidities are registered according to a slightly modified version of the Charlson Comorbidity index.[12] Comorbid diseases were defined as life shortening diseases present at the time of colorectal cancer diagnosis.

Study population

All patients who underwent surgical resection for primary stage I-III colorectal cancer (C18-20) between 2008-2013 were included. Patients were excluded if they had an unknown stage of disease (n=633), if they were treated with local tumour destruction (polypectomy, transanal endoscopic microsurgery (TEM), transanal excision (TAE)) (n=2,855) or if date of resection was missing (n=46).

Stage was based on the pathological TNM classification; clinical information was used if pathology data were missing. Patients were stratified by tumour localization: colon (C18) and rectum (rectosigmoid and rectum, C19-C20). Patients were divided into age groups: <65, 65-74, 75-84 and ≥85 years. The oldest age category was based on the selection of the oldest old of the colorectal cancer patients while the other age categories were chosen to create equal distributions of patients between age groups. Primary treatment of colon cancer was classified as surgery, surgery with adjuvant chemotherapy or other. Rectal cancer treatments were classified as surgery, surgery with neoadjuvant radiotherapy, surgery with neoadjuvant chemoradiotherapy or other. Furthermore, detailed information was available on urgency of the resection (emergency resection <24h after presentation) for patients with colon cancer.

Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database (GBA). Follow-up was completed until January 1st, 2017.

Survival definitions

Survival was defined as the time from the date of resection to the date of death or last follow-up date (January 1st, 2017) for patients who were still alive.

Overall survival was defined for the different age groups as the probability of surviving from all causes of death.

Relative survival was calculated for the different age groups as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, gender and year) general population.[13] Relative survival is the preferred way to describe the prognosis of elderly cancer patients, as it takes into account the risk of dying from other causes than the disease of interest.
Conditional survival was defined for the different age groups as the relative survival among patients who survived the first year after surgical resection.

Statistical analyses

Differences in patient and tumour characteristics across the different age groups were evaluated using χ^2 tests after stratification by tumour localization.
Overall survival was calculated using the Kaplan-Meier method. Furthermore, relative survival and conditional relative survival were calculated using the Pohar Perme method.[14] Relative excess risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times, adjusting for gender, age, period of diagnosis, stage, treatment and emergency of resection (the latter only for colon cancer). Additionally, analyses for RER were repeated for the subgroup of patients adjusting for the number of comorbidities. Postoperative 30-day mortality and 1-year overall mortality were calculated as well as the 1-year excess mortality (observed - expected deaths / number of patients).
P values below 0.05 were considered statistically significant. Analysis was performed in STATA (version 13.0, Statcorp LP, College Station, TX).

RESULTS

Over the period 2008-2013, 57,558 patients were diagnosed with primary non-metastatic colorectal cancer, of whom 52,296 (91%) patients underwent surgical resection: 36,464 colon cancer patients and 15,832 rectal cancer patients. For rectal cancer, younger patients were more likely to undergo resection. The proportions undergoing resection in the age groups <65, 65-74, 75-84 and ≥85 years for colon cancer were 95%, 95%, 93% and 89% (p<0.0001), respectively, while for rectal cancer the proportions were 90%, 88%, 80% and 57% (p<0.0001).
Table 1 shows the distribution of patient and tumour characteristics of patients who underwent surgical resection for colorectal cancer by age groups and tumour localization. Mean age for colon cancer patients was 71 (standard deviation 11.1) years and 41% was ≥75 years of age. For rectal cancer patients the mean age was 67 (standard deviation 11.0) years and 27% was ≥75 years of age. A higher proportion of female patients was found in the oldest old age groups, especially in colon cancer patients. For colon cancer, undergoing

TABLE 1 Patient and tumour characteristics of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013 according to age (n=52,296).

	<65 years		65-74 years		75-84 years		≥85 years		
	n	(%)	n	(%)	n	(%)	n	(%)	*p* value
COLON CANCER									
Total	9,847	(27)	11,607	(32)	11,775	(32)	3,235	(9)	
Gender									<0.0001
Male	5,263	(53)	6,393	(55)	5,813	(49)	1,265	(39)	
Female	4,584	(47)	5,214	(45)	5,962	(51)	1,970	(61)	
Period of diagnosis									<0.0001
2008-2009	3,293	(33)	3,555	(31)	3,770	(32)	1,088	(33)	
2010-2011	3,311	(34)	3,853	(33)	3,993	(34)	1,122	(35)	
2012-2013	3,243	(33)	4,199	(36)	4,012	(34)	1,025	(32)	
Stage									<0.0001
Stage I	1,887	(19)	2,599	(22)	2,482	(21)	533	(16)	
Stage II	3,831	(39)	4,758	(41)	5,399	(46)	1,610	(50)	
Stage III	4,129	(42)	4,250	(37)	3,894	(33)	1,092	(34)	
Treatment									<0.0001
Surgery only	5,369	(55)	7,836	(67)	10,396	(88)	3,213	(99)	
Surgery + adjuvant CT	4,366	(44)	3,665	(32)	1,313	(11)	15	(1)	
Other‡	112	(1)	106	(1)	66	(1)	7	(1)	
Emergency resection *									<0.0001
Emergent	849	(9)	783	(7)	794	(7)	347	(11)	
Elective	8,830	(91)	10,660	(93)	10,842	(93)	2,836	(89)	
Surgical procedure **									<0.0001
Open resection	6,063	(62)	7,351	(64)	8,160	(70)	2,455	(76)	
Laparoscopic resection	3,687	(38)	4,166	(36)	3,534	(30)	757	(24)	
Number of comorbidities ***									<0.0001
0	690	(49)	416	(24)	261	(15)	51	(13)	
1	393	(28)	487	(28)	390	(390)	97	(24)	
≥2	331	(23)	812	(48)	1,044	(62)	253	(63)	
RECTAL CANCER									
Total	6,209	(39)	5,385	(34)	3,612	(23)	626	(4)	
Gender									<0.0001
Male	3,851	(62)	3,537	(66)	2,109	(58)	298	(47)	
Female	2,385	(38)	1,848	(34)	1,503	(42)	328	(53)	
Period of diagnosis									<0.0001
2008-2009	2,099	(33)	1,700	(31)	1,204	(33)	232	(37)	
2010-2011	2,106	(34)	1,822	(34)	1,186	(33)	227	(36)	
2012-2013	2,004	(33)	1,863	(35)	1,222	(34)	167	(27)	

TABLE 1 Patient and tumour characteristics of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013 according to age (n=52,296). *(Continued)*

	<65 years	65-74 years	75-84 years	≥85 years	
	n (%)	n (%)	n (%)	n (%)	*p* value
Stage					<0.0001
Stage I	1,015 (16)	1,046 (19)	735 (20)	131 (21)	
Stage II	1,417 (23)	1,397 (26)	1,157 (32)	225 (36)	
Stage III	3,777 (61)	2,942 (55)	1,720 (48)	270 (43)	
Treatment					<0.0001
Surgery only	590 (10)	759 (14)	888 (25)	293 (47)	
Surgery + neoadjuvant RT	2,593 (42)	2,518 (47)	2,026 (56)	314 (50)	
Surgery + neoadjuvant CTRT	2,725 (43)	1,892 (35)	630 (17)	19 (3)	
Other‡	301 (5)	216 (4)	68 (2)	0 (0)	
Surgical procedure **					<0.0001
Open resection	3,632 (59)	3,327 (62)	2,305 (64)	438 (70)	
Laparoscopic resection	2,490 (41)	1,987 (38)	1,276 (36)	184 (30)	
Number of comorbidities ***					<0.0001
0	486 (57)	256 (32)	100 (19)	7 (11)	
1	231 (27)	268 (33)	153 (28)	17 (24)	
≥2	147 (16)	273 (35)	287 (53)	45 (65)	

CT chemotherapy, RT radiotherapy, CTRT chemoradiotherapy

* Included in the analysis but results not shown emergency resection unknown (n=168).

** Included in the analysis but results not shown surgical approach unknown (n=484).

*** Included stage I-III colorectal cancer patients diagnosed in the south-eastern part of the Netherlands and who underwent surgical resection (n=7,495).

‡ other (colon cancer): surgery with adjuvant radiotherapy, chemotherapy followed by radiotherapy or surgery with neoadjuvant chemotherapy; other (rectal cancer): surgery with adjuvant chemotherapy.

an emergency resection was associated with age; patients in the youngest and oldest age groups had slightly higher proportions emergency resections (p<0.0001). Furthermore, for both colon and rectal cancer, stage differed significantly, especially an increase in stage II and a decrease in stage III patients appeared with increasing age. Furthermore, a higher proportion of patients underwent open resection in the older age groups. The use of adjuvant chemotherapy in colon cancer patients and neoadjuvant chemoradiotherapy in rectal cancer patients decreased with advancing age groups. In the subgroup of patients of the Eindhoven area, the number of comorbid diseases increased with age.

Survival

Median follow-up time for patients included was 60 months. Survival curves for overall survival (Figure 1), relative survival (Figure 2) and conditional relative survival (Figure 3) are shown according to the different age groups <65, 65-74, 75-84 and ≥85 years. For colon cancer patients, the crude observed 5-year overall survival rates were 82%, 73%, 56% and 35% (p<0.0001), respectively; for rectal cancer patients the crude observed 5-year overall survival rates were 82%, 74%, 56% and 38% (p<0.0001). Differences in survival between the age groups were less prominent in relative survival. However, advanced age still reduced relative survival. For colon cancer, the 5-year relative survival rates were 85%, 81%, 75% and 75%, respectively; for rectal cancer the 5-year relative survival rates were 84%, 82%, 75% and 81%. The age-related differences disappeared in conditional relative survival. For colon cancer, 5-year conditional relative survival rates were 86%, 85%, 87% and 101%, among the age groups <65, 65-74, 75-84 and ≥85 years respectively; for rectal cancer the 5-year conditional relative survival rates were 84%, 83%, 84% and 109%. Five-year conditional relative survival rates among patients in the oldest old age group exceeded 100% for both colon and rectal cancer patients, indicating a higher survival rate than the general population.

For colon cancer, analyses were repeated excluding patients who underwent emergency resection (n=2,767). Higher 5-year survival rates for overall survival, relative survival and conditional relative survival among patients who underwent elective surgical resection were observed, compared to the overall study population. Furthermore, age-related differences on survival did not change. Marginal differences in 5-year relative survival rates were found and the differences disappeared when patients survived the first year after resection (data not shown).

Relative excess risks of death

Table 2 shows RER of death for relative and conditional relative survival by age groups. An increased RER of death was observed in the elderly as compared to younger patients for colon and rectal cancer. When RER was calculated for patients who survived the first year after surgical resection, differences in RER disappeared for all age groups for colon and rectal cancer. When analyses were repeated with the older age groups taken together as one group, similar results were found for colon cancer (RER conditional relative survival ≥75 versus <65 years 1.0 (0.88-1.14)) and rectal cancer (RER conditional relative survival ≥75 versus <65 years 1.4 (0.94-1.48)).

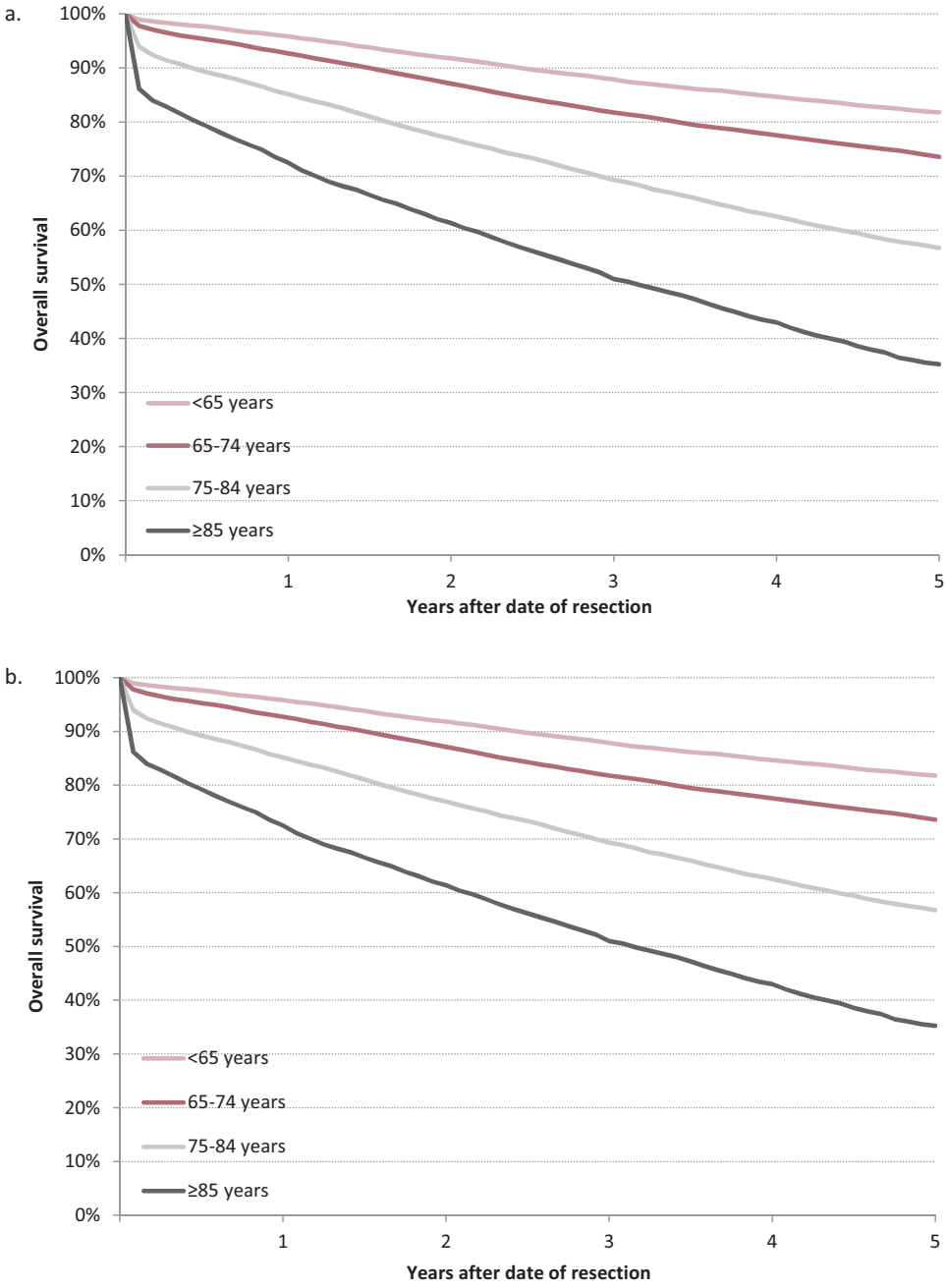

FIGURE 1 Overall survival according to age of patients who underwent surgical resection for stage I-III colon (a) or rectal (b) cancer (n=52,296).

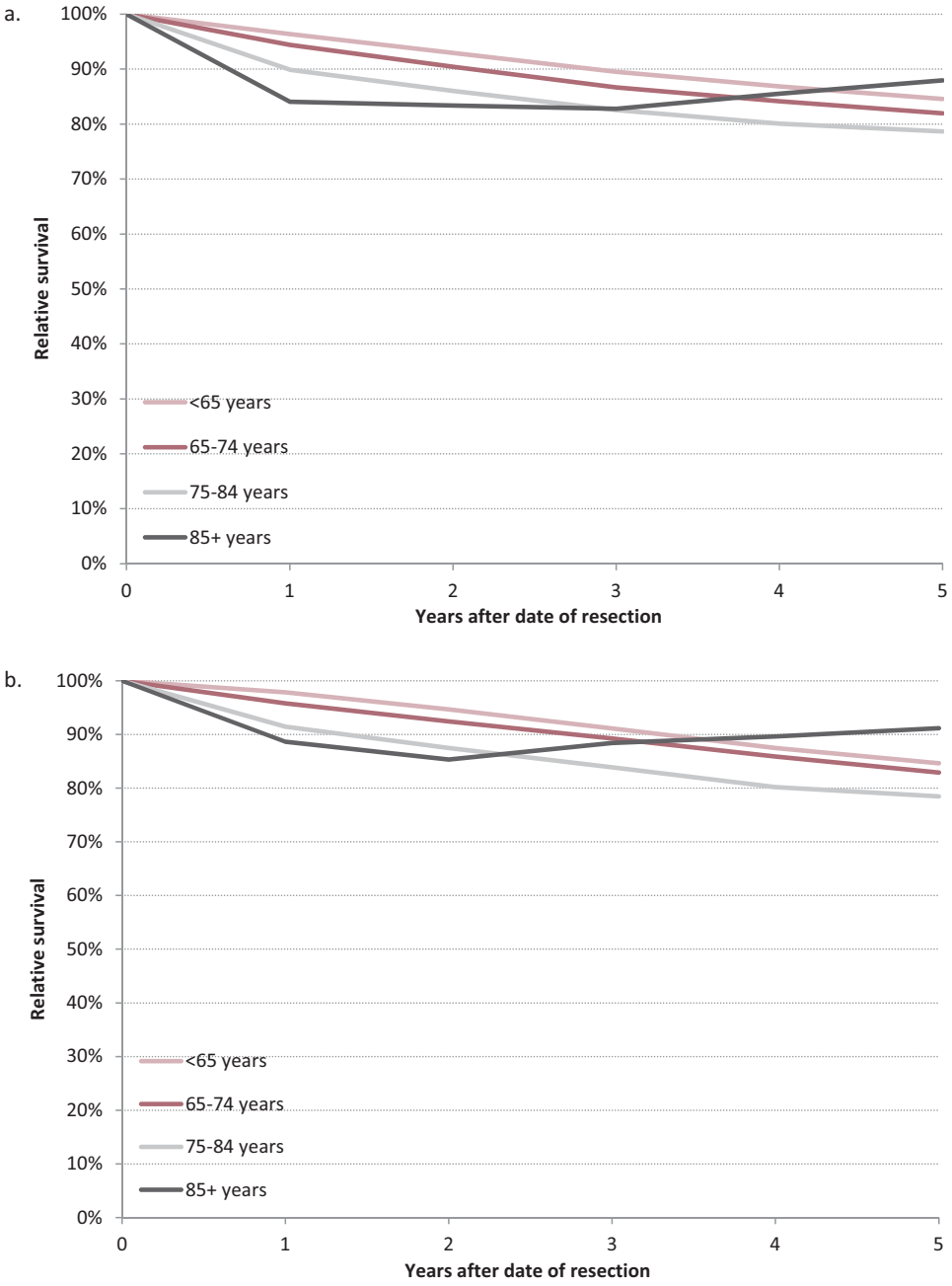

FIGURE 2 Relative survival according to age of patients who underwent surgical resection for stage I-III colon (a) or rectal (b) cancer (n=52,296).

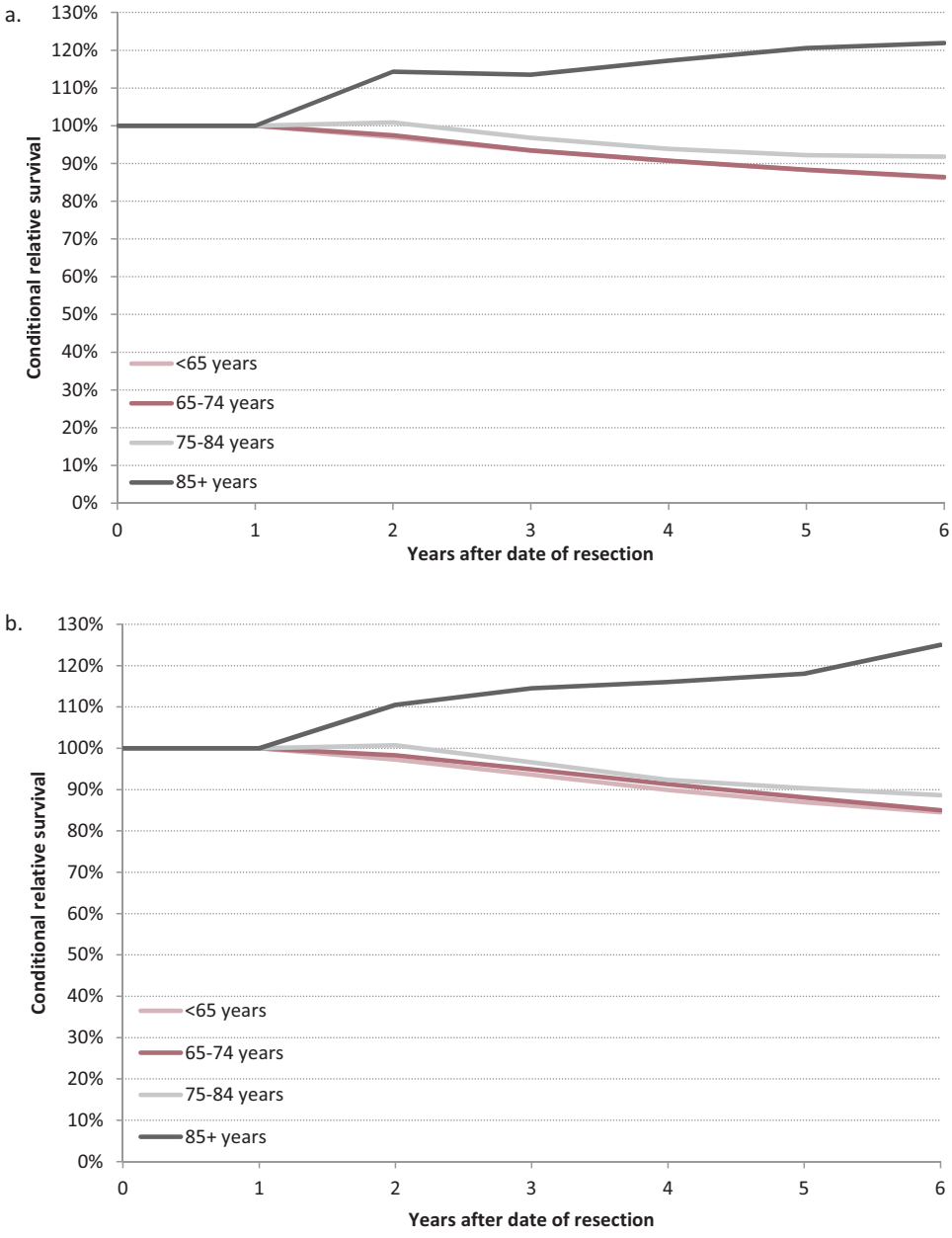

FIGURE 3 Conditional survival according to age of patients who underwent surgical resection for stage I-III colon (a) or rectal cancer (b) (n=47,293).

TABLE 2 Relative excess risks of death (RER) for relative and conditional relative survival of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013 according to age (n=52,296).

	RS	95% CI	CRS	95% CI
COLON CANCER				
<65 years	reference		reference	
65-74 years	1.2	1.13-1.32	1.1	1.00-1.21
75-84 years	1.7	1.56-1.83	1.1	0.95-1.20
≥85 years	2.1	1.80-2.38	1.1	0.98-1.76
RECTAL CANCER				
<65 years	reference		reference	
65-74 years	1.2	1.03-1.29	1.0	0.96-1.25
75-84 years	1.7	1.50-1.94	1.1	0.99-1.79
≥85 years	2.1	1.24-3.65	1.1	0.46-1.96

RS relative survival, CRS conditional relative survival, CI confidence interval
[2] Adjusted for gender, period of diagnosis, stage, treatment, surgical approach and emergency of resection (the latter for colon cancer only).

TABLE 3 Relative excess risks of death (RER) for relative and conditional relative survival of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013, in the south-eastern part of the Netherlands, according to age (n=7,495).

	RS	95% CI	CRS	95% CI
COLON CANCER				
<65 years	reference		reference	
65-74 years	1.1	0.86-1.33	1.0	0.77-1.30
75-84 years	1.1	0.88-1.41	0.9	0.69-1.28
≥85 years	1.2	0.84-1.67	0.6	0.29-1.22
RECTAL CANCER				
<65 years	reference		reference	
65-74 years	1.2	0.89-1.66	1.0	0.65-1.38
75-84 years	2.1	1.54-2.95	1.8	0.97-2.64
≥85 years	4.5	2.52-7.90	1.6	0.42-5.88

RS relative survival, CRS conditional relative survival, CI confidence interval
[2] Adjusted for gender, period of diagnosis, stage, treatment, number of comorbidities, surgical approach and emergency of resection (the latter for colon cancer only).

As a subanalysis, analyses were repeated including patients of the Eindhoven area including information on the presence of comorbid diseases (n=7,495). As shown in Table 3, age-related differences in RER for relative survival and conditional relative survival disappeared after adjustment for the number of comorbidities among patients with colon

cancer. For rectal cancer, an increased risk of death remained in the older age groups with a more pronounced association in the oldest old age group (RER relative survival 75-84 versus <65 years 2.1 (1.54-2.95) and RER relative survival ≥85 versus <65 years 4.5 (2.52-7.90)). RER conditional relative survival did not differ between age groups.

Excess mortality

Table 4 shows risk factors for overall postoperative 30-day and 1-year mortality, and 1-year excess mortality by tumour localization. Postoperative 1-year mortality rates doubled or tripled compared to postoperative 30-day mortality rates (colon cancer: 10.7% versus 4.2%; rectal cancer: 7.1% versus 2.3%). For both colon and rectal cancer patients, age and tumour stage were significant factors for postoperative 30-day and 1-year mortality (p<0.0001 for all variables) (Table 4). Additionally, increased 30-day and 1-year mortality were observed when colon cancer patients underwent an emergency resection, when colorectal cancer patients underwent open resection or when comorbidities were present at time of diagnosis (p<0.0001 for all variables). Furthermore, 30-day and 1-year mortality rates decreased over the period of diagnosis 2008-2009, 2010-2011 and 2012-2013. For colon cancer patients, the postoperative 30-day mortality rates were 4.9%, 4.2% and 3.4% and the 1-year mortality rates were 11.9%, 10.5% and 9.6% respectively, while for rectal cancer patients the proportions of postoperative 30-day mortality were 3.0%, 2.3% and 1.7% and the 1-year mortality rates were 8.0%, 7.0% and 6.4%.

The difference between observed and expected deaths (excess mortality) one year after surgical resection was highest in the older age groups, in patients with stage III colorectal cancer tumours and when patients underwent open resection for both colon and rectal cancer. Moreover, colon cancer patients undergoing emergency resection had high excess mortality. Subanalysis showed that patients with two or more concomitant diseases present at diagnosis had highest excess mortality.

As a subanalysis, analyses were repeated with the older age groups taken together as one group (≥75 years). For colon cancer patients, the postoperative 30-day mortality and 1-year mortality rates in this age group were 7.7% and 17.6%, respectively, while for rectal cancer patients the postoperative mortality rates were 5.5% and 14.8%. The proportions of excess mortality one year after surgical resection in this age group were 11.9% for colon cancer patients and 9.5% for rectal cancer patients.

TABLE 4 Overall 30-day mortality, 1-year mortality and excess mortality rates of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013 according to age (n=52,296).

		Postoperative mortality (%)				Excess mortality (%)
	n	<30 days	*p* value	1st year	*p* value	1st year
COLON CANCER						
Overall	36,464	4.2		10.7		
Gender			0.054		0.084	
Male	18,734	4.4		10.9		7.7
Female	17,730	3.9		10.3		7.7
Age			<0.0001		<0.0001	
<65 years	9,847	1.0		4.1		3.6
65-74 years	11,607	2.2		7.2		5.7
75-84 years	11,775	6.0		14.8		10.5
≥ 85 years	3,235	13.8		27.3		17.3
Stage			<0.0001		<0.0001	
Stage I	7,501	3.3		6.7		3.8
Stage II	15,598	4.3		9.5		6.3
Stage III	13,365	4.4		14.1		11.5
Emergency resection †			<0.0001		<0.0001	
Emergent	2,773	11.9		23.2		20.7
Elective	33,168	3.5		9.6		6.5
Surgical approach			<0.0001		<0.0001	
Open resection	24,029	5.4		13.3		10.2
Laparoscopic resection	12,144	1.8		5.5		2.8
Number of comorbidities			<0.0001		<0.0001	
0	1,418	1.8		4.9		3.0
1	1,367	2.8		7.0		4.3
≥2	2,440	5.7		14.8		11.3
RECTAL CANCER						
Overall	15,832	2.3		7.1		
Gender			<0.0001		<0.0001	
Male	9,795	2.8		7.8		5.5
Female	6,037	1.7		5.8		3.9
Age			<0.0001		<0.0001	
<65 years	6,209	0.6		2.7		2.2
65-74 years	5,385	1.8		6.0		4.4
75-84 years	3,612	4.7		13.2		8.9
≥ 85 years	626	10.1		23.1		12.9

TABLE 4 Overall 30-day mortality, 1-year mortality and excess mortality rates of patients who underwent surgical resection for stage I-III colon or rectal cancer diagnosed in the period 2008-2013 according to age (n=52,296). *(Continued)*

		Postoperative mortality (%)				Excess mortality (%)
	n	<30 days	*p* value	1st year	*p* value	1st year
Stage			<0.0001		<0.0001	
Stage I	2,927	2.4		5.3		2.9
Stage II	4,196	2.8		8.0		5.5
Stage III	8,709	2.1		7.4		5.4
Surgical approach			<0.0001		<0.0001	
Open resection	9,702	3.0		8.4		6.1
Laparoscopic resection	5,937	1.4		5.0		2.9
Number of comorbidities			<0.0001		<0.0001	
0	849	0.7		4.1		2.7
1	669	1.7		5.6		3.6
≥2	752	5.2		14.0		11.1

n/a not analyzed
* Included in the analysis but results not shown emergency resection unknown (n=168).
** Included in the analysis but results not shown surgical approach unknown (n=484).
*** Included stage I-III colorectal cancer patients diagnosed in the south-eastern part of the Netherland and who underwent surgical resection (n=7,495).

DISCUSSION

In this nationwide population-based study, we analyzed survival differences of patients with non-metastatic colorectal cancer between different age groups. It considers overall-, relative- and conditional relative survival. We found that the substantial age-related differences in survival rates present in overall survival, were less prominent in 5-year relative survival and disappeared in 5-year conditional relative survival among the different age groups.

Postoperative 1-year mortality rates (10.7% for colon cancer and 7.1% for rectal cancer) were doubled to tripled compared to postoperative 30-day mortality (4.2% for colon cancer and 2.3% for rectal cancer). Postoperative mortality was higher with increasing age; after one year, almost a quarter (27.3% for colon cancer and 23.1% for rectal cancer) of the patients in the oldest age group had died. Thus, there is a substantial high mortality rate during the first postoperative year and surgery has a prolonged impact on survival. These findings are in accordance with previous studies.[3, 15-18]

In a previous Dutch population-based study by Dekker et al., postoperative 1-year mortality rates were higher compared to our study for both colon as well as rectal cancer patients aged 75 years and older (colon cancer: 23.2% versus 17.6%, and rectal cancer:

20.1% versus 14.8%). The former study may be regarded as a population-based cohort in a previous decade and allows us to study transitions in time. Thirty-day mortality rates in patients aged 75 years or older were more or less comparable between the studies (colon cancer: 7.7% versus 7.5%, and rectal cancer: 5.5% versus 3.7%).[3] Unfortunately, data on emergency resection were not available in the study of Dekker et al. We cannot rule out that emergency procedures not only have a direct effect on mortality but also have a prominent, more delayed impact on mortality. The decrease in postoperative 1-year mortality over the years may reflect a period effect due to changes in selection, surgical techniques or peri- and postoperative care in elderly patients. Laparoscopic techniques are now widely implemented. Several meta-analyses or randomized clinical trials (RCT's) on postoperative mortality comparing open versus laparoscopic techniques showed a non-significant trend in favor of laparoscopic surgery.[19, 20] Recently, Gietelink et al. showed in a large population-based study that especially in elderly and frail patients laparoscopic resection reduced the risk of postoperative 30-day mortality by reducing cardiopulmonary postoperative complications.[21] The excess of deaths within 1-year probably reflects the complex interaction between major surgery, comorbidities, physiologic reserve-capacity and resilience of elderly patients, even after eliminating the malignant disease. It has been shown that, with increasing age, not only mortality but also postoperative morbidity increases.[4, 22] This may induce a delayed and indirect effect on mortality unrolling yet in several months after surgery.

We found higher rates of excess mortality in the first postoperative year among older patients, patients with stage III colorectal cancer, patients with comorbidities and patients whom underwent an emergency resection. These findings are comparable with previous studies, in which significant risk factors for 1-year mortality were identified: comorbidities, stage III colorectal cancer, emergency resection, postoperative surgical complications, and a prolonged postoperative hospital stay.[23-27] Furthermore, a study by Morris et al. showed that in colorectal cancer patients diagnosed in England, Sweden or Norway, the excess mortality was most evident within the first 3 moths after diagnosis and for the oldest patients.[28]

overall survival is defined as the probability of surviving from all causes of death and therefore may overestimate the impact of cancer on survival. Therefore, relative survival is used to adjust for mortality due to other causes than cancer. Results of this study showed that crude 5-year relative survival for patients aged 75 years and older was worse than for patients younger than 75 years. In our study, crude conditional relative survival in the oldest old patients (≥85 years) remained above 100% once patients survived the first postoperative year. This effect probably reflects the selection of the fittest or most resilient in this age group by colorectal cancer surgery and its recovery process.

In line with previous studies [3, 23], adjusted RERs for conditional relative survival did not differ along the age-groups, indicating that differences between survival rates are determined by mortality in the first postoperative year. Since postoperative complications are a more probable cause for early mortality, one can conclude that colorectal cancer itself is not the main cause of the age-related differences in survival.[29] Moreover, other studies found no differences in long-term cancer-specific survival between different age groups among patients with colorectal cancer.[30, 31]

In a subanalysis including colon cancer patients diagnosed in the Eindhoven area, adjusted RERs for relative survival revealed a different impact of the presence of comorbidities on colon and rectal cancer survival in the older age groups (≥75 years). In elderly colon cancer patients (≥75 years) differences in RERs for relative survival disappeared after adjustment for the number of comorbidities; however, in rectal cancer patients age-related differences in relative survival remained. Although resection rates in patients with rectal cancer were lower compared to patients with colon cancer. Apparently, the interaction between cancer stage, surgical interventions and comorbidities is more life threatening in rectal cancer. A major impact of the surgical procedure itself or an increase in complication rate induced by combining surgery and radiotherapy in rectal cancer may be underlying. A previous Dutch population-based study supports the latter explanation.[32]

The results of this study should be interpreted with consideration of certain limitations. Previous studies identified postoperative complications as risk factors for death during the first postoperative year.[17, 23] Unfortunately, data on postoperative complications were not available in the nationwide cancer registry. Also, in patients with rectal cancer a shift towards other surgical procedures may occur, especially in the very old, i.e. Hartmann's procedure. This might affect the incidence of postoperative complication and mortality as clinicians assume a lesser risk for complications with this procedure. Furthermore, our population-based study using data of the NCR limits comparisons, either direct between subgroups/characteristics within the study population or indirect with historical population-based data. Especially risk of selection bias and omitting of relevant parameters may occur. For instance data on frailty or dependency of patients are lacking in the registry. Both are not covered by information on the presence of comorbidities at cancer diagnosis, and are associated with complications and postoperative mortality.[33] The main strength of this study is that information on emergency resection and comorbidities is present in our dataset, making it possible to take these variables into account in multivariable analyses. We found that differences in RER for relative survival disappeared after adjustment for the number of comorbidities present at time of diagnosis. We showed that emergency resection and the presence of comorbidities not only had a prominent impact on postoperative 1-year mortality and 1-year excess mortality, but also accounted for the survival differences observed between age groups. Furthermore, we used a large dataset

including more than 50,000 colorectal cancer patients, of which almost 4,000 patients were 85 years or older. To the best of our knowledge, our study included one of the largest cohorts of patients aged 85 years and older described in literature.

Results of this study showed that mortality, especially within the first year after surgery remains high in patients aged ≥75 years. Comparison with a historical cohort showed similar 30-day mortality rates but an improvement over time in mortality rates within 1 year after colorectal cancer surgery. Age-related differences in survival disappeared after adjustment for expected death from other causes and first-year mortality. This suggests that surgery has a greater and prolonged impact on survival postoperatively in elderly. Although our study cannot determine which factors determined this improvement, it underlines survival in elderly after major surgery is modifiable.

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PART II

DETERMINANTS OF SURVIVAL

4

Treatment and outcome of synchronous colorectal carcinomas: a nationwide study

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Annals of Surgical Oncology 2017; 25(2):414-421

ABSTRACT

Background

Synchronous colorectal carcinomas occur in 1- 8% of patients diagnosed with colorectal cancer. This study evaluated treatment patterns and patient outcomes in synchronous colorectal cancer compared with solitary colorectal cancer patients.

Patients and methods

All patients diagnosed with primary colorectal cancer between 2008 and 2013, who underwent elective surgery, were selected from the Netherlands Cancer Registry. Using multivariable regressions, the effects of synchronous colorectal cancer were assessed for both short-term outcomes (prolonged postoperative hospital admission, anastomic leakage, postoperative 30-day mortality, administration of neoadjuvant or adjuvant treatment) and 5-year relative survival.

Results

Out of 41,060 colorectal cancer patients, 1,969 patients (5%) had synchronous colorectal cancer. Patients with synchronous colorectal cancer were older (mean age 71 ±10.6 years versus 69 ±11.4 years), more often male (61% versus 54%), and diagnosed with more advanced tumour stage (stage III-IV 54% versus 49%) compared with solitary colorectal cancer (all p<0.0001). In 50% of the synchronous colorectal cancers, an extended surgery was conducted (n=934). Synchronous colorectal cancers with at least one stage II-III rectal tumour less likely received neoadjuvant (chemo)radiotherapy (78% versus 86%; adjusted OR 0.6(0.48-0.84)) and synchronous colorectal cancers with at least one stage III colon tumour less likely received adjuvant chemotherapy (49% versus 63%; adjusted OR (0.7(0.55-0.89)). Synchronous colorectal cancers were independently associated with decreased survival (RS 77% versus 71%; adjusted RER 1.1(1.01-1.23)).

Conclusion

The incidence of synchronous colorectal cancers in the Dutch population is 5%. Synchronous colorectal cancers were associated with decreased survival compared with solitary colorectal cancer. The results emphasize the importance identifying synchronous tumours, preferably before surgery to provide optimal treatment.

INTRODUCTION

In the western world, colorectal cancer is the third and second most common cancer among men and women, and it is the second and third most common cause of cancer death.[1] Patients with primary colorectal cancer can have more than one lesion at the time of initial presentation.[2] Previous studies report a frequency of synchronous colorectal cancers varying from 1 to 8%.[2-7] Part of this variation can be explained by differences in definitions, selection criteria, patient populations and time periods studied. Risk factors for developing synchronous colorectal cancers are largely unknown, although familial polyposis and ulcerative colitis with dysplasia have been suggested to influence synchronous colorectal cancer development.[8, 9]

For stage I-III colorectal cancer patients, surgery of the primary treatment is the cornerstone of curative treatment. Neoadjuvant (chemo)radiotherapy is recommended in Dutch and American treatment guidelines for patients with stage II-III rectal cancer, whereas adjuvant chemotherapy is recommended for patients with stage III colon cancer.[10, 11]

A preoperative diagnosis of synchronous colorectal cancers may modify the type of surgical procedure and influence clinical decision making on the use of additional treatments. Moreover, synchronous colorectal cancers more often may require extended surgery and, if overlooked, may be diagnosed as early metachronous cancers, possibly at a more advanced stage.

Conflicting evidence exists about whether synchronous colorectal cancers have the same prognosis in survival as solitary colorectal cancer patients.[2, 6, 12, 13] Many clinical series were based on single centre numbers and the analysis of less than 50 patients.[4, 5, 14] The objectives of this study were to investigate, in depth, the various clinicopathological features of synchronous colorectal cancer patients compared with solitary colorectal cancer patients, and its association with treatment patterns, short-term postoperative outcomes, and long-term survival.

PATIENTS AND METHODS

Data source

Data from the nationwide population-based Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organisation (IKNL), were used. Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and national level.

Anatomical site of the tumour is registered according to the International Classification of Disease–Oncology (ICD-O).[15] The TNM (tumour-node-metastasis) classification is used

for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[16] Furthermore, detailed information was available on: emergency resection (<24h after presentation) and anastomotic leakage as a surgical complication. Anastomotic leakage was recorded as such if a surgical intervention or readmission was necessary within 2 months after primary anastomosis. Data on prolonged postoperative hospital admission (>14 days; yes/no) were available for patients diagnosed in 2012-2013. Prolonged postoperative hospital admission after surgery served as a proxy for a complicated postoperative period.

Definition of synchronous colorectal cancer

A slightly modified version of the Warren and Gates criteria were used to define multiple colorectal cancer.[17] Synchronous colorectal cancer was defined as two or more invasive tumours that are diagnosed simultaneously or within six months. Multiple independent tumours in the same segment of the colon and rectum are regarded as different malignancies and are counted as two or more primary cancers. For every synchronous colorectal cancer patient, the most extensive tumour according to TNM stage was designated as the index tumour in the analyses. When synchronous colorectal cancer patients were diagnosed with at least one of the lesions as stage IV, all tumours were classified as stage IV.

Study population

All patients diagnosed with primary colorectal cancer between 2008 and 2013 were included (Figure 1). Patients for whom tumour stage was unknown (n=2,379), who were not treated by resection (n=9,017), who underwent local tumour treatments (e.g., TEM, polypectomy; n=1,904) or who underwent emergency resection (n=2,709) were excluded. Synchronous colorectal cancer patients were excluded from the analyses if the dates of resection differed for the tumours (n=130).

Patients were categorized into two groups accordingly: solitary or synchronous colorectal cancer. Patients were divided into age groups: <65, 65-74, 75-84 and ≥85 years. Disease stage was based on the pathological TNM classification. Tumour localization was categorized into anatomical subsites: colon ascendens (C18.0-18.2); colon transversum (C18.3-18.5); colon descendens (C18.6-18.7); unknown or overlapping subsites of the colon (C18.8-18.9); and rectum (C19-20).

Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database (GBA). Follow-up was completed until January 1st, 2017.

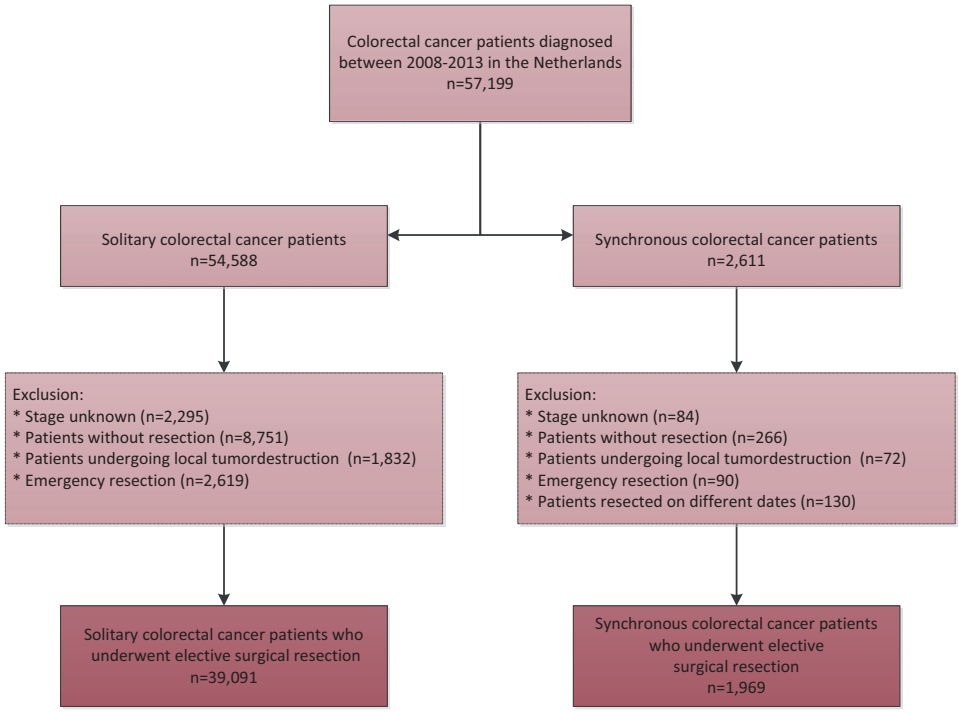

FIGURE 1 Overview of patients included in the study.

Statistical analyses

Differences in patient and tumour characteristics were evaluated using χ^2. A priori outcomes of interest were type of surgical procedure, prolonged postoperative hospital admission, anastomic leakage, postoperative 30-day mortality, and administration of neoadjuvant or adjuvant treatment and were analyzed between synchronous and solitary colorectal cancer patients using univariable (χ^2 tests) and multivariable analyses (logistic regression models).

Survival was defined as the time from the date of resection to death or last follow-up date for patients who were still alive. Relative survival was defined as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, gender, and year) general population. Relative survival was calculated using the Pohar Perme method.[18] Relative excess risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times, adjusting for age, gender, period of diagnosis, stage (most advanced tumour in synchronous colorectal cancer), location of tumour (most advanced tumour in synchronous colorectal cancer), type of surgical procedure, and (neo)adjuvant treatment.

P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) and STATA (version 13.0, Statcorp LP, College Station, TX) were used for all analyses.

RESULTS

From 2008 to 2013, 41,060 patients were diagnosed with primary colorectal cancer and underwent elective surgery. Of these, 1,969 (4.8%) patients met the definition for synchronous colorectal cancer. Patient and tumour characteristics are presented in Table 1. Synchronous colorectal cancer patients were slightly older (mean age 71 ±10.6 years versus 69 ±11.4 years), more often male, and diagnosed with more advanced tumour stage (stage III-IV) compared with solitary colorectal cancer patients (all p<0.0001).

TABLE 1 Patient and tumour characteristics of patients with solitary or synchronous colorectal cancer (n=41,060).

	Solitary CRC		Synchronous CRC				
			2 sCRC		>2 sCRC		
	n	(%)	n	(%)	n	(%)	*p* value
Total	39,091		1,865		104		
Gender							<0.0001*
Male	20,945	(54)	1,132	(61)	65	(63)	
Female	18,146	(46)	733	(39)	39	(37)	
Age							<0.0001*
<65 years	13,284	(34)	430	(23)	26	(25)	
65-74 years	12,576	(32)	632	(34)	33	(32)	
75-84 years	10,599	(27)	656	(35)	38	(36)	
≥85 years	2,632	(7)	147	(8)	7	(7)	
Stage (index tumour in sCRC)							<0.0001*
I	6,659	(17)	263	(14)	18	(17)	
II	12,689	(33)	593	(32)	33	(32)	
III	14,629	(37)	752	(40)	37	(36)	
IV	5,114	(13)	257	(14)	16	(15)	
Location of tumour (index tumour in sCRC)							<0.0001*
Colon ascendens	10,333	(26)	499	(27)	35	(33)	
Colon transversum	4,642	(12)	291	(15)	23	(22)	
Colon descendens	11,151	(29)	571	(31)	27	(28)	
NOS/other	452	(1)	93	(5)	0	(0)	
Rectum	12,313	(32)	411	(22)	19	(17)	

* *p*<0.05 between solitary and synchronous CRC
sCRC synchronous colorectal cancer

Patients with two synchronous colorectal cancers

Of the synchronous colorectal cancer patients, the majority (n=1,865, 95%) had two tumours. Table 2 gives an overview of the anatomical and stage distribution of the first and second tumour of patients with two synchronous colorectal cancers.

TABLE 2 Stage (a) and anatomical (b) distribution of first and second tumours in patients with two synchronous colorectal cancers (n=1,865).

a. Stage first and second tumour	n	(%)
III-III	451	(24)
II-II	360	(19)
I-I	253	(14)
IV-IV	241	(13)
I-II	223	(12)
I-III	172	(9)
II-III	110	(6)
Other *	55	(3)
b. Tumour location first and second tumour	**n**	**(%)**
Colon descendens-Colon descendens	353	(19)
Colon ascendens-Colon ascendens	253	(13)
Rectum-Colon descendens	236	(13)
Rectum-Rectum	193	(10)
Colon descendens-Colon ascendens	171	(9)
Colon transversum-Colon ascendens	136	(7)
Colon descendens-Colon transversum	129	(7)
Colon transversum-Colon transversum	123	(7)
Rectum-Colon ascendens	108	(6)
Rectum-Colon transversum	57	(3)
Other**	106	(6)

* Other = Stage I/II/III/IV tumour in combination with an unknown tumour stage
** Other = Unknown or overlapping subsites of the colon (C18.8-18.9) in combination with other segments of the colon or rectum

Most of the synchronous colorectal cancer patients were diagnosed with at least one stage III/IV tumour (n=1,009, 54%). Of these patients, 451 (43%, 24% of total) were diagnosed with two stage III tumours and 241 (23%, 13% of total) were diagnosed with two stage IV tumours.

Half of the synchronous tumours were located in similar segments of the large bowel (n=922, 50%). In 1,222 (66%) patients, both tumours were localized in the colon, of which 729 (60%; 39% of total) were in one colon segment. In 193 (10%) patients, both tumours were situated in the rectum.

Figure 2 shows the type of surgical procedures for the different anatomical sites in patients with two synchronous colorectal cancers compared with solitary colorectal cancer patients. As expected, (sub)total (proto)colectomy was most often performed if synchronous tumours were located in different segments of the colon. Extended surgery (e.g., (sub)total colectomy, protocolectomy or combined resections) was performed in 50% (n=934) of the patients with two synchronous colorectal cancers compared with 2% (n=577) in solitary colorectal cancer (p<0.0001).

TABLE 3 Crude percentages and adjusted odds ratios* for treatment variables and short-term postoperative outcomes among patients with solitary or synchronous colorectal cancer (n=41,060).

				Multivariable analysis	
Variable	**Total n**	**Crude (%)**	***p* value**	**OR***	**95% CI**
a. Neoadjuvant (chemo)radiation [1]					
Solitary CRC	9,286	85.9	<0.0001*	reference	
Synchronous CRC	327	78.0		0.6	0.48-0.84
b. Surgical approach (laparoscopic versus open resection) [2]					
Solitary CRC	33,678	45.4	<0.0001*	reference	
Synchronous CRC	1,644	34.9		0.9	0.83-1.06
c. Surgical approach (laparoscopic converted to open resection versus laparoscopic resection) [3]					
Solitary CRC	15,282	16.7	<0.0001*	reference	
Synchronous CRC	574	22.7		1.0	0.81-1.31
d. Prolonged postoperative hospital stay (>14 days) [4]					
Solitary CRC	11,858	16.7	<0.0001*	reference	
Synchronous CRC	679	23.0		1.2	0.92-1.45
e. Anastomotic leakage [5]					
Solitary CRC	31,001	4.9	0.48	reference	
Synchronous CRC	2,397	5.3		0.9	0.74-1.13
f. Postoperative mortality [6]					
Solitary CRC	34,531	4.7	0.42	reference	
Synchronous CRC	1,142	5.3		0.7	0.54-1.01
g. Adjuvant chemotherapy [7]					
Solitary CRC	8,260	63.1	<0.0001*	reference	
Synchronous CRC	564	48.6		0.7	0.54-0.87

OR Odds Ratio; CI Confidence Interval; sCRC synchronous CRC

* p<0.05 between solitary and synchronous CRC

*Adjusted for gender, age, stage (index tumour in sCRC), location of tumour (index tumour in sCRC) and type of surgical procedure.

[1]Included patients with stage II-III rectal cancer (n=9,613); [2]Included patients with stage I-III CRC who underwent laparoscopic or open resection (n=35,322); [3]Included patients with stage I-III CRC who underwent laparoscopic resection or laparoscopic converted to open resection (n=15,856); [4]Included patients diagnosed in 2012-2013 (n=12,537); [5]Included patients who underwent surgical resection with primary anastomosis (n=33,398); [6]Included patients with stage I-III CRC who underwent surgical resection (n=35,673); [7]Included patients with stage III colon cancer (n=8,824).

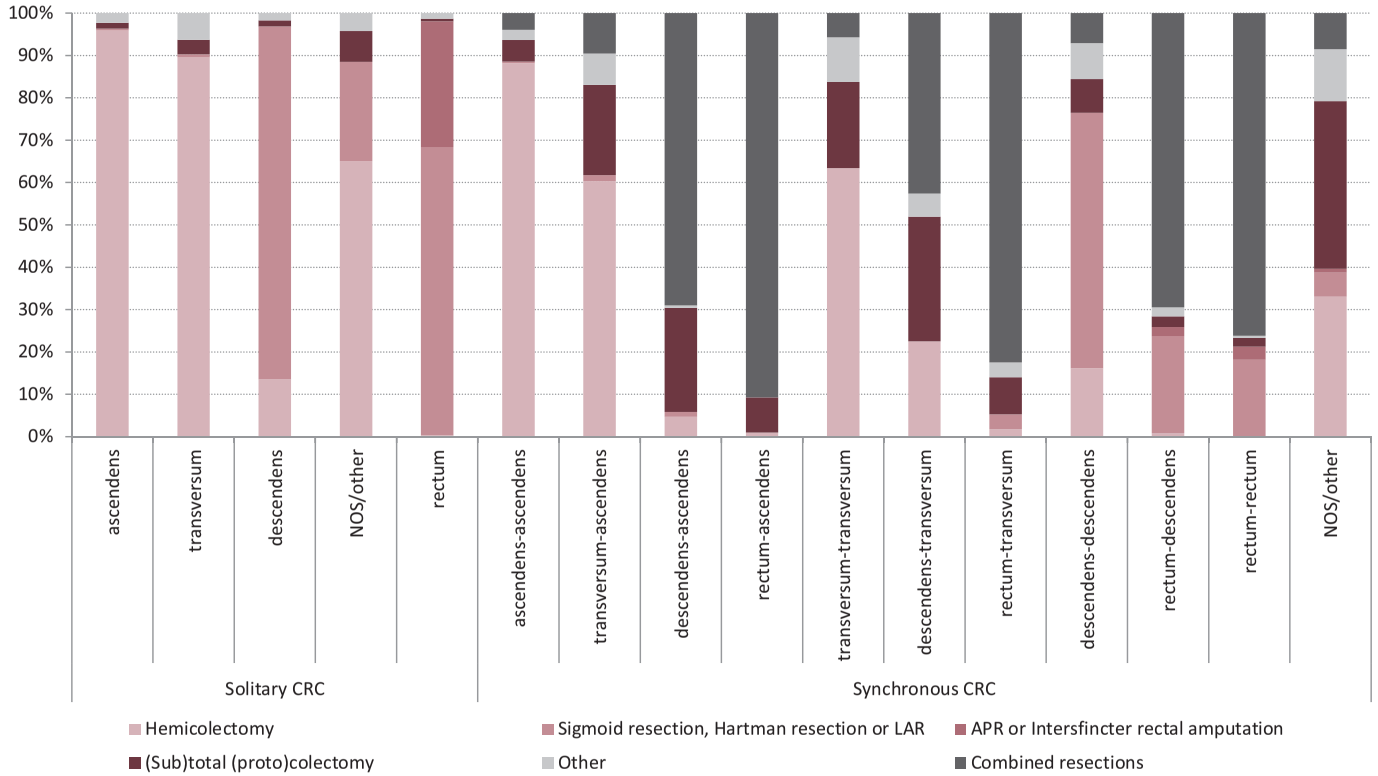

FIGURE 2 Type of surgical resection for the different anatomical sites of solitary (n=39,091) or 2 synchronous colorectal cancer (n=1,865).

LAR = Low anterior resection; APR = abdominal perineal resection; Other = resection not specified; Combined resections = when two synchronous tumours were removed using two different type of surgical procedures.

Treatment variables and short-term outcomes

Table 3 presents observed proportions and adjusted odds ratios (OR) of surgical approach, prolonged postoperative hospital stay, presence of anastomotic leakage, postoperative mortality and administration of neoadjuvant or adjuvant treatment among solitary and synchronous colorectal cancer.

Synchronous colorectal cancer patients with at least one stage II-III rectal tumour (index tumour) were less likely to receive neoadjuvant treatment compared with solitary colorectal cancer patients (Table 3a). Of the synchronous colorectal cancer patients receiving neoadjuvant treatment, the majority (n=185, 57%) was diagnosed with stage III rectal tumour as index tumour. In 88 patients (49%) with stage III rectal tumour as index tumour, both tumours were situated in the rectum. Of these patients, 45 patients (52%) were treated with neoadjuvant radiotherapy, and 42 patients (48%) received neoadjuvant chemoradiotherapy. In 97 patients (51%) with stage III rectal tumour as index tumour, one tumour was located in the rectum and the other tumour was located in a colon segment. Of these patients, the majority (n=56, 61%) was treated with neoadjuvant radiotherapy, whereas 41 patients (39%) received neoadjuvant chemoradiotherapy. The administration of adjuvant chemotherapy was lower in synchronous colorectal cancer patients with at least one stage III colon tumour (index tumour), even after case-mix adjustment (Table 3f).

Survival

Median follow-up time for patients included was 60 months. For solitary colorectal cancer patients the 5-year relative survival rate was 77% (Supplementary Figure 1a), while the proportion of 5-year relative survival for synchronous colorectal cancer patients was 71% (Supplementary Figure 1b).

After case-mix adjustment, synchronous colorectal cancers were associated with an increased RER of death (adjusted RER synchronous versus solitary colorectal cancer 1.1 (1.01-1.23)). In addition, after stratification by tumour stage, the association between increased risk of death and having more than one colorectal tumour remained in patients with stage I-III synchronous colorectal cancer (stage I RER 1.1 (95%CI 1.01-1.58), stage II RER 1.2 (1.03-1.38), stage III RER 1.2 (1.03-1.20), stage IV RER 1.1 (0.89-1.17)).

DISCUSSION

In this nationwide population-based study, synchronous colorectal cancer was prevalent in 5% of patients with colorectal cancer. We evaluated treatment patterns, short-term patient outcomes and 5-year relative survival in synchronous and solitary colorectal cancer patients. We found a decreased use of neoadjuvant and adjuvant treatment in

synchronous colorectal cancer patients. Furthermore, synchronous colorectal cancers were independently associated with a decrease in survival.

Definitions of synchronous colorectal cancer tend to differ in the literature. The prevalence of synchronous colorectal cancer ranged from approximately 1% to 8%.[2-7] Synchronous and metachronous cancers often were mixed together in previous studies.[4, 8, 19-23] Synchronous colorectal cancer is generally defined as two or more distinct colorectal tumours diagnosed within 6 months after initial diagnosis.[2, 5, 6, 8, 22-25] In other studies, colorectal cancers diagnosed within a year of the initial diagnosis were classified as synchronous, and in others, those diagnosed simultaneously at time of surgery.[6, 7, 26, 27] We considered patients with two or more invasive colorectal cancers, diagnosed simultaneously or within 6 months, as synchronous colorectal cancer.

In the present study, 61% of the synchronous colorectal cancer patients were male, compared with 54% of the solitary colorectal cancer patients. Most other studies also reported that synchronous colorectal cancer were more frequent in men than women.[2, 5-7] However, some studies showed no association between gender and the presence of synchronous colorectal cancers.[23, 26] It is unclear whether the male predominance reflects an increased risk factor to develop synchronous colorectal cancer or a greater exposure of men to environmental risk factors associated with synchronous colorectal cancer. Furthermore, we found that synchronous colorectal cancer patients were older and diagnosed with more advanced tumour stage compared with solitary colorectal cancer. These findings are comparable with other studies.[5-7, 26]

In 50% of the synchronous colorectal cancer patients, tumours were located in similar segments of the large bowel. In line with previous Dutch studies of Van Leersum et al. and Mulder et al., we found that synchronous colorectal cancer patients were more likely to undergo extended surgery.[6, 7] We found that patients with synchronous tumours that were located in different segments of the large bowel, mostly required (sub)total (proto) colectomy or extended surgery. One could expect that when tumours were located in the same or adjacent segment, the choice for surgery will be simple, either a hemicolectomy or an extended hemicolectomy with the adjacent segment. However, if, for instance, one tumour is located in the right colon while the other tumour is simultaneously located in the rectum, either a (sub)total (proto)colectomy can be performed, or two separate resections with two anastomoses can be performed. The latter can result in a higher risk of anastomotic leakage. We found no associations between having synchronous colorectal cancer and the presence of anastomotic leakage.

Remarkably, in this study, synchronous colorectal cancer patients with at least one stage II-III rectal tumour less often received neoadjuvant (chemo)radiotherapy compared with those with solitary rectal tumours. At the same time, patients with a stage III rectal tumour as index tumour, who were eligible for neoadjuvant chemoradiotherapy, and a tumour

situated in a colon segment, more often received neoadjuvant radiotherapy compared to synchronous colorectal cancer patients in which both tumours were located in the rectum (61% versus 52%). It is possible that patients with a stage III rectal tumour as index tumour and a tumour located in the colon were less often treated with neoadjuvant chemoradiotherapy to avoid the postponement of surgery and treatment of the colon tumour.

Synchronous colorectal cancer patients with at least one stage III colon tumour were associated with a lower probability of receiving adjuvant chemotherapy compared with solitary colon tumours. We do not have an obvious explanation for this finding, and no data are available from previous studies. One might expect that synchronous colorectal cancer patients may be highly susceptible to adjuvant therapy. The proportion of solitary colorectal cancer patients who were treated with adjuvant chemotherapy was 63% compared with 49% in synchronous colorectal cancer patients. The relatively low utilization of adjuvant chemotherapy overall in the Netherlands could be carried over and be amplified in patients with synchronous colorectal cancer. Explanations could be that synchronous colorectal cancer patients were in worse general health or had more surgical complications of the extended surgery, although a prolonged hospital stay was not observed.

Five-year survival for synchronous colorectal cancer patients was worse than for solitary colorectal cancer patients (76% versus 69%). Conflicting results have been reported regarding long-term prognosis of synchronous colorectal cancer patients. The majority of the studies showed no difference in survival rates between synchronous and solitary colorectal cancer.[2, 6, 12, 13, 28, 29] Some studies reported worse survival for synchronous colorectal cancer. [26, 30, 31] A previous Dutch study of Liu et al. showed that overall survival of patients with one colon cancer was significantly better than those with two, irrespective of lag-time between the two colon cancers.[32] Poor prognosis of synchronous colorectal cancer is thought to be caused by the relatively frequent distant metastasis that occur in synchronous colorectal cancer patients.[26]

The main strength of this study is the use of a large dataset including approximately 2000 synchronous colorectal cancer patients. We believe that this is the largest cohort published on this subject. Moreover, the objectives of this study were to investigate, in depth, the effects of synchronous colorectal cancer on choice of treatment and short- and long-term patients' outcomes. Clinical implications in terms of treatment and prognosis of synchronous colorectal cancer patients were seldom analyzed in large cohorts.[4, 5, 8, 23, 24]

Some limitations of this study should be acknowledged. The main limitation is the lack of data on the presence of inherited syndromes (Lynch, FAP, HNPCC). These inherited syndromes are known to be predisposing conditions for synchronous colorectal cancer.[5] Although the NCR collects a huge variety of potential case-mix factors, we cannot

exclude that other factors, such as functional status, patient preferences, and specific postoperative complications other than anastomotic leakage, may have influenced our results as well.

Information on differences in patient and treatment outcomes between solitary and synchronous colorectal cancer on a national level is relevant, because a preoperative diagnosis of synchronous colorectal cancers may modify or extend the type of surgical procedure and influence clinical decision making of the use of additional treatments. It is important to identify the presence of synchronous tumours, preferably before surgery, to provide an optimal treatment. Preoperative total colonoscopy should be performed, if possible, in all patients with colorectal cancer to detect synchronous tumours. Moreover, results of this study showed that synchronous colorectal cancers are an independent determinant of survival, indicating the relevance of this variable in case-mix adjustment models.

In conclusion, we showed that synchronous colorectal cancer occurred in 5% of patients with colorectal cancer. Synchronous colorectal cancer patients were associated with extended surgery, less (neo)adjuvant treatment, and a decrease in survival compared with solitary colorectal cancer.

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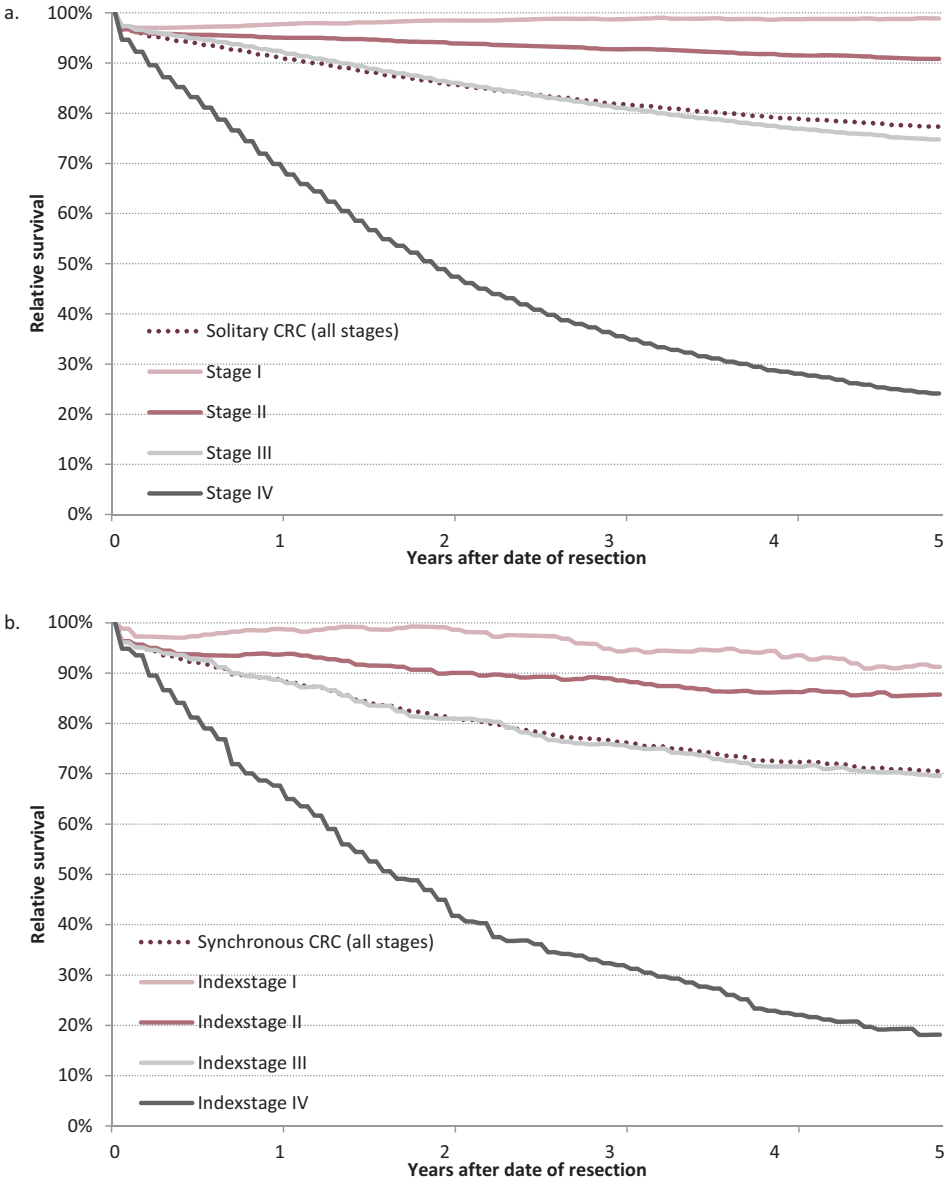
SUPPLEMENTARY FIGURES



SUPPLEMENTARY FIGURE 1 Five-year relative survival for patients with solitary (n=39,091) (a) or synchronous colorectal cancer (n=1,969) (b) stratified by tumour stage (index tumour in sCRC).

5

No difference in overall survival between hospital volumes for colorectal cancer patients in the Netherlands

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Diseases of the Colon and Rectum 2016; 59(10):943-952

ABSTRACT

Background

High-volume hospitals have been associated with improved patient outcomes for tumours with a relatively low incidence that require complex surgeries, such as oesophageal and pancreatic cancer. The volume-outcome association for colorectal cancer is under debate.

Objective

This study investigates whether hospital volume for colorectal cancer is associated with surgical care characteristics and 5-year overall survival.

Design

This is a population-based study.

Settings

Data were gathered from the Netherlands Cancer Registry. Hospitals were grouped by volume for colon (<50; 50-74; 75-99 and ≥100 resections/year) and rectum (<20; 20-39 and ≥40 resections/year).

Patients

All patients with primary non-metastatic colorectal cancer who underwent resection between 2005-2012 were included.

Main outcome measures

Differences in surgical approach, anastomotic leakage and postoperative 30-day mortality between hospital volumes were analyzed using χ^2 tests and multivariable logistic regression analyses. Cox proportional hazard models were used to investigate the effect of hospital volume on overall survival.

Results

This study included 61,394 colorectal cancer patients. In 2012, 31 of the 91 hospitals performed less than 50 colon cancer resections/year and 21 of the 90 hospitals performed less than 20 rectal cancer resections/year. No differences in anastomotic leakage between hospital volumes were observed. Only small differences between hospital volumes were revealed for conversion of laparoscopic to open resection (OR <50 versus ≥100 resections/year 1.25 (95%CI 1.06-1.46) and postoperative 30-day mortality (colon: OR <50 versus ≥100 resections/year 1.17 (1.02-1.35); rectum: OR <20 versus ≥40 resections/year 1.42 (1.09-1.84)). No differences in overall survival were found between hospital volumes.

Limitations

Although we adjusted for several patient and tumour characteristics, data on surgeon volume, data regarding local recurrences, specific postoperative complications other than anastomotic leakage and on comorbidity were not available.

Conclusion

In the Netherlands, no differences in 5-year survival were revealed between hospital volumes for non-metastatic colorectal cancer patients.

INTRODUCTION

In the last decade, there has been an increasing interest in improving quality of cancer care and the need for reliable parameters thereof. Differences in hospital volume and its relation with patient outcomes have been studied extensively in the ongoing debate of centralization of surgical care.[1-3] Especially in tumours with a relatively low incidence that require complex surgeries, such as oesophageal and pancreatic cancer, patients have better short- and long-term outcomes when operated in high-volume hospitals.[4-9]

In 2011 the Dutch Society for Surgery established a minimum volume norm of 50 colorectal cancer resections/year per hospital. Additionally, for rectal cancer a minimum volume norm of 20 resections/year per hospital is required.[10] For colorectal cancer patients, the volume-outcome association is under debate.

A Cochrane review from 2012 showed that 5-year overall survival was higher for colorectal cancer patients treated in high-volume hospitals. For rectal cancer patients only, 5-year overall survival but not postoperative mortality was higher in high-volume hospitals. The quality of the evidence was regarded low in this review, and evidence was based on studies with a large heterogeneity in volume definitions.[11]

Since it is still not clear to what extent hospital volume differences between hospitals lead to differences in short- and long-term patient outcomes, we aimed to investigate whether hospital volume determines surgical care characteristics, postoperative 30-day mortality and long-term survival in colorectal cancer patients in the Netherlands.

Based on previous literature, we hypothesize that high-volume hospitals are not associated with better overall survival rates. Furthermore, we hypothesize there is no association between surgical care characteristics (e.g. presence of anastomotic leakage and postoperative 30-day mortality) and hospital volumes.

METHODS

Data source

Data from the nationwide population-based Netherlands Cancer Registry (NCR) were used, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and national level. Anatomical site of the tumour is registered according to the International Classification of Disease–Oncology (ICD-O).[12] The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[13]

Study population

All patients who underwent surgical resection for primary stage I-III colorectal cancer (C18-20) between 2005-2012 were included. Data for the evaluation of surgical care (e.g. surgical approach, emergency resection and anastomotic leakage) were available in the NCR since 2008, therefore we limited our selection for these analyses to patients who underwent surgical resection in 2009-2012. Patients who underwent surgical resection without primary anastomosis were excluded from the analyses regarding anastomotic leakage (n=2,981).

Disease stage was based on the pathological TNM classification. Patients were stratified by tumour localization: colon (C18) and rectum (rectosigmoid and rectum, C19-20). Tumour localization was categorized into anatomical subsites: proximal colon (C18.0-18.3); transverse colon and splenic flexure (C18.4-18.5); distal colon (C18.6-1.87); unknown or overlapping subsites of the colon (C18.8-18.9); rectosigmoid (C19.9); and rectum (C20.9). Surgical care characteristics were recorded for the following categories: surgical approach (laparoscopic resection versus intent for laparoscopic but conversion to open resection versus open resection); presence of an anastomotic leakage and postoperative 30-day mortality. Anastomotic leakage was only recorded as such if a surgical intervention or readmission was necessary within two months after primary anastomosis.

Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database (GBA). Follow-up was completed until January 1st, 2015.

Hospital volumes

After stratification by tumour localization, the number of resections/year per hospital over the period 2005-2012 were calculated. Hospitals were divided per year into separate categories for colon and rectal cancer, based on their annual hospital volume. Hospital volume for colon cancer was divided into four categories: <50; 50-74; 75-99 and ≥100 resections/year. Hospital volume for rectal cancer was divided into three categories: <20; 20-39 and ≥40 resections/year. The lowest category for colon cancer was based on the Dutch minimum volume norm for colorectal cancer, since there were no minimum requirements available for colon cancer separately. The lowest category for rectal cancer was based on the Dutch minimum volume norm for rectal cancer. The higher categories for both colon and rectal cancer were chosen to create equal distribution of patients between hospital volume categories.

All hospitals in the Netherlands were included. Hospitals that merged in the period 2005-2012 were counted as separate until the date of the merge and as one after the merge or the subsequent year if this was during the year.

Statistical analyses

Differences in patient and tumour characteristics, observed proportions of anastomotic leakage and postoperative 30-day mortality between hospital volumes were calculated using χ^2 tests after stratification by tumour localization. Additionally, for patients with a tumour located in the colon, differences in surgical approach between hospital volumes were analyzed using the same methods. Multivariable logistic regression models were used to determine adjusted odds ratios (OR) for surgical approach, presence of anastomotic leakage and postoperative 30-day mortality adjusting for gender, age, T stage, N stage, differentiation grade, tumour location and neoadjuvant treatment (the latter for rectal cancer only).

Crude 1-, 3- and 5-year overall survival was calculated using the Kaplan-Meier method and differences in overall survival outcomes were assessed with the log-rank test. Overall survival was also determined using Cox proportional hazard models. Patients who survived the first 30 days after the date of resection were included in the survival analyses. Follow-up time was defined as the time between 30 days after resection and either date of death or last follow-up date for patients who were still alive. Patient and tumour characteristics influencing survival were included as covariates in the model to discriminate independent risk factors for death.

P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

Results

Over the period 2005-2012, 61,496 patients underwent surgical resection for primary non-metastatic colorectal cancer: 41,015 colon cancer patients and 20,481 rectal cancer patients. Table 1 presents the number of hospitals per hospital volume per year, showing a decreasing trend in low-volume hospitals. Figure 1 shows the annual average hospital volume, per hospital, in the period 2005-2012, combined with the annual minimum and maximum (range) hospital volume, per hospital, for colon (a) and rectal (b) cancer.

TABLE 1 Total number of hospitals per annual hospital volume of colon and rectal cancer in 2005-2012 (n=61,496).

Hospital volume/year	2005		2006		2007		2008		2009		2010		2011		2012	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
COLON CANCER																
Less than 50	65	(68)	54	(57)	54	(57)	47	(50)	46	(50)	37	(41)	35	(38)	31	(34)
50-74	18	(19)	29	(31)	25	(27)	31	(33)	22	(24)	27	(30)	22	(24)	26	(29)
75-99	10	(11)	10	(11)	13	(14)	12	(13)	18	(20)	14	(15)	17	(19)	15	(16)
100 or more	2	(2)	1	(1)	2	(2)	4	(4)	6	(6)	13	(14)	17	(19)	19	(21)
Total hospitals performing colon cancer resections	95		94		94		94		92		91		91		91	
RECTAL CANCER																
Less than 20	43	(45)	38	(40)	32	(34)	35	(38)	29	(32)	28	(31)	24	(27)	21	(23)
20-39	37	(39)	38	(40)	44	(47)	43	(47)	47	(51)	45	(49)	44	(49)	46	(51)
40 or more	15	(16)	18	(20)	18	(19)	14	(15)	16	(17)	18	(20)	22	(24)	23	(26)
Total hospitals performing rectal cancer resections	95		94		94		92		92		91		90		90	

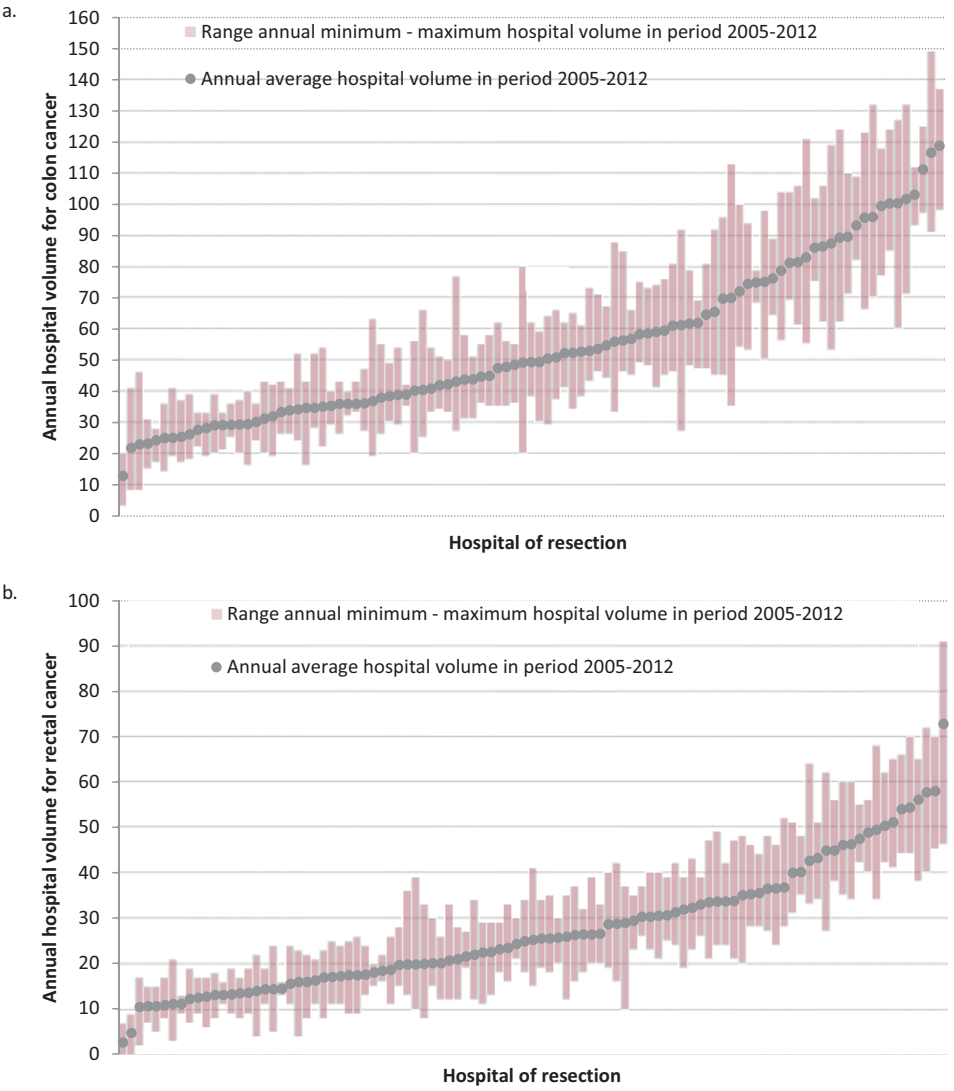

FIGURE 1 The annual average hospital volume, per hospital, in the period 2005–2012, combined with the annual minimum and maximum (range) hospital volume, per hospital, for colon cancer (a) and rectal cancer (b) (n = 61,496).

Table 2 shows the distribution of patient and tumour characteristics of the patients who underwent surgical resection for colorectal cancer by hospital volume and tumour localization. Statistically significant differences were found between hospital volumes for colon as well as rectal cancer with regard to age, period of resection, T stage, N stage and differentiation grade.

TABLE 2 Patient and tumour characteristics of patients who underwent surgical resection for colon or rectal cancer (n=61,496).

	Hospital volume/year								*p* value
	<50/yr		50-74/yr		75-99/yr		≥100/yr		
	n	(%)	n	(%)	n	(%)	n	(%)	
COLON CANCER									
Total	8,279	(20)	11,645	(29)	8,663	(21)	12,428	(30)	
Gender									0.59
Male	4,269	(51)	5,908	(51)	4,403	(51)	6,296	(51)	
Female	4,010	(49)	5,737	(49)	4,260	(49)	6,132	(49)	
Age									0.001*
< 60 years	1,425	(17)	1,937	(17)	1,399	(16)	1,895	(15)	
60-69 years	2,213	(27)	3,076	(26)	2,215	(26)	3,283	(26)	
70-79 years	2,750	(33)	4,029	(35)	2,975	(34)	4,416	(36)	
≥ 80 years	1,891	(23)	2,603	(22)	2,074	(24)	2,834	(23)	
Period of resection									<0.0001*
2005-2006	2,674	(33)	2,723	(23)	1,934	(23)	1,248	(10)	
2007-2008	2,204	(26)	3,171	(27)	1,993	(23)	2,133	(17)	
2009-2010	1,942	(23)	2,835	(25)	2,340	(26)	3,656	(30)	
2011-2012	1,459	(18)	2,916	(25)	2,396	(28)	5,391	(43)	
T stage									0.010*
T1	598	(7)	873	(8)	601	(7)	903	(7)	
T2	1,329	(16)	1,864	(16)	1,377	(16)	1,907	(15)	
T3	5,192	(63)	7,257	(62)	5,604	(65)	7,629	(64)	
T4	1,160	(14)	1,651	(16)	1,081	(12)	1,689	(14)	
N stage									0.018*
N0	5,206	(63)	7,471	(64)	5,681	(65)	7,896	(64)	
N1	2,012	(24)	2,789	(24)	2,018	(23)	3,093	(25)	
N2	1,061	(13)	1,385	(12)	1,027	(12)	1,439	(11)	
Differentiation grade									<0.0001*
Well/moderated	6,218	(75)	8,699	(75)	6,574	(76)	9,310	(75)	
Poor/undifferentiated	1,235	(15)	1,932	(16)	1,376	(16)	1,902	(15)	
Unknown	826	(10)	1,014	(9)	713	(8)	1,216	(10)	
Tumour location									0.79
Colon ascendens	3,187	(38)	4,401	(38)	3,284	(38)	4,819	(39)	
Colon transversum	1,513	(18)	2,162	(18)	1,599	(18)	2,200	(17)	
Colon descendens	3,446	(42)	4,878	(42)	3,633	(42)	5,197	(42)	
Colon NOS/other	133	(2)	204	(2)	147	(2)	212	(2)	

TABLE 2 Patient and tumour characteristics of patients who underwent surgical resection for colon or rectal cancer (n=61,496). *(Continued)*

	Hospital volume/year			*p* value
	<20/yr	20-39/yr	≥40/yr	
	n (%)	n (%)	n (%)	
RECTAL CANCER				
Total	2,545 (13)	8,830 (43)	9,106 (44)	
Gender				0.73
Male	1,525 (60)	5,366 (61)	5,503 (60)	
Female	1,020 (40)	3,464 (39)	3,603 (40)	
Age				0.027*
< 60 years	627 (24)	2,148 (14)	2,174 (24)	
60-69 years	781 (31)	2,764 (32)	2,991 (32)	
70-79 years	757 (30)	2,734 (31)	2,788 (31)	
≥ 80 years	380 (15)	1,184 (13)	1,153 (13)	
Period of resection				<0.0001*
2005-2006	782 (31)	2,072 (23)	1,772 (20)	
2007-2008	626 (25)	2,245 (25)	2,176 (24)	
2009-2010	611 (24)	2,295 (27)	2,252 (24)	
2011-2012	526 (20)	2,218 (25)	2,906 (32)	
T stage				0.0001*
T1	241 (9)	886 (10)	1,067 (12)	
T2	872 (34)	2,939 (34)	2,935 (32)	
T3	1,332 (52)	4,553 (51)	4,623 (51)	
T4	100 (4)	452 (5)	481 (5)	
N stage				0.045*
N0	1,649 (65)	5,896 (67)	6,184 (68)	
N1	603 (24)	1,955 (22)	1,972 (22)	
N2	293 (11)	979 (11)	950 (10)	
Tumour location				<0.0001*
Rectosigmoid	405 (16)	1,270 (14)	1,101 (12)	
Rectum	2,140 (84)	7,560 (86)	8,005 (88)	

* $p<0.05$ between hospital volume categories

Surgical approach in colon cancer patients

Table 3a presents observed proportions and adjusted odds ratios of laparoscopic resection by hospital volume. The distribution of surgical approach differed between hospital volumes ($p<0.0001$). Moreover, among patients initially treated laparoscopically, a higher proportion of patients underwent conversion from laparoscopic to open resection in low-volume hospitals compared to high-volume hospitals ($p=0.011$) (Table 3b).

TABLE 3 Crude percentages and adjusted odds ratios[2] for laparoscopic resection (a) and conversion from laparoscopic to open resection (b) among colon cancer patients; anastomotic leakage (c) and postoperative 30-day mortality (d) among colon and rectal cancer patients.

				Multivariable analysis	
		Crude (%)	*p* value	OR[2]	95% CI
a.	Laparoscopic resection[a]				
	COLON CANCER		<0.001*		
	<50/yr	42.2		1.04	0.96-1.13
	50-74/yr	43.4		1.10	1.03-1.18
	75-99/yr	38.2		0.88	0.82-0.95
	≥100/yr	40.8		reference	
b.	Conversion from laparoscopic to open resection[b]				
	COLON CANCER		0.020*		
	<50/yr	20.2		1.25	1.06-1.46
	50-74/yr	19.4		1.20	1.05-1.37
	75-99/yr	18.5		1.14	0.98-1.33
	≥100/yr	16.9		reference	
c.	Anastomotic leakage[c]				
	COLON CANCER		0.81		
	<50/yr	8.2		0.95	0.81-1.10
	50-74/yr	8.4		0.99	0.88-1.13
	75-99/yr	8.4		0.97	0.85-1.11
	≥100/yr	8.6		reference	
	RECTAL CANCER		0.97		
	<20/yr	13.2		1.03	0.79-1.34
	20-39/yr	13.2		0.97	0.83-1.15
	≥40/yr	13.4		reference	
d.	Postoperative mortality[d]				
	COLON CANCER		0.029*		
	<50/yr	4.4		1.17	1.02-1.35
	50-74/yr	4.7		1.24	1.09-1.41
	75-99/yr	4.3		1.10	0.96-1.27
	≥100/yr	3.9		reference	
	RECTAL CANCER		0.007*		
	<20/yr	3.4		1.42	1.09-1.84
	20-39/yr	2.6		1.12	0.92-1.36
	≥40/yr	2.3		reference	

OR Odds ratio, CI Confidence interval

[2] Adjusted for gender, age, year of surgical resection T stage, N stage, differentiation grade, tumour location and neoadjuvant treatment (the latter for rectal cancer only).

[a] Included patients diagnosed between 2009-2012 (n=20,589).

[b] Included patients diagnosed between 2009-2012 who underwent laparoscopic resection (n=9,162).

[c] Included patients diagnosed between 2009-2012 who underwent surgical resection with primary anastomosis (n=26,871).

[d] Included patients diagnoses between 2005-2012 (n=61,496).

Anastomotic leakage

Table 3c presents observed proportions and adjusted odds ratios of anastomotic leakage by hospital volume and tumour localization. For both colon and rectal cancer patients no differences were found between hospital volumes (colon *p*=0.81; rectum *p*=0.97).

Postoperative mortality

Table 3d presents observed proportions and adjusted odds ratios for postoperative 30-day mortality by hospital volume and tumour localization. For both colon and rectal cancer, postoperative mortality was marginally higher in low-volume hospitals (colon *p*=0.029; rectum *p*=0.007).

Survival

Median follow-up time for patients included was 60 months. For colon cancer patients, crude 1-, 3- and 5-year observed survival rates were similar between hospital volumes: 94, 81 and 71% (*p*=0.49) (Figure 2a). For rectal cancer patients, crude 1-, 3- and 5-year observed survival rates were also similar between hospital volumes: 96, 84 and 74% (*p*=0.71) (Figure 2b). Table 4 shows adjusted hazard ratios for death by hospital volume. The risk of death was not correlated with hospital volume for both colon and rectal cancer patients.
When the analyses were repeated with the hospitals that performed colon <50 resections/year or rectum <20 resections/year versus hospitals that performed colon ≥50 resections/year or rectum ≥20 resections/year, similar results were found for overall survival (data not shown).

TABLE 4 Cox regression analysis for the relation of the number of patients who underwent surgical resection for colon or rectal cancer per hospital per year and the risk of death of colon and rectal cancer patients in the Netherlands, 2005-2012 (n=58,218).

	Adjusted	
Hospital volume	**HR[2]**	**95% CI**
COLON CANCER		
<50/yr	1.03	0.97-1.08
50-74/yr	1.02	0.97-1.06
75-99/yr	0.99	0.94-1.04
≥100/yr	reference	
RECTAL CANCER		
<20/yr	0.98	0.91-1.07
20-39/yr	1.00	0.95-1.06
≥40/yr	reference	

HR Hazard ratio, CI Confidence interval
* p < 0.05 between hospital volume categories.
[2] Adjusted for gender, age, year of surgical resection, T stage, N stage, differentiation grade and tumour location.

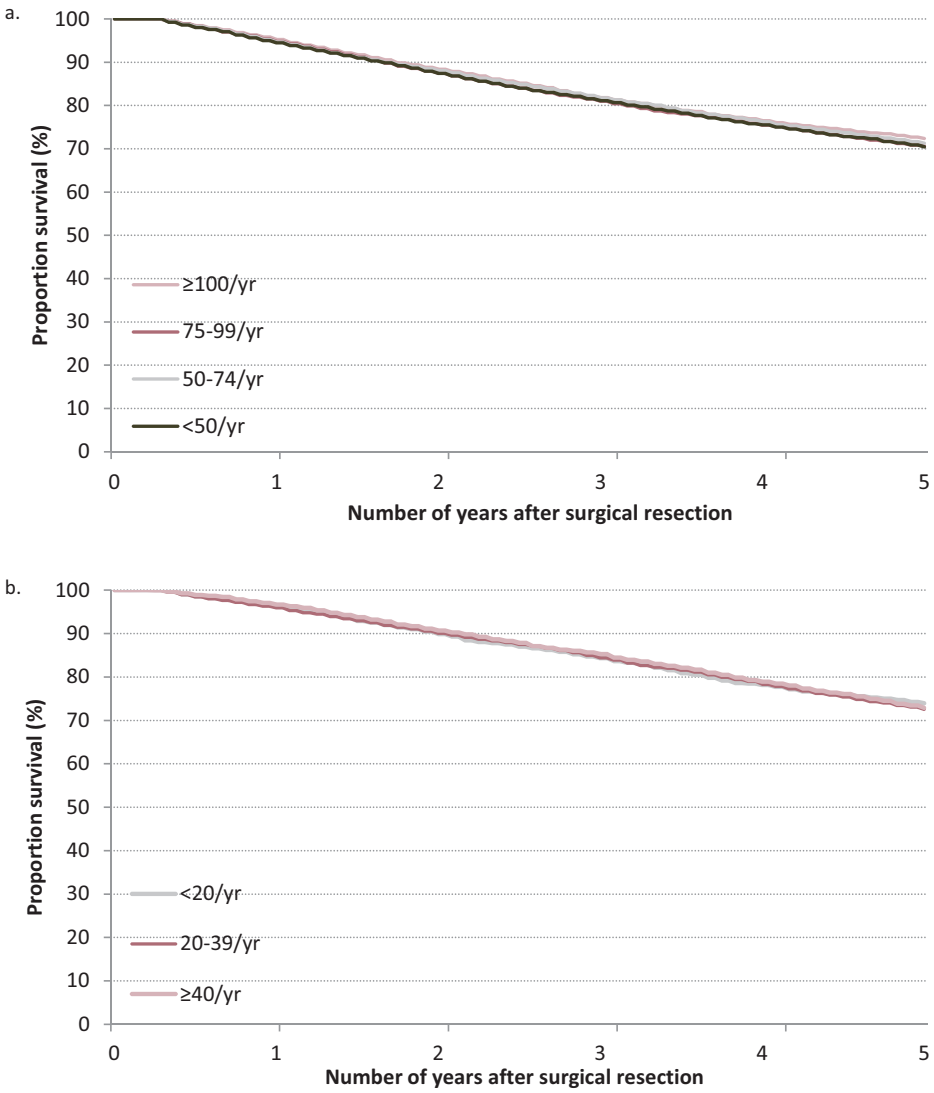

FIGURE 2. Crude overall survival of patients with colon (a) and rectal (b) cancer according to hospital volume categories in the Netherlands, 2005-2012 (n=58,218).

Subgroup analyses excluding patients who underwent emergency resection

As a sensitivity analysis, all analyses were repeated for the period 2009-2012 excluding patients who underwent emergency resection. Similar results were found for surgical approach, presence of anastomotic leakage, postoperative 30-day mortality and overall survival (data not shown).

DISCUSSION

In this population-based study covering the entire Netherlands in the period 2005-2012, we analyzed to what extent hospital volumes lead to differences in short- and long-term patient outcomes. We found no differences in overall survival between hospitals that did and did not meet the Dutch minimum volume norms for colorectal cancer. However, marginal differences were found between hospital volumes in surgical approach and postoperative 30-day mortality.

Our data were based on all consecutive non-metastatic colorectal cancer patients, who underwent resection in the Netherlands between 2005-2012. Conflicting evidence exists as to whether hospital volume is associated with differences in postoperative mortality and overall survival in colorectal cancer. The variation in results between studies may be caused by the hospital volume categories that are differently defined in the literature. The cut-off for "low-volume" ranged from ≤25 to ≤90 colorectal cancer resections, and the number of colorectal cancer resections considered as "high-volume" ranged from ≥25 to ≥110.[11] Furthermore, the low-volume thresholds used in this study would place Dutch hospitals in high-volume categories in most studies originating from the United States (US).[1, 14, 15] Other studies categorized hospitals based on the colorectal cancer hospital volume[16, 17], whereas we intentionally separated colon and rectal cancers due to differences in surgical procedures. A subgroup analysis in a meta-analysis of the Cochrane collaboration, where studies were grouped according to continent of origin, showed that studies originating from other countries than the US had no significant hospital volume effect on 5-year survival, whereas US data suggested a potential benefit for high-volume hospitals.[11] Similar to the results found in non-US studies, we demonstrated no better survival in high-volume hospitals. Moreover, patient selection varied between studies, some only included patients older than 65 years with colorectal cancer.[18, 19] Furthermore, we excluded patients with metastatic disease while others have included these.[19-23]

For colon cancer patients who were initially treated laparoscopically, we found a slightly higher proportion of patients (4%) converted from laparoscopic to open resection in hospitals with <50 resections/year compared to hospitals with ≥100 resections/year. Van Erning et al. showed a similar trend in a population-based study in the southern part of the Netherlands.[24] Laparoscopic resection is proven to be safe, with comparable disease-free and overall survival compared to open resection.[25, 26] However, conversion to open resection is associated with increased morbidity, longer length of hospital stay and shorter disease-free survival.[27-29] The technique of laparoscopic resection is still in progress, hence it is likely that variance in proportions of laparoscopic resection between hospitals will decrease.

Interestingly, marginal differences in postoperative mortality rates were present between hospital volumes for patients with colon or rectal cancer. For rectal cancer patients, this

was in line with a previous Dutch study of Elferink et al.[30]. In this study patients who were operated in hospitals with ≥50 resections/year had lower odds of dying within 30 days compared to patients who were operated in hospitals with <25 resections/year. When these results are compared with our results, it seems that the postoperative mortality rates have not been changed over time. More studies found an association between postoperative mortality and hospital volumes.[1, 14, 21-23, 31, 32] A possible explanation could be that a higher standard of care is provided in high-volume hospitals by more specialised and experienced surgeons and by technically more advanced equipment. Another possible explanation could be that low-volume hospitals with higher postoperative mortality rates are less skilled to recognize and manage serious complications once they occur, a phenomenon known as failure to rescue (FTR).[33] Nevertheless, Henneman et al. recently showed that annual average hospital volume was not significantly associated with FTR in the Netherlands.[34] We found no associations between hospital volumes and the presence of anastomotic leakage, even though lower rates of postoperative complications in high/volume hospitals were expected. Data on other specific postoperative complications were not available. Finally, elderly patients and patients with comorbidities were reported to be associated with higher risk of postoperative mortality, but this was not associated with hospital volume.[24]

The main strengths of this study are the use of a large dataset including more than 60,000 colorectal cancer patients and the inclusion of all hospitals in the Netherlands. Furthermore, the lowest volume categories in our study were based on the Dutch minimum volume norms. We calculated the annual hospital volume according to tumour location, instead of calculating an average over the included years.

Due to the increasing incidence of colorectal cancer[35], hospital volumes became substantially higher through the years. Moreover, during the study period some hospitals have merged, thereby increasing their annual hospital volume. In anticipation of the mergers, hospitals might collaborate and make agreements about referral of patients who need complex surgeries. This could have led to a higher number of complex patients treated in certain hospitals, which may have led to a worse outcome in these hospitals. Although the number of referred patients may be small and one might expect to see a minor effect, we have adjusted for several patient and tumour characteristics in our analyses.

However, some shortcomings of our study should be noted. We could not adjust for hospital volume of local recurrences (mainly for rectal cancer), which are mostly treated in a limited number of hospitals, thereby underestimating the volume of these hospitals. Moreover, a recent Dutch study by Homan et al., suggested a trend towards higher involved circumferential resection margin in rectal cancer patients of 13% in low-volume hospitals (<20/yr) versus 6% in high-volume hospitals (>40/yr) in a small area of the

Netherlands.[36] However, data on completeness of the surgical resection, as well as, data regarding local recurrence were not routinely available in the nationwide cancer registry. Furthermore, we cannot exclude that other factors, such as variation in comorbidities between patients treated in different hospitals, may have influenced our results as well. Moreover, we studied the number of resections on hospital level and not on surgeon level. Several studies showed that postoperative mortality was lower for surgeons with a higher caseload of colon cancer patients, regardless of the hospital volume of the hospital in which the surgeons practiced.[15, 22, 31, 37-39] This suggests that an association between hospital volumes and postoperative mortality could be mediated by surgeon volume. Unfortunately, data on surgeon volume were not available.

Due to the large dataset, one might dispute whether the statistically significant differences that were present between hospital volumes are clinically relevant. For example, the difference in postoperative mortality between lowest and highest volume hospitals was approximately 1%. Future studies should focus on the identification of processes associated with good outcomes and factors causing variation between individual hospitals. However, identification of these processes and their effect on quality of care remains challenging.

In conclusion, no differences in 5-year overall survival were revealed between hospital volumes for non-metastatic colorectal cancer patients. However, marginal differences in surgical approach and postoperative 30-day mortality were present between hospital volumes. Exploring factors causing variation between hospitals will provide more insight in the quality of care debate on whether undergoing a resection in a low-volume hospital is a risk factor for unfavourable patient outcomes.

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6

Development and validation of prediction models for postoperative 90-day mortality and overall survival in colorectal cancer patients

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ABSTRACT

Background

The aim of this study was to develop and validate a prediction model for postoperative 90-day mortality and overall survival for colon and rectal cancer patients to facilitate clinical decision making in the pre- and postoperative setting.

Methods

All patients diagnosed with primary non-metastatic colorectal cancer between 2008-2014 that underwent resection were selected from the Netherlands Cancer Registry. A modeling and a validation group were randomly constituted for development and validation of the models. Results from multivariable logistic regression and cox regression analyses served as the basis for development of the prediction model. Discrimination and calibration were assessed. Bootstrapping was used for internal validation. External validation was performed by regression analyses on the validation cohorts.

Results

This study included 60,758 colorectal cancer patients. The final models for postoperative 90-day mortality and overall survival included gender and age of the patient, stage of the primary tumour, urgency of resection (colon cancer), surgical approach (laparoscopic versus open), type of surgery, anastomotic leakage, (neo)adjuvant treatments, presence of multiple tumours, and radical removal of the tumour. Concordance indices for postoperative mortality were 0.80 and 0.79 in colon and rectal cancer, respectively. Corresponding indices for overall survival were 0.69 and 0.67, respectively. Model predictions were well calibrated. Estimates in the validation group did not differ significantly from the modelling cohort.

Conclusion

The validated prediction models can be used as instruments to predict postoperative 90-day mortality and overall survival and aid to clinical decision-making for tailored treatment in colorectal cancer patients.

INTRODUCTION

Colorectal cancer is one of the most frequent cancers in the Netherlands with more than 15,000 newly diagnosed cases in 2015. It is also one of the most frequent causes of cancer death with approximately 4,900 deaths in 2014.[1] The corner stone of curative treatment for colorectal cancer patients is surgical resection. Surgery for colorectal cancer has a highly variable risk of mortality within the first three months postoperatively depending on the risk profile of the individual patient. Factors that influence long-term prognosis of colorectal cancer patients include age, tumour stage, location of the tumour and treatment characteristics.[2-5]

Most of the published prediction models in colorectal cancer have focused on the pre-operative setting.[6-9] However, it is not only at the time of diagnosis that important decisions have to be made regarding type, timing and intensity of different treatment modalities. Risk profiles have change significantly in the postoperative setting compared to the pre-operative setting. For example, anastomotic leakage impacts on prognosis and including such variables enables adaptation of the individual risk assessment postoperatively. This can help patients, caregivers, and physicians to make informed decisions in this setting.

Statistical prediction models can be applied to calculate the overall probability of a specific outcome.[10] These prediction models are tailored to the profile of an individual patient. To facilitate uptake in clinical practice, a representation of the underlying model can be used for the development of a web-based calculator or user-friendly graphical interfaces. Many previous studies led to a successful application of prediction models for oncology prognostics.[11-16]

Prognostic models to predict overall survival among colorectal cancer patients are scarce.[17-20] Furthermore, currently available prediction models for postoperative mortality in colorectal cancer patients have several limitations. Most prediction models used the outcome postoperative 30-day mortality, instead of postoperative 90-day mortality. Studies have shown that a substantial proportion of short-term mortality occurs between one and three months postoperatively.[21-23] Moreover, statistical modelling approaches were used with often small sample sizes. These approaches have their drawbacks related to selecting potential predictors based on significance testing thereby ignoring potential interactions between predictors.[9, 24-27]

The aim of this study was to develop and validate prediction models to estimate postoperative 90-day mortality and 5-year overall survival for stage I-III colon and rectal cancer patients. The postoperative mortality prediction model was designed to predict dying within 90 days after undergoing a surgical resection for colorectal cancer. The prediction model with the outcome overall survival was designed to predict the likelihood of surviving at least five years after undergoing a surgical resection for colorectal cancer, excluding patients who died within 90 days post-surgery.

METHODS

Data source

Data from the nationwide population-based Netherlands Cancer Registry (NCR) were used, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and national level.
Anatomical site of the tumour is registered according to the International Classification of Disease–Oncology (ICD-O).[28] The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[29]

Study population

All patients who underwent surgical resection for primary non-metastatic colorectal cancer (C18 and C20) between 2008-2014 were included. Patients were excluded if the date of resection was missing (n=64) or if tumour stage was unknown (n=28).
Disease stage was based on the pathological TNM classification. Patients were stratified by tumour localization: colon (C18) and rectum (C20). Tumour localization was categorized into anatomical subsites: proximal colon (C18.0-18.3); transverse colon and splenic flexure (C18.4-18.5); distal colon (C18.6-1.87); unknown or overlapping subsites of the colon (C18.8-18.9) and rectum (C20.9).
Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database (GBA). Follow-up was completed until January 1st, 2017.

Statistical analyses

Model development and validation

Incomplete data were imputed using a multiple imputation strategy, as the omission of patients who have one or more predictor variables missing from the analyses can cause a considerable loss of precision and may bias the results. The number of imputation was set to 20.
Potential predictors were preselected based on clinical reasoning and evidence from previous studies, instead of observed significant relations with outcome variables in the dataset. This method results in higher external validity and less over-fitting of the developed model (i.e. the model performs well for the data it was developed in, but that performance will degrade considerably when it is applied to future patients).[30-32]
A random sample of about 50% of the population was used for model building (modelling set); the data of the remaining patients were used for validation purposes (validation set).

To reduce the number of predictors in the models, backward stepwise deletion was applied based on the Wald test. A liberal *P* value of 0.20 was used as recommended by prediction modelling guidelines.[31] Non-significant variables were included if they improved accuracy of the model.

Multivariable logistic regression analyses were used to develop a prediction model for postoperative 90-day mortality. Cox proportional hazard models were used to determine the association between potential predictors and 5-year overall survival. To exclude postoperative mortality from survival analyses, patients who died within 90 days postoperatively were excluded from survival analyses. Follow-up time was defined as the time between 90 days after resection and either date of death or last date of follow-up (January 1st, 2017) for patients who were still alive.

Assessment of model performance

Model performance was quantified in the modeling groups with respect to discrimination and calibration. The Brier score was used as an overall performance measure to calculate the disagreement between expected rates and the binary variable postoperative 90-day mortality. A Brier score of 0 indicates a perfect model, while 0.25 indicates a non-informative model. For the outcome measure postoperative 90-day mortality, discrimination was assessed by calculating the area under the receiver operating curve (AUC). Furthermore, overall fit of the postoperative mortality models was evaluated using the Hosmer-Lemeshow (H-L) goodness-of-fit test in deciles. Plotting the difference between the observed and predicted probabilities was used for graphical assessment of the calibration. The performance ability of the model for overall survival was evaluated by Harrell's concordance index (C-index). The C-index has a scale of 0 to 1 with 1 representing perfect discrimination and 0 for no discrimination ability.[33] Calibration of the cox models was assessed by comparing observed (Kaplan-Meier) and predicted survival probabilities in several prognostic groups derived by placing cutpoints on the prognostic index (linear predictor of the Cox model).[34]

Internal validity of the models was determined using bootstrap techniques.[32, 35] Random bootstrap samples were drawn with replacement from the modeling set (n=1,000). After internal validation, the regression coefficients were corrected for optimism with the heuristic shrinkage factor γ of van Houwelingen and le Cessie.[36] This makes it more likely that the model will best withhold in future studies with similar settings and patients.[35]

External validation was performed by regression analyses on the validation cohorts. The performance as well as the calibration of the models were assessed in the validation cohorts.

Statistical analyses were performed in STATA (version 13.0, Statcorp LP, College Station, TX) and SPSS Statistics for Windows (version 22.0).

TABLE 1 Patient and tumour characteristics of the eligible patients by tumour localization (n=60,744).

	Colon		Rectum	
Variable	n	% of total	n	% of total
Total	43,551		17,193	
Gender				
Male	22,473	52	10,775	63
Female	21,092	48	6,418	37
Age (years; mean ± SD)		70.8 ± 11.0		66.9 ± 10.9
Pathological T stage				
T1	3,685	8	2,820	16
T2	7,312	17	5,752	34
T3	26,483	61	7,967	46
T4	6,071	14	646	4
Pathological N stage				
N0	27,557	64	11,581	68
N1	10,540	24	3,849	22
N2	5,240	12	1,703	10
Postoperative 90-day mortality	2,368	5	563	3
Vital status				
Alive	29,221	67	12,453	72
Deceased	14,344	33	4,740	28
Follow-up (months; median (IQR))	48.2 (29.6-72.7)		51.8 (33.3-75.2)	

RESULTS

Between 2008 and 2014, 60,758 patients underwent surgical resection for primary non-metastatic colorectal cancer: 43,565 colon cancer patients and 17,193 rectal cancer patients. Patient and tumour characteristics are displayed in Table 1 for colon and rectal cancer separately. Table 2 shows that random sampling provided well-balanced groups. The number of missing values per predictor variable is also presented.

Due to high correlation between 'T-stage' and 'additional resection', and higher influence of 'T-stage' on the risk of postoperative mortality, 'additional resection' was omitted from the models. Moreover, 'type of surgery' among colon cancer patients showed high correlation with the 'presence of multiple tumours', therefore these variables were combined. Inclusion of interaction terms did not improve the model.

Postoperative 90-day mortality

After backward elimination, the following predictors were added in the model for colon cancer patients: gender; age; pathological T-stage; pathological N-stage; urgency of resection; surgical approach (laparoscopic versus open); type of surgery (segmental versus subtotal) combined with presence of multiple tumours and anastomotic leakage (among patients who underwent surgical resection with primary anastomosis). For rectal cancer, predictors constituting the final model were gender; age; pathological T-stage; pathological N-stage; surgical approach; type of surgery and anastomotic leakage. Corresponding odds ratios (OR) and regression coefficients are listed in Table 3.

Discrimination and calibration were assessed for the modelling groups for both colon as well as rectal cancer. The AUC was 0.80 (95%CI: 0.79-0.82) for colon cancer and 0.79 (95%CI: 0.76-0.82) for rectal cancer, which indicates good discriminative ability. Calibration was considered adequate (Supplementary Figure 1a and 1b). For the deciles, the average expected to observed ratio was 7.06 (p=0.53) for colon cancer and 8.34 (p=0.40) for rectal cancer, indicating a high agreement between the predictions and observations.

Internal validation in the index group with 1000 times bootstrapping revealed for the estimates a shrinkage factor of (1158.52-15/1158.52)≈0.99 for colon cancer, and (194.72-14/194.72)≈0.93 for rectal cancer. This indicates that 1% for colon cancer and 7% for rectal cancer was fit due to noise. We used the shrinkage factors for over-optimism (Table 3). External validation resulted in a Brier score of 0.0464 for colon cancer and 0.0281 for rectal cancer, an AUC of 0.81 (95%CI: 0.79-0.82) for colon cancer and 0.80 (95%CI: 0.77-0.84) for rectal cancer. The average expected to observed ratio was 9.28 (p=0.32) for colon cancer and 7.77 (p=0.46) for rectal cancer (Supplementary Figure 1a and 1b).

Overall survival

After backward elimination, the following predictors were added in the model for colon cancer patients: gender; age; tumour stage; urgency of resection; tumour location, adjuvant chemotherapy (among stage III colon cancer patients); presence of multiple tumours; radicality and anastomotic leakage. For rectal cancer, predictors constituting the final model were gender; age; tumour stage; neoadjuvant treatment (among stage II-III rectal cancer patients); anastomotic leakage and radicality. Corresponding hazard ratios and regression coefficients are listed in Table 4.

Performance was assessed for the modelling groups for colon and rectal cancer. The C-index was 0.69 for colon cancer and 0.67 for rectal cancer, which indicates good discriminative ability.

Internal validation in the index group with 1000 times bootstrapping revealed for the estimates a shrinkage factor of (2560.85-16/2560.85)≈0.99 for colon cancer, and (573.73-15/573.73)≈0.97 for rectal cancer. This indicates that 1% for colon cancer and 3% for rectal

TABLE 2 Characteristics per predictor variable for the modelling and the validation group by tumour localization (n=60,758).

	COLON CANCER					RECTAL CANCER			
	Modeling set		Validation set			General discussion		Validation set	
	n	% of total	n	% of total		n	% of total	n	% of total
Total	21,753	49.9	21,812	50.1	Total	8,557	49.8	8,636	50.2
Gender					Gender				
Male	11,177	51.4	11,296	51.8	Male	5,363	62.7	5,412	62.7
Female	10,576	48.6	10,516	48.2	Female	3,194	37.3	3,224	37.3
Age					Age				
<65 years	5,692	26.2	5,729	26.3	<65 years	3,270	38.2	3,416	39.6
65-74 years	7,097	32.6	7,097	32.5	65-74 years	3,020	35.3	2,980	34.5
75-84 years	7,083	32.6	7,146	32.8	75-84 years	1,956	22.9	1,942	22.5
≥ 85 years	1,881	8.6	1,840	8.4	≥ 85 years	311	3.6	298	3.5
Pathological T stage					Pathological T stage				
T1	1,845	8.5	1,840	8.4	T1	1,411	16.5	1,409	16.3
T2	3,711	17.1	3,601	16.5	T2	2,807	32.8	2,945	34.1
T3	13,119	60.3	13,364	61.3	T3	4,006	46.8	3,961	45.9
T4	3,066	14.1	3,005	13.8	T4	330	3.9	316	3.7
Missing	12	0.1	2	0.0	Missing	3	0.0	5	0.1
Pathological N stage					Pathological N stage				
N0	13,622	62.6	13,935	63.9	N0	5,717	66.8	5,864	67.9
N1	5,338	24.5	5,202	23.8	N1	1,934	22.6	1,915	22.2
N2	2,673	12.3	2,567	11.8	N2	878	10.3	825	9.6
Missing	120	0.6	108	0.5	Missing	28	0.3	32	0.4
Tumour location					Neoadjuvant treatment [b]				
Caecum/ascending colon	8,252	37.9	8,094	37.1	Short course radiotherapy	3,877	45.3	3,854	44.6
Hepatic flexure/transverse colon	3,043	14.0	3,128	14.3	Chemoradiotherapy	2,975	34.8	3,083	35.7
Splenic flexure/descending colon	1,849	8.5	1,963	9.0	Other	225	2.6	245	2.8
Sigmoid colon	8,128	37.4	8,153	37.4	No neoadjuvant treatment	1,480	17.3	1,454	16.8
NOS/other	481	2.2	474	2.2					
Urgency of surgery					Surgical approach				
Elective	19,814	91.1	19,872	91.1	Open surgery	3,671	42.9	3,716	43.0
Emergency	1,609	7.4	1,641	7.5	Laparoscopic surgery	4,795	56.0	4,840	56.0
Missing	330	1.5	299	1.4	Missing	104	1.2	97	1.1

TABLE 2 Characteristics per predictor variable for the modelling and the validation group by tumour localization (n=60,758). *(Continued)*

	COLON CANCER					RECTAL CANCER			
	Modeling set		Validation set			General discussion		Validation set	
	n	% of total	n	% of total		n	% of total	n	% of total
Surgical approach					Type of surgery				
Open surgery	8,051	37.0	8,165	37.4	LAR	4,698	54.9	4,817	55.8
Laparoscopic surgery	13,516	62.1	13,476	61.8	Hartmann	843	9.9	806	9.3
Missing	186	0.9	171	0.8	APR	2,740	32.0	2,794	32.4
Type of surgery					Other	289	3.4	236	2.7
Segmental	18,447	84.8	18,411	84.4	Anastomotic leakage[c]				
Subtotal	635	2.9	674	3.1	No	5,704	66.7	5,761	66.7
Other	2,671	12.3	2,727	12.5	Yes	416	4.9	460	5.3
Anastomotic leakage					No anastomosis (APR)	2,740	32.0	2,794	32.4
No	19,138	88.0	19,065	87.4	Missing	964	11.3	927	10.7
Yes	1,297	6.0	1,393	6.4	Presence of multiple tumours				
Missing	1,318	6.1	1,354	6.2	No	8,430	98.5	8,522	98.7
Adjuvant treatment [a]					Yes	140	1.6	131	1.5
No adjuvant chemotherapy	3,202	14.7	3,112	14.3	Radical removal tumour				
Adjuvant chemotherapy	4,857	22.3	4,718	21.6	Yes (R0)	8,102	94.7	8,229	95.3
No adjuvant treatment	13,694	63.0	13,982	64.1	No (microcopic = R1)	278	3.2	256	3.0
Presence of multiple tumours					No (macroscopic = R2)	33	0.4	28	0.3
No	21,043	96.7	21,112	96.8	Missing	157	1.8	140	1.6
Yes	710	3.3	700	3.2					
Radical removal tumour									
Yes (R0)	20,735	95.3	20,814	95.4					
No (microscopic = R1)	351	1.6	356	1.6					
No (macroscopic = R2)	163	0.7	132	0.6					
Missing	504	2.3	510	2.3					

[a] No adjuvant treatment: included stage I-II colon cancer patients.

[b] No neoadjuvant treatment: included stage I rectal cancer patients.

[c] No anastomosis: included rectal cancer patients who underwent surgical resection without primary anastomosis (APR).

TABLE 3 Logistic regression estimates to predict postoperative 90-day mortality among colon and rectal cancer patients (n=60,758).

	Model development			Bootstrapping		Recalibration	
	OR	95% CI	Regression coefficient	OR	Regression coefficient	OR	Regression coefficient
COLON CANCER							
Intercept	0.01	0.00-0.01	-5.071	0.01	-5.234	0.01	-5.081
Gender							
Male	reference			reference		reference	
Female	0.78	0.68-0.88	-0.255	0.76	-0.281	0.77	-0.265
Age							
<65 years	reference			reference		reference	
65-74 years	2.38	1.85-3.07	0.869	2.69	0.988	2.36	0.859
75-84 years	6.27	4.97-7.93	1.836	7.16	1.969	6.21	1.826
≥ 85 years	14.27	11.07-18.39	2.658	16.62	2.810	14.13	2.648
Pathological T stage							
T1	reference			reference		reference	
T2	1.03	0.75-1.41	0.028	1.00	-0.005	1.02	0.018
T3	1.08	0.82-1.44	0.081	1.11	0.106	1.07	0.071
T4	1.33	0.97-1.81	0.283	1.29	0.252	1.31	0.273
Pathological N stage							
N0	reference			reference		reference	
N1	1.17	1.00-1.36	0.156	1.21	0.192	1.16	0.146
N2	1.43	1.19-1.73	0.358	1.45	0.373	1.42	0.348
Urgency of resection							
Elective	reference			reference		reference	
Emergency	2.70	2.27-3.22	0.995	2.52	0.925	2.68	0.985
Surgical approach							
Laparoscopic surgery	reference			reference		reference	
Open surgery	2.27	1.92-2.69	0.821	2.27	0.821	2.25	0.811
Type of surgery							
Segmental	reference			reference		reference	
Subtotal (solitary CRC)	1.64	1.21-2.22	0.495	1.79	0.583	1.62	0.485
Subtotal (synchronous CRC)	2.05	1.07-3.91	0.716	2.96	1.086	2.03	0.706
Other	0.99	0.81-1.21	-0.009	0.90	-0.109	0.98	-0.019
Anastomotic leakage							
No	reference			reference		reference	
Yes	6.41	5.42-7.58	1.858	6.81	1.918	6.35	1.848

TABLE 3 Logistic regression estimates to predict postoperative 90-day mortality among colon and rectal cancer patients (n=60,758). *(Continued)*

	Model development			Bootstrapping		Recalibration	
	OR	95% CI	Regression coefficient	OR	Regression coefficient	OR	Regression coefficient
RECTAL CANCER							
Intercept	0.01	0.01-0.02	-4.554	0.01	-4.528	0.01	-4.626
Gender							
Male	reference			reference		reference	
Female	0.46	0.35-0.62	-0.767	0.42	-0.867	0.43	-0.839
Age							
<65 years	reference			reference		reference	
65-74 years	3.76	2.44-5.82	1.326	3.91	1.363	3.50	1.253
75-84 years	9.77	6.38-14.95	2.279	10.81	2.380	9.08	2.206
≥ 85 years	16.94	9.93-28.90	2.829	18.74	2.931	15.75	2.757
Pathological T stage							
T1	reference			reference		reference	
T2	1.05	0.69-1.61	0.053	1.05	0.053	0.98	-0.020
T3	1.12	0.74-1.68	0.111	1.12	0.113	1.04	0.039
T4	1.50	0.80-2.82	0.408	1.26	0.231	1.40	0.336
Pathological N stage							
N0	reference			reference		reference	
N1	1.22	0.91-1.65	0.202	1.24	0.213	1.14	0.129
N2	2.01	1.41-2.87	0.700	2.17	0.776	1.87	0.627
Surgical approach							
Laparoscopic surgery	reference			reference		reference	
Open surgery	1.43	1.10-1.86	0.357	1.35	0.304	1.33	0.285
Type of surgery							
LAR	reference			reference		reference	
Hartmann	1.57	1.10-2.22	0.448	1.75	0.562	1.46	0.376
APR	1.18	0.88.159	0.169	1.46	0.376	1.10	0.096
Other	1.70	0.92-3.13	0.530	2.13	0.758	1.58	0.457
Anastomotic leakage[c]							
No	reference			reference		reference	
Yes	4.01	2.60-6.18	1.389	4.04	1.395	3.65	1.296

[c] Included rectal cancer patients who underwent surgical resection with primary anastomosis.

TABLE 4 Regression estimates to predict overall survival among colon and rectal cancer patients (n=60,758).

	Model development			Bootstrapping		Recalibration	
	HR	95% CI	Regression coefficient	HR	Regression coefficient	HR	Regression coefficient
COLON CANCER							
Gender							
Male	reference			reference		reference	
Female	0.82	0.78-0.87	-0.196	0.82	-0.199	0.81	-0.206
Age							
<65 years	reference			reference		reference	
65-74 years	1.45	1.34-1.57	0.373	1.48	0.389	1.44	0.363
75-84 years	2.48	2.29-2.68	0.908	2.52	0.926	2.45	0.898
≥ 85 years	4.54	4.12-5.00	1.513	4.70	1.548	4.49	1.503
Stage							
I	reference			reference		reference	
II	1.31	1.21-1.42	0.268	1.30	0.260	1.29	0.258
III	2.95	2.71-3.21	1.081	1.82	0.600	2.92	1.071
Tumour location							
Caecum/ascending colon	reference			reference		reference	
Hepatic flexure/transverse colon	1.02	0.95-1.10	0.021	1.04	0.039	1.01	0.011
Splenic flexure/descending colon	0.96	0.87-1.06	-0.043	0.96	-0.046	0.95	-0.053
Sigmoid colon	0.88	0.83-0.93	-0.129	0.86	-0.151	0.87	-0.140
NOS/other	1.15	0.97-1.37	0.141	1.08	0.073	1.14	0.131
Urgency of surgery							
Elective	reference			reference		reference	
Emergency	1.62	1.48-1.76	0.479	1.55	0.441	1.60	0.469

TABLE 4 Regression estimates to predict overall survival among colon and rectal cancer patients (n=60,758). *(Continued)*

	Model development			Bootstrapping		Recalibration	
	HR	95% CI	Regression coefficient	HR	Regression coefficient	HR	Regression coefficient
Anastomotic leakage							
No	reference			reference		reference	
Yes	1.20	1.08-1.34	0.186	1.21	0.190	1.19	0.176
Adjuvant chemotherapy [a]							
No	reference			reference		reference	
Yes	1.61	1.49-1.75	0.476	1.56	0.446	1.59	0.466
Presence of multiple tumours							
No	reference			reference		reference	
Yes	1.07	0.92-1.23	0.065	1.09	0.082	1.06	0.055
Radical removal tumour							
Yes (R0)	reference			reference		reference	
No (microscopic = R1)	3.00	2.61-3.45	1.098	2.90	1.064	2.97	1.088
No (macroscopic = R2)	4.17	3.37-5.15	1.427	4.35	1.469	4.13	1.417
RECTAL CANCER	reference			reference		reference	
Gender	0.78	0.71-0.85	-0.249	0.75	-0.292	0.76	-0.279
Male							
Female	reference			reference		reference	
Age	1.49	1.33-1.67	0.399	1.55	0.439	1.45	0.369
<65 years	2.89	2.57-3.24	1.061	2.95	1.082	2.80	1.030
65-74 years	5.69	4.74-6.84	1.740	5.41	1.687	5.52	1.709
75-84 years							
≥ 85 years	reference			reference		reference	

TABLE 4 Regression estimates to predict overall survival among colon and rectal cancer patients (n=60,758). *(Continued)*

	Model development			Bootstrapping		Recalibration	
	HR	95% CI	Regression coefficient	HR	Regression coefficient	HR	Regression coefficient
Stage	1.42	1.21-1.67	0.351	1.48	0.395	1.38	0.320
I	1.96	1.69-2.28	0.673	2.10	0.741	1.90	0.643
II							
III	reference			reference		reference	
Neoadjuvant treatment [b]	1.17	1.05-1.30	0.153	1.11	0.106	1.13	0.123
Short radiotherapy	1.35	1.19-1.53	0.300	1.37	0.316	1.31	0.269
Chemoradiation	1.88	1.14-3.09	0.631	3.22	1.168	1.82	0.600
Other							
No neoadjuvant treatment	reference			reference		reference	
Anastomotic leakage[c]	1.15	0.93-1.43	0.142	1.18	0.164	1.12	0.112
No							
Yes	reference			reference		reference	
Radical removal tumour	2.25	1.83-2.77	0.811	1.95	0.669	2.18	0.781
Yes (R0)	6.07	4.01-9.18	1.803	6.81	1.918	5.89	1.772
No (microscopic = R1)							
No (macroscopic = R2)							

[a] Included stage III colon cancer patients.
[b] Included stage II-III rectal cancer patients.
[c] Included rectal cancer patients who underwent surgical resection with primary anastomosis.

cancer was fit due to noise. Shrinkage factors were used to correct for over-optimism (Table 4). Calibration of the models were good in each dataset. For both the modelling set as the validation set, the actual survival for both colon and rectal cancer is more or less similar to the predicted survival probabilities (supplementary Figure 2a and 2b). External validation on the validation group resulted in a C-index of 0.69 for colon cancer and 0.68 for rectal cancer.

Sensitivity analyses

In order to determine whether the number of missing values in certain variables led to different conclusions and/or results, sensitivity analyses were performed by comparing outcomes of the imputed data set with the use of complete case analysis. Analyses showed similar results for all datasets; therefore, we concluded that imputation did not lead to radically different results (data not shown).

Web-based calculator

Final models were used to propose a web-based calculator, which can be applied to predict postoperative 90-day mortality and overall survival in the postoperative setting. Supplementary Figure 3 provides an example of the nomogram which show the risk of postoperative 90-day mortality of a theoretical female colon cancer patient aged between 75 and 84 years, with a pT4N1 tumour, who underwent an elective, open hemicolectomy, and who had an anastomotic leakage as postoperative complication.

DISCUSSION

In this study, we were able to create four practical, simple to use prediction models for primary non-metastatic colon and rectal cancer patients that underwent surgical resection, based on data from 60,758 colorectal cancer patients diagnosed between 2008-2014 in the Netherlands. Variables predicting postoperative 90-day mortality included gender and age of the patient, pathological T-stage and pathological N-stage of the primary tumour, urgency of resection (colon cancer), surgical approach (laparoscopic versus open), type of surgery and anastomotic leakage. Predictors constituting the final model to estimate 5-year overall survival included gender and age of the patient, tumour stage of the primary tumour, urgency of resection (colon cancer), tumour location (colon cancer), adjuvant chemotherapy (stage III colon cancer), presence of multiple tumours (colon cancer), radicality, anastomotic leakage and neoadjuvant treatment (stage II-III rectal cancer). The predictors in our models are filtered from the nationwide population-based NCR and are readily available in (Dutch) clinical practice and for use of the web-based calculator, without any extra efforts or data gathering. Discrimination and calibration of the models

were satisfactory. Use of these models is recommended to predict postoperative 90-day mortality and 5-year overall survival among stage I-III colorectal cancer patients.

Risk prediction models to predict the prognosis of colorectal cancer patients after surgery are scarce and are focused on advanced colorectal cancer.[17, 18, 20] On the contrary, a wide variety of risk prediction models to predict postoperative mortality among colorectal cancer patients has been developed in the past decades.[24, 37-42] One of the largest previous models to predict postoperative mortality was developed in 2012, including more than 900,000 patients undergoing colon or rectal resection, of whom one-third had colorectal cancer. Several other risk prediction models are available to calculate postoperative mortality among colorectal cancer patients undergoing surgery, like the POSSUM, P-POSSUM, CR-POSSUM, ACPGBI and the CCF-CRC scoring system.[24, 40, 41, 43] These models either used postoperative 30-day mortality or in-hospital mortality as an outcome and were developed to use in a preoperative setting. We developed models to be used in a postoperative setting and used postoperative 90-day mortality as an endpoint for our mortality prediction models. We believe that death within 90 days after surgery is more likely to capture deaths that occur after prolonged critical care support and that it is sufficiently close to the date of resection that it will capture almost exclusively deaths related to surgical resection. For this purpose, anastomotic leakage was included in the prediction models, which is mostly diagnosed in the early postoperative period. This has been reported as an independent predictor of both short term and long term survival, as well as disease recurrence. A previous study from Visser et al. showed that the majority of the colorectal cancer patients (15 out of 17 patients) who died within 90 days had a postoperative complication.[22]

This study had a number of strengths including data on many variables associated with the risk of dying within 90 days post-surgery and survival. Both significance testing and literature research were part of the predictor selection process, thereby contributing to actual appropriate prediction models. Also, the prediction models were developed based on nationwide population-based data, including events in various geographic regions and hospitals types in the Netherlands. This gives a representative data set of high quality. Due to the large sample size, the discriminatory ability of the models is expected to remain high when it is applied in new settings such as other countries or time-intervals. However, re-calibration of the models is always needed. The sample size of the validation cohort was appropriately large, as a minimum of 100 events and 100 nonevents was suggested for external validation samples by Vergouwe et al.[44]

Nevertheless, several limitations in this study should be addressed. Information on other known risk factors such as comorbidity, ASA score and the development of recurrences were unavailable in the NCR and could not be taken into account. However, when these variables will become available in the NCR in the near future, these variables can be

incorporated to update the prediction models. For some predictors we had a number of missing values (i.e. anastomotic leakage and radicality of the primary tumour). Furthermore, anastomotic leakage is likely to be underestimated, as thorough retrospective analysis of the patient files on this endpoint revealed an incidence of anastomotic leakage of up to 20% in rectal cancer patients that were treated in 2011 in the Netherlands, as found in a recent snapshot study.[45] But these 'missed' leakages might have been subclinical with less impact on the outcome parameters of the present models (90-day mortality and overall survival). We considered missing values to be missing at random and considered the effect on model development and performance to be minor. This was confirmed by comparing the performance parameters calculated with complete case analysis with the imputed data set. We were not yet able to assess the next steps within prognostic modelling: usefulness and clinical impact of the models. Although the model developments were thorough, the individual risk estimates need to be interpreted with caution. Further research is therefore required to evaluate the accuracy and reliability of these prediction models in daily clinical practice.

We developed and validated prediction models to predict the probability of postoperative 90-day mortality and to predict the likelihood of surviving at least five years after undergoing colorectal cancer surgery among non-metastatic colorectal cancer patients. As proposed in this study, results can be used to develop web-based calculators to provide both patients and surgeons with valuable information in the follow-up period after colorectal cancer surgery. These calculators are simple to use in everyday practice for postoperative counseling and can aid clinical decision making and help develop individual follow-up schedules, thereby lowering the burden of both patients and health care providers.

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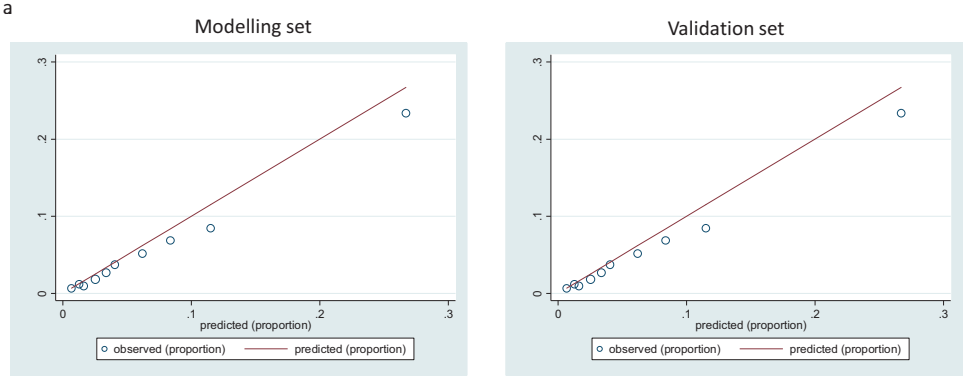
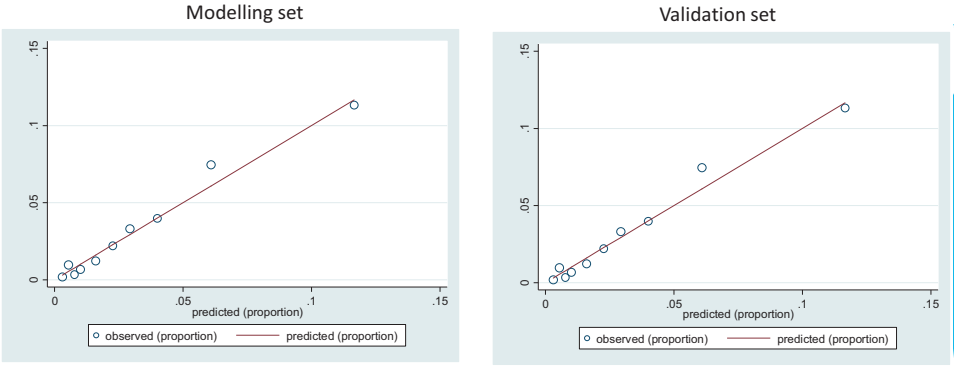
SUPPLEMENTARY FIGURES

a

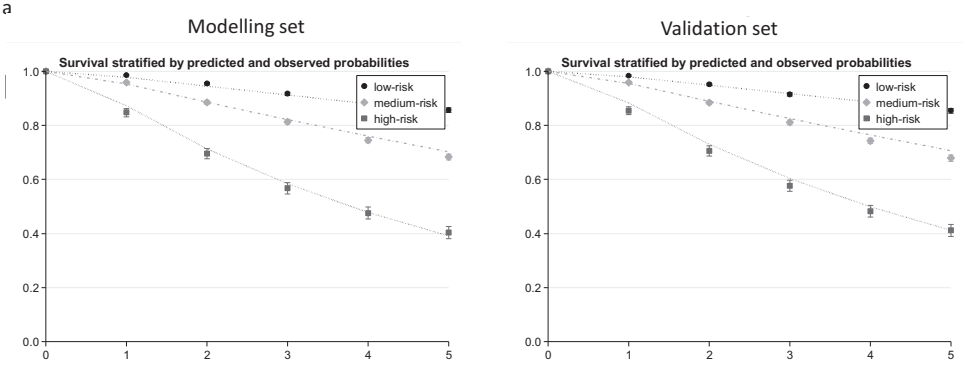


b.



SUPPLEMENTARY FIGURE 1 Calibration plots of the Logistic regression models in the modelling and derivation datasets for colon (a) and rectal (b) cancer to predict postoperative 90-day mortality.

a



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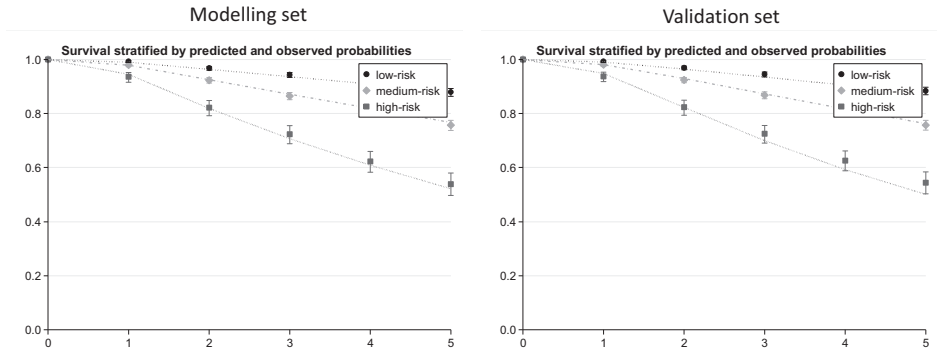
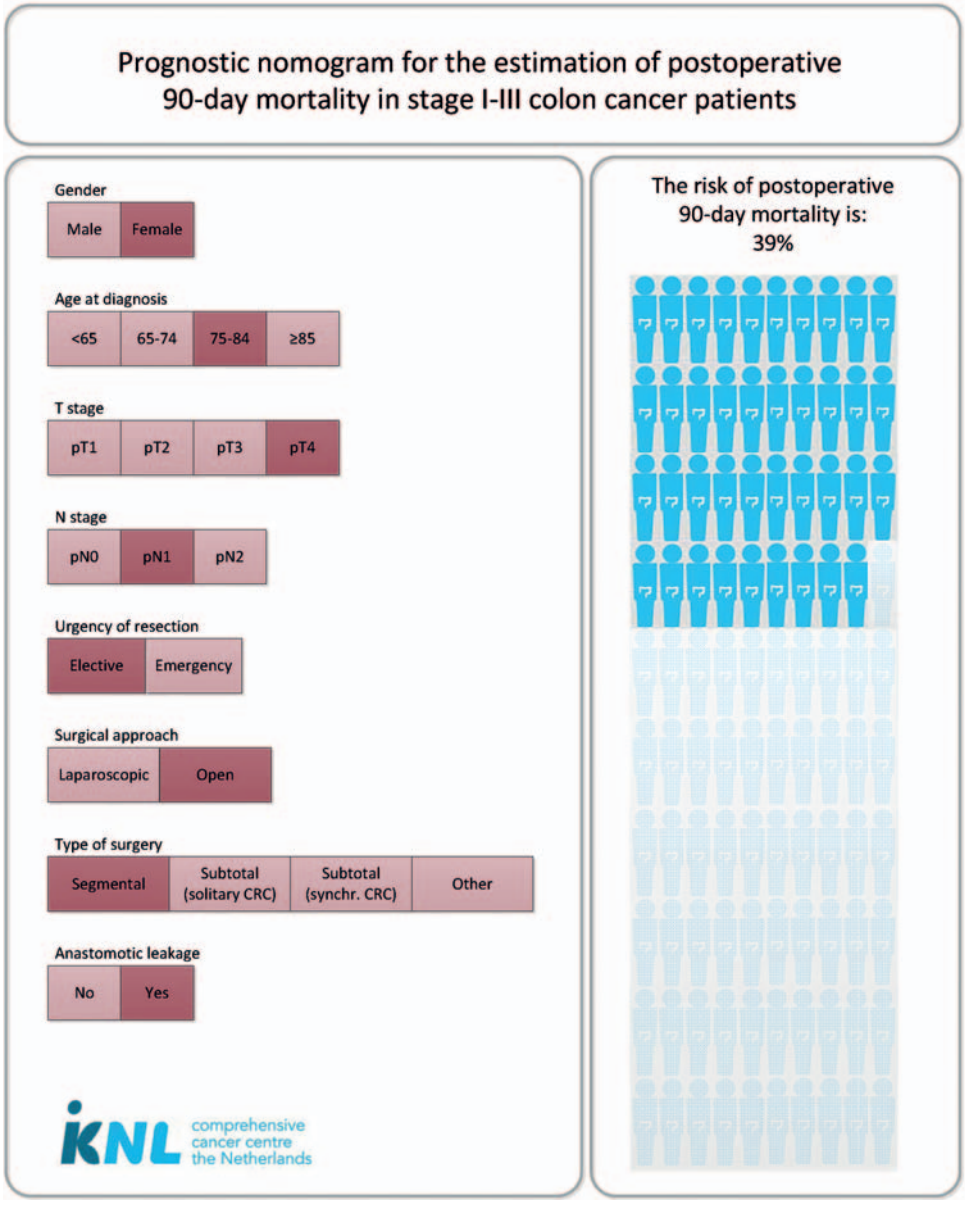


SUPPLEMENTARY FIGURE 2 Calibration of the Cox models in the modelling and validation datasets for colon (a) and rectal (b) cancer to predict 5-years overall survival. Dashed lines represent predicted survival probabilities, and vertical capped lines denote Kaplan-Meier estimates with 95% confidence intervals. Three prognosis groups are plotted: the "Good" group (darkest lines), the "Intermediate"group (medium-dark lines), and the "Poor" group (paler lines).



SUPPLEMENTARY FIGURE 3 Print screen from the nomogram, providing the risk of postoperative 90-day mortality

7

Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer

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European Journal of Cancer 2015; 51(17):2553-61

ABSTRACT

Background

Currently available data suggest that delaying the start of adjuvant chemotherapy in colon cancer patients has a detrimental effect on survival. We analyzed which factors impact on the timing of adjuvant chemotherapy and evaluated the influence on overall survival.

Patients and methods

Stage III colon cancer patients who underwent resection and received adjuvant chemotherapy between 2008-2013 were selected from the Netherlands Cancer Registry. Timing of adjuvant chemotherapy was subdivided into: ≤4, 5-6, 7-8, 9-10, 11-12 and 13-16 weeks post-surgery. Multivariable regressions were performed to asses the influence of several factors on the probability of starting treatment within 8 weeks post-surgery and to evaluate the association of timing of adjuvant chemotherapy with 5-year overall survival.

Results

6,620 patients received adjuvant chemotherapy, 14% commenced after 8 weeks. Factors associated with starting treatment after 8 weeks were older age (OR 65-74 versus <65 years 1.3 (95%CI: 1.14-1.58); OR ≥75 versus <65 years 1.6 (1.25-1.94)), emergency resection (OR 1.8 (1.41-2.32)), anastomotic leakage (OR 8.1 (6.14-10.62)), referral to another hospital for adjuvant chemotherapy (OR 1.9 (1.36-2.57)) and prolonged postoperative hospital admission (OR 4.7 (3.30-6.68)). Starting 5-8 weeks post-surgery showed no decrease in overall survival compared to initiation within 4 weeks (HR 5-6 weeks 0.9 (0.79-1.11); HR 7-8 weeks 1.1 (0.91-1.30)). However, commencing beyond 8 weeks was associated with decreased overall survival compared to initiation within 8 weeks (HR 9-10 weeks 1.4 (1.21-1.68); HR 11-12 weeks 1.3 (1.06-1.59); HR 13-16 weeks 1.7 (1.23-2.23)).

Conclusion

Our data support initiating adjuvant chemotherapy in stage III colon cancer patients within 8 weeks post-surgery.

INTRODUCTION

Adjuvant chemotherapy has been shown to decrease recurrence rates and improve overall survival after surgical resection for patients with stage III colon cancer.[1-3] The time interval from surgery to the initiation of chemotherapy has been proposed as an important factor that could affect the overall outcome.[4-6] In most clinical trials adjuvant chemotherapy was generally allowed to initiate within 4-8 weeks, routinely providing time for wound healing; however, results showed that in daily clinical practice delays in commencing treatment may occur.[7-9]

The guidelines from the European Society for Medical Oncology (ESMO) recommend adjuvant chemotherapy should start as early as possible starting from the fourth week up to a maximum of 8-12 weeks post-surgery. If the start of adjuvant chemotherapy is delayed for more than 12 weeks, treatment should be given on the basis of an individual decision taking into account the relatively limited likelihood of benefit against the potential toxicity.[10] The Dutch guideline for the treatment of colorectal cancer 2014 recommends that adjuvant chemotherapy should start between 6 and 8 weeks after surgical resection, and certainly within 12 weeks following surgical resection.[11]

Several population-based studies have shown that a delayed initiation of adjuvant chemotherapy is associated with an unfavourable long-term overall survival, cancer-specific survival and disease-free survival.[12-17] Results from a meta-analysis has indicated that the relative overall survival decreased by every 4-week delay in the administration of adjuvant chemotherapy.[18] However, in this meta-analysis there was heterogeneity among the different studies in the cut-off points for the timing of adjuvant chemotherapy, ranging from 8 weeks to more than 12 weeks, as well as in the primary location (colon versus rectum) and stage of disease (II versus III).

Various patient and tumour characteristics may act as influencing factors for timing of adjuvant chemotherapy, including age, comorbidity, tumour grade, tumour size and postoperative complications.[19] Identification of these factors can propose modifiable parameters to minimize delay in initiation of adjuvant chemotherapy.

Due to the absence of randomized data, it has not been firmly established whether there is a time window beyond which adjuvant chemotherapy is of little or no value for long-term outcomes. On the other hand, there is also no evidence that starting adjuvant chemotherapy early (i.e. 4-6 weeks post-surgery) is associated with better outcomes than starting somewhat later, giving the patient more time to recover from surgery. Irrespective of these uncertainties, the timing of adjuvant chemotherapy is often used as a quality indicator.[20]

We analyzed data from a large, population-based cancer registry of patients who are known to benefit most from adjuvant chemotherapy, i.e. with stage III colon cancer. Using these data, we investigated factors affecting timing of adjuvant chemotherapy and evaluated its influence on overall survival.

PATIENTS AND METHODS

Data from the nationwide Netherlands Cancer Registry (NCR) were used, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR is a population-based registry based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR).

Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records. The quality of the data is high due to thorough training of the registration team and computerized consistency checks at regional and national level. Anatomical site of the tumour is registered according to the International Classification of Disease-Oncology (ICD-O).[21] The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis.[22] Furthermore, detailed information was available on: urgency of the resection (emergency resection <24h after presentation); surgical procedure (laparoscopic versus open resection) and anastomotic leakage as a surgical complication. Data on type of chemotherapy (oxaliplatin-based versus non-oxaliplatin-based) was available for patients diagnosed in the South-eastern part of The Netherlands. Data on prolonged postoperative hospital admission (>14 days; yes/no) was available for patients diagnosed in 2012-2013. Prolonged postoperative hospital admission after surgical resection served as a proxy for a complicated postoperative period.

Study population

We selected all patients with colon cancer and lymph node metastases, but without distant metastases at presentation (stage III), diagnosed in The Netherlands in 2008-2013 who underwent surgical resection and received adjuvant chemotherapy (Figure 1). Patients were excluded if they had received local chemotherapy (n=4) or neoadjuvant chemotherapy (n=31). In addition, patients were excluded if the date of chemotherapy initiation was missing (n=1,051) or if chemotherapy was started more than 16 weeks after the surgical resection to ensure that treatment was for adjuvant therapy (n=49). The timing to adjuvant chemotherapy was calculated from the date of surgical resection to the date of initiation of adjuvant chemotherapy. The timing of adjuvant chemotherapy was subdivided into six categories: within 4 weeks; 5-6 weeks; 7-8 weeks; 9-10 weeks; 11-12 weeks and 13-16 weeks from surgical resection. Information on type of adjuvant chemotherapy was available for a subgroup of patients (n=725) and were included as a subgroup analysis. Patients of whom information on prolonged postoperative hospital admission was available (n=2,584) were included as a subgroup analysis. Additionally, patients who underwent surgical resection without receiving adjuvant chemotherapy were included in the crude survival analyses to show overall survival of this group (n=4,899; total n=11,519).

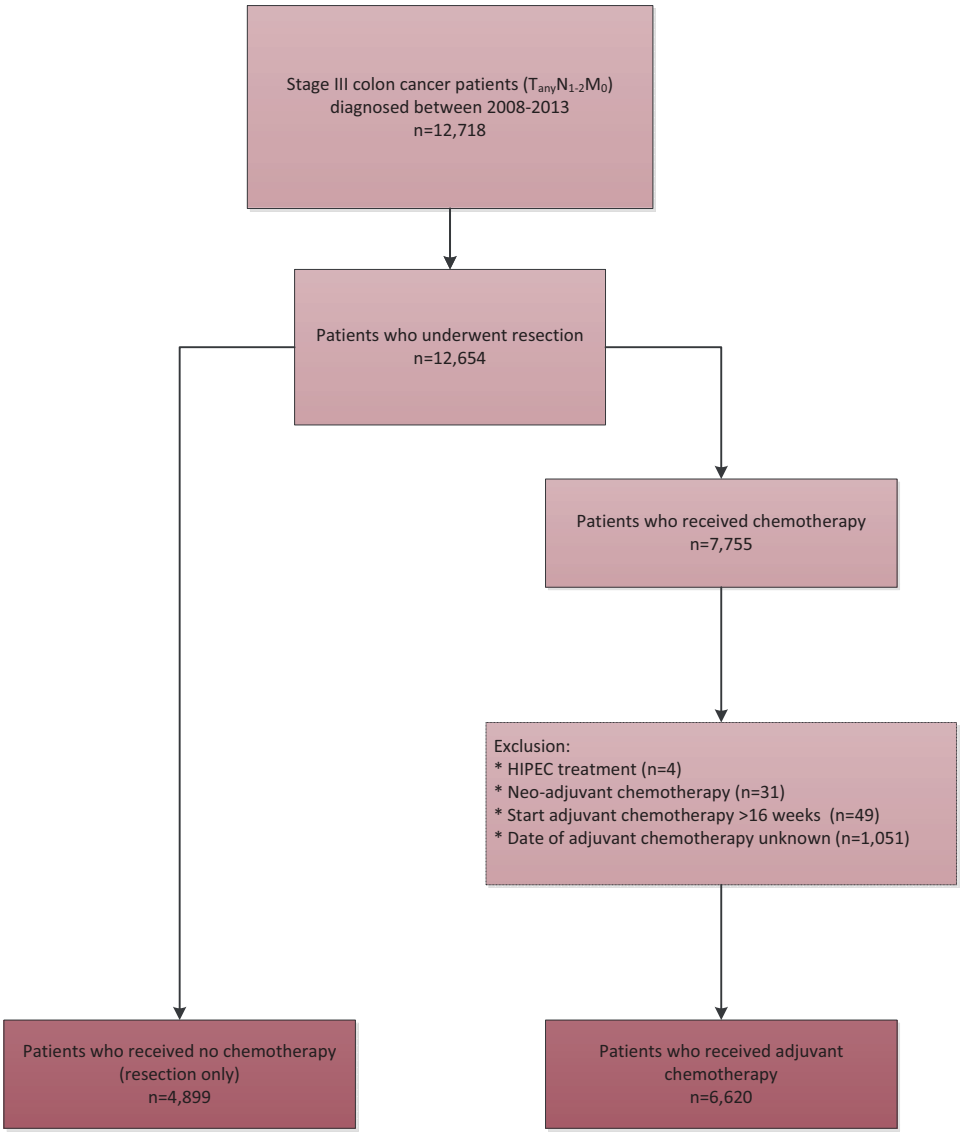

FIGURE 1 Consort diagram of patients selection.

Stage was based on the pathological TNM classification. Tumour localization was categorized into three subsites: proximal colon (C18.0-C18.5), distal colon (C18.6-C18.7) and colon other/not otherwise specified (C18.8-C18.9). Patients were divided into age groups: <65, 65-74 and ≥75 years. The study period was divided biannually into three time periods in order to calculate a possible trend over the years in timing of adjuvant chemotherapy.

Statistical analyses

Differences in clinical, pathological and treatment-related characteristics across the different timings of adjuvant chemotherapy were evaluated using chi-squared tests. Multivariable logistic regression analysis was conducted to assess the independent influence of several patient and clinical characteristics on the probability of starting adjuvant chemotherapy beyond 8 weeks post-surgery. Similar methods were used in a subgroup analysis to evaluate differences in type of chemotherapy across the different timings of adjuvant chemotherapy.

Survival was defined as the date of resection to death or last follow-up date (January 1st, 2015) for patients who were still alive. Crude 5-year overall survival was estimated for the different groups using the Kaplan-Meier method and differences in overall survival outcomes were assessed with the log-rank test.

A multivariable Cox proportional hazards regression model was used to evaluate the relationship between timing of adjuvant chemotherapy and overall survival, with adjustment for clinical, pathological and treatment-related characteristics. *P* values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Over the period 2008-2013, 6,620 patients underwent surgical resection for stage III ($T_{any}N_{1-2}M_0$) colon cancer, and received adjuvant chemotherapy. Mean age of the population was 70 (standard deviation 7.8) years, 14% was ≥75 years of age and 53% was male. The median timing of adjuvant chemotherapy was 5.6 weeks post-surgery. A total of 1,106 patients (17%) commenced treatment within 4 weeks after resection. The majority of the patients (n=4,512, 69%) started chemotherapy between 5 and 8 weeks after resection. A total of 1,002 patients (14%) started treatment after 8 weeks, of whom 165 patients (16%, 2% of total) started treatment between 13 and 16 weeks after resection. Figure 2 presents the distribution of timing of adjuvant chemotherapy in weeks.

Factors associated with timing of adjuvant chemotherapy

In univariable analyses, age, period of diagnosis, T-stage, tumour location, surgical procedure, urgency of resection, presence of an anastomotic leakage and being referred to another hospital for adjuvant chemotherapy all had a significant impact on the timing of adjuvant chemotherapy. In addition, in the subgroup of patients (diagnosed in 2012-2013), a higher proportion of patients with prolonged postoperative hospital admission was found when adjuvant chemotherapy was started beyond 6 weeks (Table 1) ($p<0.0001$). Gender, N stage, differentiation grade and histology of the primary tumour were not

associated with timing of adjuvant chemotherapy (Table 1). Type of chemotherapy was not associated with timing of adjuvant chemotherapy in the subgroup of patients for whom information on type of chemotherapy was available (p=0.918).

In a multivariable logistic regression model (Table 2), elderly patients (≥65 years of age) (adjusted odds ratio (OR) 65-74 versus <65 years 1.3 (95%CI 1.14-1.58) and OR ≥75 versus <65 years 1.6 (1.25-1.94)), patients who underwent an emergency resection (OR 1.8 (1.41-2.32)), patients who suffered from an anastomotic leakage (OR 8.1 (6.14-10.62)) and patients who were referred to another hospital for adjuvant chemotherapy (OR 1.9 (1.36-2.57)) were more likely to start chemotherapy later than 8 weeks post-surgery. Furthermore, in the subgroup of patients (diagnosed in 2012-2013) with information on prolonged postoperative hospital admission, the latter was also associated with a timing of adjuvant chemotherapy of more than 8 weeks (OR 4.7 (3.30-6.68)). Furthermore, patients undergoing a laparoscopic resection (OR 0.5 (0.43-0.61)) were more likely to start adjuvant chemotherapy earlier. Time to start of adjuvant chemotherapy did not differ according to type of chemotherapy in the subgroup of patients with information on type of chemotherapy (OR 1.1(0.65-1.55).

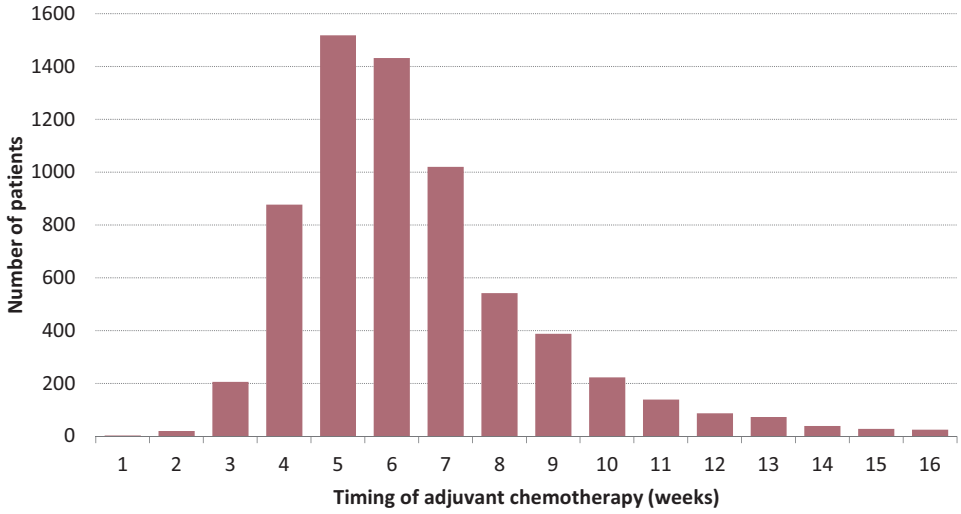

FIGURE 2 Distribution of the time (in weeks) after surgical resection to the start of adjuvant chemotherapy, for patients diagnosed with stage III colon cancer in the Netherlands, 2008-2013 (n=6,620).

TABLE 1 Demographic and clinical variables according to timing of adjuvant chemotherapy for patients diagnosed with stage III colon cancer in the Netherlands, 2008-2013 (n=6,620).

	Timing of adjuvant chemotherapy						*p* value
	≤4 weeks	5-6 weeks	7-8 weeks	9-10 weeks	11-12 weeks	13-16 weeks	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Total	1,106 (17)	2,950 (45)	1,562 (24)	611 (9)	226 (3)	165 (2)	
Gender							0.979
Male	587 (53)	1,564 (53)	841 (54)	327 (53)	125 (55)	86 (52)	
Female	519 (47)	1,386 (47)	721 (46)	284 (47)	101 (45)	79 (48)	
Age							0.001*
<65 years	493 (45)	1,449 (49)	682 (44)	264 (43)	88 (39)	72 (43)	
65-74 years	432 (39)	1,139 (39)	657 (42)	254 (42)	94 (42)	70 (43)	
≥75 years	181 (16)	362 (12)	223 (14)	93 (15)	44 (19)	23 (14)	
Period of diagnosis							0.001*
2008-2009	261 (24)	697 (24)	454 (29)	168 (28)	62 (28)	46 (28)	
2010-2011	371 (33)	1,075 (36)	558 (36)	199 (33)	80 (35)	65 (40)	
2012-2013	474 (43)	1,178 (40)	550 (35)	244 (39)	84 (37)	54 (32)	
T stage							0.022*
T1	16 (2)	62 (2)	36 (2)	8 (1)	3 (1)	2 (1)	
T2	103 (9)	256 (9)	123 (8)	46 (8)	18 (8)	12 (7)	
T3	788 (71)	2,083 (70)	1,070 (69)	423 (69)	145 (64)	105 (63)	
T4	199 (18)	549 (19)	333 (21)	134 (22)	60 (27)	46 (29)	
N stage							0.440
N1	686 (62)	1,894 (64)	976 (62)	381 (62)	135 (60)	111 (67)	
N2	420 (38)	1,056 (36)	586 (38)	230 (38)	91 (40)	54 (33)	
Tumour location							0.011*
Proximal colon	541 (49)	1,499 (51)	847 (54)	313 (51)	130 (58)	86 (52)	
Distal colon	548 (49)	1,398 (47)	685 (44)	286 (47)	86 (38)	75 (46)	
Other/NOS	17 (2)	53 (2)	30 (2)	12 (2)	10 (4)	4 (2)	
Differentiation grade							0.218
Well/moderated	807 (73)	2,153 (73)	1,101 (70)	417 (68)	156 (69)	109 (66)	

TABLE 1 Demographic and clinical variables according to timing of adjuvant chemotherapy for patients diagnosed with stage III colon cancer in the Netherlands, 2008-2013 (n=6,620). *(Continued)*

	Timing of adjuvant chemotherapy						*p* value
	≤4 weeks	5-6 weeks	7-8 weeks	9-10 weeks	11-12 weeks	13-16 weeks	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Poor /undifferentiated	208 (19)	585 (20)	336 (22)	143 (24)	51 (23)	40 (24)	
Unknown	91 (8)	212 (7)	125 (8)	51 (8)	19 (8)	16 (10)	
Histology of primary tumour							0.696
Non-mucinous adenocarcinoma	940 (85)	2,495 *5)	1,316 (84)	500 (82)	188 (83)	137 (83)	
Mucinous adenocarcinoma	139 (13)	396 (13)	206 (13)	97 (16)	35 (16)	24 (15)	
Unknown	27 (2)	59 (2)	40 (3)	14 (2)	3 (1)	4 (2)	
Surgical procedure							<0.0001*
Open resection	585 (53)	1,714 (58)	1,014 (65)	452 (74)	171 (76)	132 (80)	
Laparoscopic resection	521 (47)	1,236 (42)	548 (35)	159 (16)	55 (24)	33 (20)	
Urgency of resection *							<0.0001*
Elective	1,040 (93)	2,708 (92)	1,395 (89)	513 (84)	191 (84)	140 (84)	
Emergency	59 (5)	228 (7)	154 (9)	92 (14)	32 (14)	23 (12)	
Unknown	7 (1)	14 (1)	13 (1)	6 (1)	3 (2)	2 (2)	
Anastomotic leak **							<0.0001*
No	1,068 (96)	2,803 (95)	1,391 (90)	494 (81)	182 (80)	120 (73)	
Yes	8 (1)	39 (1)	80 (5)	65 (11)	33 (15)	30 (18)	
Unknown	30 (3)	108 (4)	91 (5)	52 (8)	11 (5)	15 (9)	
Hospital AC equal to hospital resection							<0.0001*
No	1,075 (97)	2,839 (96)	1,491 (96)	576 (95)	208 (93)	148 (90)	
Yes	31 (3)	111 (4)	71 (4)	35 (5)	18 (7)	17 (10)	
Prolonged hospital admission (>14 days)							<0.0001*
No	467 (98)	1,141 (97)	459 (83)	172 (71)	56 (67)	36 (66)	
Yes	7 (2)	37 (3)	91 (17)	72 (29)	28 (33)	18 (34)	

AC Adjuvant chemotherapy

* Not included in the analysis: urgency of resection unknown and anastomotic leak unknown.

** Included patients diagnosed in 2012-2013 (n=2,584).

TABLE 2 Crude percentages and adjusted odds ratios[2] for timing of adjuvant chemotherapy beyond 8 weeks post-surgery among resected stage III colon cancer patients receiving adjuvant chemotherapy (n=6,620).

	Timing of AC >8 weeks	Multivariable analysis	
	Crude (%)	OR[2]	95% CI
Gender			
Male	15	reference	
Female	15	1.0	0.87-1.18
Age			
<65 years	14	reference	
65-74 years	16	1.3	1.14-1.58
≥75 years	17	1.6	1.25-1.94
Period of diagnosis			
2008-2009	16	reference	
2010-2011	15	0.9	0.78-1.15
2012-2013	15	0.9	0.71-1.04
T stage			
T1	10	reference	
T2	14	1.2	0.65-3.52
T3	14	1.1	0.65-3.23
T4	16	1.2	0.62-3.23
N stage			
N1	15	reference	
N2	15	0.9	0.78-1.08
Tumour location			
Proximal colon	15	reference	
Distal colon	15	1.0	0.83-1.14
Other/NOS	20	1.5	0.94-2.44
Differentiation grade *			
Well/moderated	14	reference	
Poor /undifferentiated	17	1.2	0.98-1.44
Histology of primary tumour *			
Non-mucinous adenocarcinoma	15	reference	
Mucinous adenocarcinoma	17	1.2	0.91-1.62
Surgical procedure			
Open resection	18	reference	
Laparoscopic resection	10	0.5	0.43-0.61
Urgency of resection *			
Elective	14	reference	
Emergency	26	1.8	1.41-2.32

TABLE 2 Crude percentages and adjusted odds ratios[2] for timing of adjuvant chemotherapy beyond 8 weeks post-surgery among resected stage III colon cancer patients receiving adjuvant chemotherapy (n=6,620). *(Continued)*

	Timing of AC >8 weeks	Multivariable analysis	
	Crude (%)	OR[2]	95% CI
Anastomotic leak *			
No	13	reference	
Yes	50	8.1	6.14-10.62
Hospital AC equal to hospital resection			
No	15	reference	
Yes	25	1.9	1.36-2.57
Prolonged hospital admission (>14 days) **			
No	11	reference	
Yes	47	4.7	3.30-6.68

AC Adjuvant chemotherapy, CI Confidence interval, OR Odds ratio
[2]Adjusted for all variables listed.
* Included in the analysis but results not shown tumour grade unknown, histology of primary tumour unknown, urgency of resection unknown and anastomotic leak unknown.
** Included patients diagnosed in 2012-2013 (n=2,584).

Timing of adjuvant chemotherapy and survival

Median follow-up time was 60 months. Figure 3 shows the crude 5-year overall survival rates according to the initiation of adjuvant chemotherapy within 4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks or 13-16 weeks. The crude observed 5-year overall survival rates were 75%, 76%, 72%, 64%, 61% and 54%, respectively, while the proportion of 5-year overall survival among patients who underwent surgery only (n=4,899) was 39%. To overcome immortal time bias between patients who received adjuvant chemotherapy and patients who underwent resection only; only patients who survived the first 16 weeks after the date of resection were included in a subgroup analysis. Similar results for overall survival were found (data not shown).

After case-mix adjustment (Table 3), timing of adjuvant chemotherapy beyond 8 weeks was associated with an increased hazard of death (HR 9-10 versus ≤8 weeks 1.4 (1.21-1.68); HR 11-12 versus ≤8 weeks 1.3 (1.06-1.59) and HR 13-16 versus ≤8 weeks 1.7 (1.23-2.23)). In addition, initiation of adjuvant chemotherapy between 5 and 8 weeks post-surgery showed no decrease in overall survival compared to initiation within 4 weeks (HR 5-6 versus ≤4 weeks 0.9 (0.79-1.11) and HR 7-8 versus ≤4 weeks 1.1(0.91-1.30)). After stratification, no effect of age on hazard ratios of death for timing of adjuvant chemotherapy beyond 8 weeks was found (data not shown).

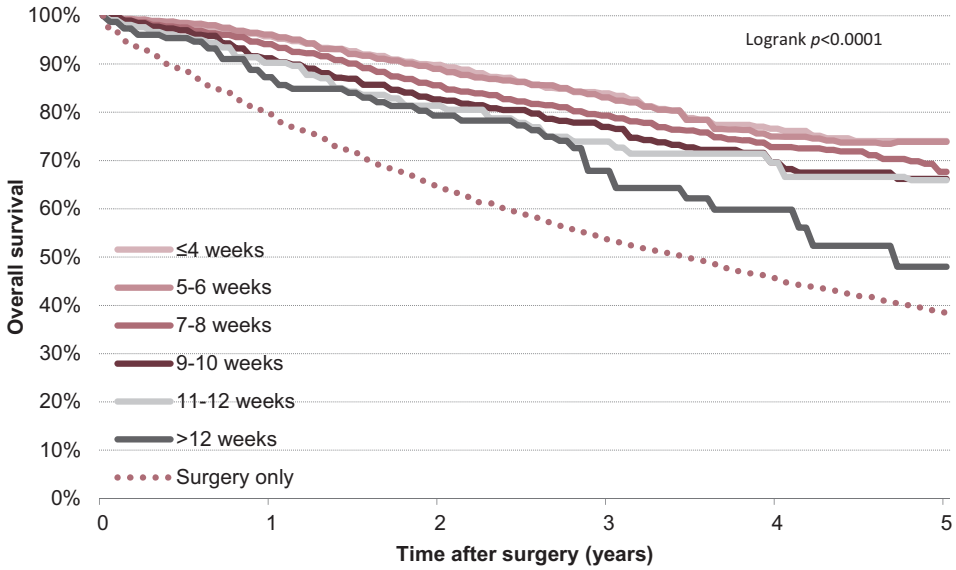

FIGURE 3 Crude overall survival according to whether adjuvant chemotherapy was initiated within 4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks, 13-16 weeks (n=6,620) or patients undergoing surgery only (n=4,899).

TABLE 3 Crude 5-year overall survival and adjusted hazard ratios[2] for death among stage III resected colon cancer patients receiving adjuvant chemotherapy (n=6,620).

Variable	Crude 5-year survival	Multivariable analysis	
	(%)	HR[2]	95% CI
Timing of AC			
≤4 weeks	75	1.0	reference
5-6 weeks	76	0.9	0.79-1.11
7-8 weeks	72	1.1	0.91-1.30
≤8 weeks	74	1.0	reference
9-10 weeks	64	1.4	1.21-1.68
11-12 weeks	61	1.3	1.06-1.59
13-16 weeks	54	1.7	1.23-2.23

AC Adjuvant chemotherapy, CI Confidence interval, HR Hazard ratio

[2]Adjusted for gender, age, period of diagnosis, T stage, N stage, tumour location, differentiation grade, histology of tumour, surgical procedure, urgency of resection, anastomotic leak, hospital AC equal to hospital resection.

DISCUSSION

Currently available data suggest that a start of adjuvant chemotherapy later than 8 weeks post-surgery in stage III colon cancer patients is associated with poorer survival. We identified factors that influenced the probability of starting adjuvant chemotherapy beyond 8 weeks, and studied the effect of the timing of adjuvant chemotherapy on survival. We found that initiating adjuvant chemotherapy beyond 8 weeks was associated with a decrease in overall survival, even when relevant prognostic factors were taken into account. However, the timing of adjuvant chemotherapy had no effect on overall survival when this was started anytime within 8 weeks of surgery.

Different cut-offs for the initiation of adjuvant chemotherapy were used in previous studies leading to different definitions of a delayed start of chemotherapy, ranging from 8 to 12 weeks.[2, 23] Other studies also included rectal cancer patients [18, 24, 25], or high-risk stage II colon cancer patients[26]. Since the benefit of adjuvant chemotherapy in patients with stage II colon cancer and in rectal cancer is less obvious or even questionable, the effect of timing of adjuvant chemotherapy on outcome may be diluted or masked in studies that included these patients. In our study, only 14% of the patients started adjuvant chemotherapy beyond 8 weeks of surgery, which is less compared to the 19-42% which has been observed in studies performed in other countries.[14, 27]

Patient age, emergency resection, surgical procedure (laparoscopic versus open resection), a complicated postoperative recovery (suffering from anastomotic leakage and/or prolonged postoperative hospital stay) and receiving adjuvant chemotherapy in a different hospital than in which surgery was performed were all identified as factors that have an impact on timing of adjuvant chemotherapy. These findings are comparable with other studies.[6, 17, 28] Hendren et al. found that the presence of surgical complications was related to a delayed start and omission of adjuvant chemotherapy in stage III colorectal cancer patients.[29] In a study including rectal cancer patients, the duration of postoperative hospital stay was also strongly associated with a delayed start of adjuvant chemotherapy.[26] In line with previous studies of Poylin et al.[30] and Lacy et al.[31], we found a lower odds for starting adjuvant chemotherapy beyond 8 weeks when patients underwent a laparoscopic resection in stead of an open resection.

The timing of adjuvant chemotherapy had no effect on overall survival when this was started anytime within 8 weeks of surgery. This is in accordance with a study of Hershman et al., who found no survival gain in patients receiving adjuvant chemotherapy within 4 weeks compared to patients receiving adjuvant chemotherapy between 5-8 weeks.[14] The 5-year survival proportion of patients starting adjuvant chemotherapy between 13 and 16 weeks was 54% in our study, while the proportion of 5-year survival among patients who underwent surgery only was 39%.

Previous studies have shown similar results using population-based data on a regional and/or hospital level. This is the first large nationwide observational study to describe the effect of timing of adjuvant chemotherapy in resected stage III colon cancer patients on long-term survival. An important limitation of this study however is its observational nature. The effects observed may be highly susceptible to selection bias, e.g. less fragile patients receiving adjuvant chemotherapy first. Although we adjusted for several patient and tumour characteristics, data about functional status, specific postoperative complications other than anastomotic leakage and comorbidity were not available. Therefore an analysis of the effect of timing of adjuvant chemotherapy on long-term outcomes may be subject to residual confounding. We hypothesize that patients starting chemotherapy beyond 8 weeks post-surgery were in worse general health, have had more surgical complications and had an inherently worse prognosis, which may have influenced the results. Another limitation of our study is that for 1,051 patients date of chemotherapy initiation was missing and were therefore excluded. However, results of our study indicate that case-mix did not differ between this group and included patients.

We did not find a negative effect on survival of initiating adjuvant chemotherapy between 5-8 weeks post-surgery compared to initiation within 4 weeks. Therefore we hypothesize the presence of a time window in which patients can recover from surgery and give them physically and emotionally more time to prepare for the next step in the treatment process. A prospective cohort study in which patients are followed over time, and in which more information about unmeasured confounders and modification of the identified factors is available, would be valuable. A national population-based colorectal cancer registry is currently in development in The Netherlands.

Our data support the inclusion of the timing of adjuvant chemotherapy as a quality indicator for cancer treatment. It is important that multidisciplinary teams (MDTs) should seek for the optimal timing of adjuvant chemotherapy taking social and frailty aspects of the patients into account.[32] Efforts should be made to ensure that the process of adjuvant chemotherapy treatment is based on shared decision-making between patients and providers whenever possible and appropriate.

In conclusion, our data support the initiation of adjuvant chemotherapy in stage III colon cancer within 8 weeks of surgery.

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8

Summary, general discussion and future perspectives

In this chapter the main findings of the studies included in this thesis are summarized and several methodological considerations are highlighted that should be taken into account when interpreting the results. We discuss the results in a broader context including possible implications for clinical practice and future research.

SUMMARY OF THE MAIN FINDINGS

Part I of this thesis starts with an overview of colorectal cancer survival in the Netherlands. **Chapter 2** provides an overview of the remarkable changes in epidemiology, treatment and survival of colorectal cancer in the Netherlands in the period 1989 to 2014. There has been an increase in the age standardized incidence of both colon and rectal cancer in the past 25 years, most marked by male colon cancer patients. The annual colorectal cancer mortality decreased over time, both in males and females. More than 90% of patients diagnosed with non-metastasized colorectal cancer underwent resection (including local excision such as polypectomy and transanal endoscopic microsurgery (TEM)). The use of adjuvant chemotherapy for stage III colon cancer increased (14 % to 60%), as well as the use of neoadjuvant radiotherapy and chemoradiotherapy for stage II/III rectal cancer (14% to 60% and 2% to 66% respectively). The administration of systemic therapy and metastasectomy increased for patients diagnosed with stage IV colorectal cancer. The 5-year relative survival increased for both colon and rectal cancer (53% to 62% for colon cancer; 51% to 65% for rectal cancer), with the largest improvement in stages II and III, and the most obvious gain in survival within the first 12 months after diagnosis.

In **chapter 3**, survival rates among non-metastatic colorectal cancer patients whom underwent resection and were diagnosed between 2008 and 2013 in the Netherlands, are compared between age groups. For this study, patients were grouped by age: <65, 65-74, 75-84 and ≥85 years. The substantial age-related differences in survival rates existing in 5-year overall survival (82%, 73%, 56% and 35% for colon cancer; 82%, 74%, 56% and 38% for rectal cancer), were less prominent in 5-year relative survival (85%, 81%, 75% and 75% for colon cancer; 84%, 82%, 75% and 81% for rectal cancer) and disappeared in conditional relative survival (i.e. surviving the first year after surgical resection) (86%, 85%, 87% and 101% for colon cancer, 84%, 83%, 84% and 109% for rectal cancer) among the different age groups. An increased relative excess risk (RER) of death was observed in the elderly as compared to younger patients for colon and rectal cancer. When RER was calculated for patients who survived the first year after surgery, differences in RER disappeared for all age groups for colon and rectal cancer. Postoperative 1-year mortality rates were doubled or tripled compared to postoperative 30-day mortality (10.7% versus 4.2% for colon cancer; 7.1% versus 2.3% for rectal cancer). The excess mortality of the first postoperative year was highest in the older age groups (17.3% for colon cancer; 12.9% for

rectal cancer), in patients with stage III colorectal cancer tumours (11.5% for colon cancer; 5.4% for rectal cancer) and when patients underwent open resection for both colon and rectal cancer (10.2% for colon cancer; 6.1% for rectal cancer). Moreover, colon cancer patients undergoing emergency resection experienced highest excess mortality (20.7%). Subanalysis showed that patients with two or more concomitant diseases present at diagnosis also had high excess mortality (11.3% for colon cancer; 11.1% for rectal cancer). Results of this study suggest that surgery has a greater and prolonged impact on survival postoperatively in elderly. Colorectal cancer itself may not be the main cause of age-related differences in survival, and it appears that survival in elderly after major surgery may be modifiable.

Part II of this thesis focusses on determinants of survival. In **chapter 4**, the objective was to evaluate short-term outcomes (prolonged postoperative hospital admission, anastomotic leakage, postoperative 30-day mortality, administration of neoadjuvant or adjuvant treatment) and 5-year relative survival in patients with synchronous colorectal cancer compared to patients with solitary colorectal cancer. All patients diagnosed with primary colorectal cancer between 2008 and 2013 who underwent elective surgery were selected from the Netherlands Cancer Registry. Synchronous colorectal cancer was defined as two or more invasive tumours, diagnosed simultaneously or within six months. Out of 41,060 colorectal cancer patients, 5% had synchronous colorectal cancer. Patients with synchronous colorectal cancer were older, more often male and diagnosed with more advanced tumour stage compared to solitary colorectal cancer. Half of the patients with synchronous colorectal cancer underwent an extended surgery. Synchronous colorectal cancer patients with at least a stage II-III rectal tumour were less likely to receive neoadjuvant (chemo)radiotherapy and synchronous colorectal cancers patients with at least one stage III colon tumour were less likely to receive adjuvant chemotherapy. Synchronous colorectal cancer was independently associated with decreased survival (relative survival 77% versus 71% in solitary colorectal cancer; adjusted RER 1.1, 95% CI 1.01-1.23). The results emphasize that information on differences in short- and long-term outcomes between solitary and synchronous colorectal cancer is relevant since a preoperative diagnosis of synchronous colorectal cancers may modify or extend the type of surgical procedure and influence clinical decision making of the use of additional treatments. The study confirmed the importance of identifying synchronous tumours, preferably prior to surgery, to provide optimal treatment.

In **chapter 5** the association between hospital volume for colorectal cancer and surgical care characteristics and between hospital volume and overall survival were investigated. In this nationwide study all patients with primary non-metastatic colorectal cancer who underwent resection between 2005 and 2012 were included. Hospitals were grouped by

volume for colon (<50; 50-74; 75-99 and ≥100 resections/year) and rectum (<20; 20-39 and ≥40 resections/year). During the study period a decreasing trend in low-volume hospitals was observed in the Netherlands. In 2012, 31 of the 91 hospitals performed less than 50 colon cancer resections per year, and 21 of the 90 hospitals performed less than 20 rectal cancer resections per year. No differences in 5-year overall survival between hospital volumes for both colon and rectal cancer were found. However, marginal differences were found between hospital volumes in surgical approach (conversion of laparoscopic to open) (20.2% versus 16.9%, adjusted odds ratio (OR) <50 versus ≥100 resections/year 1.3, (1.06-1.46) for colon cancer) and postoperative 30-day mortality (4.4% versus 3.9%, adjusted OR <50 versus ≥100 resections/year 1.2, (1.02-1.35) for colon cancer; 3.4% versus 2.3%, adjusted OR <20 versus ≥40 resections/year 1.4, (1.09-1.84) for rectal cancer).

In the study described in **chapter 6** we developed and validated prediction models to estimate postoperative 90-day mortality and overall survival for colon and rectal cancer patients. This study included all primary colorectal cancer patients diagnosed and resected between 2008 and 2014 in the Netherlands. Variables predicting postoperative 90-day mortality included gender and age of the patient, pathological T-stage and pathological N-stage of the primary tumour, urgency of resection (colon cancer), surgical approach (laparoscopic versus open), type of surgery and anastomotic leakage. Predictors constituting the final model to estimate 5-year overall survival included gender and age of the patient, tumour stage of the primary tumour, urgency of resection (colon cancer), tumour location (colon cancer), adjuvant chemotherapy (stage III colon cancer), presence of multiple tumours (colon cancer), radicality, anastomotic leakage and neoadjuvant treatment (stage II-III rectal cancer). Results of this study can be used to develop web-based calculators which can be applied to calculate the overall probability of postoperative mortality and survival in the period after colorectal cancer surgery. This information may be valuable to both patients and surgeons to help in clinical decision making and to develop individual follow-up schedules.

The last study included in this thesis investigated factors affecting timing of adjuvant chemotherapy and evaluated the influence on overall survival among patients with stage III colon cancer who underwent resection and received adjuvant chemotherapy between 2008 and 2013 in the Netherlands (**chapter 7**). Timing of adjuvant chemotherapy was subdivided into: ≤4, 5-6, 7-8, 9-10, 11-12 and 13-16 weeks post-surgery. The median timing of adjuvant chemotherapy was 5.6 weeks post-surgery. Fourteen percent of the patients started treatment more than 8 weeks after resection. Factors associated with starting treatment after 8 weeks were older age, emergency resection, anastomotic leakage, referral to another hospital for adjuvant chemotherapy and prolonged postoperative hospital admission. The crude observed 5-year overall survival rates for the different timings of adjuvant chemotherapy were 75%, 76%, 72%, 64%, 61% and 54%, respectively.

After case-mix adjustment, starting between 5 and 8 weeks post-surgery showed no decrease in overall survival compared to initiation within 4 weeks (HR 5-6 weeks 0.9 (0.79-1.11); HR 7-8 weeks 1.1 (0.91-1.30)). However, commencing later than 8 weeks was associated with decreased overall survival compared to initiation within 8 weeks (HR 9-10 weeks 1.4 (1.21-1.68); HR 11-12 weeks 1.3 (1.06-1.59); HR 13-16 weeks 1.7 (1.23-2.23)). These results support the initiation of adjuvant chemotherapy in stage III colon cancer patients within 8 weeks post-surgery.

Methodological considerations

The studies in this thesis have several strengths and weaknesses related to the data sources and study design that were used.

Strengths and limitations of the data sources

Netherlands Cancer Registry

The studies that are described in this thesis are based on data from the Netherlands Cancer Registry (NCR). Since 1993, the southeast part of the Netherlands registers comorbid conditions present at time of cancer diagnosis.[1, 2] This is unique compared to other cancer registries worldwide.

Register-based observational studies often have large sample sizes and great statistical power. Second, the registry covers virtually all cases. However, the data are collected independent of research questions, and as a result important information might be lacking.[3] In the data used, for instance, additional information on the development and treatment of recurrences, performance status, specific treatment details (e.g. used chemotherapeutic agents, postoperative complications, reasons (not) to undergo specific treatments) and disease related symptoms were not collected.

Study design

All studies in this thesis had an observational design and the following advantages and disadvantages of this approach should be considered. Randomized clinical trials (RCTs) are considered the gold standard for establishing efficacy of new therapies. RCTs have strict inclusion criteria for participation which hampers the generalizability of the outcomes in routine practice.[4, 5] The observational nature of population-based studies has limitations in establishing causality (internal validity) but contributes to better generalizability (external validity), as all patients are included and treatment decisions are based on clinical and patient preferences. Thus, population-based studies provide a unique insight into the effects of treatments in everyday clinical practice.[6-8]

The NCR allows the evaluation of outcomes in the general patient population and provides information regarding the use, safety and outcomes in the real world. Especially for large groups of patients who do not meet the eligibility criteria from RCTs, observational studies are of utmost importance. Nevertheless, several biases are inherent to population-based observational studies and should be considered when interpreting the results of the studies included in this thesis.

Bias and confounding

Here, the most important biases and how these biases were dealt with are discussed.

Selection bias

Selection bias may either refer to the selective recruitment of patients into the study who are not a representative of the population intended to be analyzed, or to systematic differences between baseline characteristics of the groups that are compared in the study. Data were extracted from the nationwide NCR, which collects data on all newly diagnosed cancer patients. Therefore, the NCR will be a representative of the population as seen in everyday clinical practice and the influence of the first type of selection bias was limited. In one study, we used data derived from the southeast area of the Netherlands (*chapter 3*). This area comprises about 2.4 million inhabitants (~15% of the Dutch population) and encompasses 10 community hospitals. Although no academic hospitals are included in this region, the data from this area are believed to be representative for the total population of colorectal cancer patients in the Netherlands.

The second type of selection bias is present in all studies included in this thesis in which patients were grouped according to a certain oncological treatment (*chapters 3-5, 7*). There were significant differences on several patient and tumour characteristics such as age and stage. Attempts to limit this potential form of selection bias were made by using statistical techniques to adjust for these imbalances between treatment groups. Statistical regression models were used to produce estimates of treatment effects adjusted for a large number of relevant patient and tumour characteristics (covariates) that were available in the NCR. Due to lack of information on other prognostic factors, these analyses cannot fully rule out selection bias.

In addition to overall survival, we included relative survival and excess mortality analyses in some studies (*chapters 2-4*). Relative survival and excess mortality analyses use overall survival and the total number of deaths, respectively, and then adjust for the expected survival and number of deaths in the underlying population using population life-tables. Therefore, these outcomes might be less prone to selection bias than overall survival.

Immortal time bias

Studies presented in this thesis have been exposed to immortal time bias since the time between cancer diagnosis and treatment initiation was taken into account in some of the survival analyses. During this period, death could not occur, since patients must have been alive to receive treatment. A period of 'immortal time' was present. This bias may result in an overestimation of the effect of a treatment.

To minimize immortal time bias, the starting points for survival analyses were chosen as adequately as possible. For studies including only patients with colorectal cancer who underwent resection (*chapters 3, 4, 6 & 7*), the date of resection of the primary tumour was used to evaluate overall or relative survival between groups. Moreover, in some studies we included conditional survival (condition of surviving a certain period) (*chapters 3, 5 & 7*).

Stage migration

One should consider potential stage migration and related forms of bias (lead time bias) when interpreting trends in treatment and survival. Improvements in diagnostic techniques (for example screening programs) in a later period may result in detection of tumours that would previously had remained silent or unidentified. Patients with this type of tumours will be added to the group of colorectal cancer patients, thereby improving the survival rate of the group of healthy people (as the patients with poorer prognosis have been removed). At the same time, the group of colorectal cancer patients will also show an improvement in survival, as the patients with formerly silent or unidentified tumours probably had better prognosis than the average patient in the colorectal cancer group. This results in an apparent improved survival within each group over time, while no actual improvement has taken place. In chapter 2, survival of all stages combined still improved, indicating that the increase of survival is not only the result of stage migration.

Residual confounding

Due to lack of randomization in the studies in this thesis, we were only able to adjust for known and observed characteristics in our statistical analyses, while other unobserved characteristics might also have influenced outcomes.[8] For instance, no information on functional status and specific postoperative complications other than anastomotic leakage were available.

GENERAL DISCUSSION

The research underlying this thesis aimed to reveal aspects of colorectal cancer survival in the Netherlands by presenting trends in incidence, mortality, treatment and survival, as well as to investigate the impact of determinants of the disease on outcome of treatment and long-term survival, using real-world data from the Netherlands Cancer Registry.

The aging population leads to a challenge in colorectal cancer survival

Real-world data from the Netherlands showed that survival of colorectal cancer patients improved over the last decades, which could be attributed to advancements in diagnostics and treatment. The most obvious gain in survival in later years is observed in the first year after diagnosis. The absolute number of colorectal cancer patients in the Netherlands is still increasing rapidly, as a result of the implementation of a nationwide screening program in 2014 and aging of the population.[9] Due to the increasing uptake of screening in the Netherlands, incidence rates will rise further the forthcoming years, after which it is likely to decrease among elderly, similar to what is seen in the US.[10-12] Mortality rates are expected to decrease further because of the screening program, by earlier detection and thereby more curative and less invasive treatment options.[13] However, colorectal cancer is still the second leading cause of cancer-related death.[9]

Colorectal cancer is predominantly a problem of the elderly: almost half of the cases occur in patients aged 75 years or older.[9] The incidence increases with advancing age, doubling every 7 years in patients aged 50 years or older. The elderly population is very heterogeneous and tends to have more advanced disease stage.[14] Limited evidence-based guidelines are available for the age group 70 years or older[15], as older patients with colorectal cancer are generally excluded from randomized clinical trials and the fit ones who are recruited are not representative of the general elderly population. Many uncertainties still remain regarding the optimal treatment, therefore, chosing between treatment options in elderly colorectal cancer patients can be challenging. It is important to carefully weigh the risks and benefits of potential treatments in individual patients, a practice which most certainly leads to variation in care. For instance, although adjuvant chemotherapy has been the standard of care for stage III colon cancer patients since 1990[16], the probability to receive chemotherapy following surgical resection declines with increasing age[17-20] and varies between hospitals[20-22].

When feasible, resection of the primary tumour is the preferred curative treatment option for non-metastasized colorectal cancer. The chances of undergoing a surgical resection is known to decrease with increasing age.[23] The age-related difference may be caused by an expectation of poorer outcome in elderly patients due to poor performance status, presence of comorbidities or higher stage of the disease. We demonstrate that

the resection rates became lower in the older age group, especially in the oldest age group. Among patients with stage I-III colon cancer, the proportion undergoing resection in those aged 75-84 years was 93%, while the resection rate in patients aged 85 years or older was 89%. For stage I-III rectal cancer patients, resection rates decreased from 80% in patients aged 75-84 years to 57% in those aged 85 years or older. A study of Speelman et al. also reported lower resection rates in older age groups over time in the Netherlands.[24] This suggests increased availability of other treatment options, and better selection of patients through improved diagnostic accuracy and preoperative staging.[25-29] According to a report from the National Bowel Cancer Audit, the proportion of patients with colorectal cancer undergoing major resection showed a steady decrease.[30] This was caused by a mixture of early-stage disease, patient frailty and advanced cancer. For instance, for a subgroup of patients with small rectal tumours, less invasive local resections have become good alternatives to major surgical resections.[31, 32] Furthermore, for elderly patients with rectal cancer, (chemo)radiotherapy followed by watchful waiting might be an alternative treatment option.[31, 33]

Although excellent results of colorectal cancer surgery in elderly patients are reported[34, 35], comorbidity and frailty challenge surgical management in these patients.[36, 37] In combination with the start of the Dutch ColoRectal Audit (DCRA) in 2009, this may have led to a change in habits and opinions of surgeons, in which they became more careful in operating these fragile group of patients. This thesis demonstrates that postoperative mortality was higher with increasing age. The highest mortality rate in the elderly occurs during the early postoperative period.[23, 38, 39] Importantly, in line with prior population-based studies[39-41], when elderly patients survived the first year after surgery, survival was comparable to younger patients. This emphasizes that surgical treatment of colorectal cancer in the aging population remains a formidable challenge, and the chances of a successful outcome with a good quality of life over the remaining life span need to be weighed against the risk of potential complications with a detrimental outcome.

Clinical features affecting colorectal cancer treatment and survival

Chronic diseases like diabetes mellitus, mental health problems and cardiovascular diseases are an increasing problem in the Western world and generally more common among the elderly than younger adults. Many of these diseases are not life threatening in the short term, consequently, many people live with, rather than die from, chronic health conditions. Cancer itself often is a chronic disease with long-term consequences for health and quality of life. Cancer and other comorbid conditions share many common risk factors (e.g. older age, smoking, obesity) and therefore cancer often co-occurs with so called benign chronic conditions.[42] Furthermore, some biological mechanisms that are associated with comorbidity may predispose to cancer (e.g. hepatitis B, diabetes,

tuberculosis).[43-45] With the aging of the population, comorbidity among colorectal cancer patients is common. As shown in this thesis, the proportion of Dutch colorectal cancer patients with two or more concomitant diseases varied from 35% in those aged 65-74 years to 51% in those aged 85 years or older.

The co-existence of cancer and other chronic conditions has substantial implications for treatment choices and outcomes. Cancer patients with comorbidity are generally more likely to receive an altered, less intensive oncological treatment compared to patients without comorbidity. For instance, previous studies have found that the administration of chemotherapy among colorectal cancer patients is lower among patients with comorbidity, independent of age.[46-49] Cancer patients with comorbidity have poorer survival[48, 50] and quality of life[51, 52]. Furthermore, delivery of care to patients with multiple problems requires a greater diversity of expertise resulting in greater costs of care for both patients as well as the health care system. Between 2003 and 2011 the annual direct costs of cancer (including benign neoplasms) already doubled from 2.2 billion euros to 4.1 billion euros. The share of costs in total cost of Dutch health care was 5.0% in 2003 and 6.1% in 2011.[53]

Previous malignancy is a common comorbid disease in colorectal cancer patients. As mentioned above, early detection of cancer as well as developments in oncological treatment have resulted in a prolonged survival period of time after many types of cancer. Cancer patients who survive 5 or more years without recurrences or metastasis are regarded as 'clinically cured'. However, cancer survivors are at increased risk for a variety of late effects after treatment, some life-threatening, such as the development of secondary tumours. As the number of cancer survivors increases, there is an increase in patients with multiple malignancies or second tumours. This concerns particularly nations with a well-functioning health care system like the Netherlands. The relatively good survival rates and the presence of appropriate diagnostic facilities increase the likelihood of multiple cancers occurring and being detected within one patient. Colorectal cancer is one of the most prevalent second cancers among long-term cancer survivors in the Netherlands.[54] A second cancer diagnosis may impair survival and undoubtedly result in more complex oncological treatment.

In this thesis we elaborate on the treatment and outcome of synchronous colorectal cancers and show that 5% of the colorectal cancer patients were diagnosed with a second colorectal cancer within 6 months after the index tumour. In line with previous studies, these patients were more likely to undergo extended surgery[55, 56] and received less intensive (neo)adjuvant treatment compared to patients with one colorectal tumour. Conflicting results have been reported regarding long-term prognosis of patients with multiple colorectal tumours.[55, 57, 58] We found that synchronous colorectal cancers were associated with a decrease in survival. A previous Dutch study of Liu et al. showed that compared to the general population, a higher risk of developing a second colorectal

tumour was observed in all subsites of colon and rectum among previous patients with colorectal cancer.[59] The elevated risk of developing a second colorectal tumour can be partly explained by a surveillance effect during 2-5 years of follow-up, since patients with colorectal cancer are routinely followed up to 5 years.[15] These findings hint the relevance of detecting synchronous colorectal tumours at diagnosis and emphasizes the importance of closely monitoring patients with prior colorectal cancer in order to achieve early detection of and treatment for a possible second colorectal tumour.

Quantity versus quality: the ongoing debate about variation in care

Quality of cancer care is a broad term and is difficult to measure. However, in this thesis we have made a starting point by revealing the impact of both clinical (patient- and tumour related) and demographic (hospital) determinants on patterns of care and survival, thereby considering multiple components that are involved in the process of quality of cancer care. Evidence from clinical trials is used to determine the right treatment for patients with cancer. Evidence-based guidelines are developed to guide and assist medical specialists in their decision-making. Nevertheless, in the current era of an aging population and increasing presence of comorbidities, personalized medicine is more often needed making it more difficult to determine whether patient care complies with the underlying philosophy of the guidelines. And even if patient care meet the terms of guidelines and evidence-based medicine, the outcome remains dependent on how well treatment is delivered.

With cancer incidence on the rise, quality of cancer care ranks highly on the political agenda in most European countries. There has been an increasing interest in improving quality of cancer care and the need to further identify reliable parameters to gain insight in differences in quality of care between institutions. One example is the positive association between improved survival and centralization of complex surgical cancer care in high volume hospitals in tumours with relatively low incidence such as esophageal and pancreatic cancer, which has led to the introduction of volume quota for surgery in several countries.[60-62] In the Netherlands, in all hospitals patients with colorectal tumours are operated on. The number of colorectal cancer resections per year per hospital is much higher in the Netherlands compared to the United States, where higher hospital volume was associated with better colorectal cancer survival. The hospitals within the lowest volume categories in this thesis would be placed in high volume categories in most studies originating from the United States.[63, 64] We found no differences in overall survival between hospital volumes for colorectal cancer patients and only minor differences between hospital volumes in postoperative mortality. In general, our thesis implies that for the current situation in the Netherlands, hospital volume is not a critical factor to be taken into account for future colorectal cancer survival outcome and should not be used

as an indicator reflecting the quality of colorectal cancer care. However, the conclusions of this study are not applicable for all colorectal cancer patients. A substantial proportion of patients with locally advanced rectal cancer are recommended to be referred to specialized centres in the Netherlands, since these surgical procedures are more complex. By referring these patients, sufficient expertise is build in the high volume hospitals and bad outcomes are avoided in low volume hospitals.[65] A study of Birkmeyer et al. described the potential processes of care that may explain improved outcomes in high volume hospitals for complex surgery.[66] One of the main attributes for improved surgical outcome was adequate resources imbedded in a multidisciplinary approach. Therefore, in many guidelines concerning cancer care, a multidisciplinary approach is advocated to arrange proper care by a range of professionals with different backgrounds.[67, 68] Other factors described by Birkmeyer et al. were case-mix and the level of personnel's expertise and skills. Knowledge, experience and skills of individual medical specialists providing care for cancer patients might vary in such a way that it leads to variation between hospitals and in outcome. Although evidence-based guidelines were developed to transfer the best available knowledge on cancer care to all medical specialists treating these patients, recommendations in guidelines are not always followed leading to inter-hospital variation, which is observed in previous Dutch studies.[20, 69-72] The central question remains whether inter-hospital variation is inappropriate or reflects good quality of care. Individualized treatment, especially among elderly or fragile cancer patients, is often considered to be beneficial. In many instances this might lead to alternative oncological treatment or even withholding treatment. If this prevents treatment related complications without exposing the patient to a disproportionate risk of tumour recurrence or death, this might be considered good quality of care. For example, for stage III colon cancer patients, the time interval from surgery to the initiation of chemotherapy has been proposed as an important factor that could affect the overall outcome. In this thesis we showed that initiating adjuvant chemotherapy beyond 8 weeks was associated with a decrease in survival. Interestingly, a negative effect on survival of initiating adjuvant chemotherapy between 5 and 8 weeks post-surgery compared to initiation within 4 weeks was not found. Therefore, a time window seems useful and safe in which patients can recover from surgery and give them physically and emotionally more time to prepare for the next step in the treatment process. As shown in a previous study of Hendren et al., surgical complications are associated with a delay in the administration of adjuvant chemotherapy.[73] Since we have shown that the timing of adjuvant chemotherapy had no effect on survival when this was started anytime within 8 weeks of surgery, it still seems beneficial to start adjuvant chemotherapy in patients with complicated postoperative recovery.

Improvement in quality of care may have different meanings across the various stakeholder groups. What a patient defines as quality of care may not always correspond with how

politicians or caregivers interpret (measures of) quality of care. Over the last decennium, patients are increasingly being involved in treatment decisions by shared-decision making between doctor and patient.[74] A key element of shared-decision making is the exchange of information on possible treatment options and expected benefits (survival) and harms (mortality, morbidity) of each option. Statistical prediction models can be applied to gain insight and to calculate the overall probability of a specific outcome. In this thesis we developed and validated prognostic models to predict postoperative 90-day mortality and overall survival among stage I-III colorectal cancer patients who underwent resection. Results can be used to develop web-based calculators which are simple to use in everyday practice and may provide both patients and surgeons with relevant information to make a shared treatment plan.

FUTURE PERSPECTIVE

Colorectal cancer was once seen as a single entity, however, nowadays it should be divided in multiple subgroups. Elderly represent a large part of colorectal cancer patients. Comorbidities, which are particularly frequent in elderly, increase the complexity of cancer treatment and survival. As mentioned above, the aging population and thereby the increasing number of comorbidities in colorectal cancer patients should become one of the focus points for future colorectal cancer research. Although it is important to individualize treatment decisions to fit the needs of each patient as much as possible, until now we are still unable to fully discern from current evidence why medical specialists choose to discontinue, alter or even reject oncological treatment in elder colorectal cancer patients. Inter-hospital variation is present in colorectal cancer care and suggests there is room for improvement in outcome. However, to improve quality of cancer care, the whole care process should be analyzed. Focusing on only one factor (e.g. surgery) is insufficient and certainly will not guarantee a better quality of cancer care. Furthermore, next to quantitative outcome measures such as survival and mortality, quality outcome measures like quality of life and preservation of independence are becoming equally, if not, more important. It is important that medical specialists recognize the need to treat the whole patient and not just the tumour. Side-effects of both the cancer and the treatment should be relieved and quality of life of the patient should be maintained whenever and so far as possible. Medical specialists must continue to take into account patient's preferences regarding treatment and communicate effectively with the patient.

Age should not be a limiting factor in the treatment of colorectal cancer patients. The management of the heterogeneous older patient population requires a stepwise approach at different stages in which a geriatrician should be involved. In a previous study the need for geriatric screening and assessment and the feasibility of including geriatrics in the process of oncological care has been shown.[75] The inclusion of geriatrics and geriatric

assessments provides further refinement of the selection of the elderly who could benefit from standard oncological treatments based on morbidity profiles or define the level of needed care tailored to the patient's clinical and physical status. Furthermore, efforts should be made to optimize timing to surgery to better study the patient's clinical situation by thorough preoperative assessment (e.g. physical and cognitive status) and to provide additional supportive measures when needed (e.g. optimization of cardiovascular and pulmonary comorbidities, and improve nutritional status) to reduce surgical risk and improve the prognosis of the patient.

In order to realize personalized cancer treatment, efforts should be made to design prospective observational studies and clinical trials for the heterogeneous colorectal cancer patient population, in which patient characteristics and outcomes should be evaluated, including quality of life. Currently, a national population-based prospective cohort study (PLCRC) is running in the Netherlands, in which colorectal cancer patients are followed over time, and from which information about long-term clinical data, tissue and blood samples, and patient-reported outcome measures will be available. Moreover, population-based studies using data like the Netherlands Cancer Registry, will remain necessary to offer insight in everyday clinical practice. The Netherlands Cancer Registry largely extended its dataset for all colorectal cancer patients diagnosed from 2015 onwards. It now includes more detailed information regarding diagnostic processes, treatment and long-term follow-up regarding tumour progression and recurrence. This offers the unique possibility to further evaluate the effect of patient, clinical and hospital features on treatment choice and long-term survival. Despite a growing body of data, it is of utmost importance to evaluate whether continuous registration of all of this data is needed for research purposes. The validity and prognostic significance of certain data items may be lacking. Therefore it is trivial that datasets are evaluated and refined to ensure their clinical relevance.

CONCLUDING REMARKS

This thesis reports numerous real-world aspects of colorectal cancer survival in the Netherlands. Colorectal cancer survival has improved in the Netherlands in the past 25 years, due to advancements in diagnostics and treatment. It is shown that when elderly patients survived the first year after surgery, survival was comparable to younger patients. It is also shown that the presence of synchronous colorectal cancers is associated with a decrease in survival. We also demonstrate the effect of variation in demographic determinants (hospital volume and timing to adjuvant chemotherapy) on colorectal cancer survival. However, many other aspects of colorectal cancer care were only marginally or not at all addressed in this thesis. This means that, although this thesis is finished now, the work continues.

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A

APPENDIX

Nederlandse samenvatting

Dutch summary

INLEIDING

Darmkanker is wereldwijd een veelvoorkomende vorm van kanker en komt vooral voor in de westerse wereld. Darmkanker is een ziekte die voornamelijk ouderen treft; ongeveer 50% van alle patiënten is bij diagnose 75 jaar of ouder. In de afgelopen decennia is het aantal nieuwe patiënten met darmkanker in Nederland meer dan verdubbeld; van 7.100 patiënten in 1990 naar 15.800 patiënten in 2015. Naar verwachting zal het aantal nieuwe patiënten per tijdseenheid en per aantal van de bevolking (zogeheten ''incidentie'') verder stijgen als gevolg van toenemende vergrijzing van de bevolking en het landelijke bevolkingsonderzoek naar darmkanker dat in 2014 is geïntroduceerd.

Darmkanker wordt onderverdeeld in tumoren in de dikke darm (colontumoren) en tumoren in de endeldarm (rectumtumoren). Er zijn verschillende soorten behandelingen mogelijk bij darmkanker. De locatie in het darmkanaal en het stadium van de tumor zijn belangrijke factoren die een rol spelen bij het maken van een behandelkeuze. Bij vrijwel alle patiënten met darmkanker wordt de tumor chirurgisch verwijderd. Hierbij kunnen voorafgaand aan de operatie (neo-adjuvant) of na de operatie (adjuvant) aanvullende behandelingen nodig zijn (chemotherapie, radiotherapie of een combinatie van beide, zogeheten chemoradiotherapie).

Door verbeteringen in diagnostiek en behandeling zijn de overlevingskansen van patiënten met darmkanker sinds eind jaren '80 toegenomen. De 5-jaarsoverleving van patiënten met darmkanker steeg van 52% in de periode 1989-1994 naar 63% in de periode 2010-2014. De overleving van patiënten met darmkanker is vooral afhankelijk van het stadium bij diagnose. In de periode 2010-2014 lag de kans om 5 jaar na diagnose nog in leven te zijn tussen 93% voor patiënten gediagnosticeerd met stadium I darmkanker tot 13% voor patiënten gediagnosticeerd met stadium IV darmkanker.

Ondanks alle positieve ontwikkelingen rond diagnostiek en behandeling, blijft de mate van voorkomen (zogeheten ''morbiditeit'') en het aantal sterftegevallen (zogeheten ''mortaliteit'') van deze tumor hoog in Nederland. Om de prognose van patiënten met darmkanker te verbeteren, is het belangrijk beter inzicht te krijgen welke factoren van invloed zijn op de dagelijkse zorg en de overleving van patiënten met darmkanker. Hierbij kunnen zowel patiënt- als klinisch gerelateerde factoren, alsmede ziekenhuisfactoren van invloed zijn op de overleving. Het evalueren van het effect van verschillende klinische factoren en ziekenhuisfactoren geeft nieuwe inzichten aan medische specialisten en ziekenhuizen om de kwaliteit van de darmkankerzorg en overlevingskansen van deze patiënten verder te optimaliseren.

DOEL VAN DIT PROEFSCHRIFT

Het doel van dit proefschrift is i) inzicht geven in de overlevingscijfers en ii) factoren identificeren die invloed kunnen uitoefenen op de kwaliteit van dagelijkse kankerzorg en prognose van patiënten met darmkanker in Nederland. Om deze onderzoeksvragen te beantwoorden, hebben wij gebruik gemaakt van data uit de Nederlandse Kankerregistratie (NKR) van het Integraal Kankercentrum Nederland (IKNL). We bestudeerden trends in incidentie, mortaliteit, behandeling en overleving (**deel I**). Daarnaast is de impact van een aantal klinische factoren en ziekenhuisfactoren op de behandelkeuze en overleving van patiënten met darmkanker geanalyseerd (**deel II**).
Er zijn verschillende manieren om de overleving te analyseren. In dit proefschrift is gebruik gemaakt van de zogeheten 'ruwe' overleving (ongecorrigeerd voor patiëntkenmerken), de relatieve overleving (benadering voor ziekte-specifieke overleving, waarbij gecorrigeerd wordt voor de normale levensverwachting op basis van sterfte naar leeftijd en geslacht) en de conditionele overleving (overleving op voorwaarde dat een patiënt reeds een bepaalde periode heeft overleefd).

BELANGRIJKSTE BEVINDINGEN VAN DIT PROEFSCHRIFT

In **deel I** van dit proefschrift wordt een overzicht gegeven van darmkanker overleving in Nederland. De studie beschreven in **hoofdstuk 2** geeft inzicht in de ontwikkelingen op het gebied van incidentie, mortaliteit, behandeling en overleving van patiënten met darmkanker in Nederland over de afgelopen 25 jaar. Uit deze studie blijkt dat de incidentie van colon- en rectumtumoren is gestegen en de mortaliteit aan beide tumoren is gedaald. Bij meer dan 90% van de patiënten met stadium I-III darmkanker werd de tumor chirurgisch verwijderd. Daarnaast kregen patiënten in recentere periodes steeds vaker een aanvullende behandeling, zoals adjuvante chemotherapie bij patiënten met een stadium III colontumor en neo-adjuvante radiotherapie en chemoradiatie bij patiënten met een stadium II-III rectumtumor. Ook patiënten met stadium IV darmkanker zijn intensiever behandeld, waarbij zowel het chirurgisch verwijderen van uitzaaiingen als het gebruik van chemotherapie aanzienlijk toenamen. Tevens heeft de opkomst van ''doelgerichte middelen'' (targeted therapy) voor een nog breder scala aan systemische behandelopties gezorgd. Mede daardoor is de relatieve 5-jaars overleving verbeterd voor colontumoren van 53% in de periode 1989-1994 naar 62% in de periode 2010-2014, en voor rectumtumoren van 51% naar 65% over dezelfde periodes.
In **hoofdstuk 3** evalueren we welke verschillen in overleving er zijn tussen de verschillende leeftijdsgroepen. In deze studie werden alle patiënten opgenomen die gediagnosticeerd zijn met niet-gemetastaseerde darmkanker tussen 2008 en 2013 en die hiervoor een operatie kregen. Patiënten werden ingedeeld in vier leeftijdscategorieën: <65, 65-

74, 75-84 en ≥85 jaar. We vonden een lagere ruwe 5-jaarsoverleving bij de oudere leeftijdsgroepen voor zowel colon- als rectumtumoren. Deze verschillen in overleving tussen leeftijdsgroepen waren minder uitgesproken wanneer wij keken naar de relatieve 5-jaarsoverleving. Bij patiënten die het eerste jaar na een operatie hebben overleefd, zijn de verschillen in overleving tussen leeftijdsgroepen verdwenen.

In **deel II** van dit proefschrift beschrijven we onderzoek naar determinanten die impact hebben op de keuze van een behandeling en de overleving van patiënten met darmkanker. In **hoofdstuk 4** onderzochten wij de impact op het behandeltraject en de overleving van meerdere darmtumoren tegelijkertijd of meer dan één tumor binnen 6 maanden bij diagnose (synchrone tumoren). Voor deze studie namen wij alle patiënten mee die gediagnosticeerd waren met darmkanker tussen 2008 en 2013 en die hiervoor een operatie kregen. In totaal werd bij 5% van deze patiënten (n=1969) synchrone darmtumoren gevonden. De helft van de patiënten met een synchrone darmtumor kreeg een uitgebreidere operatie in vergelijking tot patiënten met een één darmtumor. Daarnaast bleek dat patiënten met synchrone darmtumoren minder vaak neo-adjuvante (chemo)radiotherapie of adjuvante chemotherapie krijgen. De studie toonde ook aan dat patiënten met meerdere darmtumoren een slechtere relatieve 5-jaarsoverleving hadden in vergelijking met patiënten met een enkele darmtumor. De resultaten van deze studie laten zien dat synchrone darmtumoren invloed hebben op het type operatie en de besluitvorming omtrent additionele behandelingen. De studie bevestigt het belang om synchrone tumoren zo vroeg mogelijk op te sporen, indien mogelijk al vóór de operatie.
In **hoofdstuk 5** hebben we onderzocht of het ziekenhuisvolume samenhangt met de kortetermijn uitkomsten en overleving van patiënten met darmkanker. Ziekenhuizen werden gegroepeerd op basis van het aantal operaties bij patiënten met colontumoren (<50, 50-74, 75-99, en ≥100 operaties per jaar) en rectumtumoren (<20, 20-39 en ≥40 operaties per jaar). We vonden geen verschillen tussen ziekenhuisvolumes in de ruwe 5-jaarsoverleving van patiënten met niet-gemetastaseerde darmkanker. Er waren echter wel kleine verschillen te zien in de postoperatieve 30-dagenmortaliteit. Nader onderzoek is nodig om na te gaan wat de klinische relevantie van deze verschillen is. Het verkennen van deze factoren kan meer inzicht geven in het debat over de kwaliteit van zorg en de vraag of een operatie in een zogeheten 'laag-volume ziekenhuis' een risicofactor vormt voor ongunstige uitkomsten voor de patiënt.
In **hoofdstuk 6** ontwikkelden en valideerden wij een predictiemodel (voorspellend model) om de postoperatieve 90-dagen mortaliteit en de ruwe 5-jaarsoverleving van patiënten met niet-gemetastaseerde darmkanker te kunnen voorspellen. Factoren die de postoperatieve 90-dagen mortaliteit kunnen voorspellen zijn geslacht en leeftijd van de patiënt, tumorgrootte en uitzaaiingen in de lymfeklieren, urgentie van de operatie,

operatiemethode (laparoscopisch of open), type operatie (segment van de darm verwijderen of totale darm verwijderen) en het optreden van een complicatie (lekkage van de darminhoud op de locatie waar een nieuwe verbinding van de darm is aangelegd, zogeheten ''naadlekkage''). Voorspellende factoren voor de 5-jaarsoverleving waren geslacht en leeftijd van de patiënt, stadium, urgentie van de operatie, locatie van de tumor, het krijgen van (neo)adjuvant (chemo)radiotherapie, aanwezigheid van synchrone darmtumoren, mate waarin de tumor volledig wordt verwijderd (zogeheten ''radicaliteit van de operatie'') en optreden van naadlekkage. De resultaten van deze studie kunnen worden gebruikt om online calculators te ontwikkelen die de patiënt en medisch specialist ondersteunen bij de individuele besluitvorming omtrent het behandel- en vervolgtraject van patiënten met darmkanker.

In **hoofdstuk 7** van dit proefschrift is onderzocht welke demografische en klinische variabelen van invloed zijn op de tijd die verstreken is tot het krijgen van adjuvante chemotherapie. Daarbij is ook gekeken of een langer tijdsinterval geassocieerd is met een slechtere overleving van patiënten met een stadium III colontumor. Veertien procent van de patiënten startte 8 weken of later na de operatie met adjuvante chemotherapie. Patiënten die binnen 8 weken na de operatie starten met adjuvante chemotherapie, laten een betere ruwe 5-jaarsoverleving zien in vergelijking met patiënten die na 8 weken of later met deze behandeling beginnen. Vanaf 5 tot 8 weken na de operatie werd geen daling van de ruwe 5-jaarsoverleving waargenomen in vergelijking met het starten met adjuvante chemotherapie binnen 4 weken. Deze tijd kan nuttig worden besteed aan het herstellen van de operatie en voorbereiding op de volgende stap in het behandelproces.

In het laatste hoofdstuk van dit proefschrift zijn alle resultaten van de studies bediscussieerd in een bredere context en is ingegaan op enkele recente ontwikkelingen. Tenslotte zijn een aantal mogelijke implicaties voor de kliniek en toekomstig onderzoek belicht (**hoofdstuk 8**).

CONCLUSIE

Dit proefschrift geeft inzicht in verschillende klinische en demografische aspecten bij de overleving van patiënten met darmkanker in Nederland. Het toont aan dat in de afgelopen 25 jaar de incidentie en relatieve 5-jaarsoverleving van darmkankerpatiënten is gestegen, mede dankzij nieuwe inzichten en ontwikkelingen in diagnostiek en behandeling. Dit proefschrift toont aan dat de verschillen in 5-jaarsoverleving tussen jongere en oudere patiënten verdwijnen, indien patiënten het eerste jaar na een operatie hebben overleefd. Ook laat dit proefschrift zien dat meerdere darmtumoren ten tijde van diagnose ertoe kunnen leiden dat patiënten minder intensief worden behandeld en tevens geassocieerd zijn met een slechtere overleving. Tenslotte laat het onderzoek in dit proefschrift het effect

zien van variatie in bijvoorbeeld ziekenhuisvolume en de tijd tot het starten van adjuvante chemotherapie op darmkankeroverleving. Veel andere aspecten met betrekking tot de zorg voor patiënten met darmkanker blijven echter onbesproken in dit proefschrift. Toekomstig onderzoek blijft noodzakelijk om het effect van patiënt-, klinische- en ziekenhuisfactoren op behandelkeuzes en overleving continu te evalueren, met als einddoel uitkomsten van zorg voor patiënten met darmkanker voortdurend te blijven verbeteren.

Dankwoord

Acknowledgements

Waar voor velen van jullie het lezen van mijn proefschrift hier begint, betekenen deze pagina's voor mij een afsluiting van een bijzondere periode. De afgelopen 3,5 jaar voelden als een achtbaan vol emoties en wijze lessen. Met veel trots zeg ik nu dat mijn proefschrift is afgerond! Ik wil iedereen bedanken die heeft bijgedragen aan dit proefschrift, maar een aantal personen wil ik in het bijzonder benoemen.

Allereerst wil ik mijn promotoren en mijn copromoter hartelijk bedanken voor hun begeleiding tijdens mijn promotietraject.
Prof. Dr. Lemmens, beste Valery, wat is de tijd snel gegaan! De afgelopen periode was voor mij niet altijd even makkelijk. Ondanks je volle agenda stond je altijd voor mij klaar en wist je mij hernieuwde energie te geven als ik het even niet meer zag zitten. Het is een voorrecht met jou te mogen samenwerken! Jouw menselijkheid, geduld en positieve benadering bewonder ik enorm. Bedankt voor alles wat ik tot nu toe van je mocht leren, het vertrouwen dat je in mij stelt en bovenal, de ruimte die je mij elke keer weer geeft verder te groeien. Samen met Peter bedenk je steeds weer een manier mij in het diepe te gooien, waarna het me nog altijd lukt om boven te komen. Ik kijk vol enthousiasme uit opnieuw kopje onder te gaan en nog meer van je te mogen leren!
Prof. Dr. Huijgens, beste Peter, ruim 4 jaar geleden maakte ik kennis met je in jouw K5, waar ik gedurende het hele gesprek zenuwachtig op het puntje van mijn stoel zat (zoals je weet, is dit inmiddels veranderd). Met je aanstekelijke enthousiasme en zekerheid wist je mij te overtuigen onderzoeker te worden. Ik kan NU oprecht tegen je zeggen dat ik hier geen seconde spijt van heb gehad. Het is een eer je laatste (but not least) promovenda te mogen zijn. Ik heb veel van je mogen leren de afgelopen jaren. Jouw (Amsterdamse) eigenwijsheid, directheid, onuitputtelijke energie en toegankelijkheid kan ik enorm waarderen. Dank je wel voor al je hulp en het vertrouwen dat je mij keer op keer geeft!
Dr. van Erning, beste Felice, vanaf dag 1 kon ik bij jou terecht met al mijn vragen over SAS en colorectaal carcinoom. Jouw kennis op het gebied van epidemiologie en oncologie heeft mij enorm geholpen. Ik vind het dan ook niet meer dan logisch dat jij mijn copromoter bent vandaag. Bedankt voor de gezellige onderonsjes en fijne samenwerking!

De leden van de leescommissie, Prof. Dr. C. Verhoef, Prof. Dr. J.H.W. de Wilt en Prof. Dr. M. Koopman, wil ik bedanken voor de bereidheid om mijn proefschrift te beoordelen. Daarnaast wil ik Prof. Dr. A.H.J. Mathijssen, Dr. H.A.A.M. Maas en Dr. M.G.H. van Oijen bedanken voor het zitting nemen in de commissie.

Co-auteurs Christiane Buskens, Nelleke Brouwer, Geert-Jan Creemers, Jan Willem Dekker, Marloes Elferink, Yvette van Gestel, Vincent Ho, Niek Hugen, Danique Kortbeek, Huub Maas, Robert Matthijsen, Iris Nagtegaal, Martijn van Oijen, Kees Punt, Harm Rutten,

Pieter Tanis, Rob Verhoeven, Hans de Wilt en David Zimmerman wil ik bedanken voor de waardevolle input aan de artikelen in dit proefschrift en de prettige samenwerking.

Lieve heer en mevrouw Lohman, we hebben veel gesprekken gevoerd over mijn toekomst aan uw tafel 17 in het restaurant van mijn ouders. Met uw wijze woorden wist u mij elke keer weer te raken en te motiveren om door te pakken. Mede dankzij u sta ik hier vandaag! Ik kan niet beschrijven hoe dankbaar ik ben voor al uw hulp.

In de afgelopen jaren is er geen dag geweest dat ik niet met plezier naar mijn werk ben gegaan. Dit heb ik mede te danken aan mijn leuke en betrokken collega's bij IKNL. Beste Avinash, Gina, Jan Maarten, Kay, Irma, Kelly, Lindy, Marianne, Marilyn, Marissa, Vincent en alle anderen, dank voor de belangstelling in mijn promotieonderzoek, maar vooral voor alle superleuke koffiepauzes, (brainboost)lunches, etentjes en VrijMiBo's! Ook mijn GE-collega's, Erica, Geraldine, Jonne, Lydia, Louis, Margreet, Marjorie, Marloes, Nienke, Pauline, Otto en Rob, bedankt voor de fijne samenwerking, alle inhoudelijke discussies en de gezelligheid.
Uiteraard wil ik alle datamanagers van de Nederlandse Kankerregistratie bedanken. Door jullie nauwkeurige en consequente registratie beschikken wij over een onuitputtelijke, betrouwbare dataset waarmee wij als onderzoekers waardevol onderzoek kunnen doen.

Dan mijn paranimfen, wat ben ik blij dat jullie op deze belangrijke dag bij mij willen staan (op minimaal 7 cm hakhoogte ☺)! Dank jullie wel voor jullie vriendschap en steun, jullie zijn top! Lieve Maite, mijn partner-in-crime, mijn Zeeuwse bitchbuddy, wat kunnen wij toch ontzettend veel met elkaar delen, van guilty pleasures tot aan serious talk. Met jou op kantoor wordt de werkdag een stuk zonniger! Ik zal onze koffieleut-momentjes en lange-lunches onwijs gaan missen. Lieve Mirian, onze (voormalig) klein-Zwitserland, maar inmiddels toegetreden tot de republiek der bitches. Ook wij hebben de afgelopen jaren veel ups-and-downs met elkaar gedeeld. Je bent ontzettend lief en betrokken. Bedankt dat ik mijn hart altijd bij je kan luchten.

Lieve vrienden, kennissen, schoonfamilie, broers en schoonzussen, neefjes en nichtjes, bedankt voor jullie support en interesse de afgelopen jaren in mijn werk. Maar vooral bedankt voor alle afleiding en ontspanning die ik van tijd tot tijd nodig had.

Lieve mama, het was niet altijd even makkelijk voor je om te begrijpen dat ik mijn eigen weg wilde kiezen. Toch ben je altijd trots op mij geweest. Hopelijk maakt mijn verdediging het een beetje goed dat ik ben gestopt met mijn rechten studie. Bedankt voor al je liefde, steun en goede zorgen de afgelopen 32 jaar.

Lieve papa, het zal vandaag heel zwaar zijn omdat je er helaas niet bij kunt zijn. Ik hoop dat je boven een mooi wolkje hebt uitgekozen om toch een eersterangs plekje te bemachtigen. Dank je wel voor een luisterend oor, je meelevendheid, je steun, je liefde en je vertrouwen in mij, ook al begreep je niet altijd wat ik nou eigenlijk aan het doen was. Mijn doorzettingsvermogen en harde werken heb ik ongetwijfeld van jou gekregen. Ik hoop dat je apetrots op mij bent!

Lieve Jill, jij bent mijn grootste geschenk(je)! Ook al ben je pas 8 maanden in ons leven, je hebt ons zoveel vreugde en liefde gebracht. Dank je wel voor alle keren dat je lief naast me lag te slapen zodat ik mijn proefschrift kon afronden. Ik beloof je dat mijn laptop de komende tijd weer plaats zal maken voor onze speel-, lach- en knuffelsessies. Ik ben stapelgek op jou!

Lieve Mertin, mijn hubby, wat hebben wij ontzettend veel meegemaakt samen, we zijn er altijd sterker uitgekomen. Je helpt me keer op keer weer waar je kunt (soms met wat hulp van de Rabo) en blijft geduldig wanneer ik het je weer moeilijk maak. Je weet me te kalmeren en te motiveren wanneer ik dat het hardst nodig heb. Aan jou ben ik denk ik de meeste dank verschuldigd. Dank je wel dat je altijd met een knuffel voor mij klaarstaat, elke keer weer een glimlach op mijn gezicht kunt toveren en onvoorwaardelijk veel van mij houdt. Weet dat je mij intens gelukkig maakt. Ik hou superveel van jou, voor altijd!

Amanda
Februari 2018

Curriculum vitae auctoris

CURRICULUM VITAE AUCTORIS

Amanda C.R.K. Bos was born on the 10th of January 1986 in Amsterdam, the Netherlands. In 2004, she finished secondary education at the Sint Vituscollege in Bussum. Subsequently, she started her Bachelor in Law at the Vrije Universiteit in Amsterdam. In 2008, she started her Bachelor Biomedical Sciences at the same institution. After receiving her Bachelor's degree in 2012, she sharted her Master in Health Sciences (specialization International Public Health) at the Vrije Universiteit in Amsterdam. During her master she conducted her scientific internship at the Netherlands Cancer Institute in Amsterdam. After obtaining her Master's degree, she sharted her PhD research at the Netherlands Comprehensive Cancer Organisation (IKNL) in 2014. Her research focused on quality of care and colorectal cancer survival in the Netherlands using real-world data. During her PhD training she followed several epidemiological courses. Currently, she is chair of the colorectal cancer project team and is working as a researcher at IKNL.

List of publications

PUBLICATIONS INCLUDED IN THIS THESIS

1. **Bos ACRK**, Kortbeek D, van Erning FN, Zimmerman DDE, Lemmens VEPP, Dekker JWT & Maas HAAM. Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying. *Submitted*.

2. **Bos ACRK**, Ho VKY, van Erning FN, Buskens CJ, Tanis PJ, van Oijen MGH & Lemmens VEPP. Development and validation of prediction models for postoperative 90-day mortality and overall survival in colorectal cancer patients. *Submitted*.

3. Brouwer NPM, **Bos ACRK**, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, de Wilt JHW & Verhoeven RHA. Survival continuously improves during 25 years of treating colorectal cancer patients. Results from the Dutch Cancer Registry. *Submitted*.

4. **Bos ACRK**, Matthijsen RA, van Erning FN, van Oijen MGH, Rutten HJ & Lemmens VEPP. Treatment and outcome of synchronous colorectal carcinomas: a nationwide study. Annals of Surgical Oncology, 2017; 25(2):414-421.

5. **Bos ACRK**, van Erning FN, Elferink MA, Rutten HJ, van Oijen MGH, de Wilt JHW & Lemmens VEPP. No difference in overall survival between hospital volumes for patients with colorectal cancer in the Netherlands. Diseases of Colon and Rectum, 2016; 59(10):943-52.

6. **Bos ACRK**, van Erning FN, van Gestel YR, Creemers GJ, Punt CJ, van Oijen MGH & Lemmens VEPP. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. European Journal of Cancer, 2015; 51(17):2553-61.

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1. van der Vlugt M, Grobbee EJ, Bossuyt PMM, **Bos ACRK**, Kuipers EJ, Lansdorp-Vogelaar I, Spaander MCW & Dekker E. Risk of oral and upper gastrointestinal cancers in persons with positive results from a fecal immunochemical test in a colorectal cancer screening program. Clinical Gastroenterology and Hepatology, 2018; *Epub ahead of print*.

2. Babei M, Jansen L, Balavarca Y, Sjövall A, **Bos ACRK**, van de Velde T, Moreau M, Liberale G, Goncalves AF, Bento MJ, Ullrich CM, Schrotz-King P, Lemmens VEPP, Glimelius B & Brenner H. Neoadjuvant therapy in rectal cancer patients with clinical stage II to III across European countries: variations and outcomes. Clinical Colorectal Cancer, 2017; S1533-0028(17):30050-6.

3. Fles R, **Bos ACRK**, Supriyati, Rachmawati D, Waliyanti E, Tan IB, Haryana SM, Schmidt MK & Dewi FST. The role of Indonesian patients' health behaviors in delaying the diagnosis of nasopharyngeal carcinoma. BMC Public Health, 2017; 17(1):510.

4. van der Vlugt M, Grobbee EJ, Bossuyt PMM, **Bos ACRK**, Bongers E, Spijker W, Kuipers EJ, Lansdorp-Vogelaar I, Spaander MCW & Dekker E. Interval colorectal cancer incidence among subjects undergoing multiple rounds of fecal immunochemical testing. Gastroenterology, 2017; 153(2):439-447.

5. Van Erning FN, Elferink MA, **Bos ACRK** & Lemmens VEPP. RE: Primary tumor location as a prognostic factor in metastatic colorectal cancer. Journal National Cancer Institute, 2015; 107(9).

PhD Portfolio

SUMMARY OF PHD TRAINING

Name PhD student:	A.C.R.K. Bos
Erasmus MC Department:	Public Health/Netherlands Comprehensive Cancer Organisation (IKNL)
PhD period:	September 2014 – February 2018
Promotors:	Prof. Dr. V.E.P.P. Lemmens & Prof. Dr. P.C. Huijgens
Copromotors:	Dr. F.N. van Erning

	Year	Workload hours (ECTS)
Courses		
Basic course in Oncology, NVvO	2015	40 (1.4)
Clinical Prediction models: Theory and Practice - Maastricht University	2015	24 (0.9)
Scientific integrity – Erasmus MC	2016	8 (0.3)
Internal course on survival analysis – by Paul Dickman from Karolinska Institute Sweden at IKNL	2016	24 (0.9)
Oral presentations		
IKNL symposium 'NKR in beeld'	2016	32 (1.1)
ESSO	2016	32 (1.1)
UEGW	2016	32 (1.1)
Presenting regional reports about colorectal cancer	2015-2017	64 (2.3)
Poster presentations		
1 poster European Congres of Pathology	2015	32 (1.1)
2 posters EMCCC	2016	32 (1.1)
1 poster NCT-retreat	2016	32 (1.1)
1 poster Health RI	2017	8 (0.3)
International conferences		
EMCCC, Amsterdam, the Netherlands	2014	32 (1.1)
ESSO, Krakow, Poland	2016	32 (1.1)
EMCCC, Amsterdam, the Netherlands	2016	32 (1.1)
IACR, Utrecht, the Netherlands	2017	24 (0.9)

	Year	Workload hours (ECTS)
Dutch seminars and conferences		
IKNL symposium 'NKR in beweging'	2015	8 (0.3)
Erasmus MC-IKNL symposium Prof. dr. V.E.P.P. Lemmens	2015	6 (0.2)
Universiteit Twente-IKNL symposium Prof. Dr. S. Siesling	2015	8 (0.3)
IKNL symposium 'NKR in beeld'	2016	8 (0.3)
Federaday 'Cancer and numbers'	2016	8 (0.3)
IKNL symposium 'NKR naar buiten'	2017	8 (0.3)
5 D's Congress	2018	8 (0.3)
Teaching		
Lectures for registry clerks	2015-2017	72 (2.7)
Other tasks		
Extending the registry and assessing the quality of the extended registry for colorectal cancer	2015-2017	280 (10)
Answering questions of registry clerks about the extended registry	2015-2017	40 (1.4)
Making regional reports about colorectal cancer for hospitals	2015-2017	280 (10)
Giving input for web-based tool 'NKR online' specifically for colorectal cancer	2016-2017	240 (8.6)
Total		1456 (51.6)