

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/24307> holds various files of this Leiden University dissertation

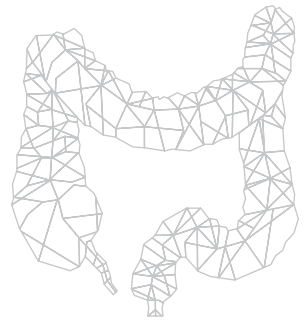
Author: Broek, Colette van den

Title: Optimisation of colorectal cancer treatment

Issue Date: 2014-02-27

Optimisation of colorectal cancer treatment

Colette van den Broek



Drukwerk

Optima Grafische Communicatie, Rotterdam

2013 Colette van den Broek | Leiden | The Netherlands

Alle rechten voorbehouden. Niets uit deze opgave mag worden verveelvoudigd, opgeslagen in een geautoriseerd gegevensbestand of openbaar gemaakt, in enige vorm of op enige wijze, hetzij elektronisch, mechanisch, door fotokopieën, opnamen of op enige andere wijze, zonder voorafgaande schriftelijke toestemming van de auteur.

All rights reserved. No part of this thesis may be reproduced or transmitted without the prior permission of the author.

ISBN 978-94-6169-468-3

Optimisation of colorectal cancer treatment

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 27 februari 2013
klokke 15.00 uur

door
Colette Bernadine Maria-Theresia van den Broek
geboren te 's Hertogenbosch in 1984

PROMOTIECOMMISSIE

Promotor

Prof. Dr. C.J.H. van de Velde

Co-promotores

Dr. E. Bastiaannet

Dr. G.J. Liefers

Beoordelingscommissie

Dr. A.J.M. de Craen

Prof. Dr. A.J. Gelderblom

Prof. Dr. C.A.M. Marijnen

Prof. Dr. H.J.T. Rutten

Academisch Ziekenhuis Maastricht

Catharina Ziekenhuis Eindhoven

Overige commissieleden

Dr. J.E.A. Portielje

Haga Ziekenhuis Den Haag

Prof. Dr. M. Verheij

Antoni van Leeuwenhoek Ziekenhuis Amsterdam

Vrije Universiteit Amsterdam

CONTENTS

Introduction

1	General introduction and outline of this thesis	9
---	---	---

Part I Colorectal cancer; treatment and survival

2	Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients - a large population-based study from 1990 to 2008 <i>Acta Oncologica</i>	21
3	Adjuvant chemotherapy use in stage III colon cancer patients <i>Submitted for publication</i>	39
4	The survival gap between middle-aged and elderly colon cancer patients. Time trends in treatment and survival <i>European Journal of Surgical Oncology</i>	57
5	Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients <i>Annals of Surgical Oncology</i>	75
6	Impact of the interval between short course radiotherapy and surgery on outcomes of rectal cancer patients <i>European Journal of Cancer</i>	89

Part II International comparisons in colorectal cancer treatment and survival

7	The EURECCA project: Data items scored by European colorectal cancer audit registries <i>European Journal of Surgical Oncology</i>	111
8	Differences in preoperative treatment administration of rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands <i>Submitted for publication</i>	121
9	A comparison of high dose rate endorectal brachytherapy, short course radiotherapy and chemoradiation on the outcome of rectal cancer patients <i>Submitted for publication</i>	141

Discussion

10.	General discussion and future perspectives	155
	Summary	167
	Summary in Dutch (Nederlandse samenvatting)	179

Appendices

List of contributing authors	189
List of publications	193
Acknowledgements (Dankwoord)	197
Curriculum vitae	199



Introduction

Chapter 1

General introduction and outline of this thesis

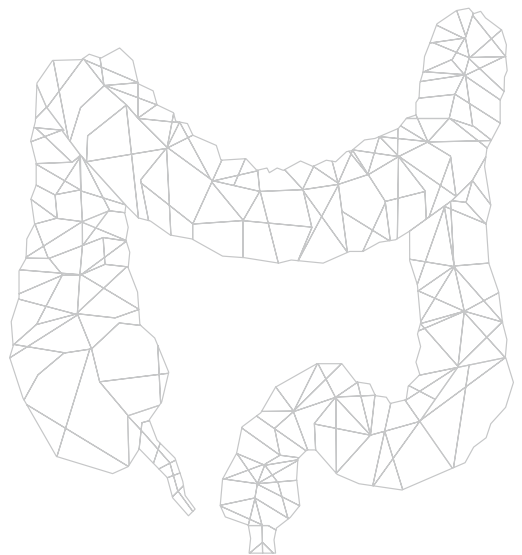
Partly published in Colorectal Cancer. 2013 Aug;2(4):371-6
Improving the outcome of colorectal cancer: the European
Registration of Cancer Care (EURECCA) project

Colette B.M. van den Broek

Petra G. Boelens

Anne J. Breugom

Cornelis J.H. van de Velde



GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Colorectal cancer is one of the most common cancers in Europe and the incidence is still growing. It is the third most common diagnosed cancer in males, and the second in females. Besides, it is the second most important cause of cancer death in Europe.¹ The incidence rates vary across Europe, with higher rates in developed countries, as compared to developing countries.² These geographic differences appear to be attributable to the differences in dietary and environmental exposures. In the Netherlands the incidence is high as compared to other European countries with an incidence of over 57 per 100 000 per year (European Standardized Rate).

Age is a major risk factor for colorectal cancer. The highest incidence is between 70 and 79 years of age, which makes it a disease of the elderly patient (see figure 1). Together with the fact that our population is ageing it is anticipated that the number of elderly patients with colorectal cancer will grow during the coming years.³

Approximately two thirds of the colorectal cancer incidence occurs in the colon, and about one third occurs in the rectosigmoid and rectum. Stage of disease is based on the growth of the tumour into the wall of the intestine, tumour growth in lymph nodes, and tumour growth into other organs.⁴ About 25% of the patients will present with lymph node metastases without distant metastases at time of diagnosis, these patients are diagnosed as stage III colorectal

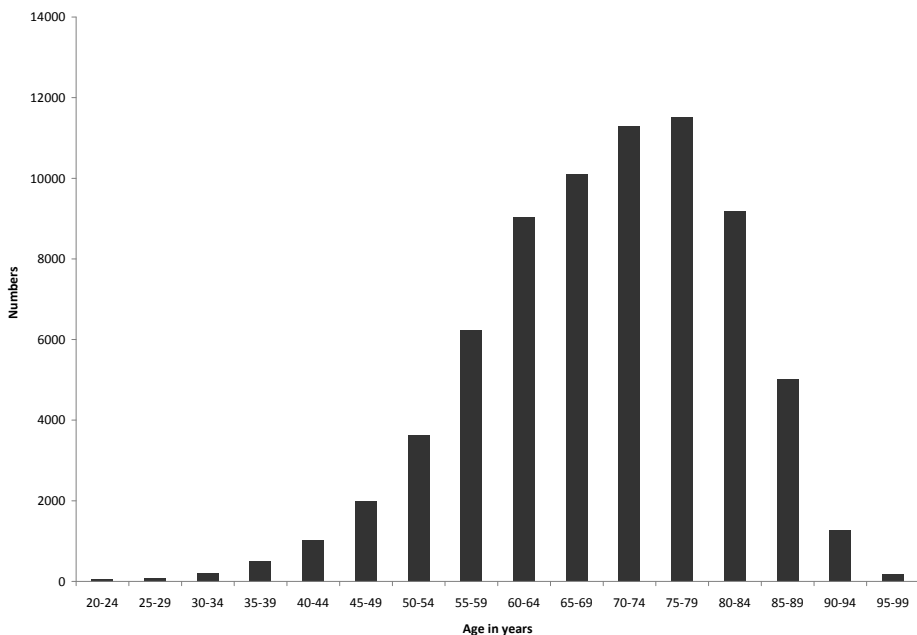


Figure 1: Crude number of new cases per 5-year age group from 2005 until 2010

cancer. Furthermore, approximately 20 to 25% of the patients with colorectal cancer will have distant metastases at time of diagnosis, most often in the liver and/or lungs, also called stage IV colorectal cancer. Patients without distant and lymph node metastases have stage I or stage II disease, depending on the growth of the tumour in the wall of the intestine and surrounding structures.

Over the past decades survival has improved as a result of several changes in the therapy of colorectal cancer. The EUROCARE working group has shown improvement in survival of colorectal cancer patients in Europe, Survival substantially increased over time in all European regions. In general, increases were more pronounced in younger than in older patients, for earlier than for more advanced cancer stages and for rectum than for colon cancer.⁵ With all the multidisciplinary approaches to treat colorectal cancer, it has to be emphasized that surgery remains the mainstay of curative colorectal cancer. To improve the overall outcome of colorectal cancer, one can focus on improvement of treatment or enhancement of quality of care; both parts will be discussed in this thesis.

PART I COLORECTAL CANCER; TREATMENT AND SURVIVAL

Since colon and rectal cancer are treated as different entities, they will be discussed separately in this thesis. In the treatment of early colon cancer, the first step is the surgical removal of the tumour and loco regional lymph nodes. Nowadays the classical abdominal resection is increasingly replaced by laparoscopic surgery. Besides, for early stages of colon cancer advanced endoscopic techniques such as endoscopic mucosal resection, endoscopic submucosal dissection, or even endoscopic mucosal ablation are described as less invasive experimental alternatives of colectomy.⁶⁻⁸ Additionally, advances have been made in perioperative care with the implementation of fast track programmes for colorectal surgery.^{9,10}

In the beginning of the 1990's Moertel et al showed in a randomised clinical trial that stage III patients treated with adjuvant chemotherapy have a significant decrease in recurrence and an improvement in survival.¹¹ Since then, the use of adjuvant chemotherapy has been incorporated in guidelines. Since the mid 2000's the use of adjuvant chemotherapy for high risk stage II patients has been implemented in the Dutch guidelines.¹² High risk stage II patients are defined as patients with a T4 tumour, poor differentiation, perforation or obstruction at time of diagnosis, less than 10 lymph nodes examined, and/or angio-invasion. The time trends in the use and costs of adjuvant chemotherapy, and survival for stage III colon cancer patients in the Netherlands from 1990-2008 are shown in *Chapter 2*. Factors associated with omitting adjuvant chemotherapy in these patients are described in *Chapter 3*.

The improvement in survival over time is accompanied by changes in treatment, although in subgroups, such as elderly patients and patients with comorbidities, these changes in treatment have occurred in a lesser extent.¹³ *Chapter 4* consists of a retrospective study comparing

the survival improvement of younger, middle-aged, and elderly over time. In general, survival of elderly colorectal cancer patients is worse as compared to younger patients. *Chapter 5* shows the importance of the first postoperative year on the survival differences between older and younger colorectal cancer patients.

As in colon cancer, surgical removal of the tumour is the main curative treatment for rectal cancer patients. Phil Quirke in 1986 identified that there was a high positive predictive value of the circumferential resection margin involvement for the subsequent development of locally recurrent cancer and poor survival.¹⁴ Conventional resection consisted of blunt dissection, which failed to clear the pelvis of mesorectal disease and resulted in an increased risk of positive lateral margins.¹⁵ Consequently, the total mesorectal excision (TME) technique, which is defined by embryological planes, and with a sharp dissection, has been introduced.¹⁶ Since introducing the TME technique, the local recurrences have decreased from 15-50% to below 10%.¹⁷⁻²¹

The preferred type of resection depends on the anatomical location of the tumour, all using TME resection. Tumours located in the lower rectum, near the anal sphincter, should undergo an abdominal perineal resection (APR) in most cases, resulting in a permanent colostomy. For tumours in the middle or upper part of the rectum, a low anterior resection (LAR) is indicated. With this surgical method the anal sphincter remain will be preserved.

In the Swedish Rectal Cancer trial patients included from 1987 until 1990 had a significant lower local recurrence rate when treated with preoperative, short course, 5 x 5 Gy radiotherapy (27% in surgery only compared with 11% for patients treated with preoperative radiotherapy followed by immediate surgery).²² In the 1990's the Dutch Colorectal Cancer Group designed a trial using standardised TME surgery; the Dutch TME trial.²³ After the Swedish Rectal Cancer trial had demonstrated the beneficial effect of radiotherapy, the remaining question was whether radiotherapy was still beneficial in combination with standardised, good, TME surgery.^{22,24} The results of the Dutch TME trial demonstrated improved local control, with an even lower local recurrence rate for patients treated with preoperative radiotherapy. For patients with a negative resection margin, the effect of radiotherapy was irrespective of the distance from the anal verge and led to an improved cancer-specific survival, which was nullified by an increase in other causes of death, resulting in an equal overall survival. Nevertheless, preoperative short term radiotherapy significantly improved ten year survival in patients with a negative circumferential margin and TNM stage III.²⁵ Since the introduction of preoperative radiotherapy, the interval between short course radiotherapy has been discussed as this could result in differences in outcome. *Chapter 6* addresses the impact of the interval between preoperative short course radiotherapy and surgery on outcome of rectal cancer patients in two time periods.

Besides radiotherapy, also chemoradiation (45-50 Gy of radiotherapy combined with chemotherapy) is often used as preoperative treatment for locally advanced rectal cancer patients. In contrast to short course radiotherapy followed by immediate surgery, chemoradiation

followed by surgery in six to eight weeks does induce downstaging.^{26,27} For locally advanced rectal cancer and patients with more than four lymph nodes expected to be positive the Dutch guidelines recommends chemoradiation.¹²

Since the use of adjuvant chemotherapy in stage III colon cancer patients is recommended, the National Institute of Health (NIH) recommend that adjuvant chemotherapy should be used in rectal cancer patients as well, based upon the results of a few small trials in the USA.²⁸⁻³⁰ These conclusions have been criticised since the trials are well underpowered, patients were included before the TME technique was introduced, and radiotherapy, if given, was delivered postoperatively. Nowadays, preoperative radiotherapy or preoperative chemoradiation, depending on the mesorectal fascia involvement, is considered to be the gold standard.³¹ Although the effect of adjuvant chemotherapy could be similar in rectal as in colon cancer, there is little direct evidence to support this since the introduction of preoperative treatment. A recent Cochrane review has shown that rectal cancer patient treated without preoperative treatment do benefit from adjuvant chemotherapy, while for rectal cancer patients treated with preoperative treatment, this remains unknown.³²

PART II INTERNATIONAL COMPARISONS IN COLORECTAL CANCER TREATMENT AND SURVIVAL

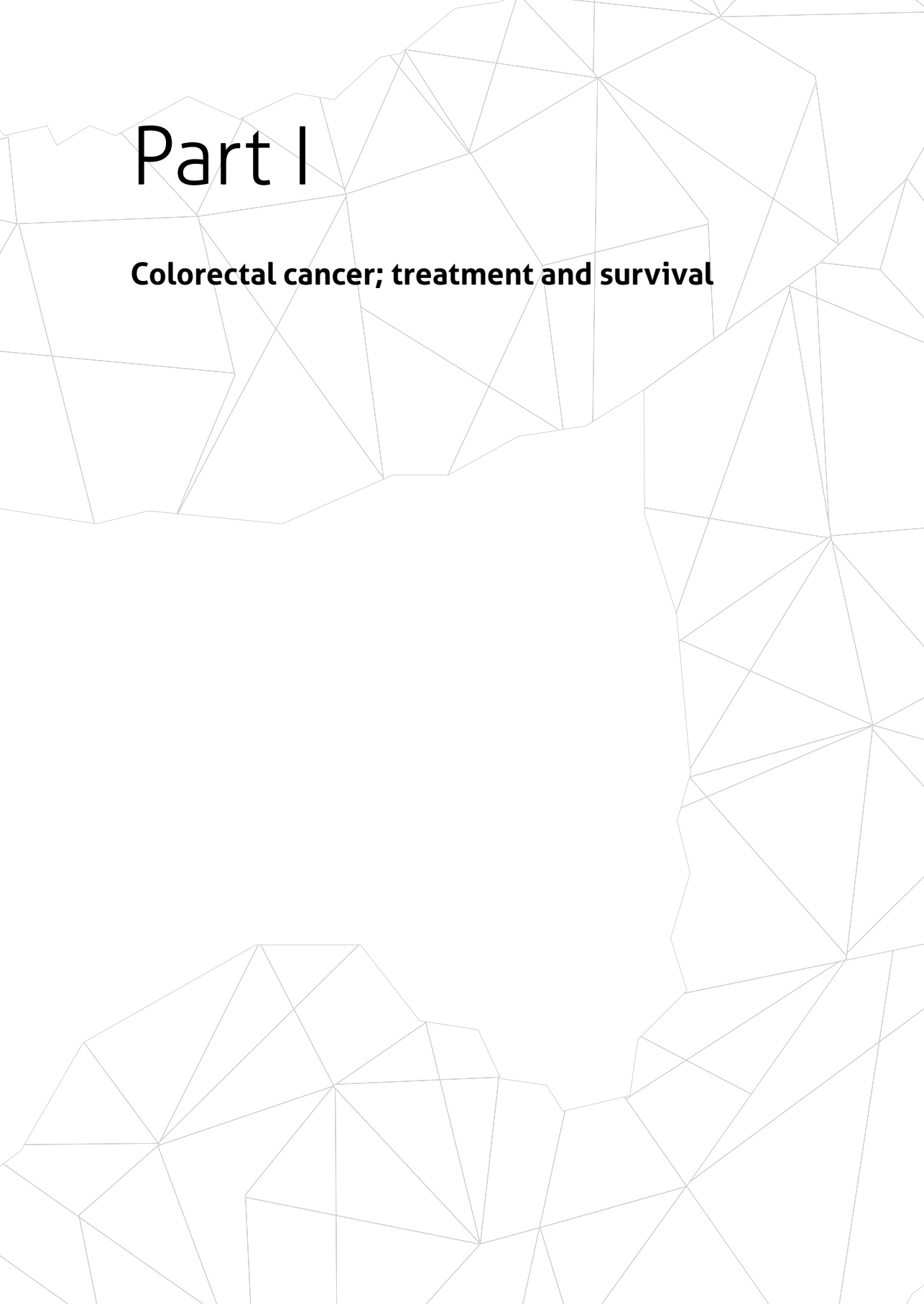
Quality of health care has a high priority on the political agenda of most European countries. Surgical quality assurance program, also called surgical audit, is a quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. Major improvements have been achieved with national audits.³³⁻³⁵ However, although all the national audits achieved excellent results, differences in treatment and outcome remain between European countries.³⁶ This suggests that further improvement is possible. To reduce the differences between the countries by identifying and spreading 'best practice', the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The goal is to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics linked to outcome registration.³⁷ The EURECCA project makes use of existing national audit registrations and started with colorectal cancer, at this moment European audit projects of other solid tumour types, such as breast cancer, gastric cancer, oesophageal cancer, and pancreatic cancer, are developed. *Chapter 7* describes the 'core dataset' (variables that are included by at least 8 of the 9 audit registries) of EURECCA colorectal. The cumulative experience of EURECCA's participants could be used to identify a 'core dataset' that covers all important aspects needed for high quality auditing and at the same time lacking needless data items that only consumes administrative effort. After defining the 'core dataset', the next

step is to compare treatment and survival between countries. The first EURECCA analyses are described in *Chapter 8*, which is a comparison of the use of preoperative treatment for rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands. Currently, randomised controlled trials (RCT's), systematic reviews, and meta-analyses are seen as the highest level of evidence. Unfortunately, randomised controlled trials are costly, time consuming, subgroups may be underrepresented in trials, and certain research questions remain unanswered by randomised clinical trials. A relatively new analysis in medicine is an instrumental variable analysis. In randomised controlled trials the type of treatment is assigned randomly, which makes sure that both treatment groups are comparable. Therefore, the results of both treatment arms can be compared in a randomised controlled trial. Since in observational studies the type of treatment is not randomly assigned to the patients, but probably based on patients' characteristics, treatment results cannot be compared without confounding by indication in most cases. An instrumental variable is a factor which is not related to both patients' characteristics and prognosis, and therefore can function as a pseudo randomisation.^{38,39} The prognosis of different treatment strategies can then be compared. In *Chapter 9* a new preoperative treatment for rectal cancer used in a specialised clinic in Canada has been compared with standard of care in a specialised clinic in the Netherlands. This study should be hypothesis generating to lead to a randomised controlled trial comparing the treatment strategies.

REFERENCE LIST

- 1 Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; **46**: 765-81.
- 2 Jemal A, Bray F, Center MM et al. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90.
- 3 The statistics about cancer in the Netherlands registred by the Netherlands Cancer Registry. <http://www.cijfersoverkanker.nl/> (accessed April 25 2013).
- 4 Sobin LH, Hermanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. *Cancer* 1988; **61**: 2310-4.
- 5 Brenner H, Bouvier AM, Foschi R et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EURO CARE study. *Int J Cancer* 2012; **131**: 1649-58.
- 6 Kim MN, Kang JM, Yang JI et al. Clinical features and prognosis of early colorectal cancer treated by endoscopic mucosal resection. *J Gastroenterol Hepatol* 2011; **26**: 1619-25.
- 7 Kobayashi N, Yoshitake N, Hirahara Y et al. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012; **27**: 728-33.
- 8 Moss A, Bourke MJ, Williams SJ et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011; **140**: 1909-18.
- 9 Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008; **248**: 189-98.
- 10 Kehlet H, Slim K. The future of fast-track surgery. *Br J Surg* 2012; **99**: 1025-6.
- 11 Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**: 352-8.
- 12 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed April 25 2013).
- 13 van Steenberghe LN, Elferink MA, Krijnen P et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol* 2010; **21**: 2206-12.
- 14 Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **2**: 996-9.
- 15 Havenga K, DeRuiter MC, Enker WE, Welvaart K. Anatomical basis of autonomic nerve-preserving total mesorectal excision for rectal cancer. *Br J Surg* 1996; **83**: 384-8.
- 16 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-82.
- 17 Enker WE. Total mesorectal excision--the new golden standard of surgery for rectal cancer. *Ann Med* 1997; **29**: 127-33.
- 18 Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998; **133**: 894-9.
- 19 Kapiteijn E, Marijnen CA, Colenbrander AC et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. *Eur J Surg Oncol* 1998; **24**: 528-35.
- 20 McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis* 1995; **10**: 126-32.
- 21 Pahlman L, Glimelius B. Local recurrences after surgical treatment for rectal carcinoma. *Acta Chir Scand* 1984; **150**: 331-5.
- 22 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; **336**: 980-7.
- 23 Kapiteijn E, Kranenbarg EK, Steup WH et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch

- Colorectal Cancer Group. *Eur J Surg* 1999; **165**: 410-20.
- 24 Folkesson J, Birgisson H, Pahlman L et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; **23**: 5644-50.
 - 25 van Gijn W., Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
 - 26 Marijnen CA, Nagtegaal ID, Klein KE et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001; **19**: 1976-84.
 - 27 Theodoropoulos G, Wise WE, Padmanabhan A et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. *Dis Colon Rectum* 2002; **45**: 895-903.
 - 28 Douglass HO, Jr., Moertel CG, Mayer RJ et al. Survival after postoperative combination treatment of rectal cancer. *N Engl J Med* 1986; **315**: 1294-5.
 - 29 Fisher B, Wolmark N, Rockette H et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988; **80**: 21-9.
 - 30 Krook JE, Moertel CG, Gunderson LL et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; **324**: 709-15.
 - 31 Valentini V, Glimelius B. Rectal cancer radiotherapy: towards European consensus. *Acta Oncol* 2010; **49**: 1206-16.
 - 32 Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; **3**: CD004078.
 - 33 Pahlman L, Bohe M, Cedermark B et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**: 1285-92.
 - 34 Wibe A, Møller B, Norstein J et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; **45**: 857-66.
 - 35 Wibe A, Carlsen E, Dahl O et al. Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis* 2006; **8**: 224-9.
 - 36 Sant M, Allemani C, Santaquilani M et al. EURO-CARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; **45**: 931-91.
 - 37 van Gijn W., van de Velde CJ. Quality assurance through outcome registration in colorectal cancer: an ECCO initiative for Europe. *Acta Chir Lugosl* 2010; **57**: 17-21.
 - 38 Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000; **29**: 722-9.
 - 39 Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol* 2009; **62**: 1226-32.



Part I

Colorectal cancer; treatment and survival

Chapter 2

Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients - a large population-based study from 1990 to 2008

Colette B.M. van den Broek

Esther Bastiaannet

Jan Willem T. Dekker

Johanneke E.A. Portielje

Anton J.M. de Craen

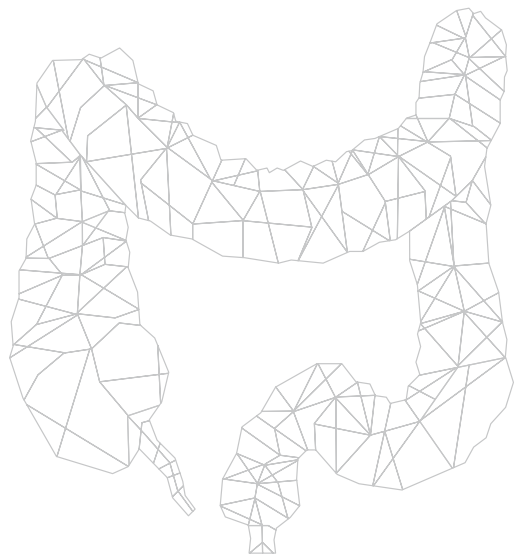
Marloes A.G. Elferink

Cornelis J.H. van de Velde

Gerrit-Jan Liefers

Ellen Kapiteijn

Acta Oncol. 2013 Jun;52(5):941-9



ABSTRACT

Background

Use of adjuvant chemotherapy for stage III colon cancer has increased since several trials have shown the beneficial effect on survival. In this population-based study we show time trends in the administration and costs of chemotherapy and relative survival of patients with stage III colon cancer.

Methods

All patients surgically treated for adenocarcinoma of the colon stage III between 1990 and 2008 in the Netherlands were included. Relative survival (using period analyses) and Relative Excess Risks of death (RER) were calculated. The costs of chemotherapy were estimated.

Results

A total of 24,111 colon cancer patients with stage III were included in the cohort. The administration (from 9.5% in 1990 to 61.8% in 2008; $p < 0.001$) and costs of chemotherapy (from € 38,467 in 1990 to € 3,876,150 in 2008) increased during the study period. Multivariable relative survival improved for patients receiving adjuvant chemotherapy (RER 0.93; 95% CI 0.92-0.94; $p < 0.001$). In contrast, relative survival remained stable for patients, younger than 80 years, who did not receive chemotherapy (RER 1.00; 95% CI 1.00-1.01; $p = 0.3$). Patients aged 80 years and older without chemotherapy, relative survival increased during the study period (RER 0.98; 95% CI 0.97-0.99; $p < 0.001$).

Conclusion

Both the administration, the costs of chemotherapy and the survival of patients with stage III colon cancer increased over time. Whereas the costs and administration of chemotherapy increased extensively, relative survival increased to a lesser extent. For patients treated with adjuvant chemotherapy relative survival increased equally in all age groups.

INTRODUCTION

Colorectal cancer is one of the most frequently diagnosed cancers in the Netherlands with more than 12,000 new patients annually. Approximately, two thirds of the patients are diagnosed with colon cancer and approximately a quarter of these patients are diagnosed with stage III disease.¹ After potentially curative surgery without adjuvant treatment, 50-60% of these patients will relapse.² Over 50% of the patients diagnosed with colon cancer are aged 70 years or older.

Moertel et al. were first to show a significant decrease in recurrence and improvement in survival of stage III colon cancer patients with the use of adjuvant fluorouracil and levamisole.³ Afterwards, several studies have shown that levamisole can be replaced by folinic acid, whereas low dose folinic acid is as effective as high dose. Besides, it was shown that adjuvant chemotherapy for half a year achieves similar results in terms of relapse and improvement of survival as chemotherapy for one year.^{4,5} In 2004 the MOSAIC-trial was published, which randomised between fluorouracil and folinic acid with or without oxaliplatin. The addition of oxaliplatin showed a significant increase in disease-free survival and overall survival for stage III colon cancer patients.⁶ A meta-analysis of recent trials showed no difference between oral or intravenous fluorouracil, and one trial included in the meta-analysis showed a trend towards an advantage in disease-free survival for oral fluorouracil (capecitabine).⁷

In the Netherlands adjuvant chemotherapy for stage III colon cancer patients was incorporated in the guidelines in the mid-1990s without age limits.⁸ The guidelines advised half a year of fluorouracil in combination with folinic acid as adjuvant treatment. Revisions of the guidelines were made in 2004, when FOLFOX (a combination of fluorouracil, folinic acid and oxaliplatin) was advised. Since 2008 the guidelines included that intravenous fluorouracil could be replaced with oral fluorouracil (capecitabine). Furthermore, in case of high age and/or comorbidities, the medical oncologist can choose for monotherapy with oral fluorouracil.⁸ In the aforementioned adjuvant trials, treatment was shown to be cost-effective, but elderly patients were usually not included. A large proportion of the elderly patients with stage III colon cancer do not receive adjuvant chemotherapy, although some studies showed a benefit for the elderly in terms of recurrence and survival.^{9,10} In this population-based study we show time trends for young and elderly patients in the administration and costs of chemotherapy, and the survival of stage III colon cancer patients.

PATIENTS AND METHODS

Patients and follow-up

Patients were selected from the Netherlands Cancer Registry (NCR). The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the registry of

histo- and cytopathology (PALGA-system). The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completed case ascertainment. Information on patient characteristics, such as gender and date of birth, as well as tumour characteristics, such as date of diagnosis, anatomical location (International Classification of Diseases for Oncology (ICD-O)), histology, stage (clinical and pathological TNM classification), grade, and primary treatment, were obtained routinely from the medical records, around nine months after diagnosis. The information about the primary treatment included whether patients received chemotherapy, but no information about the number of cycles or which drugs were retrieved. Completeness of data was estimated to be at least 95%.¹¹ The vital status was obtained either directly from medical records or through linkage of the cancer registry data with the municipal population registry which registers information on inhabitants' vital status.

Stage was based on pathological TNM classification (5th edition); if pathological stage was unknown, clinical TNM-stage was used. In approximately 1.2% of the patients the pN-stage were missing, resulting in the use of cN-stage. From 2003 the percentage of missing pN-stage decreased to approximately 0.2% per year. Patients were divided in four age groups (<60, 60-69, 70-79, and ≥80 years). Tumour localization was categorized into the following anatomical locations: proximal colon; consisting of caecum, appendix, ascending colon, hepatic flexure, and transverse colon (ICD-O C18.0-C18.4), distal colon; consisting of splenic flexure, descending colon, and sigmoid colon (ICD-O C18.4-C18.7), and Not Otherwise Specified (NOS); consisting of unknown location or overlapping anatomical locations of the colon (ICD-O C18.8 and C18.9). Type of hospital was divided into two groups. Most patients were treated in non-university hospitals.

Patients with their first primary invasive colon cancer (adenocarcinoma; ICD-O C18) stage III (T1-4, N1-3, M0) diagnosed between January 1st 1990 and December 31st 2008 and surgically treated were selected from the NCR (n=24,111). At least 98.8% of the included patients were treated with curative surgery.

Statistical analyses

Differences between the age groups were tested with a Chi-Square test. Statistical significance was defined as $p < 0.05$. Follow-up time was calculated as the time from diagnosis to death, last date of follow-up or last date of linkage with the municipal population registry (January 1st 2010). For survival analyses, overall survival and relative survival were calculated. Overall survival analyses were carried out by the Kaplan-Meier method and multivariable Cox proportional hazard models with any death as event. Relative survival was calculated by the Hakulinen method, as the ratio of the observed survival among the cancer patients and the survival that would have been expected based on the corresponding (age, sex, and year) general population. National life tables were used to estimate the expected survival. 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. Period analysis was conducted for patients diagnosed between 2005 and 2008.¹² The multivariable relative survival analysis was stratified for age groups and adjuvant chemotherapy, as the model showed statistical interaction between year of diagnosis, adjuvant chemotherapy, and age.

Costs of chemotherapy per vial or tablet were retrieved from the pharmacy at the Leiden University Medical Center for three years: 1990, 1999, and 2008. The costs presented in this study are solely the costs of the chemotherapy and were calculated per average person (height of 1.70 m, weight of 76 kg, 1.90 m² body surface). The number of patients receiving chemotherapy was retrieved from the present dataset. The different types of chemotherapy and completion rate were unknown in the dataset retrieved from the NCR and were therefore retrieved from the 'Quality Information System Colorectal Cancer' project from the Comprehensive Cancer Centre the Netherlands, location Leiden, and extrapolated to the dataset from the NCR. The 'Quality Information System Colorectal Cancer' project was a project from 2004 until 2006 collecting detailed information about chemotherapy (type, dose and completion) of colorectal cancer patients in this region. Percentages from this project have been used to calculate the results in the current study, assuming that this region is representative for all the Netherlands. Patients who did not complete their chemotherapy were calculated to have had half of the courses of chemotherapy.

RESULTS

A total of 24,111 colon cancer patients with stage III were included in the cohort. Median age of the patients at diagnosis was 70 (range 11-100) years. The age distribution was stable over time from 1990 to 2008 ($p=0.7$). The sex distribution was different within the age groups, with more females in the elderly age group ($p<0.001$, table 1). The distribution of anatomical tumour location changed with age, younger patients were more often diagnosed with distal tumours, while elderly patients were more often diagnosed with proximal tumours ($p<0.001$). With increasing age, patients were more often diagnosed with higher T-stage ($p<0.001$) and lower N-stage ($p<0.001$).

Administration of chemotherapy

The administration of chemotherapy increased from 22.2% in 1990 to 92.3% in 2008 for patients younger than 60 years; from 12.8% to 84.5% for patients aged 60 to 69 years; from 4.2% to 58.8% for patients aged 70 to 79 years; and from 0.5% to 5.6% for patients of 80 years and older ($p<0.001$ for each age group, figure 1). The odds of receiving adjuvant chemotherapy, adjusted for sex, age, anatomical location, differentiation, T-stage, N-stage, and hospital type, increased significantly in all age groups. The following factors were negatively

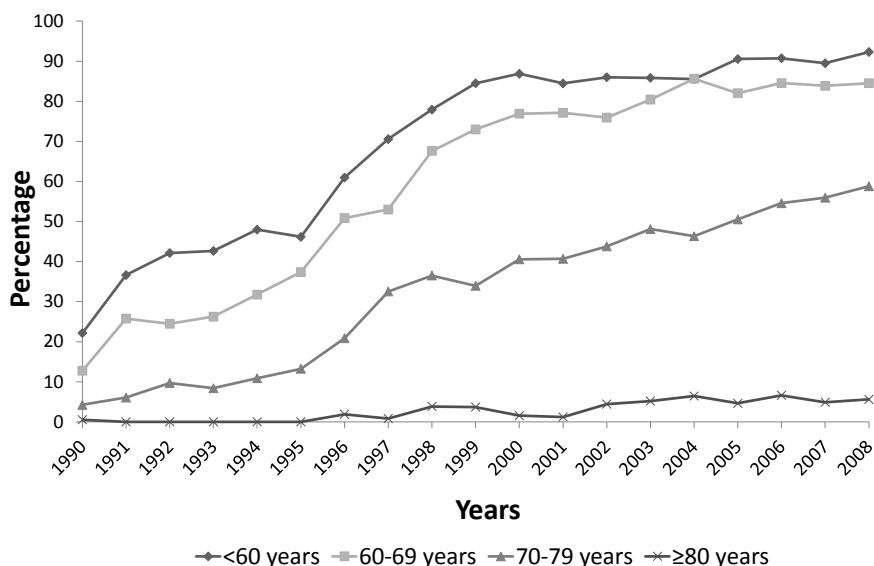
Table 1: Patient characteristics

	<60 years	%	60-70 years	%	70-80 years	%	≥80 years	%	p-value
Sex									<0.001
Male	2621	50.9	3420	53.7	3730	47.1	1564	33.5	
Female	2524	49.1	2943	46.3	4198	52.9	3111	66.5	
Period									0.7
1990-1996	1532	29.8	1881	29.6	2341	29.5	1415	30.3	
1997-2002	1647	32.0	2000	31.4	2579	32.5	1455	31.1	
2003-2008	1966	38.2	2482	39.0	3008	38.0	1805	38.6	
Grade									<0.001
I	339	6.6	450	7.1	473	6.0	270	5.7	
II	3193	62.1	4078	64.1	4950	62.4	2752	58.9	
III	1197	23.3	1394	21.9	1912	24.1	1303	27.9	
Unknown	416	8.1	441	6.9	593	7.5	350	7.5	
Anatomical location									<0.001
Proximal	2301	44.7	3081	48.4	4399	55.5	2895	61.9	
Distal	2742	53.3	3170	49.8	3397	42.8	1697	36.3	
NOS*	102	2.0	112	1.8	132	1.7	83	1.8	
T-stage									<0.001
1	66	1.3	73	1.2	61	0.8	41	0.9	
2	385	7.5	487	7.6	589	7.4	274	5.9	
3	3875	75.3	4787	75.2	5904	74.5	3416	73.1	
4	805	16.6	997	15.7	1351	17.0	932	19.9	
Unknown	14	0.3	19	0.3	23	0.3	12	0.2	
N-stage									<0.001
1	3589	69.8	4520	71.0	5796	73.1	3453	73.9	
2	1435	27.9	1706	26.8	1986	25.1	1123	24.0	
3	121	2.3	137	2.2	146	1.8	99	2.1	
Chemotherapy									<0.001
Yes	3775	73.4	4066	63.9	2822	35.6	142	3.0	
No	1370	26.6	2297	36.1	5106	64.4	4533	97.0	
Total	5145	21.3	6363	26.4	7928	32.88	4675	19.4	

* Not Otherwise Specified and unknown location

associated with the administration of chemotherapy in younger patients (<70 years): increasing age, T4-stage, and tumours with unknown location. On the contrary, higher N-stage was associated with more frequent administration of adjuvant chemotherapy in younger patients. Patients aged 70 years or older received more frequently adjuvant chemotherapy with a higher N-stage, while in contrary, increasing age, female gender, and T4-stage were associated with less frequent administration of chemotherapy.

In 1990, less than 10% of all patients (all ages) received chemotherapy. As shown in table 2, a higher percentage of patients aged younger than 60 years were treated with adjuvant



Years of diagnosis	<60 years	60-69 years	70-79 years	≥80 years
OR over time* (95%CI)	1.23 (1.22-1.25)	1.22 (1.21-1.24)	1.19 (1.18-1.21)	1.17 (1.13-1.22)
p-value	<0.001	<0.001	<0.001	<0.001

* Adjusted for sex, age, grade, anatomical location, T-stage, N-stage, and hospital type.

Figure 1: Percentage of chemotherapy given per age group

Table 2: Type of chemotherapy in 1990, 1999, and 2008, per age group

	No. of patients in 1990 (% of chemo)	No. of patients in 1999 (% of chemo)	No. of patients in 2008 (% of chemo)
Total no. of patients < 60 years	185	271	338
5-FU*	41 (22.2%)	229 (84.5%)	7 (2.0%)
FOLFOX-4	0 (0.0%)	0 (0.0%)	53 (15.7%)
CapOX	0 (0.0%)	0 (0.0%)	222 (65.7%)
Capecitabine mono	0 (0.0%)	0 (0.0%)	30 (8.9%)
Total no. of patients with chemotherapy	41 (22.2%)	229 (84.5%)	312 (92.3%)
Total no. of patients 60-69 years	251	322	504
5-FU*	32 (12.8%)	235 (73%)	10 (2.0%)
FOLFOX-4	0 (0.0%)	0 (0.0%)	72 (14.2%)
CapOX	0 (0.0%)	0 (0.0%)	276 (54.8%)
Capecitabine mono	0 (0.0%)	0 (0.0%)	68 (13.5%)
Total no. of patients with chemotherapy	32 (12.8%)	235 (73%)	426 (84.5%)
Total no. of patients 70-79 years	284	477	563
5-FU*	12 (4.2%)	162 (34%)	20 (3.5%)
FOLFOX-4	0 (0.0%)	0 (0.0%)	46 (8.2%)
CapOX	0 (0.0%)	0 (0.0%)	125 (22.2%)
Capecitabine mono	0 (0.0%)	0 (0.0%)	140 (24.9%)

Table 2 (*continued*)

	No. of patients in 1990 (% of chemo)	No. of patients in 1999 (% of chemo)	No. of patients in 2008 (% of chemo)
Total no. of patients with chemotherapy	12 (4.2%)	162 (34%)	331 (58.8%)
Total no. of patients ≥80 years	190	271	357
5-FU*	1 (0.5%)	10 (3.7%)	4 (1.1%)
FOLFOX-4	0 (0.0%)	0 (0.0%)	0 (0.0%)
CapOX	0 (0.0%)	0 (0.0%)	4 (1.1%)
Capecitabine mono	0 (0.0%)	0 (0.0%)	12 (3.4%)
Total no. of patients with chemotherapy	1 (0.5%)	10 (3.7%)	20 (5.6%)
Total no. of patients in each year with chemotherapy	86 (9.5%)	636 (47.4%)	1089 (61.8%)

* 5-FU in combination with folinic acid

chemotherapy in 1990, and the percentage of patients receiving chemotherapy decreased with increasing age. In 1999 almost 50% of all patients received chemotherapy (all ages), which also decreased with increasing age. In both 1990 and 1999 patients were only treated with a combination of fluorouracil and folinic acid. In 2008 over 60% of all patients (all ages) received adjuvant chemotherapy. Since the guidelines have been revised in 2004 and 2008, patients in 2008 were treated more often with FOLFOX, CapOx (combination of capecitabine and oxaliplatin) or capecitabine as monotherapy (table 2). With increasing age, patients more often received capecitabine as a monotherapy and less often a combination of capecitabine with oxaliplatin or FOLFOX.

Costs of chemotherapy

Due to the low percentage of patients receiving chemotherapy in 1990 and the low costs for these chemotherapeutics (off patent), the costs were relatively low, € 38,467 (figure 2). The estimated costs per patient (total costs divided through the number of patients treated) in 1990 were € 459 for patients younger than 60 years, € 445 for patients between 60 and 69 years, € 427 for patients between 70 and 79 years, and € 285 for patients 80 years and older, as shown in attachment 1. With increasing age, fewer patients completed six months of chemotherapy, resulting in lower costs per patient with increasing age. Guidelines of adjuvant chemotherapy were widely incorporated in 1999, as is shown in figure 1. The costs for chemotherapy in the present dataset for 1999 were approximately € 262,040. The estimated costs of chemotherapy per person were between € 264 and € 426 for the different age groups. In 2008, the costs of chemotherapy were higher due to the frequent use of capecitabine, an oral 5-fluorouracil analogue, which is still under a patent. Furthermore, oxaliplatin was widely incorporated as adjuvant chemotherapy in addition to fluorouracil and folinic acid (FOLFOX). The estimated costs per person in 2008 varied between € 1,933 and € 3,800 and total costs were estimated to be € 3,876,150.

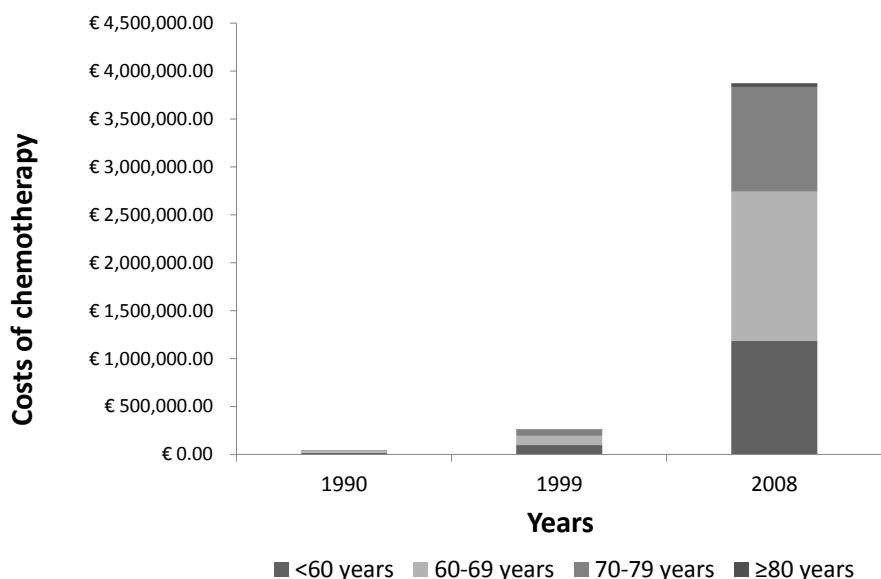
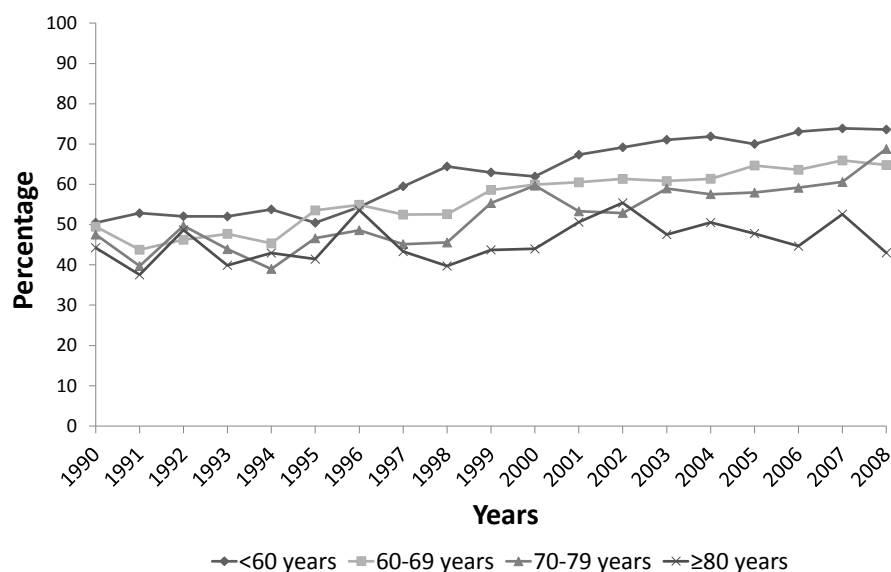


Figure 2: Changes of total costs of chemotherapy over time

Survival

Five year overall survival for colon cancer patients with stage III increased over time from 38.7% in 1990-1996, to 45.9% in 1997-2002, and to 51.6% in 2003-2008 (HR over incidence periods=0.82; 95% CI=0.80-0.84; $p<0.001$). The five year relative survival increased from 47.3% in 1990-1996, to 55.3% in 1997-2002, and to 62.2% in 2003-2008 (RER over incidence periods=0.96; 95% CI=0.96-0.97; $p<0.001$, figure 3). The improvement of relative survival was less pronounced with increasing age with a RER of 0.94 (95% CI 0.93-0.95; $p<0.001$) for patients younger than 60 years, RER of 0.95 (95% CI 0.95-0.96; $p<0.001$) for patients 60-70 years, RER of 0.96 (95% CI 0.95-0.97; $p<0.001$) for patients between 70-80 years and a RER of 0.99 (95% CI 0.98-1.00; $p=0.01$) for patients of 80 years and older.

The multivariable relative survival analyses were adjusted for sex, age, grade, anatomical location, T-stage, N-stage, and hospital. The multivariable relative survival of patients receiving chemotherapy increased for each age group over time (table below figure 3). However, the multivariable relative survival of in patients not receiving chemotherapy was less consistent over time. Whereas the survival of patients aged 60 to 69 years who did not receive chemotherapy decreased over time, the survival of patients aged 80 years or older has improved over time. Relative survival of the other age groups not receiving chemotherapy remained stable over time. Of the patients that did not receive adjuvant chemotherapy, female patients had a better relative survival. Relative survival decreased with higher grade, T-stage, and N-stage in both the group of patients receiving adjuvant chemotherapy, as well as the group of patients not receiving adjuvant chemotherapy ($p<0.001$).



	Chemotherapy		No chemotherapy	
	RER (95% CI)	p-value	RER (95% CI)	p-value
<60 years	0.93 (0.91-0.94)	<0.001	1.01 (1.00-1.03)	0.2
60-69 years	0.94 (0.93-0.96)	<0.001	1.02 (1.00-1.03)	0.01
70-79 years	0.92 (0.89-0.94)	<0.001	1.00 (0.99-1.00)	0.3
≥80 years	0.83 (0.73-0.94)	0.003	0.98 (0.97-0.99)	<0.001

* Adjusted for sex, age, grade, anatomical location, T-stage, N-stage, and hospital type.

Figure 3: Relative survival over time per age group, with multivariable relative survival per age group in the table

DISCUSSION

In this nationwide population-based study covering a period of 18 years, we showed that both administration of chemotherapy and survival of patients with stage III colon cancer increased during the study period. Whereas the administration of chemotherapy increased considerably during the period, survival increased to a lesser extent. New chemotherapeutics were introduced during the study period, which led, together with the increased use of chemotherapy, to increasing costs of chemotherapy per patient.

Administration of chemotherapy

The changes in administration of chemotherapy and survival of colon cancer found in this study are in line with earlier studies in the Netherlands and other European countries.^{13,14}

The results of randomized clinical trials published during the study period have been implemented in guidelines and clinical practice, resulting in a large increase in the use of adjuvant chemotherapy. Our observation that elderly patients less frequently received chemotherapy as compared to younger patients is in line with previous studies.^{15,16} There are several reasons why elderly patients are less likely to receive adjuvant chemotherapy; they include the presence of comorbidities, frailty, the absence of supportive caregivers, and a decrease in patients' general condition and cognitive ability.¹⁷ In addition, elderly patients seem to be less willing to accept the negative side-effects of chemotherapy, resulting in more frequent patient refusal, and some medical oncologists will probably offer elderly less often adjuvant chemotherapy.¹⁸ However, fit elderly colon cancer patients may benefit equally from adjuvant chemotherapy without increased toxicity.^{9,10} Over time, patients were more often treated with FOLFOX, CapOx, or capecitabine mono therapy, according to the results of the MOSAIC trial, the NSABP C-07 trials, and the adjustments in the guidelines.^{6,8,19} The addition of oxaliplatin showed an improved disease-free survival for stage III colon cancer patients.^{6,19} Since subgroups analyses of these two studies have shown that elderly patients with an age of 70 years and older are less likely to benefit from the addition of oxaliplatin, elderly patients in our study indeed received less often oxaliplatin in addition to oral fluorouracil with folinic acid, or in addition to capecitabine.^{20,21} Furthermore, capecitabine monotherapy has shown to be at least as effective as intravenous fluorouracil in combination with folinic acid.⁷

Costs of chemotherapy

The costs of chemotherapy are expected to be an underestimation since only the costs for the medication, and no hospital or material costs, were included. Furthermore, patients who did not complete the chemotherapy were calculated to have had fifty percent of the expected chemotherapy costs, which also might have led to an underestimation. Despite these limitations, costs of chemotherapy have increased considerably during the study period, especially in the last period, due to the use of newer chemotherapeutics. Cost-effectiveness cannot be calculated with the design of this study. However, we observe high costs for the adjuvant chemotherapy (between € 1,933 and € 3,800 per person in 2008). Recently, Pandor et al. have shown in their systematic review that the use of oral fluorouracil is cost-effective, based on quality adjusted life years (QALY's).²²

The end of the patent on oral fluorouracil, capecitabine, in December 2013, will probably result in lower costs per person. Furthermore, subset analyses of recent studies have shown that oxaliplatin might not be effective in elderly colon cancer patients^{20,21} which could decrease the costs in the coming years.

Overall, the improvement in survival found in this study was accompanied by an approximately 100-fold increase in costs of chemotherapy. Currently, the question is how much more costs can be accepted. The proportion between the improvement in survival and the increase in costs should be balanced. Perhaps, other ways to improve survival, such as perioperative care

or low-cost drugs such as aspirin²³, should be implemented first, since these improvements might be relatively cheap and less toxic in comparison to new chemotherapeutics.

Survival

The considerable improvement in five year relative survival of patients who received chemotherapy over time with 7% for patients younger than 60 years, 6% for patients between 60 and 69 years, 8% for patients between 70 and 79 years, and 17% for patients 80 years and older, is thought to be at least in part attributable to the increased use of adjuvant chemotherapy. Stage migration and improved perioperative care probably played an additional role, although these data were not available. Although the percentage of patients receiving chemotherapy increased most for patients younger than 60 years and less with increasing age, elderly patients who did receive chemotherapy had the highest increase in relative survival, indicating differences in the selection of patients receiving chemotherapy within each age group.

In the adjuvant studies that demonstrated decreased colon cancer relapse and increased overall survival, the mean age was below 65 years and the small number of older patients does not allow drawing firm conclusions on the benefits of adjuvant therapy in elderly patients.¹⁰ For patients not receiving adjuvant chemotherapy the relative survival remained almost stable, although there was an age disparity in time trends of relative survival. For patients aged younger than 80 years relative survival decreased or remained stable over time. The use of adjuvant therapy for these patients increased from approximately 10% to 80%. Hence, the selection of patients has changed over time from broad representation of unselected stage III patients who received no chemotherapy to a small group of highly selected patients for whom adjuvant therapy was not deemed beneficial for survival because of factors associated with an unfavourable outcome itself, such as comorbidities.

For patients aged 80 years and older, relative survival increased over time for both those who did and those who did not receive adjuvant chemotherapy. Improved survival might be due to increased life expectancy and improved perioperative care. Besides, stage migration with improved detection of metastases during the preoperative work-up might have contributed as well.^{14,24} However, we have to interpret these retrospective data with caution. Nevertheless, these patients deserve more attention and research regarding adjuvant treatment.

Strengths and limitations

This population-based study has some limitations. Firstly, it lacks details concerning emergency surgery and the presence of comorbidities. Both are associated with increased postoperative complications and mortality and reduced administration of chemotherapy. Elderly patients are more likely to undergo emergency surgery and also the incidence of comorbidity increases with age.²⁵ Secondly, the costs of chemotherapy and the number of patients completing chemotherapy per age group were estimated. Furthermore, the costs of complications and

additional costs, such as material and hospital stay, were not taken into account. This probably resulted in an underestimation of the actual costs of chemotherapy.

Thirdly, stage migration probably played a role in the survival changes over time, as lymph node detection has improved and advanced diagnostic methods might have increased recognition of metastases.^{14,24} It is unknown which part of the improvement in survival over time can be explained by stage migration, and which part can be attributed to changes in treatment. Nevertheless, this study has several strengths. It is a large population-based study, which used stratification according to age groups with comparison between younger and elderly patients and the receipt of chemotherapy over a long period of time, so that time trends could be studied. Furthermore, this is the first study to present the absolute costs of chemotherapy for colon cancer patients in the Netherlands.

CONCLUSION

In conclusion, the administration of chemotherapy and costs increased considerably over time, although many elderly patients still do not receive adjuvant chemotherapy. The relative survival of patients receiving chemotherapy increased over time, while the relative survival of patients who did not receive chemotherapy remained almost stable. Although administration of chemotherapy increased considerably during the study period, relative survival increased to a lesser extent. In our study we show that elderly patients who did receive adjuvant chemotherapy have at least equal improvement in relative survival as compared to younger stage III colon cancer patients, suggesting that there are differences in the selection of patients receiving adjuvant chemotherapy in each age group. Furthermore, the current results show the importance of selecting patients for whom chemotherapy is expected to be beneficial.

ACKNOWLEDGEMENTS

The authors would like to thank L.G.M. van der Geest from the Comprehensive Cancer Center the Netherlands, location Leiden and the steering group of the 'Quality Information System Colorectal Cancer' project for the estimation of the type of chemotherapy received by the patients and the number of patients completing chemotherapy. Furthermore, the authors would like to thank P.A.F. Vis from the pharmacy in the Leiden University Medical Center for helping to collect the costs of the chemotherapeutics in each year and W.B. van den Hout who helped us with the implications of the increase in costs of chemotherapy.

REFERENCE LIST

- 1 The statistics about cancer in the Netherlands registered by the Netherlands Cancer Registry. <http://www.cijfersoverkanker.nl/> (accessed February 3 2012).
- 2 Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al.: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004;22:3408-3419.
- 3 Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al.: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352-358.
- 4 Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group: *Lancet* 2000;355:1588-1596.
- 5 O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, et al.: Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; 15:246-250.
- 6 Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al.: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350:2343-2351.
- 7 Cassidy J, Saltz L, Twelves C, Van Cutsem E, Hoff P, Kang Y, et al.: Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients. *Ann Oncol* 2011;22: 2604-2609.
- 8 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed February 3 2012).
- 9 Papamichael D, Audisio R, Horiot JC, Glime-lius B, Sastre J, Mitry E, et al.: Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009;20:5-16.
- 10 Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al.: A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001;345:1091-1097.
- 11 Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ: Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993;22:369-376.
- 12 Brenner H, Hakulinen T: Up-to-date long-term survival curves of patients with cancer by period analysis. *J Clin Oncol* 2002;20:826-832.
- 13 Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al.: Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: The EURO-CARE study. *Int J Cancer* 2011.
- 14 van Steenbergen LN, Lemmens VE, Rutten HJ, Wymenga AN, Nortier JW, Janssen-Heijnen ML: Increased adjuvant treatment and improved survival in elderly stage III colon cancer patients in The Netherlands. *Ann Oncol* 2012.
- 15 Lemmens VE, van Halteren AH, Janssen-Heijnen ML, Vreugdenhil G, Repelaer van Driel OJ, Coebergh JW: Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005;16:767-772.
- 16 van Steenbergen LN, Elferink MA, Krijnen P, Lemmens VE, Siesling S, Rutten HJ, et al.: Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol* 2010; 21:2206-2212.
- 17 Droz JP, Aapro M, Balducci L: Overcoming challenges associated with chemotherapy treatment in the senior adult population. *Crit Rev Oncol Hematol* 2008;68 Suppl 1:S1-S8.
- 18 Yellen SB, Cella DF, Leslie WT: Age and clinical decision making in oncology patients. *J Natl Cancer Inst* 1994;86:1766-1770.
- 19 Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al.: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer:

- results from NSABP C-07. *J Clin Oncol* 2007; 25:2198-2204.
- 20 Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al.: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109-3116.
 - 21 Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al.: Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011;29: 3768-3774.
 - 22 Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P: The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. *Health Technol Assess* 2006;10:iii-xiv, 1.
 - 23 Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, et al.: Use of aspirin postdiagnosis improves survival for colon cancer patients. *Br J Cancer* 2012;106:1564-1570.
 - 24 Derwinger K, Carlsson G, Gustavsson B: Stage migration in colorectal cancer related to improved lymph node assessment. *Eur J Surg Oncol* 2007;33:849-853.
 - 25 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group: *Lancet* 2000; 356:968-974.

Attachment 1: costs of chemotherapy in 1990, 1999, and 2008, per age group

	No. in 1990 (% of chemo)	Costs (€)	No. in 1999 (% of chemo)	Costs (€)	No. in 2008 (% of chemo)	Costs (€)
< 60 years	185 (22.2%)		271 (84.5%)		338 (92.3%)	
5-FU*	41	€ 18,806.04	229	€ 97,570.98	7	€ 2,703.89
FOLFOX-4	0	€ 0.00	0	€ 0.00	53	€ 142,184.60
CapOX	0	€ 0.00	0	€ 0.00	222	€ 931,891.38
Capecitabine mono	0	€ 0.00	0	€ 0.00	30	€ 108,917.76
Total	41	€ 18,806.04	229	€ 97,570.98	312	€ 1,185,697.63
Per patient		€ 458.68		€ 426.07		€ 3,800.31
60-69 years	251 (12.8%)		322 (73%)		504 (84.5%)	
5-FU*	32	€ 14,247.00	235	€ 97,042.14	10	€ 3,932.93
FOLFOX-4	0	€ 0.00	0	€ 0.00	72	€ 187,349.12
CapOX	0	€ 0.00	0	€ 0.00	276	€ 1,125,056.54
Capecitabine mono	0	€ 0.00	0	€ 0.00	68	€ 240,526.72
Total	32	€ 14,247.00	235	€ 97,042.14	426	€ 1,556,865.31
Per patient		€ 445.22		€ 412.95		€ 3,654.61
70-79 years	284 (4.2%)		477 (34%)		563 (58.8%)	
5-FU*	12	€ 5,128.92	162	€ 64,782.90	20	€ 7,374.24
FOLFOX-4	0	€ 0.00	0	€ 0.00	46	€ 115,420.44
CapOX	0	€ 0.00	0	€ 0.00	125	€ 493,354.26
Capecitabine mono	0	€ 0.00	0	€ 0.00	140	€ 487,784.32
Total	12	€ 5,128.92	162	€ 64,782.90	331	€ 1,094,933.26
Per patient		€ 427.41		€ 399.89		€ 3,307.96
≥80 years	190 (0.5%)		271 (3.7%)		357 (5.6%)	
5-FU*	1	€ 284.94	10	€ 2,644.20	4	€ 983.23
FOLFOX-4	0	€ 0.00	0	€ 0.00	0	€ 0.00
CapOX	0	€ 0.00	0	€ 0.00	4	€ 10,441.36
Capecitabine mono	0	€ 0.00	0	€ 0.00	12	€ 27,229.44
Total	1	€ 284.94	10	€ 2,644.20	20	€ 38,654.03
Per patient		€ 284.94		€ 264.42		€ 1,932.70
Total costs population	86	€ 38,466.90	636	€ 262,040.22	1089	€ 3,876,150.23

* 5-Fu in combination with folinic acid

Chapter 3

Adjuvant chemotherapy use in stage III colon cancer patients

Colette B.M. van den Broek

Catherine C.E.M. Puylaert

Esther Bastiaannet

Anton J.M. de Craen

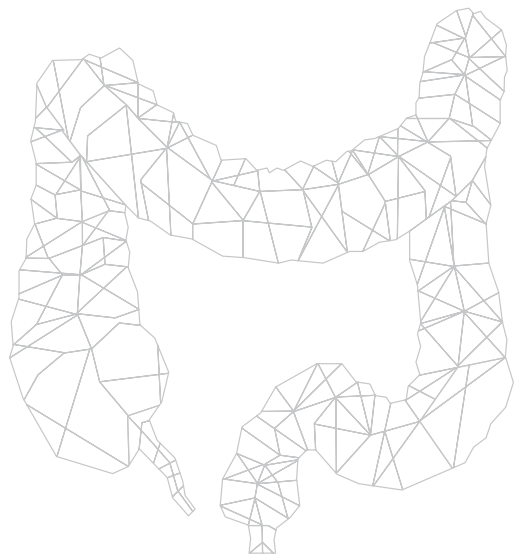
Cornelis J.H. van de Velde

Gerrit-Jan Liefers

Johanneke E.A. Portielje ¹ Department of Surgery, Leiden

University Medical Center, Leiden, the Netherlands

Submitted for publication



ABSTRACT

Background

According to the Dutch guidelines, patients with stage III colon cancer are advised to receive adjuvant chemotherapy. Even though, only about 60% of the patients do receive this treatment. The present study compares characteristics and causes of death of patients who received adjuvant chemotherapy versus patients who did not. In addition, cumulative incidence of recurrence, with death as a competing risk was studied.

Methods

All patients from two hospitals in the mid-western part of the Netherlands, diagnosed with stage III colon cancer between 2000 and 2009 and treated with curative surgery were selected. Patient characteristics, including comorbidities and treatment preferences, tumour characteristics, and follow-up were extracted from the medical records. These characteristics were compared between the treatment groups using chi-squared test. Competing-risks regression models were used to assess Sub Hazard Ratios (SHR) for recurrence rates between treatment groups with death as competing risk, adjusted for the possible confounding factors.

Results

A total of 348 patients were included. Median age was 73 years (range 33 to 93). Over half of the patients have been treated with adjuvant chemotherapy (50.6%). Patients who received adjuvant chemotherapy were significantly younger ($p < 0.001$), had less comorbidities ($p < 0.001$), and were more often living together with a partner ($p < 0.001$). Patients who received no adjuvant chemotherapy had a reduced overall survival, and cause of death was more often due to other causes than colon cancer. The cumulative incidence of colon cancer recurrence, with death as a competing risk, did not differ between the treatment groups ($p = 0.7$).

Conclusion

Patients who received no adjuvant chemotherapy had worse survival, but most of these patients died due to competing causes. Remarkably, cumulative incidence of recurrence, with death as competing risk was similar in both treatment groups. Prospective research is needed to evaluate which patient characteristics predict risks and benefits of adjuvant chemotherapy.

INTRODUCTION

In developed countries, colon cancer is one of the most common types of cancer. The incidence of colon cancer increases with age, and therefore the number of patients is expected to rise along with increasing life expectancy. In the Netherlands, colon cancer is diagnosed in over 8000 persons annually, with node positive or stage III disease in approximately a quarter of these patients.¹ Unfortunately, about 50% to 60% of the patients with stage III colon cancer have disease recurrence within five years of operation when treated with surgery only.²

Large randomised controlled trials have demonstrated relative risk reductions of 40% for recurrence and 33% relative risk reductions for mortality in patients with stage III colon cancer who received adjuvant chemotherapy.³⁻⁶ Subsequently, it has been shown that the addition of oxaliplatin further improves disease control.^{7,8} Since 1997 the Dutch guidelines recommend adjuvant chemotherapy for patients with stage III colon cancer after surgery. No age limitation is stated in these guidelines.⁹

Data from the Netherlands Cancer Registry indicate that administration of adjuvant chemotherapy has increased steadily over time. Still, only 62% of stage III colon cancer patients are treated with adjuvant chemotherapy.¹⁰ The percentage of patients that receives adjuvant chemotherapy after surgery for colon carcinoma with lymph node metastases declines with increasing age; while approximately 85% of patients under the age of 65 years receive adjuvant chemotherapy, this is approximately 25% above 75 years of age.^{10,11} Several reasons have been suggested to explain why these patients do not receive adjuvant chemotherapy, including age and comorbidities. In order to study the reasons to withhold adjuvant chemotherapy, the characteristics of all patients with stage III colon cancer treated with surgery in two hospitals in the mid-western part of the Netherlands have been studied. Delivery of adjuvant chemotherapy, cancer recurrences, and additionally causes of death were studied.

METHODS

Data collection

All patients with primary stage III colon cancer (Tumour Lymph Node Metastasis (TNM) classification from the UICC and C18.0 –C18.9 ICD-10) diagnosed between 2000 and 2009, treated with radical resection in a large teaching hospital and a university hospital in the mid-western part of the Netherlands were included in this study. Patients were identified from the Netherlands Cancer Registry (NCR). The NCR is based on notification of all new diagnosed malignancies in the Netherlands by the registry of histo- and cytopathology (PALGA-system). The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completed case ascertainment.

The following data were collected from the medical records and registered on a CRF (case report form); date of birth, gender, date of diagnosis, clinical and pathological TNM-stage, grade, location of the tumour in the colon, number of lymph nodes resected and number positive, comorbidities, prescribed medication, housing situation, and marital status. Besides, treatment information such as ASA-score, surgical radicality, surgical complications (subdivided into anastomotic leakage, postoperative bleeding, infectious complications, cardiovascular complications, neurological complications, pneumonia, urinary tract infection, trombo-embolism, death, and other), administration and type of adjuvant chemotherapy, and complications from chemotherapy (subdivided into neuropathy, hand-foot-syndrome, fatigue and other), were collected. Comorbidity was counted as the number of comorbidities per person, and calculated as a Charlson comorbidity score.¹² Polypharmacy was deemed present when a patient used five or more prescribed medications at the time of colon cancer diagnosis. Marital status was divided into married, living together, or LAT-relationship; single or divorced; widowed; or unknown marital status. Housing situation was divided into together with partner; living alone; nursing home; other (including living with children or siblings); or unknown housing situation. Reasons to withhold adjuvant chemotherapy were collected from the record or medical correspondence. Follow-up information was collected including date of local and distant recurrences, location of recurrences, number of recurrences, vital status, date of vital status, and cause of death. Causes of death were divided into seven major groups; primary tumour, complications of surgery, complications of chemotherapy, second primary tumour, heart failure, and other causes of death. Death due to postoperative complications was defined as death and postoperative complication within 30 days of surgery. Death due to complications of chemotherapy was defined as death within 30 days after administration of chemotherapy or death as a result of prolonged complications after chemotherapy. Age at time of surgery was divided into four groups; <60 years, 60-69 years, 70-79 years, and ≥80 years.

Patients were excluded if there were no positive lymph nodes found (N0), if distant metastases were discovered before, during, or within four weeks after surgery (M1), if the carcinoma was located in the rectosigmoid (C19.0) or rectum (C20.0), if colon cancer was present in the medical history, or if the tumour was not an adenocarcinoma. Figure 1 shows the selection of the patients included in current study. A total of 348 patients were included.

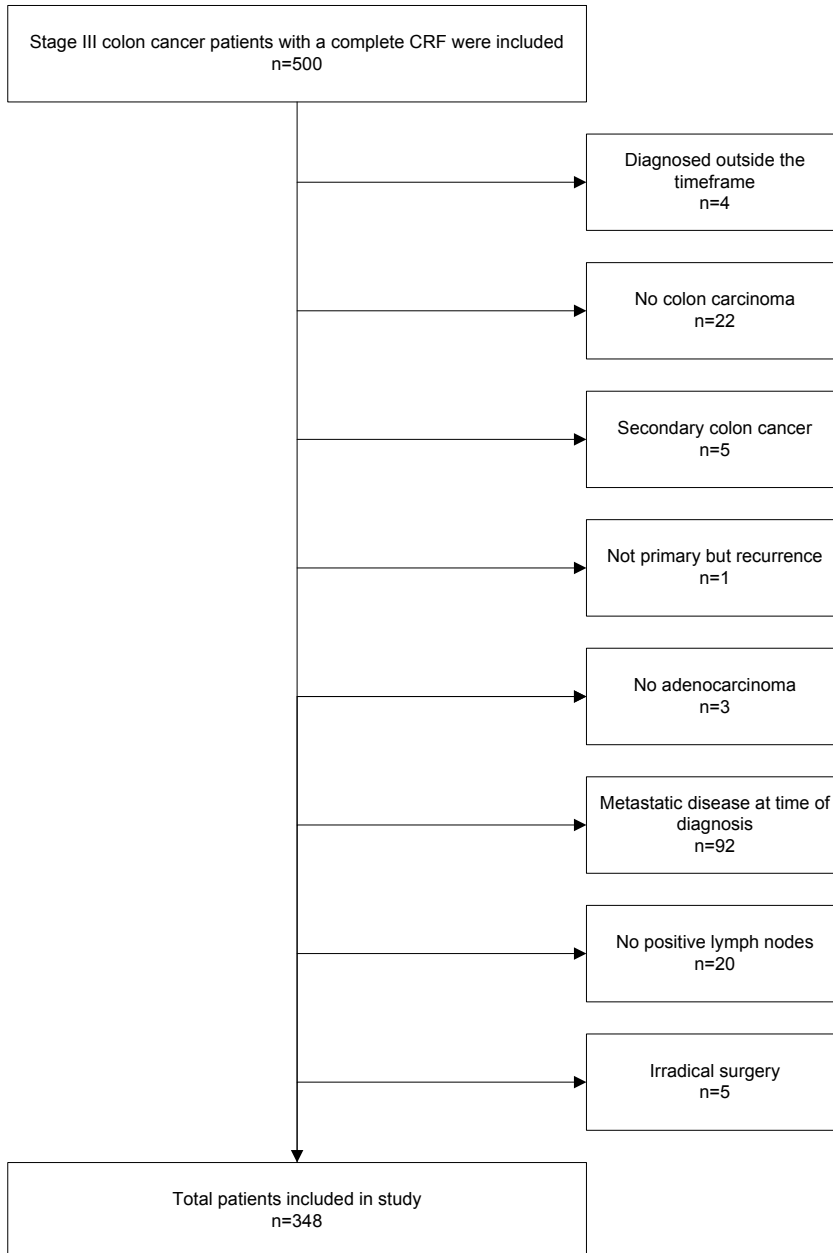


Figure 1: Flowchart for the inclusion of the patient population

Statistical analyses

The characteristics were compared between the treatment groups using chi-squared test. Motives for suboptimal treatment and treatment adaptations were described. Time to recurrence was defined as time from date of surgery to date of recurrence. Follow-up for survival was calculated as time from date of surgery to date of death or last contact. In calculating recurrence rates we accounted for death as competing risk.¹³ Competing-risks regression models were used to assess Sub Hazard Ratios (SHR) for recurrence rates between treatment groups, adjusted for the following risk factors; age at surgery, gender, pathological tumour stage, nodal stage, and grade.

RESULTS

Characteristics

A total of 348 patients were included in the study. In table 1 the patient characteristics are shown. Over 60% of the patients were aged 70 years or older, with a median age of 73 years (range from 33 years to 93 years). Slightly more than half of the patients included were female (51.4%). Almost two thirds of the included patients had one or more comorbidities at the time of colon cancer diagnosis (62.4%). The most common comorbid conditions were cardiovascular disease (36.5%), diabetes mellitus (17.0%), pulmonary disease (14.7%), and cerebrovascular disease (13.2%). Just over half of the patients had a Charlson comorbidity score of one or more (55.5%). The median Charlson comorbidity score was 1, with a range from 0 to 5. Almost a quarter of the patients underwent emergency surgery (23.3%). Patients who underwent emergency surgery more often had postoperative complications as compared to patients who underwent elective surgery (61.7% versus 28.7%). Besides, those patients slightly more often underwent reoperation (9.9% versus 6.4%).

Adjuvant treatment

Approximately half of the included patients received adjuvant chemotherapy (50.6%). In table 2, the characteristics of the treatment groups are compared. The median age of patients who received adjuvant chemotherapy was 66 years versus 80 years in the group who received no adjuvant chemotherapy. There were no significant differences between the patients in gender, T-stage, N-stage, and occurrence of emergency surgery. However, patients who received adjuvant chemotherapy were more often married and living with their partner, as compared to patients who received no adjuvant chemotherapy, who were more often widowed and living alone or in a nursing home ($p < 0.001$). Of the patients who received no adjuvant chemotherapy, 97 (75.8%) have had postoperative complications. Of patients who received adjuvant chemotherapy, only 31 (24.2%) have had postoperative complications.

Table 1: Patient characteristics

	Number of patients	Percentage
Age group		
<60 years	63	18.1
60-69 years	73	21.0
70-79 years	124	35.6
≥80 years	88	25.3
Gender		
Men	169	48.6
Women	179	51.4
Marital status		
Married, living together, or LAT-relationship	188	54.0
Single or divorced	35	10.1
Widowed	72	20.7
Unknown	53	15.2
Housing situation		
Together with partner	176	50.6
Living alone	105	30.2
Nursing home	22	6.3
Other	3	0.8
Unknown	42	12.1
T-stage		
1 or 2	28	8.0
3	275	79.0
4	44	12.6
Unknown	1	0.3
N-stage		
1	258	74.1
2	90	25.9
Comorbidity		
0	131	37.6
1	111	31.9
2 and more	103	29.6
Unknown	3	0.9
Charlson comorbidity score		
0	152	43.7
1	78	22.4
2 or 3	83	23.8
4 and more	32	9.2
Unknown	3	0.9
Polypharmacy		
Yes	92	26.4
No	246	70.7
Unknown	10	2.9
Emergency surgery		
Elective surgery	251	72.1
Emergency surgery	81	23.3
Unknown	16	4.6
Chemotherapy		
Yes	176	50.6
No	172	49.4
Total	348	100.0

Table 2: Patient characteristics according to adjuvant chemotherapy

	No adjuvant chemotherapy (n=172)		Adjuvant chemotherapy (n=176)		p-value
	Number of patients	Percentage	Number of patients	Percentage	
Age group					<0.001
<60 years	3	1.8	60	34.1	
60-69 years	15	8.7	58	33.0	
70-79 years	69	40.1	55	31.2	
≥80 years	85	49.4	3	1.7	
Gender					0.587
Men	81	47.1	88	50.0	
Women	91	52.9	88	50.0	
Marital status					<0.001
Married, living together, or LAT-relationship	79	45.9	109	61.9	
Single or divorced	17	9.9	18	10.2	
Widowed	56	32.6	16	9.1	
Unknown	20	11.6	33	18.8	
Housing situation					<0.001
Together with partner	69	40.1	107	60.8	
Living alone	73	42.5	32	18.2	
Nursing home	20	11.6	2	1.1	
Other	0	0.0	3	1.7	
Unknown	10	5.8	32	18.2	
T-stage					0.183
1 or 2	16	9.3	12	6.8	
3	129	75.0	146	82.9	
4	27	15.7	17	9.7	
Unknown	0	0.0	1	0.6	
N-stage					0.112
1	134	77.9	124	70.5	
2	38	22.1	52	29.5	
Comorbidity					<0.001
0	30	17.4	101	57.4	
1	59	34.3	52	29.5	
2 and more	83	48.3	20	11.4	
Unknown	0	0.0	3	1.7	
Charlson comorbidity score					<0.001
0	44	25.6	108	61.4	
1	44	25.6	34	19.3	
2 or 3	57	33.1	26	14.8	
4 and more	27	15.7	5	2.8	
Unknown	0	0.0	3	1.7	
Polypharmacy					<0.001
Yes	73	42.4	19	10.8	
No	94	54.7	152	86.4	
Unknown	5	2.9	5	2.8	
Emergency surgery					0.430
Elective surgery	120	69.8	131	74.4	
Emergency surgery	45	26.1	36	20.5	
Unknown	7	4.1	9	5.1	
Total	172	49.4	176	50.6	

Table 3: Types of postoperative complications stratified by the prescription of adjuvant chemotherapy

	No adjuvant chemotherapy (n=172)		Adjuvant chemotherapy (n=176)	
	Number of patients	Percentage	Number of patients	Percentage
None	79	45.9	144	81.8
Anastomotic leakage	11	6.4	4	2.3
Postoperative bleeding	5	2.9	1	0.6
Infectious complication	15	8.7	13	7.3
Cardiovascular	5	2.9	0	0.0
Neurological	4	2.3	0	0.0
Pneumonia	9	5.2	1	0.6
Urinary tract infection	6	3.5	4	2.3
Trombo-embolism	1	0.6	1	0.6
Other	12	7.0	6	3.4
Death	24	14.0	0	0.0
Unknown	1	0.6	2	1.1

Table 3 shows the type of complications and the percentage of patients with this complication stratified for the treatment with adjuvant chemotherapy.

The most common reasons to withhold adjuvant chemotherapy for patients who had survived at least 30 days after surgery were a combination of high age and comorbidity (67.3%), surgical complications (12.9%), or refusal by the patient or family (8.2%).

Type of adjuvant chemotherapy was fluorouracil and leucovorin in the majority of patients, with or without oxaliplatin (22.2% and 52.8%, respectively); the remaining patients received either capecitabine monotherapy (12.5%), or a combination of capecitabine and oxaliplatin (8.5%). With increasing age, patients more often received capecitabine monotherapy. Almost half of the patients receiving adjuvant chemotherapy experienced a complication (83 patients, 47.2%), resulting in dose reduction in 40 patients (22.7%), and in reduced numbers of cycles in 28 patients (15.9%). Complications of chemotherapy and changes in the dose and cycles of chemotherapy were not significantly associated with age ($p=0.6$) or the number of comorbidities ($p=0.9$).

Table 4: Recurrences and causes of death according to adjuvant chemotherapy

	No chemotherapy N (%)	Chemotherapy N (%)	p-value
Median follow-up (range)	2.2 years (0 – 12.5)	5.1 years (0.1 – 12.0)	
Recurrence			0.042
No	117 (68.0)	116 (65.9)	
Yes	46 (26.8)	58 (33.0)	
Unknown	9 (5.2)	2 (1.1)	
Dead			<0.001
No	56 (32.6)	115 (65.3)	
Yes	116 (67.4)	61 (34.7)	
Causes of death			<0.001
Colon cancer	37 (31.9)	43 (70.5)	
Complications surgery	23 (19.8)	0 (0.0)	
Complications chemotherapy	0 (0.0)	4 (6.5)	
Other tumour	5 (4.3)	7 (11.5)	
Heart failure	7 (6.0)	0 (0.0)	
Other	28 (24.2)	5 (8.2)	
Unknown	16 (13.8)	2 (3.3)	

Outcome

Median follow-up was 3.5 years (range from 0 to 12.5 years). The median follow-up for patients who received no adjuvant chemotherapy was 2.2 years (range from 0 to 12.5 years), while the median follow-up of those who received adjuvant chemotherapy was 5.1 years (range from 0.1 to 12.0 years). Table 4 and figure 2 show the causes of death according to adjuvant chemotherapy. The primary cause of death of patients who received adjuvant chemotherapy was colon cancer including recurrences (70.5%). In comparison, patients who received no adjuvant chemotherapy died due to colon cancer including recurrences (31.9%), complications of surgery (19.8%), cardiovascular disease (7.8%), and due to other causes, such as cerebral vascular event and sepsis.

As shown in table 4, in total, 104 patients had recurrence of the disease during follow-up (29.9%). Slightly more patients treated with adjuvant chemotherapy had a recurrence during follow-up (58 out of 176, 33.0%), as compared to patients who received no adjuvant chemotherapy (46 out of 172, 26.7%, $p=0.06$). As shown above, patients who received no adjuvant chemotherapy died more often due to other causes of death than the primary tumour. Figure 3 shows the cumulative incidence of recurrence with death as competing risk according to the use of adjuvant chemotherapy. The unadjusted SHR showed that there is no significant difference in the recurrence rate between the treatment groups, when death was taken into account as competing risk for recurrence (SHR 1.15; 95% CI 0.77-1.70; $p=0.5$). After adjustment for potential confounders such as age, gender, pathological tumour stage, nodal stage, and grade, the SHR did not materially change (SHR 1.09; 95% CI 0.64-1.86; $p=0.7$).

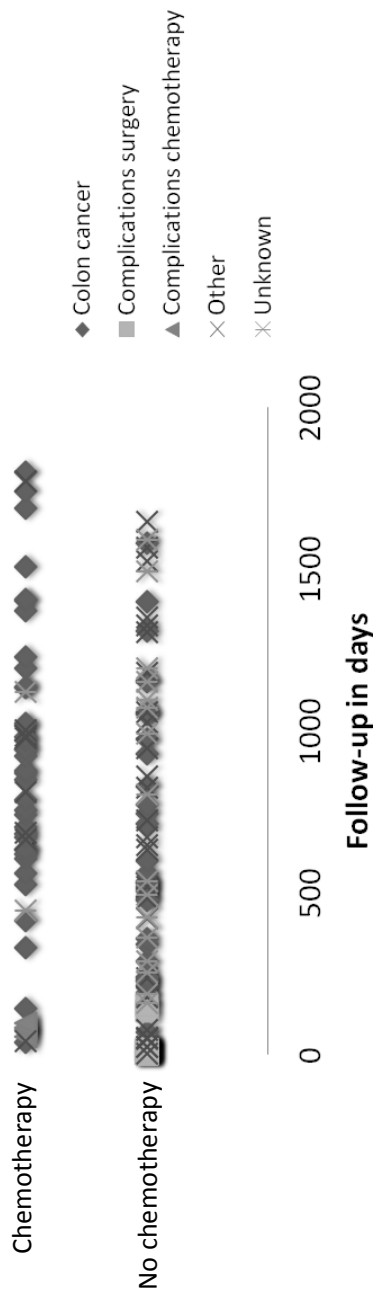


Figure 2: Causes of death over time according to adjuvant chemotherapy

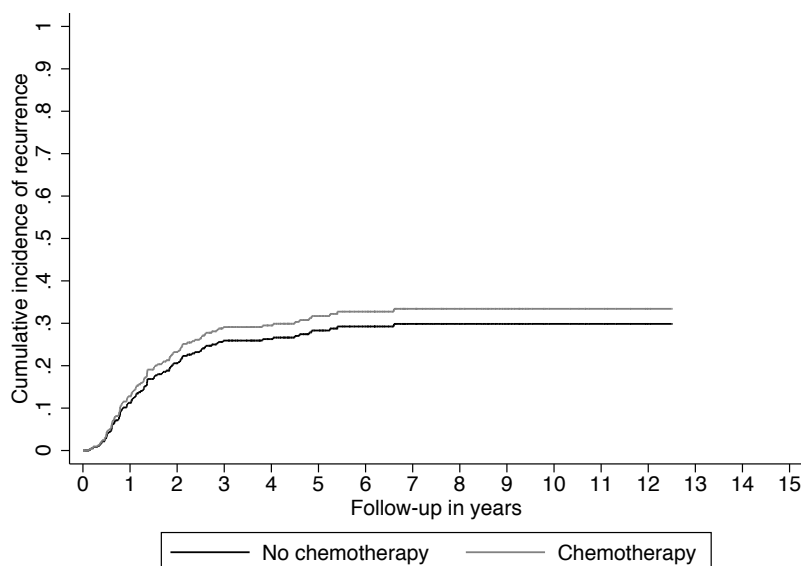


Figure 3: The cumulative incidence of recurrence according to adjuvant chemotherapy

DISCUSSION

In this population-based cohort of stage III colon cancer patients, almost half of the patients received no guideline recommended adjuvant chemotherapy after radical surgery. Main reasons for withholding adjuvant chemotherapy were surgical complications, comorbidities, and high age. Patient who received no adjuvant chemotherapy died more often due to competing causes, such as surgical complications, while patients who received adjuvant chemotherapy died more often due to the primary tumour. The cumulative incidence of recurrence was similar between the treatment groups, when death was taking into account as competing risk. The Dutch guidelines recommend adjuvant chemotherapy for all patients with stage III colon cancer irrespective of age. The finding that only half of these patients received adjuvant chemotherapy in our cohort, is in line with previous studies, although slightly lower than in the national cohort.^{10,14,15} With increasing age and the presence of comorbidities, adjuvant chemotherapy was more frequently omitted, which also has been shown by others.^{14,16-19}

In line with other studies, almost two thirds of the patients had one or more comorbidities at time of the diagnosis (62.4%).^{11,20,21} Furthermore, postoperative complications were associated with withholding adjuvant chemotherapy both in our study and in the literature.^{22,23} Besides age, comorbidities, and surgical complications, our study showed that marital status, and living status affected the initiation of adjuvant chemotherapy. Widowed patients and patients living alone or in a nursing home received less often adjuvant chemotherapy. Only

two studies, by our knowledge, have shown a relationship between marital status and living status and receipt of adjuvant chemotherapy in stage III colon cancer.^{24,25} Widowed patients or patients living alone might refrain from treatment since both doctors and the patients themselves are worried about dependency during chemotherapy. Improving professional support and out of hospital care during treatment might help these patients to benefit from adjuvant treatment, aiming to reduce their recurrence risk.

The decision to start adjuvant chemotherapy should be made jointly by doctors and patients.²⁶ Elderly patients seem to be less willing to accept the side-effects of chemotherapy, resulting in more frequent patient refusal. Patient refusal occurred in 8.2% of patients who received no adjuvant therapy. Refusal was more prevalent at higher age. Besides, clinicians might less often discuss adjuvant chemotherapy with elderly patients.^{16,24,27} However, it has been demonstrated that fit elderly colon cancer patients may benefit equally from adjuvant chemotherapy without increased toxicity.^{3,26}

Most of the patients in the present study received a combination of fluorouracil and leucovorin as adjuvant chemotherapy, as this was the guideline recommended treatment for stage III colon cancer until 2004.⁹ The addition of oxaliplatin was advised since 2004, and therefore, more patients received a combination of fluorouracil, leucovorin, and oxaliplatin by the end of our study. With increasing age, however, patients more often received fluorouracil with leucovorin or capecitabine as monotherapy. Of note, benefits of the addition of oxaliplatin in patients over the age of 70 have recently been disputed.^{8,28}

The goal of adjuvant therapy is to reduce recurrences and improve survival. In our study 29.9% of the patients developed a recurrence, which is similar in other studies.²⁹⁻³¹ For individual patients, doctors must carefully weigh benefits and risks of adjuvant chemotherapy. The potential reduction in recurrence risk must be weighed against potential risk of severe side effects and toxicities. Additionally, they must be aware that competing causes of death obliterate the intended effect of adjuvant chemotherapy. Hence, increasing age and comorbidities are expected to decrease the potential benefit of adjuvant treatment. Even though colon cancer recurrences were more frequent among patients who received adjuvant chemotherapy as compared to those who received no adjuvant chemotherapy, it may be deduced that doctors and patients decide upon adjuvant treatment for those with the largest risk of recurrence. Cumulative incidence of recurrence was equal in those treated with adjuvant chemotherapy and those without, however, from these results, it cannot be determined whether more patients could have profited from adjuvant treatment and survival would have been better with more liberal prescription of adjuvant chemotherapy.

Furthermore, elderly patients are not only interested in their life expectancy, but also in quality of life including independent life expectancy.³² In order to improve care in our aging population, geriatric health problems should be specifically addressed and geriatric medicine should become an integral part of everyday oncology practice. Besides, the goal of future studies on this subject should be to minimize recurrences and to optimize quality of life.

Strengths and limitations

This descriptive, population based study gives a clear insight in the reasons to withhold adjuvant chemotherapy in stage III colon cancer patients and provides insight in the outcome of these patients. However, since this is a retrospective, observational study, this resulted in certain limitations: not all characteristics could be retrieved from medical records, and some variables, such as the reason why patients received no adjuvant chemotherapy, were missing. Therefore, we have described the missing variables, and sensitivity analyses have been performed in order to decide whether the missing values affected the outcome. This study has compared the cumulative incidence of recurrence with death as a competing risk. We are aware that data on colon cancer recurrence might be underestimated with increasing age and increasing number of comorbidities as follow up for recurrences may be better in patients fit enough to undergo future treatments. Therefore, it is to be expected that the number of recurrences might be underestimated in patients who received no adjuvant chemotherapy. This would result in higher cumulative incidence of recurrence in the patient who received no adjuvant chemotherapy.

CONCLUSION

In conclusion, these results highlight that in a population based cohort of patients with stage III colon cancer, patients who received adjuvant chemotherapy differ with respect to age, comorbidities and living status from patients who received no adjuvant chemotherapy. A large part of patients with surgical complications subsequently received no adjuvant chemotherapy. Patient who received no adjuvant chemotherapy had worse survival, but most of these patients died due to competing causes. Interestingly, cumulative incidence of recurrence, with death as competing risk was similar in both treatment groups. In all patients, but especially in those who are old or have comorbidities, benefits and disadvantages of adjuvant chemotherapy must be carefully weighed as the effectiveness of adjuvant therapy depends not only on drug activity, but also on side effects and life expectancy. In our aging society it will become even more important to develop tools to estimate remaining life expectancy in order to facilitate the selection of patients for adjuvant treatments. Risks and benefits of adjuvant treatment in elderly patients should be studied in prospective studies that relate outcome and quality of life to geriatric parameters and comorbidities.

REFERENCE LIST

- 1 The statistics about cancer in the Netherlands registered by the Netherlands Cancer Registry. <http://www.cijfersoverkanker.nl/> (accessed May 24 2013).
- 2 Benson AB, III, Schrag D, Somerfield MR et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; **22**: 3408-19.
- 3 Sargent DJ, Goldberg RM, Jacobson SD et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001; **345**: 1091-7.
- 4 Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**: 352-8.
- 5 O'Connell MJ, Mailliard JA, Kahn MJ et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; **15**: 246-50.
- 6 Taal BG, Van TH, Zoetmulder FA. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *Br J Cancer* 2001; **85**: 1437-43.
- 7 Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**: 2343-51.
- 8 Yothers G, O'Connell MJ, Allegra CJ et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011; **29**: 3768-74.
- 9 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed May 24 2013).
- 10 van den Broek CB, Bastiaannet E, Dekker JW et al. Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients - a large population-based study from 1990 to 2008. *Acta Oncol* 2013; **52**: 941-9.
- 11 van Steenberghe LN, Rutten HJ, Creemers GJ et al. Large age and hospital-dependent variation in administration of adjuvant chemotherapy for stage III colon cancer in southern Netherlands. *Ann Oncol* 2010; **21**: 1273-8.
- 12 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-83.
- 13 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007; **26**: 2389-430.
- 14 van Gils CW, Koopman M, Mol L et al. Adjuvant chemotherapy in stage III colon cancer: guideline implementation, patterns of use and outcomes in daily practice in The Netherlands. *Acta Oncol* 2012; **51**: 57-64.
- 15 van den Broek CB, Dekker JW, Bastiaannet E et al. The survival gap between middle-aged and elderly colon cancer patients. Time trends in treatment and survival. *Eur J Surg Oncol* 2011; **37**: 904-12.
- 16 Droz JP, Aapro M, Balducci L. Overcoming challenges associated with chemotherapy treatment in the senior adult population. *Crit Rev Oncol Hematol* 2008; **68 Suppl 1**: S1-S8.
- 17 Lemmens VE, van Halteren AH, Janssen-Heijnen ML et al. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005; **16**: 767-72.
- 18 Keating NL, Landrum MB, Klabunde CN et al. Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? *J Clin Oncol* 2008; **26**: 2532-7.
- 19 Krzyzanowska MK, Regan MM, Powell M, Earle CC, Weeks JC. Impact of patient age and comorbidity on surgeon versus oncologist preferences for adjuvant chemotherapy for stage III colon cancer. *J Am Coll Surg* 2009; **208**: 202-9.
- 20 van Leersum NJ, Janssen-Heijnen ML, Wouters MW et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. *Int J Cancer* 2013; **132**: 2157-63.
- 21 van Gestel YR, Lemmens VE, de Hingh IH et al. Influence of comorbidity and age on 1-, 2-,

- and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Ann Surg Oncol* 2013; **20**: 371-80.
- 22 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; **356**: 968-74.
 - 23 Elferink MA, van Steenberg LN, Krijnen P et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. *Eur J Cancer* 2010; **46**: 1421-9.
 - 24 Winget M, Hossain S, Yasui Y, Scarfe A. Characteristics of patients with stage III colon adenocarcinoma who fail to receive guideline-recommended treatment. *Cancer* 2010; **116**: 4849-56.
 - 25 Sanoff HK, Carpenter WR, Sturmer T et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012; **30**: 2624-34.
 - 26 Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; **20**: 5-16.
 - 27 Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. *J Natl Cancer Inst* 1994; **86**: 1766-70.
 - 28 Andre T, Boni C, Navarro M et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27**: 3109-16.
 - 29 Hoeben KW, van Steenberg LN, van de Wouw AJ et al. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. *Ann Oncol* 2013; **24**: 974-9.
 - 30 Kobayashi H, Mochizuki H, Sugihara K et al. Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. *Surgery* 2007; **141**: 67-75.
 - 31 O'Connell MJ, Campbell ME, Goldberg RM et al. Survival following recurrence in stage II and III colon cancer: findings from the ACCENT data set. *J Clin Oncol* 2008; **26**: 2336-41.
 - 32 Pasetto LM, Falci C, Compostella A et al. Quality of life in elderly cancer patients. *Eur J Cancer* 2007; **43**: 1508-13.

Chapter 4

The survival gap between middle-aged and elderly colon cancer patients.

Time trends in treatment and survival.

Colette B.M. van den Broek

Jan Willem T. Dekker Esther Bastiaannet

Pieta Krijnen

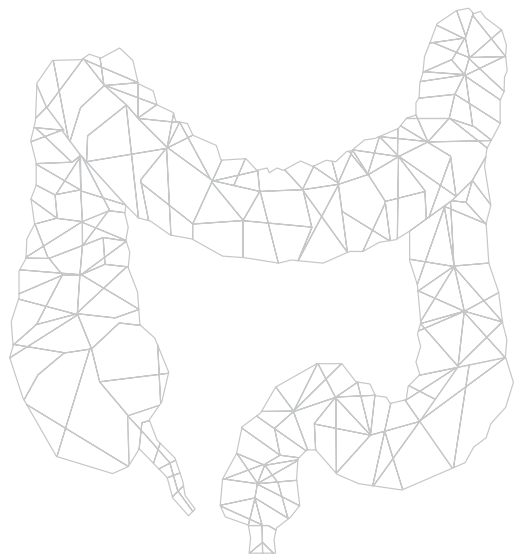
Anton J.M. de Craen

Rob A.E.M. Tollenaar

Cornelis J.H. van de Velde

Gerrit-Jan Liefers ¹ Department of Surgery, Leiden University
Medical Centre, Leiden, the Netherlands.

Eur J Surg Oncol. 2011 Oct;37(10):904-12



ABSTRACT

Background

For several types of cancer, including colon cancer, the survival gap between middle-aged patients and elderly patients widened between 1988 and 1999 in Europe. The aim of our study was to describe treatments and compare survival rates over time (1991-2005) between middle-aged (<65 years), aged (65-74 years) and elderly (≥ 75 years) colon cancer patients in the mid-western part of the Netherlands to assess whether this survival gap further increased.

Methods

All 8926 patients with invasive colon cancer diagnosed between 1991 and 2005 were selected from the Comprehensive Cancer Centre West. Relative survival was calculated. Relative Excess Risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution.

Results

There were no significant changes in the treatment for stage I and II colon. Patients with stage III and IV more often received chemotherapy over time (from 9.6% to 54.3% and from 7.5% to 44.2% for all ages, respectively), while less stage IV patients were operated on (from 73.1% to 55.2%). Relative five year survival increased significantly for middle-aged patients (RER=0.97, 95%CI=0.95-0.98, $p<0.001$), borderline significantly (RER=0.98, 95% CI=0.97-0.99, $p=0.05$) for elderly patients and not significantly for aged patients (RER=0.99, 95%CI=0.97-1.00, $p=0.08$) after adjustment for sex, age, grade, stage, and treatment.

Conclusion

The survival gap earlier found by the EURO CARE is confirmed for the mid-western part of the Netherlands, even after adjustment for age, sex, grade, stage and treatment. However, present study does not show an increase in the survival gap between middle-aged and elderly patients.

INTRODUCTION

Colorectal cancer is the second most commonly diagnosed cancer in the Netherlands.¹ The incidence in the Netherlands is more than 57 per 100 000 persons per year (European Standardized Rate) and increases with age. There is an incidence peak around 74–80 years and approximately half of colorectal patients are over 70 years of age.

The EUROCARE Working Group has compared five-year relative survival between elderly (70–84 years) and middle-aged cancer patients (55–69 years).² They observed a significant survival improvement between 1988 and 1999 for all cancers combined and for almost every cancer site including colon cancer. Survival increased at a slower rate in the elderly. As a result the gap in survival between middle-aged and elderly patients widened. In particular middle-aged women showed more marked improvements than elderly women for colon cancer.² Differences in survival for colon cancer may be explained by variations in tumour factors, patient characteristics and therapy. Elderly patients receive adjuvant chemotherapy less frequently and more often discontinue treatment.³ Moreover, the administration of adjuvant treatment for elderly stage III colon cancer patients is influenced by socioeconomic status, gender, and comorbidity.⁴ Besides, comorbidity also influences surgical eligibility and other treatment options.

In recent years the focus on elderly colon cancer patients has increased. Several studies have concluded that age per se is not a contraindication for more aggressive or adjuvant treatment.⁵ Therefore, the past ten years more elderly patients are considered for extensive therapy in routine clinical practice.⁵ As a consequence an improved outcome for elderly patients might be expected. We hypothesized that the gap in survival between middle-aged and elderly patients as observed in the EUROCARE data between 1988 and 1999 might be decreasing. Hence, the aim of our study was to describe treatments and compare survival rates over time between middle-aged (<65 years), aged (65–74 years) and elderly (≥75 years) colon cancer patients.

PATIENT AND METHODS

Patients and follow-up

Patients were selected from the regional cancer registry of the Comprehensive Cancer Centre West (CCCW) covering the mid-western part of the Netherlands. The nationwide Dutch network and registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collects data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports,

using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centres. Cancer registry data show actual variations in patterns of staging, treatment and survival by age. Therefore, these data offer a scope for improvement of care and for creating guidelines, in addition to randomized clinical trials.⁶

From the regional cancer registry, patients with their first primary invasive colon cancer were selected (International Classification of Diseases for Oncology (ICD-O) code C18.0), diagnosed between 1991 and 2005 ($n = 8926$). CCCW established vital status either directly from the patients' medical record or through linkage of cancer registry data with the municipal population registries which record information on their inhabitants' vital status (last linkage at December 31st 2009). Stage was based on pathological information; clinical information was used if pathology data were missing.

Statistical analyses

Patients were divided into middle-aged (younger than 65 years), aged (65-74 years) and elderly (75 years and older). We chose to divide the patients into those three age groups, so differences between middle-aged and elderly patients would be more pronounced. Differences between age groups were tested with Chi-Square tests. Statistical significance was defined as $p \leq 0.05$. The study period was divided into three five year strata for the analyses of the treatment data; 1991-1995, 1996-2000, and 2001-2005. Treatment was divided into no treatment, surgery only, surgery and chemotherapy, chemotherapy only, and other (radiotherapy, in combination with surgery and/or chemotherapy). Changes over time were assessed for stage at diagnosis and age.

For survival analyses, 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 cancer of interest.⁶ Relative survival was calculated by the Hakulinen method as the ratio of the observed survival among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Patients diagnosed between 1991 and 2004 were selected for five years survival analyses ($n=8197$). Patients diagnosed in 2005 were excluded from survival analyses by year, because five year follow-up was not available. Relative Excess Risks of death (RER) were estimated using a multivariate generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Relative Excess Risks of death over time were calculated according to age and according to year of incidence stratified for age groups, with their 95% confidence interval (95%CI). The RER was adjusted for sex, age, grade, and stage. Models with and without adjustment for treatment are shown to assess the effect of therapy on the RER. Model fit was assessed for each multivariable analysis. Based on the model fit, continuous or categorical data were selected for the analyses.

RESULTS

Patient characteristics

Between 1991 and 2005, 8926 patients with incident primary colon cancer were registered in the database of the Comprehensive Cancer Centre West (CCCW) in the Netherlands. The characteristics of the patients are shown in table 1. The male to female ratio changed over time from 0.8 to 1.0. The age distribution was stable from 1991 to 2005 ($p=0.08$). The distribution between men and women changed with age, with relatively more elderly women diagnosed than men. The median age at diagnosis was 72 years (range 7-101 years) and stable over time. Patients between 65 and 75 years at time of diagnosis were more often diagnosed with grade II, and less often with unknown grade ($p<0.001$). Stage distribution was associated with age, with more elderly patients having an unknown stage of disease. Elderly patients did not have

Table 1: Characteristics of patients diagnosed in the period 1991-2005 according to age.

	Age groups						p-value
	<65 years	%	65-74 years	%	≥75 years	%	
Sex							<0.001
Male	1311	51.0	1328	51.8	1571	41.4	0.08
Female	1259	49.0	1236	48.2	2221	58.6	
Year							
1991-1995	794	30.9	829	32.3	1162	30.6	<0.001
1996-2000	791	30.8	844	32.9	1240	32.7	
2001-2005	985	38.3	891	34.8	1390	36.7	
Grade							
I	151	5.9	158	6.2	219	5.8	<0.001
II	1466	57.0	1610	62.8	2212	58.3	
III	428	16.7	396	15.4	649	17.1	
Unknown	525	20.4	400	15.6	712	18.8	
Stage							
I	320	12.5	386	15.1	480	12.7	<0.001
II	799	31.1	922	36.0	1502	39.6	
III	644	25.1	634	24.7	819	21.6	
IV	619	24.1	488	19.0	590	15.6	
Unknown	188	7.3	134	5.2	401	10.6	
Surgery							
No	271	10.5	242	9.4	630	16.6	<0.001
Yes	2299	89.5	2322	90.6	3162	83.4	
Chemotherapy							
No	1760	68.5	2125	82.9	3661	96.6	<0.001
Yes	810	31.5	439	17.1	131	3.4	
Total	2570	28.8	2564	28.7	3792	42.5	

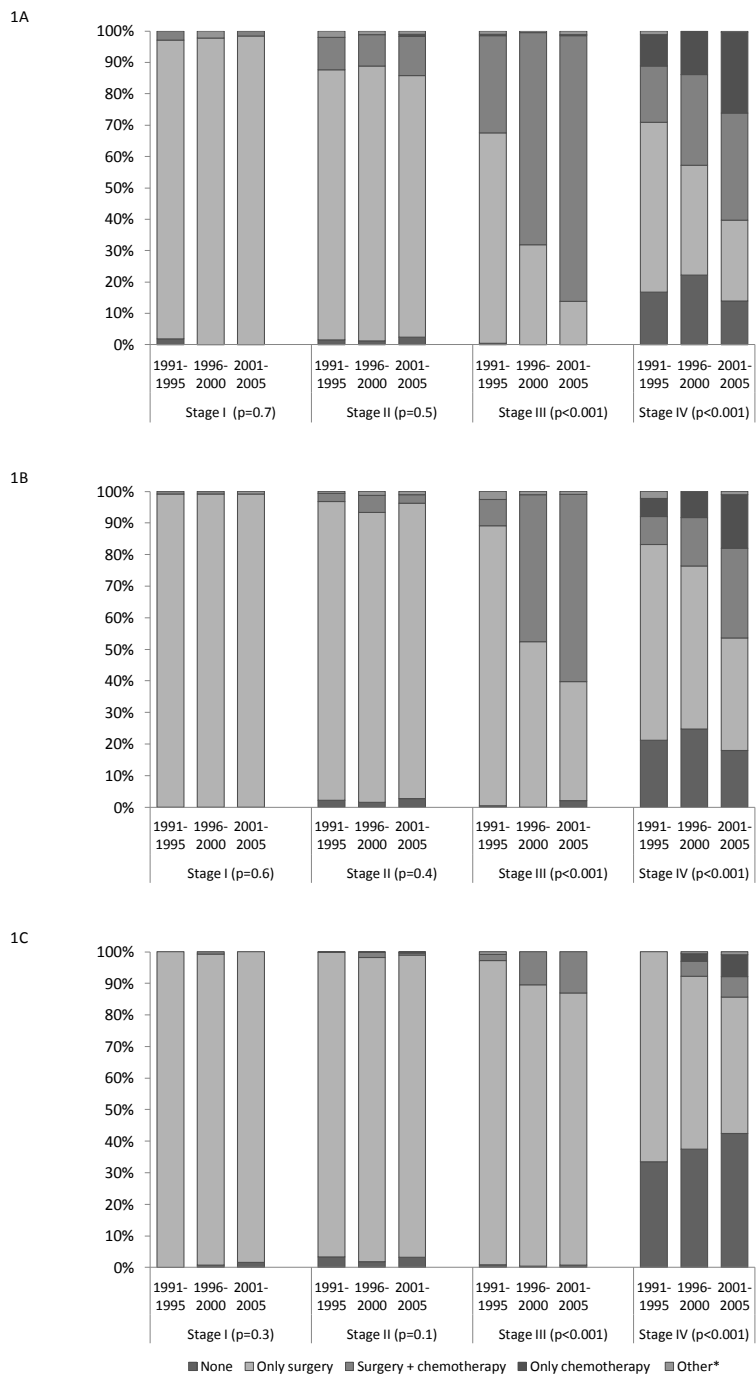


Figure 1: Changes in treatment over the years according to age: (a) Middle-aged patients (<65 years), (b) Aged patients (65-74 years), and (c) Elderly patients (75 years and older)

more advanced disease at time of diagnosis. Elderly patients were less frequently operated on their colon cancer compared with middle-aged and aged patients, while use of chemotherapy gradually declined over the age strata.

Treatment

Changes in treatment over time for the three age groups are shown in figure 1. During the study period, almost all patients with stage I to III colon cancer underwent resection of their primary tumour (98.5%). Over time, there were no significant changes in treatment for stage I and II in all age groups. Patients with stage III colon cancer received significantly more often surgery with adjuvant chemotherapy over time: from 31% to 85% among the middle-aged patients ($p<0.001$), from 8% to 59% among the aged patients ($p<0.001$), and from 2% to 13% for the oldest patients ($p<0.001$). Resection rates of stage IV colon cancer patients (with or without chemotherapy) decreased over time: from 73% to 60% among middle-aged patients ($p=0.02$), from 73% to 64% among aged patients ($p=0.2$), and from 67% to 51% among elderly patients ($p=0.004$). The use of chemotherapy only for stage IV colon cancer increased: from 10% to 26% in the middle-aged patients ($p<0.001$), from 6% to 17% in the aged patients ($p=0.002$), and from 0% to 7% in the elderly patients ($p<0.001$). Elderly patients with stage IV colon cancer received more often no treatment compared to middle-aged patients, 17% in the middle-aged and aged group compared to 38% in the elderly group ($p<0.001$).

Survival

Overall, there was a significant increase in the five year relative survival from 54.9% in 1991-1995, to 56.5% in 1996-2000, and to 57.9% in 2001-2004 ($p=0.03$). The five year relative survival of men increased from 52.5% in 1991-1995 to 58.9% in 2001-2004 ($p=0.02$), the five year relative survival of women remained stable in the same period from 56.7% to 57.0% ($p=0.5$). After adjustment for age (as a continuous variable in the model), grade, and stage, men showed a significant increase in five year relative survival over time with a RER of 0.98 (95%CI=0.97-0.99, $p<0.001$). Women did not show a significant increase in their five year relative survival with a RER of 0.99 (95%CI=0.98-1.00, $p=0.1$). After additional adjustment for treatment, both men and women showed a small, but significant increase in five year relative survival over time with a RER of 0.99 (95%CI=0.97-1.00, $p=0.02$) for men and a RER of 0.99 (95%CI=0.98-1.00, $p=0.03$) for women.

Stratified for stage, relative survival did not increase for stage I colon cancer (figure 2). In stage II colon cancer both aged and elderly showed a significant improvement in their unadjusted relative survival. After adjusting for sex, age, and grade, only aged patients still showed a significant improvement in their relative survival, while after additional adjustment for treatment, both aged and elderly patients showed an improved relative survival. In stage III colon cancer for all age groups unadjusted relative survival increased significantly. After adjustment for sex,

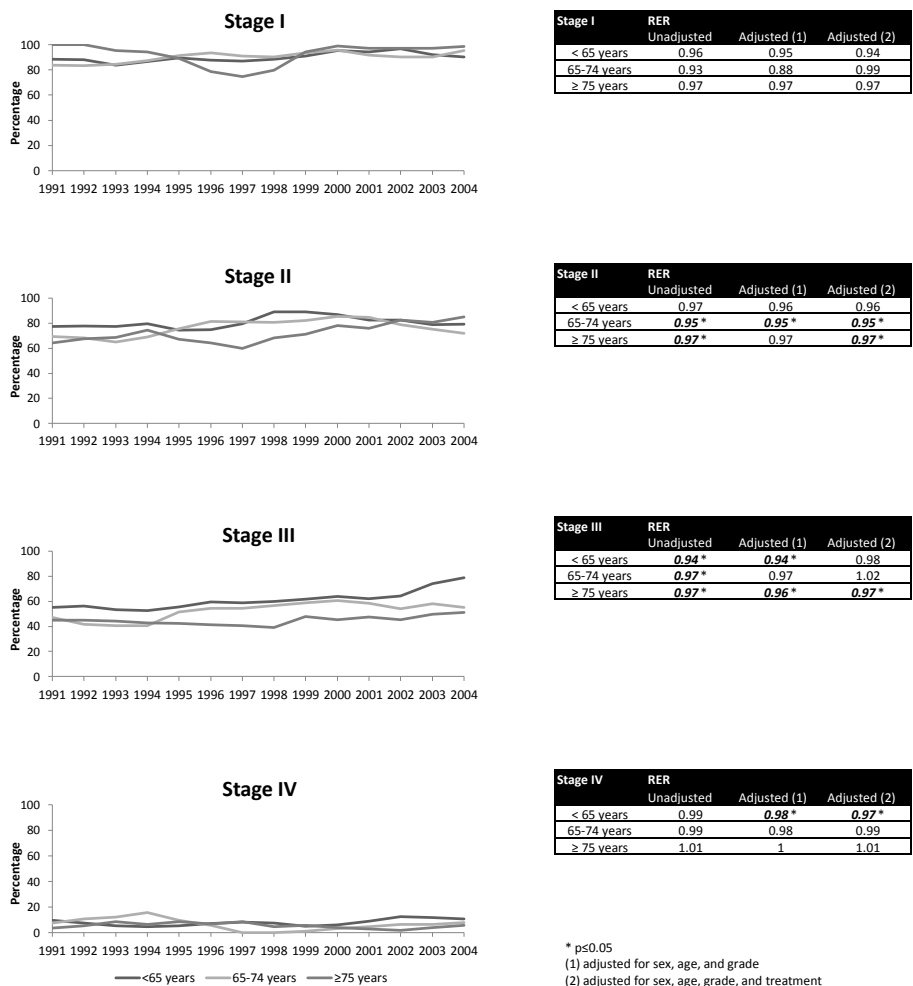


Figure 2: Unadjusted relative 5-year survival per stage and per age group in 3-year moving means, combined with tables with unadjusted and adjusted RER

age, and grade both middle-aged and elderly patients showed an increased relative survival, and after additional adjustment for treatment, only elderly patients showed an increased relative survival. Unadjusted relative survival in stage IV colon cancer did not increase in any of the age groups, after adjustment for sex, age and grade only middle-aged patients had an increased relative survival, which remained after additional adjustment for treatment. For comparison with the EURO CARE study, which showed a widening survival gap between 1988 and 1999, we calculated the adjusted RER over time, with 1991 as reference, stratified by age groups. (figure 3(a)) None of the age groups showed a significant increase in their adjusted relative survival between 1991 and 2004 after adjustment for sex, age, grade, and

3A

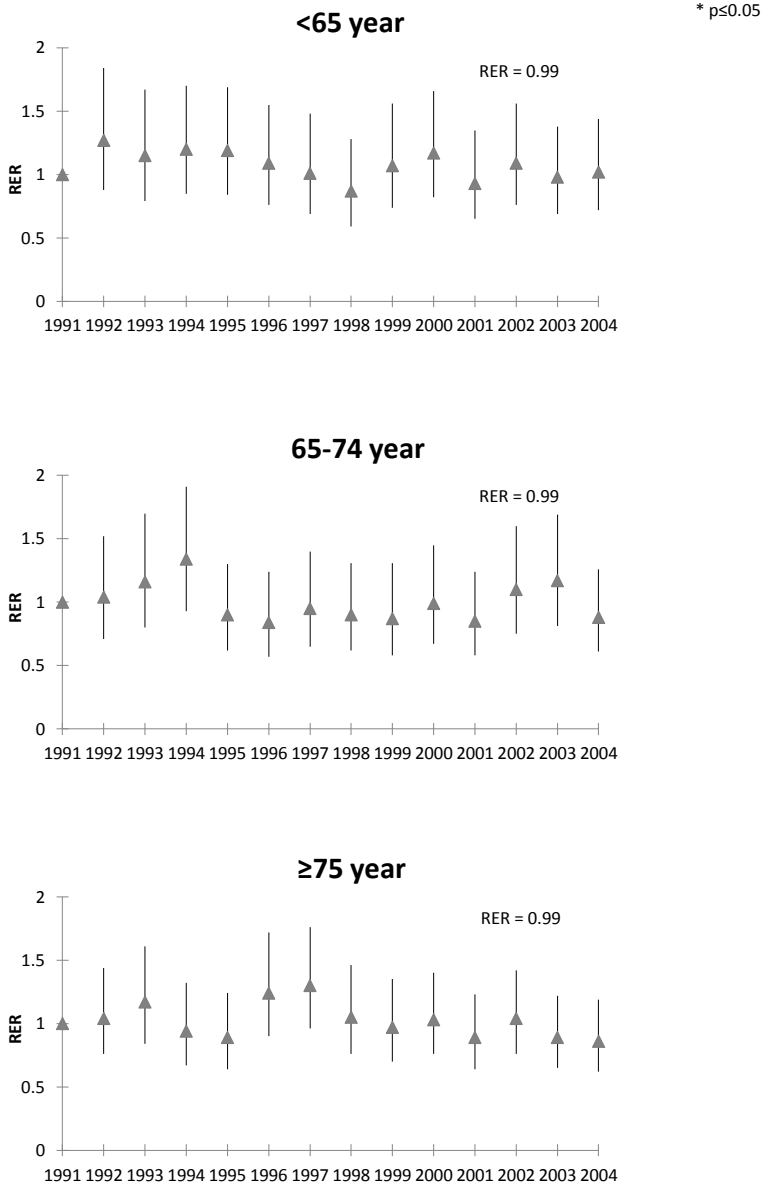


Figure 3a: Adjusted RER and 95% CI per age group over time, with 1991 of each age group as a reference. Adjusted for sex, age, grade, and stage

3B

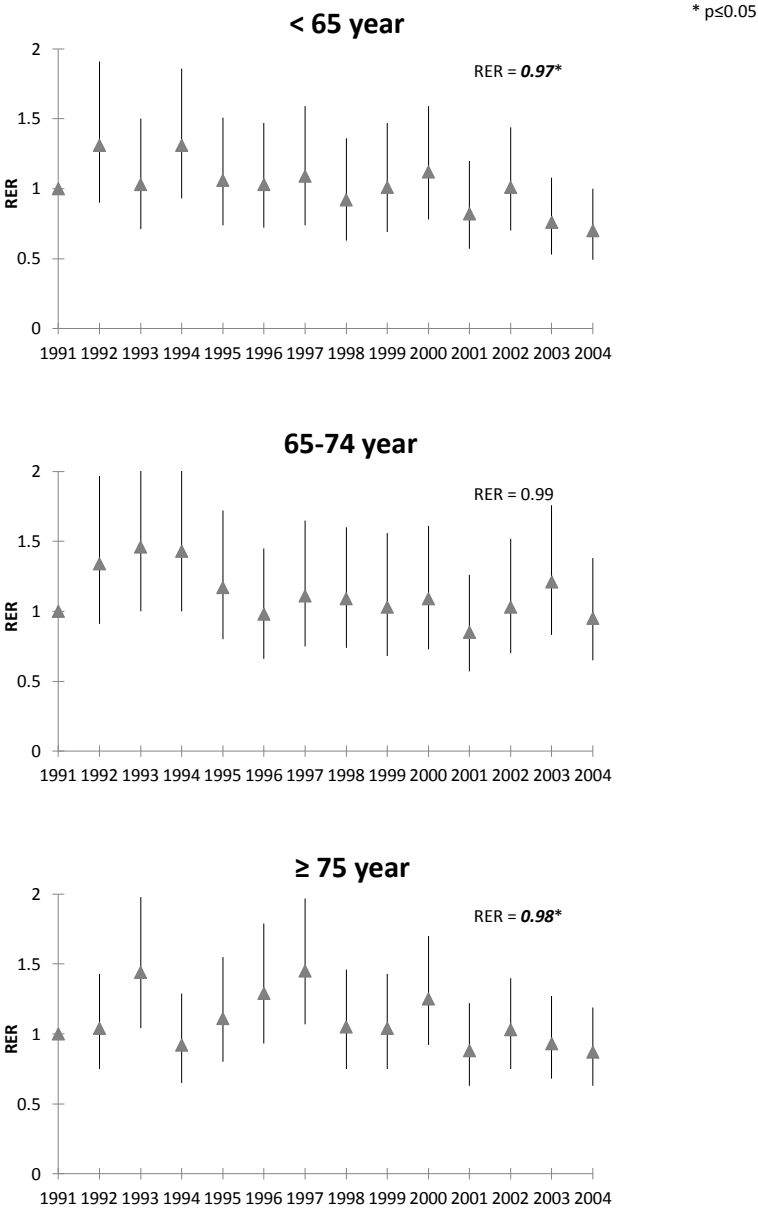


Figure 3b: Adjusted RER and 95% CI per age group over time, with 1991 of each age group as a reference. Adjusted for sex, age, grade, stage, and treatment

stage. After additional adjustment for treatment (figure 3(b)) both middle-aged patients (< 65 years) and elderly patients (≥ 75 years) showed a significant increase in their adjusted relative survival between 1991 and 2004 (RER=0.97, 95%CI=0.95-0.98, $p<0.001$ and RER=0.98, 95%CI=0.97-0.99, $p=0.05$, respectively). There was no significant increase in adjusted relative survival for patients aged between 65 and 75 years (RER=0.99, 95%CI=0.97-1.00, $p=0.08$). We calculated the RERs over time per age group adjusted for sex, grade, and stage without treatment (table 2a) and with treatment (table 2b), with middle-aged patients (<65 years) as reference. Aged and elderly patients always showed a lower survival than middle-aged patients in all years. When there is a significant difference in the RERs, the survival of the aged or elderly patients is significant worse than the survival of the middle-aged patients. The higher the RER is, the larger the difference in survival between age groups. Looking at the study period of the EURO CARE, until 1999, we see a gap between the survival of middle-aged patients and elderly patients, which is the largest in 1997 and 1998. In more recent years, the gap between middle-aged and elderly patients is still present, with 2001 and 2002 comparable with 1997 and 1998, even when adjusted for treatment, but the gap has not further increased.

DISCUSSION

In this population-based study covering the mid-western region of the Netherlands over a period of 15 years, substantial changes in treatment of colon cancer were found. Adjuvant chemotherapy for patients with stage III disease increased over time, resection rates remained stable over time for patients with stage I, II, and III disease in all age groups, while resection rates among metastatic patients decreased, and administration of chemotherapy for stage IV colon cancer patients increased for all age groups. Moreover, survival increased significantly over time for middle-aged and elderly patients after adjusting for age, sex, grade, stage and treatment. The adjusted survival of aged patients did not increase significantly over the years. However, the present study did not show a further increase in the survival gap between middle-aged and elderly patients.

Treatment

During the study period, some major changes in the adjuvant treatment of colon cancer have occurred. After Moertel et al.⁷ published the first clinically important survival benefit of one year adjuvant therapy with fluorouracil and levamisole for patients with stage II and III colon cancer, the United States quickly adopted this as standard therapy for stage III colon cancer patients. However, in the Netherlands adjuvant chemotherapy for stage III colon cancer was incorporated in the guidelines from the mid 1990's and since 2005 the guideline also includes adjuvant chemotherapy for high risk stage II patients.⁸ The changes in the guidelines

Table 2: RER over time per age group, with middle-aged patients (<65 years) as reference.

(a) Adjusted for sex, grade and stage

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
All														
Reference	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
stages														
Adjusted RER	1.4	1.2	1.4	1.6*	1.0	1.2	1.4	1.5*	1.6*	1.2	1.7*	1.4	1.9*	1.4
Adjusted RER	2.7*	1.5*	2.1*	1.5*	1.9*	2.0*	3.0*	2.7*	2.4*	2.0*	3.2*	2.9*	2.0*	2.3*

* p≤0.05

(b) Adjusted for sex, grade, stage and treatment

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
All														
Reference	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
stages														
Adjusted RER	1.4	1.2	1.5	1.3	1.2	1.1	1.1	1.4	1.4	1.0	1.4	1.1	1.5*	1.2
Adjusted RER	2.2*	1.3	1.6*	1.1	1.8*	1.6*	2.1*	2.2*	1.5*	1.2	1.8*	2.0*	1.5*	1.3

* p≤0.05

for treating patients with colon cancer are visible in the data; in the period 1996-2000, for all age groups a large increase in the adjuvant treatment of stage III colon cancer patients was visible (from 31% to 68%, from 8% to 47%, and from 2 to 10% for middle-aged, aged, and elderly patients respectively), although this showed much smaller survival benefit in the cohort than expected. During the study period stage IV colon cancer patients were increasingly treated with chemotherapy and less often with surgery. Over the past three decades, stage IV colon cancer has turned from a lethal, incurable disease, into a potentially curable disease for a selected group of patients.⁹

The surgical technique for colon cancer has not changed in the Netherlands during the study period. However, in 2009 Hohenberger et al. presented their promising results about the complete mesocolic excision for patients with colon cancer.¹⁰ Possibly with use of this technique local recurrence rates might decrease and five year survival rates might increase further in the future. Also centralisation and auditing are relatively new for colon cancer in the Netherlands which might improve survival in the future.¹¹

Survival

Overall we found a small increase in relative survival for colon cancer patients over the years. However, stage migration could have influenced this study. More advanced diagnostic tools have been used in the recent years,^{12,13} possibly leading to detecting a more advanced stage of disease. Furthermore, a more extensive search for affected lymph nodes could have had a similar effect. The harvesting of more lymph nodes could also have contributed directly to an improved survival.^{14,15} Another factor that might have influenced the survival results, is the improvement of perioperative care.¹⁶ With the hypothesis that survival would not increase over time when adjusted for sex, age, grade, stage, and treatment, the data in this paper show that there are residual influences related to outcome. Even after adjusting for sex, age, grade, stage, and treatment, a significant improvement was found in relative survival of elderly patients with stage III and of middle-aged patients with stage IV colon cancer.

Changes in treatment and improvements in survival of colon cancer in the mid-western region of the Netherlands found in this study, are in line with the results of a previous study covering national data.¹⁷ Notable is that the improvement in survival and the increase in use of adjuvant treatment are more visible in middle-aged patients than in aged and elderly patients. One of the main problems found in the treatment of elderly patients is that current guidelines are based on randomized controlled trials, in which elderly patients or patients with severe comorbidity are underrepresented or excluded. The improvement in survival of middle-aged colon cancer patients over time has mostly been due to a decrease in operative mortality and an increase in the resection rate, possibly coupled with a more aggressive approach to the treatment of local and distant recurrences.¹⁸⁻²¹ Elderly patients on the other hand usually present with more advanced stage and tend to undergo more emergency surgery. Although, in the present study we could not confirm the higher stage at diagnosis, but more elderly

patients were registered with an unknown stage of disease which could include undiagnosed stage III and IV. Elderly patients are also less likely to receive adjuvant treatment and receive “suboptimal” management.²²⁻²⁷ Adjuvant chemotherapy has shown to be an effective treatment for elderly patients with stage III colon cancer, but the benefit is lower with older age.^{18,28,29} However, elderly patients do not necessarily experience greater chemotherapy-related toxicity.^{19,29}

Gap in survival between younger and elderly

EUROCARE recently reported that for colon cancer, as well as other cancer types, the survival gap between elderly (70-84 years) and middle-aged (55-69 years) patients was widening in the period between 1988 and 1999.² Due to the information available in the EUROCARE study, adjusting for several factors, like stage, was not possible. In the present study we were able to adjust for sex, age, grade, stage, and treatment. Besides, we were able to analyse more recent data. Patients were divided into three age groups instead of two; this would make the difference between middle-aged and elderly patients more visible. We found a significant difference in survival between patients middle-aged and elderly patients over all the years, even after adjusting for sex, age, grade, stage, and treatment. The largest difference in survival was between 1997 and 1998 and between 2001 and 2002. Besides the gap between 1997 and 1998, which is similar to the gap shown by the EUROCARE, we also show a more recent survival gap in 2001 and 2002, which is similar in size to the gap in 1997 and 1998. However, the survival differences between middle-aged and elderly patients are not consistent over time. The survival gap is mainly caused by an increase in survival of middle-aged patients and a stable survival of elderly patient. In the present study, this gap did not widen any further, but is stabilising. Hopefully in the future aged and elderly patients will also benefit of the increased survival, possibly due to improved treatment.

Stage distribution differs between several countries in Europe.¹³ As tumour stage is one of the most important prognostic factors in most cancer types, survival rates for several countries are difficult to compare. A new initiative is needed and founded in EURECCA, which aims to collect prospective information about colorectal cancer patients in several countries in Europe.³⁰

CONCLUSION

In the mid-western region of the Netherlands no changes in treatment have occurred for stage I and II colon cancer during the study period. Patients with stage III and IV were treated with significantly more adjuvant chemotherapy over time, although less prominent for elderly patients, while the resection rate of patients with stage IV decreased for all age groups. The survival gap earlier found by the EUROCARE is confirmed for the mid-western part of the Netherlands, even after adjusting for several confounders. However, the present study did not

show a further increase in the survival gap between middle-aged and elderly patients. The near future will have to show if a more extensive and hopefully better tailored treatment can help elderly to close this gap.

ACKNOWLEDGEMENTS

The authors would like to thank Eelco Collette and the GeriOnNe foundation.

This work was carried out with support of ECCO, ESSO and the Bontius Foundation.

REFERENCE LIST

- 1 The statistics about cancer in the Netherlands registred by the Netherlands Cancer Registry. <http://www.cijfersoverkanker.nl/> (accessed August 5 2010).
- 2 Quaglia A, Tavilla A, Shack L et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. *Eur J Cancer* 2009; 45: 1006-16.
- 3 Muss HB, Biganzoli L, Sargent DJ, Aapro M. Adjuvant therapy in the elderly: making the right decision. *J Clin Oncol* 2007; 25: 1870-5.
- 4 Lemmens VE, van Halteren AH, Janssen-Heijnen ML et al. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005; 16: 767-72.
- 5 Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; 20: 5-16.
- 6 Louwman WJ, Vulto JC, Verhoeven RH et al. Clinical epidemiology of breast cancer in the elderly. *Eur J Cancer* 2007; 43: 2242-52.
- 7 Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; 322: 352-8.
- 8 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed August 5 2010).
- 9 Mahmoud N, Bullard DK. Metastasectomy for stage IV colorectal cancer. *Dis Colon Rectum* 2010; 53: 1080-92.
- 10 Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. *Colorectal Dis* 2009; 11: 354-64.
- 11 van Gijn W, Gooiker GA, Wouters MW et al. Volume and outcome in colorectal cancer surgery. *Eur J Surg Oncol* 2010; 36 Suppl 1: S55-S63.
- 12 Ciccolallo L, Capocaccia R, Coleman MP et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut* 2005; 54: 268-73.
- 13 Gatta G, Capocaccia R, Sant M et al. Understanding variations in survival for colorectal cancer in Europe: a EURO CARE high resolution study. *Gut* 2000; 47: 533-8.
- 14 Derwinger K, Carlsson G, Gustavsson B. Stage migration in colorectal cancer related to improved lymph node assessment. *Eur J Surg Oncol* 2007; 33: 849-53.
- 15 Namm J, Ng M, Roy-Chowdhury S et al. Quantitating the impact of stage migration on staging accuracy in colorectal cancer. *J Am Coll Surg* 2008; 207: 882-7.
- 16 King PM, Blazeby JM, Ewings P et al. The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. *Colorectal Dis* 2006; 8: 506-13.
- 17 van Steenbergen LN, Elferink MA, Krijnen P et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol* 2010.
- 18 Bouvier AM, Launoy G, Lepage C, Faivre J. Trends in the management and survival of digestive tract cancers among patients aged over 80 years. *Aliment Pharmacol Ther* 2005; 22: 233-41.
- 19 Guyot F, Faivre J, Manfredi S et al. Time trends in the treatment and survival of recurrences from colorectal cancer. *Ann Oncol* 2005; 16: 756-61.
- 20 Mitry E, Bouvier AM, Esteve J, Faivre J. Benefit of operative mortality reduction on colorectal cancer survival. *Br J Surg* 2002; 89: 1557-62.
- 21 Mitry E, Bouvier AM, Esteve J, Faivre J. Improvement in colorectal cancer survival: a population-based study. *Eur J Cancer* 2005; 41: 2297-303.
- 22 Survival of Cancer Patients in Europe: The EURO CARE-2 study. *IARC Sci Publ* 1999; 1-572.
- 23 Anderson JH, Hole D, McArdle CS. Elective versus emergency surgery for patients with colorectal cancer. *Br J Surg* 1992; 79: 706-9.
- 24 Biganzoli L, Aapro M. Adjuvant chemotherapy in the elderly. *Ann Oncol* 2003; 14 Suppl 3: iii1-iii3.

- 25 Hessman O, Bergkvist L, Strom S. Colorectal cancer in patients over 75 years of age--determinants of outcome. *Eur J Surg Oncol* 1997; 23: 13-9.
- 26 Mulcahy HE, Patchett SE, Daly L, O'Donoghue DP. Prognosis of elderly patients with large bowel cancer. *Br J Surg* 1994; 81: 736-8.
- 27 Ozoux JP, de CL, Perrier M et al. Surgery for carcinoma of the colon in people aged 75 years and older. *Int J Colorectal Dis* 1990; 5: 25-30.
- 28 Karim-Kos HE, de VE, Soerjomataram I et al. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008; 44: 1345-89.
- 29 van Steenbergen LN, Lemmens VE, Louwman MJ, Straathof JW, Coebergh JW. Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands. *Eur J Cancer Prev* 2009; 18: 145-52.
- 30 van Gijn W, van de Velde CJ. Improving quality of cancer care through surgical audit. *Eur J Surg Oncol* 2010; 36 Suppl 1: S23-S26.

Chapter 5

Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients

Jan Willem T. Dekker

Colette B.M. van den Broek

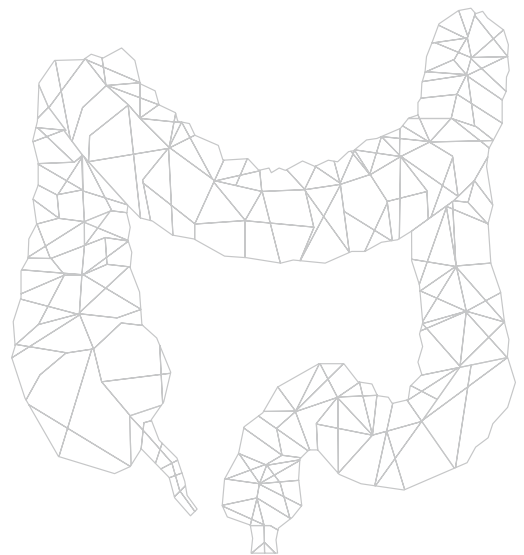
Esther Bastiaannet

Lydia G.M. van de Geest

Rob A.E.M. Tollenaar

Gerrit-Jan Liefers

Ann Surg Oncol. 2011 Jun;18(6):1533-9



ABSTRACT

Background

Elderly colorectal cancer patients have worse prognosis than younger patients. Age-related survival differences may be cancer or treatment related, but also due to death from other causes. This study aims to compare population-based survival data for young (<65 years), aged (65–74 years), and elderly (≥75 years) colorectal cancer patients.

Methods

All patients operated for stage I–III colorectal cancer between 1991 and 2005 in the western region of the Netherlands were included. Crude survival, relative survival, and conditional relative survival curves, under the condition of surviving one year, were made for colon and rectal cancer patients separately. Furthermore, 30-day, 1 year, and 1 year excess mortality data were compared.

Results

A total of 9,397 stage I–III colorectal cancer patients were included in this study. Crude survival curves showed clear survival differences between the age groups. These age-related differences were less prominent in relative survival and disappeared in conditional relative survival (CRS). Only in stage III disease did elderly patients have worse CRS than young patients. Furthermore, significant age-related differences in 30-day and 1 year excess mortality were found. Thirty-day mortality vastly underestimated one year mortality for all age groups.

Conclusion

Elderly colorectal cancer patients who survive the first year have the same cancer-related survival as younger patients. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Treatment of elderly colorectal cancer patients should focus on perioperative care and the first postoperative year.

INTRODUCTION

The number of elderly people in the population and the incidence of colorectal cancer are increasing. Therefore, it is to be expected that the number of elderly colorectal cancer patients will further increase. Various population-based studies show that survival of elderly colorectal cancer patients is worse compared with younger patients. Differences in survival by age group in colorectal cancer may be explained by variations in tumour factors, patient characteristics, and therapy. Elderly colorectal cancer patients tend to have more advanced disease stage.¹ Besides, they have more comorbidity and are treated less aggressively than their younger counterparts.² Comorbidity influences surgical eligibility and other treatment options.³ Furthermore, it represents a greater risk of non-cancer-related mortality. Elderly patients less frequently receive adjuvant chemotherapy and more often discontinue treatment before completion.⁴

Notwithstanding all these differences, several studies found similar disease-specific survival for elderly and young colorectal cancer patients.⁵⁻⁷ This would indicate that the excess mortality in elderly colorectal cancer patients is due to competing causes of death. To gain better insight into survival differences between age groups, the present study aims to compare population-based survival data of colorectal cancer patients for different age groups. It considers not only overall and relative survival but also conditional relative survival under the condition of surviving one year. Furthermore, this study focuses on age-related differences in 30-day and one year mortality.

PATIENTS AND METHODS

Patient and follow-up

Patients were selected from the regional cancer registry of the Comprehensive Cancer Centre West (CCCW) covering the western part of the Netherlands. The nationwide Dutch Network and Registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. Cancer registry data show actual variations in patterns of staging, treatment, and survival by age and therefore offer scope for improvement of care and for creating guidelines, in addition to randomized clinical trials.⁸

From the regional cancer registry, patients diagnosed between 1991 and 2005 with their first, primary, stage I, II or III colon or rectal cancer who were surgically treated were selected. Vital

status was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries which record information on their inhabitants' vital status. Stage was based on pathological information; clinical information was used if pathology data were missing.

Statistical analyses

Patients were divided into younger than 65 years, 65–74 years, and 75 years and older. Differences between characteristics were tested with chi-squared tests. Overall survival was calculated with death due to any cause as event. Relative survival is the preferred way to describe the prognosis of elderly cancer patients, as it takes into account the risk of dying from causes other than the disease of interest.⁸ Relative survival was calculated by the Hakulinen method as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, sex, and year) general population. National life tables were used to estimate expected survival. Conditional relative survival was calculated for patients who survived the first year. Relative excess risks of death (RER) were estimated using a multivariate generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Finally, 30-day and one year overall mortality were calculated as well as the one year excess mortality as (observed – expected deaths)/(number of patients).

RESULTS

From 1 January 1991 through 31 December 2005 in the CCCW region 9,611 stage I–III colorectal cancer patients were diagnosed and 9,397 (97.8%) were operated, being 6,405 patients with colon cancer and 2,992 with rectal cancer. These patients had median age of 72 years (range 7–100 years) for colon cancer and 69 years (range 18–98 years) for rectal cancer patients. Patient characteristics according to age group for colon and rectum separately are shown in table 1. The percentage of female patients was significantly higher in the oldest age groups, especially for colon cancer patients. The number of treated colon cancer patients increased over the years. Tumour grade was evenly divided for rectal cancer but not for colon cancer patients, with more grade III in the elderly. In this cohort, younger patients had higher tumour stage than the elderly, although the percentage of patients with unknown stage of disease was higher in the elderly (data not shown). Use of adjuvant chemotherapy decreased with advancing age groups. Radiotherapy for rectal cancer patients was comparable for the young and aged groups and was lower in the elderly group.

Figure 1 shows survival curves for overall survival (a), relative survival (b), and conditional relative survival (c) for colon and rectal cancer patients in the different age groups. Differences in survival between age groups for colorectal cancer patients disappeared when a correction

Table 1: Characteristics colon and rectal cancer patients whom received surgery diagnosed in the period 1991-2005 according to age

	Colon cancer				Rectal cancer				p-value	p-value
	<65.0 years Number	%	65-75 years Number	%	≥75 years Number	%	<65.0 years Number	%		
Sex										
Male	889	51.1	964	50.3	1123	40.8	603	57.6	513	57.5
Female	851	48.9	952	49.7	1626	59.2	444	42.4	379	42.5
Year										
1991-1995	539	31.0	624	32.6	831	30.2	307	29.3	295	33.1
1996-2000	531	30.5	642	33.5	930	33.8	326	31.1	281	31.5
2001-2005	670	38.5	650	33.9	988	36.0	414	39.6	316	35.4
Grade										
Grade I	123	7.1	129	6.7	184	6.7	62	5.9	44	4.9
Grade II	1150	66.1	1326	69.2	1808	65.8	720	68.8	652	73.1
Grade III	284	16.3	276	14.4	505	18.3	169	16.1	122	13.7
Unknown	183	10.5	185	9.7	252	9.2	96	9.2	74	8.3
Stage										
Stage I	317	18.2	386	20.1	476	17.3	310	29.6	333	37.3
Stage II	782	44.9	902	47.1	1459	53.1	318	30.4	285	32.0
Stage III	641	36.9	628	32.8	814	29.6	419	40.0	274	30.7
Treatment										
Only surgery	1219	70.1	1610	84.0	2661	96.8	447	42.7	471	52.8
Surgery + RT	12	0.7	18	0.9	4	0.2	449	42.9	370	41.5
Surgery + CT	504	28.9	287	15.0	84	3.0	68	6.5	34	3.8
Surgery + CT + RT	5	0.3	1	0.1	0	0.0	83	7.9	17	1.9
Overall	1740	27.2	1916	29.9	2749	42.9	1047	35.0	892	29.8
										35.2

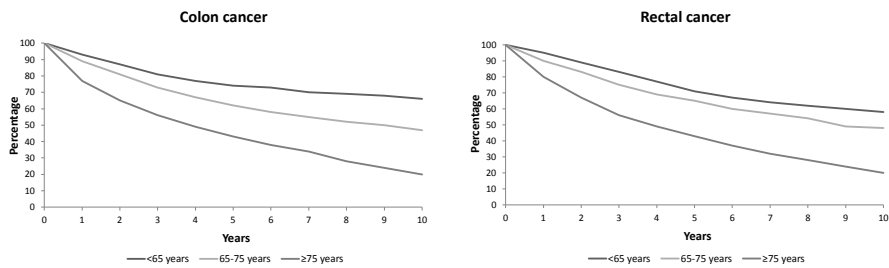


Figure 1a: Overall survival according to age for stage I - III patients operated for colon and rectal cancer

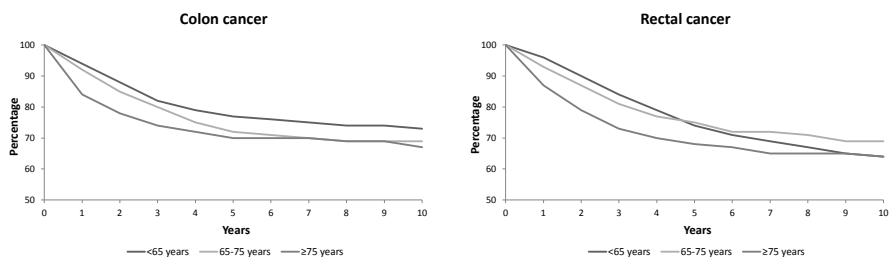


Figure 1b: Relative survival according to age for stage I -III patients operated for colon and rectal cancer

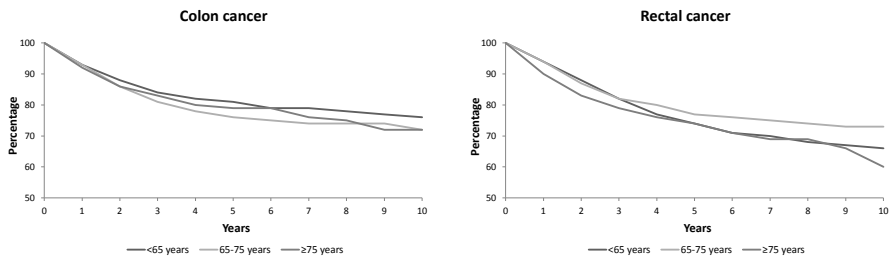


Figure 1c: Conditional relative survival (conditioning on patients who survived 1 year) according to age for stage I -III patients operated for colon and rectal cancer

was made for death from other causes under the condition of surviving one year. As shown in table 2, the elderly patients had a RER of 1.6 (95% confidence interval (CI) 1.4–1.9; $p < 0.001$) as compared with the young patients for colon cancer and 1.4 (95% CI 1.2–1.7; $p < 0.001$) for rectal cancer. When relative survival was calculated for patients who survived the first year, relative excess risks were around 1.0 (RER 1.1, $p = 0.2$ for colon; RER 1.1, $p = 0.3$ for rectal cancer).

Table 2: Patients stage I-III who received surgery

Colon cancer	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
65-74	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (0.6-2.4)	1.2 (0.6-2.5)	1.2 (0.9-1.5)	1.3 (1.0-1.8)	1.4 (1.2-1.7)	1.3 (1.0-1.6)
p-value	0.01	0.03	0.7	0.5	0.2	0.04	<0.001	0.02
75+	1.6 (1.4-1.9)	1.1 (0.9-1.4)	1.2 (0.5-2.8)	N.A.	1.8 (1.4-2.2)	1.3 (0.9-1.8)	2.0 (1.6-2.3)	1.4 (1.1-1.8)
p-value	<0.001	0.2	0.7	0.99	<0.001	0.1	<0.001	0.003
Rectal cancer	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
65-74	1.0 (0.8-1.2)	0.9 (0.7-1.1)	0.8 (0.4-1.8)	0.6 (0.3-1.5)	1.2 (0.8-1.6)	1.1 (0.8-1.7)	1.2 (0.9-1.5)	1.1 (0.8-1.4)
p-value	0.8	0.2	0.6	0.3	0.4	0.6	0.1	0.6
75+	1.4 (1.2-1.7)	1.1 (0.9-1.4)	1.7 (0.8-3.6)	0.3 (0.1-7.0)	1.6 (1.1-2.2)	1.4 (0.9-2.2)	1.8 (1.4-2.3)	1.5 (1.2-2.0)
p-value	<0.001	0.3	0.2	0.5	0.009	0.1	<0.001	0.002

RS=relative survival, CS=conditional survival, N.A.=not addressed due to small numbers

Going into more detail by considering different stages, a significant difference in conditional relative survival remained for stage III patients for both colon and rectal cancer.

Table 3 shows overall 30-day, 1 year, and 1 year excess mortality according to type of tumour in reference to baseline factors. Gender was a significant factor for first-year mortality in rectal cancer, with more male patients dying. Age was the most significant factor for all three mortality endpoints for both colon and rectal cancer patients. Tumour grade did not influence 30-day mortality but was a significant factor for one year mortality for both colon and rectal cancer patients. Tumour stage also influenced 30-day mortality for colon cancer patients, but not for rectal cancer patients. Thirty-day and one year mortality rates decreased over the years (data not shown). For colon cancer patients this was only significant ($p<0.05$) for one year mortality rates for all age groups (lowest RER 0.94). For rectal cancer patients, 30-day mortality was significantly reduced ($p<0.01$) for the elderly (RER 0.89). One year mortality for the young and aged patients (lowest RER 0.93) was significantly improved ($p=0.03$), however not for the elderly patients ($p=0.3$; RER 0.98).

Table 3: Overall 30-day and 1-year mortality and relative 1-year mortality according to type of tumour

	Colon cancer				Rectal cancer			
	Overall mortality		Excess mortality		Overall mortality		Excess mortality	
	N	† ≤30 d	† 1 st year	† 1 st year	N	† ≤30 d	† 1 st year	† 1 st year
Sex								
Male	2976	4.6	15.7	11.3	1639	2.1	13.2	9.4
Female	3429	4.1	14.5	10.9	1353	1.3	9.9	6.9
Age								
<65 years	1740	1.4	6.8	6.1	1047	0.2	5.1	4.4
65-75 years	1916	2.4	10.8	8.5	892	1.4	9.5	7.2
≥75 years	2749	7.5	23.2	16.0	1053	3.7	20.1	13.1
Grade								
I	436	2.1	9.9	6.0	162	3.1	8.0	4.9
II	4284	4.4	12.6	8.5	2140	1.8	10.2	6.6
III	1065	4.7	25.2	21.3	440	1.6	22.3	19.5
Unknown	620	4.8	18.2	14.8	250	1.2	8.4	5.2
Stage								
I	1179	1.7	8.0	4.0	1023	1.5	7.6	3.8
II	3143	5.0	13.5	9.2	966	2.4	12.7	9.1
III	2083	4.8	21.4	18.0	1003	1.5	14.9	12.1

DISCUSSION

Crude survival is a solid outcome measure that shows evident age-related differences. However, crude survival will overestimate the impact of cancer on survival, because it also includes mortality due to other causes. To adjust for this, relative survival is used, defined as the ratio of observed to expected survival. This reduces age-related differences in colorectal cancer survival. However, the results of age-related relative survival are still largely influenced by early mortality (defined as mortality in the first postoperative year). Postoperative complications are a more probable cause for early mortality than the colorectal cancer itself in stage I–III patients (who, in general, had curative surgery). Therefore, to get a clear image of the impact of colorectal cancer on survival for different age groups, we used conditional relative survival under the condition of surviving one year. As a result, age-related differences in survival disappeared, indicating that probably colorectal cancer itself is not the main cause of age-related differences in survival. This is in line with earlier studies that found no age-related differences in cancer-specific survival.⁵⁻⁷ However, this remains intriguing, since many papers indicate that differences in survival between the young and the elderly can be attributed to undertreatment in the elderly.^{1,9} Our study confirms these variations in treatment and that conditional survival in stage III patients is indeed significantly worse in the elderly.

Nonetheless, the excess mortality in the first postoperative year was the main determining factor for age-related survival differences.

Postoperative Mortality

The 30-day mortality rates for the different age groups in the present study are in accordance with earlier findings by other studies.^{10,11} However, the most striking finding of this analysis is the fact that 30-day mortality vastly underestimates one year mortality for all age groups. Apparently, the impact and consequences of treatment have a prolonged effect on mortality. This effect is very strong even for patients in the youngest group. With increasing age, also the excess mortality increases. It has been shown earlier that, with increasing age, not only mortality but also postoperative morbidity increases.¹²⁻¹⁴ Furthermore, Manku et al. showed that in-hospital complications had prognostic significance.¹⁵ In 517 patients who underwent noncardiac surgery, they found that postoperative complications caused mortality up to 3 months after surgery, with a sustaining effect on survival. Greenblatt et al. studied stage I–III colon cancer patients from the Surveillance, Epidemiology, and End Results–Medicare database and found that readmission was strongly associated with one year mortality.¹⁶ The same variables that predicted readmission in this study also predicted one year mortality (male gender, comorbidity, emergent admission, prolonged hospital stay, blood transfusion, ostomy, and discharge to a nursing home). Kunitake et al. showed that patients older than 80 years were readmitted almost twice as much as patients younger than 65 years.¹⁷ Furthermore, in their study, 75% of readmissions were not related to the surgery itself. With the present study, all these studies seem to imply that, for a significant number of patients, the assault of surgery has delayed effects that can cause mortality beyond the scope of the surgery.

Stage III Patients

Only in stage III patients were age-related differences found in conditional relative survival. Here, differences in (neo)adjuvant therapy between the age groups were most apparent. This is in line with earlier studies that show that elderly patients are undertreated.⁴ This undertreatment of elderly patients could explain the age-related differences in conditional relative survival for stage III patients. However, also in stage III patients, first-year mortality remains a crucial factor for survival. The difference in conditional relative survival between young and elderly stage III patients was 10.4% for colon and 5.6% for rectal cancer, while the differences in one year excess mortality rates were 17.2% and 12.0%, respectively.

Limitations

An obvious limitation of this study is the lack of information on emergency surgery and comorbidity. Both are associated with increased postoperative complications and mortality. They will not only have had a prominent influence on early mortality for all age groups, but they probably account for the differences between the age groups as well. Elderly patients are

more likely to undergo emergency surgery, and also the incidence of comorbidity increases with age.¹⁰ Nevertheless, the strength of this study is that it shows the essence of age-related survival and early mortality differences in a large population-based cohort.

Clinical Implications

The results of this study could provide a focus for future studies and have implications for the clinical setting. As age-related differences in mortality are most apparent for the first postoperative year, this is where the focus must be in treating elderly colorectal cancer patients. Although some risk factors may not be modifiable, others relate to care processes. More attention should be given to patient selection and careful preoperative evaluation, followed by medical optimization, proper timing of surgery, and planning of perioperative care. Furthermore, appropriate referral to high-volume or dedicated centers should be considered if it is anticipated that patients will require a higher level of resources and care following surgery. Quality enhancement programs could focus on particular complications. These should not only try to prevent the occurrence of perioperative complications but also focus on early identification and adequate treatment of complications to avoid related mortality.¹⁸

The excess mortality of the first postoperative year forms a clear indication of the prolonged impact of the perioperative period, especially when complications occur. Therefore, we should anticipate preoperatively the level of functioning after discharge.¹³ The targets of treatment for elderly patients should extend beyond the in-hospital period, and continued attention should be given to comorbidity and complications in the post-hospital period.

The prolonged impact of the perioperative period could also have a profound effect on functional status and quality of life. For elderly patients these issues should be evaluated with care, especially when they have limited life expectancies. However, for the majority of patients, age per se is not a contraindication for surgery, not least because surgery for colorectal cancer is often the best way to ensure palliation.

CONCLUSION

This study can help to comprehend the challenge of treating elderly colorectal cancer patients. When survival data for colorectal cancer are corrected for expected death from other causes and first-year mortality, age differences disappear. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Only for stage III disease did elderly patients fare worse, probably as a result of less extensive adjuvant treatment. The overall difference between the younger and elderly age groups is that, within the elderly group, there is an excess mortality of about 10% the first year. Further studies are necessary to elucidate the aetiology of these differences and whether they may be modifiable. This study implies that, in

treating elderly stage I–III colorectal cancer patients, the focus should be on the perioperative process and the first postoperative year.

REFERENCE LIST

- 1 Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; 20: 5-16.
- 2 Lemmens VE, Janssen-Heijnen ML, Houterman S et al. Which comorbid conditions predict complications after surgery for colorectal cancer? *World J Surg* 2007; 31: 192-9.
- 3 Janssen-Heijnen ML, Maas HA, Houterman S et al. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer* 2007; 43: 2179-93.
- 4 Muss HB, Biganzoli L, Sargent DJ, Aapro M. Adjuvant therapy in the elderly: making the right decision. *J Clin Oncol* 2007; 25: 1870-5.
- 5 Vironen J, Kellokumpu S, Andersson LC, Kellokumpu I. Comparison of a peanut agglutinin test and an immunochemical faecal occult blood test in detecting colorectal neoplasia in symptomatic patients. *Scand J Clin Lab Invest* 2004; 64: 140-5.
- 6 Puig-La C J, Jr, Quayle J, Thaler HT et al. Favorable short-term and long-term outcome after elective radical rectal cancer resection in patients 75 years of age or older. *Dis Colon Rectum* 2000; 43: 1704-9.
- 7 Violi V, Pietra N, Grattarola M et al. Curative surgery for colorectal cancer: long-term results and life expectancy in the elderly. *Dis Colon Rectum* 1998; 41: 291-8.
- 8 Louwman WJ, Vulto JC, Verhoeven RH et al. Clinical epidemiology of breast cancer in the elderly. *Eur J Cancer* 2007; 43: 2242-52.
- 9 Aparicio T, Navazesh A, Boutron I et al. Half of elderly patients routinely treated for colorectal cancer receive a sub-standard treatment. *Crit Rev Oncol Hematol* 2009; 71: 249-57.
- 10 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; 356: 968-74.
- 11 Tan JJ, Foo AY, Cheong DM. Colorectal clinical pathways: a method of improving clinical outcome? *Asian J Surg* 2005; 28: 252-6.
- 12 Rutten HJ, den DM, Lemmens VE, van d, V, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol* 2008; 9: 494-501.
- 13 Bentrem DJ, Cohen ME, Hynes DM, Ko CY, Bilimoria KY. Identification of specific quality improvement opportunities for the elderly undergoing gastrointestinal surgery. *Arch Surg* 2009; 144: 1013-20.
- 14 Cohen AM. Management of colorectal cancer. *Compr Ther* 1990; 16: 43-50.
- 15 Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. *Anesth Analg* 2003; 96: 583-9, table.
- 16 Greenblatt DY, Weber SM, O'Connor ES et al. Readmission after colectomy for cancer predicts one-year mortality. *Ann Surg* 2010; 251: 659-69.
- 17 Kunitake H, Zingmond DS, Ryoo J, Ko CY. Caring for octogenarian and nonagenarian patients with colorectal cancer: what should our standards and expectations be? *Dis Colon Rectum* 2010; 53: 735-43.
- 18 Birkmeyer JD, Sharp SM, Finlayson SR, Fisher ES, Wennberg JE. Variation profiles of common surgical procedures. *Surgery* 1998; 124: 917-23.

Chapter 6

Impact of the interval between short course radiotherapy and surgery on outcomes of rectal cancer patients

Colette B.M. van den Broek

Thomas A. Vermeer

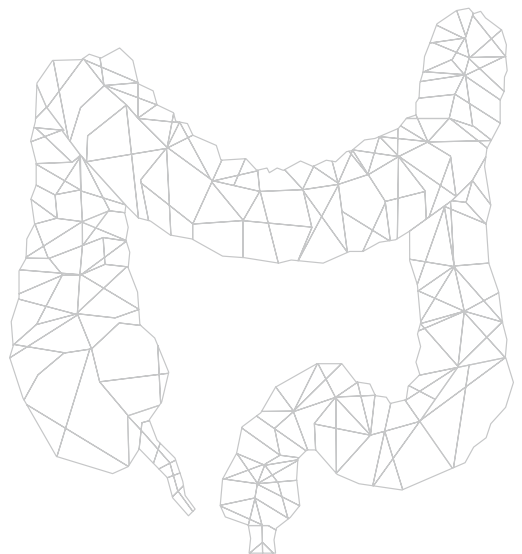
Esther Bastiaannet

Harm J.T. Rutten

Cornelis J.H. van de Velde

Corrie A.M. Marijnen ¹ Department of Surgery, Leiden University
Medical Center, Leiden, the Netherlands

Eur J Cancer. 2013 Oct;49(15):3131-9



ABSTRACT

Background

Preoperative radiotherapy has proven to reduce local recurrences after curative surgery for rectal cancer. Radiotherapy is generally well tolerated, although postoperative morbidity and mortality was increased in some patients. Current study was undertaken to analyse whether the interval between preoperative radiotherapy and surgery influences postoperative mortality and recurrence for two cohorts.

Methods

All Dutch patients included in the TME-trial receiving radiotherapy for resectable rectal cancer were included in this study (n=642). The verification set consisted of all patients receiving short course radiotherapy for resectable rectal cancer in two radiotherapy clinics in the Netherlands (n=600). Univariate and multivariable survival analyses for overall survival, disease-free survival, local recurrence-free survival, and non-cancer related survival were calculated.

Results

Patients aged 75 years and older treated during the TME-trial showed a worse overall and non-cancer-related survival when surgically treated 4-7 days after the last fraction of radiotherapy. No differences in survival between the interval groups were found in the verification set.

Conclusion

Present study found that elderly patients aged 75 years and older operated 4-7 days after the last fraction of radiotherapy had a higher chance of dying due to non-cancer-related causes during the TME-trial as compared to patients with an interval of 0-3 days. In the verification set similar differences could not be confirmed, which could be due to awareness of the clinicians who avoided delayed surgery after radiotherapy since the results have been presented during congresses. A longer than recommended interval between radiotherapy and surgery should be avoided. Besides, the verification set suggests that radiotherapy duration of 7 days is acceptable.

INTRODUCTION

In the treatment of rectal cancer, local recurrences are a major problem, occurring in 15-45% of the rectal cancer patients without TME surgery and radiotherapy.¹⁻⁴ These local recurrences often have severe disabling symptoms and are difficult to treat. To reduce local recurrences after curative surgery, several studies have used either preoperative or postoperative radiotherapy.^{5,6} In a large Swedish trial, short course preoperative RT has proven to be more effective compared to postoperative radiotherapy with conventional surgery.⁷ The TME-trial and the CRO7 trial showed, additionally, that with total mesorectal excision (TME) surgery, preoperative radiotherapy improved local control even further.^{8,9} Preoperative radiotherapy has been given in varying regimens, either short course (25 Gy in 5 fractions during one week) or long course combined with chemotherapy (45-50 Gy during five weeks).^{10,11} Radiotherapy is generally well tolerated, although postoperative morbidity and mortality is increased in some patients.^{8,12-17} The increased postoperative mortality may be contributed to the use of anterior-posterior beams, resulting in large irradiated volumes, from the earlier trials.^{12,14} A more recent study has shown that short course radiotherapy has significant impact on the perioperative leukocyte response.¹⁸ Short course radiotherapy followed by surgery after 5 or more days since the last fraction of radiotherapy was significantly correlated with leukopenia or falling leukocytes rates on day one postoperatively. The patients with an abnormal leukocyte response developed sepsis more often (31% versus 13% in patients with a normal leukocyte response), and had an increased risk of death within 90 days after surgery compared to patients with a normal leukocyte response, suggesting that surgery should occur within 5 days after the last day of radiotherapy.

This study was undertaken to analyse whether the interval between preoperative radiotherapy and surgery, or the duration of radiotherapy (5 or 7 days) influences the outcome of patients regarding one year postoperative mortality and five year local recurrence free survival and disease free survival for two cohorts; patients from the TME-trial from 1996-1999 (DUT-KWF-CKVO-9504, EORTC-40971, EU-96020) and patients from a more recent cohort from 2000 until 2010 as a verification set.

PATIENTS AND METHODS

Patients and follow-up

Dataset from the TME-trial

From January 1996 until December 1999 1861 patients with resectable rectal cancer without evidence of distance disease were randomly assigned to TME preceded by 5×5 gray radiotherapy or TME alone. There was no age limitation. For this subset analysis, only Dutch patients

receiving preoperative radiotherapy are included (n=642), since the follow-up of the Dutch patients has been more thorough and complete.

Verification set

From January 2000 until July 15th 2010, all patients receiving short course preoperative radiotherapy for resectable rectal cancer without evidence of distant metastases followed by TME surgery at Leiden University Medical Center and Catherina Hospital Eindhoven were included retrospectively. Information on the patients' characteristics, such as gender and date of birth, as well as tumour characteristics, location (according to the International Classification of Diseases for Oncology (ICD-O)), histology, stage (clinical and pathological TNM classification 5th edition), grade, and primary treatment, were obtained from the medical records. The vital status was obtained either directly from the patients' medical record or through linkage of the hospital with the municipal population registry which records information on their inhabitants' vital status. Exclusion criteria were: patients without information available on their vital status (n=2), patients without information on the date of radiotherapy or surgery (n=30), and missing data on the age (n=2).

For both datasets, stage was based on pathological TNM classification. For patients in whom pathological stage was unknown, clinical stage was used. Patients were divided in two age groups (<75 years and ≥75 years). The majority of the patients were operated 1, 2, 3, 4, or 5 days after the last fraction of radiotherapy. To compare the effect of the interval, we have divided the patients into four groups. Patients operated within 3 days since the last day of radiotherapy, from 4 until 7 days, from 8 until 27 days, and from 28 days or more (in line with one of the arms of the Stockholm III trial¹⁹).

Radiotherapy duration has been divided into two groups: 5 days (Monday till Friday) or 7 days of radiotherapy (with a weekend included). Overall treatment time (OTT, as shown in figure 1) has been divided into two groups: OTT ≤10 days (with the exception of a radiotherapy duration of 8 days) or OTT >10 days (as shown in table 1 with the light grey shaded area). A radiotherapy duration of 8 days was in violation with the protocol and has therefore been included as an OTT>10 days. An interval between radiotherapy and surgery ≥8 days (dark shaded grey area in table 1) has been excluded from the OTT analyses since this was in violation with the recommendations.

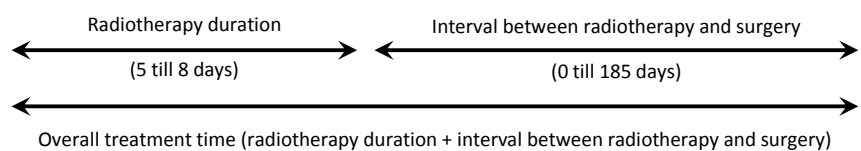


Figure 1: Relation between duration of radiotherapy, interval between radiotherapy and surgery, and overall treatment time

Table 1a: Relation between radiotherapy duration and the interval between radiotherapy and surgery during the TME-trial

		Interval between radiotherapy and surgery										Total
		0	1	2	3	4	5	6	7	8-27	≥ 28	
Radiotherapy duration	5	-	2	12	204	172	99	38	12	4	3	546 (85.0%)
	6	-	3	5	1	5	2	-	1	-	-	17 (2.6%)
	7	-	18	27	8	3	3	1	1	1	1	63 (9.8%)
	8	1	6	4	2	1	1	1	-	-	-	16 (2.5%)
Total		1	29	48	215	181	105	40	14	5	4	642

The area is light shaded grey area in case of OTT >10 days, and the dark shaded grey area has been excluded from the OTT analyses. Both were in violation with the protocol. Radiation duration of 8 days was in violation with the protocol and these patients were therefore included in the OTT > 10 days.

Table 1b: Relation between radiotherapy duration and the interval between radiotherapy and surgery during the verification set (2000 until 2010)

		Interval between radiotherapy and surgery										Total
		0	1	2	3	4	5	6	7	8-27	≥ 28	
Radiotherapy duration	5	-	2	3	179	61	2	7	6	5	10	275 (45.8%)
	6	-	1	-	2	-	-	-	-	-	-	3 (0.5%)
	7	1	86	116	16	14	19	4	9	13	23	301 (50.2%)
	8	1	14	4	-	-	-	-	-	-	2	21(3.5%)
Total		2	103	123	197	75	21	11	15	18	35	600

The area is light shaded grey area in case of OTT >10 days, and the dark shaded grey area has been excluded from the OTT analyses. Both were in violation with the recommendations. Radiation duration of 8 days was in violation with the protocol and these patients were therefore included in the OTT > 10 days.

When patients received radiotherapy for 5 days, from Monday till Friday, surgery was either performed on Monday (within 3 days since the last fraction of radiotherapy), or later in that week (from 4 until 7 days since the last fraction of radiotherapy).

Statistical analyses

All analyses were performed with STATA 10. Differences between the groups were tested with a Chi-Squared test. Follow-up was calculated as the time from surgery to death or date of last contact. Overall survival, disease-free survival, local recurrence-free survival, and non-cancer related survival (including death due to postoperative complications) were calculated, by using Kaplan-Meier survival curves, for both univariate and multivariable survival analyses. Overall survival and non-cancer related mortality were truncated at one year, since recently a study has shown that postoperative mortality can be increased up to one year after surgery due to differences in comorbidities and fragility.²⁰ Disease-free survival and local recurrence-free survival were truncated at five years, since recurrences or metastases are not expected to occur often within one year after surgery. Univariate and multivariable survival analysis was performed using a Cox proportional hazard model. Statistical significance was defined as

$p < 0.05$. All analyses are done separately for the group of patients from the TME trial and the verification set.

RESULTS

Dataset from the TME-trial

Patients

A total of 642 patients from the TME-trial were included in this study. The median follow-up since surgery of these patients was 9.1 years (range 0.01-13.7 years). The median age of the patients at time of surgery was 65.1 years (range 26.6-89.0 years).

Radiotherapy duration and interval between radiotherapy and surgery

Table 1a demonstrates the relationship between the duration of radiotherapy and the interval between the last fraction of radiotherapy and surgery for patients during the TME-trial. Most patients received radiotherapy from Monday till Friday, so 5 days continuously (85.0%). For the other patients the radiotherapy duration was 6 days (2.6%), 7 days (9.8%), or 8 days (2.5%); including a weekend and/or bank holiday. Surgery within 3 days of the last fraction of radiotherapy was performed in 293 patients of the 642 patients, an interval of 4 to 7 days was the most common (340/642). Intervals of 8 until 27 days and 28 days or more occurred less often (5 and 4 patients, respectively).

In table 2a the characteristics of the patients divided into the four interval groups are shown. There were no significant differences between the four interval groups in age and gender during the TME-trial ($p = 0.5$ and $p = 0.2$, respectively). Pathological stage was lower in the patients with an interval of ≥ 8 days as compared to patients with an interval of < 8 days ($p < 0.001$), but no difference was detected between the group of patients with an interval of 0-3 days and 4-7 days ($p = 0.3$), neither when the interval of 28 days and more only was excluded ($p = 0.4$).

Survival

Due to small numbers in the interval group of 8 until 27 days and 28 days or more, these patients ($n = 9$) were excluded for survival analysis. 30-day mortality analyses showed no significant difference between an interval of 0-3 days and 4-7 days for all ages combined (30-day mortality for interval of 0-3 days was 2.1% and for the interval of 4-7 days 4.7%, $p = 0.08$). Neither difference in one year overall survival between an interval of 0-3 days and 4-7 days was found for all ages combined (HR 1.67; 95% CI 0.94-2.96; $p = 0.08$). However, the one year overall survival showed an age disparity (figure 2a). Where patients younger than 75 years of age showed no difference in one year overall survival between both intervals (HR 1.11; 95% CI 0.54-2.30; $p = 0.8$), patients

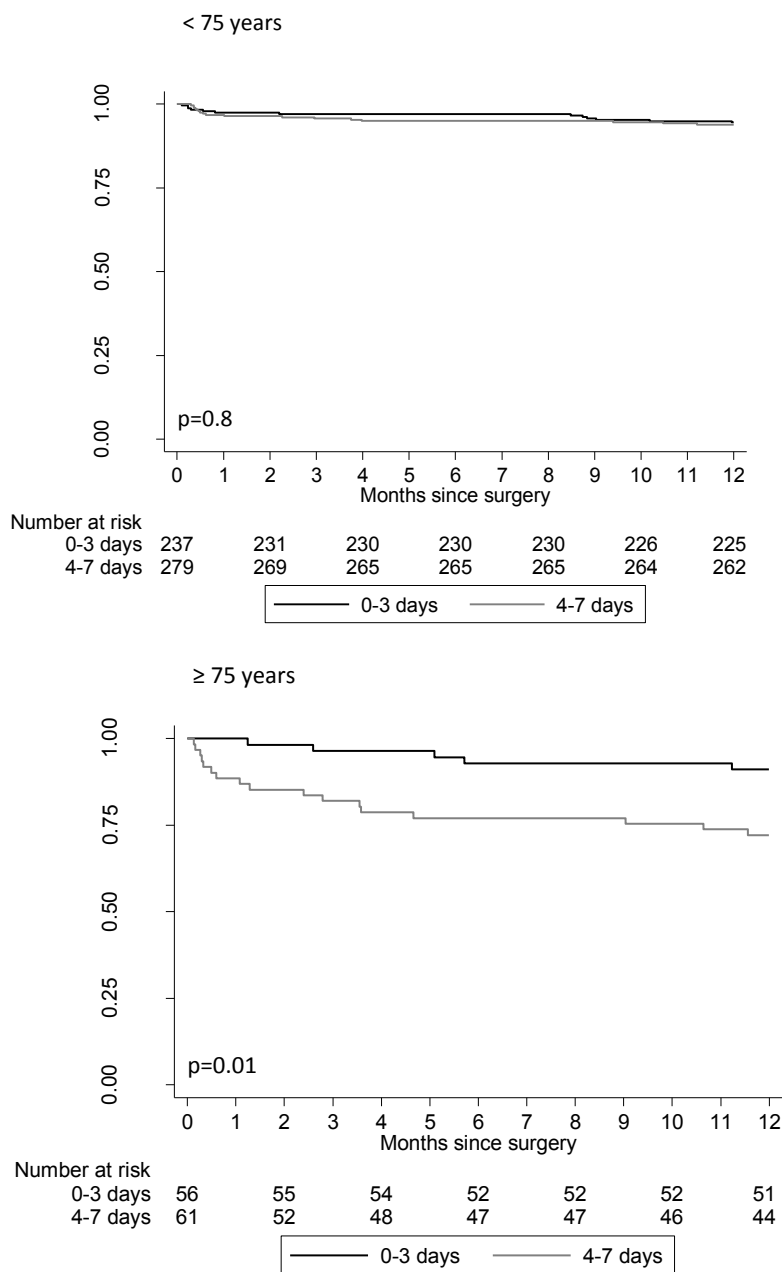


Figure 2a: Comparison of one year overall survival per interval group stratified for age group (TME-trial)

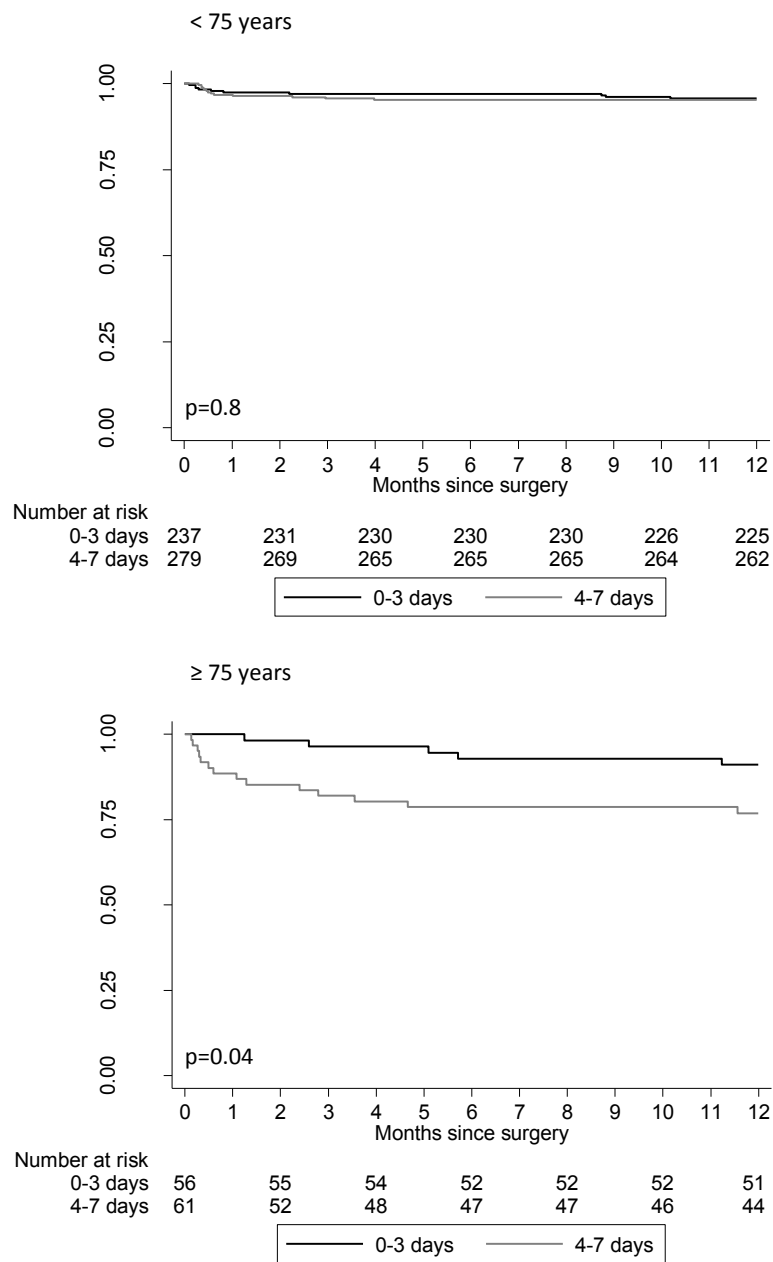


Figure 2b: Comparison of one year non-cancer related mortality per interval group stratified for age group (TME-trial)

≥75 years showed worse survival for the 4-7 days interval compared to those with 0-3 days interval (HR 3.58; 95% CI 1.32-9.71; $p=0.01$). Adjusted for age, gender, and stage these differences remained significant (HR 3.65; 95% CI 1.31-10.16; $p=0.01$). The difference between the two interval groups in elderly patients arose within the first month, which suggested non-cancer-related mortality (including postoperative complications), as confirmed in figure 2b (HR 2.92; 95% CI 1.05-8.12; $p=0.04$). No significant differences were found for both age groups between the two interval groups in five year disease-free survival (HR 1.00; 95% CI 0.71-1.39; $p=0.9$ for patients <75 years and HR 2.07; 95% CI 0.90-4.79; $p=0.09$ for patients ≥75 years), neither for the five year local-recurrence free survival (HR 0.79; 95% CI 0.37-1.67; $p=0.5$ for patients <75 years and HR 3.98; 95% CI 0.41-38.34; $p=0.2$ for patients ≥75 years).

Verification set

Patients

A total of 600 patients receiving radiotherapy between 2000 and 2010 were included in this verification set. The median follow-up since surgery of these patients was 4.3 years (range 0-11.4 years). Median age of these patients at time of surgery was 67.2 years (range 26.5-94.5 years).

Radiotherapy duration and interval between radiotherapy and surgery

In this cohort most patients received radiotherapy during 5 days (45.8%) or 7 days (50.2%) (table 1b). The remaining patients received radiotherapy during 6 days (0.5%) or 8 days (3.5%). Most patients (425/600) were operated on 0-3 days after the last fraction of radiotherapy. The interval of 4-7 days, 8-27 days, and ≥28 days were less common (112/600, 18/600, and 35/600 patients, respectively). Over time there was an increase in patients who were operated on more than 28 days after the last fraction of radiotherapy (from 2.9% in 2000, to 10.7% in 2009; $p<0.001$).

As shown in table 2b, in the verification set elderly patients of 75 years and older more often had an interval of ≥28 days, and less often ≤3 days ($p=0.006$). Furthermore, with a longer interval between the last fraction of radiotherapy and surgery, there was a decrease in pathological stage ($p<0.001$). The pooled rate of pathological complete response in patients with an interval of 28 days or more was 13% (3 of 39 patients).

Table 2a: Clinical characteristics of patients of the TME-trial

	Interval between radiotherapy and surgery								p-value
	≤3 days		4-7 days		8-27 days		≥28 days		
	N	%	N	%	N	%	N	%	
Age									0.5
<75 years	237	45.1	279	53.1	5	1.0	4	0.8	
≥75 years	56	47.9	61	52.1	0	0.0	0	0.0	
Sex									0.2
Male	185	44.3	228	54.5	4	1.0	1	0.2	
Female	108	48.2	112	50.0	1	0.5	3	1.3	
Stage									<0.001
In situ	3	30.0	5	50.0	0	0.0	2	20.0	
I	102	48.2	106	50.0	2	0.9	2	0.9	
II	94	49.5	96	50.5	0	0.0	0	0.0	
III	94	40.9	133	57.8	3	1.3	0	0.0	
Total	293	45.6	340	53.0	5	0.8	4	0.6	

Table 2b: Clinical characteristics of patients of the verification set

	Interval between radiotherapy and surgery								p-value
	≤3 days		4-7 days		8-27 days		≥28 days		
	N	%	N	%	N	%	N	%	
Age									0.006
<75 years	336	72.7	95	20.6	12	2.6	19	4.1	
≥75 years	89	64.5	27	19.6	6	4.3	16	11.6	
Sex									0.1
Male	272	74.3	64	17.5	10	2.7	20	5.5	
Female	153	65.4	58	24.8	8	3.4	15	6.4	
Stage									<0.001
In situ	4	57.1	0	0.0	0	0.0	3	42.9	
I	140	70.4	38	19.1	5	2.5	16	8.0	
II	120	67.2	37	22.2	8	3.9	12	6.7	
III	159	76.0	43	19.2	5	2.9	4	1.9	
Unknown	2	33.3	4	66.7	0	0.0	0	0.0	
Total	425	70.8	122	20.3	18	3.0	35	5.9	

Survival

Interval

The 30-day mortality for all ages combined was 1.7% for an interval of 0-3 days, 1.6% for an interval of 4-7 days and 2.9% for an interval of 28 days or more, which was not statistically different ($p=0.9$). Both the 30-day mortality and the one year overall survival of the patients

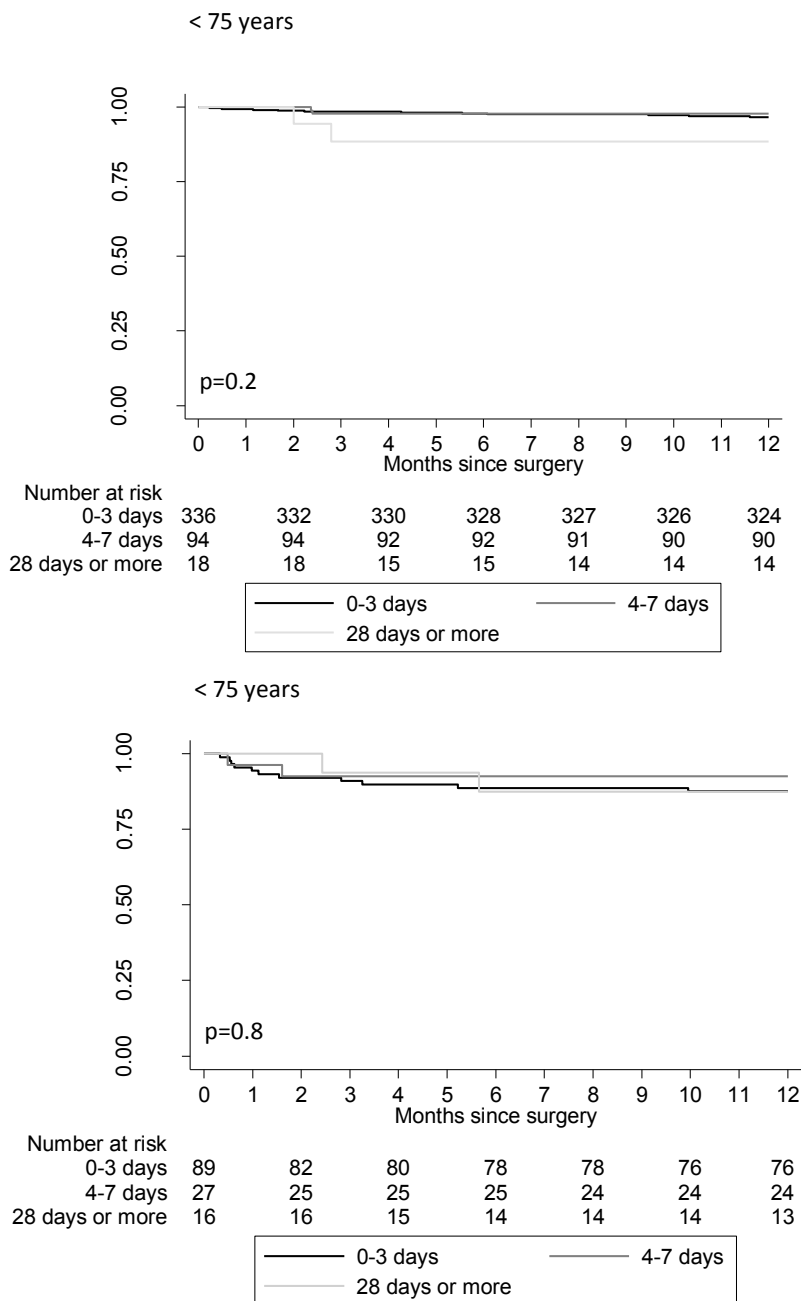


Figure 3a: Comparison of one year overall survival per interval group stratified for age group (verification set)

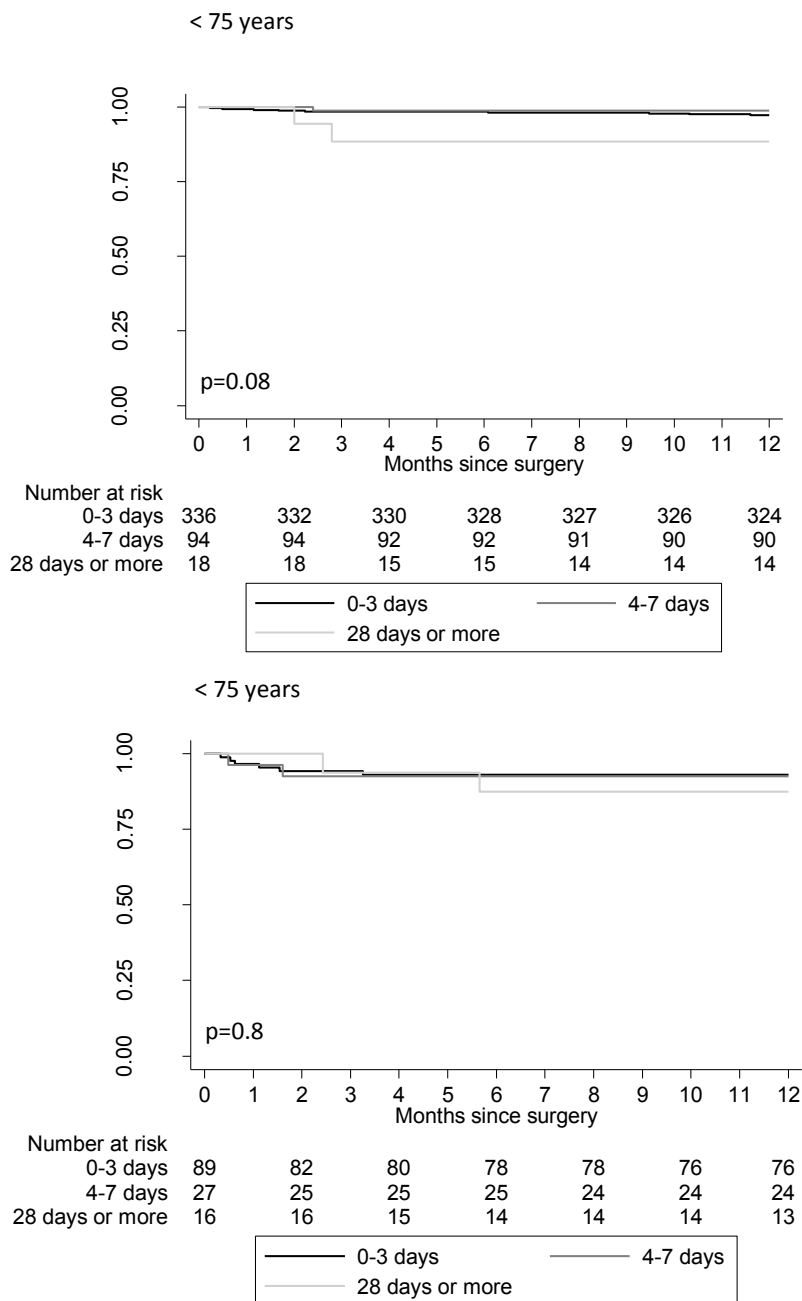


Figure 3b: Comparison of one year non-cancer related mortality per interval group stratified for age group (verification set)

from the verification set did not show the age disparity found in the dataset from the TME trial (figure 3a). Due to small numbers, patients with an interval of 8 until 27 days between radiotherapy and surgery (n=18) were excluded from survival analysis. There was no significant difference found between the interval of 0-3 days compared to 4-7 days both for patients <75 years (HR 0.65; 95% CI 0.14-2.93; p=0.6) and patients ≥75 years (HR 0.59; 95% CI 0.13-2.66; p=0.5). This remained after adjusting for age, gender, and stage. Similarly, no differences in overall survival were found between the interval of 0-3 days and ≥28 days in neither patients <75 years (HR 3.70; 95% CI 0.82-16.72; p=0.09), nor in patients ≥75 years (HR 0.97; 95% CI 0.22-4.38; p=0.9).

The non-cancer-related survival of younger and elderly patients showed no significant differences between the interval of 0-3 days compared to 4-7 days either (HR 0.40; 95% CI 0.05-3.13; p=0.4, for patients <75 years, and HR 1.08; 95% CI 0.22-5.36; p=0.9, for patients ≥75 years, respectively) (figure 3b). Besides, no differences were found in five year disease-free survival (HR 0.93; 95% CI 0.57-1.52; p=0.8, 4-7 day interval compared to 0-3 days for patients younger than 75 years, HR 0.77; 95% CI 0.29-2.05; p=0.6, 4-7 day interval compared to 0-3 days for patients of 75 years and older). Furthermore, no differences were found in five year local-recurrence free survival, (HR 0.27; 95% CI 0.04-2.06; p=0.2, HR 0.89; 95% CI 0.19-4.29; p=0.9, for younger and elderly patients with an interval of 4-7 days compared to 0-3 days, respectively).

Duration of radiotherapy

Since the TME-trial the radiotherapy treatment was more often interrupted with a weekend, which increased the duration of radiotherapy from 5 days (85.0% in the TME trial) to 7 days (50.2% in the verification set). When radiotherapy during 5 days and during 7 days were compared in the verification set, no differences were found in one year overall survival (HR 0.75; 95% CI 0.37-1.52; p=0.4), one year non-cancer-related mortality (HR 0.91; 95% CI 0.39-2.10; p=0.8), or five year local-recurrence free survival (HR 0.89; 95% CI 0.39-2.01; p=0.8). Furthermore, no differences in overall survival, non-cancer-related survival, or local-recurrence free survival were found in patients aged <75 years, neither in patients aged ≥75 years.

Overall treatment time

Since both the duration of the radiotherapy and the interval between radiotherapy and surgery have changed over time, overall treatment time (OTT, as explained in figure 1), could have been a factor influencing mortality. However, in the verification set OTT was not associated with one year overall survival, one year non-cancer-related survival, or five year local-recurrence free survival (HR 0.24; 95% CI 0.03-1.75; p=0.2, HR 0.35; 95% CI 0.085-2.62; p=0.3, and HR 1.31; 95% CI 0.45-3.87; p=0.6, respectively). When the analyses have been done separately for each age group (<75 years and ≥75 years), no differences were found either.

DISCUSSION

In this study we analysed the impact of the interval between the last fraction of short course radiotherapy and surgery on one year survival and long term recurrence, both in the TME-trial and in a verification set. Results from the TME-trial showed that elderly patients with a prolonged interval (4-7 days) between the end of radiotherapy and surgery had higher one year overall and non-cancer related mortality. In the verification set this could not be confirmed.

Although the results of the TME cohort derived from a randomised controlled trial, we have to interpret these results with caution, since these analyses have not been evaluated in a randomised setting. Therefore the finding may be simply a random finding. Another possible explanation for the results found may be that surgery was postponed in patients with a poor condition, after consultation by the anaesthetist, which would result in bias. Elderly patients are expected to have a poor condition more often, which would explain that the results were only found in patients ≥ 75 years. Because most patients were seen by the anaesthetist during admission prior to surgery, postponement of surgery by the anaesthetist should then result in a longer interval between admission and surgery for the longer interval group. However, no difference was found, with a similar median time between admission and surgery in both interval groups (2 days). Furthermore, no differences were found in age, gender, stage (see table 2a), WHO performance scores (data not shown), and toxicity (data not shown) between the two interval groups. Even though, comorbidities were not administered during the TME trial, and might explain differences between both interval groups.

For this reason we tried to confirm the above mentioned findings in a separate retrospectively collected verification set. In this verification set, no differences were found in one year overall survival and non-cancer-related survival between the interval groups. Several possible reasons could explain this. Firstly, over time perioperative care might have improved, resulting in less postoperative mortality. 30-day mortality was 2.1% in the interval of 0-3 days and 4.7% in the interval of 4-7 days, compared with 1.7% in the interval of 0-3 days, 1.6% in the interval of 4-7 days and 2.9% in the interval of 28 days or more in the verification set; suggestion that perioperative care has improved. Finally, another possibility is that due to awareness of the clinicians for the higher postoperative mortality, since the TME results have been presented on several congresses, elderly patients were less often treated with an interval between 4 till 7 days between radiotherapy and surgery in the verification set. The results showed that indeed fewer patients were operated on 4 till 7 days after the last fraction of radiotherapy, indicating that awareness of the physicians might have been present. Besides, the finding that there has been a shift in radiotherapy duration from mainly 5 days in the TME-trials to 7 days in the verification set, suggests that this was done in order to prevent logistical problems. During the TME trial most patients received radiotherapy from Monday till Friday, followed by surgery in the next week. The knowledge of possible worse outcome after an interval of more than three days might have triggered radiation oncologists to decrease the interval between

the end of radiotherapy and surgery, with nowadays only 20% of patients having an interval of 4-7 days (122 out of 600 patients), which was over 50% during the TME-trial (340 out of 642 patients). This resulted in a shift in approach; approximately 10% of the patients had a radiotherapy duration of 7 days during the TME-trial, whereas this was over 50% in the verification set. The present study therefore analysed the relation between overall treatment time and postoperative mortality and non-cancer-related mortality, demonstrating no difference, neither for the whole group, nor for the elderly. This suggests that including a weekend in radiotherapy treatment is safe.

Several other studies have studied the influence of the interval between radiotherapy and surgery. Recently the interim analyses of the Stockholm III trial have been published. In these interim analyses an increase in postoperative complications for patients surgically treated 11-17 days since the start of radiotherapy compared to patients with a shorter interval was reported. Differences in postoperative mortality were not significant due to small numbers.¹⁹ Similar, Hartley et al²¹ found in a retrospective population-based cohort that patients with an overall treatment time < 10 days had a decreased risk of complications. Additionally, Hartley et al²² published that the ratio between preoperative and postoperative neutrophil leucocyte count was significantly higher in patients without complications. Even though, they did not find an association between the neutrophil ratio and the overall treatment time. Fokstuen et al¹⁸ found clear indications that the differences between the interval groups are related to the perioperative leukocyte response. Patients with an abnormal leukocyte response developed sepsis more often and had an increased risk of death within 90 days after surgery. Besides, a longer than recommended interval also appeared to be detrimental for postoperative death independently of leukocyte response.

From the above can be concluded that there are several indications in the literature that the increased postoperative mortality after a longer interval between radiotherapy and surgery could be caused by an impaired immune response, possibly reflected in the perioperative leukocyte count of the patient.

Currently a Swedish trial studies delayed surgery after short course radiotherapy, because clear indications have been found that short course radiotherapy could cause downstaging after an interval between radiotherapy and surgery of at least four weeks.^{19,23,24} Almost certainly due to these results and the currently running trial, delayed surgery was used more often in the verification set, mainly in elderly patients. In our study there were also indications that delayed surgery induces downstaging, as patients with delayed surgery had a lower pathological stage. Furthermore, the verification set showed no differences in short term survival between direct surgery after radiotherapy (interval of 0-3 days or 4-7 days) compared to delayed surgery (interval of 28 days or more), which is in line with the results shown in the interim analyses of the Stockholm III trial.¹⁹ Possibly, the leukocyte response has normalized at the time those patients are operated on.

CONCLUSION

In conclusion, there are several indications that the interval between radiotherapy and surgery influences postoperative outcome. Results from the verification set demonstrate that avoiding a longer interval between radiotherapy and surgery and including a weekend in the radiotherapy treatment seems safe, both for postoperative mortality as for oncological outcome. Therefore we recommend to limit the interval to 3 days and accept a radiotherapy duration of 7 days. If logistically impossible, postponement surgery after more than four weeks seems an option, although results on oncological outcome have to be awaited.

REFERENCE LIST

- 1 Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. *Lancet* 1996; **348**: 1610-4.
- 2 Arnaud JP, Nordlinger B, Bosset JF et al. Radical surgery and postoperative radiotherapy as combined treatment in rectal cancer. Final results of a phase III study of the European Organization for Research and Treatment of Cancer. *Br J Surg* 1997; **84**: 352-7.
- 3 Kapiteijn E, Marijnen CA, Colenbrander AC et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. *Eur J Surg Oncol* 1998; **24**: 528-35.
- 4 Martling AL, Holm T, Rutqvist LE et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; **356**: 93-6.
- 5 Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; **358**: 1291-304.
- 6 Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol* 2003; **42**: 476-92.
- 7 Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; **36**: 564-72.
- 8 van Gijn W., Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
- 9 Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CRO7 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**: 811-20.
- 10 Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol* 2003; **42**: 476-92.
- 11 Glimelius B. Rectal cancer irradiation. Long course, short course or something else? *Acta Oncol* 2006; **45**: 1013-7.
- 12 Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Rectal Cancer Study Group. *Cancer* 1990; **66**: 49-55.
- 13 Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. Swedish Rectal Cancer Trial. *Br J Surg* 1993; **80**: 1333-6.
- 14 Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994; **30A**: 1602-6.
- 15 Marijnen CA, Kapiteijn E, van de Velde CJ et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002; **20**: 817-25.
- 16 Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Dis Colon Rectum* 1999; **42**: 403-18.
- 17 Pahlman L, Glimelius B, Graffman S. Pre- versus postoperative radiotherapy in rectal carcinoma: an interim report from a randomized multicentre trial. *Br J Surg* 1985; **72**: 961-6.
- 18 Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. *Radiother Oncol* 2009; **93**: 293-7.
- 19 Pettersson D, Cedermark B, Holm T et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010; **97**: 580-7.

- 20 Dekker JW, van den Broek CB, Bastiaannet E et al. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**: 1533-9.
- 21 Hartley A, Giridharan S, Gray L et al. Retrospective study of acute toxicity following short-course preoperative radiotherapy. *Br J Surg* 2002; **89**: 889-95.
- 22 Hartley A, Giridharan S, Srihari N, McConkey C, Geh JI. Impaired postoperative neutrophil leucocytosis and acute complications following short course preoperative radiotherapy for operable rectal cancer. *Eur J Surg Oncol* 2003; **29**: 155-7.
- 23 Hatfield P, Hingorani M, Radhakrishna G et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. *Radiother Oncol* 2009; **92**: 210-4.
- 24 Radu C, Berglund A, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. *Radiother Oncol* 2008; **87**: 343-9.



Part II

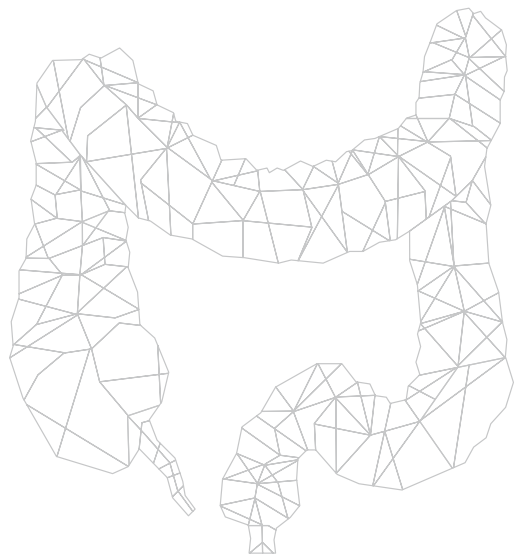
International comparisons in colorectal cancer treatment and survival

Chapter 7

The EURECCA project: data items scored by European colorectal audit registries

Willem van Gijn
Colette B.M. van den Broek
Pawel Mroczkowski
Adam Dziki
Giovani Romano
Danius Pavalkis
Michel W.J.M. Wouters
Bjørn Møller
Arne Wibe
Lars Pålman
Henrik Harling
Jason J. Smith
Freddy Penninckx
Hector Ortiz
Vincenzo Valentini
Cornelis J.H. van de Velde

Eur J Surg Oncol. 2012 Jun;38(6):467-71



ABSTRACT

Background

The EURECCA (European Registration of Cancer Care) consortium is currently formed by nine independently founded national colorectal audit registrations, of which most already run for many years. The cumulative experience of EURECCA's participants could be used to identify a 'core dataset' that covers all important aspects needed for high quality auditing and at the same time lacking needless data items that only consumes administrative effort. The aim of this study is to compare the data items used by the nine registries participating in EURECCA to identify a core dataset and explore options for future research.

Methods

All colorectal outcome registrations participating in the EURECCA project were asked to supply a list with all the data-items they score. Items were scored 'present' if they appeared literally in a registration or in case they could be calculated using other items in the same registration. The definition of a 'shared data-item' was that at least eight of the nine participating registries scored the item.

Results

The number of registered data items varied between 254 (Belgium) and 83 (Norway). Among the 45 variables were patient data, data about preoperative staging, surgical treatment, pre- or postoperative radio- and/or chemotherapy, and follow-up. Items about tumour recurrence or quality of life were scored too little to become shared data items.

Conclusion

A total of 45 items were collected by 8 or more of the participating registries and subsequently met the criteria for a shared data-item.

INTRODUCTION

In 2006, colorectal cancer caused over 200,000 deaths in Europe, making it the second most common cause of cancer related death, while its incidence is still increasing.¹ In developing countries, the rise in incidence is even higher, while they have the worst outcome.²⁻⁴ Although surgery is the cornerstone for curative treatment, there is great variability in outcomes among surgeons and institutions.

Quality of health care has a high priority on the political agenda of most European countries. Universal health care improvement initiatives, such as the development of a preoperative surgical checklist by the World Health Organization, reflect the contemporary global commitment to prioritizing high quality care within surgery.⁵

Surgical quality assurance program, also called surgical audit, is a quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. Major improvements have been achieved with national audits.⁶⁻⁸ However, although all the national audits achieved excellent results, differences in treatment and outcome remain between European countries and cannot be easily explained.⁹ To reduce those differences by identifying and spreading best practice, the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The goal is to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics linked to outcome registration. Many important topics that are unanswered by randomised controlled trials could be researched using the data of EURECCA project. The EURECCA project makes use of existing national audit registrations and started with colorectal cancer, but in the future other solid tumour types, such as breast cancer, gastric cancer, and oesophageal cancer, will follow.

Unfortunately, clinical auditing comes with a price. Despite rapid development in medical information technology, clinical auditing still is a considerable administrative burden from medical professionals. A beautifully designed but very detailed registry that turns out to be too time consuming to complete is worthless. Therefore, it is important only to register those items that really matter. When a new audit is set up, dedicated professionals might be tempted to develop a very complete, although unnecessary large dataset. Instead of reinventing the wheel, a 'core dataset' distilled from existing audits could save much energy.

The EURECCA consortium is currently formed by nine independently founded national colorectal audit registrations, most of whom already run for many years. The cumulative experience of EURECCA's participants could be used to identify a 'core dataset' that covers all important aspects needed for high quality auditing and at the same time lacking needless data items that only consumes administrative effort. Even more important than being used as a template for other audits, an EURECCA core set will give the consortium insight in what research can be performed in the near future.

The objective of this study is to compare the data items used by the nine registries participating in EURECCA to identify a core dataset and explore options for future research within the EURECCA project.

PATIENTS AND METHODS

All colorectal outcome registrations participating in the EURECCA project were asked to supply a list with all the data-items they score. These data-items were entered in a database and assigned to a main category and a subcategory. Items were scored 'present' if they appeared literally in a registration or in case they could be calculated using other items in the same registration. Secondly, the type of data (categorical, number, yes/no, free text) was scored. Software used for data input and analyses was SPSS 17 (PASW, Chicago). After all the items were entered in the database, a report was sent back to the national data managers to check for errors or incompleteness'. The corrected lists were returned and processed in the database. In the corrected and completed database, shared data items between the registries were identified as well as resemblances in data type and categories. The definition of a 'shared data-item' was that only one registry was allowed not to score the item, so at least eight of the nine participating registries scored the item.

RESULTS

All nine participating EURECCA registries (table 1) supplied lists with all recorded data items, which were entered into a database and checked for accuracy as described in the methods section. The number of registered data items varied between 254 (Belgium) and 83 (Norway) (figure 1). A total of 45 items were collected by 8 or more of the participating registries and subsequently met the criteria for a shared data-item (table 2). Among the 45 variables were patient data such as date of birth, gender, cancer type and ASA score. Furthermore, variables to score the use of endoscopy, rectal ultrasound, CT or MRI scan for preoperative staging met the shared data item criteria together with cT-stage and cM-stage. Items about the surgical treatment that met the criteria for a shared data item included date of surgery, main procedure, open or laparoscopic, the creation of an anastomosis and/or stoma and the important postoperative complication; anastomotic leakage. Eight or more out of the nine participating registries scored pTNM stage, radicality and distance of the tumour to the surgical resection plane. Registrations of administered pre- or postoperative radio- and or chemotherapy were also shared data items. Regarding follow-up, death status and date of death were shared data items. Items about tumour recurrence or quality of life were scored too little to become shared data items.

Table 1: The EURECCA consortium

Name	Country	Number of included patients (mid 2011)
Dutch Surgical Colorectal Audit (DSCA)	The Netherlands	25,000
International Quality Assurance in Colorectal Carcinoma	Germany Poland Italy (Naples) Lithuania	76,000
Norwegian Colorectal Cancer Project	Norway	26,500
Swedish Colorectal Cancer Registry	Sweden	41,000
Danish Colorectal Cancer Database	Denmark	36,500
National Bowel Cancer Audit Program (NBOCAP)	United Kingdom	200,000
Project on cancer of the Rectum (PROCARE)	Belgium	4,500
Spanish TME project	Spain	7,500
Study group for Therapies Of Rectal Malignancies (STORM)	Italy	1,500
EURECCA		418,500

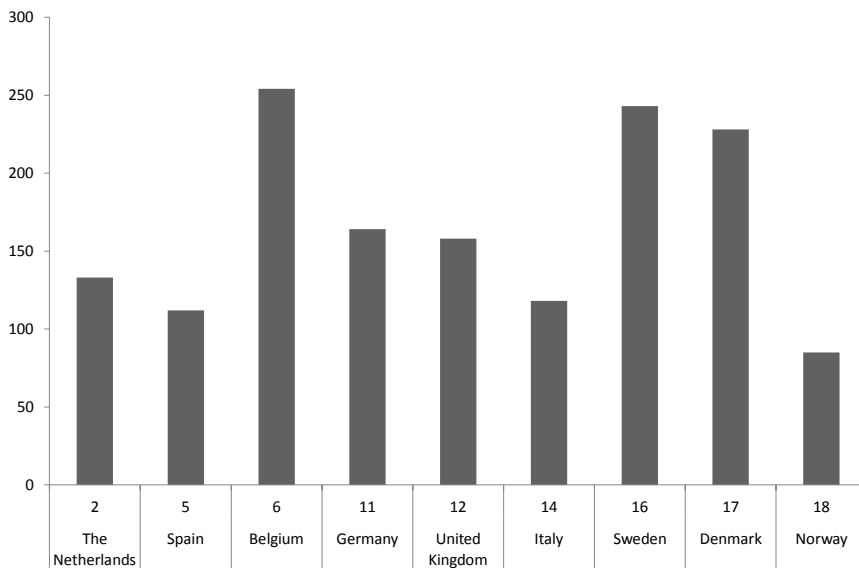
**Figure 1:** Number of recorded data-items for all EURECCA participants, including time since first registration in years

Figure 1 shows the number of recorded data-items scored by all nine EURECCA participants on the Y-axis and the number of years since first registration on the X-axis. There was no relation between time since first registration and the number of scored data items.

Table 2: Data items shared by ≥8/9 registrations

Category	Data item
Patient: administrative data	Patient number Cancer type (rectal, colon) Neoadjuvant therapy (type: none, RT, CT, RCT) Adjuvant therapy (type: none, RT, CT, RCT) Gender Patient name Hospital Date of birth Radiotherapy: type (preop / postop) and duration (long- / short-course)
Patient: preoperative medical condition	ASA score
Preoperative staging: Colonoscopy, location tumour, biopsy, complications	Endoscopy: lower limit from anal verge (cm) Endoscopy: y/n
Preoperative staging: Imaging	CT scan Ultrasound rectal MRI scan MRI - cT stage
Preoperative staging: Final preoperative staging, MDT, other	cM Clinical metastases: y/n Final preop diagnosis: CT-stage Final preop diagnosis: cM-stage
Neoadjuvant treatment: Type, technique, dose, etc	Preoperative chemotherapy Preoperative radiotherapy
Operation: Type, technique, anastomosis, stoma, etc	Operation: y/n Operation: date Main procedure (ICD10 or translatable into) Surgery: stoma (none, decompressive, permanent, loop, endtype) Surgical access for resection: (laparotomy / laparoscopy / converted laparoscopy / local excision) Surgery: Anastomosis Resection of adjacent organ
Operation: Complications	Postoperative anastomotic leakage
Postoperative staging: Pathology, final diagnosis	Primary diagnosis (ICD10) Distant metastasis Histology (SNOMED) pTNM: T pTNM: N pTNM: M Tumour stage (TNM 6th edition) Lymph nodes with metastases Lymph nodes in total Distance to surgical resection plane (CRM) Radicality operation (R0, R1, R2) Location distant metastases (liver, lung, peritonuem, omentum, ovary, lymph node)

Table 2: *Continued*

Category	Data item
Adjuvant treatment: RT, CT, RCT, type, technique, dose, etc	Postoperative chemotherapy
	Postoperative radiotherapy
Follow-up: Date, Death status, Oncological status	Death / alive
	Date of death
Total	45

DISCUSSION

After comparing the datasets of EURECCA's nine participating registries, a list of 45 data items could be identified as a shared, core dataset. A strong variation between the number of data items collected by different registries was found, ranging between 83 by Norway and 254 by Belgium. Despite the fact that the oldest registry (Norway) used the fewest data items, there was no relation between time since first registration and slimness of the dataset.

Although many important items can be mentioned that are not listed in the core dataset, the most vital variables about patient, disease, preoperative staging, operation, pathology and survival are all part of the core dataset. Furthermore, data about pre- and postoperative adjuvant treatment are also part of the core dataset.

Worldwide and also within Europe, there are many differences in the use of (neo)adjuvant treatment for cancer. For instance, for rectal cancer with an unthreatened circumferential resection margin, many patients will receive short course (5×5 Gy) preoperative radiotherapy while others will get long course radiochemotherapy and sometimes this is administered postoperatively. Using the shared data items in combination with the impressive and unprecedented amount of patients supplied by EURECCA, an inventory about differences in (neo) adjuvant treatment can be made and linked to other data such as anastomotic leakage, surgical radicality and long term survival. The EURECCA core dataset offers enough patient data to perform statistical corrections for patient and tumour factors, necessary for a fair comparison between different treatments.

While the share of elderly in the incidence of colorectal cancer is increasing every year, elderly are remarkably enough excluded from most clinical trials concerning colorectal cancer. Again, the extensive data of EURECCA's core dataset should be able to answer vital questions about the optimal treatment for elderly. Differences in treatment can be identified as well as differences in first presentation of disease, whether this is tumour stage, age, gender or incidence of a disease.

CONCLUSION

In conclusion, a valuable core data set is identified. This study shows a lean and easy to register core dataset that can help starting clinical audits setting up their database and help minimize administrative burden for existing audits. Most importantly, vital research questions will be answered in the near future using the power of EURECCA's merged data.

ACKNOWLEDGEMENTS

This work was carried out with support of ECCO and ESSO.

REFERENCE LIST

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol.* 2007; 18(3): 581-92.
2. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EURO CARE-4 study. *Lancet Oncol.* 2007; 8(9): 773-83.
3. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(6): 1688-94.
4. Verdecchia A, Guzzinati S, Francisci S, De Angelis R, Bray F, Allemani C, et al. Survival trends in European cancer patients diagnosed from 1988 to 1999. *Eur J Cancer.* 2009; 45(6): 1042-66.
5. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med.* 2009; 360(5): 491-9.
6. Wibe A, Moller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer - implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum.* 2002; 45(7): 857-66.
7. Wibe A, Carlsen E, Dahl O, Tveit KM, Weedon-Fekjaer H, Hestvik UE, et al. Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis.* 2006; 8(3): 224-9.
8. Pahlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjö Dahl R, Öjerskog B, Damber L & Johansson R: The Swedish Rectal Cancer Registry. *Br J Surg.* 2007; 94: 1285-1292.
9. van Gijn W, Wouters MW, Peeters KC, van de Velde CJ. Nationwide outcome registrations to improve quality of care in rectal surgery. An initiative of the European Society of Surgical Oncology. *J Surg Oncol.* 2009; 99(8): 491-6.

Chapter 8

Differences in preoperative treatment administration of rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands

Colette B.M. van den Broek

Willem van Gijn

Esther Bastiaannet

Bjørn Møller

Robert Johansson

Marloes A.G. Elferink

Arne Wibe

Lars Pahlman

Lene H. Iversen

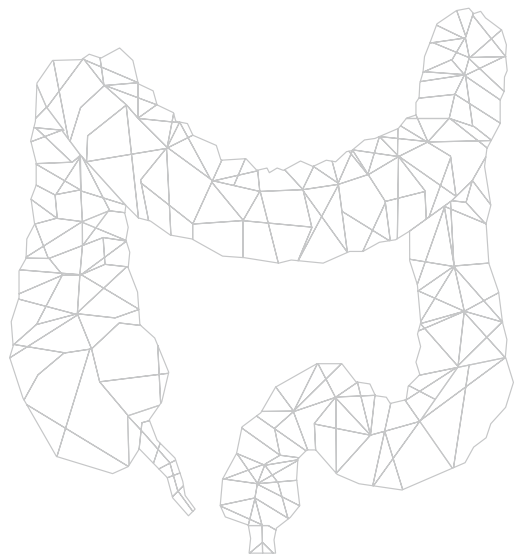
Freddy Penninckx

Vincenzo Valentini

Cornelis J.H. van de Velde

On behalf of the EURECCA consortium

Submitted for publication



ABSTRACT

Background

Several studies have shown remarkable differences in colorectal cancer survival across Europe. Most of these studies lacked information about stage and treatment. This study compared short term survival as well as differences in tumour stage and treatment strategies between five European countries: Norway, Sweden, Denmark, Belgium, and the Netherlands.

Methods

For this retrospective cohort study all patients aged 18 years or older with adenocarcinoma of the rectum without distant metastases and operated upon with a rectal resection from Norway, Sweden, Denmark, Belgium (PROCARE), and the Netherlands diagnosed in 2008 and 2009 were included. Differences in preoperative treatment between the countries were compared using univariate and multivariable logistic regression. One year univariate relative survival and one year multivariable relative excess risk (RER) were compared between the five countries.

Results

The use of preoperative short course radiotherapy and chemoradiation varied widely across the countries. The one year relative survival was significantly better for patients from Sweden compared with the Netherlands. When stratified for age groups, these differences were only present in the patients aged 75 years and older.

Conclusion

Large variation in the use of preoperative radiotherapy and chemoradiation was found between the countries. Even though, there was little variation in relative survival between the countries, except Sweden, which had a significant better one year RER among the elderly patients after adjustment. The differences in survival are expected to be caused by differences in perioperative care, selection of patients, and especially management of elderly patients. The effects of preoperative treatment are expected to be seen on long term follow-up.

INTRODUCTION

Several studies have shown remarkable differences in colorectal cancer survival across Europe.^{1,2} Although the mean European five year relative survival between 1995 and 1999 was 54.0%, it ranged from 38.8% to 59.9% between the countries.³ The variation in outcome could be explained by case mix variation, differences in socioeconomic status and variation in registration. More importantly, many countries have their own guidelines resulting in variation in treatment plans. Potentially easy modifiable factors could be stage at diagnosis (by screening) and treatment plans (by adjusting guidelines). Since the stage of disease at diagnosis is one of the most important prognostic factors, this should always be taken into account when comparing the survival of cancer patients. The differences in treatment strategies may lead to differences in survival.⁴⁻⁶ Currently, it is unknown which country has a better treatment strategy compared with the other countries.

In the last two decades clinical audits have been initiated in several European countries to improve the outcome of rectal cancer patients. These clinical audits have not only successfully identified best practice and underperforming hospitals, but also achieved amongst others, a rise in survival, nationally.⁷⁻⁹ However, variation in outcome between the European countries remains.¹⁰ The European REgistration of Cancer CAre (EURECCA) project was initiated by the European CanCer Organisation (ECCO) in order to decrease these differences and to improve cancer care through Europe.^{10,11} This project has the aim to generate the best care for all cancer patients by combining national audit structures.

Most of the previous studies concerning European survival differences lacked information about stage of disease and treatment strategies within countries and therefore, results should be interpreted with caution. The present study was undertaken to compare preoperative treatment of rectal cancer patients including the differences in tumour stage between five European countries included in the EURECCA-project: Norway (NO), Sweden (SE), Denmark (DK), Belgium (BE), and the Netherlands (NL). The five included countries had the data available, the data was accessible, and similar health care systems were present. Furthermore, short term survival (30 day and 1 year) will be compared. Variation in both preoperative treatment and survival are to be expected.

PATIENTS AND METHODS

Patients and follow-up

Patients with rectal cancer (ICD-10 C20) were extracted from national (clinical) cancer registries from NO (Norwegian Colorectal Cancer Registry), SE (Swedish Colorectal Cancer Registry), DK (Danish Colorectal Cancer Group database), BE (PROCARE) and the NL (Netherlands Cancer Registry). All of them were national clinical cancer registries, except NL, which was a national

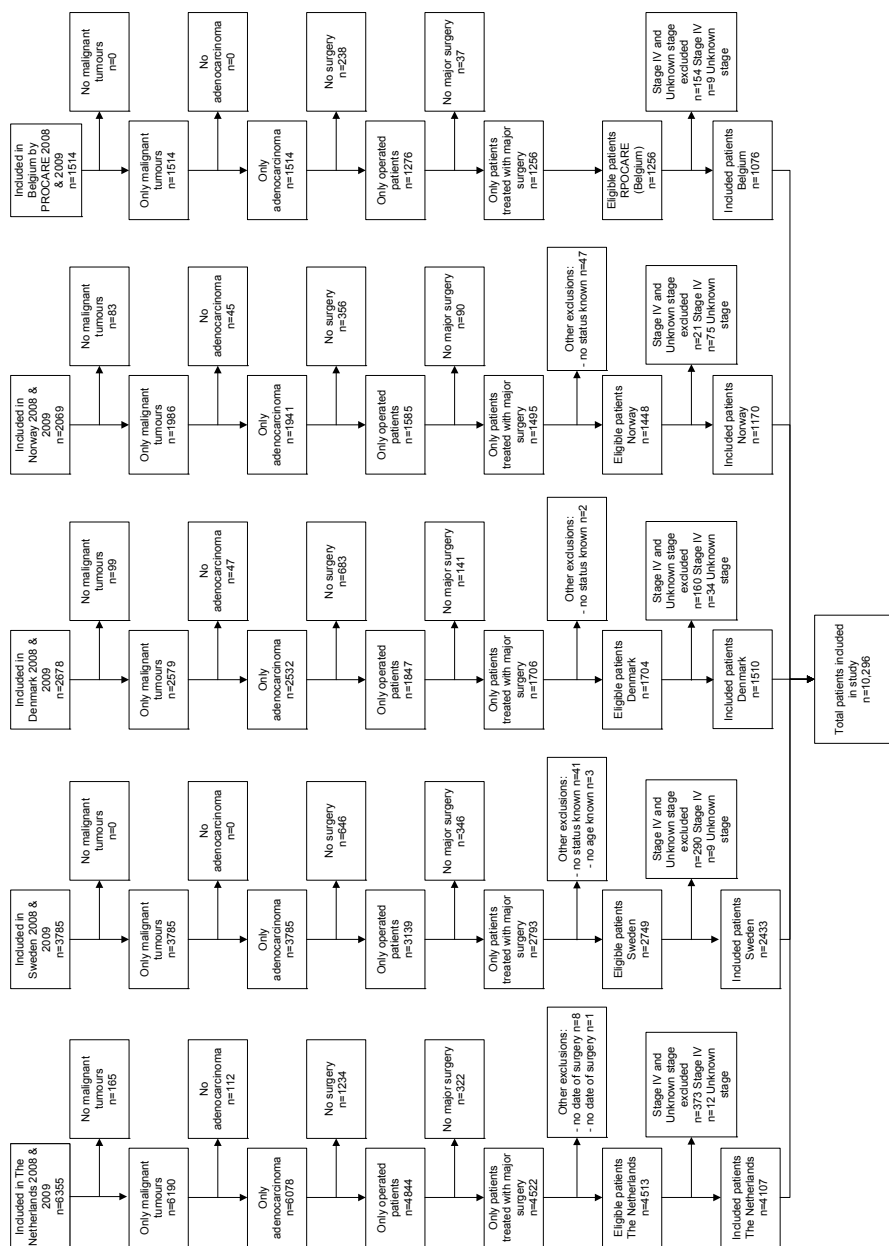


Figure 1: Flow chart of the inclusion of rectal cancer patients according to country

cancer registry. The inclusion criteria slightly differ among the countries; the Norwegian Colorectal Cancer Registry included all rectal cancer patients, the Swedish Colorectal Cancer Registry included only patients with an adenocarcinoma of the colon or rectum and no patients with premalignant tumours, the Danish Colorectal Cancer Group database included Danish patients (no residents of Greenland and Faroe Islands, nor foreigners without a civil registration number) aged 18 years and older, diagnosed at a surgical department, without metachronous colorectal cancer, the Netherlands Cancer Registry did not have any exclusion criteria, and in PROCARE the registration of patients was voluntary, besides, PROCARE only included patients with adenocarcinoma of the rectum and no premalignant tumours. From all countries patients diagnosed in 2008 and 2009 were included. Inclusion criteria in the present study were: patients aged 18 years and older with adenocarcinoma of the rectum without distant metastases, operated upon with a rectal resection (including Hartmann procedure, Low Anterior Resection, Abdominoperineal resection, and proctocolectomy with or without pouch construction), known age, stage of disease and treatment strategy, and a vital status known at date of follow-up (either date of death, or last date of linkage with the municipal or national population registries). All countries link their data with the municipal or national population registry. The last date of linkage was at least December 31st 2010, except for DK, which was November 25th 2010. The inclusion of patients is shown in the flowchart (figure 1). A total of 10,296 patients from the five countries were included in this study.

Tumour stage was based on pathology reports (pathological stage). In case pathological stage was not available, clinical stage was used. Clinical stage is based on the results of echoendoscopy and magnetic resonance imaging (MRI). If neither pathological nor clinical stage was registered, patients were defined as having an unknown stage and excluded. Clinical stage was not registered in Denmark. Preoperative treatment was divided into four groups: no preoperative treatment, preoperative radiotherapy, preoperative chemoradiation, and unknown treatment. Patients were categorized in three age groups (<65 years, 65-74 years, and ≥75 years).

Statistical analyses

Differences in the characteristics between the countries were calculated using a chi-squared test. Univariate and multivariable logistic regressions were performed to compare the use of preoperative treatment between the countries, and to compare the 30-day mortality between the countries. Follow-up was calculated from the day of surgery until death or the last day of follow-up. One year univariate relative survival analyses were made using the Hakulinen definition¹² as the ratio of the survival observed among the patients and the survival that would have been expected based on the corresponding (age, gender, and year) general population. National life tables were used to estimate expected survival. Expected survival was estimated with Ederer II method.¹³ With relative survival the excess mortality has been modelled, therefore, multivariable models can be estimated as Relative excess risks of death (RERs). RERs were

estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Multivariable analyses were adjusted for age (in one year groups, used as continuous variable in the model), gender, and stage. Follow-up was truncated at 30 days, or 1 year, respectively. Stratified multivariable RER analyses were performed for the three age groups. Sensitivity analyses have been performed, excluding BE from the analyses, to compare whether this would change the outcomes. In all analyses, a p-value of <0.05 was considered to be statistically significant.

RESULTS

Characteristics

In attachment 1, an overview of the trends in incidence and mortality of the included countries is presented. A total of 16,401 patients diagnosed with rectal cancer in 2008 and 2009 have been identified in the five clinical cancer registries. The median age of the patients was 67 years in NL, 70 years in SE, 70 years in DK, 70 years in NO, and 69 years in BE. About 20% of the patients from each country did not receive a resection of the tumour (NL 20.1%, SE 17.0%, DK 24.6%, NO 20.8%, and BE 17.0%). Non-resected patients were slightly older than the complete group; 71 years in NL, 75 years in SE, 75 years in DK, 77 years in NO, and 73 years in BE.

A total of 10,296 patients from the five countries were included in this study. Table 1 shows the characteristics. The country with the highest number of included patients was NL with 4107 (38.9%), followed by SE with 2433 patients, 1510 patients from DK, 1170 from NO, and the remaining 1076 from BE. Patients from NL had a younger age when compared to the patients of the other countries ($p<0.001$). No difference in gender distribution was found between the five countries. Both the clinical and the pathological stage distribution differed between the countries ($p<0.001$ for both), the differences for pathological stage remained statistically significant when patients with no residual tumour (ypT0 after preoperative treatment) was excluded ($p<0.001$).

Preoperative treatment

All countries used preoperative treatment, either radiotherapy or chemoradiation, for rectal cancer patients. However, in DK 71.5% of the patients did not receive any preoperative treatment, compared to 69.3% in NO, 33.4% in BE, 33.1% in SE, and 14.2% in NL ($p<0.001$) (table 1).

Overall, the proportion of patients receiving preoperative radiotherapy varied by country ($p<0.001$), with NL and SE reporting high rates of radiotherapy (52.8% and 52.3%, respectively). BE, NO, and DK had low rates (14.7%, 9.7%, and 5.6%, respectively) (table 1).

Table 1: Characteristics of the rectal cancer patients included stratified by country

	The Netherlands		Sweden		Denmark		Norway		Belgium		p-value
	N	%	N	%	N	%	N	%	N	%	
Age group											<0.001
<65 years	1782	43.4	801	32.9	538	35.6	446	38.1	414	38.5	
65-74 years	1310	31.9	822	33.8	525	34.8	329	28.1	317	29.4	
≥75 years	1015	24.7	810	33.3	447	29.6	395	33.8	345	32.1	
Gender											0.4
Male	2520	61.4	1457	59.9	916	60.7	684	58.5	648	60.2	
Female	1587	38.6	976	40.1	594	39.3	486	41.5	428	39.8	<0.001
Clinical stage											
I	689	16.8	551	22.7			235	20.1	182	16.9	
II	1154	28.1	811	33.3			272	23.2	212	19.7	
III	1058	25.8	730	30.0			406	34.7	644	59.9	<0.001
Unknown	1206	29.4	341	14.0			257	22.0	38	3.5	
Preoperative treatment											
None	583	14.2	805	33.1	1079	71.5	810	69.3	360	33.4	<0.001
Radiotherapy	2168	52.8	1273	52.3	84	5.6	114	9.7	158	14.7	
Chemoradiation	1356	33.0	346	14.2	338	22.4	246	21.0	558	51.9	
Unknown/other	0	0	9	0.4	9	0.5	0	0	0	0	
Pathological stage											<0.001
No residual tumour	245	6.0	59	2.4	0	0.0	0	0.0	124	11.5	
I	1276	31.1	668	27.5	426	28.2	385	32.9	315	29.3	
II	1126	27.4	752	30.9	561	37.2	372	31.8	266	24.7	
III	1338	32.6	929	38.2	523	34.6	334	28.6	300	27.9	
Unknown	122	2.9	25	1.0	0	0.0	79	6.7	71	6.6	
Total	4107	39.8	2433	23.6	1510	14.7	1170	11.4	1076	10.5	



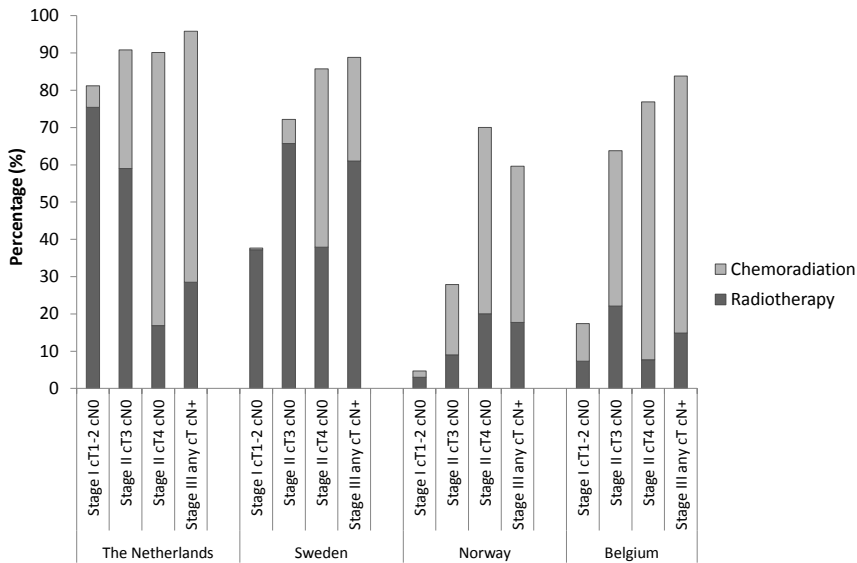


Figure 2: The use of preoperative treatment per country organised by clinical stage

Figure 2 shows the use of radiotherapy for each country organized by clinical stage. In NL radiotherapy is applied in a high amount for every stage (decreasing from 75.4% at stage I, to 28.5% at stage III), while the use of radiotherapy varied among the stages in SE (stage I 37.2%, stage II cT3 cN0 65.70.2%, stage II cT4 cN0 37.9%, and stage III 61.0%). The use of preoperative radiotherapy was low in NO (from 3.0% in stage I to 17.7% in stage III). In BE the administration of radiotherapy alone is not very common, except for clinical stage II cT3 cN0, where 22.1% of the patients received preoperative radiotherapy.

Stratified for age group (see figure 3), NL, BE, NO, and DK used preoperative radiotherapy alone more frequently with increasing age: 47.8% of patients aged <65 years received radiotherapy in NL, 10.6% in BE, in NO 9.2%, and in DK 4.1%; when the patients were aged ≥75 years, they received radiotherapy in 61.1% of the patients in NL, 19.7% of the cases in BE, in 9.6% of the cases in NO, and in 7.4% of the cases in DK. In SE this percentage was more stable and high over the age groups: it changed from 53.1% to 46.8%. For DK, BE, and NL the differences in the use of radiotherapy between patients <65 years and patients ≥75 years remained after adjustment for gender and stage (OR 1.85; $p=0.03$ for DK, OR 1.95; $p=0.002$ for BE, and OR 1.62; $p<0.001$ for NL). In NO the use of radiotherapy remained stable with increasing age after adjustment (OR 1.00; $p=0.9$). In SE the use of radiotherapy decreased with increasing age (OR 0.79; $p=0.02$).

Overall, BE had the highest usage of chemoradiation (51.9%), followed by NL (33.0%), DK (22.4%), and NO (21.0%). SE used preoperative chemoradiation the least often (14.2%)(table 1). Figure 2 also shows the proportion of patients that received chemoradiation in each country stratified for clinical stage. The proportion of patients receiving chemoradiation increased

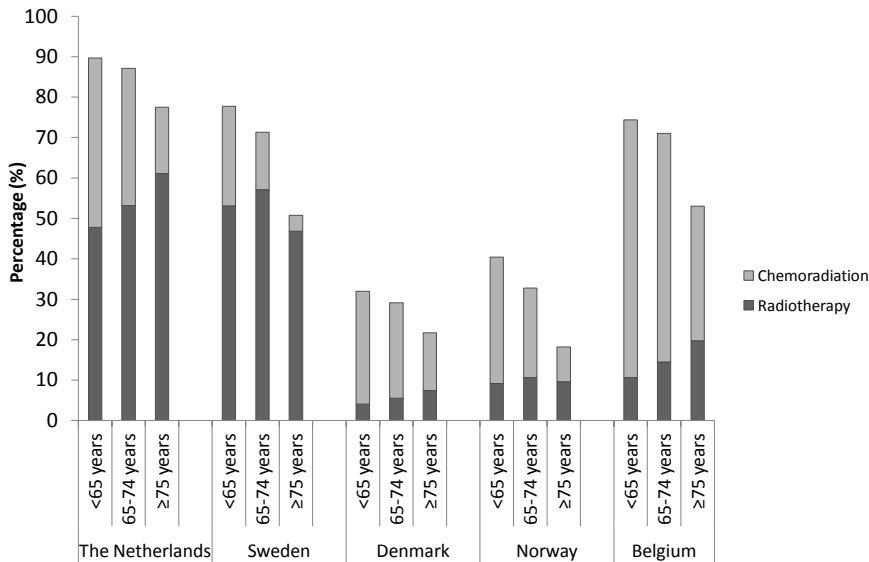


Figure 3: The use of preoperative treatment per country organised by age group

with higher clinical stages in each country, whereas stage II cT4 cN0 was treated comparable with stage III.

As shown in figure 3, stratified for age group, less chemoradiation was administered with increasing age for all countries ($p < 0.001$ for each country). In DK and SE it decreased from 27.9% and 24.6% in patients aged <65 years to 14.3% and 4.0% in patients aged ≥75 years, respectively. In NL and NO 41.9% and 31.2% of the patients aged <65 years received chemoradiation, while 16.4% and 8.6% of the patients ≥75 years received chemoradiation, respectively. In BE the percentage decreased from 63.8% to 33.3%. After adjustment for gender and stage, the use of chemoradiation remained decreased with increasing age group for each of the countries (OR 0.28; $p < 0.001$ for NL, OR 0.13; $p < 0.001$ for SE, OR 0.43; $p < 0.001$ for DK, OR 0.21; $p < 0.001$ for NO, and OR 0.30; $p < 0.001$ for BE).

Survival

The 30-day mortality rate was 2.5% in NL, 1.9% in SE, 3.0% in DK, 1.7% in NO, and 1.5% in BE, which did not differ significantly between the countries ($p = 0.08$). After adjustment for age, gender, and stage, SE, NO, and BE had a significant lower 30-day mortality rate as compared to NL (OR 0.58; 95%CI 0.41-0.83; $p = 0.003$, OR 0.53; 95% CI 0.32-0.87; $p = 0.012$, OR 0.52; 95% CI 0.30-0.89; $p = 0.017$, respectively). Whereas the 30-day mortality was comparable between DK and NL (OR 0.99; 95%CI 0.69-1.43; $p = 0.9$).

In figure 4 the relative survival according to country is shown. The relative survival at one year varied little between the countries: in NL one year relative survival was 95.6%, in SE 96.1%, in DK 95.0%, in NO 96.4%, and in BE 96.8%, which was not significant different ($p = 0.3$). After

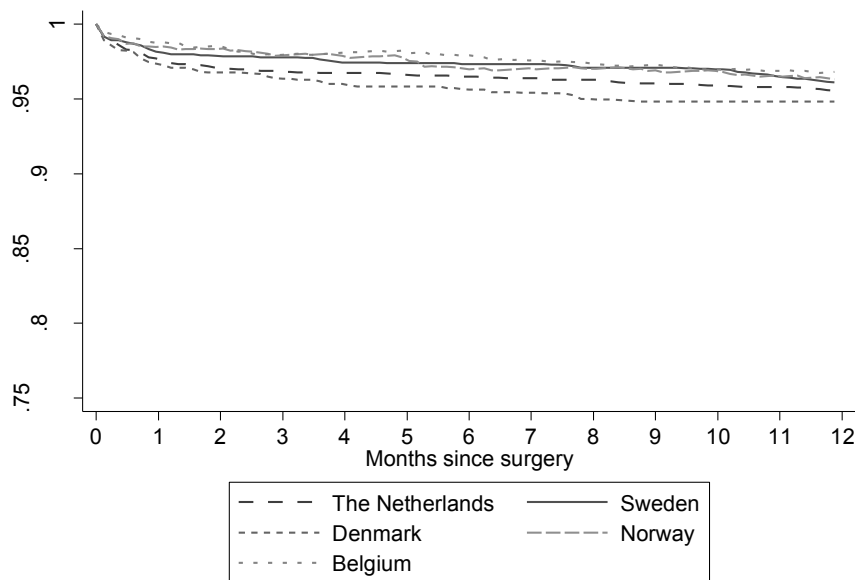


Figure 4: Graphic depiction of one year relative survival by country

adjustment, SE had a significantly better relative survival at one year compared with NL (RER 0.66; 95% CI 0.49-0.89; $p=0.007$) (table 2).

When stratified for age group, the differences in survival, adjusted for age, gender, and stage, between the countries were only present in the patients aged 75 years and older (table 2). SE had a significant better one year relative survival (RER 0.61; 95% CI 0.41-0.90; $p=0.013$) compared with NL.

The sensitivity analyses did not show differences.

DISCUSSION

Major findings in this study were the large differences in the proportion of patients receiving preoperative radiotherapy or chemoradiation between the countries. The one year relative survival was significantly better for patients from SE as compared to NL. When stratified for age groups, the differences in multivariable relative survival were only present in the patients aged 75 years and older.

Patients from NL were younger in comparison with other countries. When the datasets were compared without the selection criteria and therefore including all patients, the median age of the patients remained younger in the Netherlands (67 years in NL, 69 years in BE, and 70 years in NO, SE, and DK). Table 1 also shows that the lower age of diagnosis is not accompanied by

Table 2: One-year multivariable* RER as compared to the Netherlands

	All ages				<65 years				65-75 years				≥75 years			
	RER	95% CI	p-value	reference	RER	95% CI	p-value	reference	RER	95% CI	p-value	reference	RER	95% CI	p-value	reference
The Netherlands	1				1				1				1			
Sweden	0.66	0.49-0.89	0.007		0.50	0.22-1.15	0.1		0.80	0.42-1.53	0.5		0.61	0.41-0.90	0.01	
Denmark	0.94	0.69-1.28	0.7		0.95	0.46-1.94	0.9		1.39	0.77-2.49	0.3		0.78	0.51-1.20	0.3	
Norway	0.68	0.46-1.02	0.06		0.92	0.42-2.04	0.8		0.62	0.22-1.77	0.4		0.61	0.36-1.03	0.06	
Belgium	0.66	0.42-1.03	0.07		0.55	0.18-1.74	0.3		0.59	0.21-1.69	0.3		0.66	0.38-1.13	0.1	

* Adjusted for age, gender, and stage



lower stage at diagnosis, as would be expected if the difference would be a result of screening. Brenner et al. have reported the age distribution in several European registries for colorectal cancer.¹⁴ Compared to NO and SE, less elderly patients from NL were included in this study. A possible explanation could be that the Dutch population is younger compared to the other countries, which is shown by Eurostat.¹⁵ Another possibility is that the age distribution for rectal cancer within the countries was different, resulting in less elderly patients within NL as compared to SE, DK, NO, and BE, supported by the evidence from the ECO-website (European Statistics by the European Commission).¹⁶

The variation in the administration of both radiotherapy and chemoradiation is striking, as in DK less than 30% of the patients were treated preoperatively, in NL, on the other hand, over 85% of patients received preoperative treatment. In BE, DK and NO preoperative chemoradiation was preferred, while in NL and SE preoperative radiotherapy was mostly administered. Besides variation in treatment, also variations between the guidelines are present (attachment 2). An interesting research proposal would be to compare whether the (preoperative) treatment given by each of the countries was in accordance to the guidelines. Unfortunately, detailed information is needed, such as distance from the anal verge and threatened mesorectal fascia, are often not registered. Including these variables by the registries would make a comparison of the guideline adherence, including a comparison of the outcome of these treatment strategies, possible.

Although the results of the analyses showed that NO uses both radiotherapy alone and chemoradiation as preoperative treatment, this might be a flaw in the registration manner. Norwegian guidelines advise the use of chemoradiation as preoperative treatment. Since all guidelines are evidence-based, variation was expected to be minimal. However, it seems that the same literature can be interpreted in different ways. Besides, the difference in time of development of the guidelines could be another explanation. The Dutch and the Swedish guidelines are relatively old, and arise from the results of the Dutch TME-trial, in which the patients were randomised between total mesorectal excision (TME) surgery with and without preoperative radiotherapy.¹⁷ Since during that trial, MRI staging was not standard, preoperative staging was less accurate. Nowadays, MRI staging is widely incorporated in all five countries included. Recently, the Mercury trial has shown that with MRI staging, T3 and NO patients should not always receive preoperative treatment.¹⁸ This suggests that overtreatment was present based on the knowledge we have today in a high percentage of the patients included in the current study. Indications on overtreatment were also found in the most recent results from the TME-trial.¹⁹ Van Gijn et al. showed that preoperative radiotherapy significantly improved the cancer-specific survival in patients operated with a negative circumferential resection margin, but this benefit was offset by an increase in other causes of death, resulting in an equal overall survival compared with surgery alone. Similar data has been found in Sweden before the TME-era, indicating that radiotherapy can harm.²⁰

The wide-ranging variation in preoperative treatment could have an effect on short- and long term survival. Unadjusted survival did not differ significantly between the countries. After adjustment for age, gender, and stage, SE, NO, and BE had lower 30-day mortality as compared to NL. It has been shown before that DK has an inferior short term survival as compared to other European countries.^{21,22} SE had a significant better one year RER as compared to NL, after adjustment for several confounders. It is known that SE in general has a high quality health care with nationwide quality assurance programs, which might have contributed to the current results in short term survival.²³ But, the health care structure of SE is comparable with NO and DE. Another explanation could be the use of tobacco and alcohol.

As preoperative treatment is expected to have an effect on both the curative resection as well as on disease recurrence, it is expected to find the effects of the differences in treatment on recurrence and therefore, long term survival.²⁴ Unfortunately, long term survival was not available at the time of the study for these incidence years. Although, it is difficult to distinguish between the effect of perioperative care (defined as the general care before, during, and after surgery, such as treatment of comorbidities, fast-track regimens, and anaesthesiologic care) and the effect of preoperative treatment on survival, it is to be expected that perioperative care will probably result in survival differences within one year, since recurrences rarely occur within the first postoperative year. Patients who die within the first postoperative year are most likely to die because of non-cancer related disease. Differences found at conditional five year survival (under the condition of surviving the first postoperative year) will probably be due to preoperative and postoperative treatment, such as radiotherapy, chemoradiation, and chemotherapy, and quality of surgery.²⁵ The present study showed that the differences found in multivariable RER, when stratified according to age group, was only present in the group of patients aged 75 years and older. Elderly patients are a heterogeneous group of patients, which might vary among the countries due to differences in selection of patient which will be assessed fit enough for certain treatments as well as differences in perioperative approach. Therefore, the differences found in RER adjusted for several confounders in the current study between the countries in elderly patients are probably more related to differences in surgery, perioperative care, and differences in fitness of the elderly patients at time of surgery rather than to preoperative treatment. Unfortunately, information on perioperative care and fitness of the patients was not available in the present study. Nevertheless, at one year differences in survival between the countries can already be found, suggesting that survival can be improved in all countries.

Long term follow-up is vital, since it could show whether differences in treatment strategies also result in survival benefit. Currently, within the EURECCA consortium is ongoing on the differences in survival between the countries for the elderly patients persist in long term survival. Furthermore, the administration of adjuvant chemotherapy in rectal cancer patients is being investigated. Possibly, due to the shorter life expectancy of elderly patients, the decrease in (local) recurrences of due to preoperative radiotherapy and chemoradiation should be

carefully weighed against the treatment-related morbidity and mortality caused. One of the goals of the EURECCA consortium is to define multidisciplinary European guidelines for the treatment of colorectal cancer. During a consensus meeting in December 2012, the experts from all disciplines involved in the care for patients with colon and rectal cancer used the Delphi method in order to develop diagnostic and treatment algorithms, as a first initiative to achieve multidisciplinary European guidelines.²⁶

Strengths and limitations

Several limitations are present in this study. Unknown is to what extent the differences in characteristics are caused by time of diagnoses, leading to differences in stage at diagnosis, by variation in case-mix, especially comorbidities, and by registration. In the case of NL, patients are defined as clinical unknown stage when no MRI is available. Besides, DK did not register preoperative (clinical) TNM stage, and neither collected information about patients without residual tumour postoperatively (ypT0). But since DK had a very low administration of preoperative treatment, large differences in clinical and pathological TNM stage would not be expected. The use of staging by MRI is widely used in all five countries, which made preoperative staging more reliable. Differences in administration of preoperative treatment and survival could be partly explained by differences in performance status and comorbidities. Unfortunately, these case-mix variables were not available in this study.

Another limitation is the selection bias probably present in the PROCARE database, which is based on voluntary participation of both hospitals and clinicians. That the group of patients in PROCARE indeed is better as compared to all patients within Belgium is shown when comparing the results of PROCARE with the Belgium Cancer Registry. The median age nationally was slightly higher (70 years as compared to 69 in PROCARE) and patients from PROCARE were less often diagnosed with stage IV (15.2% in the Belgium Cancer Registry, as compared to 12.6% in PROCARE). Even though, we have chosen to include these patients in the present manuscript, since PROCARE is an important initiative and should therefore be stimulated. Recently, the Belgium government has decided that PROCARE is indeed very important, and in the next one and a half year, it should become mandatory to participate for all hospitals including all patients in Belgium. On the other hand, we understand that the voluntary base of PROCARE at this moment might induce bias. We have performed sensitivity analyses, which did not resulted in changes in the outcome of the results overall.

The strength of the current study is the large number of patients included in this study, with detailed information. To our knowledge this is the first study comparing five countries with detailed information on both rectal cancer treatment. All registries except for Belgium are national (clinical) cancer registries, with an estimated inclusion of over 95% of cases. For Belgium, a registration bias cannot be excluded since registration was based on voluntary participation.

CONCLUSION

A large variation in administration of preoperative treatment has been found between NO, SE, DK, BE, and NL. After adjustment for age, gender, and stage, Sweden had a significant better relative survival for patients aged ≥ 75 years at one year compared to the Netherlands. The differences in one year relative survival are expected to be caused by differences in perioperative care, selection of patients, and fitness of elderly patients. By comparing these items between the countries, which will be a next step of the EURECCA-project, differences in survival of elderly patients could be elucidated. To properly investigate this, randomized controlled trials (RCT's) may be considered. RCT's, however, are costly and time consuming and will not yield practice changing results within years from the start. Furthermore, older patients are underrepresented if not excluded from RCT's. International comparison of specific treatment protocols could serve as a good alternative to select 'best practices' and improve the risk/benefit ratio in the treatment of rectal cancer patients. This comparative effectiveness research can bridge the knowledge gap specifically in older cancer patients, who are by nature, heterogeneous in patient characteristics and treatment patterns.²⁷

ACKNOWLEDGEMENTS

This study was funded by European CanCer Organisation (ECCO), European Society of Surgical Oncology (ESSO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Medical Oncology (ESMO). There has been no role of the sponsors in the study design, in the collection, analysis, and interpretation of data, in writing the manuscript, or in the decision to submit the manuscript for publication.

REFERENCE LIST

- 1 Gatta G, Zigon G, Aareleid T et al. Patterns of care for European colorectal cancer patients diagnosed 1996-1998: a EURO CARE high resolution study. *Acta Oncol* 2010; **49**: 776-83.
- 2 Morris EJ, Sandin F, Lambert PC et al. A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. *Gut* 2011; **60**: 1087-93.
- 3 Sant M, Allemani C, Santaquilani M et al. EURO CARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; **45**: 931-91.
- 4 Ciccolallo L, Capocaccia R, Coleman MP et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut* 2005; **54**: 268-73.
- 5 Gatta G, Capocaccia R, Sant M et al. Understanding variations in survival for colorectal cancer in Europe: a EURO CARE high resolution study. *Gut* 2000; **47**: 533-8.
- 6 Thomson CS, Forman D. Cancer survival in England and the influence of early diagnosis: what can we learn from recent EURO CARE results? *Br J Cancer* 2009; **101 Suppl 2**: S102-S109.
- 7 Pahlman L, Bohe M, Cedermark B et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**: 1285-92.
- 8 Wibe A, Moller B, Norstein J et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; **45**: 857-66.
- 9 Bulow S. Improved survival after rectal cancer in Denmark. 2010.
- 10 van Gijn W., van de Velde CJ. Improving quality of cancer care through surgical audit. *Eur J Surg Oncol* 2010; **36 Suppl 1**: S23-S26.
- 11 van Gijn W., van den Broek CB, Mroczkowski P et al. The EURECCA project: Data items scored by European colorectal cancer audit registries. *Eur J Surg Oncol* 2012; **38**: 467-71.
- 12 Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comput Programs Biomed* 1985; **19**: 197-207.
- 13 Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. *Eur J Cancer* 2011; **47**: 2202-10.
- 14 Brenner H, Bouvier AM, Foschi R et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: The EURO CARE study. *Int J Cancer* 2011.
- 15 European Statistics by the European Commission <http://epp.eurostat.ec.europa.eu> (accessed July 30 2013).
- 16 European Cancer Observatory <http://eu-cancer.iarc.fr/> (accessed July 30 2013).
- 17 Kapiteijn E, Kranenbarg EK, Steup WH et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. *Eur J Surg* 1999; **165**: 410-20.
- 18 Taylor FG, Quirke P, Heald RJ et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. *Ann Surg* 2011; **253**: 711-9.
- 19 van Gijn W., Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
- 20 Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. *J Clin Oncol* 2005; **23**: 6126-31.
- 21 Engholm G, Kejs AM, Brewster DH et al. Colorectal cancer survival in the Nordic countries and the United Kingdom: excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000. *Int J Cancer* 2007; **121**: 1115-22.
- 22 Folkesson J, Engholm G, Ehrnrooth E et al. Rectal cancer survival in the Nordic coun-

- tries and Scotland. *Int J Cancer* 2009; **125**: 2406-12.
- 23 Socialstyrelsen. *Nationella riktlinjer för bröst-, kolorektal- och prostatacancer - Beslutsstöd för prioriteringar* 2007.
 - 24 Wong RK, Tandan V, De SS, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev* 2007; CD002102.
 - 25 Dekker JW, van den Broek CB, Bastiaannet E et al. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**: 1533-9.
 - 26 van de Velde CJ, Aristei C, Boelens PG et al. EURECCA colorectal: Multidisciplinary Mission statement on better care for patients with colon and rectal cancer in Europe. *Eur J Cancer* 2013; **49**: 2784-2790.
 - 27 Hsiao FY, Mullins CD, Onukwughu E, Pandya N, Hanna N. Comparative effectiveness of different chemotherapeutic regimens on survival of people aged 66 and older with stage III colon cancer: a "real world" analysis using Surveillance, Epidemiology, and End Results-Medicare data. *J Am Geriatr Soc* 2011; **59**: 1717-23.

Attachment 1: Trends in incidence and mortality of the included countries

		Incidence (ESR)				Mortality (ESR)			
		Men	Women	Trend over time (incidence from 2000-2007†)		Men	Women	Trend over time (mortality from 2000-2007‡)	
				Men	Women			Men	Women
The Netherlands	2008	22.3	12.3	↑(18.9)	↑(10.9)	5.8	2.9	=(5.8)	=(3.1)
	2009	22.2	12.7			5.9	3.2		
Denmark	2008	27.1	17.0	=(27.1)	=(16.9)	10.0	5.9	↓(10.4)	↓(6.1)
	2009	27.2	15.9			9.4	5.1		
Sweden	2008	19.1	12.8	=(19.3)	=(12.7)	7.5	4.3	=(7.2)	=(4.4)
	2009	19.7	12.6			7.1	4.4		
Belgium	2008	22.3	12.0	↑(21.2)	=(11.6)	4.1	2.0	↓(4.7)	↓(2.3)
	2009	22.0	11.1			NA	NA		
Norway	2008	24.9	16.8	=(25.9)	=17.0	7.6	4.4	↓(9.7)	↓(5.7)
	2009	26.8	17.2			7.8	4.1		

ESR: European Standardised rates

NA: Not applicable, no information available

† The incidence rates of 2000 until 2007 for each country, except for Belgium, they are 2004 until 2007

‡ The mortality rates of 2000 until 2007 for each country, except for Belgium, they are 2004 until 2006

Attachment 2: Guidelines for rectal cancer treatment per country

Country	Guidelines
The Netherlands	T1 N0: Only TME surgery. T2-4: Preoperative radiotherapy followed by TME surgery. <i>In case of high, small tumours, there might be chosen not to give preoperative radiotherapy.</i> <i>In case of positive circumferential resection margin (CRM) or more than 4 lymph nodes positive, there might be chosen for preoperative chemoradiation.</i> <i>There are no indications for adjuvant chemotherapy.</i>
Sweden	T1-3a/b N0-1: No preoperative treatment, only TME surgery T3c/d N1-2: In case of no involved margins, preoperative short course T3-4 any N: radiotherapy is indicated, followed by TME surgery. With compromised margins preoperative chemoradiation is indicated followed by TME surgery. <i>There are no indications for adjuvant chemotherapy, although several medical oncologists do prescribe adjuvant chemotherapy.</i>
Denmark	T1-2: Low (≤ 5 cm from the anal verge), mid (5-10 cm from the anal verge), and high (11-15 cm from the anal verge) tumours receive no preoperative treatment. Low and mid tumours receive TME surgery, while high tumours receive PME surgery. T3: Low and mid (CRM ≤ 5 mm) tumours receive preoperative chemoradiation, mid (CRM > 5 mm) and high tumours receive no preoperative treatment. T4: Low and mid tumours receive preoperative chemoradiation, while high tumours receive no preoperative treatment. <i>In selected cases preoperative radiotherapy and postoperative chemotherapy might be administered.</i>
Norway	T1-2 N0: No preoperative treatment, only TME surgery. T3: < 3 mm from the CRM preoperative chemoradiation, in case of > 3 mm from the CRM, no preoperative treatment. Followed by TME surgery. T4 or N+ outside the mesorectum: Preoperative chemoradiation followed by TME surgery. <i>Short course preoperative radiotherapy might be an alternative for old and fragile patients. In case of no preoperative treatment and perforation of the tumour or postoperative CRM ≤ 1 mm, postoperative chemoradiation is indicated. There are no indications for adjuvant chemotherapy.</i>
Belgium	T1-2 N0: No preoperative treatment, only TME surgery T3: Low tumour (≤ 5 cm from the anal verge) preoperative chemoradiation, mid and high tumours (5.1-15 cm from the anal verge) short course preoperative radiotherapy, or when the CRM < 2 mm preoperative chemoradiation followed by TME surgery. T4 or N+: Preoperative chemoradiation followed by TME surgery. <i>In case of postoperative stage of II or III adjuvant chemotherapy is advised (or a combination of chemoradiation with chemotherapy in case when patients did not receive preoperative treatment).</i>

Chapter 9

A comparison of high dose rate endorectal brachytherapy, short course radiotherapy and chemoradiation on the outcome of rectal cancer patients

Colette B.M. van den Broek

Thomas A. Vermeer

Té Vuong

Esther Bastiaannet

Laurent Azoulay

Olaf M. Dekkers

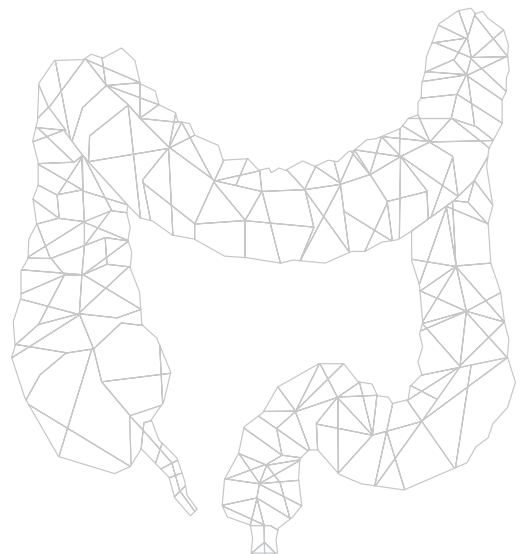
Tamim Niazi

Hetty A. van den Berg

Harm J.T. Rutten

Cornelis J.H. van de Velde

Submitted for publication



ABSTRACT

Background

Short course external beam radiotherapy decreases local recurrences in patients with rectal cancer. However, improvements should be weighed against treatment-related morbidity. The present study compared long term outcome in rectal cancer patients treated with either pre-operative short course radiotherapy (5×5 Gy) or chemoradiotherapy (CRT) in the Netherlands and a new treatment with possibly less side-effects, high dose rate endorectal brachytherapy (HDREBT), in Canada.

Methods

In total, 134 patients treated with preoperative 5×5 Gy radiotherapy (n=52) or CRT (n=82), and 141 patients treated with preoperative HDREBT (26 Gy over 4 days) were included. Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidence intervals (CIs) adjusted for potential confounders between the countries. Endpoint was five year overall survival. Besides, competing-risks regression models were used to assess Sub Hazard Ratios (SHR) for local recurrence and cancer-specific mortality between the treatment strategies, with death as competing risk.

Results

A statistically significant reduction of five year overall survival was observed in patients treated with HDREBT, compared to patients treated with 5×5 Gy or CRT (HR 0.42, 95% CI 0.20-0.90, p=0.03). With death as competing risk, the SHR for five year local recurrence was 0.56 (95% CI 0.14-2.30, p=0.42), and the SHR for five year cancer-specific mortality was 0.60 (95% CI 0.17-2.16, p=0.44).

Conclusion

In the present study, no significant differences in local recurrence and cancer-specific mortality were observed. However, superior overall survival was observed for patients treated with HDREBT, possibly due to lower treatment-related toxicities. This finding needs to be formally tested in randomized controlled trials.

INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second in women worldwide.¹ Approximately one third of these malignancies occur in the rectum, making the global rectal cancer incidence approximately 400,000/year.¹

In the past two decades, several improvements in rectal cancer treatment have been achieved. Whereas five year local recurrence rates were up to 27% until the beginning of the nineties after surgery², the introduction of total mesorectal excision (TME) decreased five year local recurrence rates to 5-11%³⁻⁵. The TME-trial showed that the addition of preoperative external beam irradiation further decreased these rates to 5.6%.⁵ However, the improvement in local control should be weighed against the risk of side-effects due to short-course external beam irradiation.^{6,7} Acute as well as late side-effects occur, including more postoperative complications (48% in patients treated with preoperative short-course radiotherapy (RT) versus 41% in patients not treated with RT⁸, and more faecal incontinence after five years (62% versus 38%, respectively)^{8,9}.

In an attempt to reduce treatment-related toxicity, high dose rate endorectal brachytherapy (HDREBT) has been explored as a neoadjuvant treatment in patients with resectable rectal cancer.¹⁰⁻¹⁵ The five year local recurrence rate was 5% and toxicity patterns seemed to be favourable as compared to external beam.^{10,15} Importantly, to our knowledge, no studies (either randomized or observational) have compared the long term effects of these therapies. Given these findings, the objective of this study is to compare the overall survival, cancer-specific mortality, and local recurrence in patients with clinical T3 rectal cancer treated with either short term preoperative radiotherapy or chemoradiotherapy (CRT) in the Netherlands, to HDREBT as routinely used in Canada.

PATIENTS AND METHODS

Patients

All patients included in the current study had clinical T3 (cT3) rectal cancer based on MR Imaging. From the Catharina Hospital in the Netherlands, 134 consecutive patients with cT3 rectal cancer based on MR Imaging were included, 52 were treated with short-course radiotherapy (5×5 Gy) followed by TME surgery, while the remaining 82 were preoperatively treated with long-course radiotherapy 25×1.8-2 Gy combined with chemotherapy followed by TME surgery. From the Jewish General hospital and McGill University Health Center in Canada, 141 consecutive patients were included. All these patients were treated with preoperative HDREBT with a daily dose of 6.5 Gy during 4 days, followed by TME surgery after 4-8 weeks. Included patients from both hospitals were surgically treated between 2005 and 2010.

According to the Dutch rectal cancer treatment guidelines, cT3 patients should receive pre-operative short-course radiotherapy. When the circumferential margin (CRM) is threatened or patients have N2 disease, patients should receive a combination of long-course radiotherapy and chemotherapy (CRT).¹⁶ Patients included from Canada received HDREBT.

None of the included patients had distant metastases at the time of diagnosis. TME surgery was performed to all patients. Age, gender, clinical N-stage, pathological T-stage, pathological N-stage, and year of surgery were collected from all the included patients. Patients were divided into three age groups (<65 years, 65-74 years, and ≥75 years).

Follow-up was measured from date of surgery to last date of follow-up or date of death, or to the date of local recurrence. The primary outcome was death from any cause. The secondary outcomes were local recurrence, regardless of the status of the systemic disease, and cancer-specific mortality. Local recurrence was defined as evidence of tumour within the pelvic or perineal area, confirmed by imaging or pathology. Cancer-specific mortality was defined as death due to rectal cancer, as defined by the treating physician. As an additional secondary analysis, the overall survival of the Dutch patients treated with either 5×5 Gy or CRT was compared.

Statistical analyses

Descriptive statistics were used to describe the characteristics of the patients from the Netherlands treated with 5×5 Gy or CRT, and Canada treated with HDREBT. Kaplan-Meier curves were constructed comparing overall survival between the countries. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the overall survival when comparing the countries. All models were adjusted for age (as a continuous variable), gender, cN-stage, and year of surgery. Competing-risks regression models were used to assess Sub Hazard Ratios (SHR) for local recurrence and cancer-specific mortality between the treatment strategies, with death as competing risk.¹⁷ Statistical significance was defined as $p < 0.05$. All analyses were performed with STATA 12.

RESULTS

A total of 275 patients with cT3 rectal cancer were included. Table 1 shows the characteristics of included patients. No significant differences between patients treated with 5×5 Gy or CRT, and treated with HDREBT were present, except clinical N-stage (cN-stage), in which patients treated with 5×5 Gy or CRT had more often signs of lymph node metastasis. In the Netherlands, elderly patients were more likely to have received 5×5 Gy than chemoradiotherapy in line with current clinical guidelines. Besides, elderly patients are more often female.

Table 2 shows the postoperative T and N (pT and pN) staging per country. Patients treated with HDREBT had lower pT stages as compared with patients treated with 5×5 Gy or CRT ($p < 0.001$),

Table 1: Characteristics of the included population

	The Netherlands Number	%	Canada Number	%	p-value
Age					0.64
<65 years	65	48.5	68	48.2	
65-74 years	45	33.6	42	29.8	
≥75 years	24	17.9	31	22.0	
Gender					0.35
Male	90	67.2	102	72.3	
Female	44	32.8	39	27.7	
Clinical T-stage					
cT3	134	100.0	141	100.0	
Clinical N-stage					0.04
Negative	65	48.5	90	63.8	
Positive	66	49.3	49	34.8	
Unknown	3	2.2	2	1.4	
Year of surgery					0.33
2005	22	16.4	25	17.7	
2006	16	12.0	28	19.9	
2007	29	21.6	23	16.3	
2008	28	20.9	20	14.2	
2009	24	17.9	29	20.6	
2010	15	11.2	16	11.3	
Total	134	48.7	141	51.3	

Table 2: Postoperative T-stage and N-stage

	The Netherlands Number	%	Canada Number	%	p-value
Pathological T-stage					<0.001
ypT0	15	11.2	45	31.9	
1	4	3.0	13	9.2	
2	37	27.6	42	29.8	
3	72	53.7	39	27.7	
4	2	1.5	2	1.4	
Unknown	4	3.0	0	0.0	
Pathological N-stage					0.11
0	83	61.9	103	73.1	
1	36	26.9	24	17.0	
2	15	11.2	14	9.9	
Total	134	48.7	141	51.3	

with a higher percentage of pathological complete responses (ypT0) (11.2% in patients treated with 5×5 Gy or CRT, as compared with 31.9% in patients treated with HDREBT) and fewer pathological T3-stage (53.7% patients treated with 5×5 Gy or CRT, 27.7% patients treated with HDREBT). The pN-stage on the other hand, did not differ significantly between both countries ($p=0.11$), although patients treated with HDREBT seemed to have slightly more pathological positive lymph nodes (73.1%, compared with 61.9% in patients treated with 5×5 Gy or CRT).

Figure 1 shows the five year overall survival for the countries. Comparing the five year overall survival between patients treated with 5×5 Gy or CRT and patients treated with HDREBT unadjusted for baseline imbalances showed a HR of 0.56 (95% CI 0.27-1.16, $p=0.12$). After adjustment for potential confounders, patients treated with HDREBT had a significant better five year overall survival (HR 0.39, 95% CI 0.16-0.93, $p=0.03$). When comparing five year cancer-specific mortality between the countries, 6/134 patients treated with 5×5 Gy or CRT died due to the rectal cancer, and 4/141 patients treated with HDREBT (HR 0.59, 95% CI 0.16-2.08, $p=0.41$). Five-year local recurrence was 5/134 in the patients treated with 5×5 Gy or CRT and 2/141 in the patients treated with HDREBT (HR 0.54, 95% CI 0.13-2.28, $p=0.41$). When death was taken into account as competing risk, the SHR for five year cancer-specific mortality was 0.60 (95% CI 0.17-2.16, $p=0.44$), and the SHR for five year local recurrence was 0.56 (95% CI 0.14-2.30, $p=0.42$).

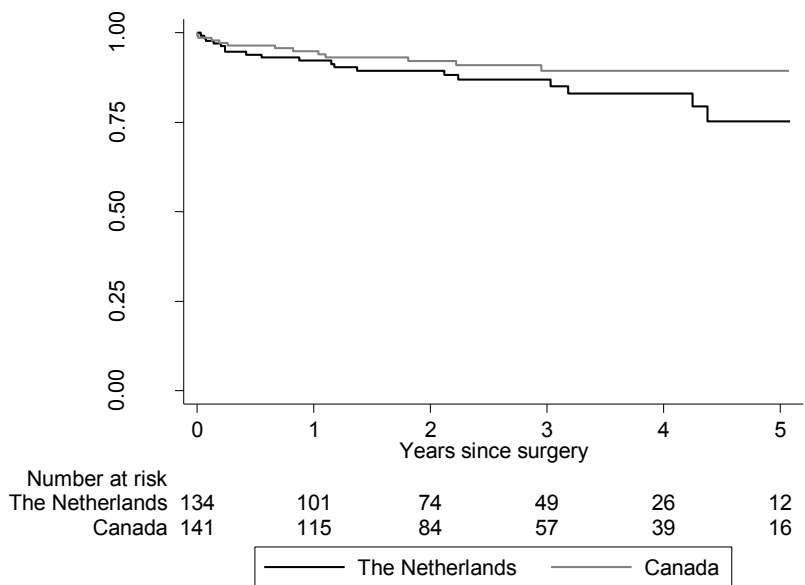


Figure 1: Kaplan-Meier of overall survival (event = death due to all causes)

There was no difference in five year overall survival between Dutch patients treated with 5×5 Gy radiotherapy and Dutch patients treated with CRT after adjustment (HR 1.18, 95% CI 0.32-4.35, $p=0.80$).

DISCUSSION

In this study, a comparison was made between the current standard preoperative therapy in the Netherlands (5×5 Gy or CRT) and a newer therapy used in Canada, HDREBT. Overall survival was better for patients treated with HDREBT. Cancer-specific mortality and local recurrence were comparable, although this comparison is based on few events, making the study underpowered to detect relevant differences. Overall, the results of this study suggest that HDREBT could be a safe alternative to CRT or 5×5 Gy in the treatment of patients with rectal cancer.

Findings from the present study add important new observations, which to our knowledge, have not been previously investigated. The results show that overall survival was better for patients treated with HDREBT, as compared with patients treated with 5×5 Gy or CRT. Besides, only a few patients had a local recurrence or died due to rectal cancer in both countries. The results of this study should be interpreted with caution, since the data are observational and type of preoperative treatment has not been randomised. The study's conclusions therefore rely on the assumption of no unmeasured confounding. We have tried to deal with the potential of confounding by design and by analysis. We used a design in which the level of comparison was between two countries. The comparison at country level emulates the principles of an instrumental variable analysis^{18,19}, which deals with (unmeasured) confounding because the instrument (in this case country) is at least partially unrelated to prognosis. In other words: we made the assumption that the cT3 patients treated in the Netherlands and in Canada were to a certain extent comparable. As a direct country comparison will not circumvent confounding completely, we also adjusted for important baseline differences between the countries. Moreover, differences in age, gender, cN-stage, and year of surgery were found when comparing the two countries at baseline. These variables were adjusted for in the analysis. Clinical N-stage was significantly different between patients treated with 5×5 Gy or CRT and HDREBT when compared preoperative ($p=0.004$), but after surgery, no significant differences in N-stage between both countries were found. Differences in preoperative N-stage could be due to difference in staging by the radiologists as accuracy of positive lymph nodes identification in rectal cancer lacks.^{20,21} In addition, the differences preoperatively could be decreased or adjusted due to the type of preoperative treatment used within the country, since preoperative treatment involves radiation on lymph nodes. Even though, the type of preoperative treatment was based on the cT-stage and in lesser extent on cN-stage.

Unexpectedly, the overall survival between the countries was significantly better for patients treated with HDREBT. We hypothesize that HDREBT is associated with lower non-cancer related deaths in comparison with external beam radiotherapy. This is an important observation as the long term results from the Dutch trial suggested that despite the improved cancer-specific survival provided by radiation therapy, these benefits were nullified by an increase in other causes of death.²² One of the main causes was secondary cancer.²² Several other studies on prostate cancer have also shown that secondary malignancies are less common after HDREBT as compared to external beam radiation.²³⁻²⁶ Furthermore, in the current study no difference between both countries is present until 4 years since surgical treatment, which suggests that short term outcome does not differ between both treatment strategies, as also shown in a comparison between patients from Canada and Sweden.²⁷

An ypT0 stage has been achieved more often for patients treated with preoperative HDREBT as compared with the treatment strategy from the Netherlands. Since 5×5 Gy is often followed by immediate surgery and downstaging is not the aim of this short course of radiation, this could explain the differences in downstaging. CRT on the other hand is followed by surgery after at least 6 weeks, similar to HDREBT, which would expect the same percentage of downstaging. However, HDREBT does induce more downstaging as compared with CRT as the mean dose given to the tumour bed was 26 Gy in 4 days, which is a much higher radiobiological dose than 45-50 Gy in 25-28 fractions.²⁸⁻³⁰

HDREBT was introduced as an attempt to reduce radiation treatment-related toxicity. The initial results showed that all patients treated with preoperative HDREBT had an acute proctitis grade 2, except one percent of patients who had an acute proctitis grade 3 and required a blood transfusion. None of the patients had to be hospitalized for treatment-related toxicity.¹⁰ A comparison between Sweden and HDREBT showed that the postoperative complications were similar between patients treated with HDREBT, 5×5 Gy and without preoperative treatment, except HDREBT had a higher rate of cardiovascular complications, but there was no increase in the postoperative deaths.²⁷ This could possibly be explained by the higher Charlson comorbidity score in the Canadian population (data not shown). Furthermore, a comparison of hormonal profile collected prospectively in 119 male patients with rectal cancer treated with either conventional CRT or HDREBT showed that HDREBT allows better hormonal sparing, less hypogonadism.³¹ And finally, interim analyses of an on-going study show that both faecal incontinence and urinary incontinence are lower in patients treated with HDREBT in comparison with patients treated with external beam radiotherapy.³² All these studies suggest that treatment-related toxicity may indeed be reduced.

CONCLUSION

Overall, HDREBT seems to be a realistic alternative in the treatment of patients with rectal cancer, whereas postoperative complications, local recurrence rates and the rates of death due to rectal cancer were low in all countries. These findings could have profound clinical implications and strongly propose a randomized controlled trial in consideration of the possible overall survival benefits suggested by this study, in addition to a lower overall treatment-related toxicity.

REFERENCE LIST

- 1 Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-917.
- 2 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; **336**: 980-7.
- 3 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-82.
- 4 MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**: 457-60.
- 5 Peeters KC, Marijnen CA, Nagtegaal ID et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; **246**: 693-701.
- 6 Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; **358**: 1291-304.
- 7 Camma C, Giunta M, Fiorica F et al. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *JAMA* 2000; **284**: 1008-15.
- 8 Marijnen CA, Kapiteijn E, van de Velde CJ et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002; **20**: 817-25.
- 9 Peeters KC, van de Velde CJ, Leer JW et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *J Clin Oncol* 2005; **23**: 6199-206.
- 10 Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. *Clin Oncol (R Coll Radiol)* 2007; **19**: 701-5.
- 11 Devic S, Vuong T, Moftah B. Advantages of inflatable multichannel endorectal applicator in the neo-adjuvant treatment of patients with locally advanced rectal cancer with HDR brachytherapy. *J Appl Clin Med Phys* 2005; **6**: 44-9.
- 12 Devic S, Vuong T, Moftah B et al. Image-guided high dose rate endorectal brachytherapy. *Med Phys* 2007; **34**: 4451-8.
- 13 Vuong T, Belliveau PJ, Michel RP et al. Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer: early results of a phase I/II study. *Dis Colon Rectum* 2002; **45**: 1486-93.
- 14 Vuong T, Devic S, Moftah B, Evans M, Podgorsak EB. High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: technical aspects. *Brachytherapy* 2005; **4**: 230-5.
- 15 Vuong T, Richard C, Niazi T et al. High Dose Rate Endorectal Brachytherapy for Patients With Curable Rectal Cancer. *Semin Colon Rectal Cancer Surg* 2010; **21**: 115-9.
- 16 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed May 31 2013).
- 17 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007; **26**: 2389-430.
- 18 Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; **19**: 537-54.
- 19 Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol* 2009; **62**: 1226-32.
- 20 Bipat S, Glas AS, Slors FJ et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology* 2004; **232**: 773-83.
- 21 Lahaye MJ, Engelen SM, Nelemans PJ et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. *Semin Ultrasound CT MR* 2005; **26**: 259-68.

- 22 van Gijn W, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
- 23 Bhojani N, Capitanio U, Suardi N et al. The rate of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localized prostate cancer: a population-based study on 17,845 patients. *Int J Radiat Oncol Biol Phys* 2010; **76**: 342-8.
- 24 Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000; **88**: 398-406.
- 25 Liauw SL, Sylvester JE, Morris CG, Blasko JC, Grimm PD. Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys* 2006; **66**: 669-73.
- 26 Zelefsky MJ, Housman DM, Pei X et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **83**: 953-9.
- 27 Hesselager C, Vuong T, Pahlman L et al. Neoadjuvant high dose endorectal brachytherapy or short course external beam radiotherapy in resectable rectal cancer. *Colorectal Dis* 2013.
- 28 Kalady MF, de Campos-Lobato LF, Stocchi L et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009; **250**: 582-9.
- 29 Moore HG, Gittleman AE, Minsky BD et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. *Dis Colon Rectum* 2004; **47**: 279-86.
- 30 Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol* 2008; **15**: 2661-7.
- 31 Yau I, Vuong T, Garant A et al. Risk of hypogonadism from scatter radiation during pelvic radiation in male patients with rectal cancer. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1481-6.
- 32 Al-Halabi H, Poggi L, Niazi T et al. Functional and Quality of Life Assessment in Rectal Cancer Patients Treated with Pre-operative Endorectal Brachytherapy and Sphincter Preserving Surgery. *Int.J.Radiat.Oncol.Biol.Phys.* 2010 **78**: S310.



Discussion

Chapter 10

General discussion, summary, and summary in Dutch

Improving the outcome of colorectal cancer: the
European Registration of Cancer Care (EURECCA)
project

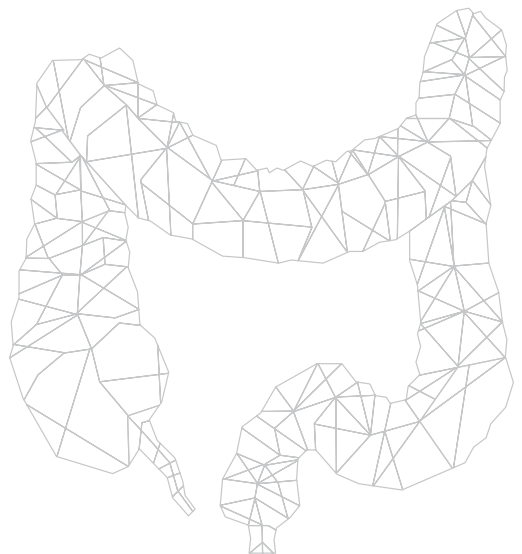
Colette B.M. van den Broek

Petra G. Boelens

Anne J. Breugom

Cornelis J.H. van de Velde

Partly published in Colorectal Cancer. 2013 Aug;2(4):371-6



GENERAL DISCUSSION

Introduction

In 2008, colorectal cancer was the third most common cancer in men (663 000 cases) and the second in women (571 000 cases) worldwide. Nowadays, these numbers are even higher. Incidence rates vary 10-fold worldwide, the highest rates being estimated in developed countries, such as in the Netherlands. Differences between developed and less developed countries are probably due to an unfavourable pattern in lifestyle and an aging population in developed countries.^{1,2} The incidence of colorectal cancer increases with higher age, with the highest incidence between 70 and 79 years of age. In the coming years the population will age further and it is estimated that by 2020 26% of the Dutch population will be 65 years or older.³ Incidence rates are substantially higher in men than in women, although stabilising in men and still increasing in women in the past decade.⁴ The difference between the incidence in males and females is probably at least partly due to differences in lifestyle pattern. In the Netherlands, approximately 13,000 patients are diagnosed with colorectal cancer yearly, and five year survival is 58% for colon cancer patients and 59% for rectal cancer patients.⁵

Diagnostic assessment and staging

Colorectal cancer is a curable disease when detected and treated in time. To optimise the outcome of colorectal cancer patients, accurate diagnosis and staging are important. This provides an opportunity for screening, which is already advised in the US and the UK and is being implemented in many other European countries.^{6,7} In the end of 2009 the Dutch Health Council advised the government that mass screening in the Netherlands should be conducted using biannual immunochemical faecal occult blood test for men and women aged 55 to 75 years.⁸ The introduction of the screening will be between 2013 and 2019. In patients with a positive test result at screening, optimal diagnostics (especially colonoscopy) will follow, and, if necessary, treatment. The aim of the screening is reduced colorectal cancer mortality by detecting cancers at an earlier stage. Screening will probably result in an increased workload for both gastroenterologists and pathologists, and possibly also surgeons, due to increased finding of adenomatous polyps. Besides, costs will increase due to the screening itself, as well as, the treatment of patients with a positive screening. Screening could, on the long term, result in decreased costs of colorectal cancer treatment, when tumours are found at an earlier stage. Therefore, fewer patients would be diagnosed with an advanced stage of disease, needing more extensive treatment. Overall, screening could improve outcome, but the effectiveness of screening remains under discussion, as is also the case in for example breast cancer and prostate cancer.⁹ In breast cancer and prostate cancer the incidences have increased due to the introduction of screening, and have not returned to prescreening levels. Besides, the relative fraction of early stage cancer has increased, while the incidence of more

advanced tumours has not decreased. Therefore, results of the introduction of screening should be analysed carefully in order to achieve optimal results.

Once the diagnosis is established, the extent of the primary tumour, regional lymph nodes, as well as distant metastases should be determined, also called staging, to provide a framework for discussing therapy and prognosis. Besides, uniform staging provides a common language with which doctors can communicate about a patient's case, and to compare treatment strategies and outcomes.¹⁰ National clinical guidelines state that for diagnostic assessment of colorectal cancer all patients should undergo physical examination, colonoscopy for colon cancer and endoscopy for rectal cancer, and imaging procedures of the abdomen, liver, and thorax. Furthermore, all patients need to be discussed in a multidisciplinary meeting.¹¹ Based on the results of diagnostic assessment, the stage is determined. There are different types of staging: clinical staging, based on the physical examination, imaging tests, and biopsies of affected areas, and pathological staging, which can only be done in patients who have had surgery to remove the tumour. In pathological staging, both the information of clinical staging and the surgery are combined. Finally, since nowadays colorectal cancer patients more often are treated with neoadjuvant treatment, restaging is become more common and is used to determine the extent of the disease after neoadjuvant treatment.

Currently, the Tumour, Nodes, and Metastasis (TNM) staging system is considered the most robust tool for prediction of prognosis and for decisions on the delivery of treatment. The objectives of the TNM system have been stated as: to aid in the planning of treatment; to give some indication of prognosis; to assist in assessing the effects of treatment; to help with the exchange of information between treatment centres; and to contribute to the continuing investigation of human cancers.¹² Since the knowledge of cancer is continually expanding, the TNM system is revised every few years. Unfortunately, these revisions may cause problems, since modification of a component of the system could lead to the upstaging or downstaging of the disease, resulting in a change in treatment. Besides, changes in the TNM system can also lead to an inability to compare results from new trials with older trials, or even worse, when the changes occur during an ongoing trial.¹³ As a result of the variation in definition of tumour deposit between the TNM5, TNM6 and TNM7, and their reproducibility and use in special situations, such as after neoadjuvant treatment, the Netherlands decided to continue applying the TNM5.^{11,14} Additional information needed for optimal staging, such as the R-classification, has not been included in the newer TNM versions. On the other hand, an improvement of the TNM6 as compared to the TNM5 is the distinction between stage IIA and stage IIB colon cancer patients, since the patients with a T4 N0 M0 from stage IIB do indeed have worse prognosis than those classified as T3 N0 M0. These stage IIB patients, defined as high risk, are often treated with adjuvant chemotherapy. However, other patients with stage II are also defined as high risk, and should therefore receive adjuvant chemotherapy. These patients have extramural vascular invasion or extensive extramural spread, inadequately sampled nodes (less than 10), perforation, and/or poorly differentiated histology.¹⁵ These details cannot be

identified by the TNM-system or are compromised. In addition, it is recommended to describe which TMN version is used and whether there are tumour deposits present, and describe their characteristics.¹¹ Furthermore, additional details such as needed to confirm high risk, should be described. Perhaps in the future, a different staging system could be developed including possible gene mutations, which could lead to more individually based treatment and prognosis. On the other hand, the desire is to keep the staging system simple.

Treatment of colon cancer

Surgical resection is the cornerstone of curative treatment for colon cancer. The resection rates remain high among all colon cancer patients, due to the fact that resection is the only possible curative option in the treatment of colon cancer.¹⁶ Unfortunately, resection alone will not cure all patients. Both high risk stage II patients and stage III patients should receive adjuvant chemotherapy according to the guidelines to improve their outcome.¹¹ In the current thesis, it is demonstrated that the use of adjuvant chemotherapy for stage III has increased during the past two decades, which is in line with most other European countries.^{17,18} Elderly patients with stage III colon cancer receive adjuvant chemotherapy less often. There are several reasons why elderly patients are less likely to receive adjuvant chemotherapy, as described in this thesis; they include the presence of comorbidities, frailty, the absence of supportive caregivers, and a decrease in patients' general condition and cognitive ability.^{19,20} In addition, elderly patients seem to be less willing to accept the negative side-effects of chemotherapy, resulting in more frequent patient refusal.²¹ In general, medical oncologist agree with the recommendations in the national guidelines for adjuvant chemotherapy for the relatively young and healthy patients with stage III colon cancer, but their opinion differs widely on recommendations for patients who are older and sicker.²² Consequently, the likelihood of the older patients to receive adjuvant chemotherapy depends on the attitude and opinion of the medical oncologist treating the patient. However, fit elderly colon cancer patients may benefit equally from adjuvant chemotherapy without increased toxicity.^{23,24}

Over time, the optimal combination of chemotherapy has been extended. Moertel et al. were the first to show a decrease in recurrences and improved survival with the use of fluorouracil and levamisole in stage III colon cancer patients.²⁵ Afterwards, several studies have shown that levamisole can be replaced by folinic acid, whereas low dose folinic acid is as effective as high dose. Besides, it was shown that adjuvant chemotherapy for half a year achieves similar results in terms of relapse and improvement of survival as chemotherapy for one year.^{26,27} In 2004 the MOSAIC-trial was published, which randomised between fluorouracil and folinic acid with or without oxaliplatin. The addition of oxaliplatin showed a significant improve in disease-free survival and overall survival for stage III colon cancer patients.²⁸ Recently, subgroup analyses of two studies have shown that the elderly patients are less likely to benefit from the addition of oxaliplatin.^{29,30} Furthermore, a meta-analysis of recent trials showed no difference between oral or intravenous fluorouracil, and one trial included in the meta-analysis showed

a trend towards an advantage in disease-free survival for oral fluorouracil (capecitabine).³¹ Therefore, elderly patients more often receive fluorouracil in combination with folinic acid, or capecitabine as monotherapy^{17,20}, which is in line with the advice of the Dutch guidelines.¹¹ In general, five year survival has improved for all colon cancer patients over time.³² For stage III colon cancer patients the five year relative survival improved approximately 7% in the past 18 years, which is thought to be at least in part attributable to the increased use of adjuvant chemotherapy.¹⁷ Besides adjuvant chemotherapy, also stage-migration and improved peri-operative care, defined as care before, during, and the first days after surgery, have possibly attributed to this improvement in survival. In an attempt to further improve outcome of these patients, treatment can be individualized. To prevent both overtreatment and undertreatment of certain subgroups, which includes elderly colon cancer patients and patients with comorbidities, a geriatric assessment might be helpful in decision making. Overall, the selection of patients receiving adjuvant chemotherapy should be objectified in prospective studies and discussed. Furthermore, to compare the outcome of patients treated with and without adjuvant chemotherapy, recurrence and quality of life should be important outcomes. Survival will be less informative, since the patients not treated with adjuvant chemotherapy are expected to have inferior survival due to the decreased fitness of them in comparison with patients who do receive adjuvant chemotherapy.

Treatment of rectal cancer

There are four major goals to achieve in the treatment of patients with rectal cancer; local control, long term survival, preservation of the anal sphincter, bladder and sexual function, and optimal quality of life.³³ Treatment of rectal cancer has been subject of research for the past two decades. The Dutch TME-study from 1996 to 1999 was the first study to achieve quality control on radiotherapy, surgery, and pathology.³⁴ With the change in pathology approach, the extent of the disease in each patient became clearer. Besides, this trial had quality control on surgical procedure, implementing a new surgical technique, the total mesorectal excision (TME). The goal of this surgical technique is to remove the rectum along with its blood vessels and surrounding lymph nodes within an intact visceral fascial that envelopes around the mesorectal fat and thereby obtaining a negative circumferential resection margin which is associated with improved local control.³⁵ Another improvement of the TME technique as compared to the traditional blunt dissection is that the autonomic nerves can be preserved, and therefore urinary and sexual function as well. However, surgery alone still resulted in unacceptable rates of locoregional recurrences. The Dutch TME-trial reported reduced local recurrences by implementing short course preoperative radiotherapy. The ten year follow-up of the Dutch TME trial, showed indeed a decrease in local recurrence for patients treated with preoperative radiotherapy followed by TME-surgery (5%), as compared to patients treated with only TME-surgery (11%, $p < 0.001$).³⁴ Even though, the overall survival did not differ between both groups. The interval between preoperative radiotherapy and surgery, however,

remains a subject of research. As also described in this thesis, patients during the TME-trial aged 75 years or older who had an interval of 4-7 days had a significant worse overall and non-cancer-related survival as compared to patients in the same age group with an interval of 0-3 days.³⁶⁻³⁸ Furthermore, a current trial is investigating whether an interval of more than four weeks could induce downstaging, without worse survival. The interim analyses of this trial show that the compliance was acceptable and severe acute toxicity was uncommon.³⁸ There are several indications in the literature that the increased postoperative mortality after a longer interval between radiotherapy and surgery could be caused by an impaired immune response, possibly reflected in the perioperative leucocyte count of the patient.^{39,40}

In case of suspected mesorectal fascia involvement, short course radiotherapy followed by immediate surgery is not a good option. Hypofractionated preoperative radiotherapy followed by immediate surgery has not shown to lead to downstaging of the tumour.⁴¹ Therefore, radical resection cannot be achieved in those patients. Long course, or hyperfractionated, radiation followed by delayed surgery after 4-12 weeks reduces tumour size, which increased the change of a complete resection. Several phase II studies have shown that the addition of chemotherapy to long course radiotherapy results in downsizing and downstaging.⁴²⁻⁴⁵ The Dutch guidelines advise the use of long course radiotherapy in combination with fluorouracil based chemotherapy, also called chemoradiation, for patients with suspected mesorectal fascia involvement, and therefore a possible positive circumferential resection margin (CRM), or in case the patient has four or more lymph nodes which are suspected to be tumour positive.¹¹ The addition of oxaliplatin might be associated with even a higher pathological complete response rate^{46,47}, but is associated with more acute toxicity.⁴⁸ Overall, neoadjuvant short course radiotherapy alone followed by direct surgery compared to neoadjuvant chemoradiation followed by delayed surgery enhances pathological response and thereby improves radical resections in stage II and III rectal cancer. Survival, both disease-free survival and overall survival, was comparable between both treatment groups.⁴⁹ Besides, the effects of neoadjuvant chemoradiation on functional outcome and quality of life are not completely clear. For that reason, future trials should be addressed on that topic. Throughout Europe, several countries prefer chemoradiation over short course radiotherapy as neoadjuvant treatment even when mesorectal fascia involvement is not suspected. The differences of the use of neoadjuvant treated among rectal cancer patients from five European countries was striking, as described in this thesis.

Current Dutch guidelines advice neoadjuvant short course radiotherapy for all rectal cancer patients, with the exception of T1 N0 and small tumours located high in the rectum. The use of neoadjuvant chemoradiation is advised for patients with suspected mesorectal fascia involvement. Since toxicity is common after neoadjuvant chemoradiation for rectal cancer patients with a high risk for recurrence, a new study, the RAPIDO trial, is aiming to decrease the toxicity and improve survival with an experimental treatment. In this study the intervention arm will be short term radiotherapy (5 days), followed by six cycles of chemotherapy, to decrease the

size of the rectal tumour and to treat possible (micro)metastases. The smaller tumour will then be removed by surgery. The intervention arm will be compared with standard of care. The clinicians can optionally give adjuvant chemotherapy. Since the beginning of 2013 the accrual of this study is ongoing, with an aim of 850 patients to participate in the study. The datacenter at Leiden University Medical Center is the organising center. Besides centers in the Netherlands, also centers from Norway, Sweden, Slovenia, and Spain are participating.⁵⁰

In another attempt to reduce treatment-related toxicity from short course radiotherapy, high dose rate endorectal brachytherapy (HDREBT) has been explored as a neoadjuvant treatment in patients with resectable rectal cancer.⁵¹⁻⁵⁵ A study of Vuong et al. has shown that the five year local recurrence rate was 5% and toxicity patterns seemed to be favourable as compared to external beam radiotherapy (only grade 2 and in one percent of the patients grade 3 proctitis).⁵³ In this thesis, a comparison of the long term results between cT3 rectal cancer patients from the Netherlands treated with short course radiotherapy or chemoradiation, compared with cT3 rectal cancer patients from Canada treated with high dose rate endorectal brachytherapy has been described. No significant differences in local recurrence and cancer-specific mortality were observed. However, superior overall survival was observed in patients from Canada possibly due to a decrease in treatment related toxicities. Overall, HDREBT seems to be a realistic alternative in the treatment of rectal cancer patients, and the results are a strong rationale for a randomised controlled trial.

Another relatively new approach to treat locally advanced rectal cancer is to apply intraoperative radiotherapy boost to a specific area. This treatment allows the deliverance of a radiation boost, biologically comparable to an additional 30–40 Gy fractionated irradiation, to a well-defined volume under direct vision, with a possibility to shield or remove dose-sensitive structures. However, the equipment needed is expensive and the logistics are complex. The results of a pooled analyses show that the outcome of these patients is promising.⁵⁶

Even though colon and rectal cancer are treated as different entities, they are comparable in some aspects, as they appear similar macroscopically. Besides, metastatic colorectal cancer shows similar response to chemotherapy both for colon and rectal cancer. Adjuvant chemotherapy is standard of care for stage III colon cancer. Adjuvant chemotherapy for rectal cancer is still subject of research. Although it is assumed that the effects of postoperative adjuvant chemotherapy are similar in rectal cancer to the results achieved in colon cancer, there is little evidence to support this. Recently, a Cochrane review has indicated that the evidence supports adjuvant chemotherapy for rectal cancer patients treated without neoadjuvant radiotherapy or chemoradiation.⁵⁷ For rectal cancer patients treated with neoadjuvant treatment sufficient evidence is lacking. There have been some trials on this subject, but the results have not been published yet. The results of three individual trials are expected to be published in 2013 and 2014. An individual patient meta-analysis will be performed with the patients from a Dutch trial, an English trial, and an Italian trial by 2014.

Follow-up

Despite potentially curative surgery and the use of (neo)adjuvant chemotherapy and/or radiation therapy, more than 40% of patients who present with stage II or III disease will have a disease recurrence following primary therapy.⁵⁸ The aim of follow-up after primary treatment is to diagnose local and distant recurrences, and second primaries when the patient is still asymptomatic and potentially eligible for curative treatment. There is considerable variability among physicians in the use of follow-up studies after potentially curative resection of CRC⁵⁹⁻⁶³ and in the guidelines from major societies.⁶⁴⁻⁶⁹ Multiple surveillance strategies have been published at costs ranging from a few hundred to several thousand dollars per patient.^{70,71} A survival benefit from such an approach has in fact been shown in three separate meta-analyses.⁷²⁻⁷⁴ However, several comments can be made on those studies; first, the selection of patients are not consistent, and second, the standard treatment arm of these studies had more intensive follow-up as compared to our current guidelines. Overall, the optimal frequency and duration of surveillance is difficult to determine due to the heterogeneity of programmes assessed in the studies.

Elderly patients often have several comorbid conditions at time of colorectal cancer diagnoses. The presence of these concomitant diseases have an impact on both crude and relative survival, which is not purely due to differences in the treatment of these patients.¹⁶ Because of this, there is discussion about the follow-up of elderly colorectal cancer patients. Whereas in young patients they might die of the recurrence of disease, elderly patients and patients with comorbidities perhaps need less intense or no follow-up since they might probably not die of the recurrence. In Denmark patients over 75 years of age rarely are followed after surgery.

Old age and comorbidities

The fastest growing part of the population in Western countries are people aged 65 years or older, and the highest incidence of colorectal cancer is among those between 70 and 80 years old. In recent years the focus on elderly colorectal cancer patients has increased. It is important to realise that the elderly population forms a very heterogeneous group of patients. Not only can chronological age be very different from biological age, but also the definition of elderly varies widely from ≥ 65 years to ≥ 80 years in different studies. Chronological age alone is therefore not the primary influence on outcome. The combination of comorbidities present and a decreased physical reserve to recover from adverse events that may occur, may rather determine the outcome of elderly patients.^{23,75} This is also referred to as biological age. Hence chronicle age itself should not be a contraindication for more aggressive or adjuvant treatment. Comorbidities, on the other hand, are of critical importance in the care of a patient. The presence of comorbidity effects treatment decisions^{22,76-78}, and the prognosis⁷⁹⁻⁸³. As the prevalence of comorbid conditions is increasing among colorectal cancer patients, individualised care becomes more important. In order to accomplish improved personalised medicine,

more knowledge about and attention to the role of comorbidity in colorectal cancer in both research and care is needed.^{81,84}

Besides age-related treatment differences, several studies have shown age-related differences in relative survival as well. In this thesis it was reported that although the survival of elderly colon cancer patients (75 years and older) has improved over the time period of 1990 to 2005, the survival-gap as compared to middle-aged patients (younger than 65 years) remains. There might be two explanations for the differences in relative survival among aged and elderly patients. First of all, elderly might still be undertreated, resulting in worse survival. This can probably not be completely prevented, since frailty and comorbidities could impede the use of chemotherapy, radiotherapy or a combination of both. Secondly, elderly patients have a higher risk of excess mortality. In this thesis, we show that the differences in survival are most apparent in the first postoperative year, probably due to a prolonged impact of the insult of surgery in elderly patients.⁸⁵

In order to improve the survival of elderly colorectal cancer patients, in the future there should be more focus on non-cancer related survival, such as treatment of comorbidities. In this way the balance in physiological resources could be optimised. Due to the heterogeneity of elderly colorectal cancer patients, there is hardly any clinical trial data on elderly patients and evidence based treatment guidelines specifically for the elderly are currently lacking.^{86,87} As elderly patients are characterized by a large variation in health status, recent developments should focus on geriatric screening instruments to predict the tolerance to treatment⁸⁸⁻⁹⁰, followed by multidisciplinary treatment, focussing on the perioperative care of not only colorectal cancer itself, but also the comorbid conditions.

Quality assurance

Quality control on surgery, radiotherapy, and pathology has been introduced in trials, followed by incorporation in the general care.^{91,92} Furthermore, there have been several improvements by introducing high volume clinics.^{93,94} As an alternative to volume based referral, hospitals and surgeons can also improve their results by learning from their own outcome statistics and those from colleagues treating a similar patient group. An audit is a quality instrument that collects detailed clinical data from different healthcare providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. In this way, 'best practices' can be identified, communicated, and broadly adopted. After case-mix adjustments, a fair judgement can be made on the quality of cancer treatments. Hospitals and surgeons can be faced with their own results compared to those of colleagues treating the same patient category. Another important advantage is the fact that audit registries include the entire patient population which makes it possible to perform research on patient groups that are usually excluded from clinical trials (such as elderly patients and patients with comorbidities). Although all these national and regional audit structures have achieved excellent results, differences in outcome between European countries remain which cannot be easily explained.

A joined international network has been initiated to generate the best care for all cancer patients, founded as the European Registration of Cancer Care (EURECCA). EURECCA was initiated in colorectal cancer, but has expanded to Upper GI, breast, and hepatic, pancreatic, and biliary cancer. The initiative and the first results of a comparison between treatment strategies for rectal cancer are described in this thesis. Next, the selection of patients receiving adjuvant chemotherapy in colon stage II and rectal cancer will be compared across the countries. In the future EURECCA wants to expand to other cancer types, and the ultimate goal would be to achieve an European audit with feedback to the countries, hospitals, and clinicians about their results in comparison with other countries, after case-mix adjustment.

CONCLUSION AND FUTURE PERSPECTIVES

For the past two decades both colon and rectal cancer have been a subject of research. This resulted in several diagnostic and treatment improvements for both colon and rectal cancer, which led to improved outcome. Even though, several further improvements are to be expected in the coming decades. First of all, screening will be initiated in the Netherlands, possibly leading to a detection of more early tumours, which might need a different approach. Secondly, elderly patients and patients with comorbidities, which will be a growing group of patients in the next ten years, will probably need different care since not all treatments will be tolerated and fewer side effects might be accepted. Furthermore, the past five to ten years have led to significant advances in the understanding of biological, molecular, genetics, and pathogenesis. Genetic based tumour markers will lead to further characterised cancer, and will be accompanied by tailored treatment. Already the genetic testing for KRAS, and several other similar RAS mutations, are being implemented clinically to determine which patients should undergo treatment with monoclonal antibodies against EGFR. In parallel with these advances in understanding colorectal cancer, DNA sequencing has increased exponentially. By examining tumours and identifying common genetic mutations and molecular pathway perturbations, cancer development will be better understood. This will allow the development of more accurate screening tests, diagnostic tests, and identification of new and specialised treatments. Overall, these advances will lead to more complex treatment strategies which need to be individualised based on patient- and tumour characteristics.

Trials are important to answer specific research questions, but for individualised patient care trials will probably not provide the needed information. Large population based datasets can provide the needed information by identifying the optimal treatment strategy for certain subgroups. An audit is a quality instrument that collects detailed clinical data from different healthcare providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or clinicians. The audit structure will include all patients. Audits have achieved excellent results on national level. A next step will be to combine these national

audits. The combined audit structure will provide a network in which 'best practices' can be compared and identified, including for certain subgroups.

To achieve optimal care for all patients, multidisciplinary care is the only way. Current and future research will lead to advances in colorectal cancer screening, diagnosing, treatment, and outcome. By comparing multidisciplinary audit structures across countries, optimal treatment strategies within subgroups can be identified. Furthermore, optimal communication between clinicians and between patient and clinician will be the optimal strategy to achieve shared decision making in combination with personalised medicine.

SUMMARY

In the Western World, colorectal cancer is a major health problem. The incidence is high and expected to grow even further in the upcoming years.⁵ Besides, the incidence increases with increasing age, which makes it a disease of the older patient. Together, it is anticipated that the number of elderly patients with colorectal cancer will grow during the coming years, while there are no specific clinical guidelines for the elderly. Evidence from population-based studies clearly demonstrates that older patients are more often inadequately staged, undergo fewer elective operations⁹⁵ and are less likely to receive adjuvant chemotherapy and/or radiotherapy than their younger counterparts⁹⁶⁻¹⁰⁰. Current guidelines are derived from (randomised) trials in which elderly patients or patients with severe comorbidity are excluded or underrepresented.^{100,101}

PART I COLORECTAL CANCER; TREATMENT AND SURVIVAL

Over the past two decades the treatment of colon cancer has changed substantially. Moertel et al²⁵ have shown that adjuvant chemotherapy has a beneficial effect on survival. The guidelines in the Netherlands have changed in 1997 and adjuvant chemotherapy is now advised for all patients diagnosed with stage III colon cancer, regardless of the age of a patient. Since the adjustment of the guidelines, the use of adjuvant chemotherapy has increased. The aim of *Chapter 2* was to describe the time trends in the use and costs of adjuvant chemotherapy. A total of 24,111 patients diagnosed with stage III colon cancer between 1990 and 2008 were included in this retrospective cohort study. Both the administration (from 9.5% in 1990 to 61.8% in 2008) and the estimated medicine costs of chemotherapy (from € 38,467 in 1990 to € 3,876,150 in 2008) increased during the study period. Elderly patients received less adjuvant chemotherapy as compared to younger patients. Multivariable analyses showed that the relative survival improved for all patients receiving adjuvant chemotherapy (RER 0.93; 95% CI 0.92-0.94). In contrast, relative survival remained stable for patients, younger than 80 years, who did not receive chemotherapy (RER 1.00; 95% CI 1.00-1.01). In patients aged 80 years and older treated without chemotherapy, relative survival improved during the study period (RER 0.98; 95% CI 0.97-0.99). Concluding, the administration of chemotherapy, the costs of chemotherapy and the survival of patients with stage III colon cancer increased over time. Whereas the costs and administration of chemotherapy increased extensively, relative survival improved to a lesser extent. For patients treated with adjuvant chemotherapy relative survival improved equally in all age groups.

Even though the Dutch guidelines advise to treat all stage III colon cancer patients with adjuvant treatment, a large proportion of these patients are not treated adherent to this guideline. The percentage of patients not receiving adjuvant chemotherapy increases with

age. In *Chapter 3* factors associated with not receiving adjuvant chemotherapy were studied as well as causes of death and recurrences of this population. A total of 348 consecutive stage III colon cancer patients diagnosed between 2000 and 2009 from two hospitals in the mid-western region of the Netherlands were included. Most patients were between 70 and 79 years of age (35.6%) and slightly more women were included (51.4%). Just over half of the patients received adjuvant chemotherapy (50.6%). After adjustment for several confounders, elderly patients and patients with one or more comorbidities were less likely to receive adjuvant chemotherapy. Patients who did not receive adjuvant chemotherapy died earlier, and more often due to other causes than the primary tumour. Adjuvant chemotherapy is prescribed in order to prevent recurrence of disease. Patients need to be alive to develop a recurrence. Therefore a so-called competing risk analyses has been performed, with death as competing risk in order to develop a recurrence. Patients who did and who did not receive adjuvant chemotherapy had a comparable cumulative incidence of recurrence, when death was taken into account as a competing risk. This study showed that the selection of patients who are eligible for adjuvant chemotherapy is of great importance in order to decrease recurrences. Further research should focus on objectifying the selection of the patients treated with and without adjuvant chemotherapy. Besides, decreasing recurrences in both patients treated with and without adjuvant chemotherapy, and optimising the quality of life of these patients should be a focus of further research.

Recently, the EUROCARE working group has shown that the survival of colon cancer patients has improved between 1988 and 1999. When they compared the five year relative survival between elderly (70-85 years) and middle-aged patients (55-69 years), survival improved in both age groups, although in lesser extent in the elderly, resulting in a survival gap.¹⁰² *Chapter 4* aimed to describe treatment and compare survival rates over time (1991-2005) between middle-aged (<65 years), aged (65-74 years), and elderly (≥75 years) colon cancer patients in the mid-western region of the Netherlands, to assess whether the survival gap has increased over time. A total of 8926 patients with invasive colon cancer were included in the present study. Over time no treatment changes occurred for stage I and II, while the use of chemotherapy increased for stage III and IV. Surgical procedures were less often performed for stage IV over time. Survival differences between middle-aged and elderly patients were present and the survival gap from the EUROCARE was thereby confirmed. Nevertheless, the differences between both age groups remained stable over time, which means that the gap between middle-aged and elderly patients did not increase.

The survival of elderly colon cancer patients is worse as compared to younger patients. Similar results have been found for elderly rectal cancer patients. *Chapter 5* included all stage I-III colorectal cancer patients diagnosed between 1991 and 2005 in the mid-western region of the Netherlands (n=9397). As expected, both overall and relative survival of elderly patients (aged 75 years or older), was worse as compared to patients younger than 65 years. These 'age related' differences disappeared in conditional relative survival, under the condition

that the patients should have survived the first postoperative year. Only in stage III disease, elderly patients had a worse conditional relative survival than young patients, probably due to differences in the use of adjuvant treatment. In conclusion, elderly colorectal cancer patients that survive the first year, have the same cancer related survival as younger patients. So, decreased survival in the elderly is mainly due to differences in early mortality. Treatment of elderly colorectal cancer patients should therefore focus on perioperative care and the first postoperative year.

As in colon cancer, the treatment of rectal cancer has changed substantially in the past two decades. Surgical resection has been improved by Phil Quirke and Bill Heald in 1986.^{35,103} Between 1987 and 1990, the Swedish rectal cancer trial has shown that preoperative short course radiotherapy decreases recurrence rates (27% in surgery only compared with 11% for patients treated with preoperative radiotherapy followed by immediate surgery).¹⁰⁴ The Dutch TME trial showed that with standardised total mesorectal excision (TME) surgery, preoperative radiotherapy still improves local control.³⁴ Since the introduction of preoperative radiotherapy, the interval between short course radiotherapy has been discussed as this could result in differences in outcome. *Chapter 6* addresses the impact of the interval between preoperative short course radiotherapy and surgery on outcome of rectal cancer patients in two time periods, during the TME trial and a more recent verification set. A total of 642 patients from the TME trial were included, and 600 patients from the verification set from two radiotherapy clinics in the Netherlands. During the TME trial, patients aged 75 years and older had a worse overall and non-cancer-related survival when surgically treated 4 to 7 days after the last fraction of radiotherapy. No differences in survival between the interval groups were found in the verification set. Several trials have found similar results.^{40,105} The results in the verification set may be different due to awareness of the clinicians, who avoided delayed surgery after radiotherapy since the results have been presented during congresses. Therefore, a longer than recommended interval between radiotherapy and surgery should be avoided.

PART II INTERNATIONAL COMPARISONS IN COLORECTAL CANCER TREATMENT AND SURVIVAL

Randomised controlled trials, systematic reviews, and meta-analyses are seen as the highest level of evidence. Unfortunately, randomised controlled trials are costly, time consuming, subgroups may be underrepresented in trials, and certain research questions remain unanswered by randomised clinical trials. Another option to identify optimal treatment is comparing treatment strategies. When all factors except the treatment strategy are comparable between regions or countries, the region or country can be seen as a pseudo randomisation, and the prognosis of different treatment strategies can then be compared. Overall, trials are important to answer specific research questions, but for individualised patient care trials might not

provide the needed information. In that case, large population based datasets can provide information about the optimal treatment of subgroups, such as elderly and patients with comorbidities. Audits might provide the detailed clinical information to compare treatment strategies and the results can be fed back to hospitals and clinicians, who can thereby further improve their outcome.

Major improvements have been achieved with national audits.¹⁰⁶⁻¹⁰⁸ However, although all the national audits achieved excellent results, differences in treatment and outcome remain between European countries.¹⁰⁹ To reduce the differences between the countries by identifying and spreading 'best practice', an international, multidisciplinary, outcome-based quality improvement program has been initiated: European Registration of Cancer Care (EURECCA).¹¹⁰ The EURECCA project makes use of existing national audit registrations and started with colorectal cancer, but also other solid tumour types, such as breast cancer, gastric cancer, oesophageal cancer, and hepato biliary (HPB) cancer and pancreatic cancer, have recently been initiated. *Chapter 7* describes the 'core dataset' of EURECCA colorectal. A total of 45 shared data items are identified. Among the 45 shared data items were patients' data, data about preoperative staging, surgical treatment, preoperative and postoperative treatment, and follow-up. The first EURECCA analyses are described in *Chapter 8*. The aim of this study was to compare the use of preoperative treatment for rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands. Several studies have shown differences in colorectal cancer survival, but most of these studies lacked of details about stage and treatment. All rectal cancer patients without distant metastases and operated on with a rectal resection from Norway, Sweden, Denmark, Belgium, and the Netherlands were included (n=10,296). The use of preoperative radiotherapy and chemoradiation varied widely across the countries. The variation in one year relative survival did not vary much. Sweden had a significant better one year relative survival after adjustment for age, gender, and stage as compared to the Netherlands. When stratified for age group, only patients aged 75 years or older from Sweden had a better one year relative survival after adjustment. The differences in one year survival are expected to be caused above all by differences in perioperative care, selection of patients, and especially management of elderly patients, and not by differences in the use of preoperative treatment. Effects of preoperative treatment will probably be visible in long term survival, unfortunately, this is not available yet.

In *Chapter 9* a new preoperative treatment for rectal cancer, high dose rate endorectal brachytherapy (HDREBT), used in a specialised clinic in Canada has been compared with standard of care in a specialised clinic in the Netherlands. In the Netherlands short course external beam radiotherapy and chemoradiation are standard of care. Short course external beam radiotherapy improved survival and decreased recurrences in rectal cancer, but improvements should be weighed against treatment related morbidity. High dose rate endorectal brachytherapy (HDREBT) is a targeted form of radiation therapy. Since the comparison of treatment would include biases such as confounding by indication and selection bias, this study has

compared treatment strategies from two specialised clinics. In total 141 patients from Canada treated with preoperative HDREBT, 26 Gy over 4 days, and 134 Dutch patients treated with either preoperative 5×5 Gy radiotherapy (n=52), or chemoradiation (n=82) were included, all diagnosed with a clinical T3 rectal carcinoma based on MRI-imaging. A statistically significant difference in five year overall survival was observed, with patients treated with HDREBT having better survival than patients from the Netherlands after adjustment (HR 0.42, 95% CI 0.20-0.90). Again patients should be alive in order to develop a recurrence at five years or to die due to the rectal cancer. Therefore, competing risk analyses have been performed for five year local recurrence and cancer-specific mortality. With death as competing risk, there were no significant differences in five year local recurrence and five year cancer-specific survival between the treatment strategies. Concluding, HDREBT seems to be a realistic alternative in the treatment of rectal cancer patients. The difference in five year overall survival between both countries might be possibly due to treatment related toxicities. These findings could have profound clinical implications and strongly suggest a randomised controlled trial in which the treatments can be compared.

Due to the research performed in the past and the ongoing research, more and more subgroups are being identified with screening, increasing age of the patients and the presence of comorbidities among the patient, besides, research in the past ten years has led to significant advances in the understanding of biology, molecular background, genetics, and pathogenesis of colorectal cancer. In the future, patient care has to become more multidisciplinary. Every involved specialism should be included in the audit structures. By comparing multidisciplinary audit structures across countries, optimal treatment strategies for subgroups can be identified. Besides optimal treatment strategies, the opinion of the patient should be incorporated achieving optimal personalised medicine.

REFERENCE LIST

- 1 International Agency for Research on Cancer. GLOBOCAN 2008. <http://globocan.iarc.fr/> (accessed April 25 2013).
- 2 van Steenbergen LN, Lemmens VE, Louwman MJ, Straathof JW, Coebergh JW. Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands. *Eur J Cancer Prev* 2009; **18**: 145-52.
- 3 Website of the Dutch government with information about public health and health care <http://www.nationaalkompas.nl/bevolking/vergrijzing/toekomst/> (accessed May 10 2013)
- 4 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108.
- 5 The statistics about cancer in the Netherlands registred by the Netherlands Cancer Registry. <http://www.cijfersoverkanker.nl/> (accessed April 25 2013).
- 6 Levin B, Lieberman DA, McFarland B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008; **58**: 130-60.
- 7 West NJ, Boustiere C, Fischbach W, Parente F, Leicester RJ. Colorectal cancer screening in Europe: differences in approach; similar barriers to overcome. *Int J Colorectal Dis* 2009; **24**: 731-40.
- 8 Gezondheidsraad. Bevolkingsonderzoek naar darmkanker. Den Haag: Gezondheidsraad; 2009. 2013.
- 9 Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA* 2009; **302**: 1685-92.
- 10 American Joint Committee on Cancer. <http://www.cancerstaging.org/mission/whatis.html> (accessed April 25 2013).
- 11 Dutch guidelines for the treatment of oncology. <http://www.oncoline.nl> (accessed April 25 2013).
- 12 Sobin LH, Hermanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. *Cancer* 1988; **61**: 2310-4.
- 13 Quirke P, Williams GT, Ectors N et al. The future of the TNM staging system in colorectal cancer: time for a debate? *Lancet Oncol* 2007; **8**: 651-7.
- 14 Nagtegaal ID, Quirke P, Schmol HJ. Has the new TNM classification for colorectal cancer improved care? *Nat Rev Clin Oncol* 2012; **9**: 119-23.
- 15 American Society of Clinical Oncology. <http://www.asco.org/> (accessed April 25 2013).
- 16 Lemmens VE, Janssen-Heijnen ML, Verheij CD et al. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. *Br J Surg* 2005; **92**: 615-23.
- 17 van den Broek CB, Bastiaannet E, Dekker JW et al. Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients - a large population-based study from 1990 to 2008. *Acta Oncol* 2012.
- 18 Brenner H, Bouvier AM, Foschi R et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EURO-CARE study. *Int J Cancer* 2012; **131**: 1649-58.
- 19 Droz JP, Aapro M, Balducci L. Overcoming challenges associated with chemotherapy treatment in the senior adult population. *Crit Rev Oncol Hematol* 2008; **68 Suppl 1**: S1-S8.
- 20 Hoeben KW, van Steenbergen LN, van de Wouw AJ et al. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. *Ann Oncol* 2013; **24**: 974-9.
- 21 Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. *J Natl Cancer Inst* 1994; **86**: 1766-70.
- 22 Keating NL, Landrum MB, Klabunde CN et al. Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? *J Clin Oncol* 2008; **26**: 2532-7.
- 23 Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer

- patient: SIOG expert recommendations. *Ann Oncol* 2009; **20**: 5-16.
- 24 Sargent DJ, Goldberg RM, Jacobson SD et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001; **345**: 1091-7.
 - 25 Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**: 352-8.
 - 26 Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet* 2000; **355**: 1588-96.
 - 27 O'Connell MJ, Mailliard JA, Kahn MJ et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; **15**: 246-50.
 - 28 Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**: 2343-51.
 - 29 Andre T, Boni C, Navarro M et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27**: 3109-16.
 - 30 Yothers G, O'Connell MJ, Allegra CJ et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011; **29**: 3768-74.
 - 31 Cassidy J, Saltz L, Twelves C et al. Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients. *Ann Oncol* 2011; **22**: 2604-9.
 - 32 van den Broek CB, Dekker JW, Bastiaannet E et al. The survival gap between middle-aged and elderly colon cancer patients. Time trends in treatment and survival. *Eur J Surg Oncol* 2011; **37**: 904-12.
 - 33 Tulchinsky H, Rabau M. Rectal cancer: progress over the past two decades. *Isr Med Assoc J* 2006; **8**: 711-2.
 - 34 van Gijn W, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
 - 35 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-82.
 - 36 Hartley A, Giridharan S, Gray L et al. Retrospective study of acute toxicity following short-course preoperative radiotherapy. *Br J Surg* 2002; **89**: 889-95.
 - 37 Hartley A, Giridharan S, Srihari N, McConkey C, Geh JI. Impaired postoperative neutrophil leucocytosis and acute complications following short course preoperative radiotherapy for operable rectal cancer. *Eur J Surg Oncol* 2003; **29**: 155-7.
 - 38 Pettersson D, Cedermark B, Holm T et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010; **97**: 580-7.
 - 39 Pettersson D, Glimelius B, Iversen H et al. Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III Trial. *Br J Surg* 2013.
 - 40 Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. *Radiother Oncol* 2009; **93**: 293-7.
 - 41 Marijnen CA, Nagtegaal ID, Klein KE et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001; **19**: 1976-84.
 - 42 Movsas B, Hanlon AL, Lanciano R et al. Phase I dose escalating trial of hyperfractionated pre-operative chemoradiation for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 1998; **42**: 43-50.
 - 43 Movsas B, Diratzouian H, Hanlon A et al. Phase II trial of preoperative chemoradiation with a hyperfractionated radiation boost in locally advanced rectal cancer. *Am J Clin Oncol* 2006; **29**: 435-41.

- 44 Myerson RJ, Valentini V, Birnbaum EH et al. A phase I/II trial of three-dimensionally planned concurrent boost radiotherapy and protracted venous infusion of 5-FU chemotherapy for locally advanced rectal carcinoma. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1299-308.
- 45 Ngan SY, Burmeister BH, Fisher R et al. Early toxicity from preoperative radiotherapy with continuous infusion 5-fluorouracil for resectable adenocarcinoma of the rectum: a Phase II trial for the Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2001; **50**: 883-7.
- 46 Martijnse IS, Dudink RL, Kusters M et al. T3+ and T4 rectal cancer patients seem to benefit from the addition of oxaliplatin to the neo-adjuvant chemoradiation regimen. *Ann Surg Oncol* 2012; **19**: 392-401.
- 47 Gerard JP, Chapet O, Nemoz C et al. Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen: the Lyon R0-04 phase II trial. *J Clin Oncol* 2003; **21**: 1119-24.
- 48 Ryan DP, Niedzwiecki D, Hollis D et al. Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901. *J Clin Oncol* 2006; **24**: 2557-62.
- 49 Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; **93**: 1215-23.
- 50 Information about trials sponsored by the Dutch Colorectal Cancer Group. <http://www.dccg.nl/trials/rapido> (accessed April 25 2013).
- 51 Devic S, Vuong T, Moftah B. Advantages of inflatable multichannel endorectal applicator in the neo-adjuvant treatment of patients with locally advanced rectal cancer with HDR brachytherapy. *J Appl Clin Med Phys* 2005; **6**: 44-9.
- 52 Devic S, Vuong T, Moftah B et al. Image-guided high dose rate endorectal brachytherapy. *Med Phys* 2007; **34**: 4451-8.
- 53 Vuong T, Richard C, Niazi T et al. High dose rate endorectal brachytherapy for patients with curable rectal cancer. *seminars in colon & rectal surgery* 2010; **21**: 115-9.
- 54 Vuong T, Devic S, Moftah B, Evans M, Podgorsak EB. High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: technical aspects. *Brachytherapy* 2005; **4**: 230-5.
- 55 Vuong T, Kopeck N, Ducruet T et al. Conformal therapy improves the therapeutic index of patients with anal canal cancer treated with combined chemotherapy and external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; **67**: 1394-400.
- 56 Kusters M, Valentini V, Calvo FA et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. *Ann Oncol* 2010; **21**: 1279-84.
- 57 Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; **3**: CD004078.
- 58 Benson AB, Schrag D, Somerfield MR et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; **22**: 3408-19.
- 59 Johnson FE, Longo WE, Vernava AM et al. How tumor stage affects surgeons' surveillance strategies after colon cancer surgery. *Cancer* 1995; **76**: 1325-9.
- 60 Johnson FE, Novell LA, Coplin MA et al. How practice patterns in colon cancer patient follow-up are affected by surgeon age. *Surg Oncol* 1996; **5**: 127-31.
- 61 Johnson FE, McKirgan LW, Coplin MA et al. Geographic variation in patient surveillance after colon cancer surgery. *J Clin Oncol* 1996; **14**: 183-7.
- 62 Vernava AM, III, Longo WE, Virgo KS et al. Current follow-up strategies after resection of

- colon cancer. Results of a survey of members of the American Society of Colon and Rectal Surgeons. *Dis Colon Rectum* 1994; **37**: 573-83.
- 63 Virgo KS, Wade TP, Longo WE et al. Surveillance after curative colon cancer resection: practice patterns of surgical subspecialists. *Ann Surg Oncol* 1995; **2**: 472-82.
 - 64 Anthony T, Simmang C, Hyman N et al. Practice parameters for the surveillance and follow-up of patients with colon and rectal cancer. *Dis Colon Rectum* 2004; **47**: 807-17.
 - 65 Benson AB, Desch CE, Flynn PJ et al. 2000 update of American Society of Clinical Oncology colorectal cancer surveillance guidelines. *J Clin Oncol* 2000; **18**: 3586-8.
 - 66 Duffy MJ, van DA, Haglund C et al. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. *Eur J Cancer* 2003; **39**: 718-27.
 - 67 Richard CS, McLeod RS. Follow-up of patients after resection for colorectal cancer: a position paper of the Canadian Society of Surgical Oncology and the Canadian Society of Colon and Rectal Surgeons. *Can J Surg* 1997; **40**: 90-100.
 - 68 Tornqvist A, Ekelund G, Leandroer L. The value of intensive follow-up after curative resection for colorectal carcinoma. *Br J Surg* 1982; **69**: 725-8.
 - 69 Tveit KM, Kataja VV. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of rectal cancer. *Ann Oncol* 2005; **16 Suppl 1**: i20-i21.
 - 70 Richert-Boe KE. Heterogeneity of cancer surveillance practices among medical oncologists in Washington and Oregon. *Cancer* 1995; **75**: 2605-12.
 - 71 Virgo KS, Vernava AM, Longo WE, McKirgan LW, Johnson FE. Cost of patient follow-up after potentially curative colorectal cancer treatment. *JAMA* 1995; **273**: 1837-41.
 - 72 Figueredo A, Rumble RB, Maroun J et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. *BMC Cancer* 2003; **3**: 26.
 - 73 Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2007; CD002200.
 - 74 Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002; **324**: 813.
 - 75 Ramesh HS, Pope D, Gennari R, Audisio RA. Optimising surgical management of elderly cancer patients. *World J Surg Oncol* 2005; **3**: 17.
 - 76 Ananda S, Field KM, Kosmider S et al. Patient age and comorbidity are major determinants of adjuvant chemotherapy use for stage III colon cancer in routine clinical practice. *J Clin Oncol* 2008; **26**: 4516-7.
 - 77 Lemmens VE, van Halteren AH, Janssen-Heijnen ML et al. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005; **16**: 767-72.
 - 78 Sarfati D, Hill S, Blakely T et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. *BMC Cancer* 2009; **9**: 116.
 - 79 Hines RB, Shanmugam C, Waterbor JW et al. Effect of comorbidity and body mass index on the survival of African-American and Caucasian patients with colon cancer. *Cancer* 2009; **115**: 5798-806.
 - 80 Iversen LH, Norgaard M, Jacobsen J, Laurberg S, Sorensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006--a population-based cohort study. *Dis Colon Rectum* 2009; **52**: 71-8.
 - 81 Janssen-Heijnen ML, Maas HA, Houterman S et al. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer* 2007; **43**: 2179-93.
 - 82 Lemmens VE, Janssen-Heijnen ML, Houterman S et al. Which comorbid conditions predict complications after surgery for colorectal cancer? *World J Surg* 2007; **31**: 192-9.

- 83 Zingmond D, Maggard M, O'Connell J et al. What predicts serious complications in colorectal cancer resection? *Am Surg* 2003; **69**: 969-74.
- 84 van Leersum NJ, Janssen-Heijnen ML, Wouters MW et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. *Int J Cancer* 2013; **132**: 2157-63.
- 85 Dekker JW, van den Broek CB, Bastiaannet E et al. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**: 1533-9.
- 86 Audisio RA, Bozzetti F, Gennari R et al. The surgical management of elderly cancer patients; recommendations of the SIOG surgical task force. *Eur J Cancer* 2004; **40**: 926-38.
- 87 Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; **20**: 5-16.
- 88 Extermann M. Basic assessment of the older cancer patient. *Curr Treat Options Oncol* 2011; **12**: 276-85.
- 89 Extermann M, Boler I, Reich RR et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 2012; **118**: 3377-86.
- 90 Hurria A, Cohen HJ, Extermann M. Geriatric Oncology Research in the Cooperative Groups: A Report of a SIOG Special Meeting. *J Geriatr Oncol* 2010; **1**: 40-4.
- 91 Kapiteijn E, Kranenbarg EK, Steup WH et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. *Eur J Surg* 1999; **165**: 410-20.
- 92 Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-49.
- 93 Birkmeyer JD, Siewers AE, Finlayson EV et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**: 1128-37.
- 94 von Meyenfeldt EM, Gooiker GA, van GW et al. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. *J Thorac Oncol* 2012; **7**: 1170-8.
- 95 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; **356**: 968-74.
- 96 Biganzoli L, Aapro M. Adjuvant chemotherapy in the elderly. *Ann Oncol* 2003; **14 Suppl 3**: iii1-iii3.
- 97 Neugut AI, Matasar M, Wang X et al. Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. *J Clin Oncol* 2006; **24**: 2368-75.
- 98 Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol* 2002; **20**: 1192-202.
- 99 Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 2001; **93**: 850-7.
- 100 Sundararajan V, Mitra N, Jacobson JS et al. Survival associated with 5-fluorouracil-based adjuvant chemotherapy among elderly patients with node-positive colon cancer. *Ann Intern Med* 2002; **136**: 349-57.
- 101 Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23**: 3112-24.
- 102 Quaglia A, Tavilla A, Shack L et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. *Eur J Cancer* 2009; **45**: 1006-16.
- 103 Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **2**: 996-9.

- 104 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; **336**: 980-7.
- 105 Pettersson D, Cedermark B, Holm T et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010; **97**: 580-7.
- 106 Pahlman L, Bohe M, Cedermark B et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**: 1285-92.
- 107 Wibe A, Moller B, Norstein J et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; **45**: 857-66.
- 108 Wibe A, Carlsen E, Dahl O et al. Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis* 2006; **8**: 224-9.
- 109 Sant M, Allemani C, Santaquilani M et al. EURO-CARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; **45**: 931-91.
- 110 van Gijn W, van de Velde CJ. Improving quality of cancer care through surgical audit. *Eur J Surg Oncol* 2010; **36 Suppl 1**: S23-S26.

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

In de westerse wereld is colorectaal carcinoom een belangrijk gezondheidsprobleem. De incidentie is hoog en zal naar verwachting nog verder toenemen in de komende jaren.¹ Daarnaast stijgt de incidentie met toenemende leeftijd, waardoor het voornamelijk een ziekte van de ouderen is. Samen leidt dit tot een verdere toename van het aantal oudere patiënten met colorectaal carcinoom in de komende jaren. Echter, leeftijdsspecifieke behandelrichtlijnen zijn niet beschikbaar. Bewijs uit 'population-based' onderzoek laat duidelijk zien dat oudere patiënten vaker inadequaats gestageerd worden², minder vaak electieve operaties ondergaan en minder vaak pre- of postoperatief worden behandeld met chemotherapie of radiotherapie in vergelijking met jongere patiënten³⁻⁷. Huidige richtlijnen zijn gebaseerd op (gerandomiseerde) trials, oudere patiënten en patiënten met comorbiditeit worden vaak geëxcludeerd of ondervertegenwoordigd in trials.⁸

DEEL I COLORECTAAL CARCINOOM; BEHANDELING EN OVERLEVING

Over de afgelopen 20 jaar is de behandeling van het coloncarcinoom aanzienlijk veranderd. Begin jaren 1990 hebben Moertel e.a.⁹ laten zien dat adjuvante chemotherapie een gunstig effect heeft op de overleving. De richtlijnen in Nederland zijn daarop in 1997 aangepast en adjuvante behandeling met chemotherapie wordt nu geadviseerd voor alle patiënten met stadium III coloncarcinoom, ongeacht de leeftijd van de patiënt. Het doel van *Hoofdstuk 2* was het beschrijven van de tijd trends in het gebruik en de kosten van adjuvante chemotherapie. In totaal 24.111 patiënten met stadium III coloncarcinoom gediagnosticeerd tussen 1990 en 2008 zijn geïnccludeerd in deze retrospectieve cohort studie. Zowel de het gebruik (van 9,5% in 1990, naar 61,8% in 2008), als de geschatte medicijnkosten van chemotherapie (van €38,467 in 1990, naar €3.876.150 in 2008), zijn toegenomen over de studieperiode. Met toenemende leeftijd werd er minder chemotherapie gebruikt. Multivariabele analyses van de relatieve overleving lieten een verbetering zien voor alle patiënten behandeld met adjuvante chemotherapie (RER 0,93; 95% CI 0,92-0,94). Voor patiënten jonger dan 80 jaar die geen adjuvante chemotherapie kregen, daarentegen, bleef de relatieve overleving stabiel (RER 1,00; 95% CI 1,00-1,01). De relatieve overleving van patiënten ouder dan 80 jaar zonder adjuvante chemotherapie behandeld is toegenomen over de studieperiode (RER 0,98; 95% CI 0,97-0,99). Concluderend; het gebruik van adjuvante chemotherapie, de kosten van chemotherapie en de overleving van de patiënten met stadium III coloncarcinoom zijn over de tijd toegenomen. Waar het gebruik en de kosten van chemotherapie aanzienlijk zijn toegenomen, is de relatieve overleving in mindere mate verbeterd. Patiënten behandeld met adjuvante chemotherapie hadden een gelijkmatige verbetering van de overleving in alle leeftijdsgroepen.

Ondanks dat de Nederlandse richtlijnen adviseren om alle patiënten met stadium III coloncarcinoom met adjuvante chemotherapie te behandelen, krijgt een groot deel van de patiënten geen aanvullende behandeling met chemotherapie. Het percentage patiënten wat niet behandeld wordt met adjuvante chemotherapie neemt toe met toenemende leeftijd. In *Hoofdstuk 3* worden de factoren bestudeerd die geassocieerd zijn met het onthouden van adjuvante chemotherapie, daarnaast zijn ook de doodsoorzaken en de recidieven van deze populatie bestudeerd. In totaal 348 opeenvolgende patiënten met stadium III coloncarcinoom gediagnosticeerd tussen 2000 en 2009 van twee ziekenhuis in de mid-westerse regio van Nederland werden geïnccludeerd. De meeste patiënten waren tussen 70 en 79 jaar oud (35,6%) en iets meer vrouwelijke patiënten werden geïnccludeerd (51,4%). Net iets meer dan de helft van de patiënten hebben adjuvante chemotherapie gehad (50,6%). Oudere patiënten en patiënten met één of meer comorbiditeiten werden minder met adjuvante chemotherapie behandeld. Dit effect bleef zichtbaar na correctie voor mogelijke confounders. Patiënten die niet behandeld werden met adjuvante chemotherapie stierven vaker eerder, en meer als gevolg van complicaties en hartfalen. Adjuvante chemotherapie is een behandeling voor het voorkomen van recidieven na een in opzet curatieve operatie. Om een recidief te krijgen, moet een patiënt in leven zijn. Daarom is een zogenaamde 'competing risk' analyse uitgevoerd, waarbij dood een 'competing risk', ofwel concurrerend risico, is. Patiënten die geen adjuvante chemotherapie ontvingen hadden een vergelijkbare cumulatieve incidentie voor het krijgen van een recidief, wanneer dood als een concurrerend risico werd meegenomen. Deze studie toont aan dat de selectie van patiënten die geschikt zijn voor adjuvante chemotherapie van groot belang is om zo recidieven te voorkomen. Verder onderzoek zou zich moeten richten op het objectiveren van de selectie van de patiënten die wel en niet met adjuvante chemotherapie behandeld worden. Daarnaast moet het verminderen van recidieven in zowel patiënten die wel en niet behandeld zijn met adjuvante chemotherapie, en het optimaliseren van de kwaliteit van leven van deze patiënten een focus van verder onderzoek zijn.

Recentelijk heeft de EURO CARE working group laten zien dat de overleving van patiënten met coloncarcinoom verbeterd is tussen 1988 en 1990. Echter, wanneer zij de relatieve vijf jaar overleving vergeleken tussen oudere patiënten (70 tot 85 jaar) en patiënten van middelbare leeftijd (55 tot 69 jaar), bleek dat de overleving van beide leeftijdsgroepen was verbeterd over de tijd, maar in mindere mate bij de oudere patiënten, waardoor een overlevingskloof is ontstaan.¹⁰ *Hoofdstuk 4* had als doel om de behandeling en overleving over de tijd (1991-2005) te beschrijven tussen jongere (<65 jaar), middelbare (65 tot 74 jaar), en oudere (≥75 jaar) patiënten met coloncarcinoom in de mid-westerse regio van Nederland, om zo te bepalen of de overlevingskloof is toegenomen over de tijd. In totaal 8.926 patiënten met invasief coloncarcinoom zijn geïnccludeerd in deze studie. Over de tijd vonden geen veranderingen in de behandeling van stadium I en II coloncarcinoom plaats, terwijl er een toename was in het gebruik van adjuvante chemotherapie voor stadium III en IV. Stadium IV patiënten werden over de tijd minder vaak geopereerd. Verschillen in de overleving tussen jongere en oudere

patiënten was aanwezig en daarmee was de overlevingskloof van de EUROCORE bevestigd. Desondanks, de verschillen tussen de leeftijdsgroepen bleven stabiel over de tijd, wat betekent dat de kloof tussen jongere en oudere patiënten met coloncarcinoom niet is toegenomen. De overleving van oudere patiënten met coloncarcinoom is slechter in vergelijking met jongere patiënten. Vergelijkbare verschillen zijn gevonden bij oudere patiënten met rectumcarcinoom. *Hoofdstuk 5* heeft alle stadium I-III colorectaal carcinoom patiënten gediagnosticeerd tussen 1991 en 2005 in de mid-westerse regio van Nederland geïncludeerd ($n=9.397$). Zoals verwacht, was zowel de overall als de relatieve overleving van oudere patiënten (75 jaar en ouder) slechter in vergelijking met patiënten jonger dan 65 jaar. Deze leeftijd gerelateerde verschillen verdwenen bij conditionele relatieve survival, onder de conditie dat de patiënten het eerste jaar na de operatie overleefd moeten hebben. Alleen bij stadium III hadden oudere patiënten een slechtere conditionele relatieve survival, waarschijnlijk door de verschillen in het gebruik van adjuvante behandeling. Concluderend hebben oudere patiënten die het eerste postoperatieve jaar overleven een vergelijkbaar kanker-gerelateerde overleving als jongere patiënten. De lagere overleving van oudere patiënten is dus voornamelijk door verschillen in vroege mortaliteit. De behandeling van oudere colorectaal carcinoom patiënten moet zich daarom focussen op de perioperatieve zorg en het eerste postoperatieve jaar.

Net als voor het coloncarcinoom is de behandeling van het rectumcarcinoom aanzienlijk veranderd in de afgelopen 20 jaar. De chirurgische verwijdering is verbeterd mede door Phil Quirke en Bill Heald in 1986.^{11,12} De Zweedse rectumcarcinoom trial liet tussen 1987 en 1990 zien dat preoperatieve radiotherapie een afname geeft van het aantal lokaal recidieven (27% in de groep alleen behandeld met chirurgie, vergeleken met 11% in de groep behandeld met preoperatieve radiotherapie direct gevolgd door chirurgie).¹³ De Nederlandse TME trial liet zien dat met gestandaardiseerde totale mesorectale excisie (TME) chirurgie, preoperatieve radiotherapie nog altijd lokale controle verbeterd.¹⁴ Sinds de introductie van kortdurende preoperatieve radiotherapie, wordt het interval tussen de radiotherapie en de chirurgie bediscussieerd, aangezien het interval mogelijk invloed zou kunnen hebben op de uitkomsten. *Hoofdstuk 6* beschrijft de impact van het interval tussen kortdurende preoperatieve radiotherapie en chirurgie op de uitkomst van rectumcarcinoom patiënten gedurende twee tijdsperiodes, tijdens de TME trial en tijdens een meer recente verificatie set. In totaal waren 642 patiënten van de TME trial geïncludeerd, en 600 patiënten van de verificatie set uit twee radiotherapeutische centra in Nederland waren geïncludeerd. Gedurende de TME trial hadden patiënten van 75 jaar en ouder een slechtere overall en niet-kanker-gerelateerde overleving wanneer ze 4 tot 7 dagen na de laatste fractie radiotherapie geopereerd werden. In de verificatie set werden geen verschillen in overleving tussen de verschillende interval-groepen gevonden. De resultaten in de verificatie set kunnen beïnvloed zijn door besef van de clinici aangezien de resultaten van de TME trial op verschillende congressen gepresenteerd zijn, waardoor vertraagde chirurgie na radiotherapie wellicht vermijd werd. Daarnaast hebben

verschillende andere trials vergelijkbare resultaten gevonden.^{15,16} Alles bij elkaar zou een langer dan geadviseerd interval tussen radiotherapie en chirurgie vermeden moeten worden.

DEEL II INTERNATIONALE VERGELIJKINGEN VAN DE BEHANDELING EN OVERLEVING VAN COLORECTAAL CARCINOOM

Gerandomiseerde gecontroleerde trials, systematische reviews, en meta-analyses worden gezien als de hoogste 'levels of evidence'. Helaas zijn gerandomiseerde gecontroleerde trials kostbaar, tijdrovend, sommige subgroepen zijn vaak ondervertegenwoordigd in trials, en bepaalde onderzoeksvragen blijven onbeantwoord door gerandomiseerde trials. Een andere optie om optimale behandeling te identificeren is het vergelijken van behandelingsstrategieën. Wanneer alle factoren behalve de behandelingsstrategie vergelijkbaar zijn tussen regio's of landen, kan de regio of het land gezien worden als een pseudorandomisatie, waardoor de uitkomsten van de verschillende behandelingsstrategieën met elkaar vergeleken kunnen worden. Concluderend, zijn trials belangrijk om specifieke onderzoeksvragen te beantwoorden, maar bij geïndividualiseerde patiënten zorg kunnen trials niet de benodigde informatie geven. In dat geval, kunnen grote 'population-based' datasets ons wel informeren over de optimale behandeling van bepaalde subgroepen, zoals oudere patiënten of patiënten met comorbiditeit. Audits kunnen gedetailleerde klinische informatie bieden om daarmee behandelingsstrategieën te vergelijken en de resultaten kunnen terug gekoppeld worden aan de ziekenhuizen en specialisten, die daardoor hun uitkomsten verder kunnen verbeteren.

Grote verbeteringen zijn behaald met behulp van nationale audits.¹⁷⁻¹⁹ Landelijk hebben audits dan wel uitstekende resultaten bereikt, verschillen in de behandelingen en uitkomsten tussen de verschillende Europese landen blijven bestaan.²⁰ Om de verschillen tussen de landen te minimaliseren door middel van het identificeren en verspreiden van 'best practice' is een internationaal, multidisciplinair, uitkomstgebaseerd kwaliteitsverbeteringsprogramma geïnitieerd: European REgistration of Cancer Care (EURECCA).²¹ Het EURECCA-project gebruikt bestaande nationale audit registraties en is begonnen met colorectaal carcinoom registraties, daarnaast zijn andere solide tumoren, zoals mammacarcinoom, maagcarcinoom en oesophaguscarcinoom geïnitieerd, maar in de toekomst zullen onder andere HPB (hepatobiliare) carcinen en pancreascarcinomen, volgen. *Hoofdstuk 7* beschrijft de 'core dataset' van EURECCA colorectaal. In totaal 45 gedeelde variabelen zijn geïdentificeerd. Onder deze 45 variabelen vallen data-items over patiëntkarakteristieken, preoperatieve stadiëring, chirurgische behandeling, preoperatieve en postoperatieve behandeling, en follow-up. De eerste EURECCA-analyses zijn beschreven in *Hoofdstuk 8*. Het doel van deze studie was het vergelijken van het gebruik van preoperatieve behandeling tussen Noorwegen, Zweden, Denemarken, België, en Nederland voor patiënten met een rectumcarcinoom. Diverse studies hebben verschillen in de overleving van colorectaal carcinoom patiënten tussen landen laten zien, maar bij de

meeste van die studies ontbrak informatie over stadium en behandeling. Alle patiënten met een rectumcarcinoom zonder afstandsmetastasen en geopereerd aan de tumor door middel van een rectumresectie uit Noorwegen, Zweden, Denemarken, België, en Nederland werden geïnccludeerd (n=10.296). Het gebruik van preoperatieve radiotherapie en chemoradiatie varieerde sterk tussen de landen. De éénjaars overleving varieerde in minder mate. Zweden had een significant betere overleving in vergelijking met Nederland na correctie voor leeftijd, geslacht, stadium. Gestratificeerd naar leeftijdsgroep, hadden alleen de patiënten van 75 jaar en ouder uit Zweden een betere éénjaars overleving na correctie. Naar verwachting worden de verschillen in éénjaars overleving veroorzaakt door verschillen in perioperatieve zorg, selectie van patiënten, en in het bijzonder de behandeling van oudere patiënten, en niet zozeer door verschillen in het gebruik van preoperatieve behandeling.

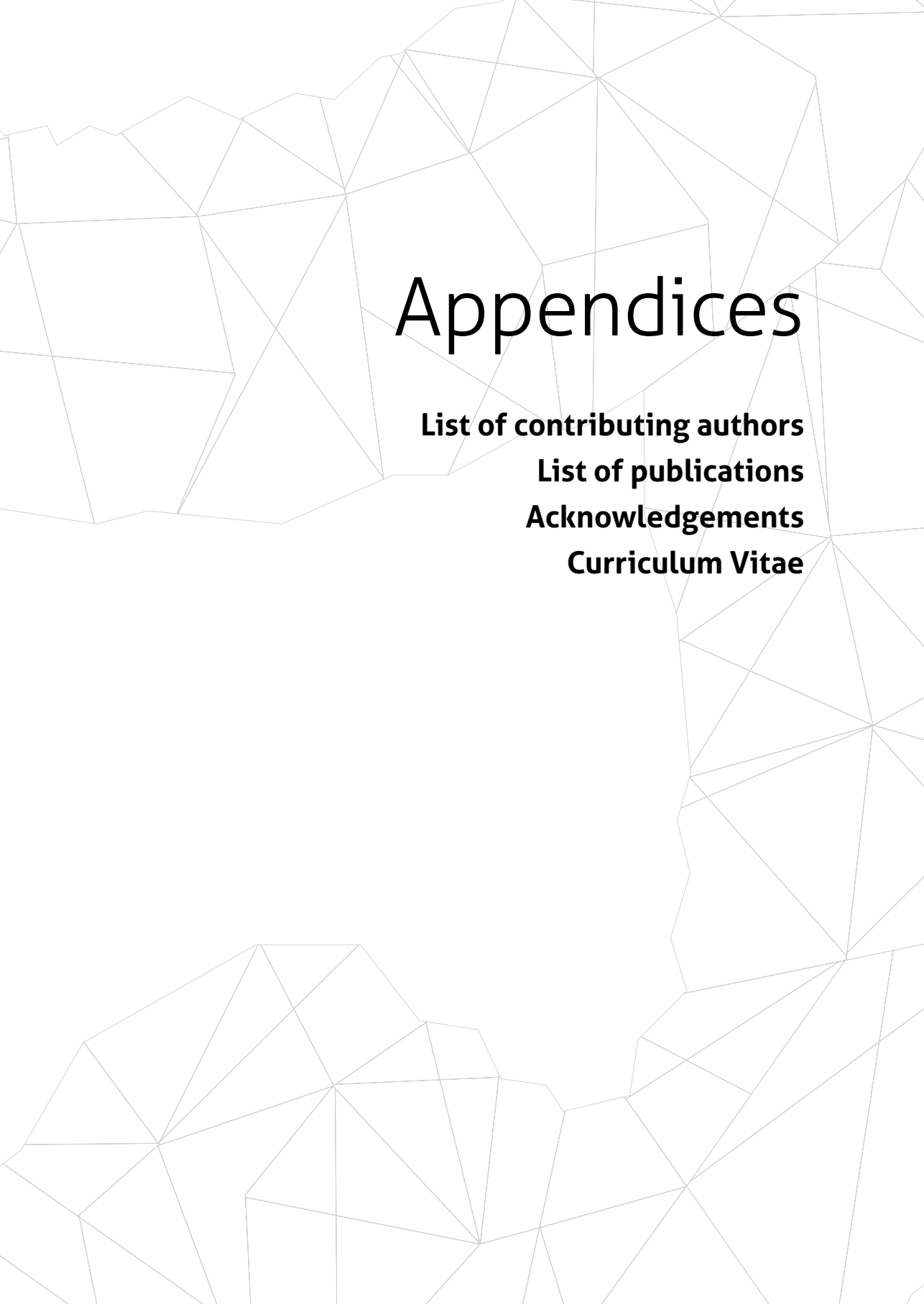
In *Hoofdstuk 9* is een nieuwe preoperatieve behandeling voor het rectumcarcinoom, 'high dose rate endorectal brachytherapy' (HDREBT), gebruikt in een gespecialiseerde kliniek in Canada, vergeleken met de standaard behandeling in een gespecialiseerde kliniek in Nederland. In Nederland zijn kortdurende preoperatieve radiotherapie en chemoradiatie de standaard zorg. Kortdurende radiotherapie verbeterde de overleving en verminderde het aantal recidieven, maar deze verbeteringen moeten worden afgewogen tegen de morbiditeit door de behandeling. HDREBT is een gerichte wijze van radiotherapie. In totaal 141 Canadese patiënten behandeld met preoperatieve HDREBT, 26 Gy over 4 dagen, en 134 Nederlandse patiënten behandeld met of preoperatieve 5×5 Gy radiotherapie (n=52), of chemoradiatie (n=82) werden geïnccludeerd, allen hadden zij een cT3 rectumcarcinoom op basis van de MRI beelden. Geen verschillen in lokale recidieven en niet-kankergelateerde overleving werden gevonden tussen Nederland en Canada (5 uit 134 versus 2 uit 141, en 6 uit 134 versus 4 uit 141, respectievelijk). Een statistisch significant verschil in vijf jaar overall overleving was gevonden, waarbij patiënten uit Canada een betere overleving hadden dan de patiënten uit Nederland na correctie (HR 0,42; 95% CI 0,20-0,90, p=0,03). HDREBT lijkt daarmee een realistisch alternatief voor de behandeling van patiënten met rectumcarcinoom. De verschillen in vijf jaar overall overleving tussen beide landen zijn mogelijk door de behandeling gerelateerde toxiciteit. Deze bevindingen kunnen grote klinische implicaties hebben; echter een gerandomiseerde trial kan hier definitief antwoord op geven.

Als gevolg van onderzoek uit het verleden en het lopende onderzoek, zullen in de toekomst een toenemend aantal subgroepen geïdentificeerd worden met screening, toenemende leeftijd van de patiënten en de aanwezigheid van comorbiditeiten bij patiënten, daarnaast heeft onderzoek in de afgelopen tien jaar ertoe geleid dat significante vooruitgang is geboekt in het begrijpen van de biologie, moleculaire achtergrond, genetica, en pathogenese van het colorectaal carcinoom. In de toekomst zal patiëntenzorg meer multidisciplinair worden. Ieder betrokken specialisme zou deel moeten nemen aan de auditstructuren. Door multidisciplinaire auditstructuren tussen landen te vergelijken kunnen optimale behandelingsstrategieën voor iedere subgroep geïdentificeerd worden. Naast optimale behandelingsstrategieën, zal ook de

mening van de patiënt opgenomen moeten worden, om zo optimaal 'personalised medicine' te bereiken.

REFERENTIE LIJST

- 1 Statistieken over kanker in Nederland geregistreerd door de Nederlandse Kanker-Registratie. <http://www.cijfersoverkanker.nl/> (Geraadpleegd 25 april 2013).
- 2 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; **356**: 968-74.
- 3 Biganzoli L, Aapro M. Adjuvant chemotherapy in the elderly. *Ann Oncol* 2003; **14 Suppl 3**: iii1-iii3.
- 4 Neugut AI, Matasar M, Wang X et al. Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. *J Clin Oncol* 2006; **24**: 2368-75.
- 5 Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol* 2002; **20**: 1192-202.
- 6 Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 2001; **93**: 850-7.
- 7 Sundararajan V, Mitra N, Jacobson JS et al. Survival associated with 5-fluorouracil-based adjuvant chemotherapy among elderly patients with node-positive colon cancer. *Ann Intern Med* 2002; **136**: 349-57.
- 8 Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23**: 3112-24.
- 9 Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**: 352-8.
- 10 Quaglia A, Tavilla A, Shack L et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. *Eur J Cancer* 2009; **45**: 1006-16.
- 11 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-82.
- 12 Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **2**: 996-9.
- 13 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; **336**: 980-7.
- 14 van Gijn W., Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575-82.
- 15 Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. *Radiother Oncol* 2009; **93**: 293-7.
- 16 Pettersson D, Cedermark B, Holm T et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010; **97**: 580-7.
- 17 Pahlman L, Bohe M, Cedermark B et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**: 1285-92.
- 18 Wibe A, Moller B, Norstein J et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; **45**: 857-66.
- 19 Wibe A, Carlsen E, Dahl O et al. Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis* 2006; **8**: 224-9.
- 20 Sant M, Allemani C, Santaquilani M et al. EURO-CARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; **45**: 931-91.
- 21 van Gijn W., van de Velde CJ. Improving quality of cancer care through surgical audit. *Eur J Surg Oncol* 2010; **36 Suppl 1**: S23-S26.



Appendices

List of contributing authors

List of publications

Acknowledgements

Curriculum Vitae

LIST OF CONTRIBUTING AUTHORS

L. Azoulay	Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, Quebec, Canada & Department of Oncology, McGill University, Montreal, Quebec, Canada
E. Bastiaannet	Department of Surgery & Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands
H.A. van den Berg	Department of Radiotherapy, Catherina Hospital Eindhoven, Eindhoven, the Netherlands
P.G. Boelens	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
A.J. Breugom	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
A.J.M. de Craen	Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands
J.W.T. Dekker	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
O.M. Dekkers	Department of Epidemiology, Leiden University Medical Center, Leiden, the Netherlands
A. Dziki	Department of General and Colorectal Surgery, Medical University of Lodz, Lodz, Poland. On behalf of the International Quality Assurance Project for Colorectal Cancer (Poland)
M.A.G. Elferink	Department of Research, Comprehensive Cancer Center The Netherlands, Utrecht, the Netherlands
L.G.M. van de Geest	Comprehensive Cancer Centre West, Leiden, the Netherlands
W. van Gijn	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
H. Harling	Department of Surgery K, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark. On behalf of the Danish Colorectal Cancer Database
L.H. Iversen	Department of Surgery, P Aarhus University Hospital, Aarhus, Denmark. On behalf of the Danish Colorectal Cancer Database
R. Johansson	Department of Radiation Science, Oncology, Umeå° University, Umeå°, Sweden. On behalf of the Swedish ColoRectal Cancer Registry
G.J. Liefers	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
E. Kapiteijn	Department of Clinical Oncology, Leiden University Medical Center, Leiden, the Netherlands
P. Krijnen	Comprehensive Cancer Centre West, Leiden, the Netherlands

C.A.M. Marijnen	Department of Clinical Oncology, Leiden University Medical Center, Leiden, the Netherlands
B. Møller	Department of Clinical and Registry-based Research, Cancer Registry of Norway, Institute of Population-based Cancer Research, Oslo, Norway. On behalf of the Norwegian Colorectal Cancer Project
P. Mroczkowski	Department of General, Visceral and Vascular Surgery, Otto-von-Guericke-University of Magdeburg, Magdeburg, Germany. On behalf of the International Quality Assurance Project for Colorectal Cancer (Germany)
T. Niazi	Department of Radiation Oncology, Jewish General Hospital, McGill University, Montréal, Quebec, Canada
H. Ortiz	Department of Surgery, Complejo Hospitalario de Pamplona, Universidad Publica de Navarra, Pamplona, Navarra, Spain. On behalf of the Spanish Rectal Cancer Project
L. Pählman	Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. On behalf of the Swedish ColoRectal Cancer Registry
D. Pavalkis	Department of Surgery, University of Medicine Kaunas, Kaunas, Lithuania. On behalf of the International Quality Assurance Project for Colorectal Cancer (Lithuania)
F. Penninckx	Department of Abdominal Surgery, University Hospital Gasthuisberg Leuven, Belgium. On behalf of the Belgian Project On Cancer Of The Rectum (PROCARE)
J.E.A. Portielje	Department of Clinical Oncology, Haga Hospital, The Hague, the Netherlands
C.C.E.M. Puylaert	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
G. Romano	Department of oncologic surgery, National Cancer Institute, "Fond. G. Pascale", Napoli, Italy. On behalf of the International Quality Assurance Project for Colorectal Cancer (Italy)
H.J.T. Rutten	Department of Surgery, Catherina Hospital Eindhoven, Eindhoven, the Netherlands
J.J. Smith	Department of Surgery, West Middlesex University Hospital, London, United Kingdom. On behalf of the National Bowel Cancer Audit Program (NBOCAP)
R.A.E.M. Tollenaar	Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
V. Valentini	Department of Radiotherapy, Catholic University of the Sacred Heart, Rome, Italy. On behalf of the Study group for Therapies Of Rectal Malignancies (STORM)

- C.J.H. van de Velde** Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
- T.A. Vermeer** Department of Surgery, Catherina Hospital Eindhoven, Eindhoven, the Netherlands
- T. Vuong** Department of Radiation Oncology, Jewish General Hospital, McGill University, Montréal, Quebec, Canada
- A. Wibe** Department of Cancer Research and Molecular Medicine Norwegian, University of Science and Technology, and Department of Surgery, St. Olavs Hospital, Trondheim, Norway. On behalf of the Norwegian Colorectal Cancer Project
- M.W.J.M. Wouters** Department of Surgical Oncology, Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands. On behalf of the Dutch Surgical Colorectal Audit (DSCA)

LIST OF PUBLICATIONS

J.W.T. Dekker, C.B.M. van den Broek, E. Bastiaannet, L.G.M. van de Geest, R.A.E.M. Tollenaar, G.J. Liefers: Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol*. 2011 Jun; 18(6): 1533-9.

C.B.M. van den Broek, J.W.T. Dekker, E. Bastiaannet, P. Krijnen, A.J.M. de Craen, R.A.E.M. Tollenaar, C.J.H. van de Velde, G.J. Liefers: The survival gap between middle-aged and elderly colon cancer patients. Time trends in treatment and survival. *Eur J Surg Oncol*. 2011 Oct;37(10):904-12.

W. van Gijn, C.B.M. van den Broek, P. Mroczkowski, A. Dziki, G. Romano, D. Pavalkis, M.W.J.M. Wouters, B. Møller, A. Wibe, L. Pählman, H. Harling, J.J. Smith, F. Penninckx, H. Ortiz, V. Valentini, C.J.H. van de Velde: The EURECCA project: Data items scored by European colorectal cancer audit registries. *Eur J Surg Oncol*. 2012 Jun;38(6):467-71.

E. Bastiaannet, K. Sampieri, O.M. Dekkers, A.J.M. de Craen, M.P.P. van Herk-Sukel, V.E.P.P. Lemmens, C.B.M. van den Broek, J.W. Coebergh, R.M.C. Herings, C.J.H. van de Velde, R. Fodde & G.J. Liefers: Use of aspirin postdiagnosis improves survival for colon cancer patients. *Br J Cancer*. 2012 Apr 24;106(9):1564-70.

C.B.M. van den Broek, E. Bastiaannet, J.W.T. Dekker, J.E.A. Portielje, A.J.M. de Craen, M.A.G. Elferink, C.J.H. van de Velde, G.J. Liefers, E. Kapiteijn: Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients – a large population-based study from 1990 to 2008. *Acta Oncol*. 2013 Jun;52(5):941-9.

M.S. Reimers, E. Bastiaannet, M.P.P. van Herk-Sukel, V.E.P.P. Lemmens, C.B.M. van den Broek, C.J.H. van de Velde, A.J.M. de Craen, G.J. Liefers: Aspirin use after the diagnosis improves survival in older colon cancer patients: a retrospective cohort study. *J Am Geriatr Soc*. 2012 Dec;60(12):2232-6.

C.J.H. van de Velde, C.B.M. van den Broek: Quality assurance in rectal cancer treatment. *Dig Dis*. 2012;30 Suppl 2: 126-31.

H.S. Snijders, C.B.M. van den Broek, M.W.J.M. Wouters, E.M. Meershoek-Klein Kranenbarg, T. Wiggers, H.J.T. Rutten, C.J.H. van de Velde, R.A.E.M. Tollenaar, J.W.T. Dekker: An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? *Eur J Surg Oncol*. 2013 Jul;39(7):715-20.

C.B.M. van den Broek, Petra G. Boelens, Anne J. Breugom, Cornelis J.H. van de Velde: Improving the Outcome of Colorectal Cancer: the European Registration of Cancer Care (EURECCA) Project. *Colorectal Cancer*. 2013 August;2(4):371-6.

C.J.H. van de Velde, C. Aristei, P.G. Boelens, R.G. Beets-Tan, L. Blomqvist, J.M. Borrás, C.B.M. van den Broek, G. Brown, J.W. Coebergh, E. van Cutsem, E. Espin, J. Gore-Booth, B. Glimelius, K. Haustermans, G. Henning, L.H. Iversen, J.H. van Krieken, C.A.M. Marijnen, P. Mroczkowski, I. Nagtegaal, P. Naredi, H. Ortiz, L. Pahlman, P. Quirke, C. Rödel, A. Roth, H.J.T. Rutten, H.J. Schmoll, J.J. Smith, P.J. Tanis, C. Taylor, A. Wibe, M.A. Gambacorta, E. Meldolesi, T. Wiggers, A. Cervantes, V. Valentini: EURECCA colorectal: Multidisciplinary Mission statement on better care for patients with colon and rectal cancer in Europe. *Eur J Cancer*. 2013 Sep;49(13):2784-90.

C.B.M. van den Broek, T.A. Vermeer, E. Bastiaannet, H.J.T. Rutten, C.J.H. van de Velde, C.A.M. Marijnen: Impact of the interval between short course radiotherapy and surgery on outcomes of rectal cancer patients. 2013 Oct;49(15):3131-9.

C.J.H. van de Velde, P.G. Boelens, J.M. Borrás, J.W. Coebergh, A. Cervantes, L. Blomqvist, R.G.H. Beets-Tan, C.B.M. van den Broek, G. Brown, E. Van Cutsem, E. Espin, K. Haustermans, B. Glimelius, L.H. Iversen, J.H. van Krieken, C.A.M. Marijnen, G. Henning, J. Gore-Booth, E. Meldolesi, P. Mroczkowski, I. Nagtegaal, P. Naredi, H. Ortiz, L. Pahlman, P. Quirke, C. Rödel, A. Roth, H.J.T. Rutten, H.J. Schmoll, J.J. Smith, P.J. Tanis, C. Taylor, A. Wibe, T. Wiggers, M.A. Gambacorta, C. Aristei, V. Valentini: Multidisciplinary Management: European Consensus Conference Colon & Rectum. *Eur J Cancer*. 2013 Oct 31. Epub ahead of print.

A.J. Breugom, P.G. Boelens, C.B.M. van den Broek, A. Cervantes, E. Van Cutsem, H.J. Schmoll, V. Valentini, C.J.H. van de Velde. Quality assurance in the treatment of colorectal cancer: the EURECCA initiative. 2013 Invited for publication *Ann Oncol*.

C.B.M. van den Broek, T.A. Vermeer, T. Vuong, E. Bastiaannet, L. Azoulay, O.M. Dekkers, T. Niazi, H.A. van den Berg, H.J.T. Rutten, C.J.H. van de Velde. A comparison of high-dose-rate endorectal brachytherapy, short course radiotherapy and chemoradiation on the outcome of rectal cancer patients. 2013 Submitted

C.B.M. van den Broek, W. van Gijn, E. Bastiaannet, B. Møller, R. Johansson, M.A.G. Elferink, A. Wibe, L. Pahlman, L.H. Iversen, F. Penninckx, V. Valentini, C.J.H. van de Velde. On behalf of the EURECCA consortium: A comparison of the administration of preoperative treatment and short term outcomes of rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands. 2013 Submitted for publication.

J.W.T. Dekker, G.A. Gooiker, E. Bastiaannet, C.B.M. van den Broek, P.W. de Graaf, L.G.M. van de Geest, C.J.H. van de Velde, R.A.E.M. Tollenaar, G.J. Liefers: The prolonged impact of the insult of surgery for colorectal cancer in elderly patients. 2013 Submitted for publication.

C.B.M. van den Broek, C.C.E.M. Puylaert, E. Bastiaannet, A.J.M. de Craen, C.J.H. van de Velde, G.J. Liefers, J.E.A. Portielje: Characteristics and outcome of stage III colon cancer patients; a comparison between patients who did and who did not receive guideline recommended adjuvant chemotherapy. 2013 Submitted for publication.

ACKNOWLEDGEMENTS

Finally, these are pages that will be read by most of you. This is the moment to thank all the people that have supported me for the past four years. I would like to thank everyone who has contributed to this thesis for his or her time, effort, energy, creativity, enthusiasm, and support. Some of them I would like to acknowledge especially for their involvement.

Allereerst en bovenal prof. dr. C.J.H. van de Velde, die mij de afgelopen jaren intensief heeft begeleid en gestuurd gedurende mijn promotie onderzoek. Beste professor, uw optimisme en drive bewonder ik enorm. Zonder uw ideeën, internationale betrokkenheid, en nauwe samenwerking zou dit proefschrift nooit compleet zijn geweest. Dank u voor deze onderzoeksmogelijkheden en ik hoop in de toekomst nog meer van u te mogen leren!

Dr. G.J. Liefers, beste Gerrit-Jan, jij hebt me aangestoken met enthousiasme voor het onderzoek doen. Jouw tomeloze energie en nieuwe inzichten in voor mij onbegrijpelijke resultaten, hebben dit proefschrift enorm geholpen.

Dr. Ir. E. Bastiaannet, beste Esther, co-promotor! Dit proefschrift had geen analyses gehad zonder jouw (oneindige) geduld en goede uitleg. Altijd had je tijd om mijn vragen te beantwoorden en na te denken over resultaten en analyses.

Leden van de leescommissie, graag wil ik jullie allen hartelijk danken voor de aandacht en tijd die u hebt besteed aan het inzien en beoordelen van dit proefschrift.

Mijn dank gaat uit naar alle andere coauteurs, bedankt voor de prettige samenwerking.

Enkele coauteurs wil ik in het bijzonder noemen, waaronder Ton de Craen, jouw kritische blik heeft mijn ogen vaak geopend. Johanneke Portielje, jij bent het korte lijntje met het Haga ziekenhuis, de samenwerking met jou heeft nieuwe ideeën en onderzoeken gebracht. Ellen Kapiteijn, jij bracht mij de medisch oncologische kennis bij die ik miste bij het schrijven. Corrie Marijnen, jij leerde mij de radiotherapie kennen waardoor mijn toekomstperspectief is veranderd. Harm Rutten, het gebruik van jouw gedetailleerde data gaf mij de mogelijkheid tot meer onderzoek. Té Vuong and the other authors from Canada thank you for the opportunity to perform research with your data. Jan-Willem Dekker, jouw enthousiasme en doorzettingsvermogen heeft mij net dat extra duwtje in de rug gegeven. Willem van Gijn, het snel heen en weer sturen van een manuscript, heeft de snelheid er bij mij in gehouden. Dank jullie allemaal voor de samenwerking!

I would like to thank all the participants of EURECCA colorectal, especially prof. Vincenzo Valentini, prof. Lars Pålman, prof. Arne Wibe, prof. Lene Iversen, prof. Freddy Penninckx, dr. Bjørn Møller, and dr. Robert Johansson. Thank you for the pleasant cooperation, quick responses, and suitable comments.

Alle (ex-)collega's uit het LUMC, AvL en AMC wil ik natuurlijk bedanken voor de gezellige lunches, alle koffiemomentjes, en de prettige samenwerking!

Daarnaast wil ik alle vrienden bedanken die mij hebben bijgestaan en hun best deden om mijn onderzoeksverhalen te begrijpen. In het bijzonder wil ik Chantal en Petra bedanken omdat

jullie vandaag aan mijn zijde staan tijdens de verdediging van mijn proefschrift. Chantal sinds mijn wetenschapsstage hebben wij elkaar kunnen steunen in het onderzoek doen, en nu ook weer sta je hier naast mij om mij te steunen! En aan mijn andere zijde Petra! Jij hebt mij door de laatste loodjes heen getrokken!

Lieve familie, ook al waren mijn bezigheden de afgelopen vier jaar niet altijd even duidelijk voor jullie, jullie steun was onvoorwaardelijk. Lieve oma, ondanks dat de afgelopen jaren niet altijd even gemakkelijk waren, bleven u en opa altijd interesse tonen in de bezigheden van alle tien kleinkinderen en partners. Lieve papa en mama en Malou, dank voor jullie steun. Jullie hebben mij gestimuleerd om te zijn wie ik nu ben. Zonder jullie had ik dit niet gekund. Querida Familia De la Cruz Beltrán, agradezco a ustedes animar a Didier el venir a los Países Bajos, en gran parte es la razón del que yo pueda lograr esta tesis. Muchas gracias por su apoyo durante los últimos cuatro años.

Lieve Didier, dankzij jou heb ik thuis de steun en rust kunnen vinden om dit te kunnen bereiken, en daarnaast ook genoeg afleiding gehad om dingen af en toe even naast mij neer te leggen.

CURRICULUM VITAE

Colette van den Broek was born on August 21st 1984 in 's-Hertogenbosch, the Netherlands. She was raised in Veghel, where she graduated from the Zwijsen College in 2002. In the same year she commenced to Life Science and Technology at the University of Leiden and at the Delft University of Technology before she got enrolled at the Medical School at the Leiden University Medical Center in 2003.

After completing her preclinical training in medicine, she started with her clinical rotations in June 2007. At the end the clinical rotations she started with her research internship on pancreatic cancer under the guidance of dr. G.J. Liefers. During this research internship her enthusiasm for clinical research developed. As part of her final clinical internship she worked three months in a health centre in San Jeronimo, Cusco, Peru.

The author obtained her medical degree in February 2010. After which she started as a PhD-student at the surgical department in the Leiden University Medical Center under the supervision of prof. dr. C.J.H. van de Velde, dr. G.J. Liefers, and dr. E. Bastiaannet. For four years she was involved in the on-going research about colorectal cancer treatment and survival, and the EURECCA-project. She studied the differences in treatment and survival of colorectal patients both within the Netherlands as between several European countries. The results of her study are presented in this thesis and have been published into various international journals.

Currently, Colette is working as a resident Radiation Oncology at the Amsterdam Medical Center.

