Improving colorectal cancer care: treatment and outcomes of patients with colorectal cancer

Breugom, A.J.

IMPROVING COLORECTAL CANCER CARE

Treatment and outcomes of patients with colorectal cancer

Anne J. Breugom

Colophon
Cover art: detail of a fresco made by Linda Overzee
(Cover) Lay-out: Ilse Modder, www.ilsemodder.nl
Printing: Gildeprint Enschede, www.gildeprint.nl

Improving colorectal cancer care - treatment and outcomes of patients with colorectal cancer
Thesis, Leiden University Medical Centre, the Netherlands, 2021

ISBN: 978-94-6419-365-7

Improving colorectal cancer care

Treatment and outcomes of patients with colorectal cancer

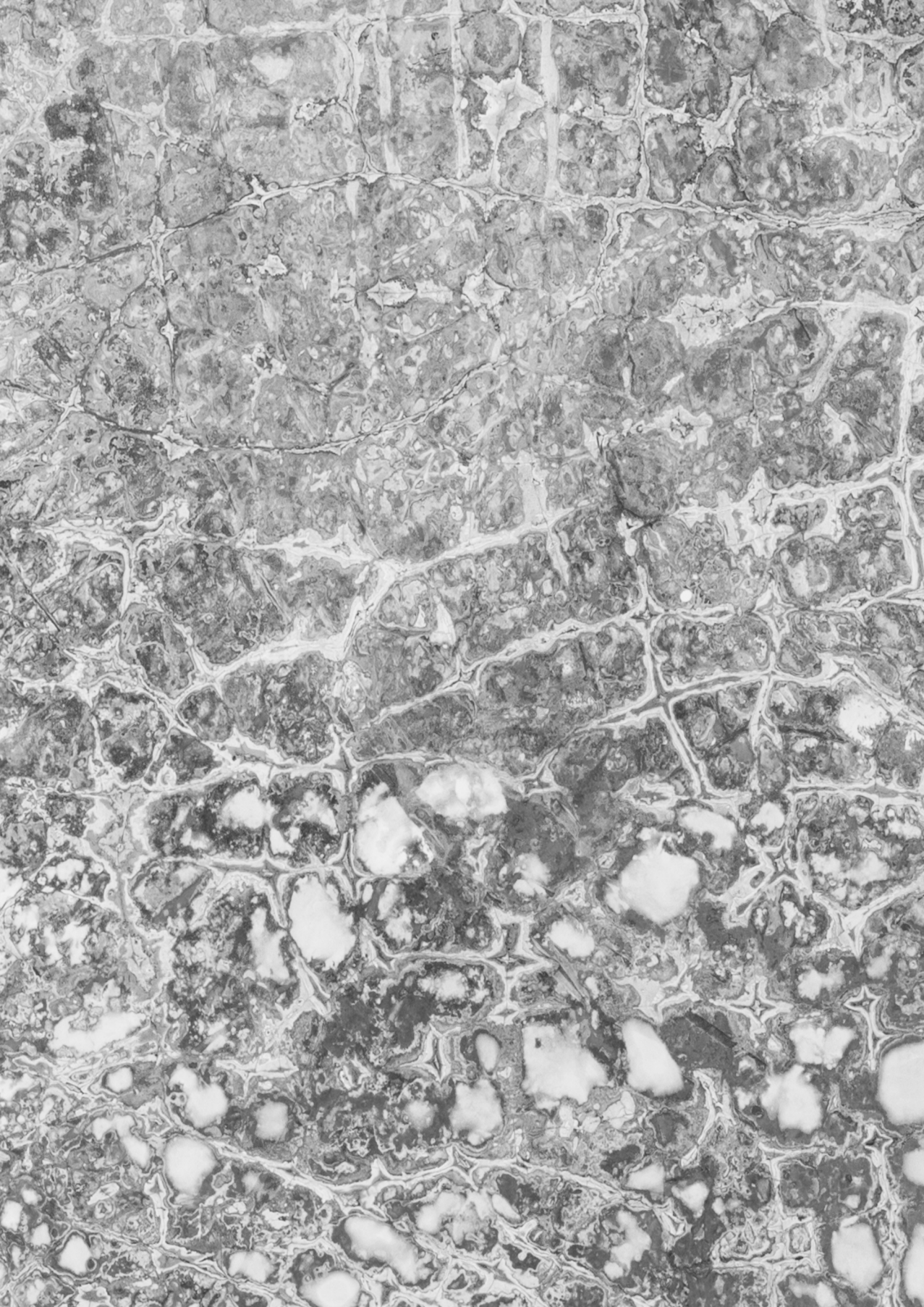
Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 8 december 2021
klokke 15.00 uur

door
Anne Johanna Breugom
Geboren te Den Haag
in 1988

Promotor:	Prof.dr. C.J.H. van de Velde
Copromotor:	dr. E. Bastiaannet
Leden promotiecommissie:	Prof.dr. J.E.A. Portielje
	Prof.dr. C.A.M. Marijnen
	Prof.dr. G.A.P. Hospers, UMC Groningen
	dr. J.W.T. Dekker, Reinier de Graaf Gasthuis

CONTENTS



1

General introduction and outline of this thesis

INTRODUCTION

Epidemiology

With a total of 1.36 million new cases worldwide in 2012, colorectal cancer is the third most common cancer in men and the second in women. Almost 55% of colorectal cancer cases occur in more developed regions. Globally, colorectal cancer ranks as the fourth most frequent cause of cancer related death with 694,000 deaths in 2012.[1]

In the Netherlands, over 13,700 patients were diagnosed with colorectal cancer in 2017. Approximately 70% of patients have a tumour located in the colon and about 20% of patients have metastatic disease at time of diagnosis. Incidence is highest among patients aged 70-74 years. Colorectal cancer incidence increased with approximately one percent per year between 1990 and 2013 in the Netherlands, while a substantially higher increase was observed in 2014 as a result of the introduction of the national screening programme and a further increase till 2015 due to gradual implementation of the screening programme.[2]

While colorectal cancer incidence increased over the past decades, survival improved as a result of changes in screening, surveillance, staging, and treatment.[3,4]

Survival of patients with colorectal cancer highly depends on the TNM (Tumour, Node, Metastasis) classification.[5] Five-year overall survival ranges from 95% for stage I disease to 11% for stage IV disease in patients with colon cancer, and from 92% for stage I disease to 14% for stage IV disease in patients with rectal cancer.[2]

Treatment

Colon cancer

Surgical resection is the only curative treatment modality for stage I-III colon cancer, which can be achieved using an open or laparoscopic approach.[6,7] For selected favourable-risk early stages of colon cancer, endoscopic mucosal resection and endoscopic submucosal resection techniques offer the potential to remove mucosal and submucosal tumours, though the risk of local recurrence is significantly higher after piecemeal resection than after en bloc resection.[8-10]

The benefit of adjuvant chemotherapy in stage III colon cancer has first been demonstrated in a study by Moertel et al. in 1990, where patients were randomly assigned to observation or to treatment with levamisole plus fluorouracil. Treatment with levamisole combined with fluorouracil reduced the risk of cancer recurrence and improved overall survival.[11] Several randomised trials followed and confirmed reduced recurrences and mortality in patients with stage III colon cancer after treatment with adjuvant fluoropyrimidine-

based chemotherapy.[12-15] Moreover, the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy further reduced the risk of recurrence and the risk of death in patients with stage III colon cancer, but resulted in more adverse events as for example peripheral polyneuropathy.[16,17] According to the European Society for Medical Oncology (ESMO) clinical practice guidelines, the standard treatment is a doublet schedule with oxaliplatin and fluoropyrimidine-based chemotherapy. When oxaliplatin is contraindicated, monotherapy with capecitabine or 5-fluorouracil/leucovorin can be an alternative treatment.[18]

On the contrary, the benefit of adjuvant chemotherapy in stage II colon cancer is less certain. Several trials included both patients with stage II and stage III disease, though the number of patients with stage II disease was much smaller. Since the risk on recurrence and mortality is lower in patients with stage II colon cancer than in patients with stage III colon cancer, the absolute benefit of adjuvant chemotherapy is smaller and therefore a larger number of patients is needed to demonstrate a significant effect. The results of a Cochrane meta-analysis showed no improvement in overall survival and recurrences, but did show a benefit in disease-free survival.[19] Moreover, the addition of oxaliplatin to 5-fluorouracil/leucovorin did not demonstrate an improvement in overall survival and disease-free survival in patients with stage II colon cancer.[20] Clinical high-risk features, defined as lymph node sampling <12, poorly differentiated tumour, vascular, lymphatic or perineural invasion, tumour presentation with obstruction or perforation, and pT4 stage, are used for decision-making for adjuvant chemotherapy for patients with stage II colon cancer. For patients presenting with at least one of these high-risk features, adjuvant chemotherapy is not routinely recommended, but could be considered, although the evidence for this is weak.[18]

Rectal cancer

As in colon cancer, radical surgical resection is the mainstay curative treatment for rectal cancer. The use of total mesorectal excision (TME) instead of the conventional blunt approach resulted in reduced local recurrence and mortality rates.[21] Depending on the anatomical location of the tumour, a radical excision using TME could be a sphincter-sparing low anterior resection (LAR) including partial or total resection of the rectum with a colorectal or coloanal anastomosis, or an abdominoperineal resection (APR) including resection of the sigmoid, rectum, and anus, followed by construction of a colostomy. For older patients with multiple comorbidities, a Hartmann procedure, including resection of the rectum with distal closure and a colostomy should be considered.

Preoperative short-course radiotherapy with conventional surgery reduced local recurrences and mortality compared with conventional surgery alone.[22] The Dutch TME trial later confirmed improved local control for patients treated with preoperative

radiotherapy and standardised total mesorectal excision. For patients with a negative resection margin, preoperative radiotherapy led to an improved cancer-specific survival, but not to an improved overall survival due to an increase in other causes of death. However, for patients with TNM stage III and a negative circumferential resection margin, ten-year overall survival was better for patients who received preoperative radiotherapy compared with TME alone.[23]

For locally advanced rectal cancer, defined as a threatened mesorectal fascia (≤1mm), or four or more lymph nodes suspected for lymph node metastases within or out the mesorectum, the goal of preoperative therapy is to downstage the tumour to be able to perform a radical resection. These patients should be considered for preoperative chemoradiotherapy, which has been shown to reduce local recurrence rates, though no improved survival and more toxicity was observed.[24,25]

The benefit of adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME is debated, which is reflected by differences in guideline recommendations across countries. Though older studies before using preoperative (chemo)radiotherapy and TME, resulting in a high locoregional recurrence rate, demonstrated a benefit of adjuvant chemotherapy, more recent studies did not.[26,27]

Metastatic colorectal cancer

Although colon and rectal cancer are considered as separate entities for stage I-III disease, this does not apply to metastatic colorectal cancer.

A selected group of patients with limited liver or lung metastases have potentially resectable disease that can be treated with curative intent, sometimes after downstaging with systemic therapy, or radiofrequency ablation.[28-30] However, for most patients, the management of metastatic colorectal cancer is limited to palliative therapy.

For patients with irresectable metastases, chemotherapy combined with bevacizumab is standard first-line treatment. Combination chemotherapy with fluoropyrimidine and oxaliplatin or irinotecan is indicated in patients with symptomatic metastases, or if concurrent lines of chemotherapy are unlikely. When patients are likely to undergo more lines of chemotherapy, sequential administration of fluoropyrimidine monotherapy, oxaliplatin and irinotecan seems to have comparable survival.[31] In patients with RAS wildtype tumours, anti-EGFR therapy can be administered as second line treatment in combination with chemotherapy or as monotherapy.[32]

For a selected group of patients with peritoneal carcinomatosis cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) and adjuvant chemotherapy

seems to improve progression-free and cancer-specific survival compared with systemic chemotherapy.[33]

Quality assurance

Quality assurance is of great importance in cancer care. Quality measurement is essential to improve care and reduce costs. Randomised controlled trials are placed at the highest level of evidence to study safety and efficacy of treatments. However, a selected group of patients are represented in trials, trials are time consuming, costly, and not always feasible. Important endpoints for cancer care include for example overall survival, disease-free survival, recurrences, and quality of life.

Besides studies using these outcome measures, monitoring the process of cancer care on a population-based level can identify variations in cancer care. The European Registration of Cancer Care, EURECCA, is an ESSO/ECCO initiative that has been founded in 2007 and is a quality assurance programme in cancer care. EURECCA is a multidisciplinary platform including health care professionals, epidemiologists, and patients and aims to improve cancer outcomes by harmonising data collection, and providing feedback.[34]

OUTLINE

Part I of this thesis studies treatment and its complications in relation to outcomes. In **Chapter 2**, we use population-based data from the Netherlands Cancer Registry to study the association between the most prevalent complications after surgery for stage I-III colon cancer and their impact on short-term survival, long-term survival, and recurrences. In **Chapter 3**, we evaluate 30-day and one-year mortality over time using population-based data from the Netherlands Cancer Registry.

Chapter 4 assesses the effect of adjuvant chemotherapy after preoperative (chemo) radiotherapy and total mesorectal excision (TME) in patients with (y)pTNM stage II or III rectal cancer included in the PROCTOR-SCRIPT study. **Chapter 5** is an individual patient data meta-analysis analysing data of four trials investigating the effect of adjuvant chemotherapy in patients with (y)pTNM stage II or III rectal cancer after preoperative (chemo)radiotherapy and surgery.

Part 2 studies patterns of care across different European countries participating in the EURECCA project by using population-based data from national cancer registries. **Chapter 6** describes the importance of quality assurance and the aims of the EURECCA project. **Chapter 7** compares adjuvant chemotherapy and relative survival of all surgically treated patients with stage II colon cancer between seven European countries.

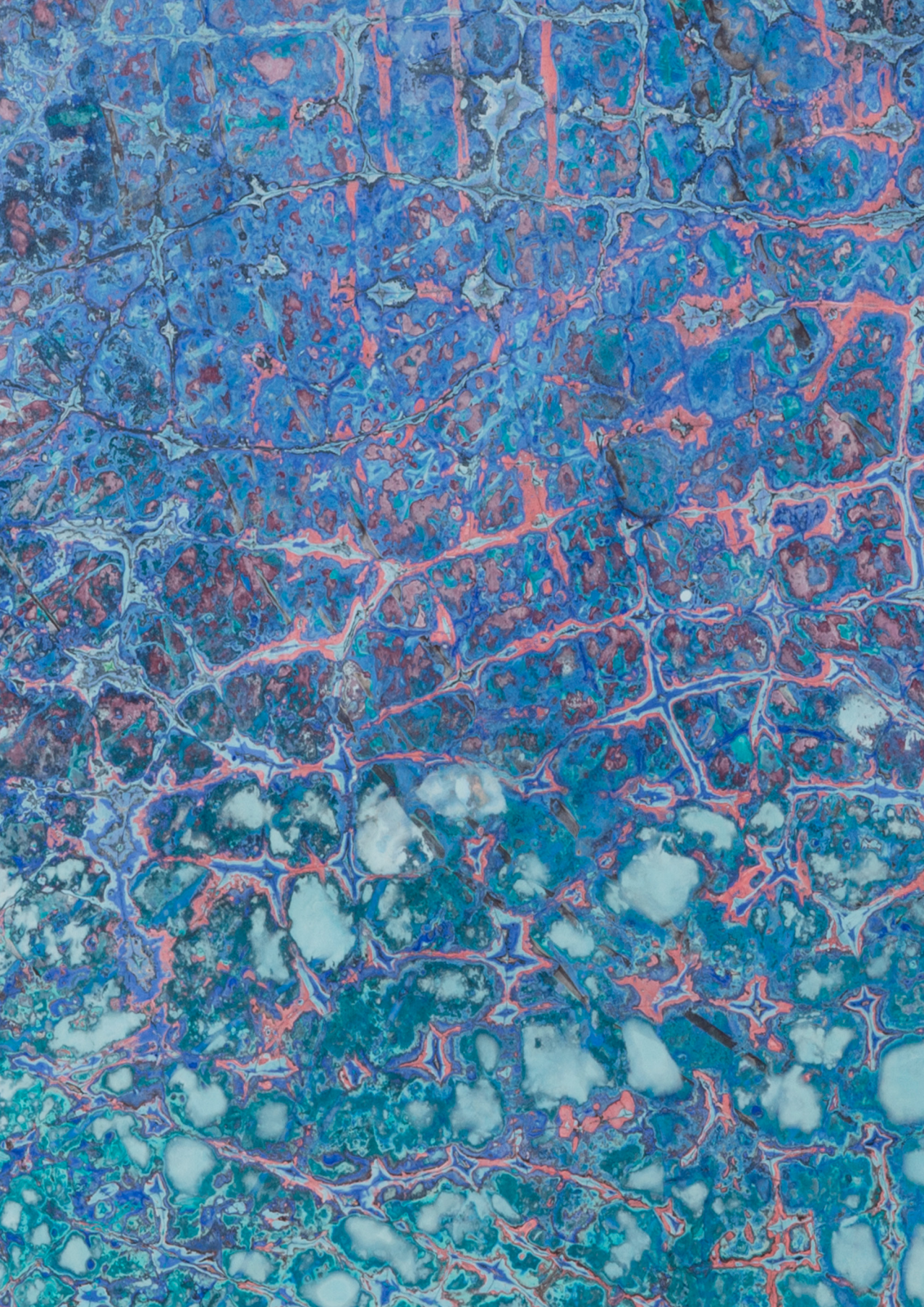
Chapter 8 evaluates patterns of care and relative survival of all surgically treated patients with stage I-III rectal cancer between eight European countries. **Chapter 9** assesses differences in treatment and overall survival of patients with incurable metastatic colorectal cancer in the Netherlands and Norway.

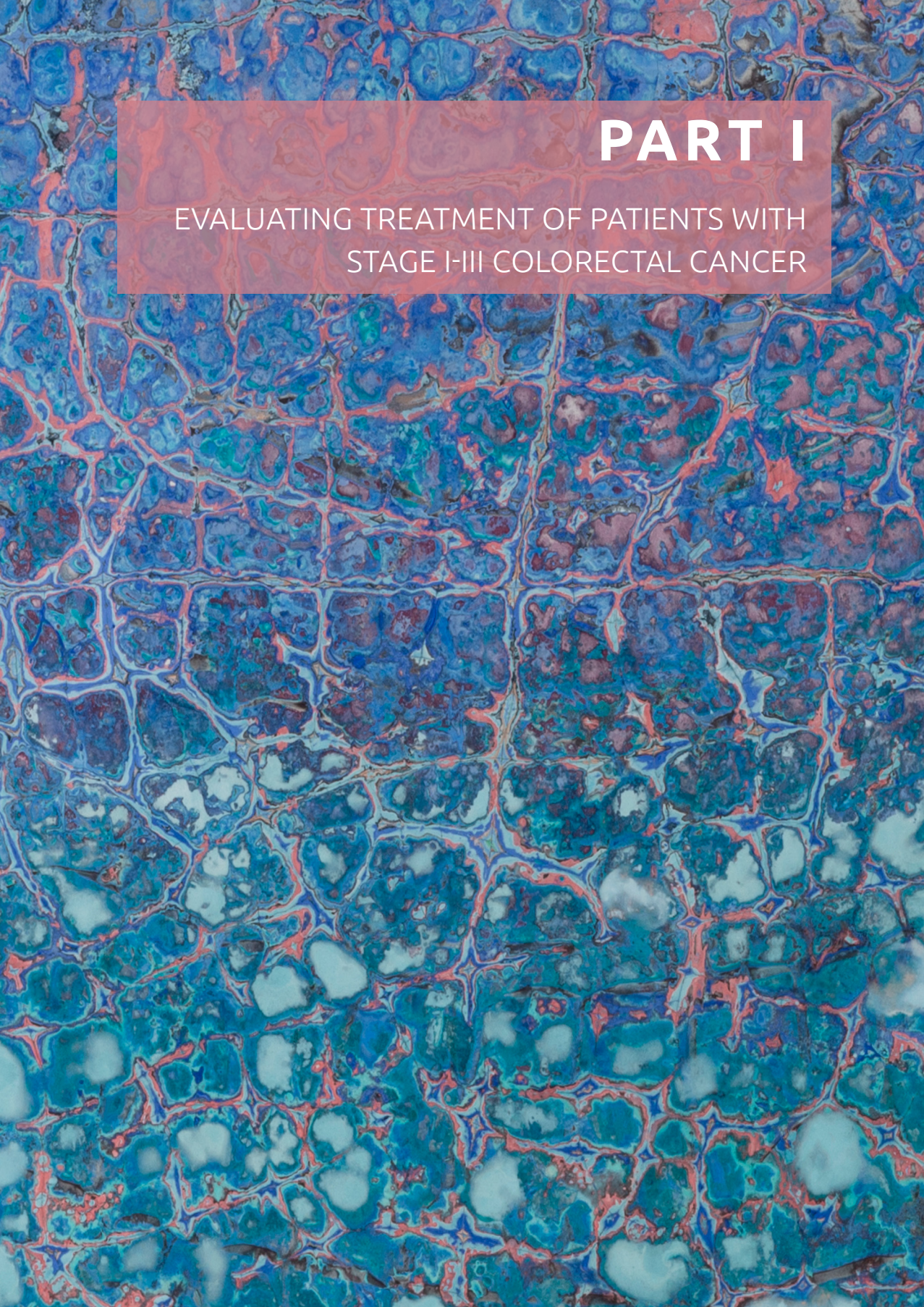
Finally, **Chapter 10** comprises a summary and general discussion of the results of the studies in this thesis and addresses future perspectives.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**(5): E359-86.
2. www.cijfersoverkanker.nl. *Accessed October* 2018.
3. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer* 2015; **51**(15): 2158-68.
4. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. 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**(10): 1345-89.
5. Gospodarowicz MK, Brierley JD, Wittekind C. TNM classification of malignant tumours: John Wiley & Sons; 2017.
6. Reza MM, Blasco JA, Andradas E, Cantero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. *Br J Surg* 2006; **93**(8): 921-8.
7. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. *Cancer Treat Rev* 2008; **34**(6): 498-504.
8. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. *Endoscopy* 2014; **46**(5): 388-402.
9. Yoda Y, Ikematsu H, Matsuda T, et al. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. *Endoscopy* 2013; **45**(9): 718-24.
10. Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. *Gastroenterology* 2013; **144**(3): 551-9; quiz e14.
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**(6): 352-8.
12. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet* 1995; **345**(8955): 939-44.
13. 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**(1): 246-50.
14. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005; **23**(34): 8671-8.
15. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
16. Shah MA, Renfro LA, Allegra CJ, et al. Impact of Patient Factors on Recurrence Risk and Time Dependency of Oxaliplatin Benefit in Patients With Colon Cancer: Analysis From Modern-Era Adjuvant Studies in the Adjuvant Colon Cancer End Points (ACCENT) Database. *J Clin Oncol* 2016; **34**(8): 843-53.
17. 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**(23): 2343-51.
18. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi64-72.
19. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. *Cochrane Database Syst Rev* 2008; (3): CD005390.
20. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol* 2012; **30**(27): 3353-60.
21. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**(8843): 457-60.
22. Swedish Rectal Cancer T, Cedermark B, Dahlberg M, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; **336**(14): 980-7.
23. 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**(6): 575-82.
24. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J*

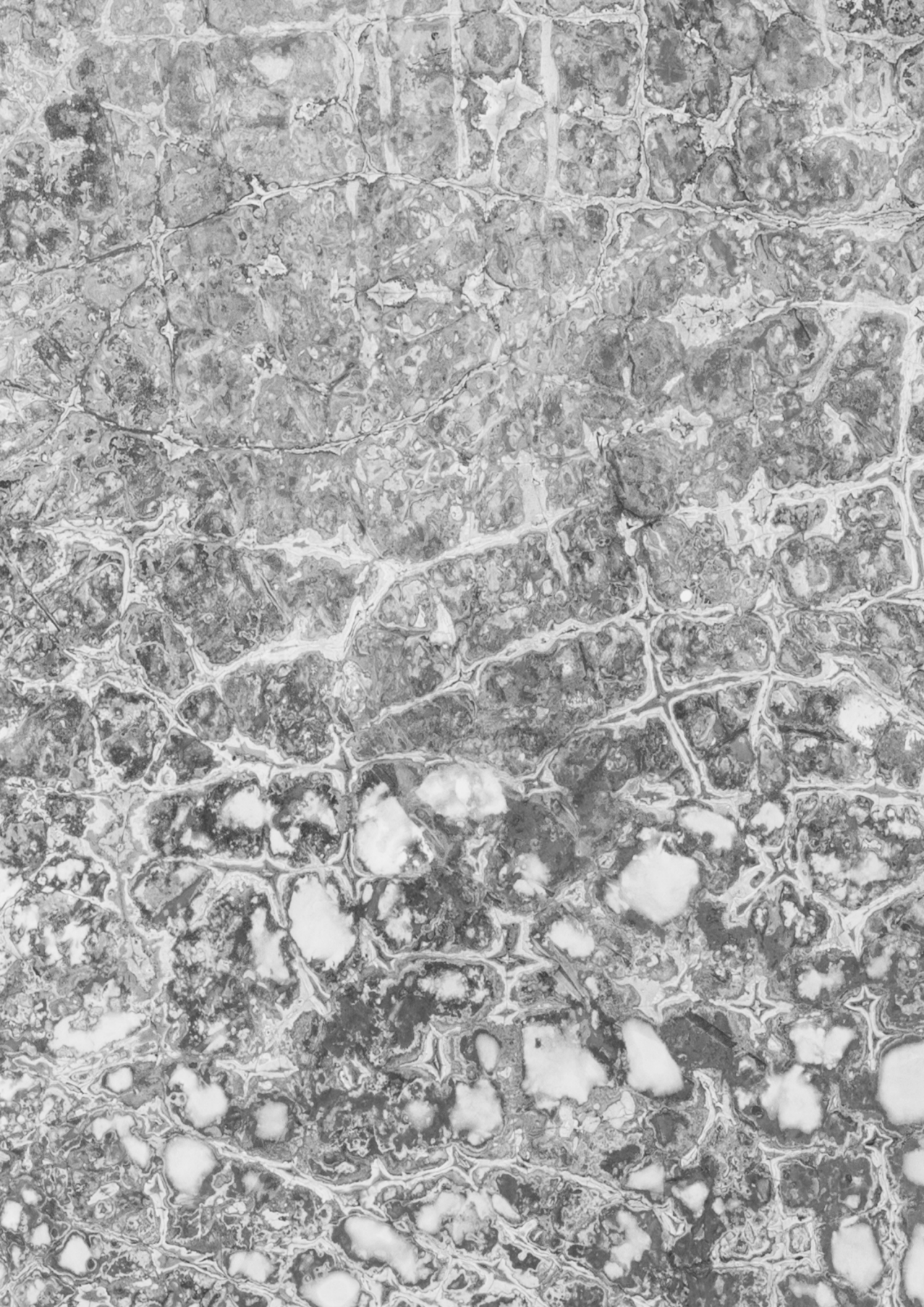
Med 2006; **355**(11): 1114-23.
25. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**(10): 1638-44.
26. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; (3): CD004078.
27. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010; **21**(9): 1743-50.
28. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; **4**: 283-301.
29. Fiorentino F, Treasure T. Pulmonary metastasectomy for colorectal cancer: making the case for a randomized controlled trial in the zone of uncertainty. *J Thorac Cardiovasc Surg* 2013; **146**(4): 748-52.
30. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. *Cochrane Database Syst Rev* 2012; (6): CD006317.
31. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**(9582): 135-42.
32. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. *Cancer Treat Rev* 2012; **38**(6): 618-25.
33. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; **15**(9): 2426-32.
34. Boelens PG, Audisio RA, Van de Velde CJ. Quality assurance in surgical oncology the EURECCA platform. *Eur J Surg Oncol* 2014; **40**(11): 1387-90.





PART I

EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER



2

Association between the most frequent complications after surgery for stage I-III colon cancer and short-term survival, long-term survival, and recurrences

A.J. Breugom
D.T. van Dongen
E. Bastiaannet
F.W. Dekker
L.G.M. van der Geest
G.J. Liefers
A.W.K.S. Marinelli
W.E. Mesker
J.E.A. Portielje
W.H. Steup
L.N.L. Tseng
C.J.H. van de Velde
J.W.T. Dekker

Annals of Surgical Oncology. 2016 Sep;23(9):2858-65.

ABSTRACT

Background

The purpose of this study was to identify the ten most frequent complications after surgery for stage I-III colon cancer and to assess the association between these complications and overall survival, conditional overall survival, and recurrences.

Methods

All patients who underwent surgery for stage I-III colon cancer in five hospitals in the Western region of the Netherlands were identified. Crude and adjusted Cox proportional hazards models were used to study the association between complications and 1-year overall survival, 5-year overall survival, 5-year conditional overall survival, and 5-year disease-free period.

Results

Data from 761 patients were used for the analyses. Complications were associated with decreased 1-year overall survival (hazard ratio (HR) 2.87, 95% CI 1.82-4.51; p<0.001), 5-year overall survival (HR 1.59, 95% CI 1.25-2.04; p<0.001), and 5-year conditional overall survival (HR 1.34, 95% CI 1.06-1.69; p=0.016), whereas an increasing number of complications had no additional impact. Anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival, anastomotic leakage, delirium, abscess, and (abdominal) sepsis with reduced 5-year overall survival, and anastomotic leakage, delirium, and abscess with reduced 5-year conditional overall survival. Anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within five years.

Conclusions

Our results demonstrate the serious impact of the most frequent complications after surgery for colon cancer on short-term and long-term outcomes. This study confirms the prolonged impact of surgery and demonstrates that complications result not only in reduced 1-year survival, but also in reduced long-term outcomes.

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed malignancies worldwide.[1] In the Netherlands, approximately 15,000 patients were diagnosed with colorectal cancer in 2014, of which almost 70% had a tumour located in the colon.[2] Surgery is the mainstay curative treatment for non-metastasised colon cancer. Depending on stage, surgery is followed by adjuvant chemotherapy.[3-5] Still ~20% of all patients with stage I-III colon cancer will eventually develop metastatic disease within 5 years.[6] Five-year overall survival ranges from 94% for patients with stage I disease to 75% for patients with stage III disease.[2]

A considerable amount of patients will suffer from postoperative complications.[7-11] Previous studies have shown an association between the occurrence of complications and decreased overall survival, whereas the association between complications and recurrences is less clear.[12-15] Importantly, Dekker et al. showed that 30-day mortality after surgery for colon or rectal cancer underestimates 1-year mortality.[16] The 1-year excess mortality rate was more than 10% for patients who underwent surgery for colon cancer, and was even much higher for subgroups.[16,17] Several risk factors have been identified for excess mortality during the first year after surgery for colon cancer, including stage III disease, comorbidity, emergency surgery, and postoperative surgical complications.[17] Moreover, readmission within 30 days after colectomy for cancer predicts 1-year mortality.[18] These results suggest a prolonged impact of surgery on survival.

Most previous studies investigating the association between complications and outcomes after surgery for colon cancer lacked detailed information for specific complications or studied surgical complications only. The association between specific complications, directly as well as indirectly related to surgery, and survival and recurrences therefore is not yet completely unravelled.

The purpose of this study was to identify the ten most frequent complications after surgery for stage I-III colon cancer and to assess the association between these complications and 1-year overall survival, 5-year overall survival, 5-year conditional overall survival (i.e., conditional on having survived the first postoperative year), and 5-year disease-free period.

PATIENTS AND METHODS

Patients

All patients with stage I-III colon cancer (ICD-10 C18), diagnosed between January 1, 2006 and December 31, 2008, and treated with curative intent in the following hospitals:

Leiden University Medical Centre, an academic hospital, HAGA Hospital, Reinier de Graaf Gasthuis, Medical Centre Haaglanden, and Groene Hart Hospital, all teaching hospitals, were included. We started with data from the Netherlands Cancer Registry. Trained data managers collected additional data from the medical records in the hospitals. We excluded patients with unknown localisation of the tumour and missing medical records. We collected data on patient characteristics, diagnosis, surgery, TNM stage, adjuvant treatment, complications, comorbidity, recurrence, and follow-up.

Age was categorised as <65 years, 65-74 years, and ≥75 years. Comorbidity was categorised as 0, 1, 2, and ≥3 comorbidities. The information on TNM stage was based on pathological reports. If pathological data were missing, clinical TNM stage was used. Complications were defined as any complication within 30 days after surgery, as well as any long-term complication registered in the medical records. Complications included both complications directly related to surgery (e.g. anastomotic leakage), as well as indirectly related to surgery (e.g. pneumonia). We categorised complications as no and yes, and the total number of complications as 0, 1, and ≥2. Furthermore, we identified the ten most frequent complications after surgery. Anastomotic leakage included both anastomotic leakage as well as faecal peritonitis and abdominal sepsis as a result of anastomotic leakage. Complications were classified as (abdominal) sepsis if (abdominal) sepsis was registered in the medical records without identifiable cause. Type of surgery was recorded as elective or emergency surgery. Recurrence included both locoregional and distant recurrence.

Endpoints were 1-year overall survival, 5-year overall survival, 5-year conditional overall survival, and 5-year disease-free period. Five-year conditional overall survival was calculated as the proportion of patients surviving five additional years under the condition of surviving the first postoperative year. Overall survival was defined as time from surgery to death of any cause, or to end of follow-up (censored). Disease-free period was defined as time from surgery to recurrence, or as time from surgery to end of follow-up, or death in case of no recurrence. Follow-up was completed through April 1, 2013.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier method.[19] The percentages 1-year overall survival, 5-year overall survival, and 5-year disease-free period were obtained from life-tables. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to study the association between complications and overall survival (truncated at 1 and 5 years), disease-free period (truncated at 5 years), and conditional overall survival (truncated at 5 years under the condition of surviving the first postoperative year). A Kaplan-Meier curve was

constructed to compare overall survival between patients with no complications, one complication, and two or more complications.

One-year overall survival, 5-year overall survival, 5-year disease-free period, and 5-year conditional overall survival analyses were adjusted for the following potential confounders: gender, age, T-stage, N-stage, grade, emergency surgery, and comorbidity. A p-value <0.05 was considered as statistical significant.

Moreover, we described the number of complications as well as the percentage 1-year overall survival, 5-year overall survival, and 5-year disease-free period for patients with and without complications by age categories.

All analyses were done with IBM SPSS Statistics, version 20.0.

RESULTS

Between January 1, 2006 and December 31, 2008, a total of 776 patients were identified. We excluded seven patients with an unknown localisation of the tumour, and eight patients with missing medical records. Data from the remaining 761 patients were used for analyses. Table 1 shows the characteristics of the patients. Median follow-up from surgery was 5.4 years (interquartile range 4.7-6.2 years).

Table 1. Patient characteristics

Characteristics	Colon cancer (*n* =761)
Gender	
Male	360 (47.3)
Female	401 (52.7)
Age	
<65 years	206 (27.1)
65-74 years	210 (27.6)
≥ 75 years	345 (45.3)
Year of diagnosis	
2006	273 (35.9)
2007	260 (34.2)
2008	228 (30.0)
T stage	
T1-T2	185 (24.3)
T3-T4	575 (75.6)
Unknown	1 (0.1)
N stage	
N0	479 (62.9)
N1	186 (24.4)
N2	94 (12.4)
Unknown	2 (0.3)

Table 1. Continued

Characteristics	Colon cancer (*n* =761)
Stage	
I	144 (18.9)
II	335 (44.0)
III	280 (36.9)
Unknown	2 (0.3)
Grade	
I	46 (6.0)
II	499 (65.6)
III	112 (14.7)
Unknown	104 (13.7)
Comorbidity	
0	179 (23.5)
1	200 (26.3)
2	159 (20.9)
≥3	223 (29.3)
Emergency surgery	
No	656 (86.2)
Yes	105 (13.8)

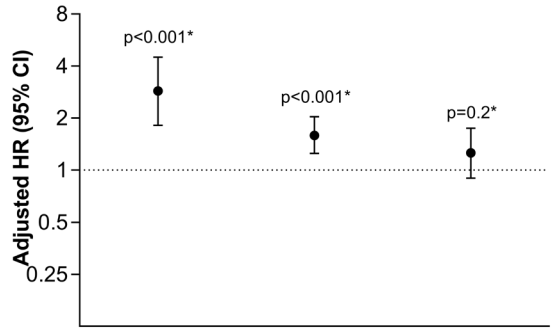
Data are presented as *n* (%)

Presence and number of complications

Complications occurred in 41.9% of the patients, of which 21,8% had one complication and 20.1% had two or more complications. More than 95% of all first complications occurred within 30 days after surgery.

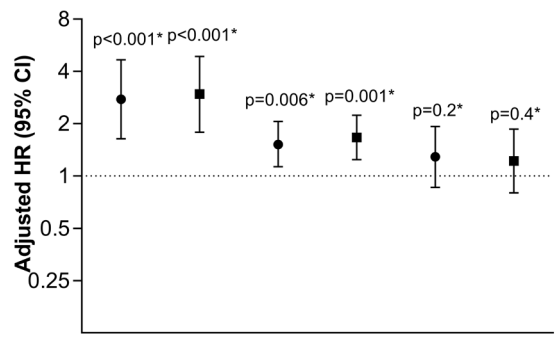
Figure 1 shows the association between complications (no and yes, as well as 0, 1, and ≥2) and survival and recurrences. Complications were associated with decreased 1- and 5-year overall survival, although an increasing number of complications had no significant additional impact on survival. One-year overall survival was 93.8% (95% CI 91.2-95.8%) for patients with no complications compared with 77.1% (95% CI 72.1-81.4%) for patients with complications (adjusted HR 2.87, 95% CI 1.82-4.51; p<0.001). For patients with one complication, 1-year overall survival was 80.1% (95% CI 73.2-85.4%) with an adjusted HR of 2.77 (95% CI 1.64-4.67; p<0.001 compared with no complications), and 73.9% (95% CI 66.1-80.1%) for patients with two or more complications (adjusted HR 2.96, 95% CI 1.79-4.89; p<0.001 compared with no complications). Five-year overall survival was 70.4% (95% CI 65.8-74.6%) for patients with no complications and 53.7% (95% CI 47.9-59.1%) for patients with complications (adjusted HR 1.59, 95% CI 1.25-2.04; p<0.001). Five-year overall survival was 57.0% (49.0-64.2%) for patients with one complication (adjusted HR 1.52, 95% CI 1.13-2.06, p=0.006 compared with no complications), and 50.0% (95% CI 41.7-57.8%) for patients with two or more complications (adjusted HR 1.67, 95% CI 1.24-2.24; p=0.001 compared with no complications). Figure 2 shows the cumulative overall survival by number of complications.

a



Complications	*n* (%)	% 1-year OS **	% 5-year OS **	% 5-year DFP **
No (ref.)	442 (58.1)	93.9%	70.4%	78.8%
● Yes	319 (41.9)	77.1%	53.7%	74.0%

b

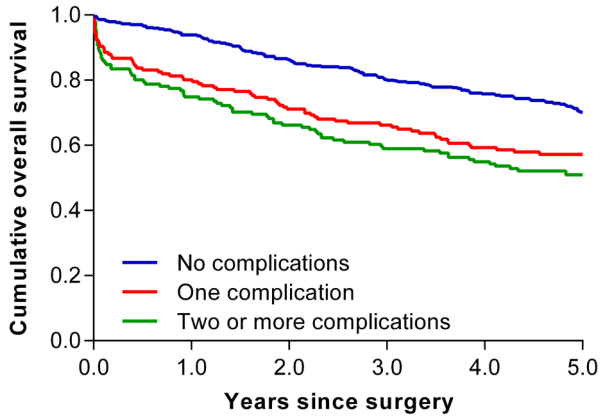


Complications	*n* (%)	% 1-year OS **	% 5-year OS **	% 5-year DFP **
No (ref.)	442 (58.1)	93.9%	70.4%	78.8%
● One	166 (21.8)	80.1%	57.0%	74.9%
■ Two or more	153 (20.1)	73.9%	50.0%	73.0%

Figure 1. Association between a. presence of complications and b. number of complications and one-year overall survival, five-year overall survival, and five-year disease-free period

* Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, and comorbidity

** Percentages obtained from life-tables



Number at risk						
No complications	442	414	379	350	321	195
One complication	166	133	118	106	92	64
Two or more complications	153	113	100	89	81	44

Figure 2. Cumulative overall survival for patients with no complications, one complication, and two or more complications

We did not detect differences in 5-year disease-free period between patients with complications (no and yes, as well as 0, 1, and ≥2) and patients without complications (Figure 1).

Supplementary table 1 describes the number of complications and the percentages 1-year overall survival, 5-year overall survival, and 5-year disease-free period for patients with and without complications by age categories.

Ten most frequent complications

Table 2 shows the association between the ten most frequent complications and survival and recurrences. The ten most frequent complications were ileus (7.0%), anastomotic leakage (5.3%), pneumonia (5.0%), excessive blood loss (5.0%), electrolyte disorders (4.1%), cardiac arrhythmia (4.1%), delirium (4.1%), abscess (3.7%), urinary tract infection (3.4%), and (abdominal) sepsis (3.3%).

In adjusted analyses, patients with anastomotic leakage (HR 3.29, 95% CI 1.83-5.91, p<0.001), excessive blood loss (HR 1.98, 95% CI 1.02-3.84; p=0.04), and (abdominal) sepsis (HR 4.09, 95% CI 2.11-7.93, p<0.001) had worse 1-year overall survival compared with patients without these specific complications.

Moreover, patients with anastomotic leakage (adjusted HR 2.74, 95% CI 1.81-4.15; p<0.001), delirium (adjusted HR 1.90, 95% CI 1.20-2.99; p=0.006), abscess (adjusted HR

1.88, 95% CI 1.11-3.17; p=0.02), and (abdominal) sepsis (adjusted HR 2.93, 95% CI 1.74-4.92; p<0.001) had reduced 5-year overall survival.

Table 2. Association between the ten most frequent complications and one-year overall survival, five-year overall survival, and five-year disease-free period

			1-year overall survival					
Complication	***n***	**(%)**	**1yr OS (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	86.9-86.8	1.00	(0.47-2.16)	1.0	0.83	(0.38-1.82)	0.6
Anastomotic leakage	40	(5.3)	88.1-65.0	3.36	(1.91-5.91)	<0.001	3.29	(1.83-5.91)	<0.001
Pneumonia	38	(5.0)	87.5-73.7	2.28	(1.18-4.37)	0.01	1.30	(0.66-2.58)	0.5
Excessive blood loss	38	(5.0)	87.7-71.1	2.53	(1.35-4.73)	0.004	1.98	(1.02-3.84)	0.04
Electrolyte disorders	31	(4.1)	86.7-90.3	0.69	(0.22-2.19)	0.5	0.64	(0.20-2.03)	0.5
Cardiac arrhythmia	31	(4.1)	87.8-64.5	3.41	(1.82-6.37)	<0.001	1.83	(0.95-3.53)	0.07
Delirium	31	(4.1)	87.8-64.5	3.38	(1.81-6.33)	<0.001	1.67	(0.85-3.26)	0.1
Abscess	28	(3.7)	87.0-82.1	1.35	(0.55-3.32)	0.5	1.11	(0.44-2.84)	0.8
Urinary tract infection	26	(3.4)	86.5-96.2	0.27	(0.04-1.91)	0.2	0.24	(0.03-1.76)	0.2
(Abdominal) sepsis NOS	25	(3.3)	88.2-48.0	6.60	(3.68-11.85)	<0.001	4.09	(2.11-7.93)	<0.001
			5-year overall survival					
Complication			**5yr OS (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	62.7-73.0	0.70	(0.41-1.19)	0.2	0.67	(0.39-1.15)	0.1
Anastomotic leakage	40	(5.3)	65.0-34.8	2.66	(1.77-3.99)	<0.001	2.74	(1.81-4.15)	<0.001
Pneumonia	38	(5.0)	63.8-55.0	1.48	(0.91-2.42)	0.1	1.06	(0.64-1.76)	0.8
Excessive blood loss	38	(5.0)	63.9-53.1	1.45	(0.88-2.36)	0.1	1.36	(0.82-2.24)	0.2
Electrolyte disorders	31	(4.1)	63.7-56.5	1.18	(0.68-2.06)	0.6	1.15	(0.65-2.02)	0.6
Cardiac arrhythmia	31	(4.1)	64.0-48.4	1.92	(1.16-3.19)	0.01	1.31	(0.78-2.21)	0.3
Delirium	31	(4.1)	64.9-28.4	3.00	(1.94-4.65)	<0.001	1.90	(1.20-2.99)	0.006
Abscess	28	(3.7)	64.2-40.7	2.00	(1.21-3.32)	0.007	1.88	(1.11-3.17)	0.02
Urinary tract infection	26	(3.4)	63.0-75.4	0.56	(0.25-1.25)	0.6	0.51	(0.22-1.15)	0.1
(Abdominal) sepsis NOS	25	(3.3)	64.7-25.7	3.71	(2.30-5.99)	<0.001	2.93	(1.74-4.92)	<0.001
						5-year disease-free period			
Complication			**5yr DFP (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	76.9-79.1	0.89	(0.47-1.68)	0.7	0.88	(0.46-1.68)	0.7
Anastomotic leakage	40	(5.3)	78.2-51.5	2.82	(1.63-4.89)	<0.001	2.66	(1.50-4.70)	0.001
Pneumonia	38	(5.0)	76.8-81.7	0.74	(0.30-1.80)	0.5	0.65	(0.26-1.60)	0.3
Excessive blood loss	38	(5.0)	77.3-71.1	1.35	(0.69-2.64)	0.4	1.84	(0.92-3.71)	0.08
Electrolyte disorders	31	(4.1)	77.6-63.7	1.68	(0.89-3.20)	0.1	2.08	(1.08-3.97)	0.028
Cardiac arrhythmia	31	(4.1)	76.7-86.0	0.60	(0.19-1.86)	0.4	0.50	(0.16-1.60)	0.2
Delirium	31	(4.1)	77.3-63.7	1.39	(0.61-3.14)	0.4	1.17	(0.49-2.77)	0.7
Abscess	28	(3.7)	77.9-50.7	2.55	(1.38-4.71)	0.003	2.04	(1.08-3.85)	0.028
Urinary tract infection	26	(3.4)	77.0-76.7	1.00	(0.44-2.26)	1.0	1.12	(0.49-2.58)	0.8
(Abdominal) sepsis NOS	25	(3.3)	77.4-56.7	2.38	(1.05-5.40)	0.04	2.13	(0.90-5.05)	0.09

*Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, comorbidity

Patients with anastomotic leakage (adjusted HR 2.66, 95% CI 1.50-4.70; p=0.001), electrolyte disorders (adjusted HR 2.08, 95% CI 1.08-3.97; p=0.028), or an abscess (adjusted HR 2.04, 95% CI 1.08-3.85; p=0.028) more often developed recurrences within

5 years after surgery compared with patients without these complications.

Conditional survival

The association between complications and 5-year overall survival under the condition of surviving the first postoperative year is shown in Table 3. Twenty-seven patients without complications died in the first postoperative year compared with 73 patients with complications (*n*=33 with 1 complication and *n*=40 with 2 or more complications). Patients with complications who survived the first postoperative year more often died after five additional years compared with patients without complications who survived the first postoperative year (adjusted HR 1.34, 95% CI 1.06-1.69; p=0.016). The adjusted HR was 1.25 (95% CI 0.94-1.66; p=0.13) for patients with one complication, and 1.45 (95% CI 1.08-1.95; p=0.013) for patients with two or more complications, both compared with patients without complications.

Patients with anastomotic leakage, delirium, or an abscess had worse 5-year overall survival under the condition of surviving the first postoperative year compared with patients without these specific complications.

Table 3. Association between complications and conditional survival

	5-year overall survival under the condition of surviving the first postoperative year					
Presence of complications	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
No	1	Reference		1	Reference	
Yes	1.34	(1.00-1.79)	0.05	1.34	(1.06-1.69)	0.016
Number of complications	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
0	1	Reference		1	Reference	
1	1.25	(0.87-1.79)	0.23	1.25	(0.94-1.66)	0.13
≥2	1.44	(1.00-2.09)	0.05	1.45	(1.08-1.95)	0.013
Ten most frequent complications						
(no vs. yes)						
Ileus	0.49	(0.23-1.05)	0.066	0.49	(0.23-1.05)	0.067
Anastomotic leakage	2.14	(1.22-3.77)	0.008	2.47	(1.38-4.42)	0.002
Pneumonia	0.88	(0.41-1.87)	0.7	0.66	(0.30-1.43)	0.3
Excessive blood loss	0.74	(0.33-1.66)	0.5	0.71	(0.31-1.62)	0.4
Electrolyte disorders	1.54	(0.84-2.82)	0.17	2.63	(0.68-10.19)	0.16
Cardiac arrhythmia	1.07	(0.47-2.40)	0.9	0.86	(0.37-1.97)	0.7
Delirium	2.94	(1.67-5.17)	<0.001	2.32	(1.29-4.20)	0.005
Abscess	2.66	(1.48-4.77)	0.001	2.80	(1.52-5.15)	0.001
Urinary tract infection	0.64	(0.26-1.56)	0.33	0.65	(0.27-1.61)	0.35
(Abdominal) sepsis NOS	2.05	(0.91-4.63)	0.08	1.91	(0.81-4.48)	0.14

*Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, comorbidity

DISCUSSION

This study shows an association between complications after surgery for stage I-III colon cancer and decreased short-term overall survival, as well as decreased long-term overall survival - even under the condition of surviving the first postoperative year. However, an increasing number of complications had no significant additional impact on survival. Of the ten most frequent complications, anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival. Anastomotic leakage, delirium, abscess, and (abdominal) sepsis were risk factors for worse 5-year overall survival, whereas anastomotic leakage, delirium, and abscess were risk factors for 5-year conditional overall survival. Moreover, anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within 5 years after surgery.

More than 40% of all patients with stage I-III colon cancer in this study suffered from at least one complication. Previous studies have shown a complication rate of approximately 30-35% after surgery for colorectal cancer.[7-11] Possible explanations for the higher rate in our study could be that some studies assessed surgical complications only, whereas other studies did not record all specific complications separately. Moreover, given that all patients underwent surgery between 2006 and 2008, there could have been improvements over time in surgery and perioperative care, resulting in fewer complications.

In line with previous studies, the results of the current study show an association between complications and decreased overall survival.[12-15] A remarkable finding of our study was that no significant differences in overall survival were found between patients with one complication and patients with two or more complications, although this might be related to sample size. Possibly, the first registered complication is the most serious complication mainly affecting survival, whereas subsequent complications are less serious or might be related to the first complication.

Several studies have shown that the impact of colorectal cancer surgery and postoperative complications goes beyond thirty-day postoperative mortality.[16,17,20-22] Importantly, up to 25% of all colorectal cancer deaths in the first postoperative year are attributed to postoperative complications.[23] Moreover, anastomotic leakage is known to be a serious complication in colorectal surgery, causing a significant increase in short-term mortality, as well as long-term mortality and recurrences[24,25] Furthermore, a recent study by Odermatt et al. shows that major postoperative complications negatively impacted long-term survival, although no association with recurrences was demonstrated.[13] The results of our study are in accordance with these results. Our study adds important information about the association between specific complications and

survival and recurrences. Moreover, we showed that there still is an association between complications and surviving five additional years after surviving the first postoperative year (5-year conditional overall survival). This finding underlines the long-term effect of complications on overall survival, and shows that the long-term overall survival is not only determined by the short-term survival.

In the present study, it was demonstrated that anastomotic leakage, excessive blood loss, and (abdominal) sepsis were risk factors for dying in the first postoperative year. These serious complications directly impact important functions to survive. Both anastomotic leakage and (abdominal) sepsis were also associated with reduced 5-year overall survival, showing the prolonged impact of complications on survival.

Furthermore, abscess and delirium were associated with decreased 5-year overall survival. Previous studies have shown that postoperative delirium is associated with prolonged hospital stay and poor functional recovery.[26] The most important risk factors for postoperative delirium known from literature are advanced age, preoperative cognitive performance, and comorbidity.[27] This implies that patients who develop delirium are more frail, as also suggested by Raats et al.[28], which could be a possible explanation for worse long-term survival.

In a retrospective analysis by Law et al, postoperative complications were found to be adversely affected with recurrences.[12] By contrast, Odermatt et al. did not demonstrate this association.[13] Although we also found no association between the presence or the number of complications and recurrences, we did demonstrate that patients with anastomotic leakage, electrolyte disorders, or abscess more often had recurrences within 5 years after surgery compared with their counterparts. The exact mechanism of the association between complications and recurrences has not been elucidated yet. It has been shown that severe postoperative surgical complications in patients with stage III colon cancer were associated with less use or discontinuation of adjuvant chemotherapy.[10] This might partly explain the association between the specific complications and recurrences for patients with high-risk stage II disease or stage III disease, although we did not demonstrate an association between the presence or number of complications and recurrences. Moreover, it is suggested that extended immunosuppression and/or angiogenic stimulation due to postoperative infectious complications could play a role in proliferation of metastatic tumour cells.[12,13,29] The finding that anastomotic leakage and abscess were associated with recurrences supports this theory. However, we could not explain the association between electrolyte disorders and recurrences.

This study has some limitations. Although we adjusted the analyses for potential confounders, there might have been residual confounding. Since not only complications

within 30 days after surgery, but also long-term complications were included, immortal time bias might have been introduced. However, we consider the risk of immortal time bias to be very low given that over 95% of all first complications occurred within 30 days after surgery. Unfortunately, we had no information on the severity of complications. However, the main strength of this study is its detailed information regarding complications. Furthermore, this study is, to our knowledge, unique in providing a comprehensive insight into the association between the most frequent complications after surgery for stage I-III colon cancer and short-term as well as long-term outcomes. Moreover, our study covered patients from several hospitals, including both university and teaching hospitals.

CONCLUSIONS

Complications are associated with decreased short-term and long-term overall survival, although an increasing number of complications had no significant additional impact on survival. Of the ten most frequent complications, anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival. Anastomotic leakage, abscess, delirium, and (abdominal) sepsis were associated with decreased 5-year overall survival, while anastomotic leakage, delirium, and abscess were associated with decreased 5-year conditional overall survival. Furthermore, anastomotic leakage, electrolyte disorders, and abscess were associated with recurrences at 5 years. This study confirms the prolonged impact of surgery and demonstrates that complications result not only in reduced 1-year survival, but also in reduced long-term outcomes.

ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL), location Leiden, and H.D.M. Murk Jansen for the collection of data.

REFERENCES

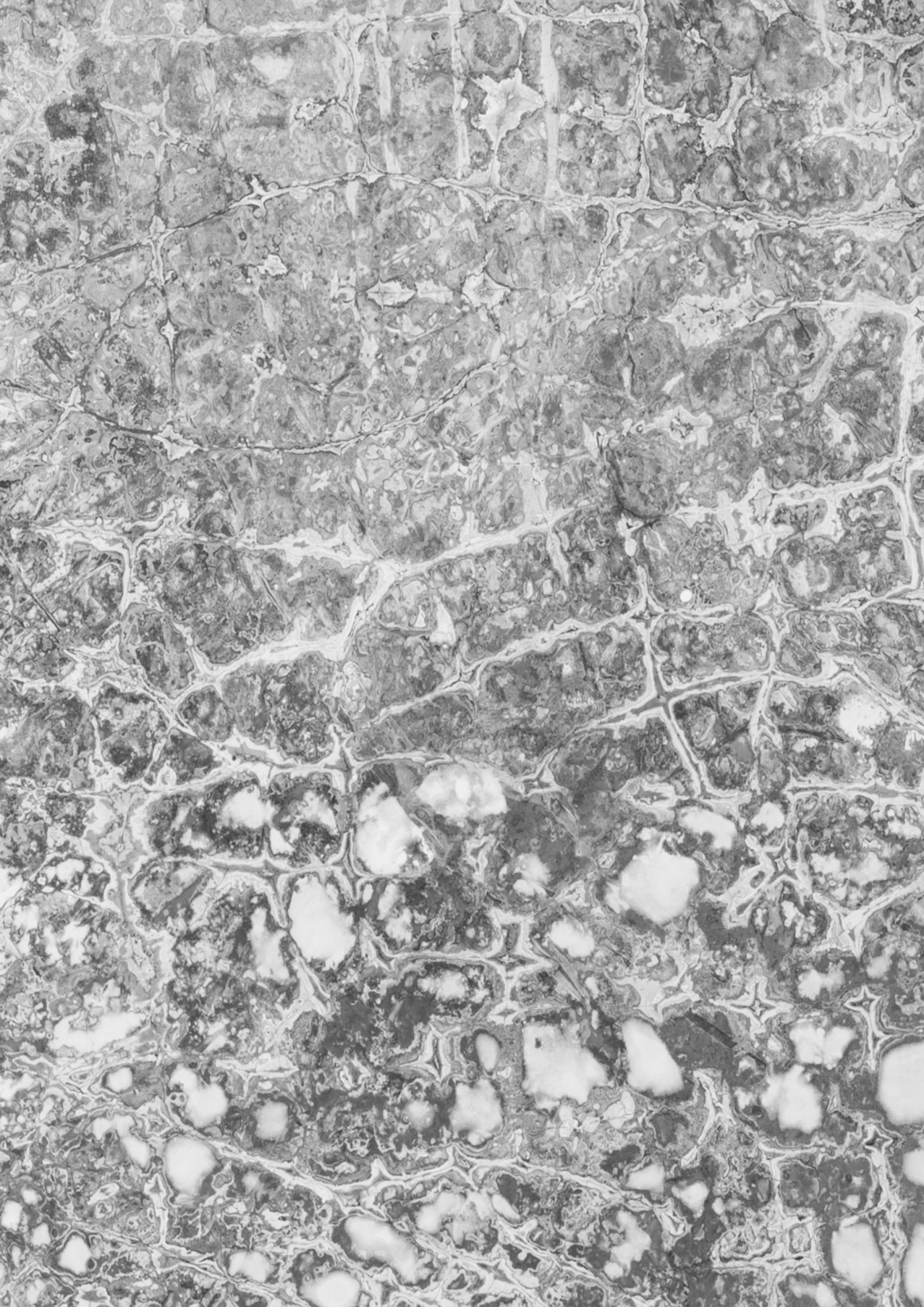
1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65:87-108.
2. Netherlands Cancer Registry. http://cijfersoverkanker.nl/selecties/Dataset_1/img559e9911e8351. Accessed July 2015.
3. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev 2008;CD005390.
4. Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; 322:352-358.
5. André 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; 27:3109-3116.
6. Elferink MA, de Jong KP, Klaase JM et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. Int J Colorectal Dis 2015; 30:205-212.
7. van Leersum NJ, Snijders HS, Henneman D et al. The Dutch surgical colorectal audit. Eur J Surg Oncol 2013; 39:1063-1070.
8. Liang J, Fazio V, Lavery I et al. Primacy of surgery for colorectal cancer. Br J Surg 2015; 102:847-852.
9. Bakker N, Cakir H, Doodeman HJ et al. Eight years of experience with Enhanced Recovery After Surgery in patients with colon cancer: Impact of measures to improve adherence. Surgery 2015; 157:1130-1136.
10. van der Geest LG, Portielje JE, Wouters MW et al. Complicated postoperative recovery increases omission, delay and discontinuation of adjuvant chemotherapy in patients with Stage III colon cancer. Colorectal Dis 2013; 15:e582-e591.
11. Al-Refaie WB, Parsons HM, Habermann EB et al. Operative outcomes beyond 30-day mortality: colorectal cancer surgery in oldest old. Ann Surg 2011; 253:947-952.
12. Law WL, Choi HK, Lee YM et al. The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer. Ann Surg Oncol 2007; 14:2559-2566.
13. Odermatt M, Miskovic D, Flashman K et al. Major postoperative complications following elective resection for colorectal cancer decrease long-term survival but not the time to recurrence. Colorectal Dis 2015; 17:141-149.
14. Alves A, Panis Y, Mathieu P et al. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. Arch Surg 2005; 140:278-83, discussion.
15. Henneman D, ten Berge MG, Snijders HS et al. Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement. J Surg Oncol 2014; 109:567-573.
16. 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; 18:1533-1539.
17. Gooiker GA, Dekker JW, Bastiaannet E et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 2012; 19:2428-2434.
18. Greenblatt DY, Weber SM, O'Connor ES et al. Readmission after colectomy for cancer predicts one-year mortality. Ann Surg 2010; 251:659-669.
19. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17:343-346.
20. Visser BC, Keegan H, Martin M et al. Death after colectomy: it's later than we think. Arch Surg 2009; 144:1021-1027.
21. Faiz O, Haji A, Bottle A et al. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. Colorectal Dis 2011; 13:779-785.
22. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? Colorectal Dis 2012; 14:1175-1182.
23. Dekker JW, Gooiker GA, Bastiaannet E et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. Eur J Surg Oncol 2014; 40:1481-1487.
24. Kube R, Mroczkowski P, Granowski D et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol 2010; 36:120-124.
25. Mirnezami A, Mirnezami R, Chandrakumaran K et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011; 253:890-

899.
26. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011; 112:1202-1211.
27. Robinson TN, Raeburn CD, Tran ZV et al. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg 2009; 249:173-178.
28. Raats JW, Steunenberg SL, Crolla RM et al. Postoperative delirium in elderly after elective and acute colorectal surgery: A prospective cohort study. Int J Surg 2015; 18:216-219.
29. Mynster T, Christensen IJ, Moesgaard F et al. Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANX05 Colorectal Cancer Study Group. Br J Surg 2000; 87:1553-1562.

SUPPLEMENTARY DATA

Supplementary table 1. Number of complications and percentages one-year overall survival, five-year overall survival, and five-year disease-free period for patients with and without complications by age categories.

	<65 years	65 – 74 years	≥75 years
Complications			
No	149 (72.3%)	129 (61.4%)	164 (47.5%)
Yes	57 (27.7%)	81 (38.6%)	181 (52.5%)
One-year overall survival			
No complications	99.3%	91.5%	90.9%
Complications	85.9%	90.1%	68.5%
Five-year overall survival			
No complications	81.5%	73.5%	58.0%
Complications	67.9%	66.3%	43.5%
Five-year disease-free period			
No complications	79.0%	80.2%	77.3%
Complications	62.8%	65.2%	84.1%



3

Decrease in 30-day and one-year mortality over time in patients aged ≥75 years with stage I-III colon cancer: a population-based study

A.J. Breugom
E. Bastiaannet
J.W.T. Dekker
M.W.J.M. Wouters
C.J.H. van de Velde
G.J. Liefers

European Journal of Surgical Oncology. 2018 Dec;44(12):1889-1893.

ABSTRACT

Background

Monitoring time trends of cancer mortality is essential. Thirty-day mortality is an important surgical outcome measure, though postoperative mortality exceeds to one year after surgery in patients with colorectal cancer. The aim of this nationwide observational study was to assess changes over time in 30-day and one-year mortality in patients with stage I-III colorectal cancer.

Methods

All surgically treated patients with stage I-III colorectal cancer, diagnosed between 2009 and 2013 were selected from the Netherlands Cancer Registry. Changes in 30-day and one-year mortality were assessed using logistic regression by tumour localisation (colon, rectum) and age group (<75 years, ≥75 years).

Results

Overall, 41,186 patients were included. Among patients with colon cancer ≥75 years, 30-day mortality decreased from 8.3% in 2009 to 6.2% in 2013 (p-value for trend =0.011), and one-year mortality from 18.5% in 2009 to 15.0% in 2013 (p-value for trend =0.007). No significant differences in mortality over time were observed for patients <75 years with colon cancer and for patients with rectal cancer.

Conclusion

Thirty-day and one-year mortality decreased over time in patients ≥75 years with stage I-III colon cancer, though the absolute decrease is small. However, 30-day mortality and in particular the one-year mortality are both still high in older patients with colorectal cancer and will need to be focused on to further improve outcomes for these patient subgroups.

INTRODUCTION

Colorectal cancer incidence increased with approximately one percent per year between 1989 and 2013 in the Netherlands, while a substantially higher increase was observed in 2014 as a result of the introduction of the national screening programme and a further increase in 2015 due to gradual implementation of the screening programme. With 15,400 patients diagnosed with colorectal cancer in 2016, it is currently the second most commonly diagnosed cancer in the Netherlands.[1]

Thirty-day postoperative mortality is widely used as an outcome measure after surgical procedures and is useful for benchmarking and quality assurance. However, previous studies suggested a continued effect of surgery on survival.[2-6] It was shown that 30-day mortality considerably underestimates postoperative mortality in patients with colorectal cancer, with one-year excess mortality (defined as one-year mortality adjusted for expected mortality in the general population) rates up to 30%.[5,6] Risk factors for excess mortality in the first postoperative year were comorbidity, stage III tumours, emergency surgery, and postoperative surgical complications.[6] Furthermore, age-related differences in colorectal cancer survival are mainly due to differences in mortality in the first postoperative year: patients ≥75 years who survived the first year had the same cancer-related survival compared to younger patients.[5] In the majority of patients with colorectal cancer, especially older patients, who died within the first year after surgery, the cause of death was attributed to the disease.[7] As it is unlikely that most of these patients had recurrent disease within the first year, the majority of these patients probably died as a result of cancer treatment.

Monitoring time trends of cancer mortality is important for cancer control. It might be possible to link changes in cancer mortality to changes in exposure to a particular risk factor, to changes in treatment guidelines, or to changes in health care including for example perioperative care for surgically treated patients, optimisation of care for specific subgroups, and non-surgical management.

Given the importance of the 30-day and one-year mortality as outcome measures after surgery for colorectal cancer, the aim of this nationwide observational study was to assess changes over time in both 30-day and one-year mortality in patients with stage I-III colorectal cancer.

METHODS

Patients

All surgically treated patients with stage I-III colorectal cancer (ICD-10 C18, C19, and C20), who were diagnosed between January 1, 2009 and December 31, 2013, were selected from the Netherlands Cancer Registry. Patients who underwent local resection of the tumour were excluded. The Netherlands Cancer Registry registers data of all newly diagnosed patients with cancer in the Netherlands. Patients are detected through the national pathology archive, after which trained registry personnel collect data from the medical records including patient, tumour, and treatment characteristics. Follow-up status is available through linkage with municipal population registers, and was complete until December 31st, 2014.

Age was categorised as <75 years and ≥75 years. Tumour localisation was defined as colon or rectum. The information on TNM stage was based on pathological reports. If pathological data were missing, clinical TNM stage was used. Emergency surgery was recorded as no, yes, or as stent or stoma followed by planned surgery. Thirty-day and one-year mortality were defined as all-cause death at or before 30 days and one year after surgery for colorectal cancer.

Statistical analyses

Analyses were stratified by tumour localisation (colon, rectum) and age (<75 years, ≥75 years).

P-value for trend was obtained by logistic regression analyses. Moreover, we assessed if mortality changed over time using crude logistic regression models with 30-day or one-year mortality as dependent variable and year of diagnosis as independent variable, with the previous year used as a reference category. These analyses were additionally adjusted for stage, emergency surgery, and age. If data were missing, patients were analysed as a separate 'unknown' group within the same variable.

A p-value <0.05 was considered as statistical significant. All analyses were done with IBM SPSS Statistics, version 20.0.

RESULTS

Between January 1, 2009 and December 31, 2013, a total of 43,513 patients were identified. We excluded 2,327 patients who underwent local resection of the tumour. Data from the remaining 41,186 patients were included. Table 1 shows the characteristics

of the patients. Of all patients, 15,162 patients were aged ≥75 years. Moreover, over 70% of patients had a tumour located in the colon.

Table 1. Patient characteristics

	All patients (*n*=41,186)	**<75 years** (*n*=26,024)	**≥75 years** (*n*=15,162)
Age (median ±SD)	71.00 ±11.19	65.00 ±8.58	80.00 ±4.28
Gender			
Male	22,390 (54.4)	14,936 (57.4)	7,454 (49.2)
Female	18,796 (45.6)	11,088 (42.6)	7,708 (50.8)
Year of diagnosis			
2009	7,514 (18.2)	4,754 (18.3)	2,760 (18.2)
2010	8,282 (20.1)	5,123 (19.7)	3,159 (20.8)
2011	8,541 (20.7)	5,457 (21.0)	3,084 (20.3)
2012	8,577 (20.8)	5,428 (20.9)	3,149 (20.8)
2013	8,272 (20.1)	5,262 (20.2)	3,010 (19.9)
Tumour localisation			
Colon	30,022 (72.9)	17,798 (68.4)	12,224 (80.6)
Rectum	11,164 (27.1)	8,226 (31.6)	2,938 (19.4)
TNM stage			
I	9,829 (23.9)	6,474 (24.9)	3,355 (22.1)
IIA	13,930 (33.8)	8,175 (31.4)	5,755 (38.0)
IIB	2,083 (5.1)	1,160 (4.5)	923 (6.1)
IIIA	1,850 (4.5)	1,338 (5.1)	512 (3.4)
IIIB	8,209 (19.9)	5,272 (20.3)	2,937 (19.4)
IIIC	4,934 (12.0)	3,372 (13.0)	1,562 (10.3)
Unknown, but no metastases	351 (0.9)	233 (0.9)	118 (0.8)
Grade			
I	2,033 (4.9)	1,258 (4.8)	775 (5.1)
II	25,156 (61.1)	15,501 (59.6)	9,655 (63.7)
III	5,031 (12.2)	2,875 (11.0)	2,156 (14.2)
IV	50 (0.1)	22 (0.1)	28 (0.2)
Unknown	8,916 (21.6)	6,368 (24.5)	2,548 (16.8)
Emergency surgery			
No	27,578 (67.0)	16,340 (62.8)	11,238 (74.1)
Yes	2,209 (5.4)	1,328 (5.1)	881 (5.8)
Stent or stoma followed by planned surgery	185 (0.4)	120 (0.5)	65 (0.4)
Unknown	11,214 (27.2)	8,236 (31.6)	2,978 (19.6)

Data are presented as median ±SD or as *n* (%).

Patients with colon cancer <75 years

Thirty-day mortality ranged from 1.4% in 2009 to 1.1% in 2013 for patients with colon cancer <75 years (p-value for trend =0.065, Figure 1a). Adjusted logistic regression showed no significant differences in 30-day mortality (Table 2).

One-year mortality was 5.0% in 2009 and 5.1% in 2013 (p-value for trend =0.058, Figure 1a). In 2010, the one-year mortality was higher compared to 2009 in adjusted analysis (OR 1.26, 95% CI 1.02-1.56, p=0.035, Table 2), and the one-year mortality in 2011 was lower compared to 2010 (adjusted OR 0.74, 95% CI 0.60-0.91, p=0.004, Table 2).

Table 2. Crude and adjusted Odds Ratios

	Year of diagnosis	Crude OR	95% CI*	p-value*	Adjusted OR	95% CI**	p-value**
Colon cancer <75 years							
30-day mortality	2009	1	(Reference)		1	(Reference)	
	2010	1.42	(0.97-2.09)	0.072	1.41	(0.96-2.07)	0.082
	2011	0.77	(0.54-1.11)	0.159	0.76	(0.53-1.08)	0.127
	2012	0.96	(0.66-1.40)	0.824	0.94	(0.64-1.37)	0.732
	2013	0.76	(0.50-1.14)	0.188	0.77	(0.51-1.17)	0.223
1-year mortality	2009	1	(Reference)		1	(Reference)	
	2010	1.27	(1.03-1.56)	0.027	1.26	(1.02-1.56)	0.035
	2011	0.77	(0.63-0.94)	0.011	0.74	(0.60-0.91)	0.004
	2012	1.16	(0.94-1.42)	0.164	1.15	(0.93-1.41)	0.193
	2013	0.90	(0.73-1.10)	0.286	0.91	(0.74-1.12)	0.375
Colon cancer ≥75 years							
30-day mortality	2009	1	(Reference)		1	(Reference)	
	2010	1.00	(0.81-1.23)	0.982	0.97	(0.79-1.20)	0.774
	2011	0.81	(0.66-1.00)	0.048	0.81	(0.65-1.01)	0.056
	2012	1.01	(0.81-1.26)	0.913	1.06	(0.85-1.32)	0.616
	2013	0.89	(0.71-1.11)	0.295	0.86	(0.68-1.08)	0.183
1-year mortality	2009	1	(Reference)		1	(Reference)	
	2010	0.98	(0.85-1.14)	0.815	0.94	(0.81-1.10)	0.456
	2011	0.89	(0.77-1.03)	0.111	0.89	(0.76-1.03)	0.117
	2012	0.99	(0.85-1.15)	0.895	1.05	(0.89-1.22)	0.581
	2013	0.90	(0.77-1.05)	0.181	0.86	(0.74-1.01)	0.072
Rectal cancer <75 years							
30-day mortality	2009	1	(Reference)		1	(Reference)	
	2010	1.10	(0.57-2.15)	0.776	1.09	(0.56-2.13)	0.807
	2011	1.11	(0.60-2.06)	0.737	1.16	(0.62-2.18)	0.638
	2012	0.94	(0.51-1.72)	0.830	0.97	(0.52-1.80)	0.927
	2013	0.78	(0.40-1.53)	0.466	0.77	(0.39-1.51)	0.440
1-year mortality	2009	1	(Reference)		1	(Reference)	
	2010	1.17	(0.83-1.64)	0.362	1.19	(0.85-1.68)	0.319
	2011	0.92	(0.67-1.27)	0.608	0.94	(0.67-1.30)	0.689
	2012	1.02	(0.73-1.41)	0.920	1.02	(0.73-1.42)	0.910
	2013	0.81	(0.57-1.15)	0.241	0.81	(0.57-1.16)	0.249
Rectal cancer ≥75 years							
30-day mortality	2009	1	(Reference)		1	(Reference)	
	2010	0.84	(0.51-1.40)	0.506	0.86	(0.52-1.44)	0.566
	2011	1.00	(0.60-1.68)	1.000	1.03	(0.61-1.75)	0.902
	2012	0.76	(0.44-1.31)	0.317	0.71	(0.41-1.23)	0.225
	2013	0.73	(0.39-1.37)	0.329	0.79	(0.42-1.49)	0.464
1-year mortality	2009	1	(Reference)		1	(Reference)	
	2010	0.84	(0.60-1.17)	0.311	0.86	(0.61-1.20)	0.369
	2011	1.06	(0.76-1.48)	0.732	1.11	(0.79-1.56)	0.568
	2012	1.01	(0.73-1.40)	0.934	0.96	(0.69-1.34)	0.803
	2013	0.81	(0.58-1.13)	0.218	0.85	(0.60-1.20)	0.355

* Previous year is used as a reference category.

** Previous year is used as a reference category adjusted for stage, emergency surgery, and age.

Patients with colon cancer ≥75 years

For patients with colon cancer ≥75 years, 30-day mortality decreased from 8.3% in 2009 to 6.2% in 2013 (p for trend =0.011), and one-year mortality from 18.5% in 2009 to 15.0% in 2013 (p-value for trend =0.007, Figure 1b).

We did not demonstrate a significant improvement in 30-day and one-year mortality using the previous year as a reference category in adjusted logistic regression analysis (Table 2).

Patients with rectal cancer <75 years

We observed no significant differences in 30-day mortality (p-value for trend =0.901) and one-year mortality (p-value for trend =0.058) for patients with rectal cancer <75 years (Figure 1c). Thirty-day mortality ranged from 1.4% in 2009 to 1.1% in 2013, and one-year mortality ranged from 5.0% in 2009 to 5.1% in 2013. Adjusted logistic regression analysis with the previous year as a reference category also showed no significant improvement in 30-day and one-year mortality (Table 2).

Patients with rectal cancer ≥75 years

For patients with rectal cancer aged ≥75 years, 30-day mortality decreased from 6.1% in 2009 to 2.9% in 2013 (p for trend =0.107), and one-year mortality from 15.3% in 2009 to 11.7% in 2013 (p-value for trend =0.490, Figure 1d). Compared to the previous year, no significant differences in 30-day and one-year mortality were observed (Table 2).

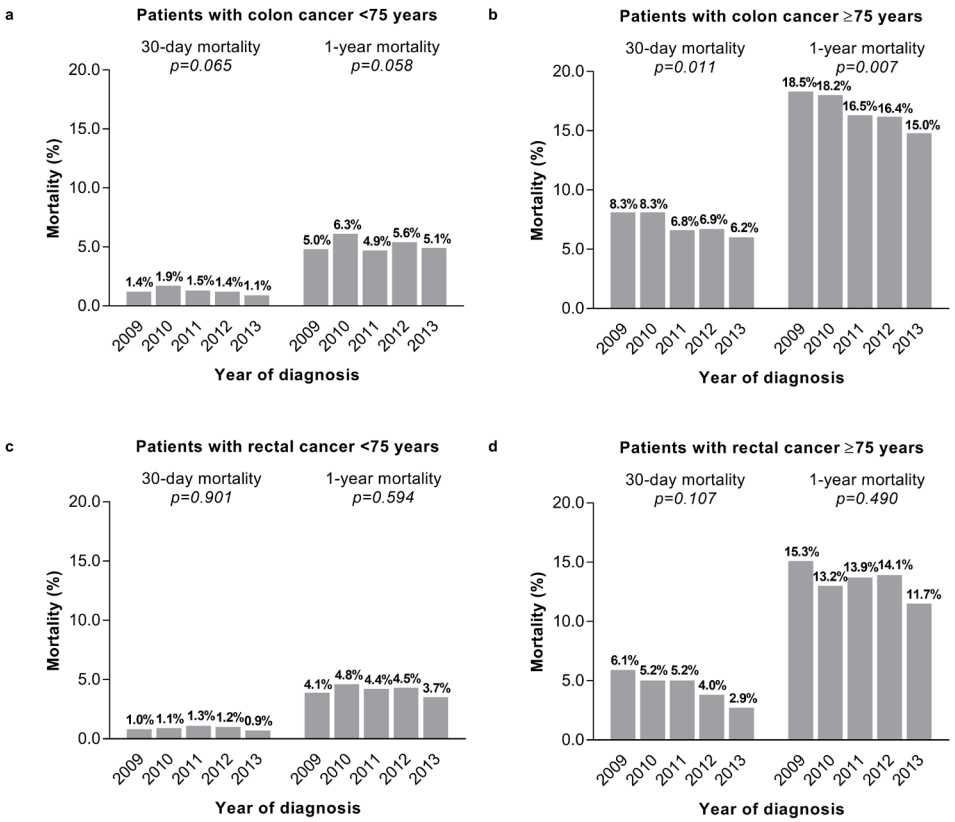


Figure 1. Time trends in 30-day and 1-year mortality for patients with a. colon cancer <75 years, b.colon cancer ≥75 years , c. rectal cancer <75 years, d. rectal cancer ≥75 years

P-values were calculated using logistic regression, and represent p for trend for year of diagnosis.

DISCUSSION

This study shows a 25% relative decrease in 30-day and a 19% relative decrease in one-year mortality over time in patients with stage I-III colon cancer aged ≥75 years, while the absolute decrease was 2.1% in 30-day mortality and 3.5% in one-year mortality.

Improving quality and safety of colorectal cancer care is an important issue. Survival improved markedly over time for patients with colorectal cancer in Europe, whilst incidence rates increased modestly.[1,8-10] The increase in survival has been mainly attributed to improvements in for example staging, access to treatment, effective treatment options, standardising care, and the introduction of high-volume care.[8,11,12] Moreover, several European countries initiated surgical audits which may also have contributed to improved survival by measuring quality of care, and reflecting on the effects of any

changes in the quality of care over time.[13] These factors could have contributed to the decrease in 30-day and one-year mortality that we observed. Moreover, in older patients, more individual selection for preoperative and postoperative treatment might have been improved over time.

For patients with rectal cancer, we observed no significant decrease over time in both 30-day and one-year mortality. Outcome of patients with rectal cancer already improved considerably over the past decades mainly as a result of the introduction of standardised total mesorectal excision, more accurate staging with MRI, and the use of preoperative (chemo)radiotherapy.[12,14-17] In this study, we demonstrated that for example the 30-day mortality rate for patients with rectal cancer <75 years was only 0.9% in 2013. However, although slightly lower than in patients with colon cancer aged ≥75 years, 30-day and one-year mortality are still high among older patients with rectal cancer.

Henneman et al. demonstrated that the mortality rate in patients with a severe complication is higher in patients with colon cancer than in patients with rectal cancer, although patients with rectal cancer have a higher complication rate.[18] In a study by van der Sijp et al., it was also shown that complications account for a higher one-year excess mortality in patients with colon cancer.[19] In our study, we observed higher 30-day and one-year mortality in patients with colon cancer, which is in line with the findings of these studies.

For patients aged younger than 75 years, we observed no significant changes over time in 30-day mortality and one-year mortality for both colon and rectal cancer, with especially low 30-day mortality rates. This indicates that a further reduction in mortality would be difficult to achieve. Moreover, there is substantial more evidence for younger patients from randomised controlled trials regarding optimal treatment compared to older patients who are often excluded from randomised controlled trials.[20] However, although not significant, it is worth noticing that in patients <75 years with colon cancer, one-year mortality did not decrease at all over time. While 30-day mortality is very low in this group, one-year mortality is still over five percent. This suggests that there might be a continued effect of surgery on survival for younger patients as well. A possible explanation could be that younger patients will be fit enough to survive complications in the acute phase, but may die during the first year after surgery as a late result of their severe complications, while older patients will also die more often in the acute phase after a complication.

Although we observed an improved 30-day and one-year mortality over time for patients with colon cancer ≥75 years, 30-day mortality and especially one-year mortality are still high for older patients with colon or rectal cancer, which is in line with previous studies.[5,6]

These studies concluded that the focus should be on the first postoperative year to improve outcomes after colorectal cancer surgery.

Comorbidity, stage III tumours, emergency surgery, postoperative surgical complications, and readmission were already identified as important factors influencing one-year mortality.[6,19,21] Moreover, older patients are at increased risk to dehydration and electrolyte abnormalities, especially when there is physiological stress, as a result of age-related pathophysiological changes combined with iatrogenic causes.[22] In older patients admitted to hospital as medical emergencies, dehydration is associated with a greater risk of in-hospital mortality.[23] Dehydration may therefore be a factor influencing 30-day mortality after surgery for colorectal cancer in older patients. Geriatric consultation can be of help in treatment decision making for older patients and may lead to more individualised and optimised treatment.[24] Further insight in modifiable risk factors for 30-day and one-year mortality in patients ≥75 years is necessary. Moreover, the period after hospital discharge will also be of great importance to improve the quality of colorectal cancer care.

The main strength of this study is the well-registered and quality assured data from the Netherlands Cancer Registry of a large number of unselected patients with stage I-III colorectal cancer. This made it possible to assess time trends of 30-day and one-year mortality, providing insight in mortality rates over time. On the contrary, we were unfortunately not able to incorporate specific patient characteristics such as comorbidity and clinical condition, as these data are not registered in the Netherlands Cancer Registry. This limits detailed analysis on specific subgroups. Moreover, no information on cause of death, as well as toxicity or complications of treatment was available. In this study, we used all-cause 30-day and one-year mortality as outcomes. However, it was previously shown that excess mortality was high among patients with colorectal cancer who died within the first postoperative year.[5,6]

In conclusion, 30-day and one-year mortality decreased over time in patients with stage I-III colon cancer aged ≥75 years. However, 30-day mortality and in particular one-year mortality are both still high in older patients with colorectal cancer and will need to be focused on to further improve outcomes for these patient subgroups.

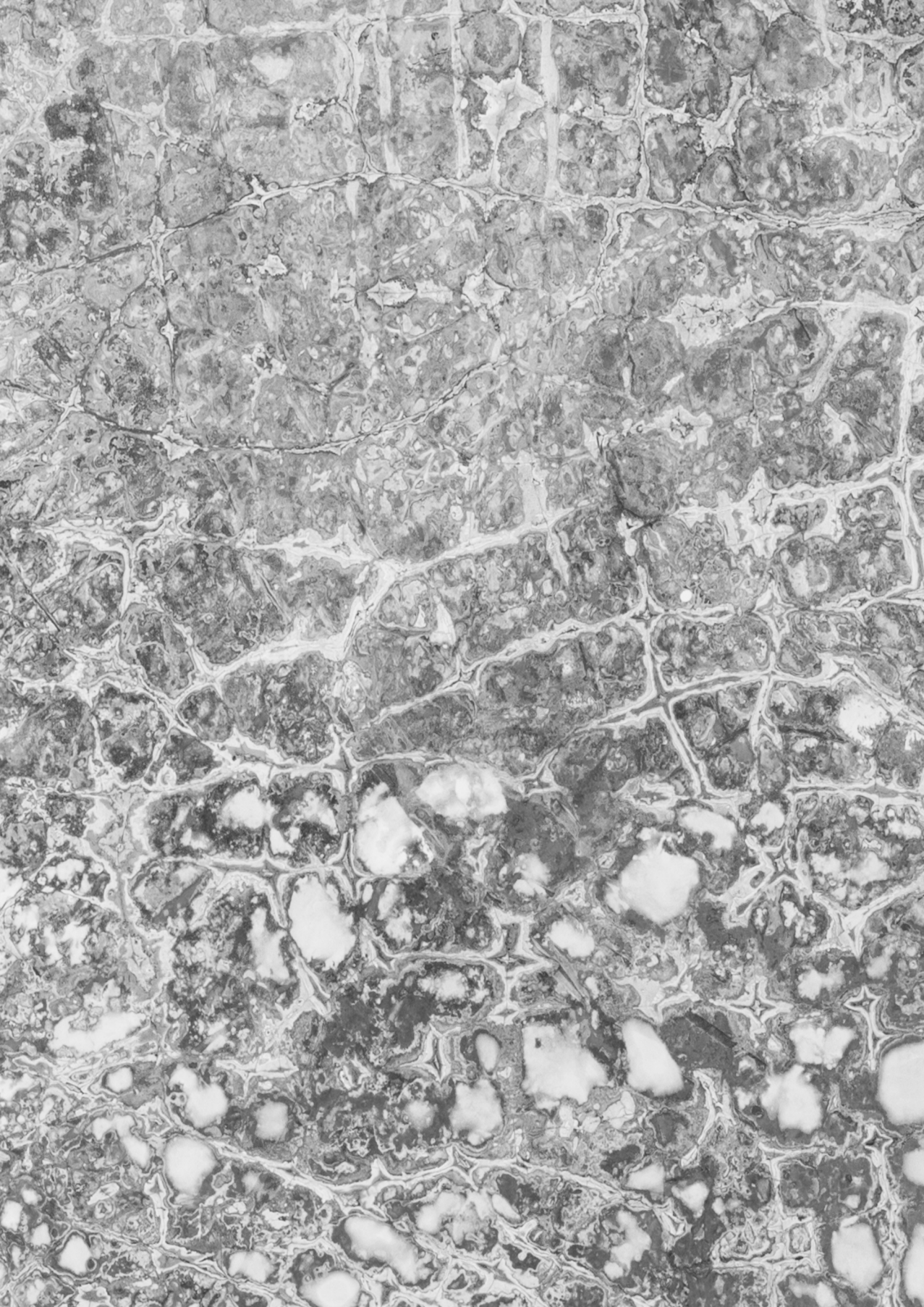
ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data.

REFERENCES

1. http://cijfersoverkanker.nl. *Accessed October* 2017.
2. Visser BC, Keegan H, Martin M, Wren SM. Death after colectomy: it's later than we think. *Arch Surg* 2009; **144**(11): 1021-7.
3. Faiz O, Haji A, Bottle A, Clark SK, Darzi AW, Aylin P. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. *Colorectal Dis* 2011; **13**(7): 779-85.
4. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? *Colorectal Dis* 2012; **14**(10): 1175-82.
5. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**(6): 1533-9.
6. Gooiker GA, Dekker JW, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* 2012; **19**(8): 2428-34.
7. Dekker JW, Gooiker GA, Bastiaannet E, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *Eur J Surg Oncol* 2014; **40**(11): 1481-7.
8. Karim-Kos HE, de VE, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. 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**(10): 1345-89.
9. 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 EUROCARE study. *Int J Cancer* 2012; **131**(7): 1649-58.
10. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2. *Eur J Cancer* 2015.
11. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**(15): 1128-37.
12. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**(8496): 1479-82.
13. Breugom AJ, Boelens PG, van den Broek CB, et al. Quality assurance in the treatment of colorectal cancer: the EURECCA initiative. *Ann Oncol* 2014; **25**(8): 1485-92.
14. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol* 2014; **32**(1): 34-43.
15. 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**(6): 575-82.
16. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**(17): 1731-40.
17. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**(28): 4620-5.
18. Henneman D, Ten Berge MG, Snijders HS, et al. Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement. *J Surg Oncol* 2014; **109**(6): 567-73.
19. van der Sijp MP, Bastiaannet E, Mesker WE, et al. Differences between colon and rectal cancer in complications, short-term survival and recurrences. *Int J Colorectal Dis* 2016; **31**(10): 1683-91.
20. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med* 2011; **26**(7): 783-90.
21. Greenblatt DY, Weber SM, O'Connor ES, LoConte NK, Liou JI, Smith MA. Readmission after colectomy for cancer predicts one-year mortality. *Ann Surg* 2010; **251**(4): 659-69.
22. El-Sharkawy AM, Sahota O, Maughan RJ, Lobo DN. The pathophysiology of fluid and electrolyte balance in the older adult surgical patient. *Clin Nutr* 2014; **33**(1): 6-13.
23. El-Sharkawy AM, Watson P, Neal KR, et al. Hydration and outcome in older patients admitted to hospital (The HOOP prospective cohort study). *Age Ageing* 2015; **44**(6): 943-7.

24. Verweij NM, Souwer ETD, Schiphorst AHW, et al. The effect of a geriatric evaluation on treatment decisions for older patients with colorectal cancer. *Int J Colorectal Dis* 2017.



4

Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomised phase III trial

A.J. Breugom
W. van Gijn
E.W. Muller
Å. Berglund
C.B.M. van den Broek
T. Fokstuen, H. Gelderblom
E. Kapiteijn
J.W.H. Leer
C.A.M. Marijnen
H. Martijn
E. Meershoek-Klein Kranenbarg
I.D. Nagtegaal
L. Påhlman
C.J.A. Punt, H. Putter
A.G.H. Roodvoets
H.J.T. Rutten
W.H. Steup, B. Glimelius
C.J.H. van de Velde
Cooperative Investigators of the Dutch Colorectal Cancer Group and the Nordic Gastrointestinal Tumour Adjuvant Therapy Group

Annals of Oncology. 2015 Apr;26(4):696-701.

ABSTRACT

Background

The discussion on the role of adjuvant chemotherapy for rectal cancer patients treated according to current guidelines is still ongoing. A multicentre, randomised phase III trial, PROCTOR-SCRIPT, was conducted to compare adjuvant chemotherapy with observation for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision (TME).

Patients and Methods

The PROCTOR-SCRIPT trial recruited patients from 52 hospitals. Patients with histologically proven stage II or III rectal adenocarcinoma were randomly assigned (1:1) to observation or adjuvant chemotherapy after preoperative (chemo)radiotherapy TME. Radiotherapy consisted of 5x5 Gy. Chemoradiotherapy consisted of 25x1.8-2 Gy combined with 5-FU based chemotherapy. Adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR), or eight courses capecitabine (SCRIPT). Randomisation was based on permuted blocks of six, stratified according to centre, residual tumour, time between last irradiation and surgery, and preoperative treatment. The primary end point was overall survival.

Results

Of 470 enrolled patients, 437 were eligible. The trial closed prematurely because of slow patient accrual. Patients were randomly assigned to observation (n=221) or adjuvant chemotherapy (n=216). After a median follow-up of 5.0 years, 5-year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group (hazard ratio (HR) 0.93, 95% CI 0.62-1.39; p=0.73). The HR for disease-free survival was 0.80 (95% CI 0.60-1.07; p=0.13). Five-year cumulative incidence for locoregional recurrences was 7.8% in both groups. Five-year cumulative incidence for distant recurrences was 38.5% and 34.7%, respectively (p=0.39).

Conclusion

The PROCTOR-SCRIPT trial could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy after preoperative (chemo) radiotherapy and TME on overall survival, disease-free survival, and recurrence rate. However, this trial did not complete planned accrual.

Funding

This work was supported by The Dutch Cancer Society (KWF 1999-03 and KWF 2003-16), the Dutch Colorectal Cancer Group, and the Swedish Cancer Society. Furthermore, Roche has provided an unrestricted educational grant.

INTRODUCTION

Locoregional recurrence rates and survival have significantly improved with the introduction of total mesorectal excision (TME) for patients with rectal cancer.[1,2] Further improvements in rectal cancer treatment were made by the possibility of more accurate staging with magnetic resonance imaging (MRI), and by the use of preoperative short-course radiotherapy or long-course chemoradiotherapy.[3-6] The addition of preoperative radiotherapy to TME surgery resulted in a more than 50% decrease in locoregional recurrences. However, the combination of preoperative (chemo)radiotherapy and TME surgery did not improve overall or disease-free survival[3,5,6], although cancer-specific survival was significantly better in patients operated with a negative circumferential margin after preoperative radiotherapy.[3]

In contrast to locoregional recurrence rates, distant metastasis rates did not improve. Up to 30% of all patients treated with curative intent for localised rectal cancer will develop distant metastases[3,5], and distant metastases are still the main cause of death after rectal cancer.[7]

Adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME surgery could eradicate micrometastases. This might reduce distant metastases, resulting in improved outcomes. Currently, there is no conclusive evidence on the benefit of adjuvant chemotherapy in rectal cancer treatment after preoperative (chemo)radiotherapy followed by TME surgery, and the debate on this subject is still ongoing.[8]

With this trial, we aim to investigate the value of adjuvant chemotherapy with fluoropyrimidine monotherapy after preoperative (chemo)radiotherapy and TME surgery.

PATIENTS AND METHODS

Study design and patients

We undertook a randomised, controlled, phase III trial in 52 hospitals. Patients were randomised to observation or adjuvant chemotherapy after preoperative (chemo) radiotherapy and TME surgery. Initially, radiotherapy was given in five factions of 5 Gy and adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR – **P**reoperative **R**adiotherapy and / **O**r adjuvant **C**hemotherapy combined with **T**ME surgery in **O**perable **R**ectal cancer). After a protocol amendment, chemoradiotherapy was also allowed and capecitabine was used as adjuvant treatment (SCRIPT – **S**imply **C**apecitabine in **R**ectal cancer after **I**rradiation **P**lus **T**ME).

Patients aged ≥18 years, with a rectal adenocarcinoma (below the level of S1/S2 on CT or MRI, or located within 15 cm from the anal verge measured during withdrawal of a flexible or rigid scope), who had preoperative (chemo)radiotherapy and TME surgery, (y)pTNM stage II or III, an R0 (PROCTOR and SCRIPT) or R1 (SCRIPT) resection, and who could start chemotherapy within six weeks after surgery, were eligible.

Exclusion criteria were Familial Adenomatosis Polyposis Coli, Hereditary Non-Polyposis Colorectal Cancer, active inflammatory bowel disease, DPD deficiency, and present or prior malignancies except for adequately treated basocellular carcinoma of the skin, or in situ carcinoma of the cervix uteri (PROCTOR: no prior malignancies, SCRIPT: at least ten years disease-free).

We obtained ethical approval from central and local ethics committees. All patients gave written informed consent.

Randomisation

Randomisation was carried out centrally at the datacentre of the Department of Surgery at the Leiden University Medical Centre. Patients were randomly assigned (1:1) to observation or adjuvant chemotherapy. Randomisation was computer-generated and based on permuted blocks of six, with stratification according to centre, residual tumour (R0/R1), time between last irradiation and surgery, and preoperative treatment.

Procedures

Preoperative radiotherapy consisted of 25 Gy in five fractions of 5 Gy, preoperative chemoradiotherapy of 45-50 Gy in 25 fractions(1.8-2 Gy) with 5-FU based chemotherapy. The Clinical Target Volume (CTV) included the primary tumour and the mesentery with vascular supply containing the perirectal, the presacral and the internal iliac nodes (up to the S1/S2 junction). If an abdominoperineal resection was planned, the inner and outer anal sphincter were included. A three or four beams technique was mandatory. Patients were treated in either prone or supine position.

Standardised TME surgery was carried out according to strict and controllable quality demands.[2,3] Standardised pathological examination was carried out.[9] A circumferential resection margin of ≤1 mm was considered positive. R1 resection was defined as both microscopic residual tumour and a circumferential resection margin (CRM) of ≤1 mm. Good TME surgery, including an intact mesorectum, no deep defects, no coning, and a smooth CRM, was performed in 82.7% (PROCTOR) and 66.0% (SCRIPT) of the patients.

Adjuvant chemotherapy consisted of leucovorin 20mg/m^2 immediately followed by 5-FU 425mg/m^2 by intravenous bolus injection daily for five days, repeated every four to five

weeks for six courses (Mayo regimen), or of 5-FU 500mg/m^2 followed by leucovorin 60mg/m^2 after 30 to 40 minutes by bolus intravenous injections daily, for two consecutive days every 14 days for 12 courses (Nordic regimen). After a protocol amendment, adjuvant chemotherapy consisted of eight courses of 1.250 mg/m^2 oral capecitabine twice daily (days 1-14 every 21 days).

All Dutch patients were assessed every 3 months after surgery during the first 2 years and annually afterwards. All Swedish patients were assessed at 1 and 3 years or every six months for three years according to the COLOFOL trial.[10] Locoregional recurrence was defined as a recurrence within the pelvic, anastomotic, or perineal area. Distant recurrence was defined as tumour growth in any other area.

End points

Primary end point was overall survival. Secondary end points were disease-free survival, overall recurrence rate, and locoregional and distant recurrence rate separately.

Statistical analyses

A total of 840 patients (294 events) was needed to detect an improvement in 5-year overall survival from 60% to 70% (alpha 0.05, two sided; power 0.90).

All analyses were carried out by intention-to-treat. A per-protocol analysis was done on patients in the observation group who survived at least 210 days (to avoid immortal time bias), and eligible patients that completed all chemotherapy cycles. A sensitivity analysis including all randomised patients was carried out on the primary end point.

Overall survival was defined as time to death (any cause), or end of follow-up (censored). Disease-free survival was defined as time to any recurrence or death, whichever occurred first, or end of follow-up (censored). Time to locoregional, distant or overall recurrence was defined as time to the specific recurrence, or end of follow-up (censored).

Overall survival and disease-free survival curves were calculated with the Kaplan-Meier method. The hazard ratios (HR) and their 95% confidence intervals (CIs), and the cumulative incidence of recurrences, were calculated with Cox proportional hazards model. In order to determine differences between PROCTOR and SCRIPT, an interaction term between randomisation and study part was used.

Statistical analyses were carried out using IBM SPSS Statistics (20.0). A p-value of ≤0.05 was considered statistically significant.

RESULTS

Between 1 March 2000 and 1 January 2013, 470 patients were included, of whom 33 were incorrectly randomised. Therefore, 437 patients (309 Dutch and 128 Swedish patients) were eligible for analyses. The trial was finally closed due to poor patient accrual without reaching the intended inclusion. Preoperative staging with CT or MRI was done in 50.6% in the PROCTOR part, while in the SCRIPT part 74.5% had a pelvic MRI scan. The median time from surgery to the start of adjuvant chemotherapy was 6.0 weeks.

Of the incorrectly randomised patients, 15 did not have ypTNM stage II or III, 13 received TME surgery without preoperative (chemo)radiotherapy, 4 had a tumour not located within 15 cm from the anal verge, and 1 received long-course radiotherapy without chemotherapy (supplementary Figure S1). Of the eligible patients, 221 patients were randomised to observation and 216 patients were randomised to adjuvant chemotherapy. The trial profile is demonstrated in supplementary Figure S1. Patient characteristics were equally distributed between the two groups (Table 1).

Table 1. Patient characteristics

Characteristics	Total (*n* = 437)	Observation (*n* = 221)	Chemotherapy (*n* = 216)
Age (years)	61.08 ± 9.03	61.08 ± 9.13	61.13 ± 8.94
Gender			
Male	270 (61.8)	139 (62.9)	131 (60.6)
Female	167 (38.2)	82 (37.1)	85 (39.4)
Preoperative treatment			
Radiotherapy	376 (86.0)	193 (87.3)	183 (84.7)
Chemoradiotherapy	61 (14.0)	28 (12.7)	33 (15.3)
Type of resection			
LAR	275 (62.9)	142 (64.3)	133 (61.6)
APR	146 (33.4)	70 (31.7)	76 (35.2)
Hartmann	16 (3.7)	9 (4.1)	7 (3.2)
Tumour location from anal verge			
< 5 cm	113 (25.9)	51 (23.1)	62 (28.7)
5 – 9.9 cm	139 (31.8)	75 (33.9)	64 (29.6)
≥ 10 cm	168 (38.4)	83 (37.6)	85 (39.4)
Unknown	17 (3.9)	12 (5.4)	5 (2.3)
CRM			
Negative	409 (93.6)	208 (94.1)	201 (93.1)
Positive	19 (4.3)	8 (3.6)	11 (5.1)
Unknown	9 (2.1)	5 (2.3)	4 (1.9)
Residual tumour			
R0	418 (95.7)	213 (96.4)	205 (94.9)
R1	19 (4.3)	8 (3.6)	11 (5.1)
(y)pTNM			
II	71 (16.2)	32 (14.5)	39 (18.1)
III	366 (83.8)	189 (85.5)	177 (81.9)

Data are presented as median ± SD or as *n* (%)

In the chemotherapy group, 73.6% (*n*=159) completed all chemotherapy cycles, 20.8% did not, while 4.6% never started chemotherapy. Information on chemotherapy compliance was missing in 0.9% (supplementary Figure S1). In 14.8%, toxicity was the reason to end chemotherapy. Capecitabine was used in 65.3% of the patients. The remaining 34.7% received 5-FU/LV (37.3% Mayo regimen, 48.0% Nordic regimen, 14.7% unknown regimen).

Follow-up was completed until 27 June 2014. Median follow-up of surviving patients was 5.0 years (range 0.02 – 13.12 years).

Overall survival

A total of 95 patients died. Five-year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group (HR 0.93, 95% CI 0.62-1.39; *p*=0.73; Figure 1A).

The per-protocol analysis demonstrated an HR of 0.77 for overall survival (95% CI 0.49-1.21; *p*=0.26). A sensitivity analysis of all patients showed an HR of 0.94 (95% CI 0.64-1.38; *p*=0.75). The effect of adjuvant chemotherapy on overall survival did not differ between PROCTOR and SCRIPT ($p_{interaction}$=0.54).

Disease-free survival

No statistically significant difference in disease-free survival was observed. Five-year disease-free survival was 55.4% for the observation group and 62.7% for the chemotherapy group (HR 0.80, 95% CI 0.60-1.07; *p*=0.13; Figure 1B). In the per-protocol analysis, the HR was 0.77 (95% CI 0.55-1.06; *p*=0.11).

There was no difference in the effect of adjuvant chemotherapy between PROCTOR and SCRIPT ($p_{interaction}$=0.49).

Recurrences

In total, there were 157 recurrences. At 5 years, the cumulative incidence for overall recurrences was 40.3% in the observation group and 36.2% in the chemotherapy group (HR 0.88, 95% CI 0.64-1.20; *p*=0.43). Similar results were found in per-protocol analysis (HR 0.87, 95% CI 0.61-1.22; *p*=0.41).

The 5-year cumulative incidence for locoregional recurrences was 7.8% in the observation group versus 7.8% in the chemotherapy group (HR 1.17, 95% CI 0.55-2.50; *p*=0.69), whereas this amounted to 38.5% and 34.7%, respectively for distant recurrences (HR 0.87, 95% CI 0.63-1.20; *p*=0.39; Figure 2). The per-protocol analysis showed an HR of 1.24 for locoregional recurrences (95% CI 0.56-2.76; *p*=0.60) and 0.85 (95% CI 0.59-1.21; *p*=0.36) for distant recurrences.

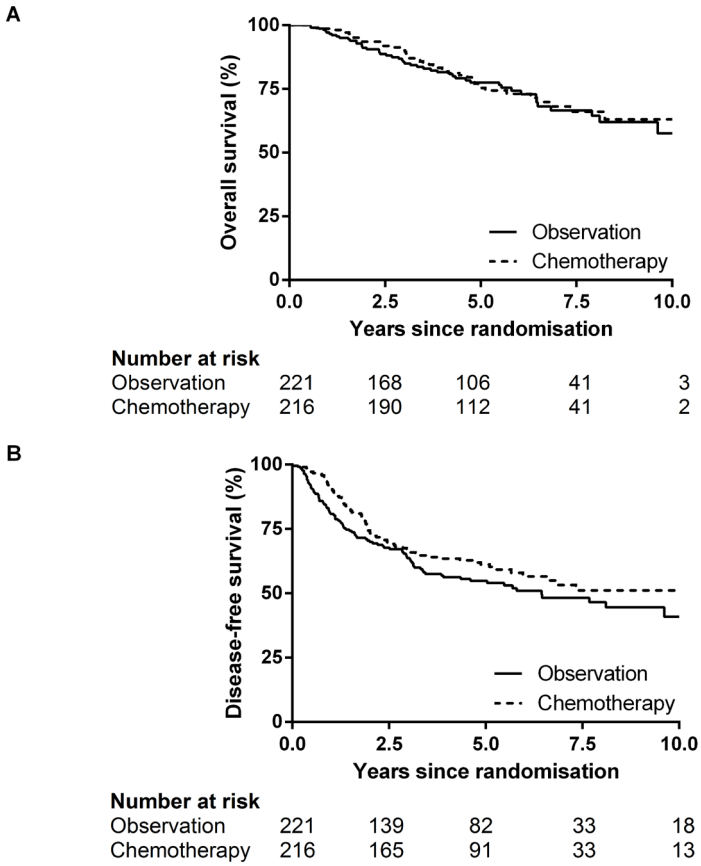


Figure 1. a. Overall survival. b. Disease-free survival

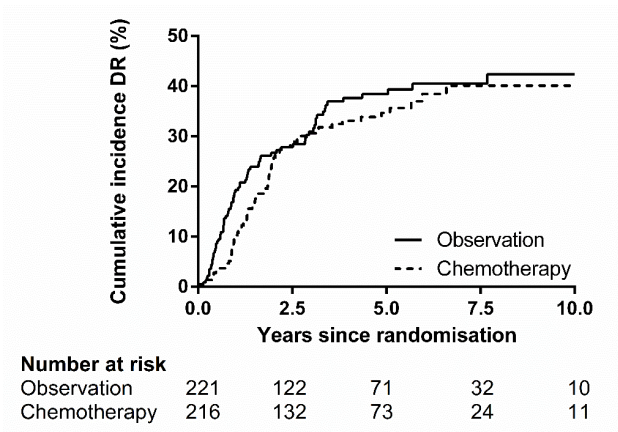


Figure 2. Cumulative incidence distant recurrence

DISCUSSION

After a median follow-up of 5 years, the PROCTOR-SCRIPT trial could not demonstrate a significant benefit in overall survival for adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME surgery in ypTNM stage II and III rectal cancer patients. Furthermore, no significant differences were demonstrated in disease-free survival, and recurrence rates.

Now that locoregional recurrence rates decreased, the focus of rectal cancer treatment is on reducing distant metastases. However, the debate on the role of adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and TME surgery is still ongoing. On the contrary, the advantage of adjuvant chemotherapy for stage III colon cancer has been clearly proven.[11-14]

Although colon and rectal tumours have histological similarities, and are in anatomical continuity, tumour biology is not the same.[15] Nevertheless, several guidelines recommend the use of adjuvant chemotherapy for rectal cancer[16-18] based on extrapolation from experience with colon cancer. In contrast, the Dutch guidelines state that there is no indication for adjuvant chemotherapy.[19]

These differences in adjuvant chemotherapy use can be explained by the fact that no conclusive evidence exists for patients treated with preoperative (chemo)radiotherapy and TME surgery.

Adjuvant chemotherapy appears to be effective in patients who neither received preoperative (chemo)radiotherapy nor standardised surgery. One study then often referred to is a Japanese trial demonstrating a benefit in disease-free and overall survival of uracil-tegafur in stage III rectal cancer patients who underwent standardised mesorectal excision, including selective lateral pelvic lymphadenectomy. None of the patients underwent preoperative radiotherapy.[20] Further, a Cochrane review of 21 trials showed a risk reduction of 17% on overall survival and 25% on disease-free survival among patients who received adjuvant chemotherapy.[21] It must be taken into account that none of the trials performed standardised TME surgery, that no standardised definition of rectum was used, and that only two of the included studies administered preoperative (chemo)radiotherapy. One of these two trials, the QUASAR, found a small improvement in survival for patients with rectal cancer who received adjuvant chemotherapy. However, of all rectal cancer patients, only 21% received preoperative radiotherapy.[22] The second trial, the EORTC 22921 trial, did not demonstrate a benefit of adjuvant chemotherapy after 5 years.[23]

The results of the present trial are consistent with results of three trials investigating the role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery[6,24,25], and support the conclusions made by Bujko et al. in a systematic review.[8] First, the EORTC 22921 trial did not demonstrate any clinically relevant nor statistically significant benefit of adjuvant 5-FU/LV in overall survival, disease-free survival, or recurrence rates. Ten-year overall survival was 48.4% in the observation group and 51.8% in the chemotherapy group.[6] Secondly, the CHRONICLE trial randomised 113 patients who received preoperative chemoradiotherapy between observation and adjuvant CAPOX. This trial closed prematurely because of poor patient accrual. After 3 years, no significant differences in disease-free and overall survival could be detected.[25] Thirdly, an Italian trial, randomised patients between observation and adjuvant 5-FU/LV after preoperative chemoradiotherapy and surgery, and did also not find differences in overall survival and distant recurrences after 10 years.[24]

The lack of effect of adjuvant chemotherapy in rectal cancer has often been attributed to poor compliance. In the current trial, 73.6% of the patients randomised to chemotherapy completed all cycles. In comparison, chemotherapy compliance was 43% in the EORTC 22921 trial, 48% in the CHRONICLE trial, and about 55% received three to six chemotherapy cycles in the Italian trial.[6,23-25] The difference in chemotherapy compliance can probably be explained by the fact that we randomised patients postoperatively, resulting in a selected group fit enough to start chemotherapy, although the CHRONICLE trial also randomised postoperatively. However, CHRONICLE used combination chemotherapy, which can be a possible explanation for this difference. Despite the relatively high compliance rate in our trial, no differences between the observation group and the chemotherapy group could be demonstrated.

In the current trial, fluoropyrimidine monotherapy was used as adjuvant treatment, because no clear evidence on the benefit of combination chemotherapy existed at the start of our trial. Meanwhile, the MOSAIC trial demonstrated a benefit in disease-free and overall survival of combination chemotherapy for colon cancer.[14] In the South Korean population of the recently published phase two ADORE trial, there seems to be a benefit of adjuvant FOLFOX over 5-FU/LV for patients with ypTNM stage II or III rectal cancer.[26] Besides, the results of the CAO/ARO/AIO-04 trial are awaited for the effect of combination chemotherapy on disease-free survival.[27]

This trial has some limitations. The intended inclusion of 840 patients was not reached due to poor patient accrual. Many patients and clinicians had preference for either observation or chemotherapy which resulted in a lower participation rate than anticipated. Furthermore, 5-year overall survival was better than calculated. Therefore, we would have required a larger number of events for an adequate power. The lack of

statistical power can be a possible explanation for the fact that differences between the observation and the chemotherapy group could not be detected, as for example the 7% difference in disease-free survival which might have been significant with appropriate statistical power.

Moreover, different follow-up schedules are used in the Netherlands and Sweden, which could have influenced disease-free survival and recurrence rates. In addition, the trial was amended: adjuvant chemotherapy changed from 5-FU/LV (PROCTOR) to capecitabine (SCRIPT), and patients received preoperative chemoradiotherapy or radiotherapy (SCRIPT) instead of radiotherapy only (PROCTOR). Given the similarity in study design, the similar efficacy of 5-FU/LV and capecitabine, and the fact that no differences in treatment effect existed between PROCTOR and SCRIPT, it is unlikely that these changes have influenced overall outcomes significantly.

Still considerable debate exists on the definition of the rectum, with regard to distance from the anal verge and location of peritoneal reflection. Possibly, upper rectal tumours are more similar to low sigmoid tumours that benefit from adjuvant chemotherapy. Furthermore, it would be interesting to investigate the role of adjuvant chemotherapy for stage III rectal cancer. We will perform an individual patient data meta-analysis including data of European trials to investigate if subgroups of patients benefit from adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery. Moreover, we will try to identify prognostic or predictive biomarkers in tumour material of patients included in our trial, which will give insight in tumour prognosis, and can be the basis for tailor-made treatment.

In conclusion, with the PROCTOR-SCRIPT trial we could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy regarding overall survival, disease-free survival, and recurrence rates after preoperative (chemo) radiotherapy and TME surgery in ypTNM stage II and III rectal cancer patients. However, this trial did not complete planned accrual.

REFERENCES

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**(8496): 1479-82.
2. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002; **89**(9): 1142-9.
3. 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, randomized controlled TME trial. *Lancet Oncol* 2011; **12**(6): 575-82.
4. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; **333**(7572): 779.
5. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; **30**(16): 1926-33.
6. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomized study. *Lancet Oncol* 2014; **15**(2): 184-90.
7. Elferink MA, van Steenbergen 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**(8): 1421-9.
8. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomized trials. *Ann Oncol* 2010; **21**(9): 1743-50.
9. 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**(8514): 996-9.
10. Wille-Jorgensen P, Laurberg S, Pahlman L, et al. An interim analysis of recruitment to the COLOFOL trial. *Colorectal Dis* 2009; **11**(7): 756-8.
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**(6): 352-8.
12. Taal BG, H. VT, Zoetmulder FA, group N. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *Br J Cancer* 2001; **85**(10): 1437-43.
13. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
14. André 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**(19): 3109-16.
15. Kapiteijn E, Liefers GJ, Los LC, et al. Mechanisms of oncogenesis in colon versus rectal cancer. *J Pathol* 2001; **195**(2): 171-8.
16. NCCN Clinical Practice Guidelines in Oncology, Rectal Cancer, http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. *Visited: May, 6,* 2014.
17. NICE clinical guideline, Colorectal cancer, http://www.nice.org.uk/nicemedia/live/13597/56998/56998.pdf. *Visited: May, 6,* 2014.
18. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi81-vi8.
19. Dutch guideline colorectal cancer, http://www.oncoline.nl/colorectaalcarcinoom. *Visited: May, 6,* 2014.
20. Akasu T, Moriya Y, Ohashi Y, Yoshida S, Shirao K, Kodaira S. Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. *Jpn J Clin Oncol* 2006; **36**(4): 237-44.
21. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; **3**: CD004078.
22. Gray R, Barnwell J, McConkey C, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. *Lancet* 2007; **370**(9604): 2020-9.
23. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
24. Cionini L, Sainato A, De Paoli A, al. e. Final results of randomized trial on adjuvant chemotherapy after

preoperative chemoradiation in rectal cancer. *Radiother Oncol* 2010; **96**(Suppl 1): S113-S4.
25. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: Results of a randomized phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (Xelox) versus control. *Ann Oncol* 2014.
26. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomized controlled trial. *Lancet Oncol* 2014; **15**(11): 1245-53.
27. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomized phase 3 trial. *Lancet Oncol* 2012; **13**(7): 679-87.

SUPPLEMENTARY DATA

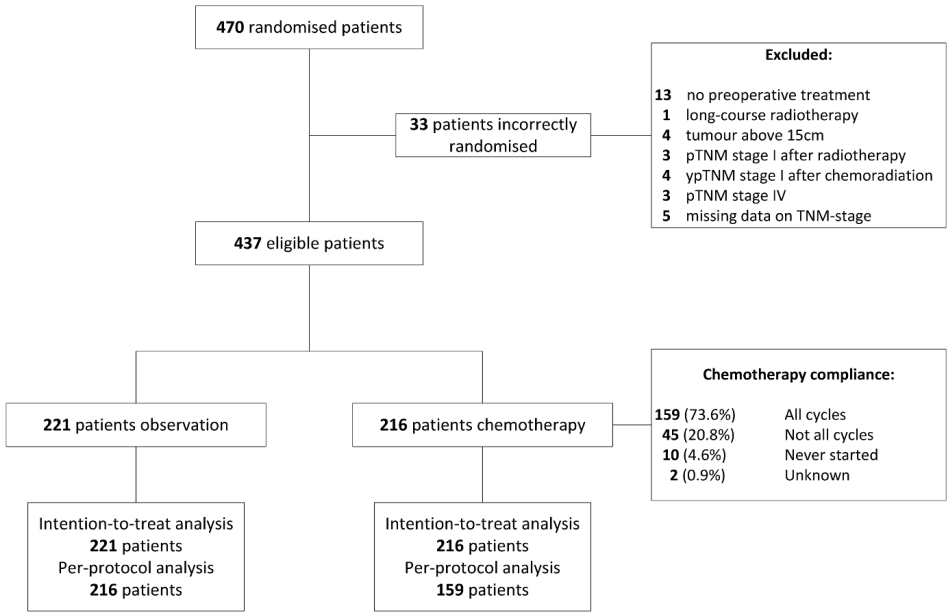
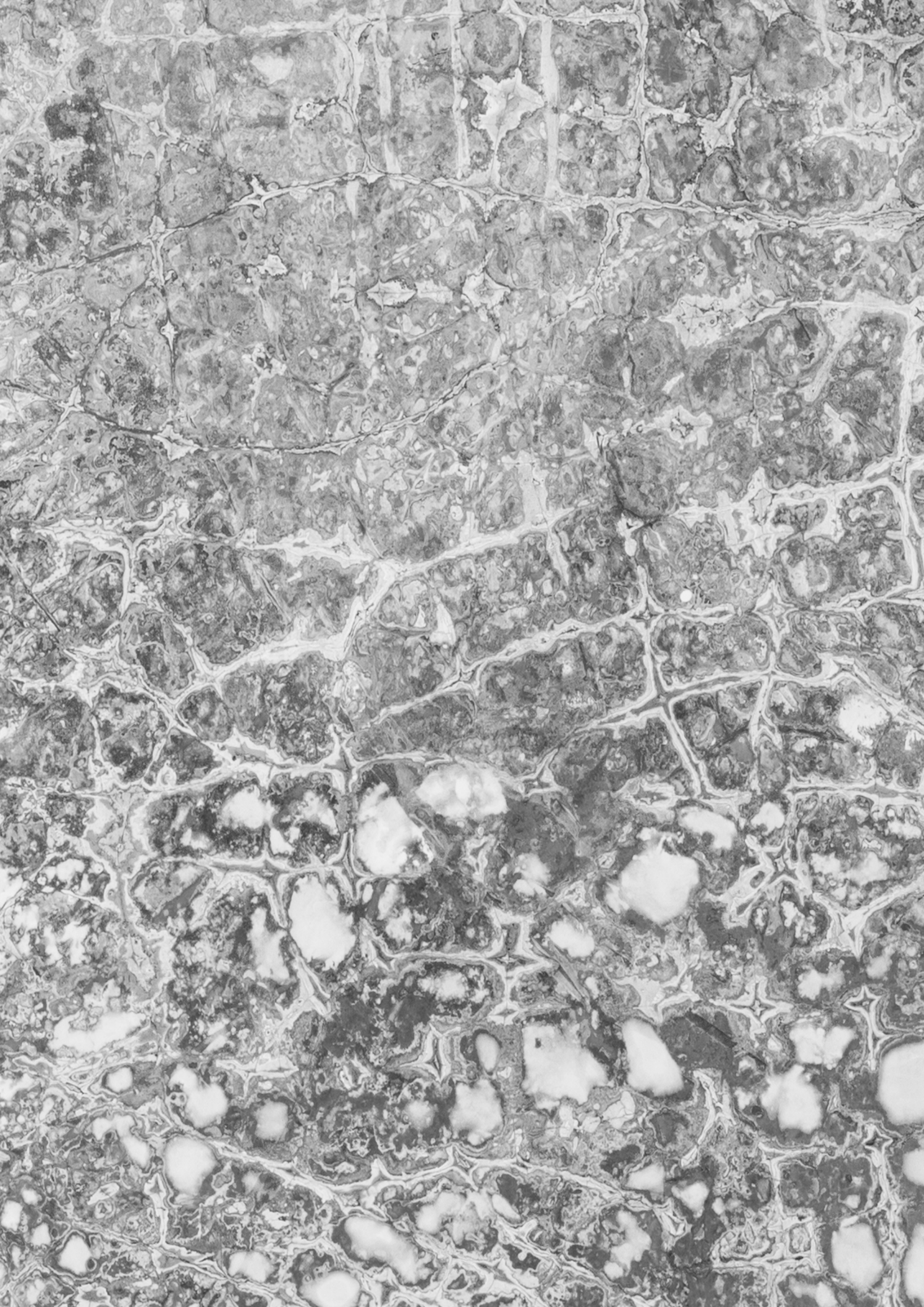


Figure 1. CONSORT diagram



5

Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

A.J. Breugom*
M. Swets*
J.F. Bosset
L. Collette
A. Sainato
L. Cionini
R. Glynne-Jones
N. Counsell
E. Bastiaannet
C.B.M. van den Broek
G.J. Liefers
H. Putter
C.J.H. van de Velde

** Authors contributed equally to the work.*

The Lancet Oncology. 2015 Feb;16(2):200-7.

ABSTRACT

Background

The role of adjuvant chemotherapy for patients with rectal cancer after preoperative (chemo)radiotherapy and surgery is uncertain. We did a meta-analysis of individual patient data to compare adjuvant chemotherapy with observation for patients with rectal cancer.

Methods

We searched PubMed, MEDLINE, Embase, Web of Science, The Cochrane Library, CENTRAL, and conference abstracts to identify European randomised, controlled, phase 3 trials comparing observation with adjuvant chemotherapy after preoperative (chemo) radiotherapy and surgery for patients with non-metastatic rectal cancer. The primary endpoint was overall survival.

Results

We analysed data from four eligible trials, including data from 1196 patients with (y) pTNM stage II or III disease, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge. We found no significant differences in overall survival between patients who received adjuvant chemotherapy and those who underwent observation (hazard ratio [HR] 0.97, 95% CI 0.81-1.17, p=0.775); there were no significant differences in overall survival in subgroup analyses. Overall, adjuvant chemotherapy did not significantly improve disease-free survival (HR 0.91, 95% CI 0.77-1.07, p=0.230) or distant recurrences (HR 0.94, 95% CI 0.78-1.14, p=0.523). However, in subgroup analyses, patients with a tumour 10-15 cm from the anal verge had improved disease-free survival (HR 0.59, 95% CI 0.40-0.85, p=0.005, $p_{interaction}$=0.107) and fewer distant recurrences (HR 0.61, 95% CI 0.40-0.94, p=0.025, $p_{interaction}$=0.126) when treated with adjuvant chemotherapy compared with patients undergoing observation.

Conclusion

Overall, adjuvant fluorouracil-based chemotherapy did not improve overall survival, disease-free survival, or distant recurrences. However, adjuvant chemotherapy might benefit patients with a tumour 10-15 cm from the anal verge in terms of disease-free survival and distant recurrences. Further research with regard to preoperative and postoperative treatment for this subgroup of patients is warranted.

Funding

None.

INTRODUCTION

Important advances have been made in the treatment of rectal cancer with the introduction of total mesorectal excision, the addition of preoperative (chemo) radiotherapy to total mesorectal excision, and the ability to more accurately stage rectal cancer with MRI.[1-9] Although locoregional recurrence and survival have improved, distant recurrence has not. About 30% of all patients treated with curative intent will eventually develop distant metastases.[3,6,9] Adjuvant chemotherapy might prevent distant metastases by eliminating circulating tumour cells and micrometastases. However, the use of adjuvant chemotherapy for patients with rectal cancer treated with preoperative (chemo)radiotherapy and surgery is debated.[10] For patients treated without preoperative (chemo)radiotherapy and total mesorectal excision, which results in high numbers of locoregional recurrences, adjuvant chemotherapy is effective. In a systematic review and meta-analysis, Petersen and colleagues showed that adjuvant chemotherapy improved overall survival (HR 0.83, 95% CI 0.76-0.91) and disease-free survival (HR 0.75, 95% CI 0.68-0.83).[11] However, their review included only two studies in which patients had had preoperative (chemo)radiotherapy.[12,13] The investigators of the EORTC 22921 study[12] did not report a benefit of adjuvant chemotherapy, while those of QUASAR[13] showed a borderline significant improvement in overall survival for patients with rectal cancer. However, in the QUASAR study, only 21% of patients with rectal cancer or both colon and rectal cancer received preoperative radiotherapy.[13] Furthermore, results of a Japanese trial also showed improved overall and disease-free survival in patients with stage III rectal cancer who were randomised to adjuvant chemotherapy after standardised mesorectal excision.[14] However, none of the patients received preoperative (chemo)radiotherapy and standardised mesorectal excision included selective lateral lymphadenectomy.[14]

By contrast, results of other trials comparing adjuvant chemotherapy and observation after preoperative (chemo)radiotherapy and total mesorectal excision did not show a benefit of adjuvant chemotherapy.[7,15-17]

We did a meta-analysis of individual patient data to investigate the effect of adjuvant fluorouracil based chemotherapy compared with observation after preoperative (chemo) radiotherapy and surgery for patients with rectal cancer.

METHODS

Search strategy and selection criteria

In cooperation with a trained librarian, we searched for published and unpublished European randomised, controlled, phase 3 trials comparing observation with adjuvant

chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with non-metastatic rectal cancer. Patients aged 18 years and older were eligible for inclusion. All available preoperative treatment regimens, as well as both total mesorectal excision and conventional surgery, were accepted for inclusion. We excluded randomised controlled trials of adjuvant chemotherapy without an observation group.

We searched PubMed, MEDLINE (OVID version), Embase (OVID version), Web of Science, The Cochrane Library, and CENTRAL from the date of their inception until June 26, 2014, for relevant articles. We also searched abstracts from the most important international meetings: ECCO, ESTRO, ESS, and ESMO. We searched for "rectal carcinoma" AND "adjuvant chemotherapy" AND "preoperative treatment". All relevant keyword variations were used for these three terms. We restricted our searches to reports published in English. Two independent reviewers (MS and AJB) screened the title and abstract of retrieved articles. Studies that seemed to meet the inclusion criteria were selected for full-text review. Disagreements between the two independent reviewers were resolved by discussion. We contacted the principal investigators of all eligible trials and requested individual patient data for baseline characteristics, tumour characteristics, preoperative treatment, surgery, adjuvant treatment, and follow-up.

Outcomes

The primary endpoint of interest was overall survival. Secondary endpoints were disease-free survival, and distant recurrences. All time-to-event variables were calculated from date of surgery. Overall survival was defined as time to death from any cause, or to end of follow-up (censored). Disease-free survival was defined as time to any recurrence or death, whichever occurred first, or end of follow-up (censored). Time to distant recurrence was defined as time to distant recurrence or end of follow-up (censored). The absence or presence of distant recurrence was confirmed by histological assessment, cytological assessment, or imaging.

Statistical analysis

To improve comparability between patients in the eligible trials, we included patients with (post-neoadjuvant) pathological TNM - ie, (y)pTNM - stage II or III disease, who had a R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located no more than 15 cm from the anal verge. We did a sensitivity analysis of the primary endpoint for all patients who were originally included in the eligible trials. We analysed data for all included patients, as well as for the following patient subgroups: (y)pTNM stage (II *vs* III), tumour location from anal verge (<5 cm *vs* 5.0-9.9 cm *vs* ≥10 cm), type of resection (low anterior resection *vs* abdominoperineal resection), nodal status ((y)pN0 *vs* (y)pN1 *vs* (y)pN2), and preoperative treatment (short-course radiotherapy *vs* long-course radiotherapy *vs* long-course chemoradiotherapy).

We calculated hazard ratios (HR) and 95% CIs for overall survival, disease-free survival, and the cause-specific risk of distant recurrence, with Cox proportional hazards regression. The regression models included strata defined by a term representing the distinct trials. We calculated the cumulative incidence of distant recurrences with death as competing risk.[18] We calculated median follow-up according to the reverse Kaplan-Meier method.[19] We did an interaction test of treatment efficacy for each subgroup for all outcome measures. We also analysed the primary endpoint by trial, with all patients who were originally included in the eligible trials. These HRs and CIs slightly differ from the original articles, because we used more recent follow-up information.

The I^2 statistic and Q to assess whether significant heterogeneity existed between the included trials.[20] We did statistical analyses with SPSS (version 20.0) and R (version 3.1.0). We considered a p-value of 0.05 or less as statistically significant.

Role of the funding source
This study had no funding. The funders of the original studies had no role in the study design, management, data analysis, and data interpretation. AJB, MS, HP, and CJHvdV had access to all study data. The corresponding author had the final responsibility for the decision to submit for publication.

RESULTS

Our initial search identified 1131 citations. We excluded 1035 citations by title because they did not meet eligibility criteria. We read the abstracts of the remaining 96 articles. Of these, three full-text randomised controlled trials were read (figure 1).[7,13,16] We also found one eligible trial that was presented during the 29th European Society for Radiotherapy and Oncology (ESTRO) congress in 2010[21], and one abstract that was presented during the European Cancer Congress in 2013.[22] We were able to obtain individual patient data for the I-CNR-RT trial, the CHRONICLE trial, the PROCTOR-SCRIPT trial, and the EORTC 22921 trial.[7,15-17] Table 1 shows the main characteristics of these trials. The risk of bias of all included studies was judged to be low.

2195 patients were included in the four trials. 1196 patients with (y)pTNM stage II or III, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15cm from the anal verge were included in our analyses. Of these 1196 patients, 598 patients had observation after surgery, and 598 patients received adjuvant chemotherapy. Table 2 shows patient characteristics. Median follow-up was 7.0 years (IQR 4.3-10.2; two patients died on day of surgery).

Table 1. Study characteristics

	I-CNR-RT	PROCTOR-SCRIPT	EORTC 22921	CHRONICLE
Preoperative treatment				
Chemoradiotherapy	25x1.8Gy + 5-FU based chemotherapy	25x1.8-2Gy + 5-FU based chemotherapy	25x1.8Gy + 5-FU based chemotherapy	45Gy + 5-FU based chemotherapy
Radiotherapy		5x5Gy / 25x1.8-2Gy	25x1.8Gy	
Adjuvant treatment**	6 courses of 5-FU (350mg/m²) and Folinic Acid (20mg/m²)	Mayo regimen: 6 courses of 5-FU (425mg/m2) and Folinic Acid (20mg/m2) Nordic regimen:12 courses of 5-FU (500mg/m2) and Folinic Acid (60mg/m2) 8 courses every three weeks of oral capecitabine (1250mg/m2) twice daily for 14 days	4 courses every three weeks of 5-FU (350mg/ m²) and Folinic Acid (20mg/ m²)w	6 courses every three weeks of oxaliplatin (130mg/m²) and oral capecitabine (1000mg/m²) twice daily for 14 days (CAPOX)
Start of accrual	September 1992	March 2000	April 1993	November 2004
End of accrual	January 2001	January 2013	March 2003	April 2008
Disease stage	Clinical stage T3,T4*	(y)pTNM II, III	Clinical stage T3,T4*	ypTNM II,III
Resection margin	R0	R0, R1	R0	R0
TME surgery performed	No	Yes	Halfway inclusion	Yes
Timing of randomisation	Before surgery	After surgery	Before surgery	After surgery
Number of patients eligible for analysis (original article)	634	437	1011	113
Number of patients eligible for analysis in this meta-analysis	245	403	473	75

* For this meta-analysis we included patients based on (y)pTNM stage

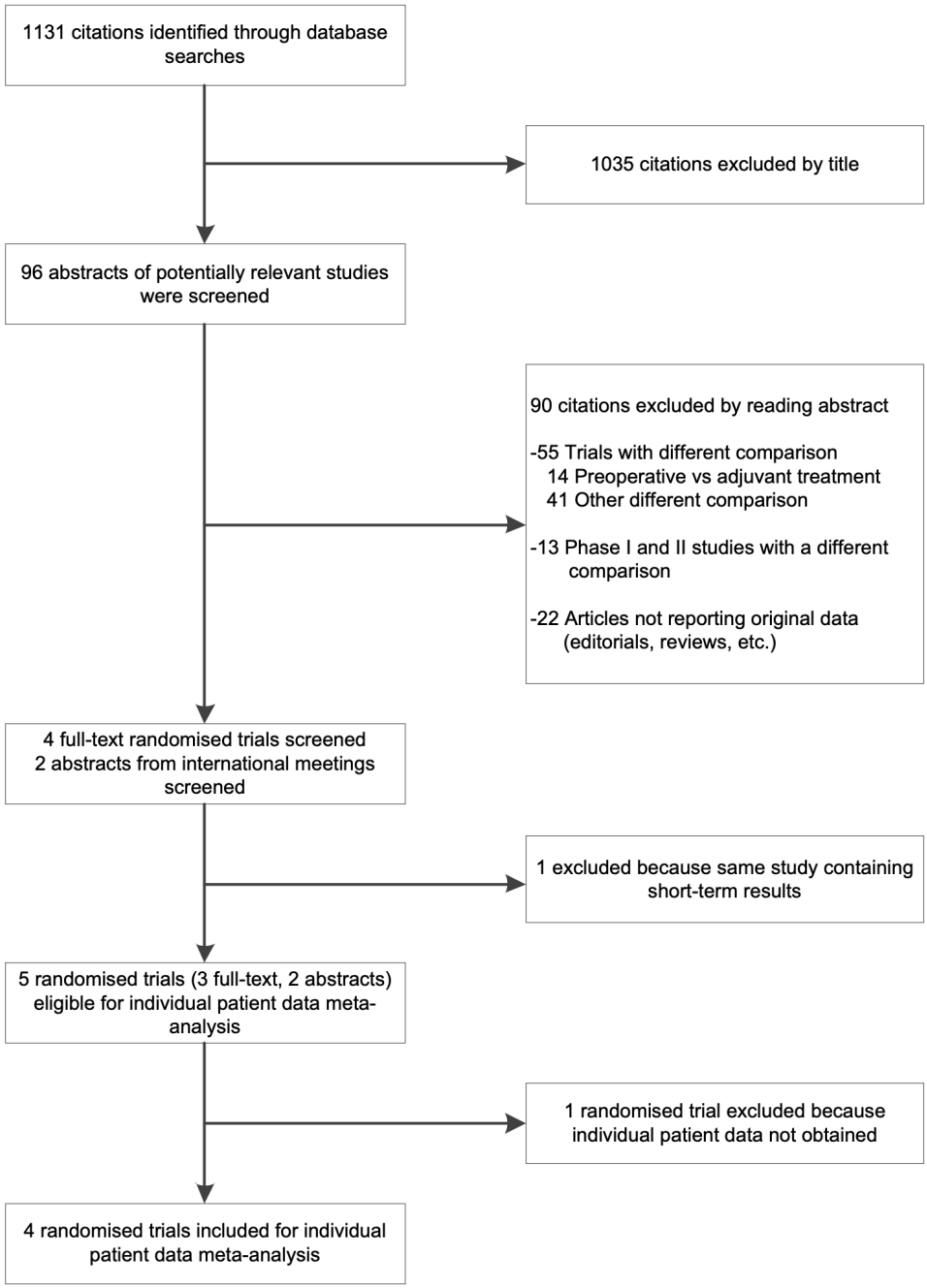


Figure 1. Study selection

Table 2. Patient characteristics

Characteristics	Total (*n* = 1196)	Observation (*n* =598)	Chemotherapy (*n* =598)
Trial			
I-CNR-RT	245 (20.5)	112 (18.7)	133 (22.2)
PROCTOR-SCRIPT	403 (33.7)	204 (34.1)	199 (33.3)
Chronicle	75 (6.3)	45 (7.5)	30 (5.0)
EORTC 22921	473 (39.5)	237 (39.6)	236 (39.5)
Age (years)	61.50 ±9.60	62.00 ±9.63	61.00 ±9.57
Gender			
Male	810 (67.7)	410 (68.6)	400 (66.9)
Female	386 (32.3)	188 (31.4)	198 (33.1)
Preoperative treatment			
25 Gy	348 (29.1)	179 (29.9)	169 (28.3)
45 Gy	267 (22.3)	134 (22.4)	133 (22.2)
45 Gy + FU based chemotherapy	581 (48.6)	285 (47.7)	296 (49.5)
Type of resection			
LAR	726 (60.7)	362 (60.5)	364 (60.9)
APR	470 (39.3)	236 (39.5)	234 (39.1)
Tumour location from anal verge			
< 5 cm	381 (31.9)	187 (31.3)	194 (32.4)
5 – 9.9 cm	519 (43.4)	256 (42.8)	263 (44.0)
≥ 10 cm	281 (23.5)	144 (24.1)	137 (22.9)
Unknown	15 (1.3)	11 (1.8)	4 (0.7)
(y)pTNM			
II	459 (38.4)	207 (34.6)	252 (42.1)
III	737 (61.6)	391 (65.4)	346 (57.9)

Data are presented as median ± SD or as *n* (%)

451 patients died. Overall, adjuvant chemotherapy provided no significant benefit in overall survival compared with observation (HR 0.97, 95% CI 0.81-1.17, p=0.775; figure 2A). In subgroup analyses, we recorded no significant differences in overall survival between the groups. Sensitivity analysis of all 2195 patients showed a HR of 0.95 (95% CI 0.82-1.09, p=0.430). Supplementary Figure 1 shows a forest plot of hazard ratios for overall survival by study. We found no heterogeneity in treatment effect between the four trials (I^2=0%, p=0.605).

580 events disease-free survival events occurred. For all included patients, we detected no significant difference in disease-free survival between patients who received adjuvant chemotherapy and those who underwent observation (HR 0.91, 95% CI 0.77-1.07, p=0.230; figure 2B). In subgroup analysis, patients with a tumour 10-15 cm from the anal verge who received adjuvant chemotherapy had improved disease-free survival (HR 0.59, 95% CI 0.40-0.85, p=0.005), with no significant interaction between distance from the anal verge (<5 cm *vs* 5-9.9 cm *vs* ≥10 cm) and treatment group (figure 2B). For the other subgroups, we recorded no significant differences in disease-free survival. The effect of adjuvant chemotherapy on disease-free survival was not heterogeneous among the four trials (I^2=0%, p=0.836).

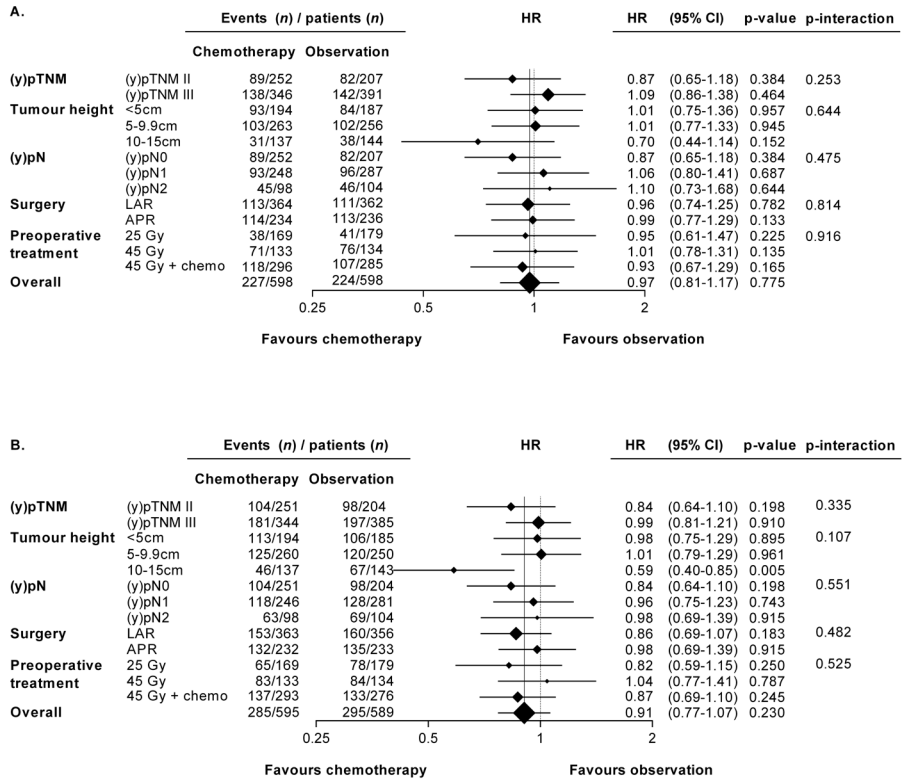


Figure 2. Overall survival a. and disease-free survival b. for all patients and by patient subgroups
The size of the diamonds represents the proportion of patients

We recorded 415 distant recurrences. Overall, we detected no significant benefit of adjuvant chemotherapy compared with observation (figure 3). At 5 years, the cumulative incidence for distant recurrences was 36.5% (95% CI 32.6%-40.8%) in the observation group and 35.5% (95% CI 31.7%-39.7%) in the chemotherapy group (HR 0.94, 95% CI 0.78-1.14, p=0.523; figures 3 and 4). However, patients with a tumour between 10 cm and 15 cm from the anal verge had a benefit with adjuvant chemotherapy in terms of distant recurrence (HR 0.61, 95% CI 0.40-0.94, p=0.025), without a significant interaction between distance from the anal verge and treatment group (figure 3). We detected no significant differences for the other subgroups between observation and adjuvant chemotherapy (figure 3). We found no heterogeneity in treatment effect on distant recurrence between the four trials (I^2=0%, p=0.617).

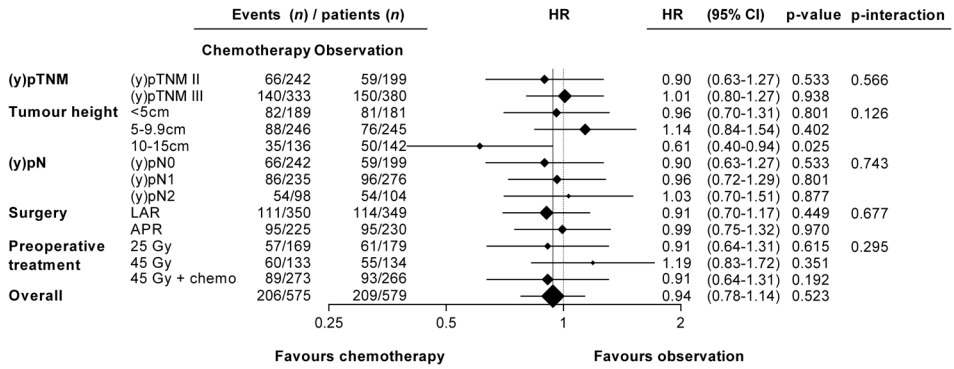


Figure 3. Distant recurrence
The size of the diamonds represents the proportion of patients

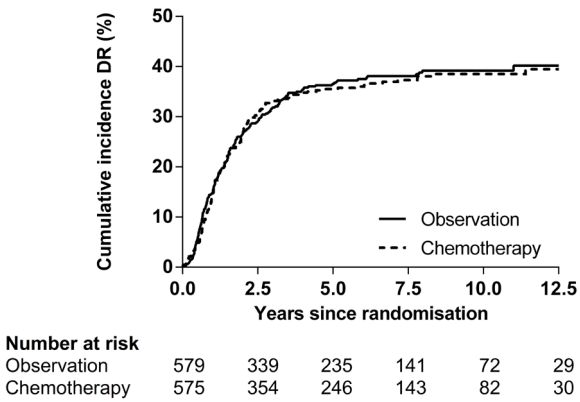


Figure 4. Cumulative incidence of distant recurrences

DISCUSSION

Our findings show that fluorouracil-based adjuvant chemotherapy has no benefit on overall survival, disease-free survival, and distant recurrences after a median follow-up of 7.0 years in patients with (y)pTNM stage II or III rectal cancer, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge. However, our findings suggest that adjuvant chemotherapy might improve disease-free survival and distant recurrences in patients with a tumour located 10-15 cm from the anal verge.

Although a clear benefit of adjuvant chemotherapy has been shown for patients with stage III colon cancer[23-26], this is not the case for patients with non-metastatic rectal cancer treated with preoperative (chemo)radiotherapy and surgery. The inconclusive evidence on the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer is shown by international differences in treatment guidelines.[27-30] Advice to give adjuvant chemotherapy to patients with stage II or III rectal cancer is based on extrapolation of results from phase 3 trials of adjuvant treatment for colon cancer[23-26], as well as from trials in patients with rectal cancer who were treated without preoperative (chemo)radiotherapy.[11]

Despite four of five European randomised controlled trials comparing adjuvant chemotherapy with observation after receiving preoperative (chemo)radiotherapy and surgery showing no benefit of adjuvant chemotherapy[7,15-17], none have individually ended the discussion about the role of adjuvant chemotherapy. This might partly be because two of these trials did not have sufficient power.[15,16] The QUASAR trial showed a borderline significant improvement in overall survival for patients with rectal cancer who were assigned to adjuvant chemotherapy, but only 21% of patients with rectal cancer or both rectal and colon cancer had preoperative radiotherapy and no patient received chemoradiotherapy.[13] By pooling individual patient data, we think that this meta-analysis is the most robust analysis to date of the role of adjuvant fluorouracil-based chemotherapy for patients with rectal cancer; combining the individual patient data increased the statistical power, and enabled us to improve comparability between patients in the four individual trials, as well as to do subgroup analyses. Although none of the studies were masked, we do not think that this affected the outcome measurements. Aside from embryological, anatomical, and physiological differences between the colon and rectum, colon and rectal cancer seem to differ in oncogenesis.[31] Rectal cancer has less microsatellite instability (MSI) and fewer BRAF mutations than does colon cancer.[32-34] Furthermore, different gene expression profiles between colon and rectal tumours have been reported.[35,36] These differences might contribute to different effects of adjuvant chemotherapy in colon and rectal cancer. By contrast, no clear differences have been detected in *KRAS* mutations between colon and rectal tumours.[37-40]

Despite the suggestion that colon and rectal tumours differ in carcinogenesis, the definition of the rectum is not consistent across countries with regard to distance from the anal verge and location of the peritoneal reflection. The findings from our subgroup analysis raise the question of whether tumours between 10 cm and 15 cm from the anal verge should be defined as colon tumours rather than rectal tumours, which might require different treatments to rectal tumours less than 10 cm from the anal verge. However, because we detected no significant interaction between distance from the anal verge and treatment group, these results are not definitive. Further investigation

of preoperative and postoperative treatment for patients with a tumour 10-15 cm from the anal verge is warranted to draw definitive conclusions for these patients. We showed no benefit of adjuvant chemotherapy for other subgroups. Patients with ypTNM 0 and ypTNM I were only included in the I-CNR-RT trial, and partly in the EORTC 22921 trial. Therefore, we could not do a meta-analysis of patients with ypTNM stage 0 and ypTNM stage I disease.

A meta-analysis of individual patient data has advantages over a meta-analysis of aggregate data, such as the possibility to obtain results for subgroups.[41] Although we think that our study provides the best available evidence, it has some limitations. A well-known challenge in randomised controlled trials is to obtain sufficient power.[42] Patients´ and clinicians' treatment preferences contributed to the fact that two trials in this meta-analysis had to stop before the intended number of patients were recruited.[15,16] Compliance to adjuvant chemotherapy is recognised as a problem of studies investigating the role of adjuvant chemotherapy in patients with rectal cancer after preoperative (chemo)radiotherapy and surgery. In the PROCTOR-SCRIPT trial (patients postoperatively randomly assigned), 73.6% of patients complied with treatment.[15] In the EORTC 22921 trial (patients preoperatively randomly assigned) 43% completed all cycles of chemotherapy[7], compared with 48% in the CHRONICLE trial (patients postoperatively randomly assigned).[16] In the I-CNR-RT trial (patients preroperatively randomly assigned), 55% of participants received three to six courses chemotherapy.[17] In theory, this low adherence to treatment could have affected our results, although we think it is unlikely to have had a significant effect. For example, in the per-protocol analysis of the PROCTOR-SCRIPT trial[15], adjuvant chemotherapy was not beneficial for patients who completed all cycles of chemotherapy. Another potential limitation is that the EORTC 22921 trial, the I-CNR-RT trial, and the PROCTOR-SCRIPT trial all had long accrual periods, and thus may have been affected by changes in practice over time. For example, total mesorectal excision was not yet the standard of care during most of the I-CNR-RT trial, and became standard of care halfway the inclusion period of the EORTC 22921 trial. Lastly, the QUASAR trial was not included in our meta-analysis, because we could not obtain the individual patient data.

If patients with a tumour 10-15 cm from the anal verge do benefit from adjuvant chemotherapy, the question is whether fluoropyrimidine monotherapy or combination chemotherapy should be administered. No clear evidence of the superiority of fluoropyrimidine monotherapy or combination chemotherapy existed at the start of most of the included trials. Three of the trials included in this meta-analysis used fluoropyrimidine monotherapy.[7,15-17] In 2009, the MOSAIC trial showed that the addition of oxaliplatin to fluorouracil and folinic acid improved disease-free survival and overall survival in patients with colon cancer.[26,43] For this reason, the CHRONICLE

trial used combination chemotherapy.[16] Findings from the ADORE trial showed that adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin) seems to be more beneficial than fluorouracil and folinic acid for patients with ypTNM stage II or III rectal cancer.[44] The results of the CAO/ARO/AIO-04 trial showed a benefit of adjuvant combination chemotherapy over fluorouracil monotherapy.[45] Because both studies did not include an observation arm, they were ineligible for this meta-analysis. The question whether adjuvant combination chemotherapy provides a benefit compared with observation thus remains unanswered. In conclusion, overall, fluorouracil-based adjuvant chemotherapy did not improve overall survival, disease-free survival and distant recurrences compared with observation for patients with (y)pTNM stage II or III rectal cancer, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm from the anal verge. However, our findings suggest that patients with a tumour located between 10 cm and 15 cm from the anal verge may benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences. Further research with regard to preoperative and postoperative treatment for this subgroup of patients is warranted.

ACKNOWLEDGEMENTS

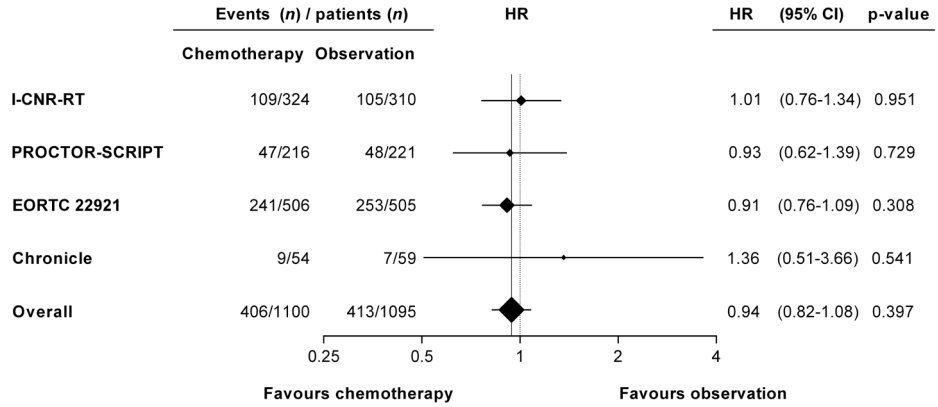
We would like to thank the investigators (including Cernusco Luna Nunzia Valentina, Department of Radiotherapy, "Centro Oncologico Fiorentino", Florence) of all trials included in this meta-analysis for providing the data. The authors thank the European Organisation for Research and Treatment of Cancer for permission to use the data from EORTC trial 22921 for this research. We would also like to thank the patients participating in the four trials included in the meta-analysis. Finally, we would like to thank J.W. Schoones, librarian at the Leiden University Medical Centre, Leiden, The Netherlands, for his help with the search strategy and literature search.

REFERENCES

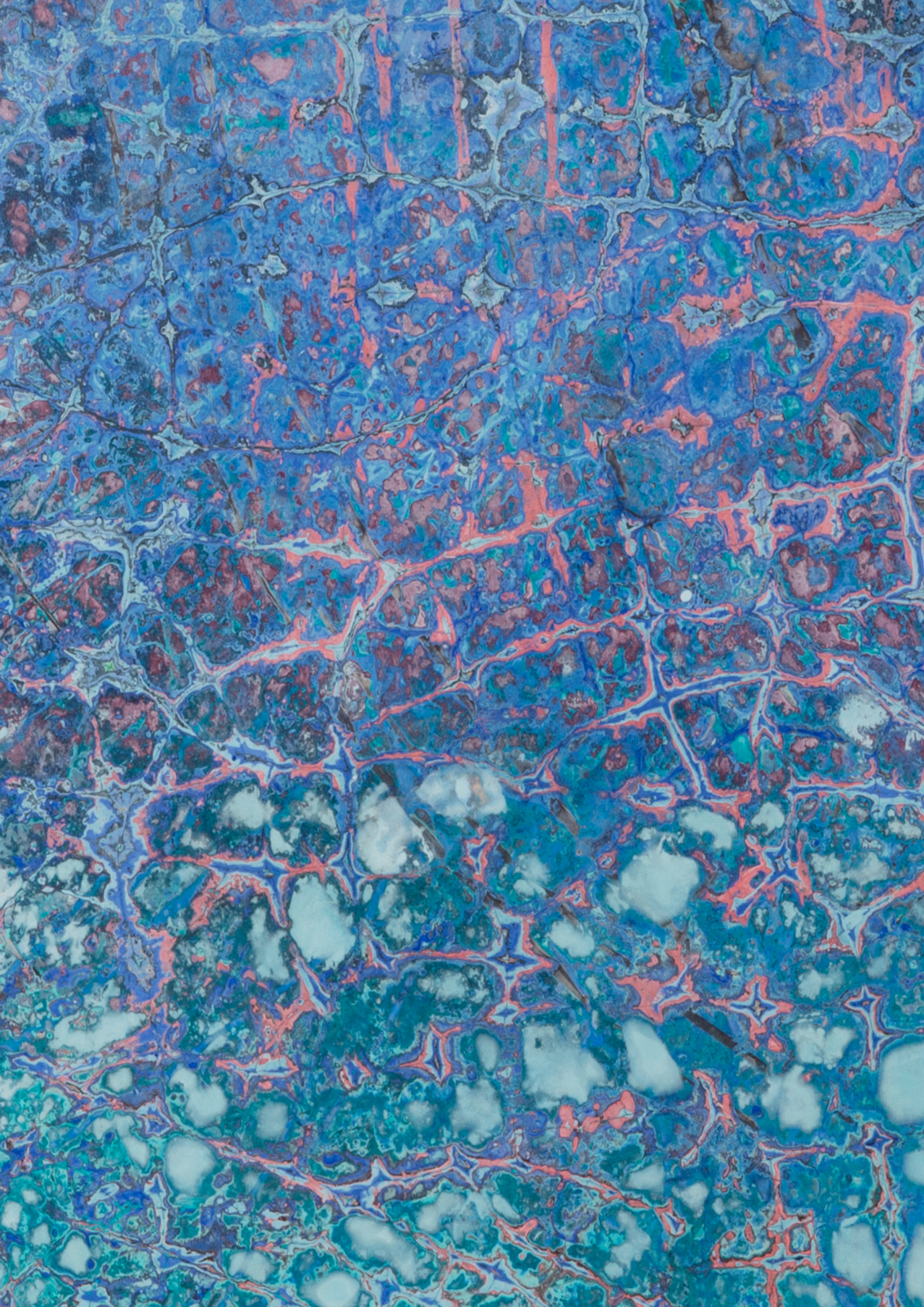
1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**(8496): 1479-82.
2. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002; **89**(9): 1142-9.
3. W. vG, 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**(6): 575-82.
4. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. 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**(10): 1215-23.
5. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**(28): 4620-5.
6. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; **30**(16): 1926-33.
7. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**(2): 184-90.
8. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; **333**(7572): 779.
9. Engelen SM, Maas M, Lahaye MJ, et al. Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge. *Eur J Cancer* 2013; **49**(10): 2311-20.
10. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010; **21**(9): 1743-50.
11. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; **3**: CD004078.
12. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
13. Group QC, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**(9604): 2020-9.
14. Akasu T, Moriya Y, Ohashi Y, Yoshida S, Shirao K, Kodaira S. Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. *Jpn J Clin Oncol* 2006; **36**(4): 237-44.
15. Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomised phase III trial. *Ann Oncol* 2014.
16. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25**(7): 1356-62.
17. Sainato A, Cernusco LNV, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**(2): 223-9.
18. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007; **26**(11): 2389-430.
19. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**(4): 343-6.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**(11): 1539-58.
21. Cionini L, Sainato A, De Paoli A, al. e. Final results of randomized trial on adjuvant chemotherapy after preoperative chemoradiation in rectal cancer. *Radiother Oncol* 2010; **96**(Suppl 1): S113-S4.
22. Breugom AJ, van den Broek CBM, van Gijn W, et al. The value of adjuvant chemotherapy in rectal cancer

patients after preoperative radiotherapy or chemoradiation followed by TME-surgery: The PROCTOR/SCRIPT study. *Eur J Cancer* 2013; **49.suppl 3:S1**.
23. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**(6): 352-8.
24. Taal BG, H. VT, Zoetmulder FA, group N. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *Br J Cancer* 2001; **85**(10): 1437-43.
25. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
26. André 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**(19): 3109-16.
27. NCCN Clinical Practice Guidelines in Oncology, Rectal Cancer, http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. *Visited: August, 28,* 2014.
28. NICE clinical guideline, Colorectal cancer, http://www.nice.org.uk/nicemedia/live/13597/56998/56998.pdf. *Visited: August, 28,* 2014.
29. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi81-vi8.
30. Dutch guideline colorectal cancer, http://www.oncoline.nl/colorectaalcarcinoom. *Visited: August, 28,* 2014.
31. Kapiteijn E, Liefers GJ, Los LC, et al. Mechanisms of oncogenesis in colon versus rectal cancer. *J Pathol* 2001; **195**(2): 171-8.
32. Kalady MF, Sanchez JA, Manilich E, Hammel J, Casey G, Church JM. Divergent oncogenic changes influence survival differences between colon and rectal adenocarcinomas. *Dis Colon Rectum* 2009; **52**(6): 1039-45.
33. Fransén K, Klintenas M, Osterstrom A, Dimberg J, Monstein HJ, Soderkvist P. Mutation analysis of the BRAF, ARAF and RAF-1 genes in human colorectal adenocarcinomas. *Carcinogenesis* 2004; **25**(4): 527-33.
34. Colombino M, Cossu A, Manca A, et al. Prevalence and prognostic role of microsatellite instability in patients with rectal carcinoma. *Ann Oncol* 2002; **13**(9): 1447-53.
35. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012; **487**(7407): 330-7.
36. Li JN, Zhao L, Wu J, et al. Differences in gene expression profiles and carcinogenesis pathways between colon and rectal cancer. *J Dig Dis* 2012; **13**(1): 24-32.
37. Baskin Y, Dagdeviren YK, Calibasi G, et al. KRAS mutation profile differences between rectosigmoid localized adenocarcinomas and colon adenocarcinomas. *J Gastrointest Oncol* 2014; **5**(4): 265-9.
38. Nagasaka T, Sasamoto H, Notohara K, et al. Colorectal cancer with mutation in BRAF, KRAS, and wild-type with respect to both oncogenes showing different patterns of DNA methylation. *J Clin Oncol* 2004; **22**(22): 4584-94.
39. M. vE, Roemen GM, Brink M, et al. K-ras mutations and RASSF1A promoter methylation in colorectal cancer. *Oncogene* 2002; **21**(23): 3792-5.
40. Patil H, Korde R, Kapat A. KRAS gene mutations in correlation with clinicopathological features of colorectal carcinomas in Indian patient cohort. *Med Oncol* 2013; **30**(3): 617.
41. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340**: c221.
42. Treweek S, Pitkethly M, Cook J, et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010; (4): MR000013.
43. 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**(28): 3768-74.
44. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; **15**(11): 1245-53.
45. Rödel C, Liersch T, Fietkau R, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *J Clin Oncol* 2014; **32**(5s): (suppl;abst 3500).

SUPPLEMENTARY DATA

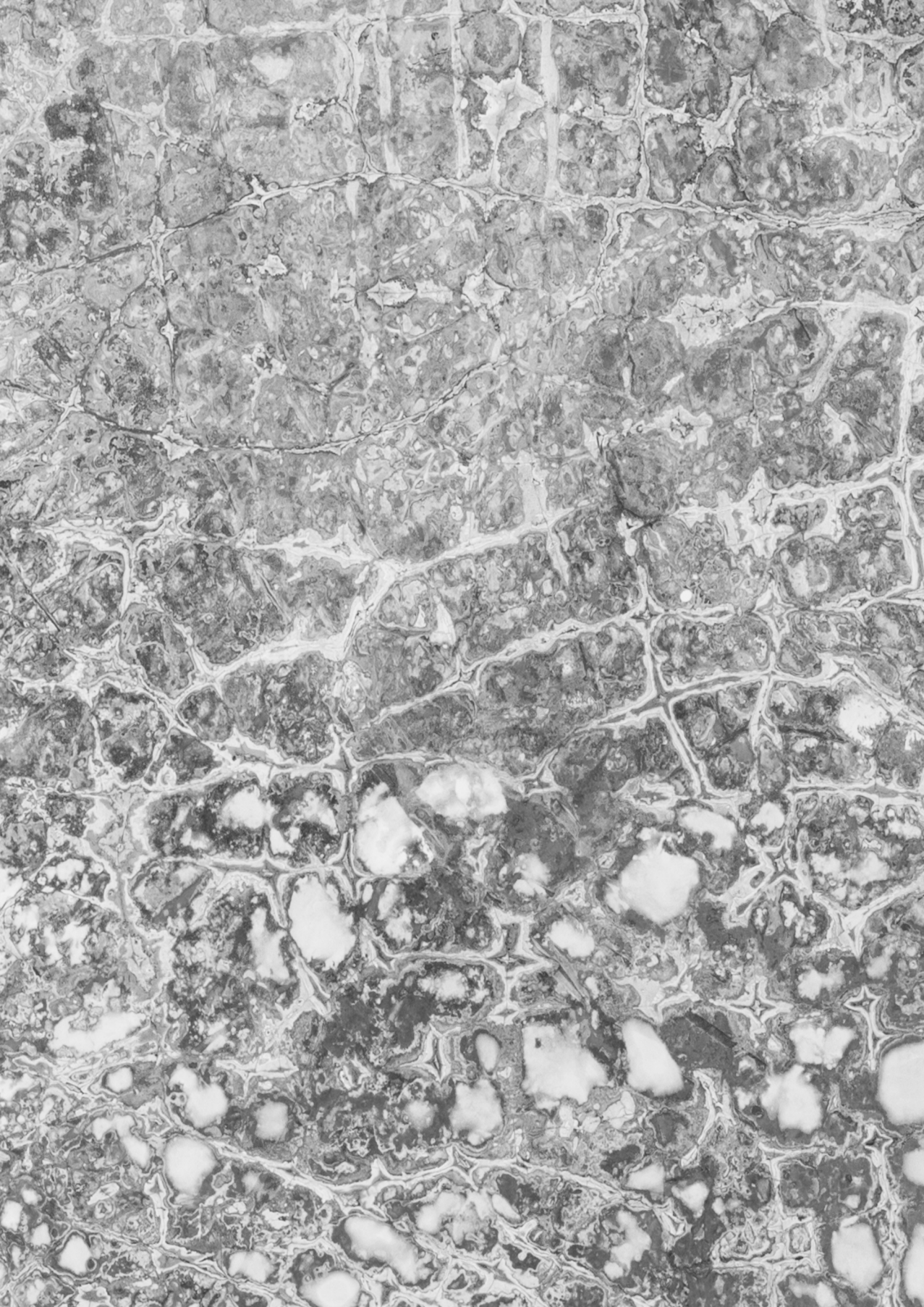


Supplementary figure 1. Overall survival by study



PART II

INTERNATIONAL COMPARISONS ON TREATMENT AND OUTCOMES OF PATIENTS WITH COLORECTAL CANCER



6

Quality assurance in the treatment of colorectal cancer: the EURECCA initiative

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

Annals of Oncology. 2014 Aug;25(8):1485-92.

ABSTRACT

Colorectal cancer is one of the most common cancers in Europe. Over the past few decades, important advances have been made in screening, staging and treatment of colorectal cancer. However, considerable variation between and within European countries remains, which implies that further improvements are possible. The most important remaining question now is: when are we, health care professionals, delivering the best available care to patients with colon or rectal cancer?

Currently, quality assurance is a major issue in colorectal cancer care and quality assurance awareness is developing in almost all disciplines involved in the treatment of colorectal cancer patients.

Quality assurance has shown to be effective in clinical trials. For example, standardisation and quality control were introduced in the Dutch TME trial and led to marked improvements of local control and survival in rectal cancer patients. Besides, audit structures can also be very effective in monitoring cancer management and national audits showed to further improve outcome in colorectal cancer patients. To reduce the differences between European countries, an international, multidisciplinary, outcome-based quality improvement programme, European Registration of Cancer Care (EURECCA), has been initiated. In the near future, the EURECCA dataset will perform research on subgroups as elderly patients or patients with comorbidities, which are often excluded from trials. For optimal colorectal cancer care, quality assurance in guideline formation and in multidisciplinary team management is also of great importance.

The aim of this review was to create greater awareness and to give an overview of quality assurance in the management of colorectal cancer.

Funding
EURECCA is supported by the European CanCer Organisation and the European Society of Surgical Oncology. There was no role of the funding sources to this manuscript.

INTRODUCTION

Important objectives of health policies are improving quality, safety, patient satisfaction and health care efficiency. To achieve this in cancer care, measuring and monitoring cancer treatment are crucial to deliver the best care to every patient and to conclude whether quality was assured. Owing to the increasing complexity of cancer care, monitoring the quality of care is also becoming more complex. Integrated care pathways can be used as a tool to measure and monitor cancer treatment and can facilitate these processes. Besides, it is needed to develop minimal required standards of good clinical practice through expert consultation and international consensus-building processes. Providing up-to-date treatment guidelines with objective information on short-term, long-term and adverse effects might contribute to improvements in quality of care.

The fact that cancer incidence still increases in Europe emphasises the importance to optimise quality of cancer care.[1,2] Currently, colorectal cancer is the second most common cancer in Europe, with 447,000 new cases and almost 215,000 deaths estimated to have occurred in 2012.[1] EUROCARE, a European collaborative research programme, which was initiated to assemble survival data collected by national and regional cancer registries, showed that considerable variation in survival between and within European countries still exists.[3,4]

In contrast to the increasing incidence of colorectal cancer, mortality reduced across Europe as a result of changes in screening, surveillance, staging, and treatment.[2,5] Over time, especially younger patients, patients with earlier tumour stages and rectal cancer patients demonstrated a better survival.[5] Therefore, more advancement could be gained by changing the focus to, for example, elderly patients, patients with advanced stages of disease and colon cancer patients. Furthermore, it is of great importance that cancer management becomes increasingly individualised, since certain patient subgroups are more vulnerable for the adverse effects of medical treatment. Besides, in future research, traditional outcome measures such as cancer-specific survival, overall survival and disease-free survival are still of great value, but might fail to explain more patient-centred end points such as quality of life and functional outcomes after cancer treatment.

WHAT IS QUALITY ASSURANCE?

Quality assurance in health care is definitely not a new concept. Probably, the first example of routine health outcome measurement with death as outcome was by Florence Nightingale who attempted to standardise nursing care in the Crimean war. In the early 1900s, Ernest Amory Codman (1869-1940), a Boston surgeon, developed the 'End Result'

idea, which he defined as: "The common sense notion that every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire, 'If not, why not?' with a view to preventing similar failures in the future".[6] This way, Codman demonstrated patient outcomes, but unfortunately, he did not receive any support and after he created an uproar at a public meeting, he was dismissed.[6] Currently, quality assurance programmes are gaining popularity and also extend to other disciplines than surgery.

Quality assurance is essential for good medical decision making and can be defined as all those planned and systematic actions necessary to achieve minimal requirements of good cancer care. Quality assurance programmes aim to optimise quality of care by determining standards and assuring that these standards are met. This will result in reduced variability and continuous quality improvement. Therefore, quality assurance programmes should become obligatory for all centres that provide colorectal cancer care.

In clinical trials, quality control already showed to be very effective.[7-13] However, another effective instrument to monitor quality of care and to improve outcome is auditing, which is closely related to quality assurance. Within an audit cycle, collected data will be compared with selected quality standards, and provides continuous feedback to participating health care professionals on these standards and on outcomes (Figure 1).

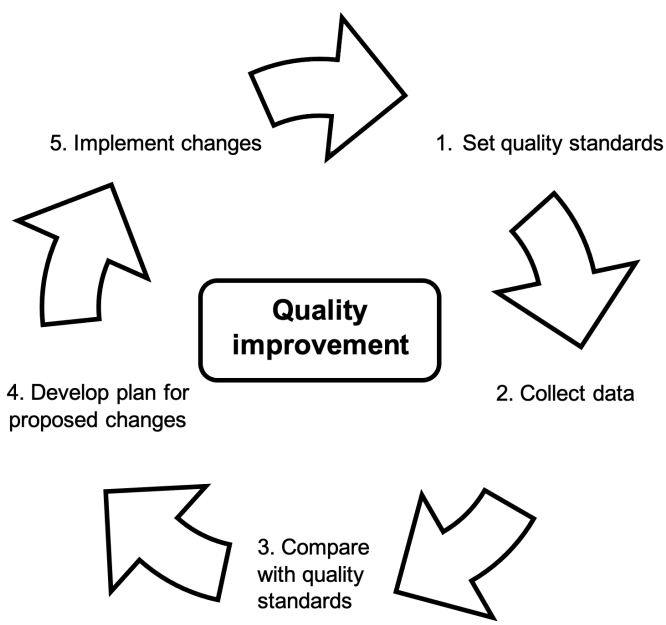


Figure 1. Audit cycle

DIFFERENCES IN QUALITY

Various publications and reports demonstrated considerable variation in outcomes of care between countries, regions and hospitals.[4,5,14,15] Birkmeyer et al. showed that undergoing surgery in a high-volume hospital for selected cardiovascular and cancer procedures, including colectomy, significantly reduced the risk of operative death.[14] In addition, several groups demonstrated that high surgeon volume was also associated with improved patient outcomes.[16]

Surprisingly, in the Swedish Uppsala trial it was found that half of the patients were operated by surgeons who performed less than one rectal cancer operation per year.[17] Consequently, rectal cancer care was centralised to centres with specialised surgeons.

The decision of concentration of colorectal cancer care is preferably not only based on caseload, but also on other outcomes. Therefore, additional information on differences in, for example, case mix between hospitals, reasons for non-adherence to guidelines and the occurrence of recurrences is very important. A comprehensive European audit as EURECCA, which will be explained later, could provide in this.

EUROPEAN AUDITS FOR COLORECTAL CANCER

Over the past few decades, audit structures are most frequently initiated in surgical oncology compared with other disciplines. Several European countries have organised national surgical colorectal cancer audits. Most of these audits were initially founded for rectal cancer because of poor outcomes before the 1990s. Main reasons for initiating these audits were to evaluate the effect of standardised TME surgery and to diminish variation in outcome.[18]

The Norwegian Rectal Cancer Project (now: the Norwegian Colorectal Cancer Project) was the first initiated national audit and included 3319 patients diagnosed with rectal cancer. Training courses and master classes were arranged and involved departments received regularly feedback together with the national average results for comparison and quality control. During this period of auditing, the proportion of TME surgery increased from 78% to 92%. Before auditing, the local recurrence rate in Norway was 28% and the mean 5-year survival rate 55%, while after 4 years of auditing, the local recurrence rate was 6% for patients who received TME surgery and the overall 4-year survival rate was 73%.[19]

Another example is the Danish Colorectal Cancer Database that included >93% of all

colorectal cancer patients. For rectal cancer, 5-year survival increased from 37% in males and 42% in females in the period 1987-1989 to 55% in males and 63% in females in the period 1994-1999.[20]

Several other European countries followed by establishing a national (colo)rectal cancer audit programme (Table 1) and showed remarkable improvements.[18,21-27]

Table 1. National audits

Audit	Country	Year of foundation
Norwegian Colorectal Cancer Project	Norway	1993
Danish Colorectal Cancer Database	Denmark	1994
Swedish Colorectal Cancer Registry	Sweden	1995
Study group for Therapies Of Rectal Malignancies	Italy	1999
International Quality Assurance in Colorectal Carcinoma	Germany, Poland, Lithuania, Italy	2000
National Bowel Cancer Audit Program	United Kingdom	2001
Project on Cancer of the Rectum	Belgium	2005
Spanish TME Project	Spain	2006
Dutch Surgical Colorectal Audit	Netherlands	2009

In the EUROCARE-4 study, colorectal cancer patients diagnosed between 2000 and 2002 demonstrated a mean 5-year relative survival of 56.2%. However, there was large variation in survival among European countries. Especially North and Central Europe showed best survival rates, while survival rates in the Czech Republic and Poland were substantial lower (45.2% and 46.0% respectively) than average. However, for countries without national coverage, the EUROCARE data are not representative for the entire colorectal cancer population. Nevertheless, the EUROCARE results point out the considerable differences in survival among European countries. These differences imply that further optimisation in colorectal cancer care is possible in order to improve outcomes and to reduce variability between European countries. EUROCARE is useful in identifying where the possibilities are to improve quality of care. However, questions such as why these differences exist and how the survival rate can be improved cannot be answered by the EUROCARE database. The challenge is to define a standardised European dataset, that will answer these questions, that will be subject of change as science progresses and that will contribute in optimising the quality of care.

THE EURECCA INITIATIVE

EURECCA is the acronym for European Registration of Cancer Care or in short European Cancer Audit.[28] By developing a European, outcome-based, multidisciplinary audit registry, EURECCA aims to reduce systematic variance by standardising and harmonising

cancer care in Europe. EURECCA works with national audit registries and national cancer registries and collects patient and treatment data, which will be analysed. Subsequently, standards will be uncovered and will be fed back (Figure 2). Besides, subgroups as for example elderly patients and patients with comorbidities are mostly excluded from trials, leaving little evidence to define good cancer care for these patient groups. Therefore, to improve quality of care for the entire population, a comprehensive audit as EURECCA, in which all patients of a population are included, could be an effective instrument and can eventually result in evidence-based medicine for these subgroups by identifying and communicating about 'best practices'.[18]

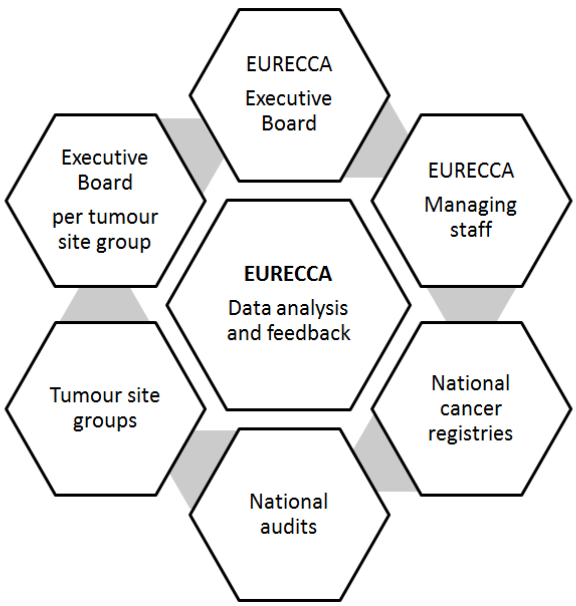


Figure 2. EURECCA structure

EURECCA has been initiated by the European Society of Surgical Oncology (ESSO) in partnership with the European Society for Radiotherapy & Oncology (ESTRO), the European Society for Medical Oncology (ESMO), the European Society of Coloproctology (ESCP), the European CanCer Organisation (ECCO), and the European Organisation for Research and Treatment of Cancer (EORTC). Patient organisations EuropaColon and EONS are also important affiliated partners.

Outcomes that will be considered within EURECCA are morbidity, mortality, recurrences and survival. Future plans are to implement more patient-centred parameters such as quality of life and functional outcomes. The collected data will be analysed in order

to identify where further quality improvement is needed and additional data will be collected to adjust for possible confounders. Furthermore, EURECCA could give insights into the amount of surgical procedures performed in each hospital and by each surgeon. Initially, EURECCA Colorectal has been established. Currently, nine audit registries in eleven countries are participating in the EURECCA project. Mid-2011, all audit registries included over 400,000 patients with colorectal cancer. In 2012, a valuable core dataset for EURECCA colorectal has been identified, consisting of a list of 45 data items including patient data, data about preoperative staging, surgical treatment, (neo)adjuvant therapy, and follow-up, to facilitate future analyses with respect to national privacy legislations.[29] In December 2012, a multidisciplinary consensus meeting for EURECCA Colorectal was held to establish treatment guidelines by using the Delphi method. Representatives of European scientific organisations involved in colorectal cancer treatment formed the multidisciplinary expert panel during the consensus meeting in order to ensure a solid basis to reach health care professionals in the field. There was voted on 465 medical statements in several rounds. In 84% large consensus was reached (>80% agreement), 6% reached moderate consensus, 7% reached minimum consensus and 3% was disagreed by >50% of the members.[30,31] Besides EURECCA Colorectal, EURECCA Breast, EURECCA Hepatopancreaticbiliary (HPB), EURECCA Upper GI, and EURECCA Urology have been initiated.

QUALITY ASSURANCE IN TRIALS

Treating within clinical trials provides us information to optimise treatment strategies. Within trials, there is standardisation, better monitoring and better quality assurance of diagnostic and treatment processes, which might result in improved outcomes. However, trials are costly, time-consuming and there is selection bias which makes the results inapplicable for the entire population.[13,32] Quality assurance was integrated in the Dutch D1-D2 gastric cancer trial and later in the Dutch TME trial.[7,8] The Dutch TME trial was initiated to investigate the effect of short-term preoperative radiotherapy in combination with TME surgery compared with TME surgery alone.[7] It was considered crucial that surgical, pathological and radiotherapeutical techniques were standardised and controlled for quality. TME surgery was taught to surgeons through workshops, symposia and video instructions. A monitoring committee ensured adherence to surgical protocols. In each hospital, the first five TME procedures were supervised by an experienced instructor surgeon. Also for radiotherapy exact descriptions of dose, volume, fields and simulation techniques were used. Pathologists were trained according to a strict protocol. Quality assurance was very successful in this trial. Local recurrence rates were reduced by >50%. Furthermore, there was an association between circumferential resection margin (CRM) involvement and outcome, which shows the importance of good surgical performance.[33,34] According to these successful results, would not it be of

great value to incorporate quality control in daily medical practice to provide the same standardised care and treatment as within trials?

Several studies have suggested that patients treated within clinical trials have better outcomes than patients who receive similar treatment outside the framework of a trial.[9-12] Patients participating in trials have better management of their disease, because of more frequent evaluation with potentially earlier detection of problems and better management of side-effects. They are also more likely to maintain the scheduled dose and frequency of treatment.[35]

QUALITY ASSURANCE IN OTHER MEDICAL DISCIPLINES

Although quality assurance in cancer care is most advanced in surgery, it is also developing in other medical disciplines, such as radiology, radiation oncology, medical oncology and pathology.

The Mercury Study Group reported that preoperative staging of rectal cancer with MRI precisely predicts whether the CRM will be clear or not[36,37] and several studies demonstrated that a positive circumferential resection margin has an adverse effect on the local recurrence rate and on overall survival.[38-40] This demonstrates the importance of preoperative staging.

In Alberta, Canada, an electronic synoptic operative report template has successfully been introduced in order to replace the narrative operative record, with standardised dropdown menus to include patient and operative data. This did not only result in information about surgical practices, but it also provides insight in the utilisation of the health care system.[41]

In radiation oncology, important features for quality assurance are, for example, the irradiated volume, portals technique, radiation modality, amount of fractions, and the total tumour dose.[32,42] As mentioned before, radiotherapy was standardised in the Dutch TME trial and led to considerable results.[33,34]

In medical oncology, the use of adjuvant chemotherapy is frequently defined in treatment guidelines, of which ESMO gives a yearly update and incorporates the most recent evidence from trials.[42,43] However, older studies indicate that about half of the patients receive non-evidence based schedules, which is for example related to age, patient preferences and comorbidities.[44] Unfortunately, there is no information available

on more actual adherence to schedules, but difficulties certainly are dose reduction, toxicity management and dose intensity. Key questions are: is the right treatment being given? Is it well done? Is the patient as well as the disease treated? Good quality of care registration could help to give an insight in these challenges. Also in pathology, quality assurance has become an important part. Currently, there are for example protocols fur cut-up and reporting, for minimum numbers of lymph nodes to be retrieved and for internal quality control.[45] However, to assure and improve quality of colorectal cancer care, further development of guidelines and multidisciplinary management could be very useful.

QUALITY ASSURANCE IN GUIDELINE FORMATION

Guidelines for cancer management, as well as early detection and screening procedures, are essential for quality improvement, optimal use of the available resources, and maximal reduction of unnecessary harm to patients. Knowledge of best measures for diagnosis and treatment is not universally available at the required highest level, and a strong, clinically highly relevant difference in expertise exists at all levels of cancer care between individuals, disciplines, hospitals, regions and countries. Therefore, in several countries national guidelines have been developed, and European scientific societies have partially adopted this process and prepare or have published international/European guidelines and treatment recommendations for the major tumour types (e.g. ESMO, EUA, or ESO). Although guidelines are not always completely up-to-date as science rapidly evolves, it is important to have guidelines as a basis for clinicians in the treatment of cancer patients. There are some major essential points of importance regarding the methodology for the development and publication of national and international recommendations. Recommendations must be based on highest available evidence. If this is not available, expert opinion is a valuable surrogate, which however is often in danger and may not be guided or dominated by 'eminence' of politically or otherwise powerful representatives of the various disciplines. Besides, multidisciplinarity of the expert panel and, in particular important in international guidelines, a balanced distribution between the members of the different countries as well as the different disciplines are also important. Furthermore, a strictly followed scheme for development of the text of the guideline is of high value, and should be based on preparation of the topics to be described by the different experts, discussion of the topics in the expert group, and development of the consensus statement in the full expert group. The most critical point is the methodology to achieve consensus, since this is always a source of potential bias. To avoid this, guidelines should use objective methods for voting of statements, for example, the 'Delphi' method (as used in the EURECCA colorectal multidisciplinary consensus conference[30,31]), followed by personal discussion in the consensus group and further rounds of voting, or the more

'simple' direct method of personal voting in the consensus group, followed by discussion and final voting (e.g. used in the ESMO guidelines for colorectal cancer).[43]

Finally, the level of evidence on which the final statement is based (level I-IV), the level of recommendation (A-D), the level of agreement and percentage of disagreement (if existent and relevant) must be noted in the final document. Correct implementation of these methodologies and a clear definition and description of the instruments and methods used are of utmost importance for the final guideline document and its reliability and use.

There might be internationally different definitions of standards, based on the accessibility of diagnostic and therapeutic options within different countries. However, the standard must be defined according to the best available data which are mostly based on best available tools for diagnosis and treatment. Besides, the document should also include recommendations for those situations where this is not the case.

QUALITY ASSURANCE IN MULTIDISCIPLINARY TEAMS

Each discipline within the colorectal cancer care process plays an important role in determining outcome. Currently, multidisciplinary cancer management, in which the full complement of services is provided timely and in a safe, effective, efficient, but in a patient-centred way, has been implemented for most of Europe and forms an important component in guidelines.[46] Multidisciplinary teams have been introduced in cancer care because cancer management has become increasingly complex. Owing to this complexity, it is important to involve different health care professionals in clinical decision making for individual patients to provide optimal medical care. Multidisciplinary teams need to consist of at least a radiation oncologist, medical oncologist, surgeon, pathologist, radiologist and a clinical nurse specialist. All new colorectal cancer patients should be discussed before neoadjuvant treatment or primary surgery as well as after surgery to decide on treatment strategies. Multidisciplinary teams should improve communication, coordination and decision making in the cancer care process between health care professionals and patients.[47] In a study by Blazeby et al., the authors showed that the most important reasons for changing decisions within a multidisciplinary team were the result of co-morbid disease, patient preferences, and the availability of additional clinical information.[48] Although multidisciplinary teams have been widely incorporated in cancer management, research into the effectiveness of multidisciplinary teams has led to inconclusive results. Hereby, it must be taken into account that poor study designs have been used to evaluate the effect of multidisciplinary cancer management. Furthermore, the findings are often confounded by changes over time

including improved treatments, and technology and service changes.[47,49] The efficacy of multidisciplinary teams needs to be studied more extensively, although it is without question that multidisciplinary discussions are of great value in cancer care. However, several studies demonstrated improvements in cancer care and diagnostic accuracy achieved by working in multidisciplinary teams.[49-55] The Mercury Study Group showed the importance of improved collaboration between different disciplines and a trained team to ensure standardisation of techniques and interpretation was demonstrated. In this study, the local recurrence rate was only 2.3% in patients with T3a/bN0 disease and even 0% in patients with T2N1, T3a/bN1 or T3bN2 disease.[36] In the UK, multidisciplinary management is associated with improved 5-year survival in colorectal cancer.[52] Furthermore, in a study by Burton et al., 26% of the patients without discussion of the MRI by a multidisciplinary team had a positive CRM compared with 1% of the patients with discussion of the MRI by a multidisciplinary team.[53]

In 2010, the National Cancer Action Team published the document 'The Characteristics of an Effective Multidisciplinary Team (MDT)' and offered recommendations regarding the multidisciplinary team itself, infrastructure for meetings, meeting organisation and logistics, patient-centred clinical decision-making and team governance.[56] By achieving recommendations as the National Cancer Action Team formulated, multidisciplinary team meetings will be more effective. Of course, EURECCA fully supports the use of multidisciplinary teams to achieve optimal colorectal cancer care for every patient.

COST EFFECTIVENESS OF QUALITY IMPROVEMENT

Professor Wibe demonstrated during the Colorectal Conference in 2007 in St. Gallen that the costs of the Norwegian Colorectal Cancer Project were EUR 120,000 per year and that the costs for every saved life were less than EUR 700.[57] In contrast, adjuvant therapy for colon cancer with fluorouracil, leucovorin and folinic acid costs around EUR 11,000 per saved life year.[58] These points out that a quality assurance project as an audit is very cost-effective compared with adjuvant chemotherapy.

Besides, an important goal of the Dutch Surgical Colorectal Audit (DSCA) is to reduce health care expenditures. The Boston Consulting Group demonstrated in a report in 2011 that complete implementation of quality registries in the Dutch healthcare system could result in a saving of EUR 2.3 billion per year in 2020.[59]

Despite relatively low costs of an audit, of course it still has to be financed. For example, the government can contribute to this, because of the cost effectiveness of auditing. Besides, an European audit as EURECCA can result in a reduction of the use

of unnecessary treatments and in an improvement of cancer outcome. Therefore, it is also interesting for health insurance companies to invest in an outcome-based European audit. Finally, cancer foundations and other grant giving institutes might be interested to contribute in quality improving initiatives.[60] Besides the financial aspect, there is also the need to identify an organisation to perform audits. Such an organisation requires expertise, uniformity and the ability to benchmark across Europe.

FUTURE PERSPECTIVES

Although there is increasing awareness of quality assurance, there is still much to improve. Multidisciplinary teams and integrated care pathways can contribute to this on hospital level, while a comprehensive European platform such as EURECCA, that organises international cancer care registry and feedback, can contribute to this on European level. EURECCA determines the core datasets per tumour type. For an optimal insight in cancer management, data on patient characteristics (comorbidities and fitness), tumour anatomy and biology, diagnosis, surgical treatment, neoadjuvant and adjuvant treatment will need to be collected. Data completeness and data accuracy are important goals to reach a good quality audit.

However, EURECCA has to deal with different privacy laws in different European countries. These laws currently limit international patient data collection. Moreover, there is no official structural funding yet for this international platform, which currently limits European expansion.

EURECCA, which is still in a developing phase, aims at rapid data processing and feedback and is patient centred. Furthermore, EURECCA aims to develop audit structures for all disciplines involved in cancer care. These audit structures are currently most advanced in surgical oncology. One of EURECCA's goals is to expand to all European countries and to cover all cancer registries and clinical audits. To achieve this, key opinion leaders are actively approached. In the near future, an international comparison on adjuvant treatment for rectal cancer and stage II colon cancer will be performed, as well as an international comparison on treatment and survival for the oldest elderly patients with colorectal cancer. Colorectal cancer screening will be subject of future research. Ultimately, EURECCA wish to establish European guidelines for the treatment of cancer patients, with as goal that these guidelines will eventually substitute national and local guidelines. To establish quality assurance in cancer management, real-time measurement and feedback are crucial and not readily available yet. Initiatives such as EURECCA, which creates a platform to realise this, are necessary in the future to reflect on cancer care and improve cancer outcome. Large database analyses will offer the possibility of

evidence-based and tailor-made treatment. Moreover, under- and overtreatment will be more easily detected.

ACKNOWLEDGEMENTS

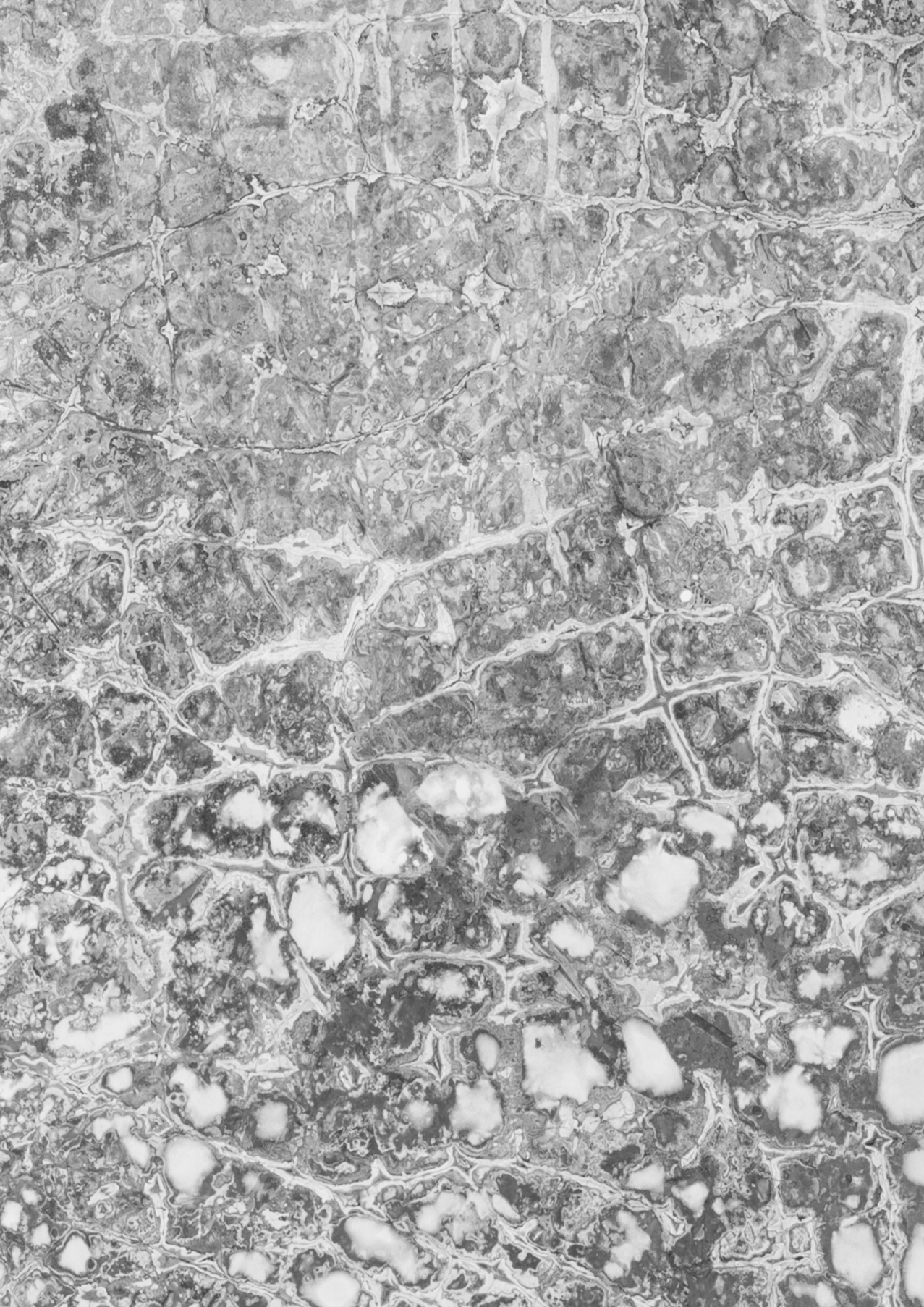
The authors would like to thank the EURECCA colorectal group; L. Påhlman, B. Glimelius, Swedish Colorectal Cancer Registration; A. Wibe, Norwegian Colorectal Cancer Registry; L.H. Iversen, Danish Colorectal Cancer Database; T. Wiggers, Dutch Surgical Colorectal Audit; H. Ortiz, Spanish Rectal Cancer Project; P. Mroczkowski, International Quality Assurance Project for Colorectal Cancer in Germany; A. Dziki, International Quality Assurance Project for Colorectal Cancer in Poland; R. Janciauskiene, International Quality Assurance Project for Colorectal Cancer in Lithuania; G. Romano, International Quality Assurance Project for Colorectal Cancer in Italy; F. Penninckx, Belgian Project On Cancer Of the Rectum (PROCARE); L. Van Eycken, Belgian Cancer Registry; J.J. Smith, P. Quirke, National Bowel Cancer Programme in the UK; M.A. Gambacorta, Department of Radiation Oncology, Università Cattolica S. Cuore, Italy; C. Aristei, Radiation Oncology Section, Department of Surgery, Radiology and Dentistry, University of Perugia, Italy; R.G.H. Beets-Tan, European Society of Radiology, Department of Radiology, Maastricht University, the Netherlands; L. Blomqvist, European Society of Radiology, Department of Diagnostic Radiology, Karolinska University Hospital, Sweden; J.M. Borras, ECCO/EPAAC Catalonian Cancer Strategy Unit, Spain; G. Brown, European Society of Radiology, Department of Radiology, The Royal Marsden NHS Foundation Trust, UK, J.W. Coebergh, Erasmus MC Rotterdam, Comprehensive Cancer Centre South, the Netherlands; E. Espin, Colorectal Surgery Unit, Hospital Valle de Hebron, Spain; J. Gore-Booth, G. Henning, EUROPA Colon; K. Haustermans, ESTRO, EORTC, Department of Radiation Oncology, University Hospitals Leuven, Belgium; J.H. van Krieken, I. Nagtegaal, ESP, Department of Pathology, Radboud University Nijmegen, the Netherlands; C.A.M. Marijnen, ESTRO, Department of Radiation Oncology, Leiden University Medical Centre, the Netherlands; R.E.M. Tollenaar, Dutch Institute of Clinical Auditing; P. Naredi, ESSO, Department of Surgery, Sahlgrenska University Hospital, Sweden; C. Rödel, ESTRO, Radiation Oncologist, University Hospital of Frankfurt, Germany; A. Roth, ESSO, Oncosurgery Unit HUG, Switzerland; H.J.T. Rutten, ESSO, Department of Surgery, Catharina Hospital Eindhoven, the Netherlands; P.J. Tanis, ESSO, Department of Surgery, Academic Medical Centre, the Netherlands; C. Taylor, EONS, St. Mark's Hospital, United Kingdom.

REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**(6): 1374-403.
2. Karim-Kos HE, E. dV, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. 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**(10): 1345-89.
3. Gatta G, Zigon G, Aareleid T, et al. Patterns of care for European colorectal cancer patients diagnosed 1996-1998: a EUROCARE high resolution study. *Acta Oncol* 2010; **49**(6): 776-83.
4. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol* 2007; **8**(9): 784-96.
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 EUROCARE study. *Int J Cancer* 2012; **131**(7): 1649-58.
6. Brand RA. Ernest Amory Codman, MD, 1869-1940. *Clin Orthop Relat Res* 2009; **467**(11): 2763-5.
7. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**(9): 638-46.
8. 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**(5): 439-49.
9. Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW. Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch Intern Med* 2008; **168**(6): 657-62.
10. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. *Cancer* 1985; **56**(7): 1710-8.
11. Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. *BMJ* 1989; **299**(6707): 1069-72.
12. Mayers C, Panzarella T, Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. *Cancer* 2001; **91**(12): 2246-57.
13. Antman K, Amato D, Wood W, et al. Selection bias in clinical trials. *J Clin Oncol* 1985; **3**(8): 1142-7.
14. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**(15): 1128-37.
15. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**(22): 2117-27.
16. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. *Br J Surg* 2007; **94**(2): 145-61.
17. 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**(6): 564-72.
18. van Gijn W, van de Velde CJ. Improving quality of cancer care through surgical audit. *Eur J Surg Oncol* 2010; **36 Suppl 1**: S23-S6.
19. 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**(7): 857-66.
20. Harling H, Bulow S, Kronborg O, Moller LN, Jorgensen T. Survival of rectal cancer patients in Denmark during 1994-99. *Colorectal Dis* 2004; **6**(3): 153-7.
21. Birgisson H, Talback M, Gunnarsson U, Pahlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. *Eur J Surg Oncol* 2005; **31**(8): 845-53.
22. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. *Br J Surg* 2007; **94**(10): 1285-92.
23. Mroczkowski P, Kube R, Schmidt U, Gastinger I, Lippert H. Quality assessment of colorectal cancer care: an international online model. *Colorectal Dis* 2011; **13**(8): 890-5.
24. Penninckx F, Van Eycken L, Michiels G, et al. Survival of rectal cancer patients in Belgium 1997-98 and the potential benefit of a national project. *Acta Chir Belg* 2006; **106**(2): 149-57.
25. Audit DSC, 2012 R. http://dsca.clinicalaudit.nl/jaarrapportage/#dica_rapportages_dsca. *(accessed August 2013)* 2013.

26. Programme NBCA. http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Bowel-Cancer-Audit-National-Report-pub-2012.pdf. *(accessed August 2013)* 2013.
27. 2006-2008 STP. http://www.aecirujanos.es/secciones/coloproctologia/proyecto_vikingo_informe_2006-2008.-pdf. *(accessed August 2013)* 2013.
28. EURECCA. www.canceraudit.eu. *(accessed August 2013)* 2013.
29. W vG, 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**(6): 467-71.
30. C.J. vdV, Boelens PG, Borras JM, et al. EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum. *Eur J Cancer* 2013.
31. 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**(13): 2784-90.
32. Poortmans PM, Davis JB, Ataman F, Bernier J, Horiot JC. The quality assurance programme of the Radiotherapy Group of the European Organisation for Research and Treatment of Cancer: past, present and future. *Eur J Surg Oncol* 2005; **31**(6): 667-74.
33. 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**(5): 693-701.
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**(6): 575-82.
35. Vardy J, Tannock IF. Quality of cancer care. *Ann Oncol* 2004; **15**(7): 1001-6.
36. 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**(4): 711-9.
37. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; **333**(7572): 779.
38. Bernstein TE, Endreseth BH, Romundstad P, Wibe A. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009; **96**(11): 1348-57.
39. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002; **89**(3): 327-34.
40. Marijnen CA, Nagtegaal ID, Kapiteijn E, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003; **55**(5): 1311-20.
41. Mack LA, Dabbs K, Temple WJ. Synoptic operative record for point of care outcomes: a leap forward in knowledge translation. *Eur J Surg Oncol* 2010; **36 Suppl 1**: S44-S9.
42. Valentini V, Glimelius B, Frascino V. Quality assurance and quality control for radiotherapy/medical oncology in Europe: Guideline development and implementation. *Eur J Surg Oncol* 2013.
43. Schmoll HJ, E. VC, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012; **23**(10): 2479-516.
44. Ottevanger PB, De Mulder PH. The quality of chemotherapy and its quality assurance. *Eur J Surg Oncol* 2005; **31**(6): 656-66.
45. van Krieken JH, Nagtegaal ID. Pathological quality assurance in gastro-intestinal cancer. *Eur J Surg Oncol* 2005; **31**(6): 675-80.
46. Lamb BW, Sevdalis N, Taylor C, Vincent C, Green JS. Multidisciplinary team working across different tumour types: analysis of a national survey. *Ann Oncol* 2012; **23**(5): 1293-300.
47. Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? *Lancet Oncol* 2006; **7**(11): 935-43.
48. Blazeby JM, Wilson L, Metcalfe C, Nicklin J, English R, Donovan JL. Analysis of clinical decision-making in multi-disciplinary cancer teams. *Ann Oncol* 2006; **17**(3): 457-60.
49. Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. *Ann Surg Oncol* 2011; **18**(8): 2116-25.
50. Forrest LM, McMillan DC, McArdle CS, Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2005; **93**(9): 977-8.
51. Newman EA, Guest AB, Helvie MA, et al. Changes in surgical management resulting from case review at a breast cancer multidisciplinary tumor board. *Cancer* 2006; **107**(10): 2346-51.

52. Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's colorectal cancer patients. *Br J Cancer* 2006; **95**(8): 979-85.
53. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? *Br J Cancer* 2006; **94**(3): 351-7.
54. Wille-Jorgensen P, Sparre P, Glenthoj A, et al. Result of the implementation of multidisciplinary teams in rectal cancer. *Colorectal Dis* 2013; **15**(4): 410-3.
55. MacDermid E, Hooton G, MacDonald M, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. *Colorectal Dis* 2009; **11**(3): 291-5.
56. Team NCA. The Characteristics of an Effective Multidisciplinary Team, www.ncin.org.uk/view?rid=136. *(accessed August 2013)* 2010.
57. A. W. Nationwide quality assurance of rectal cancer treatment. *In: Colorectal congress, 28th November 2007, St Gallen, Switzerland* 2007.
58. Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol* 2000; **18**(18): 3302-17.
59. Group BC. Rapport Zorg voor Waarde, http://www.clinicalaudit.nl/sites/default/files/Waarde%20van%20registratie.pdf. *(accessed August 2013)* 2011.
60. van de Velde CJ, van den Broek CB. Quality assurance in rectal cancer treatment. *Dig Dis* 2012; **30 Suppl 2**: 126-31.



7

Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - a EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania

A.J. Breugom
E. Bastiaannet
P.G. Boelens
L.H. Iversen
A. Martling
R. Johansson
T. Evans, S. Lawton
K.M. O'Brien
E. Van Eycken
R. Janciauskiene
G.J. Liefers
A. Cervantes
V.E.P.P. Lemmens
C.J.H. van de Velde

European Journal of Cancer. 2016 Aug;63:110-7.

ABSTRACT

Background

The aim of the present EURECCA international comparison is to compare adjuvant chemotherapy and relative survival of patients with stage II colon cancer between European countries.

Methods

Population-based national cohort data (2004-2009) from the Netherlands (NL), Denmark (DK), Sweden (SE), England (ENG), Ireland (IE), and Belgium (BE) were obtained, as well as single-centre data from Lithuania (LT). All surgically treated patients with stage II colon cancer were included. The proportion of patients receiving adjuvant chemotherapy was calculated and compared between countries. Besides, relative survival was calculated and compared between countries.

Results

Overall, 59,154 patients were included. The proportion of patients receiving adjuvant chemotherapy ranged from 7.1% to 29.0% ($p<0.001$). Compared with NL, a better adjusted relative survival was observed in SE (stage II: RER 0.53, 95% confidence interval (CI) 0.44-0.64; $p<0.001$), and BE (stage II: RER 0.84, 95% CI 0.76-0.92; $p<0.001$), and in IE for patients with stage IIA disease (RER 0.80, 95% CI 0.65-0.98; $p=0.03$).

Conclusion

The proportion of patients with stage II colon cancer receiving adjuvant chemotherapy varied largely between seven European countries. No clear linear pattern between adjuvant chemotherapy and adjusted relative survival was observed. Compared with NL, SE and BE showed an improved adjusted relative survival for stage II disease, and IE for patients with stage IIA disease only. Further research into selection criteria for adjuvant chemotherapy could eventually lead to individually tailored, optimal treatment of patients with stage II colon cancer.

Funding

EURECCA was funded by the European Society of Surgical Oncology (ESSO). The funding source had no role in the study design, data collection, analysis, interpretation of the data, writing of the manuscript, or the decision to publish.

INTRODUCTION

Colorectal cancer is the third most common cancer in males and the second in females, and it is the second cause of cancer death in Europe. In total, 447,000 new cases and 215,000 deaths are estimated to have occurred in 2012.[1] Approximately 70% of patients with colorectal cancer have a tumour in the colon.[2] Surgery is the mainstay curative treatment for colon cancer. Depending on stage, surgery may be followed by adjuvant chemotherapy with the aim of eradicating micrometastases.

The role of adjuvant chemotherapy in patients with stage III colon cancer is well established, resulting in a reduction in recurrence rate and an improvement in survival.[3-9] Nowadays, oxaliplatin combined with capecitabine or 5-fluorouracil (FU)/leucovorin (LV) is standard in the adjuvant treatment of stage III colon cancer.[10-12]

On the contrary, the role of adjuvant chemotherapy in patients with stage II colon cancer remains uncertain despite several randomised controlled trials (RCTs) exploring this subject.[13] Currently about 15% of patients with stage II colon cancer will develop metastatic disease within 5 years after diagnosis of the primary tumour.[14] According to the ESMO Clinical Practice Guidelines, adjuvant chemotherapy could be considered in patients with high-risk stage II colon cancer defined as at least one of the following characteristics: poorly differentiated tumours, pT4 disease, vascular or lymphatic or perineural invasion, obstruction or perforation, and fewer than 12 lymph nodes sampled.[12]

Previous studies have shown that colon cancer survival significantly varies across Europe, with the lowest relative survival in Eastern Europe.[15,16] These differences in relative survival might be partly attributable to differences in patterns of care among European countries.

Although RCTs are considered to be the gold standard for evaluating the effectiveness of interventions, they are costly, time consuming, not always feasible, and importantly, results cannot be extrapolated to the general population.[17] Besides, RCTs in stage II colon cancer did not give conclusive evidence concerning the effectiveness of adjuvant chemotherapy so far. As an alternative, comparative effectiveness research with large, ideally population-based, datasets could provide clues for optimal treatment strategies. The aim of the present EURECCA international comparison is to compare the use of adjuvant chemotherapy and to compare relative survival of patients with stage II colon cancer between European countries.

PATIENTS AND METHODS

Patients

National datasets from the Netherlands Cancer Registry (NL), the Danish Colorectal Cancer Group database (DK), the Swedish Colorectal Cancer Registry (SE), the English National Cancer Registration Service database Cancer Analysis System (ENG), the National Cancer Registry Ireland (IE), and the Belgian Cancer Registry (BE) were included. Moreover, we obtained single-centre data from the Hospital of Lithuanian University of Health Sciences Kaunas Clinics (LT).

We selected all patients with stage II colon cancer (ICD-10 C18), who were diagnosed between 2004 and 2009, except for patients from SE who were diagnosed between 2007 and 2009. All patients were surgically treated with curative intent.

We collected information on gender, age, year of incidence, TNM stage, tumour grade, use of adjuvant chemotherapy, and vital status at date of last follow-up. Age was categorised as <65 years, 65-74 years, and ≥75 years. The information on tumour stage was based on pathological reports (pTNM). If pathology data were missing, clinical tumour stage was used. The TNM classification 5th or 6th edition was used for staging. Stage was subclassified as IIA (T3N0M0; tumour invades through the muscularis propria into the subserosa or into non-peritonealised pericolic tissue, no regional lymph node metastasis, no distant metastasis) or IIB (T4N0M0; tumour directly invades other organs or structures, and/or perforates visceral peritoneum, no regional lymph node metastasis, no distant metastasis). No substage was available for England. Tumour grade was classified as grade I (well differentiated), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated/anaplastic). Adjuvant chemotherapy was defined as 'no' or 'yes'. For England, adjuvant treatment was defined as yes if a patient had surgery followed by chemotherapy, and as 'unknown' if a patient had surgery and no record of receiving chemotherapy after surgery, due to incomplete data on treatment.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier method.[18] The analyses were done for all patients with stage II colon cancer, as well as stratified by stage (IIA, IIB) excluding England.

We performed crude and adjusted logistic regression models to compare the proportion of adjuvant chemotherapy between the countries. Time of follow-up was calculated from date of surgery until death, or until end of follow-up (censored). Relative survival was calculated by the Ederer II method[19] as the ratio of the survival observed among

the patients with stage II colon cancer and the survival that would have been expected based on the corresponding general population (matched by country, age, gender, and year of diagnosis). National life tables from www.mortality.org were used to estimate expected survival. Relative Excess Risks (RERs) of death were estimated using an adjusted generalised linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. The country with the lowest proportion of patients receiving adjuvant chemotherapy was used as reference category.

Countries with national data were compared: NL, DK, SE, ENG, IE, and BE. Single-centre data from LT were used to describe patient characteristics and the proportion of patients receiving adjuvant chemotherapy, but not to calculate relative survival.

The analyses were adjusted for potential confounders: gender, age (continuous), and year of incidence. No information on tumour grade was available for DK. Therefore, we did not adjust for tumour grade in the adjusted logistic regression models used to compare the proportion of patients receiving adjuvant chemotherapy between the countries. However, we adjusted for tumour grade in the relative survival analysis for all countries with national data except DK.

Sensitivity analysis was performed including patients who were diagnosed between 2007 and 2009.

A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 and STATA SE 12.0.

RESULTS

In total, 59,154 patients were included; 14,217 patients from NL, 4,575 patients from DK, 3,467 patients from SE, 26,075 patients from ENG, 2,415 patients from IE, 8,232 patients from BE, and 203 patients from LT. Patient and tumour characteristics are listed in Table 1. Median follow-up was 6.7 years (IQR 5.1-8.3).

Stage II colon cancer

Figure 1a shows the proportion of patients receiving adjuvant chemotherapy and the adjusted RERs by country. The proportion of patients receiving adjuvant chemotherapy varied from 7.1% in NL to 29.0% in BE (adjusted p<0.001). No clear linear pattern was observed between adjuvant chemotherapy and adjusted RERs of death.

Table 1. Patient characteristics

	Netherlands (*n* = 14,217)	Denmark (*n* = 4,575)	Sweden (*n* = 3,467)	England (*n* = 26,075)	Ireland (*n* = 2,415)	Belgium (*n* = 8,232)	Lithuania (*n* = 203)
Gender							
Male	7,095 (49.9)	2,293 (50.1)	1,691 (48.8)	13,668 (52.4)	1,337 (55.4)	4,123 (50.1)	103 (50.7)
Female	7,122 (50.1)	2,282 (49.9)	1,776 (51.2)	12,407 (47.6)	1,078 (44.6)	4,109 (49.9)	100 (49.3)
Age (years)							
<65	3,528 (24.8)	1,025 (22.4)	728 (21.0)	5,771 (22.1)	695 (23.8)	1,746 (21.2)	66 (32.5)
65-74	4,328 (30.4)	1,471 (32.2)	969 (27.9)	7,874 (30.2)	718 (29.7)	2,329 (28.3)	73 (36.0)
≥75	6,361 (44.7)	2,079 (45.4)	1,770 (51.1)	12,430 (47.7)	1,002 (41.5)	4,157 (50.5)	64 (31.5)
Year of incidence							
2004	2,265 (15.9)	757 (16.5)	0 (0.0)	3,654 (14.0)	366 (15.2)	1,241 (15.1)	33 (16.3)
2005	2,271 (16.0)	738 (16.1)	0 (0.0)	4,191 (16.1)	385 (15.9)	1,279 (15.5)	37 (18.2)
2006	2,321 (16.3)	792 (17.3)	0 (0.0)	4,393 (16.8)	376 (15.6)	1,352 (16.4)	35 (17.2)
2007	2,354 (16.6)	748 (16.3)	1,160 (33.5)	4,555 (17.5)	412 (17.1)	1,459 (17.7)	33 (16.3)
2008	2,440 (17.2)	775 (16.9)	1,140 (32.9)	4,653 (17.8)	423 (17.5)	1,432 (17.4)	34 (16.7)
2009	2,566 (18.0)	765 (16.7)	1,167 (33.7)	4,629 (17.8)	453 (18.8)	1,469 (17.8)	31 (15.3)
TNM stage							
IIA	12,251 (86.2)	3,838 (83.9)	2,967 (85.6)	0 (0.0)	1,846 (76.4)	6,905 (83.9)	170 (83.7)
IIB	1,966 (13.8)	737 (16.1)	500 (14.4)	0 (0.0)	569 (23.6)	1,327 (16.1)	33 (16.3)
Stage II	0 (0.0)	0 (0.0)	0 (0.0)	26,075 (100.0)	0 (0.0	0 (0.0)	0 (0.0)
Tumour grade							
I	1,154 (8.1)	0 (0.0)	619 (17.9)	1,376 (5.3)	141 (5.8)	1,319 (16.0)	24 (11.8)
II	9,920 (69.8)	0 (0.0)	2,462 (71.0)	20,463 (78.5)	1,860 (77.0)	4,792 (58.2)	143 (70.4)
III	2,127 (15.0)	0 (0.0)	251 (7.2)	3,289 (12.6)	276 (11.4)	1,099 (13.4)	35 (17.2)
IV	1 (0.0)	0 (0.0)	0 (0.0)	22 (0.1)	3 (0.1)	31 (0.4)	1 (0.5)
Unknown	1,015 (7.1)	4,575 (100.0)	135 (3.9)	925 (3.5)	135 (5.6)	991 (12.0)	0 (0.0)

Data are presented as *n* (%)

Five-year relative survival with 95% confidence intervals (CI's) are listed in Table 2. Compared with NL, a better relative survival was observed in SE as demonstrated by a RER of 0.53 (95% CI 0.44-0.64; p<0.001), and BE (RER 0.84, 95% CI 0.76-0.92; p<0.001) after adjustment for potential confounders (Figure 1a; Table 2).

Sensitivity analysis including patients diagnosed between 2007 and 2009 showed similar results except for BE (adjusted RER 0.88, 95% CI 0.76-1.01; p=0.06). Compared with NL, a better relative survival was observed in SE (adjusted RER 0.56, 95% CI 0.46-0.69; p<0.001).

Stage IIA colon cancer

The proportion of patients with stage IIA colon cancer receiving adjuvant chemotherapy ranged from 4.7% in NL to 25.1% in BE (adjusted p<0.001), whereas we did not observe a clear linear pattern between the use of adjuvant chemotherapy and adjusted relative survival expressed by RERs (Figure 1b).

Five-year relative survival, as well as crude and adjusted RERs, is listed in Table 2. Compared with NL, a better adjusted relative survival was observed in SE (RER 0.45, 95% CI 0.34-0.61; p<0.001), IE (RER 0.80, 95% CI 0.65-0.98; p=0.03), and BE (RER 0.80, 95% CI 0.71-0.90; p<0.001).

Sensitivity analysis showed an adjusted RER of 0.76 (95% CI 0.59-0.97; p=0.03) for DK, an adjusted RER of 0.73 (95% CI 0.51-1.03; p=0.07) for IE, and an adjusted RER of 0.45 (95% CI 0.34-0.61; p<0.001) for SE compared with NL.

Stage IIB colon cancer

The proportion of patients with stage IIB receiving adjuvant chemotherapy varied between 22.4% in NL and 49.4% in BE (adjusted p<0.001). Again, no clear linear pattern was observed between use of adjuvant chemotherapy and adjusted RERs (Figure 1c).

Table 2 lists the 5-year relative survival and crude and adjusted RERs. We observed a better adjusted relative survival in SE (RER 0.76, 95% CI 0.59-0.97; p=0.03) and BE (RER 0.84, 95% CI 0.73-0.98; p=0.02), both compared with NL.

Sensitivity analysis showed an adjusted RER of 0.78 (95% CI 0.71-1.19; p=0.07) for SE compared with NL, and an adjusted RER of 0.96 (95% CI 0.78-1.18; p=0.70) for BE compared with NL.

Table 2. Five-year relative survival and crude and adjusted Relative Excess Risks (RERs) of death, 2004-2009

	5-yr relative survival	95% CI	Crude RER	95% CI	p-value	Adjusted RER*	95% CI	p-value
					Stage II			
The Netherlands	83.64%	(82.62-84.36%)	1	(reference)		1	(reference)	
Denmark	84.61%	(82.78-86.39%)	0.97	(0.86-1.09)	0.65	0.93**	(0.83-1.04)	0.21
Sweden	89.13%	(86.35-91.76%)	0.46	(0.37-0.58)	<0.001	0.53	(0.44-0.64)	<0.001
England	83.83%	(83.10-84.55%)	0.99	(0.92-1.06)	0.67	1.02	(0.96-1.09)	0.53
Ireland	83.03%	(80.56-85.39%)	0.99	(0.86-1.15)	0.92	1.03	(0.90-1.18)	0.68
Belgium	84.31%	(82.93-85.65%)	0.91	(0.82-1.01)	0.07	0.84	(0.76-0.92)	<0.001
					Stage IIA			
The Netherlands	86.67%	(85.59-87.72%)	1	(reference)		1	(reference)	
Denmark	88.21%	(86.24-90.10%)	0.94	(0.81-1.10)	0.43	0.89**	(0.77-1.03)	0.11
Sweden	92.19%	(89.22-94.96%)	0.38	(0.27-0.53)	<0.001	0.45	(0.34-0.61)	<0.001
Ireland	89.38%	(86.65-91.95%)	0.79	(0.63-0.98)	0.04	0.80	(0.65-0.98)	0.03
Belgium	88.02%	(86.55-89.46%	0.85	(0.75-0.97)	0.02	0.80	(0.71-0.90)	<0.001
					Stage IIB			
The Netherlands	64.80%	(61.96-67.58%)	1	(reference)		1	(reference)	
Denmark	65.68%	(60.82-70.36%)	0.95	(0.80-1.14)	0.61	0.93**	(0.78-1.10)	0.39
Sweden	70.63%	(62.64-77.99%)	0.65	(0.51-0.84)	0.001	0.76	(0.59-0.97)	0.03
Ireland	62.33%	(56.98-67.46%)	1.02	(0.85-1.22)	0.85	1.10	(0.92-1.32)	0.29
Belgium	64.81%	(61.19-68.43%)	0.94	(0.81-1.08)	0.37	0.84	(0.73-0.98)	0.02

* Adjusted for gender, age, year of incidence, grade

** Adjusted for gender, age, year of incidence

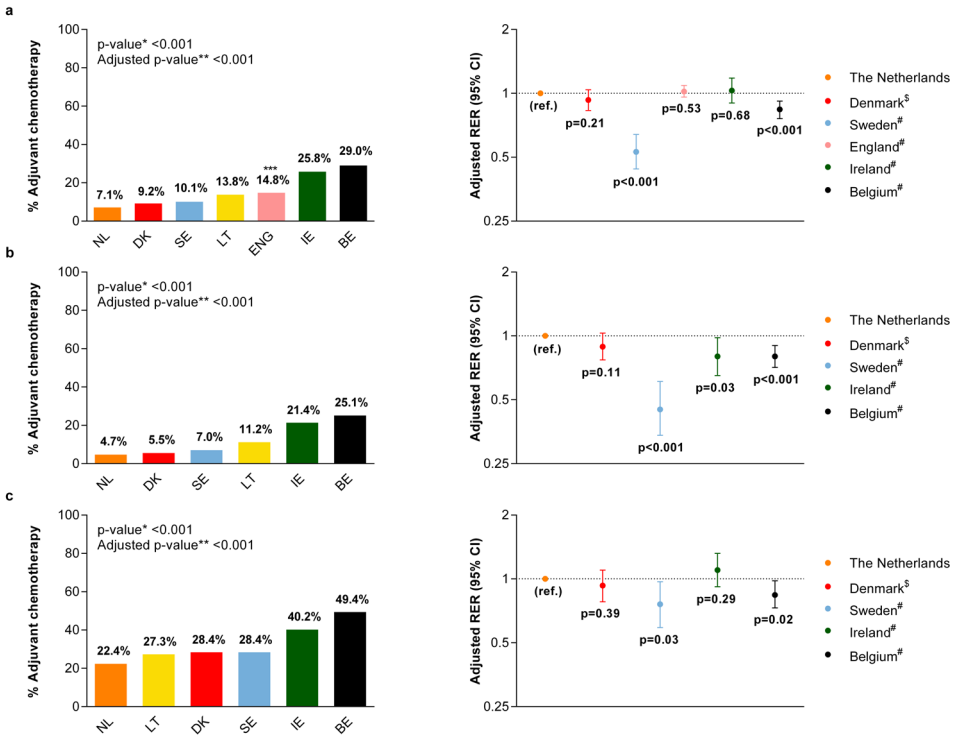


Figure 1. Proportion of patients receiving adjuvant chemotherapy and adjusted Relative Excess Risks (RERs) of death by country for patients with a. stage II colon cancer, b. stage IIA colon cancer, c. stage IIB colon cancer, 2004-2009

* p-value for comparison of NL, DK, SE, ENG, IE, and BE

** p-value for comparison of NL, DK, SE, ENG, IE, and BE adjusted for gender, age, and year of incidence

*** Unknown if remaining proportion is treated with adjuvant chemotherapy

$ Adjusted for gender, age, and year of incidence (not for grade because grade is missing for all patients in Denmark)

\# Adjusted for gender, age, year of incidence, and grade

DISCUSSION

This study shows a large variation in the proportion of patients with stage II colon cancer receiving adjuvant chemotherapy between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. No clear linear pattern between adjuvant chemotherapy and adjusted relative survival was observed. However, both Sweden and Belgium showed an improved adjusted relative survival compared with the Netherlands. In addition, Ireland showed an improved adjusted relative survival compared with the Netherlands in patients with stage IIA disease.

The benefits of adjuvant fluoropyrimidine-based chemotherapy have been clearly demonstrated for patients with stage III colon cancer.[3-7] The MOSAIC trial found an improvement of 7.5% in 5-year disease-free survival and approximately 4% in 6-year overall survival with the addition of oxaliplatin to 5-FU/LV (FOLFOX) among patients with stage III colon cancer.[9] Moreover, the NSABP C-07 trial also demonstrated a benefit from the addition of oxaliplatin to 5-FU/LV for disease-free survival, although no significant benefit for overall survival was found.[8] Oxaliplatin combined with capecitabine showed similar results as oxaliplatin combined with 5-FU/LV.[10] As a result of these studies, oxaliplatin combined with capecitabine or 5-FU/LV is nowadays standard in the adjuvant treatment of stage III colon cancer.[10-12]

For patients with stage II colon cancer, the role of adjuvant chemotherapy remains unproven. Several trials enrolled both patients with stage II and stage III disease, although the number of patients with stage II disease was much smaller than with stage III disease. Remarkably, most of these studies found a survival benefit of adjuvant chemotherapy in patients with stage III disease only. In a systematic review and meta-analysis, a better disease-free survival was found in patients with stage II colon cancer who were treated with adjuvant chemotherapy, while no improvement in overall survival was found.[13] On the contrary, a Dutch trial demonstrated improved overall survival for both stage II and stage III disease.[20]

However, medical care has evolved since the above-mentioned trials have been performed. Over time, this has led to better outcomes for patients with colon cancer.[15] These better outcomes could be partly attributed to adjuvant chemotherapy, but also to other factors such as improved preoperative staging, surgery, pathology, and perioperative care.[21-24] Furthermore, stage migration may have occurred. Therefore, the absolute benefit of adjuvant chemotherapy under current circumstances is not known.

According to the ESMO Clinical Practice Guidelines, adjuvant chemotherapy should not be routinely administered to all patients with stage II colon cancer, but could be considered in patients with high-risk stage II colon cancer.[25] All countries included in this international comparison have incorporated this recommendation in their national guidelines. It is remarkable, as shown in our study, that the proportion of patients receiving adjuvant chemotherapy varies largely between these countries. This emphasises the variation in country-specific interpretation and considerations whether or not to start treatment. Moreover, the routine to identify high-risk patients may have been implemented differently among the countries. Further, patients' reluctance to receive adjuvant chemotherapy may also vary across countries. Interestingly, a recent study by Verhoeff et al. including patients with high-risk stage II colon cancer showed that patients with pT4 disease were more likely to receive adjuvant chemotherapy compared with patients with

two or more high-risk factors, while patients with emergency surgery only, <10 lymph nodes evaluated only, or poor/undifferentiated grade only were less likely to receive adjuvant chemotherapy compared with patients with two or more risk factors. Moreover, patients aged <70 years, patients with a tumour in the distal colon, patients diagnosed in a more recent time period, and patients with less than two comorbid diseases more often received adjuvant chemotherapy.[26]

Although survival of patients with colorectal cancer in Europe improved markedly over the past years, there are still significant differences in relative survival across Europe.[15,16] However, these studies lacked information on for example TNM stage and treatment. Several possibilities to explain the differences in survival have previously been suggested. These include demographic differences, differences in lifestyle, screening or diagnostic procedures, stage at diagnosis, health-care systems, and differences in access to or use of effective treatment options.[16]

In the current study, no clear linear pattern between adjuvant chemotherapy and relative survival was observed. However, we found that Sweden had a much better relative survival compared with the Netherlands. Since we obtained data from Sweden for patients diagnosed between 2007 and 2009, we performed a sensitivity analysis including patients diagnosed between 2007 and 2009. These results also showed a better relative survival in Sweden for stage II (IIA and IIB together) and stage IIA, but the relative survival did not significantly differ for stage IIB disease. Relative survival differences between Sweden and the Netherlands cannot solely be explained by the small difference in the use of adjuvant chemotherapy. The focus on improved colon cancer treatment on a national level since 2004-2005 in Sweden, including better preoperative work-up, improved surgery with the concept of Complete Mesocolic Excision, less acute resections, and better pathology might at least partly explain the differences.[27] Moreover, other factors, not measured here, such as differences in health-care system will also play a role.

A better adjusted relative survival was also found for Belgium compared with the Netherlands, except for stage IIB disease in the sensitivity analysis. On a scale from a low to a high proportion of patients receiving adjuvant chemotherapy, the Netherlands and Belgium are two extremes. The large differences in adjuvant treatment might still partly contribute to the differences in relative survival between the Netherlands and Belgium, although we found no clear linear pattern between adjuvant chemotherapy and relative survival.

Previous comparative studies showed relatively low survival for the United Kingdom.[15,16] However, in our study we did not observe this for England. It has been suggested that the relatively low survival in the United Kingdom could be due to late detection and diagnosis,

access to treatment, especially to surgical treatment, and health inequalities.[28,29] Given that we selected patients with stage II colon cancer who were surgically treated with curative intent might be an explanation why we did not observe a worse relative survival for England. Moreover, it might be that England has different outcomes than the rest of the United Kingdom, although England comprises most of the area of the United Kingdom.

This study has some limitations. There might be unknown differences in data registration between the countries and completeness of vital follow-up. Although we adjusted the analyses for potential confounders, residual confounding by unmeasured factors cannot be entirely excluded due to the retrospective design of the study. For example, it is unknown what role differences in health-care systems between European countries play. Moreover, we had no detailed information on vascular or lymphatic or perineural invasion, obstruction or perforation, number of lymph nodes sampled, type or dose of chemotherapy, toxicity, chemotherapy compliance, comorbidity, life-style factors, performance, and quality of life, among others. As also stated by Storm et al, these variables should ideally be included in national population-based datasets to do more detailed analysis and to improve comparability between countries.[30]

On the other hand, this study is unique in comparing both treatment and relative survival between European countries for a specific disease stage. Furthermore, we used a large dataset with almost 60,000 patients from seven countries. Importantly, national data covering the whole population were obtained for six of these countries. Single-centre data from Lithuania were used to describe the proportion of patients receiving adjuvant chemotherapy, but not for relative survival analyses because these data might not be representative of the whole Lithuanian population.

In conclusion, the present population-based study, comparing both the use of adjuvant chemotherapy and relative survival of patients with stage II colon cancer between seven European countries, showed large differences in the proportion of patients receiving adjuvant chemotherapy. Moreover, no clear linear pattern between the use of adjuvant chemotherapy and relative survival was observed. Our findings should be a strong recommendation for further research into selection criteria for adjuvant chemotherapy. This could eventually lead to individually tailored, optimal treatment of patients with stage II colon cancer.

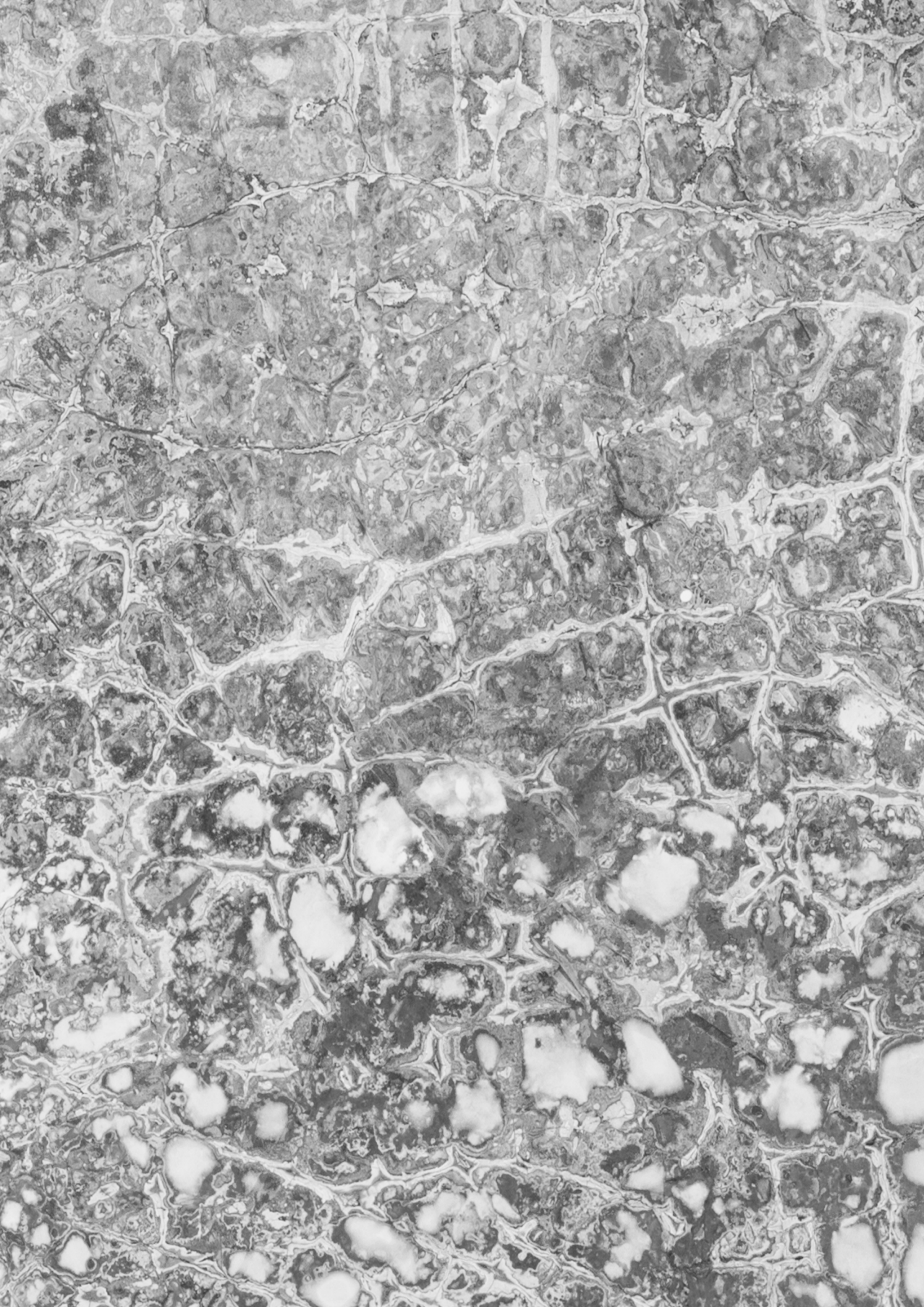
ACKNOWLEDGEMENTS

The authors thank the registration teams of the Comprehensive Cancer Centre Netherlands, the Danish Colorectal Cancer Group, the Swedish Colorectal Cancer Registry, National Cancer Registration Service Public Health England, the National Cancer Registry Ireland, the Belgian Cancer Registry, and the Hospital of Lithuanian University of Health Sciences Kaunas Clinics for the collection of data for the registries. We would like to thank dr. A.J.M. de Craen† for discussing the results.

REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**(6): 1374-403.
2. Registry NC. http://cijfersoverkanker.nl/selecties/Dataset_1/img559e9911e8351. *Accessed November* 2015.
3. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**(6): 352-8.
4. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005; **23**(34): 8671-8.
5. investigators IMPAoCCTI. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995; **345**(8955): 939-44.
6. 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**(1): 246-50.
7. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
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**(28): 3768-74.
9. André 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**(19): 3109-16.
10. Schmoll HJ, Twelves C, Sun W, et al. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. *Lancet Oncol* 2014; **15**(13): 1481-92.
11. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012; **23**(10): 2479-516.
12. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi64-vi72.
13. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. *Cochrane Database Syst Rev* 2008; (3): CD005390.
14. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 2015; **30**(2): 205-12.
15. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer* 2015.
16. Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *BMJ* 2015; **351**: h4970.
17. Sullivan P, Goldmann D. The promise of comparative effectiveness research. *JAMA* 2011; **305**(4): 400-1.
18. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**(4): 343-6.
19. Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. *Eur J Cancer* 2011; **47**(14): 2202-10.
20. Taal BG, H. VT, Zoetmulder FA, group N. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *Br J Cancer* 2001; **85**(10): 1437-43.
21. van Steenbergen LN, Elferink MA, Krijnen P, et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol* 2010; **21**(11): 2206-12.
22. 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**(4): 354-64.
23. Bertelsen CA, Neuenschwander AU, Jansen JE, et al. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol* 2015; **16**(2): 161-8.
24. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; **383**(9927): 1490-502.
25. Van Cutsem EJ, Kataja VV. ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and

follow-up of colon cancer. *Ann Oncol* 2005; **16 Suppl 1**: i16-i7.
26. Verhoeff SR, van Erning FN, Lemmens VE, de Wilt JH, Pruijt JF. Adjuvant chemotherapy is not associated with improved survival for all high risk factors in stage II colon cancer. *Int J Cancer* 2016.
27. Bernhoff R, Martling A, Sjövall A, Granath F, Hohenberger W, Holm T. Improved survival after an educational project on colon cancer management in the county of Stockholm--a population based cohort study. *Eur J Surg Oncol* 2015; **41**(11): 1479-84.
28. Gatta G, Capocaccia R, Sant M, et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. *Gut* 2000; **47**(4): 533-8.
29. Oncology TL. Is UK cancer care broken? *Lancet Oncol* 2015; **16**(13): 1273.
30. Storm HH, Engholm G, Pritzkuleit R, et al. Less pitfalls and variation in population based cancer survival comparisons within the European Union: Lessons from colorectal cancer patients in neighbouring regions in Denmark and Germany - The Fehmarn Belt project. *Eur J Cancer* 2015; **51**(9): 1188-98.



8

Oncologic treatment strategies and relative survival of patients with stage I-III rectal cancer - a EURECCA international comparison between the Netherlands, Belgium, Denmark, Sweden, England, Ireland, Spain, and Lithuania

A.J. Breugom
E. Bastiaannet
P.G. Boelens
E. Van Eycken
L.H. Iversen
A. Martling
R. Johansson
T. Evans
S. Lawton
K.M. O'Brien
H. Ortiz
R. Janciauskiene
O.M. Dekkers
H.J.T. Rutten
G.J. Liefers
V.E.P.P. Lemmens
C.J.H. van de Velde

European Journal of Surgical Oncology. 2018 Sep;44(9):1338-1343.

ABSTRACT

Introduction

The aim of this EURECCA international comparison is to compare oncologic treatment strategies and relative survival of patients with stage I-III rectal cancer between European countries.

Material and methods

Population-based national cohort data from the Netherlands (NL), Belgium (BE), Denmark (DK), Sweden (SE), England (ENG), Ireland (IE), Spain (ES), and single-centre data from Lithuania (LT) were obtained. All operated patients with (y)pTNM stage I-III rectal cancer diagnosed between 2004 and 2009 were included. Oncologic treatment strategies and relative survival were calculated and compared between neighbouring countries.

Results

We included 57,120 patients. Treatment strategies differed between NL and BE ($p<0.001$), DK and SE ($p<0.001$), and ENG and IE ($p<0.001$). More preoperative radiotherapy as single treatment before surgery was administered in NL compared with BE (59.7% vs. 13.1%), in SE compared with DK (55.1% vs. 10.4%), and in ENG compared with IE (15.2% vs. 9.6%). Less postoperative chemotherapy was given in NL (9.6% vs. 39.1%), in SE (7.9% vs. 14.1%), and in IE (12.6% vs. 18.5%) compared with their neighbouring country. In ES, 55.1% of patients received preoperative chemoradiation and 62.3% postoperative chemotherapy.

There were no significant differences in relative survival between neighbouring countries.

Conclusion

Large differences in oncologic treatment strategies for patients with (y)pTNM I-III rectal cancer were observed across European countries. No clear relation between oncologic treatment strategies and relative survival was observed. Further research into selection criteria for specific treatments could eventually lead to individualised and optimal treatment for patients with non-metastasised rectal cancer.

Funding

EURECCA was funded by the European Society of Surgical Oncology (ESSO). The funding source had no role in the study design, data collection, analysis, interpretation of the data, writing of the manuscript, or the decision to publish.

INTRODUCTION

Colorectal cancer is one of the most common cancers in Europe, with a total of 447,000 new cases and 215,000 deaths estimated to have occurred in 2012.[1] Rectal cancer accounts for approximately one third of all colorectal cancers.

The introduction of total mesorectal excision (TME) in rectal cancer treatment has led to substantial improvements in locoregional recurrence rates and survival.[2,3] The addition of preoperative short-course radiotherapy to TME further decreased the local recurrence rate by more than 50% compared with TME alone, although no overall survival benefit was demonstrated.[4] For patients with locally advanced rectal cancer, preoperative chemoradiation followed by TME became the standard treatment.[5-8] The role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME has been extensively debated over the past years. Whereas adjuvant chemotherapy has been shown to be effective in patients treated without preoperative treatment, there is currently no clear scientific evidence to support the use of adjuvant fluorouracil-based chemotherapy after preoperative (chemo)radiotherapy and TME.[9-11]

Although survival of patients with colorectal cancer improved over the past years, rectal cancer survival still varies across Europe, with Eastern Europe having the lowest relative survival rates.[12] Survival differences might be explained by several factors, such as differences in demographics, socioeconomic status, lifestyle, screening or diagnostic procedures, stage at diagnosis, and health-care systems. Moreover, these differences might be attributable to differences in access to effective treatment or differences in patterns of care among countries.[13]

Randomised controlled trials (RCTs) are the gold standard to evaluate treatment effectiveness. However, RCTs tend to be expensive, slow, not always feasible, and strict inclusion criteria limit generalisability of the results.[14] Alternatively, comparative effectiveness research with large, ideally population-based datasets can provide evidence for optimal treatment strategies.

The aim of the present EURECCA international comparison is to compare oncologic treatment strategies and to compare relative survival of patients with stage I-III rectal cancer between European countries.

PATIENTS AND METHODS

Patients

We included national datasets selected from the Netherlands Cancer Registry (NL), the Belgian Cancer Registry (BE), the Danish Colorectal Cancer Group database (DK), the Swedish Colorectal Cancer Registry (SE), the English National Cancer Registration Service database Cancer Analysis System (ENG), the National Cancer Registry Ireland (IE) and selected all patients with (y)pTNM stage I-III rectal cancer (ICD-10 C20), who were diagnosed between 2004 and 2009 and who were surgically treated with curative intent. Besides, we obtained data from the Spanish Rectal Cancer Project (ES) including 103 out of 261 hospitals in Spain, and single-centre data from the Hospital of Lithuanian University of Health Sciences Kaunas Clinics (LT). Guidelines regarding preoperative and postoperative treatment strategies differ between these countries (Supplementary table 1).

We collected information on gender, age, year of diagnosis, (y)pTNM stage, tumour grade, preoperative treatment, postoperative treatment, and vital status at date of last follow-up. Age was categorised as <65 years, 65-74 years, and ≥75 years. Information on tumour stage was based on pathological reports. Clinical TNM stage was not available for some countries and missing for a substantial part in other countries, so stratification by cTNM stage was not possible. Preoperative treatment was defined as none, radiotherapy, chemoradiation, or unknown. Postoperative treatment was defined as none, chemotherapy, radiotherapy, chemoradiation, or unknown. For Sweden, postoperative treatment was complete for 2004-2006. For England, preoperative and postoperative treatment were defined as yes if a patient had received preoperative or postoperative treatment, and as unknown if a patient had surgery and no record of receiving preoperative or postoperative treatment, as a result of incomplete data.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier method.[15] For countries with national data, the analyses were compared side-by-side for neighbouring countries. Data from ES and single-centre data from LT were used for descriptive analyses, and not compared with another country. All (y)pTNM stages were analysed together. Stratification by (y)pTNM substage was not possible due to different guideline recommendations regarding preoperative treatment strategies.

The proportion of patients receiving different types of preoperative and postoperative treatment was calculated and compared with the chi-square test. Time of follow-up was calculated from date of diagnosis until death, or until end of follow-up (censored). Relative survival was calculated by the Ederer II method as the ratio of survival observed

among the patients with stage I-III rectal cancer and the survival that would have been expected based on the corresponding general population (matched by country, age, gender, and year of diagnosis). National life tables from www.mortality.org were used to estimate expected survival. Relative Excess Risks (RERs) of death were estimated using an adjusted generalised linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Crude and adjusted RERs were calculated. We adjusted for the following potential confounders: gender, age (as a continuous variable), year of diagnosis, and tumour grade. For the comparison DK-SE, we did not adjust for tumour grade because this information was not available for DK.

A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 and STATA SE 12.0.

RESULTS

Overall, 56,878 patients were included; 11,768 patients from NL, 8,230 patients from BE, 4,761 patients from DK, 6,673 patients from SE, 20,991 patients from ENG, 1,689 patients from IE, 2,435 patients from ES, and 331 patients from LT. Table 1 shows patient and tumour characteristics. Median follow-up was 6.5 years (IQR 5.0-8.1).

Treatment strategies and relative survival for the Netherlands and Belgium
Figure 1a shows the treatment strategies, as well as the crude and adjusted relative survival for patients from NL and BE. Preoperative treatment strategy differed between NL and BE (p<0.001), with more radiotherapy as single treatment before surgery (59.7% vs. 13.1%) and less chemoradiation (19.1% vs. 38.9%) in NL compared with BE. Postoperative treatment strategy also differed between NL and BE, with more often no postoperative treatment (88.0% vs. 53.4%) and less often chemotherapy (9.6% vs. 39.1%) in NL compared with BE (p<0.001 for comparison postoperative treatment strategy NL-BE).

Five-year relative survival was 80.96% (95% CI 79.94-81.96%) in NL and 78.96% (95% CI 77.68-80.20%) in BE (Figure 2). After adjustment for potential confounders, no differences in relative survival were observed (RER 1.05, 95% CI 0.97-1.14; p=0.25, Figure 1a).

Treatment strategies and relative survival for Denmark and Sweden
Treatment strategies and relative survival for patients from DK and SE are shown in Figure 1b. In DK, a lower proportion of patients received preoperative radiotherapy as single treatment before surgery (10.4% vs. 55.1%), while a higher proportion of patients received chemoradiation (20.9% vs. 10.0%) compared with SE (p<0.001 for comparison

Table 1. Patient characteristics

	Netherlands (*n* = 11,768)	Belgium (*n* = 8,230)	Denmark (*n* = 4,761)	Sweden (*n* = 6,673)	England (*n* = 20,991)	Ireland (*n* = 1,689)	Spain (*n* = 2,435)	Lithuania (*n* = 331)
Gender								
Male	7,096 (60.3)	4,945 (60.1)	2,896 (60.8)	3,985 (59.7)	13,456 (64.1)	1,121 (66.4)	1,604 (65.9)	202 (61.0)
Female	4,672 (39.7)	3,285 (39.9)	1,865 (39.2)	2,688 (40.3)	7,535 (35.9)	568 (33,6)	831 (34.1)	129 (39.0)
Age (years)								
<65	4,818 (40.9)	2,888 (35.1)	1,754 (36.8)	2,212 (33.1)	7,339 (35.0)	712 (42.2)	930 (38.2)	113 (34.1)
65-74	3,789 (32.2)	2,562 (31.1)	1,609 (33.8)	2,110 (31.6)	7,180 (34.2)	542 (32.1)	742 (30.5)	131 (39.6)
≥75	3,161 (26.9)	2,780 (33.8)	1,398 (29.4)	2,351 (35.2)	6,472 (30.8)	435 (25.8)	763 (31.3)	87 (26.3)
Year of diagnosis								
2004	1,750 (14.9)	1,216 (14.8)	768 (16.1)	1,004 (15.0)	3,291 (15.7)	267 (15.8)	0 (0.0)	68 (20.5)
2005	1,781 (15.1)	1,322 (16.1)	775 (16.3)	1,068 (16.0)	3,429 (16.3)	278 (16.5)	0 (0.0)	85 (25.7)
2006	1,900 (16.1)	1,402 (17.0)	842 (17.7)	1,074 (16.1)	3,498 (16.7)	248 (14.7)	159 (6.5)	36 (10.9)
2007	2,082 (17.7)	1,433 (17.4)	785 (16.5)	1,174 (17.6)	3,529 (16.8)	316 (18.7)	362 (14.9)	33 (10.0)
2008	2,089 (17.8)	1,452 (17.6)	793 (16.7)	1,154 (17.3)	3,560 (17.0)	290 (17.2)	694 (28.5)	60 (18.1)
2009	2,166 (18.4)	1,405 (17.1)	798 (16.8)	1,199 (18.0)	3,684 (17.6)	290 (17.2)	1220 (50.1)	49 (14.8)
(y)pTNM stage								
I	3,782 (32.1)	2,271 (27.6)	1,261 (26.5)	1,887 (28.3)	5,711 (27.2)	275 (16.3)	817 (33.6)	55 (16.6)
II	3,274 (27.8)	2,339 (28.4)	1,721 (36.1)	2,101 (31.5)	7,023 (33.5)	300 (17.8)	771 (31.7)	136 (41.1)
III	3,915 (33.3)	2,652 (32.2)	1,718 (36.1)	2,534 (38.0)	8,257 (39.3)	422 (25.0)	847 (34.8)	139 (42.0)
I-III, unspecified	797 (6.8)	968 (11.8)	61 (1.3)	151 (2.3)	0 (0.0)	692 (41.0)	0 (0.0)	1 (0.3)
Grade								
I	493 (4.2)	1,237 (15.0)	0 (0.0)	450 (6.7)	975 (4.6)	64 (3.8)	0 (0.0)	187 (56.5)
II	5,618 (47.7)	5,018 (61.0)	0 (0.0)	2,574 (38.6)	16,669 (79.4)	1,277 (75.6)	0 (0.0)	130 (39.3)
III	1,060 (9.0)	1,025 (12.5)	0 (0.0)	287 (4.3)	2,213 (10.5)	145 (8.6)	0 (0.0)	14 (4.2)
IV	0 (0.0)	22 (0.3)	0 (0.0)	0 (0.0)	16 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	4,597 (39.1)	928 (11.3)	4,761 (100.0)	3,362 (50.4)	1,118 (5.3)	203 (12.0)	2,435 (100.0)	0 (0.0)

Data are presented as *n* (%)

preoperative treatment strategy DK-SE). Postoperative treatment strategy also varied between DK and SE (p<0.001). No postoperative treatment was given in 84.3% in DK vs. 75.8% in SE, while 14.1% of patients received postoperative chemotherapy in DK compared with 7.9% in SE. In 15.8% of patients from SE information on postoperative treatment was unknown.

Five-year relative survival was 81.65% (95% CI 80.00-83.24%) in DK and 81.18% (95% CI 79.67-82.63%) in SE (Figure 2). We observed no differences in adjusted relative survival (RER 0.95, 95% CI 0.85-1.07; p=0.38, Figure 1b).

Treatment strategies and relative survival for England and Ireland

Figure 1c shows treatment strategies and relative survival for patients from ENG and IE. In ENG, 15.2% of patients received preoperative radiotherapy as single treatment before surgery, and 15.6% received preoperative chemoradiation, compared with 9.6% and 34.6%, respectively in IE (p<0.001 for comparison preoperative treatment strategy ENG-IE). In 69.1% of patients from ENG, there was no record of receiving preoperative treatment.

Postoperative treatment strategy was also different between ENG and IE (p<0.001). A higher proportion of patients from ENG received postoperative chemotherapy compared with IE (18.5% vs. 12.6%). In 77.8% of patients from ENG there was no record of receiving postoperative treatment.

Five-year relative survival was 78.26% (95% CI 77.50-79.00%) in ENG and 76.84% (95% CI 74.05-79.50%) in IE. After adjustment for potential confounders, no difference in relative survival was observed between ENG and IE (RER 1.02, 95% CI 0.90-1.16;p=0.75, Figure 1c).

Treatment strategies and relative survival for Spain and Lithuania

Supplementary table 2 shows treatment strategies and five-year relative survival for both ES and LT. In ES, 55.1% received preoperative chemoradiation and 62.3% received postoperative chemotherapy. Five-year relative survival for ES was 81.82% (95% CI 79.00-84.46%).

In LT, 11.2% of patients received preoperative radiotherapy as single treatment before surgery, and 7.9% preoperative chemoradiation. Besides, postoperative chemotherapy was given in 12.4%, and postoperative chemoradiation in 13.6% of patients. Five-year relative survival was 84.04% (95% CI 77.21-90.12%).

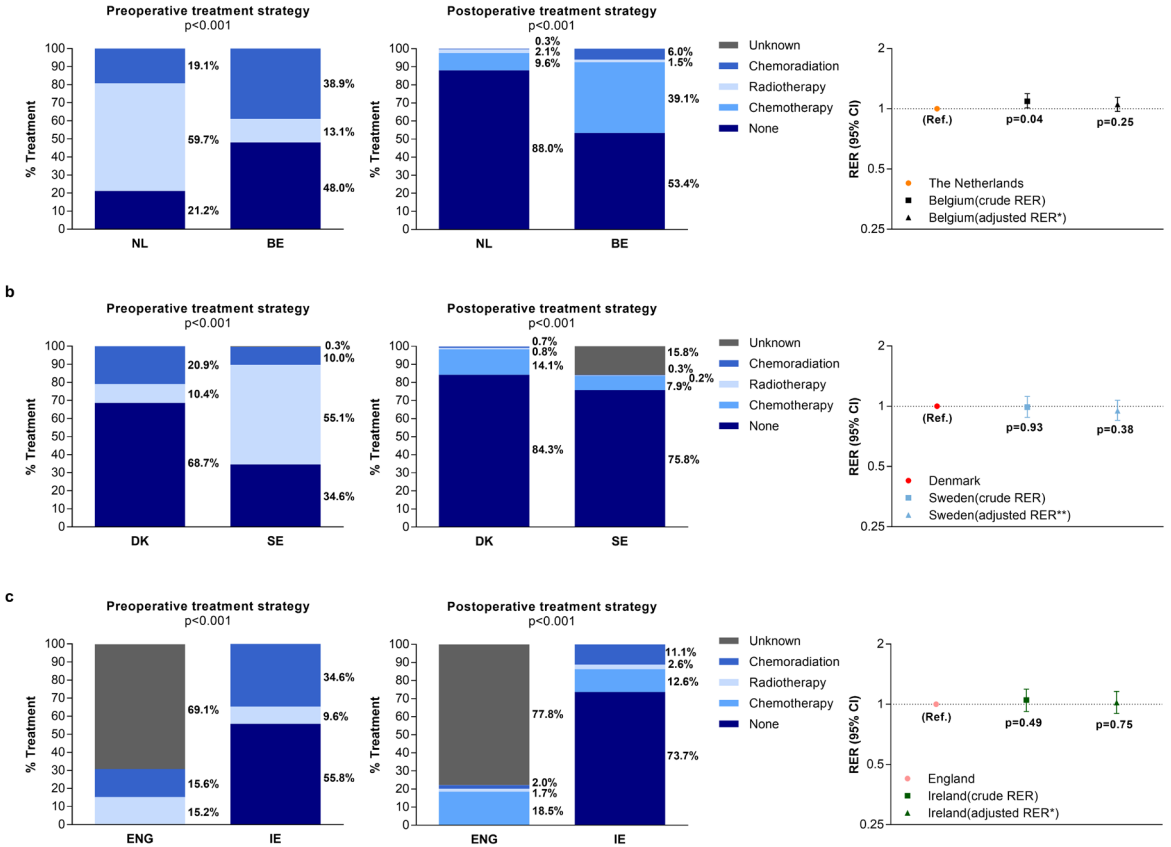


Figure 1. Treatment strategies and Relative Excess Risks (RERs) of death for a. The Netherlands and Belgium, b. Denmark and Sweden, and c. England and Ireland

* Adjusted for gender, age, year of diagnosis, grade

** Adjusted for gender, age, year of diagnosis

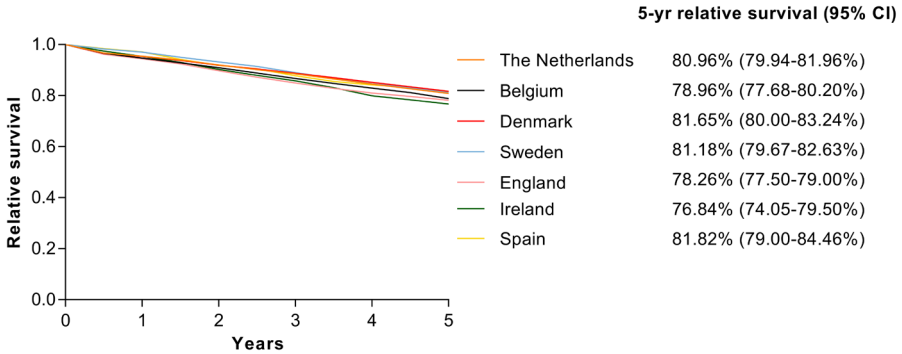


Figure 2. Relative survival

DISCUSSION

This study shows a large variation in both preoperative and postoperative oncologic treatment strategies between neighbouring countries. No differences in adjusted relative survival were observed between the Netherlands and Belgium, Denmark and Sweden, and England and Ireland. Therefore, we observed no clear relation between differences in treatment strategies and (adjusted) relative survival.

Striking differences were observed in preoperative and postoperative treatment strategies between the included European countries. More preoperative radiotherapy and less preoperative chemoradiation were given in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. In Lithuania, over eighty percent of patients received no preoperative treatment at all. Postoperative chemotherapy was more frequently administered in Belgium compared with the Netherlands, in Denmark compared with Sweden, and in England compared with Ireland. Over half of the Spanish patients received preoperative chemoradiation and about sixty percent received postoperative chemotherapy.

The observed differences in treatment strategies could at least partly be explained by differences in guidelines between the countries. Unfortunately, we were not able to compare guideline adherence with respect to preoperative treatment strategies since we had no information on clinical TNM stage, circumferential resection margin, and tumour height from the anal verge. Some guidelines have more recently been adjusted regarding pre- and postoperative treatment strategies. The Dutch guideline for example now recommends TME without preoperative treatment for patients with low risk resectable rectal cancer, defined as cT1-3N0, extramural invasion ≤5mm, and distance to the mesorectal fascia (MRF) of >1mm. For patients with intermediate risk resectable

rectal cancer (cT1-3N1 or cT3N0 with extramural invasion >5 mm, distance to the MRF >1 mm) preoperative short-course radiotherapy should be considered. Preoperative chemoradiation followed by TME is the standard of care for patients with high risk rectal cancer (cT3 with distance to the MRF ≤1 mm or cT4, and/or high probability of four or more positive lymph nodes in the mesorectum or positive lymph nodes outside the mesorectum on MRI.[16]

In addition, there are differences in guideline recommendations for postoperative chemotherapy, ranging from not recommending postoperative chemotherapy to recommending postoperative chemotherapy for patients with postoperative stage II and III disease. These guideline differences are reflected in our results.

The variation in guidelines and patterns of care regarding postoperative chemotherapy could be explained by inconclusive evidence on the effectiveness of postoperative chemotherapy after preoperative (chemo)radiotherapy and TME for patients with rectal cancer during the time period represented in the present study. In a systematic review and meta-analysis by Petersen and colleagues, a total of 21 eligible RCTs between 1975 and 2011 were identified. Patients who received adjuvant chemotherapy had improved overall survival (HR=0.83, 95% CI 0.76-0.91) and disease-free survival (HR=0.75, 95% CI 0.68-0.83) compared with patients who did not receive postoperative chemotherapy.[10] However, the majority of included studies were performed in patients who were surgically treated without preoperative treatment. Only two studies in this meta-analysis included patients who received preoperative (chemo)radiotherapy. First, the EORTC 22921 study showed no significant effect on overall survival and disease-free survival of the addition of fluorouracil-based postoperative chemotherapy after preoperative (chemo) radiotherapy in patients with clinical stage T3 or T4 resectable rectal cancer.[8] Second, the QUASAR study demonstrated a borderline significant improvement in overall survival for patients with rectal cancer treated with postoperative chemotherapy, but only a minority of these patients received preoperative radiotherapy.[17]

Interestingly, more recently published studies assessing the effectiveness of postoperative chemotherapy after preoperative (chemo)radiotherapy and surgery did not demonstrate a benefit of fluorouracil-based adjuvant chemotherapy regarding overall survival, disease-free survival, or distant recurrences.[9,11] During the accrual period of these trials there was no clear evidence of the advantage of combination chemotherapy over fluoropyrimidine monotherapy.[18,19] In a phase 2 study by Hong and colleagues, it was found that postoperative treatment with FOLFOX improved disease-free survival compared with fluorouracil and leucovorin in patients with ypTNM stage II or III rectal cancer.[20] Moreover, the German CAO/ARO/AIO-04 study also showed a significant improvement in disease-free survival with the addition of

oxaliplatin to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy in patients with clinically staged T3-4 or node positive rectal cancer, though no overall survival benefit was demonstrated.[21] However, both studies did not compare combination chemotherapy with observation. Therefore, the question whether postoperative combination chemotherapy results in better outcomes than observation remains unanswered.

Differences in patterns of care might contribute to differences in survival. Remarkably, although we observed large differences in patterns of care in the present study, no clear relation between these differences and relative survival was found. Crude analysis showed a worse relative survival for Belgium compared with the Netherlands, but no significant differences in relative survival were observed after adjustment for potential confounders. Also no differences in relative survival were observed between the other neighbouring countries.

This study has some limitations. Unfortunately, information on clinical TNM stage was either not available or missing in a considerable number of patients. As a result, we were not able to stratify the analyses by clinical stage. Moreover, we analysed all (y)pTNM stages together, because differences in preoperative treatment approaches would have resulted in incomparable data when analysing (y)pTNM substages separately. Other limitations of our study were that there might be unknown differences in data registration between the countries and that the populations of the participating countries differed to some extent. As an example, there were more patients aged 75 years and older in BE compared with NL. Although we adjusted the analyses for potential confounders, there may still be residual confounding by unidentified factors that we could not control for. For example, the impact of differences in screening or diagnostic procedures, or differences in health-care systems between the countries are unknown. Further, data on treatment was recorded as unknown in ENG if a patient had surgery and no record of receiving preoperative or postoperative treatment. During the time period 2004 – 2009 there would have been variation by region in the completeness of these data items in ENG. Therefore, no record of receiving preoperative or postoperative treatment could either mean that patients did not receive preoperative or postoperative treatment, or that it was not recorded when patients received preoperative or postoperative treatment. Information on type of surgical resection, quality of the resection, and whether the surgical resection margins were free or not would also have been relevant to adjust for taken into account that surgery is the most crucial factor for survival. Finally, we were unfortunately not able to obtain data on comorbidity, compliance to preoperative and postoperative treatment, type of chemotherapy, acute or late toxicity, and quality of life. However, our study provides unique insight into the enormous variation in patterns of care across European countries, and it is to our knowledge the first study comparing

both preoperative and postoperative treatment strategies as well as relative survival of patients with stage I-III rectal cancer. Furthermore, we used a large dataset including over fifty-seven thousand patients from eight countries. Importantly, national data covering the whole population were obtained from seven of these countries.

In conclusion, in this population-based study comparing oncologic treatment patterns and relative survival of patients with (y)pTNM I-III rectal cancer, we observed large differences in preoperative and postoperative treatment strategies across European countries. Moreover, we did not find a clear relation between oncologic treatment strategy and relative survival. Further research into selection criteria for specific treatments could eventually lead to individualised and optimal treatment for patients with non-metastasised rectal cancer.

ACKNOWLEDGEMENTS

The authors thank the registration teams of the Comprehensive Cancer Centre Netherlands, the Belgian Cancer Registry, the Danish Colorectal Cancer Group, the Swedish Colorectal Cancer Registry, National Cancer Registration and Analysis Service Public Health England, the National Cancer Registry Ireland, the Spanish Rectal Cancer Project, and the Hospital of Lithuanian University of Health Sciences Kaunas Clinics for the collection of data for the registries.

REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**(6): 1374-403.
2. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**(8496): 1479-82.
3. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**(8843): 457-60.
4. 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**(6): 575-82.
5. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**(17): 1731-40.
6. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**(28): 4620-5.
7. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009; **27**(31): 5124-30.
8. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
9. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; **16**(2): 200-7.
10. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; **3**: CD004078.
11. Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery +/- a fluoropyrimidine and surgery + a fluoropyrimidine +/- oxaliplatin. *Eur J Surg Oncol* 2015; **41**(6): 713-23.
12. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2. *Eur J Cancer* 2015; **51**(15): 2158-68.
13. Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *BMJ* 2015; **351**: h4970.
14. Sullivan P, Goldmann D. The promise of comparative effectiveness research. *JAMA* 2011; **305**(4): 400-1.
15. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**(4): 343-6.
16. Oncoline. www.oncoline.nl/colorectaalcarcinoom. *Accessed January* 2016.
17. Group QC, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**(9604): 2020-9.
18. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25**(7): 1356-62.
19. 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**(28): 3768-74.
20. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; **15**(11): 1245-53.
21. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015; **16**(8): 979-89.

Supplementary table 1. Guideline recommendations by country during the time period represented in the present study

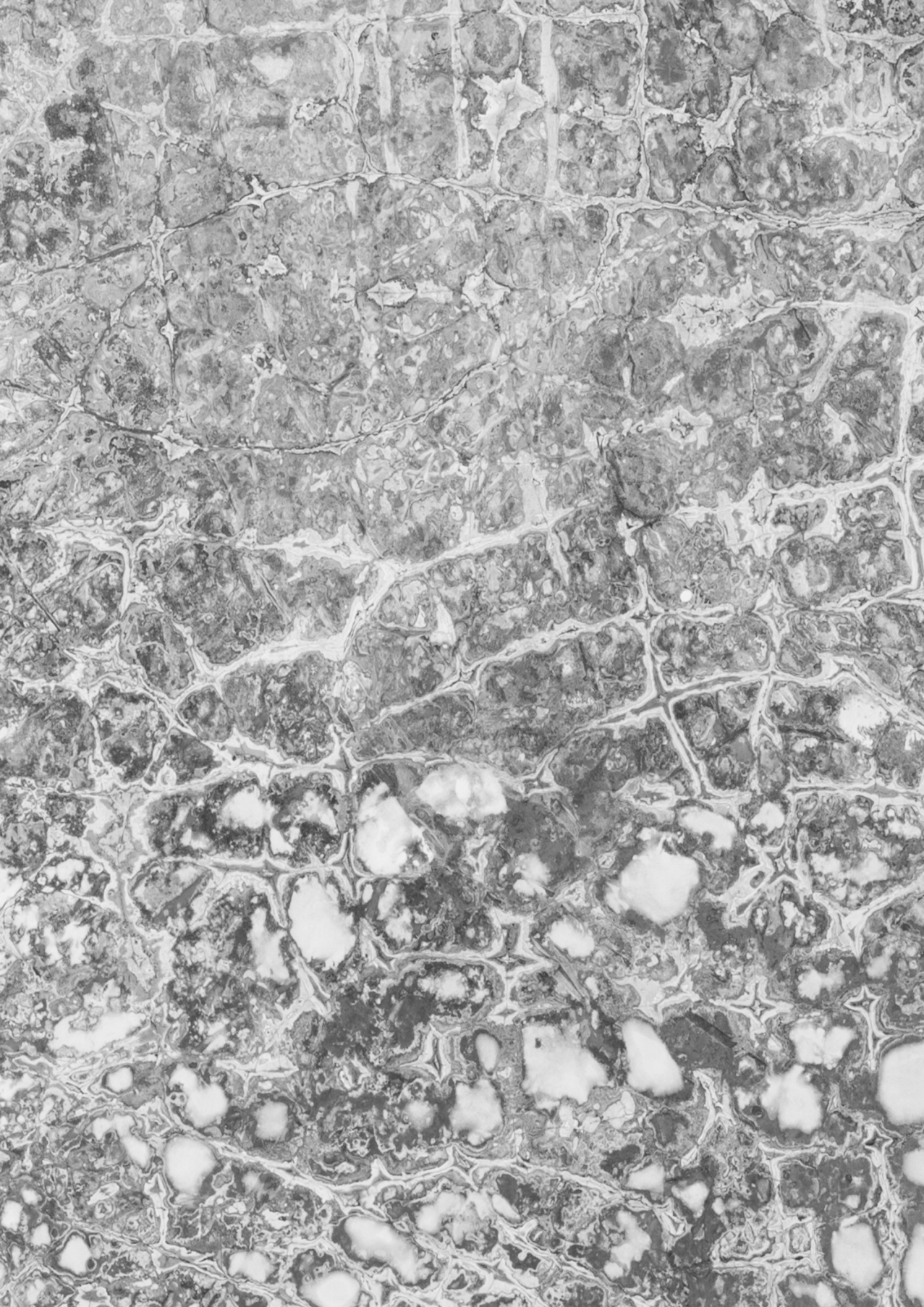
	Preoperative treatment	Postoperative treatment	Guideline adjusted?
The Netherlands	T1N0: no preoperative treatment. T2-T4: preoperative radiotherapy plus TME. In case of high, small tumours without lymph node metastases, it could be considered to omit preoperative radiotherapy. In case of positive circumferential resection margin (CRM) or more than 4 positive lymph nodes expected, preoperative chemoradiation could be considered.	Not possible to give a clear recommendation whether or not to administer postoperative chemotherapy.	Yes, 2014.
Belgium	T1-2N0: no preoperative treatment. Low tumour (0-5cm from the anal verge), T3-4N0 or TanyN+: preoperative chemoradiation. Mid and high tumours (5.1-15cm from the anal verge) T3N0 with CRM>2mm: preoperative radiotherapy. Mid and high tumours (5.1-15cm from the anal verge) T4N0 or CRM<2mm: preoperative chemoradiation. Mid and high tumours (5.1-15cm from the anal verge) TanyN+: preoperative chemoradiation.	Stage II-III: Stage II-III: (KCE 2007, Report 69 p. 38) -Postoperative chemotherapy should be considered for all patients who received preoperative radiotherapy without chemotherapy. -Postoperative chemoradiation is recommended in case a patient had no neo-adjuvant treatment.	Yes, 2016
Denmark	Until 2005: Short-course radiotherapy in mid (5-10 cm from the anal verge) and low (<5 cm from the anal verge) T3 and T4 tumours. All other: no preoperative treatment. Since 2005-2009: 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. T3: low and mid (MRF ≤ 5 mm) tumours: preoperative chemoradiation, mid (MRF > 5 mm) and high tumours: no preoperative treatment. T4: low and mid tumours: preoperative chemoradiation, high tumours: no preoperative treatment. In selected cases preoperative radiotherapy might be administered.	In selected cases postoperative chemotherapy might be administered.	Yes, 2009, 2014, 2015.
Sweden	T1-3a/b N0-1: no preoperative treatment. T3c/d N1-2: preoperative radiotherapy in case of no involved margins. T3-4Nany: with compromised margins: preoperative chemoradiation.	There are no indications for adjuvant chemotherapy.	Yes, 2014.

Supplementary table 1. Continued

	Preoperative treatment	Postoperative treatment	Guideline adjusted?
England	cT1 or cT2 or cT3a and no lymph node involvement (low risk): no preoperative treatment. any cT3b or greater, in which the potential margin is not threatened, or any suspicious lymph node not threatening the surgical resection margin, or the presence of extramural vascular invasion (moderate risk): consider preoperative radiotherapy. Consider preoperative chemoradiation for patients with tumours that are borderline between moderate (see above) and high risk (a threatened, <1mm, or breached resection margin, or low tumours encroaching onto the inter-sphincteric plane or with levator involvement). High-risk operable rectal cancer: offer preoperative chemoradiation.	Consider adjuvant chemotherapy after surgery for patients with high-risk stage II and all stage III rectal cancer.	Yes, 2014.
Ireland	T1-2N0, CRM clear: no preoperative treatment Early T3N0 or N1, CRM clear: upper and mid rectum preoperative radiotherapy or surgery only, lower rectum preoperative radiotherapy or chemoradiation and surgery CRM threatened by tumour or involved nodes or tumour beyond CRM or involved internal iliac/obturator nodes: preoperative chemoradiation and surgery.	Adjuvant chemotherapy should be considered for patients with node positive colorectal cancer. Patients with high-risk node negative disease should be individually counselled by an oncologic with regard to their level of risk and the possible benefits of fluoropyrimidine based chemotherapy.	No.
Spain	Stage II-III: preoperative chemoradiation is considered the treatment of choice.	Adjuvant chemotherapy is indicated for stage III patents who have been initially under staged.	No.
Lithuania	?	Adjuvant chemotherapy after surgery is recommended for patients with high-risk stage II and all stage III rectal cancer.	?

Supplementary table 2. Treatment strategies and five-year relative survival Spain and Lithuania

	Spain (%)	**Lithuania** (%)
Preoperative treatment		
None	42.0	81.0
Radiotherapy	2.9	11.2
Chemoradiation	55.1	7.9
Postoperative treatment		
None	31.1	66.8
Chemotherapy	62.3	12.4
Chemoradiation	6.7	13.6
Radiotherapy	0.0	7.3
Five-year relative survival (95% CI)	81.82% (79.00-84.46%)	84.04% (77.21-90.12%)



9

Treatment strategies and overall survival for incurable metastatic colorectal cancer - a EURECCA international comparison including 21,196 patients from the Netherlands and Norway

A.J. Breugom
E. Bastiaannet
M.G. Guren
H. Kørner
P.G. Boelens
F.W. Dekker
E. Kapiteijn
H. Gelderblom
I.K. Larsen
G.J. Liefers
C.J.H. van de Velde

European Journal of Surgical Oncology. 2020 Jun;46(6):1167-1173.

ABSTRACT

Background

The potential benefit of surgery of the primary tumour in patients with asymptomatic metastatic colorectal cancer is debated. This EURECCA international comparison analyses treatment strategies and overall survival in the Netherlands and Norway in patients with incurable metastatic colorectal cancer.

Methods

National cohorts (2007 – 2013) from the Netherlands and Norway including all patients with synchronous metastatic colorectal cancer were compared on treatment strategy and overall survival. Using country as an instrumental variable, we assessed the effect of different treatment strategies on mortality in the first year.

Results

Of 21,196 patients (16,144 Dutch and 5,052 Norwegian), 38.6% Dutch and 51.5% ($p<0.001$) Norwegian patients underwent resection of the primary tumour. In the Netherlands, 58.2% received chemotherapy compared with 21.4% in Norway. Radiotherapy was given in 9.5% of Dutch patients and 7.2% of Norwegian patients. Using the Netherlands as reference, the adjusted HR for overall survival was 0.96 (95% CI 0.93 – 0.99; $p=0.024$). Instrumental variable analysis showed an adjusted OR of 1.00 (95% CI 0.99 – 1.02; $p=0.741$).

Conclusions

Treatment strategies varied significantly between the Netherlands and Norway, with more surgery and less radiotherapy in Norway. Adjusted overall survival was better in Norway for all patients and patients <75 years, but not for patients ≥75 years. Instrumental variable analysis showed no benefit in one-year mortality for a treatment strategy with a higher proportion of surgery and a lower proportion of radiotherapy. Our findings emphasise the need for further research to select patients with incurable metastatic colorectal cancer for different treatment options.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with 1.4 million new cases and 694,000 cancer deaths estimated to have occurred in 2012.[1] Approximately 20% of all patients with colorectal cancer have distant metastases at diagnosis.[2] Although a selected group of patients with metastatic colorectal cancer can be treated with curative intent, treatment options are limited to palliative therapy for the majority of patients.[3] Survival of patients with incurable metastatic colorectal cancer has improved significantly over the past years with advances in systemic therapy.[4] Median overall survival is approximately five to six months with symptom-directed palliative care alone, while survival increases to 11 to 12 months with fluoropyrimidine monotherapy, and to about two years with fluoropyrimidine-based combination chemotherapy with oxaliplatin or irinotecan often combined with bevacizumab, or EGFR inhibitors (cetuximab or panitumumab).[5-10]

Surgical resection of the primary tumour in patients with incurable metastatic colorectal cancer is indicated in case of obstruction, perforation, or severe bleeding. On the contrary, the potential benefit of surgery of the primary tumour in patients with asymptomatic disease is extensively debated.[11,12]

Randomised controlled trials (RCTs) are considered to be the gold standard to evaluate treatment effectiveness. However, no results are yet available from RCTs comparing surgery versus no surgery of the primary tumour in asymptomatic patients with unresectable metastatic colorectal cancer, and well-designed trials have been unable to recruit patients by various reasons including for example a smaller patient population than anticipated and the perception of the doctor about the best treatment strategy.[13] Moreover, results from retrospective studies are at high risk of confounding by indication and should therefore be interpreted with caution.

As an alternative, instrumental variable analysis can be used, which is a promising tool to estimate treatment effects and to reduce residual confounding in comparative effectiveness research.[14,15] An instrumental variable is defined as a factor that is related to treatment, but neither directly nor indirectly related to the study outcome.[14]

The aim of the present EURECCA international comparison is to compare treatment strategies and to compare overall survival between the Netherlands and Norway in patients with incurable metastatic colorectal cancer, and to define optimal treatment strategies using country as an instrumental variable.

METHODS

Patients

National datasets with (almost) 100% coverage of incident cases from the Netherlands Cancer Registry (NL), and the Cancer Registry of Norway (NO) including detailed data from the Norwegian Colorectal Cancer Registry were included.[16,17] We selected all patients diagnosed with synchronous metastatic colorectal cancer between 2007 and 2013. To define patients with incurable metastatic disease, we excluded patients who underwent surgery of metastasis. Patients without surgery of metastatic disease or with unknown data on surgery of metastatic disease were included.

We collected information on age, gender, primary tumour localisation (colon or rectum), year of diagnosis, clinical T-stage, clinical N-stage, localisation of metastases, treatment, and vital status at date of last follow-up. Clinical T-stage was classified as T0-2, T3, T4, or unknown. Clinical N-stage was classified as N0, N+, or unknown. Localisation of metastases was defined as liver only, lung only, other but one localisation, ≥2 localisations, or unknown. Information on treatment consisted of surgery of the primary tumour, radiotherapy of the primary tumour, and chemotherapy, all defined as no, yes, or unknown.

While data on surgery and radiotherapy are of very good quality in the Norwegian Colorectal Cancer Registry, data on chemotherapy are not complete, and must be interpreted with caution.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier technique.[18] Analyses were performed for all patients, as well as stratified by localisation of the primary tumour (colon, rectum), and age (<75 years, ≥75 years).

We performed a chi-square test to compare the proportion of surgery of the primary tumour, chemotherapy, and radiotherapy of the primary tumour between the Netherlands and Norway. Overall survival was defined as time from diagnosis to death of any cause or to end of follow-up (censored). To compare overall survival between the Netherlands and Norway, we used Kaplan-Meier curves. Crude and adjusted Cox proportional hazards models were performed to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) to study the association between country and overall survival with the Netherlands as a reference category. We adjusted for the following potential confounders: age, gender, localisation of the primary tumour, and year of diagnosis. Median survival was calculated according to the Kaplan-Meier method and compared by the Log-rank test. A Kaplan–Meier curve was constructed to compare overall survival between the Netherlands and Norway.

Using country as an instrumental variable (pseudo-randomisation), we assessed the effect of different treatment strategies on mortality (yes/no) within the first year using the instrumental variable estimation procedure (ivregress) in Stata adjusted for age, gender, localisation of the primary tumour, and year of diagnosis.

As a sensitivity analysis, survival analyses were performed excluding patients with unknown data on surgery of metastatic disease.

A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 23.0 and STATA SE 12.0.

RESULTS

A total of 21,196 patients were included; 16,144 from the Netherlands, and 5,052 from Norway. Data on surgery of metastatic disease were unknown for 803 (3.8%) of these patients. Patient and tumour characteristics are shown in Table 1. Median follow-up of surviving patients was 4.3 years (IQR 2.7 – 6.1 years).

Table 1. Patient and tumour characteristics

	The Netherlands (*n*=16,144)	**Norway** (*n*=5,052)
Age (years)	70 (14-102)	72 (19-104)
Gender		
Male	9,111 (56.4)	2,671 (52.9)
Female	7,033 (43.6)	2,381 (47.1)
Localisation primary tumour		
Colon	12,007 (74.4)	3,898 (77.2)
Rectum	4,137 (25.6)	1,154 (22.8)
Year of diagnosis		
2007	2,143 (13.3)	690 (13.7)
2008	2,217 (13.7)	731 (14.5)
2009	2,221 (13.8)	727 (14.4)
2010	2,386 (14.8)	743 (14.7)
2011	2,372 (14.7)	721 (14.3)
2012	2,355 (14.6)	750 (14.8)
2013	2,450 (15.2)	690 (13.7)
Clinical T-stage		
T0-2*	556 (3.4)	262 (5.2)
T3	3,552 (22.0)	881 (17.4)
T4	3,550 (22.0)	641 (12.7)
Unknown	8,486 (52.6)	3,268 (64.7)
Clinical N-stage		
N0	2,918 (18.1)	245 (4.8)
N+	7,337 (45.4)	1,021 (20.2)
Unknown	5,889 (36.5)	3,786 (74.9)
Metastases		
Liver only	6,608 (40.9)	772 (15.3)
Lung only	753 (4.7)	156 (3.1)
Other, but one localisation	2,283 (14.1)	872 (17.3)
≥2 localisations	6,353 (39.4)	362 (7.2)
Unknown	147 (0.9)	2,890 (57.2)

Data are presented as median (minimum-maximum) or as *n* (%)

* Including one patient with T in situ

All patients

Figure 1 depicts the various treatment strategies in the Netherlands and Norway. In the Netherlands, a lower percentage of patients underwent surgery of the primary tumour compared with Norway (38.6% *vs.* 51.5%; p<0.001). Moreover, 58.2% of Dutch patients received chemotherapy. In Norway, 21.4% of patients received chemotherapy and data on chemotherapy was unknown in 41.2% of patients (p<0.001). Of all patients, 9.5% received radiotherapy of the primary tumour in the Netherlands compared with 7.2% of patients from Norway.

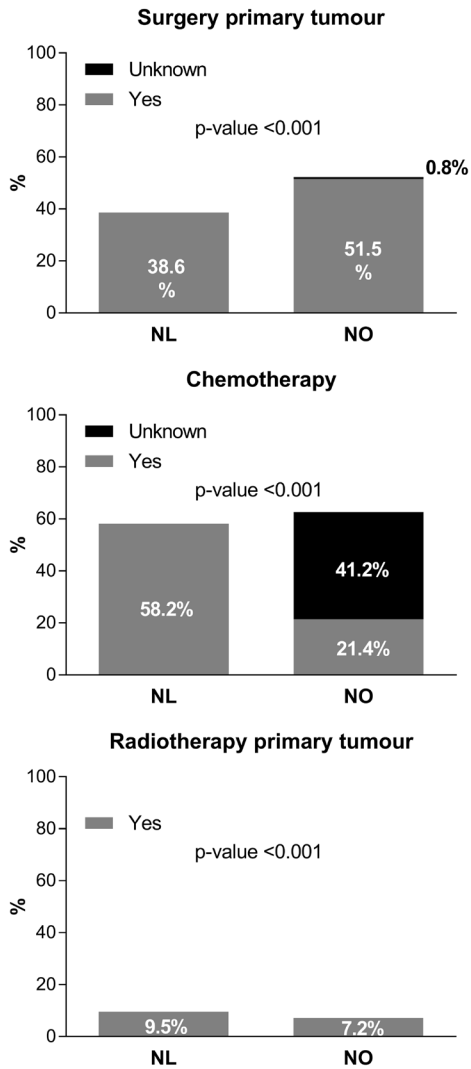
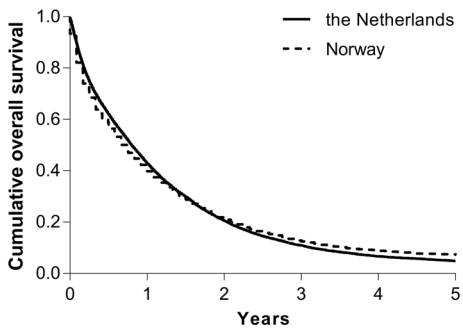


Figure 1. Treatment strategy

Median overall survival was 9.6 months in the Netherlands and 9.0 months in Norway. No difference in crude overall survival was found between the two countries (HR 0.99, 95% CI 0.96 – 1.03; p=0.731; Figure 2). After adjustment for potential confounders, the HR was 0.96 (95% CI 0.0.93 – 0.99; p=0.024) for Norway compared with the Netherlands.



Number at risk						
The Netherlands	16,144	6,923	2,809	1,242	589	307
Norway	5,052	2,021	905	444	245	139

Figure 2. Overall survival

Colon cancer

Figure 3 shows the treatment strategy in the Netherlands and Norway for patients with colon cancer. In the Netherlands, 44.9% of patients with colon cancer underwent surgery of the primary tumour compared with 55.6% in Norway (p<0.001). Chemotherapy was administered in 56.5% of Dutch patients. In Norway, 18.5% of patients received chemotherapy and data on chemotherapy was unknown in 40.4% of patients (p<0.001). Median overall survival for patients with colon cancer was 8.8 months in the Netherlands and 8.0 months in Norway (HR 1.00, 95% CI 0.96 – 1.04; p=0.958; Figure 4). After adjustment for potential confounders, the HR was 0.97 (95% CI 0.93 – 1.01; p=0.095).

Rectal cancer

Figure 3 shows treatment strategies for patients with rectal cancer. A lower percentage of patients in the Netherlands underwent surgery of the primary tumour compared with Norway (20.1% *vs.* 37.4%; p<0.001). Chemotherapy was given in 63.2% of Dutch patients. In Norway, 31.2% of patients had chemotherapy, while data on chemotherapy was unknown in 44.2% of patients (p<0.001). In the Netherlands, 37.1% of patients had radiotherapy of the primary tumour. In Norway, 31.5% of patients had radiotherapy of the primary tumour (p<0.001).

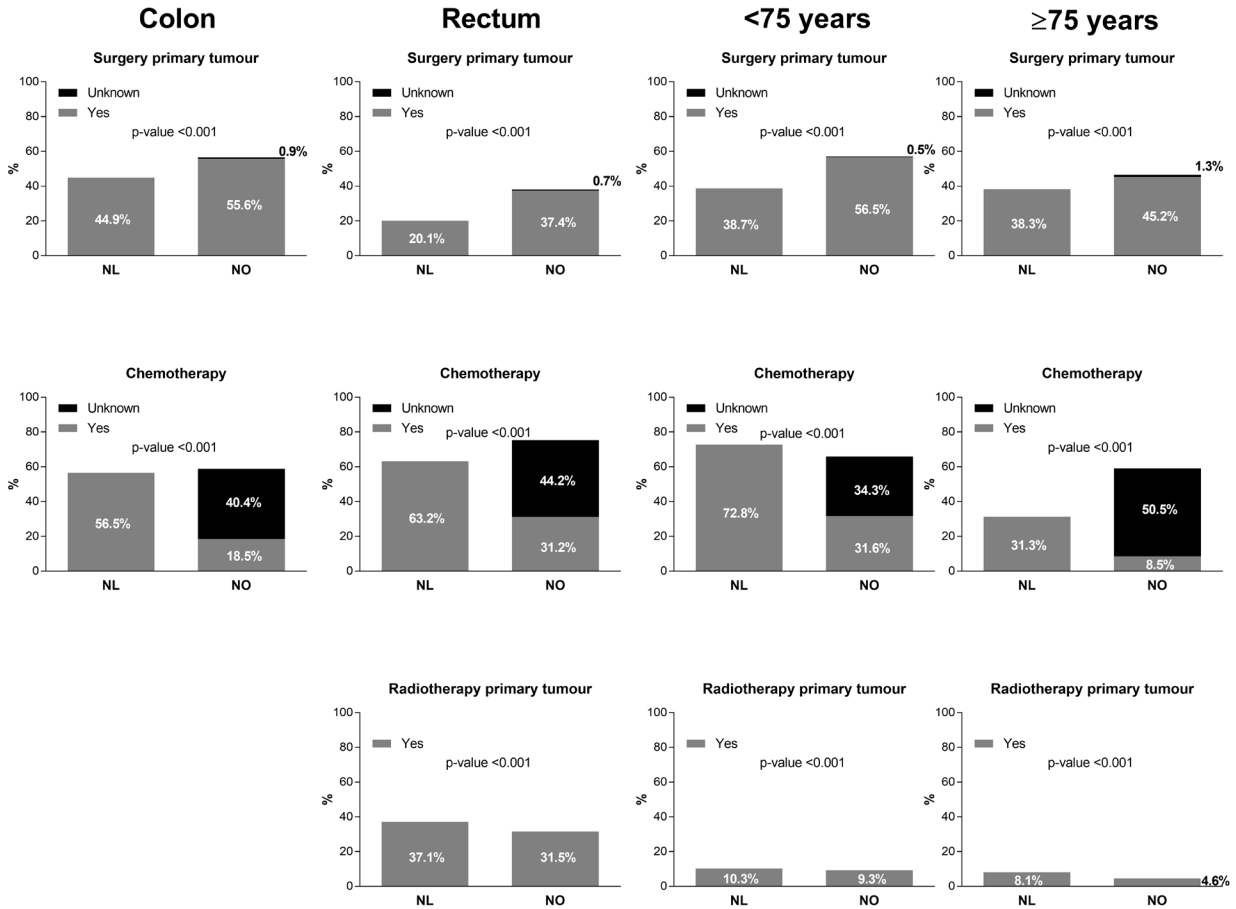


Figure 3. Treatment strategy for patients with colon and rectal cancer

Median overall survival for patients with rectal cancer was 12.0 months in the Netherlands as well as in Norway (HR 0.96, 95% CI 0.89 – 1.03; p=0.248; Figure 4). After adjustment for potential confounders, the HR was 0.95 (95% CI 0.88 – 1.02; p=0.122).

Patients <75 years

In the Netherlands, 38.7% of patients <75 years with colorectal cancer underwent surgery of the primary tumour compared with 56.5% of patients from Norway (p<0.001). Moreover, 72.8% of Dutch patients had chemotherapy. In Norway, 31.6% of patients received chemotherapy, while data on chemotherapy was unknown in 34.3% of patients (p<0.001). Radiotherapy of the primary tumour was given in 10.3% of Dutch patients and 9.3% of Norwegian patients (p<0.001; Figure 3).

Median overall survival for patients <75 years was 11.9 months in the Netherlands and 13.0 months in Norway (HR 0.89, 95% CI 0.85 – 0.93; p<0.001; Figure 4). After adjustment for potential confounders, the HR was 0.89 (95% CI 0.85 – 0.93; p<0.001).

Patients ≥75 years

In the Netherlands, 38.3% of patients ≥75 years with colorectal cancer underwent surgery of the primary tumour compared with 45.2% in Norway (p<0.001). Of all Dutch patients, 31.3% received chemotherapy. Of all Norwegian patients, 8.5% received chemotherapy and data on chemotherapy was unknown in 50.5% of patients. Radiotherapy of the primary tumour was given in 8.1% of Dutch patients and in 4.6% of Norwegian patients (Figure 3).

Median overall survival for patients ≥75 years was 6.1 months in the Netherlands and 4.9 months in Norway (HR 1.08, 95% CI 1.02 – 1.13; p=0.004; Figure 4). After adjustment for potential confounders, the HR was 1.07 (95% CI 1.01– 1.12; p=0.014).

Sensitivity analysis

When excluding patients with unknown data on surgery of metastatic disease, median overall survival was 9.6 months in the Netherlands and 10.0 months in Norway (HR 0.91, 95% CI 0.88 – 0.94; p<0.001). After adjustment for potential confounders, the HR was 0.89 (95% CI 0.86 – 0.92; p<0.001).

Instrumental variable analysis

Using instrumental variable analysis, no difference was observed between the treatment strategy in Norway compared with the treatment strategy in the Netherlands on mortality within the first year (OR of 1.00, 95% CI 0.99 – 1.02; p=0.741).

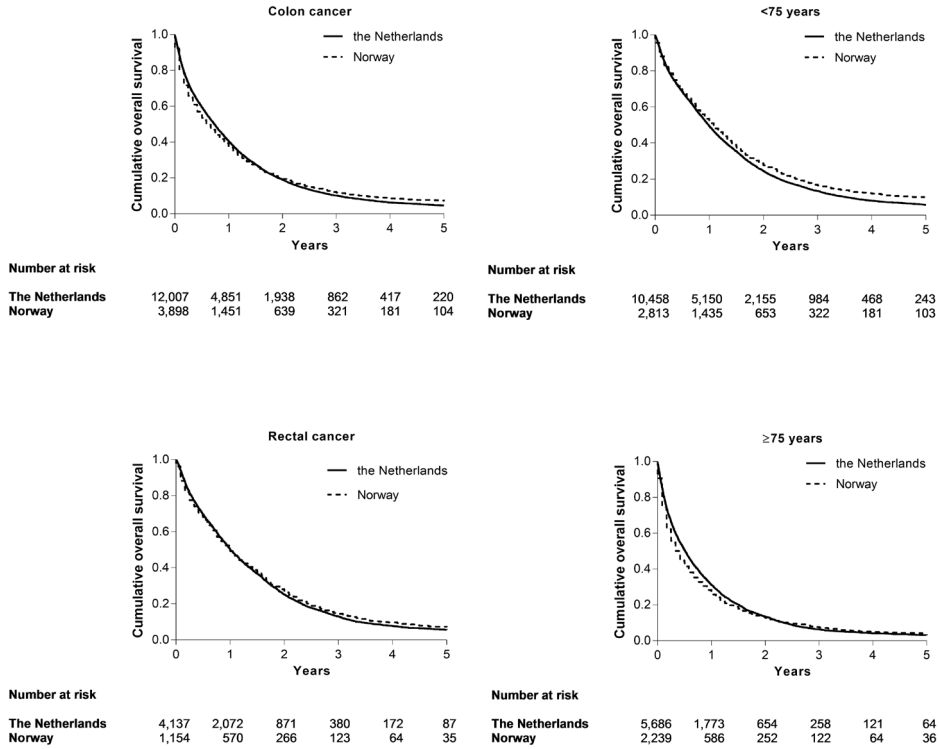


Figure 4. Overall survival by localisation (colon, rectum) and age (<75 years, ≥75 years)

DISCUSSION

This study shows remarkable variation in treatment strategies between the Netherlands and Norway for patients with incurable metastatic colorectal cancer. In Norway, more patients underwent surgery of the primary tumour compared with the Netherlands. Moreover, Dutch patients possibly received more chemotherapy, particularly in the group of patients ≥75 years; however, data on chemotherapy was unknown for about forty percent of Norwegian patients. The proportion of patients with rectal cancer receiving radiotherapy of the primary tumour was lower in Norway compared with the Netherlands.

We observed no differences in crude overall survival between the Netherlands and Norway. However, after adjustment for potential confounders, our study showed a small survival benefit in Norwegian patients, also for patients <75 years. On the contrary, patients from Norway aged ≥75 years had a worse crude and adjusted survival. Moreover,

when stratified by tumour localisation (colon or rectum), no significant difference in survival was observed, although the effect is in the same direction as for all patients. Using instrumental variable analysis no benefit in one-year mortality was found for a treatment strategy with a higher proportion of surgery of the primary tumour.

Resection of the primary tumour in asymptomatic patients with unresectable metastatic colorectal cancer has traditionally been performed to prevent subsequent complications including obstruction, perforation, or severe bleeding. A lower postoperative mortality rate was reported for elective colorectal cancer surgery than for emergency surgery in patients with metastatic disease[19], which is one of the main arguments in favour of initial resection of the primary tumour in asymptomatic patients with incurable metastatic colorectal cancer. On the contrary, the incidence of developing symptoms or tumour complications leading to emergency surgery of the primary tumour is 9-29% according to previous studies[20-22], so a considerable number of patients, in particular octo- and nonagenarians, may be spared from surgery-related morbidity or mortality by adhering to a conservative treatment policy.[23] Also, palliative radiotherapy of the rectal tumour may provide effective symptom palliation and reduce the need for surgery of the primary tumour.[24,25]

Over the last two decades, survival of patients with metastatic colorectal cancer improved greatly. Several factors may have contributed to better clinical outcomes, including improvements in the efficacy of systemic treatment, an increase in the number of patients that can be treated curatively, changes in follow-up and earlier detection of metastatic disease.[3]

Also with the advances in chemotherapeutic regimens, there is a trend toward a non-surgical management, although only 58.2% of Dutch patients received chemotherapy. Possible explanations for this could be frailty, patients' preferences, or clinical condition. A retrospective cohort study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results colorectal cancer registry demonstrated that the annual rate of surgery of the primary tumour decreased from 74.5% to 57.4% between 1988 and 2010.[26] Still, for asymptomatic patients with incurable metastatic disease, the benefit of primary tumour resection is uncertain.

In a meta-analysis of Clancy *et al.* including 21 retrospective studies examining the effect of primary tumour resection in patients with unresectable metastatic disease, resection of the primary tumour was associated with better overall survival compared with chemotherapy alone.[27] All included studies were at high risk of confounding by indication since surgery of the primary tumour was not randomised. For example, this meta-analysis showed that patients who underwent surgery of the primary tumour were likely

to have less extent of metastatic disease and could therefore have a better prognosis on forehand compared with patients who did not undergo surgery of the primary tumour. Additionally, patients in the non-surgery group had poorer performance status, more comorbidity, higher alkaline phosphatase and carcinoembryonic antigen (CEA) levels, and different sites of the primary tumour. Moreover, resection did not significantly reduce the risk of complications of the primary tumour.[28]

More recent studies using comparative effectiveness research including instrumental variable analysis also show varying results. For example, a study by Alawadi *et al.* showed that resection of the primary tumour was not associated with improved overall survival.[29] On the contrary, several other studies found a benefit for patients with incurable stage IV colorectal cancer who underwent surgery of the primary tumour.[30-32]

There are some ongoing randomised trials, as for example the CAIRO 4 study, investigating the (long-term) effects of primary tumour resection in unresectable stage IV colorectal cancer.[33-35] However, these results are still awaited. Some of these trials also included quality of life as a secondary outcome measure, which may be of additional value in the decision-making process.

Interestingly, we observed a survival benefit in Norwegian patients aged <75 years, while a worse survival was observed in Norwegian patients aged ≥75 years. This might at least partly be explained by differences in the frequency of surgery of the primary tumour between the Netherlands and Norway. In both age groups, surgery of the primary tumour is more often performed in Norway. A previous study by Dekker *et al.* showed that decreased survival in the elderly is mainly due to differences in early survival in patients who had surgery for stage I-III colorectal cancer.[36] These results are in line with a recent study by Mehta *et al.* evaluating the comparative effectiveness of initial chemotherapy versus resection of the primary tumour in older patients with metastatic colorectal cancer. It was found that chemotherapy as initial treatment resulted in similar or better two-year survival.[37] Postoperative complications are a plausible reason for early mortality. Thus, it might be that younger patients may benefit from surgery due to less postoperative mortality, while older patients die more often as a result of postoperative complications.

A lower percentage of patients with the primary tumour located in the rectum underwent primary tumour resection compared with patients with the primary tumour in the colon, which is as expected because surgery for rectal cancer is technically more difficult than surgery for colon cancer, more proximal tumours have an increased risk of bowel obstruction, and resection of the primary tumour in rectal cancer is associated with higher postoperative morbidity and negative side effects. Moreover, palliative

radiotherapy is a highly effective treatment option for local control of rectal cancer, but not for colon cancer. We observed no differences in survival between the Netherlands and Norway.

This study has some limitations. There might be unknown differences in data registration between the two countries and differences in data completeness of other treatment modalities than surgery exist. Although we adjusted the analyses for potential confounders, residual confounding by unmeasured factors cannot be excluded due to the retrospective design of the study. For example, it is unknown what role differences in health-care systems, or differences in screening or diagnostic procedures between the two countries play. Some variables are not complete in the registries, as for example chemotherapy. Ideally we would have adjusted the analyses for location and number of metastases as well. However, there was missing data for a considerable part, and this variable introduced interaction. This should be studied in future studies with a bigger dataset by stratifying on this variable. Moreover, we had no detailed information on primary tumour symptoms, emergency surgery, type or dose of chemotherapy, toxicity, chemotherapy compliance, treatment sequence, other treatment modalities such as HIPEC, comorbidity, life-style factors, and ASA classification among others. These variables should ideally be included in national population-based datasets to do more detailed analysis and to improve comparability of the data.[38] In particular, from a patient-centred perspective, quality of life and individual preferences in the presence of incurable disease are important aspects for shared decision making. Finally, the different treatment approaches with a higher proportion undergoing surgery in Norway as compared to the Netherlands may be related to non-measurable factors, e.g. clinical traditions or different expectations from the patients in the two countries. The potential differences between countries and the effect on survival can therefore not be thoroughly investigated.

On the other hand, this study is unique in comparing both treatment and overall survival as well as using instrumental variable analysis between two European countries in patients with metastatic colorectal cancer. Furthermore, we used a large dataset with over 20,000 patients with national data covering the Netherlands and Norway.

In conclusion, the present population-based study, comparing both treatment strategies and overall survival of patients with incurable metastatic colorectal cancer between the Netherlands and Norway, showed treatment variation with especially more surgery and less radiotherapy in Norway. After adjustment for potential confounders, a better overall survival was observed in Norway compared with the Netherlands for all patients, and for patients <75 years, while we observed a worse survival in Norwegian patients aged ≥75 years. This may be partly the result of differences in treatment strategies,

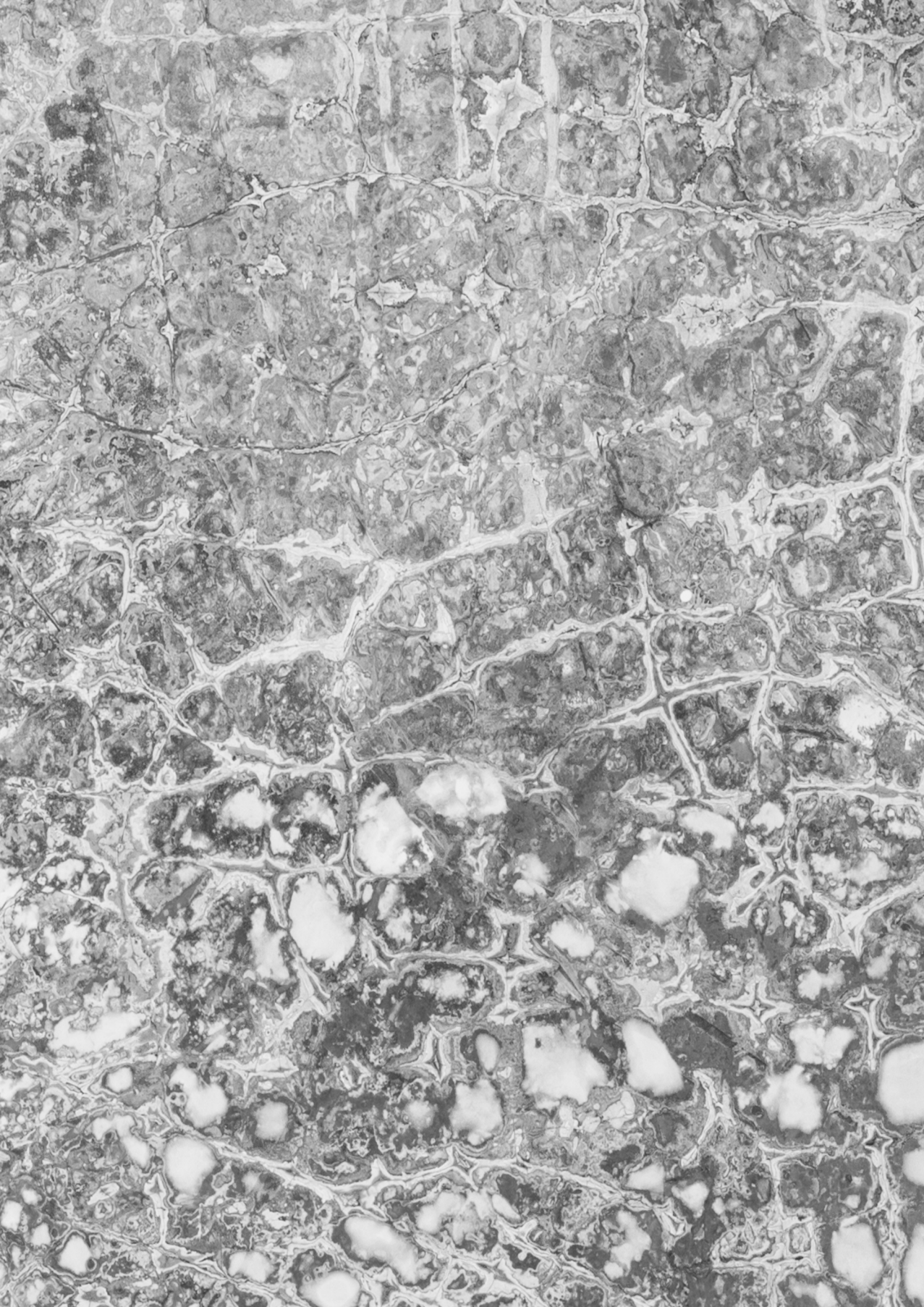
although there may be other factors as well that impact on survival. However, survival differences between the Netherlands and Norway are small and clinical relevance may be questioned.

Our findings strongly underline that further research is needed to better define how to select patients with incurable metastatic colorectal cancer for various treatment options, and in particular who will and who will not benefit from surgical treatment of the primary tumour. This could eventually lead to individually tailored, optimal treatment of patients with incurable metastatic colorectal cancer.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer* 2015; **136**(5): E359-86.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: a cancer journal for clinicians* 2016; **66**(1): 7-30.
3. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**(8): 1386-422.
4. Sorbye H, Cvancarova M, Qvortrup C, Pfeiffer P, Glimelius B. Age-dependent improvement in median and long-term survival in unselected population-based Nordic registries of patients with synchronous metastatic colorectal cancer. *Ann Oncol* 2013; **24**(9): 2354-60.
5. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ (Clinical research ed)* 1993; **306**(6880): 752-5.
6. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2000; **18**(16): 2938-47.
7. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *The New England journal of medicine* 2000; **343**(13): 905-14.
8. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet (London, England)* 2007; **370**(9582): 135-42.
9. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *The New England journal of medicine* 2004; **350**(23): 2335-42.
10. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. *Cancer treatment reviews* 2012; **38**(6): 618-25.
11. Soreide K. Resection of asymptomatic primary tumour in unresectable stage IV colorectal cancer: time to move on from propensity matched scores to randomized controlled trials. *International journal of cancer* 2016; **139**(9): 1927-9.
12. Patel S, Chang GJ. Primary Tumor Resection in Metastatic Colorectal Cancer: Please Pass the Salt. *JAMA oncology* 2015; **1**(9): 1213-4.
13. Arbman G, Pahlman L, Glimelius B. The rise and fall of a longed for clinical trial in patients with generalized colorectal cancer. *Acta Oncol* 2013; **52**(8): 1779-82.
14. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiology and drug safety* 2010; **19**(6): 537-54.
15. Boef AG, le Cessie S, Dekkers OM. [Instrumental variable analysis]. *Nederlands tijdschrift voor geneeskunde* 2013; **157**(4): A5481.
16. Guren MG, Korner H, Pfeffer F, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. *Acta Oncol* 2015; **54**(10): 1714-22.
17. The Netherlands Cancer Registry https://www.iknl.nl. Accessed August 9, 2018.
18. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Controlled clinical trials* 1996; **17**(4): 343-6.
19. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Annals of surgical oncology* 2005; **12**(8): 637-45.
20. Sarela AI, Guthrie JA, Seymour MT, Ride E, Guillou PJ, O'Riordain DS. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br J Surg* 2001; **88**(10): 1352-6.
21. Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. *Journal of the American College of Surgeons* 2003; **196**(5): 722-8.
22. Tebbutt NC, Norman AR, Cunningham D, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut* 2003; **52**(4): 568-73.
23. Sigurdsson HK, Korner H, Dahl O, Skarstein A, Soreide JA, Norwegian Rectal Cancer G. Palliative surgery for rectal cancer in a national cohort. *Colorectal Dis* 2008; **10**(4): 336-43.
24. Cameron MG, Kersten C, Vistad I, et al. Palliative pelvic radiotherapy for symptomatic rectal cancer - a

prospective multicenter study. *Acta Oncol* 2016; **55**(12): 1400-7.
25. Tyc-Szczepaniak D, Wyrwicz L, Kepka L, et al. Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study. *Ann Oncol* 2013; **24**(11): 2829-34.
26. Hu CY, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. *JAMA Surg* 2015; **150**(3): 245-51.
27. Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Annals of surgical oncology* 2014; **21**(12): 3900-8.
28. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. *The Cochrane database of systematic reviews* 2012; (8): Cd008997.
29. Alawadi Z, Phatak UR, Hu CY, et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. *Cancer* 2017; **123**(7): 1124-33.
30. t Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands. *International journal of cancer* 2016; **139**(9): 2082-94.
31. Xu H, Xia Z, Jia X, et al. Primary Tumor Resection Is Associated with Improved Survival in Stage IV Colorectal Cancer: An Instrumental Variable Analysis. *Sci Rep* 2015; **5**: 16516.
32. Tarantino I, Warschkow R, Worni M, et al. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients: A Population-Based, Propensity Score-Adjusted Trend Analysis. *Ann Surg* 2015; **262**(1): 112-20.
33. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012; **12**: 142.
34. t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014; **14**: 741.
35. Kim CW, Baek JH, Choi GS, et al. The role of primary tumor resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial. *Trials* 2016; **17**: 34.
36. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Annals of surgical oncology* 2011; **18**(6): 1533-9.
37. Mehta HB, Vargas GM, Adhikari D, Dimou F, Riall TS. Comparative effectiveness of chemotherapy vs resection of the primary tumour as the initial treatment in older patients with Stage IV colorectal cancer. *Colorectal Dis* 2017; **19**(6): O210-O8.
38. Storm HH, Engholm G, Pritzkuleit R, et al. Less pitfalls and variation in population based cancer survival comparisons within the European Union: Lessons from colorectal cancer patients in neighbouring regions in Denmark and Germany - The Fehmarn Belt project. *Eur J Cancer* 2015; **51**(9): 1188-98.



10

Summary, general discussion and future perspectives

SUMMARY

PART I: EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER

In **Chapter 2**, the most frequent complications after surgery for stage I-III colon cancer were identified, and we assessed the association between these complications and survival and recurrences. Thirty-day mortality after surgery for colon or rectal cancer underestimates one-year mortality, with stage III disease, comorbidity, and postoperative surgical complications as risk factors for excess mortality in the first year after surgery for colon cancer.[1,2]

Patients who suffered from complications had decreased one-year and five-year survival, whereas an increasing number of complications had no additional impact. Anastomotic leakage, excessive blood loss, (abdominal) sepsis, delirium, and the occurrence of an abscess were associated with long-term survival, and/or recurrences. These findings underline the prolonged impact of complications on survival and recurrences, not only one year after surgery, but also on long-term outcomes.

Chapter 3 shows a decrease in thirty-day and one-year mortality over time in patients ≥75 years with stage I-III colon cancer, though the absolute decrease was small. Especially in older patients, 30-day and one-year mortality are still high for both colon and rectal cancer. This implies that the focus should be on the first postoperative year in older patients with colorectal cancer to further improve outcomes.

Chapter 4 described the outcomes of the PROCTOR-SCRIPT trial, investigating the effectiveness of adjuvant chemotherapy compared with observation after (chemo) radiotherapy and total mesorectal excision (TME) among patients with (y)pTNM stage II or III rectal cancer. Adjuvant chemotherapy might prevent the occurrence of distant metastases, though the use of adjuvant chemotherapy for patients with rectal cancer treated with preoperative (chemo)radiotherapy is extensively debated.[3] After a median follow-up of five years, we could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy in terms of overall survival, disease-free survival, and recurrences. However, the intended inclusion was not reached due to poor patient accrual. The lack of statistical power may have prevented the detection of statistically significant differences in outcomes between observation and adjuvant chemotherapy.

Though four out of five European randomised controlled trials comparing adjuvant chemotherapy with observation after preoperative (chemo)radiotherapy and surgery in

patients with rectal cancer showed no benefit of adjuvant chemotherapy, and one trial with the majority of patients not having preoperative treatment showing a borderline significant improvement in overall survival only, none of these trials have individually ended the discussion about the role of adjuvant chemotherapy.[4-8] Therefore, in **Chapter 5**, we investigated the effectiveness of fluorouracil-based adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME in a meta-analysis including individual patient data from four of the above mentioned trials. In patients with (y)pTNM stage II or III rectal cancer, who had a R0 resection after low anterior resection or abdominoperineal resection, and a tumour located within 15 cm of the anal verge, fluorouracil-based adjuvant chemotherapy did not improve overall survival, disease-free survival, and distant recurrences compared with observation. However, subgroup analyses suggest that patients with a tumour between 10 cm and 15 cm from the anal verge might benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences.

PART II: INTERNATIONAL COMPARISONS ON TREATMENT AND OUTCOMES OF PATIENTS WITH COLORECTAL CANCER

In the second part of this thesis we compared patterns of care and survival outcomes of patients with colorectal cancer in Europe using data from countries participating in the EURECCA project.

In **Chapter 6**, we reported on quality assurance in the management of colorectal cancer and elaborated on the aims of the EURECCA project. There is considerable variation in survival outcomes between European countries.[9] Quality assurance can be defined as all those planned and systematic actions necessary to achieve minimal requirements of good cancer care. Quality assurance in the management of colorectal cancer could eventually lead to improved cancer care and less variation. The European Registration of Cancer Care, EURECCA, has been initiated to reduce differences between European countries, and collects patient and treatment data of national audit registries or national cancer registries to be analysed in order to identify where further improvement is needed.

Chapter 7 provided more insight into the use of adjuvant chemotherapy and into relative survival outcomes among patients with stage II colon cancer. Population-based national cohort data from the Netherlands, Denmark, Sweden, England, Ireland, and Belgium were obtained, as well as single-centre data from Lithuania. An interesting finding was a large variation in the proportion of patients with stage II colon cancer receiving adjuvant chemotherapy, though we observed no clear linear pattern between adjuvant chemotherapy and adjusted relative survival. Sweden and Belgium both had a better adjusted relative survival compared with the Netherlands. Although we found no clear linear pattern between adjuvant chemotherapy and relative survival, differences in the

proportion of adjuvant treatment might still partly, but not solely, contribute to these differences in survival.

In **Chapter 8**, we evaluated preoperative and postoperative treatment strategies and relative survival of patients with stage I-III rectal cancer. Neighbouring countries were compared, and showed more preoperative radiotherapy and less preoperative chemoradiation in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. Adjuvant chemotherapy was more often given in Belgium compared with the Netherlands, in Denmark compared with Sweden, and in England compared with Ireland. We observed no differences in relative survival between neighbouring countries. The variation in treatment strategies reflects the differences in national guidelines and underlines the lack of international consensus on optimal treatment strategies for stage I-III rectal cancer.

Chapter 9 described treatment strategies and overall survival of patients with incurable metastatic colorectal cancer. Treatment strategies varied between the Netherlands and Norway, with especially more surgery and less radiotherapy in Norway. Adjusted overall survival was better in Norway for all patients and for patients <75 years, but survival was worse for patients ≥75 years. Differences in treatment strategies probably contribute to differences in survival outcomes, while the effect of specific treatments may differ between younger and older patients.

Future perspectives

In the era of multidisciplinary management and shared-decision making, analyses from a unified European population-based dataset, of course combined with results from trials as well as the search for additional biomarkers will be the challenge for the future to better select subgroups of patients for treatment. More importantly, intensified neoadjuvant (chemo)radiotherapy addresses the need to monitor patients carefully with intense radiological follow-up to only intervene in case of tumour recurrence. In some patients, this can even avoid surgery in case of long-lasting complete response.

REFERENCES

1. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**(6): 1533-9.
2. Gooiker GA, Dekker JW, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* 2012; **19**(8): 2428-34.
3. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010; **21**(9): 1743-50.
4. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**(2): 184-90.
5. Quasar Collaborative G, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**(9604): 2020-9.
6. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25**(7): 1356-62.
7. Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015; **26**(4): 696-701.
8. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**(2): 223-9.
9. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer* 2015; **51**(15): 2158-68.

GENERAL DISCUSSION

Survival of patients with colorectal cancer improved markedly over the past decades, as a result of advances in screening, staging procedures, treatment, and surveillance.[1-5] However, still about 20% of patients with colorectal cancer develop metachronous metastases and 20% of all patients with colorectal cancer have metastatic disease at diagnosis.[6,7] Several treatment modalities, such as total mesorectal excision (TME) and preoperative (chemo)radiotherapy for rectal cancer, as well as adjuvant chemotherapy for stage III colon cancer, have been studied extensively and showed to improve cancer-related outcomes.[3,4,8-10] On the contrary, the effectiveness of other treatment modalities including adjuvant chemotherapy for rectal cancer and for stage II colon cancer, and surgery of the primary tumour in incurable metastatic colorectal cancer are still subject of debate.[11-13] Moreover, there is considerable short-term and long-term morbidity after (chemo)radiotherapy or surgery which should be taken into account. Further defining optimal treatment strategies is therefore of great importance. This thesis focused on improving evidence for treatment modalities that are currently subject of debate for patients with colorectal cancer. This was done using data from randomised controlled trials as well as cancer registry data.

Part I of this thesis focused on treatment, its complications, and outcomes of patients with stage I-III colorectal cancer by using trial data as well as cancer registry data.

In part II, patterns of care and survival across European countries were evaluated for patients with stage II colon cancer, stage I-III rectal cancer, and incurable metastatic colorectal cancer by analysing data from national cancer registries.

PART I: EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER

Perioperative care

Thirty-day mortality is widely accepted as a benchmark measure of outcome to determine risks and benefits of surgical procedures. However, thirty-day mortality underestimates the risk of dying in the first postoperative year after curative surgery for stage I-III colorectal cancer with excess mortality in the first year up to 30%. Comorbidity, stage III tumours, emergency surgery, and postoperative surgical complications have been identified as risk factors for excess mortality in the first year.[14] Moreover, a previous study suggested that major postoperative complications have a negative impact on long-term survival as well.[15] Interestingly, age-related differences in colorectal cancer survival are mainly due to differences in mortality in the first postoperative year; patients ≥75 years who survived the first year had the same cancer-related survival compared to younger patients.[16]

As complications are shown to be a risk factor for one-year excess mortality, we identified the most frequent complications after surgery for stage I-III colon cancer and we studied the association between complications and short-term survival, long-term survival, and recurrences in **Chapter 2**. We found that over 40% of patients had one or more complications. Complications were associated with decreased short-term overall survival and long-term overall survival, even under the condition of surviving the first postoperative year. An increasing number of complications had no additional impact on survival. Ileus, anastomotic leakage, pneumonia, excessive blood loss, electrolyte disorders, cardiac arrhythmia, delirium, abscess, urinary tract infection, and (abdominal) sepsis were the most frequent complications. Moreover, anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within five years after surgery. From this study, it can be concluded that complications not only have an effect on short-term survival, but also on long-term overall survival. Some specific complications are also associated with recurrences, though the exact mechanism has not been elucidated. Focusing on reducing complication rates could eventually lead to better outcomes.

Monitoring time trends in cancer care could be helpful in cancer control. For example, it could give insight in the relation between cancer mortality and changes in exposure to risk factors, or to changes in cancer care. In **Chapter 3**, we assessed time trends in 30-day and one-year mortality in patients with stage I-III colorectal cancer. It was found that that there was a 25% relative decrease in 30-day and 19% relative decrease in one-year mortality in patients ≥75 years with stage I-III colon cancer, while the absolute decrease was 2.1% and 3.5% in 30-day and one year mortality respectively. For younger patients, we observed low 30-day and one-year mortality rates, implying that a further reduction in mortality would be difficult to achieve. However, 30-day and one-year mortality rates are still high for older patients with stage I-III colorectal cancer. Focusing on older patients with colorectal cancer in order to select the right patients for the right treatment could further improve outcomes of colorectal cancer care.

Adjuvant chemotherapy for patients with rectal cancer

Adjuvant chemotherapy aims to prevent the occurrence of distant metastases by eliminating circulating tumour cells and micrometastases. The use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME for patients with rectal cancer has been extensively debated as a result of inconclusive evidence. This is also shown in large differences in various treatment guidelines. The Dutch guideline for example, states that there is no indication for adjuvant chemotherapy for patients with rectal cancer.[17] On the contrary, the US NCCN guideline recommends adjuvant chemotherapy for all patients with stage II or III rectal cancer after preoperative chemoradiotherapy and surgery, although it is recognised that conclusive data are lacking.[18]

Advice to give adjuvant chemotherapy to patients with stage II or III rectal cancer was based for a long time on extrapolation of results from randomised clinical trials on adjuvant chemotherapy for colon cancer, as well as on studies showing a benefit of adjuvant 5-fluorouracil (FU) based chemotherapy after radical surgery for rectal cancer before the era of standardised TME and without the use of preoperative (chemo) radiotherapy.[10,19]

In **Chapter 4**, we reported the results of the PROCTOR-SCRIPT study, a randomised controlled phase III trial. In this trial, patients aged ≥18 years with a rectal adenocarcinoma, who had preoperative (chemo)radiotherapy and TME, (y)pTNM stage II or III, and R0 (PROCTOR and SCRIPT) or R1 (SCRIPT) resection, were randomised between observation and adjuvant chemotherapy with 5-FU/LV (PROCTOR) or capecitabine (SCRIPT). After almost thirteen years, the trial was closed due to poor patient accrual without reaching the intended inclusion of 840 patients. In total, 470 patients were included, of whom 439 were eligible for analyses. After a median follow-up of five years, we could not demonstrate a significant benefit in overall survival, disease-free survival, and recurrences for adjuvant chemotherapy, though the lack of statistical power may have prevented detection of small differences.

Three other trials, the I-CNR-RT trial, the EORTC 22921 trial, and the CHRONICLE trial also compared adjuvant chemotherapy with observation after preoperative (chemo) radiotherapy and surgery. These studies all did not demonstrate a benefit of adjuvant chemotherapy.[20-22] On the contrary, the QUASAR trial found a small benefit in survival and recurrence for patients with rectal cancer, but only 21% of these patients had preoperative radiotherapy.[23]

To get more information about the role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer, we did a meta-analysis of individual patient data. The results were described in **Chapter 5**. Data from the PROCTOR-SCRIPT trial, the I-CNR-RT trial, the EORTC 22921 trial, and the CHRONICLE trial could be obtained. Patients with (y)pTNM stage II or III disease, who had a R0 resection after a low anterior resection or abdominoperineal resection, and a tumour located no more than 15cm from the anal verge, were included. Our findings showed no benefit of adjuvant chemotherapy on overall survival, disease-free survival, and distant recurrences. Although there are several limitations of the individual studies in our meta-analysis, including poor compliance to adjuvant chemotherapy, two studies without sufficient power, and a long accrual period with changes in practice over time as for example TME and type of chemotherapy, we think this meta-analysis provides the best available evidence comparing adjuvant chemotherapy with observation after preoperative (chemo)radiotherapy for patients with rectal cancer and it is unlikely

that there will be new trials investigating this subject. Therefore, we think there is no evidence for the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery.

A uniform definition of the rectum is important for optimal treatment of upper rectal tumours and distal sigmoid tumours. However, different definitions to distinguish the rectum from the sigmoid have been used in studies and guidelines. The most reported pragmatic definition of the rectum is a tumour ≤15cm from the anal verge, though the most reported ideal definition of the rectum on imaging is the sigmoid take-off.[24] In the meta-analysis in **Chapter 5**, we did a subgroup analysis comparing the effect of adjuvant chemotherapy stratified by distance of the tumour from the anal verge. We found that tumours located 10-15cm from the anal verge had a benefit with adjuvant chemotherapy regarding disease-free survival and distant recurrences. Because we detected no significant interaction between distance from the anal verge and treatment group, these results are not definitive. Nevertheless, these results raise the question if tumours located 10-15cm from the anal verge should be considered as colon tumours, though further research is warranted for definitive conclusions.

Compliance to adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery is suboptimal. In the EORTC 22921 trial 43% completed all cycles of chemotherapy, while this was 48% in the CHRONICLE trial, and 55% of patients in the I-CNR-RT trial received three to six courses of chemotherapy.[20-22] In the PROCTOR-SCRIPT trial presented in **Chapter 4**, compliance to adjuvant chemotherapy was 73.6%, which may be higher compared to the EORTC 22921 trial and I-CNR-RT trial because patients were randomised postoperatively. Compliance may be higher than in the CHRONICLE trial because in the PROCTOR-SCRIPT trial 5-FU monotherapy was used, while combination chemotherapy was used in the CHRONICLE trial.

In conclusion, based on the results reported in this thesis, there is no evidence to support the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery in patients with stage II or III rectal cancer. It is suggested that patients with a tumour located 10-15cm from the anal verge might benefit from adjuvant chemotherapy, though these results are not definitive.

PART II: INTERNATIONAL COMPARISONS ON TREATMENT AND OUTCOMES OF PATIENTS WITH COLORECTAL CANCER

Population-based observational studies

Evidence-based medicine is the use of best available research to guide clinical decision making in patients and is intended to complement clinical judgment in individual patients.

Randomised clinical trials are considered to be the gold standard to evaluate the effect of cancer treatment. However, in general, trials have strict inclusion and exclusion criteria and are therefore limited in predicting real-world outcomes.[25] On the contrary, evaluating treatment effectiveness in observational studies is disputable. Observed outcomes may be the result of differences among patients being given either one or the other treatment. Moreover, there could be residual confounding despite attempts to adjust for identified differences between two treatment groups.[26]

There are several situations in which randomised clinical trials are not feasible, and attempts have been made in order to use observational data to evaluate treatment effectiveness. A tool that can be used to estimate treatment effects and to reduce residual confounding in comparative effectiveness research is instrumental variable analysis, where an instrumental variable is defined as a factor that is related to treatment, but neither directly nor indirectly related to the study outcome.[27,28]

In **Chapter 6**, we elaborated on the EURECCA (European Registration of Cancer Care) project, which is a quality assurance programme that aims to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics in relation to outcomes in order to improve the quality of cancer care and to reduce variation in outcomes. Quality assurance programmes aim to optimise the quality of care by determining standards and assuring that these standards are met. Although several aspects of cancer treatment have been studied extensively and shown to improve outcomes, there is still considerable variation in outcomes between European countries that cannot be easily explained.[1]

To get insight into treatment strategies and outcomes between European countries for patients with stage II colon cancer, stage I-III rectal cancer, and incurable stage IV colorectal cancer (**Chapter 7, 8, 9**), we collected data of national, population-based cancer registries of countries willing to participate in the EURECCA project. Currently, over twenty European countries have a national cancer registry with coverage of the entire population. Other European countries have no complete coverage, or lack the existence of a national cancer registry. In total, cancer registries in Europe cover about 60% of the European population, though coverage increases over time.[29]

Several common variables were collected from the national cancer registries, which resulted in valuable insights into treatment strategies and outcomes. However, there are also challenges left when it comes to data comparison between European countries. As a result of privacy legislation, it is impossible for some countries to establish a national cancer registry, or it is not allowed to share data to participate in a European project as EURECCA. Moreover, not all national cancer registries collect the same data variables

and do not collect data in the same manner. Differences in access to health care and differences in health care systems imply difficulties in data comparison.

Adjuvant chemotherapy for patients with stage II colon cancer

As already described in the introduction of this thesis, there is ongoing debate about the benefit of adjuvant chemotherapy for patients with stage II colon cancer since previous studies did not demonstrate an improvement in overall survival, but only a better disease-free survival.[12] Clinicopathologic features that are associated with a worse prognosis in patients with stage II colon cancer include a pT4 stage, a poorly differentiated tumour, lymphovascular or perineural invasion, bowel obstruction or perforation, inadequate lymph node sampling (<12), and a high preoperative carcinoembryonic antigen.[30] In Europe, it is advised to consider adjuvant chemotherapy in patients who present with at least one of the high-risk features.[31]

Within the EURECCA project, we were able to obtain data from seven European countries to compare the use of adjuvant chemotherapy and to compare relative survival. The results of this international comparison are shown in **Chapter 7**. Common data variables included information on gender, age, year of incidence, TNM stage, tumour grade, and the use of adjuvant chemotherapy. Information on pathological TNM substage IIA or IIB was not available in England. Moreover, information on tumour grade was not available in Denmark and unknown in 3.5% - 12.0% in the other countries.

In this study, we observed large differences in the use of adjuvant chemotherapy between European countries. The proportion of all patients with stage II colon cancer receiving adjuvant chemotherapy ranged from 7.1% in the Netherlands to 29.0% in Belgium, while this ranged from 4.7% in the Netherlands to 25.1% in patients with stage IIA colon cancer, and from 22.4% to 49.4% in patients with stage IIB colon cancer. Although there was large variation in the proportion of patients receiving adjuvant chemotherapy between European countries, we found no clear linear pattern between the proportion of adjuvant chemotherapy and adjusted relative survival. However, a better adjusted relative survival was observed for Sweden and Belgium compared with the Netherlands, and also patients from Ireland had a better adjusted relative survival compared with the Netherlands in patients with stage IIA disease.

It is an interesting finding that the proportion of adjuvant chemotherapy differs largely between European countries, with the biggest difference between the Netherlands and Belgium. Although several high-risk features were identified to be associated with a worse prognosis and adjuvant chemotherapy is given to high-risk groups only, there is no international consensus on the exact definition of high-risk stage II colon cancer. For example, in the MOSAIC study, high-risk stage II colon cancer was defined

as the presence of at least one of the following criteria: pT4 stage, perforation, or less than 10 lymph nodes examined.[32] It would have been of value to have information on other high-risk features except tumour substage to unravel the differences in the use of adjuvant chemotherapy between European countries. Moreover, patients with stage II colon cancer with tumour microsatellite-instability do not benefit from adjuvant chemotherapy.[33] However, information on microsatellite status is not available either. Patient characteristics as for example comorbidity and physical functioning would also give insight in why differences in the use of adjuvant chemotherapy exist.

Standard adjuvant chemotherapy for patients with colon cancer consists of fluoropyrimidine (oral capecitabine or infusion of 5-FU/LV) combined with oxaliplatin. When there is a contraindication for oxaliplatin, fluoropyrimidine monotherapy could be considered.[34-36] Interestingly, the long-term results of the MOSAIC study showed only a small non-significant improvement of 3.7% in overall survival and a non-significant improvement of 5.7% in disease-free survival for combination chemotherapy compared with fluoropyrimidine monotherapy in patients with high-risk stage II colon cancer.[32] Furthermore, optimal duration of adjuvant chemotherapy for high-risk stage II colon cancer is not completely clear, although three months of adjuvant chemotherapy seems to be non-inferior to six months of adjuvant chemotherapy.[37] To identify subgroups of patients who may benefit from adjuvant chemotherapy and to identify best practices with population-based data, it would be very relevant for national cancer registries to collect more detailed data items on patient characteristics such as comorbidity, on tumour characteristics, and on treatment and its toxicity and compliance.

Our international comparison on adjuvant chemotherapy and relative survival in patients with stage II colon cancer shows large variation in the use of adjuvant chemotherapy between European countries, though no clear relation between the proportion of adjuvant chemotherapy and relative survival was demonstrated. This supports the idea that there is no indication for routine administration of adjuvant chemotherapy in patients with stage II colon cancer. Further defining selection criteria for adjuvant chemotherapy could eventually result in optimal treatment for subgroups of patients with stage II colon cancer. Registering detailed information in national cancer registries on patient and tumour characteristics as well as on treatment would be helpful to get insight which patient subgroups may benefit from adjuvant chemotherapy.

Treatment strategies for patients with stage I-III rectal cancer

Guidelines regarding preoperative and postoperative treatment strategies for patients with stage I-III rectal cancer differ between countries. It is evident that preoperative radiotherapy followed by total mesorectal excision is effective in reducing the probability of local recurrences and there is a benefit in cancer-specific survival compared with total

mesorectal excision only.[4] Moreover, for locally advanced rectal cancer, preoperative chemoradiotherapy is thought to be necessary to achieve a tumour-free circumferential resection margin, and a complete pathological response (pCR) could be achieved in almost 30% of patients with cT2 cancers and in over 15% of cT3 cancers.[38] However, the benefits of preoperative (chemo)radiotherapy should be carefully weighed against the morbidity associated with it, as for example faecal incontinence, bladder dysfunction, and sexual dysfunction.[39,40] It is therefore challenging to avoid undertreatment as well as overtreatment for patients with rectal cancer. As already discussed before, adjuvant chemotherapy after preoperative (chemo)radiotherapy and total mesorectal excision is subject of debate and large differences in European guidelines exist regarding the recommendation of adjuvant chemotherapy.

In **Chapter 8**, we did a EURECCA international comparison of oncologic treatment strategies and relative survival of patients with (y)pTNM stage I-III rectal cancer. Population-based national cohort data from seven European countries and single-centre data from one European country were obtained. Large differences in preoperative and postoperative treatment strategies for patients with stage I-III rectal cancer were observed between neighbouring European countries. More preoperative radiotherapy and less preoperative chemoradiotherapy was given in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. Single-centre data from Lithuania showed that over eighty percent of patients had no preoperative treatment. Patients from Belgium compared with the Netherlands, from Denmark compared with Sweden, and from England compared with Ireland more often received adjuvant chemotherapy. In Spain, over half of the patients had preoperative chemoradiotherapy and about sixty percent had adjuvant chemotherapy. Comparing the Netherlands and Belgium for example, adjuvant chemotherapy was given in 9.6% of patients in the Netherlands while this was 39.1% in Belgium where adjuvant chemotherapy is advised in patients without preoperative (chemo)radiotherapy and advised to be considered in patients with stage II or III disease after preoperative (chemo) radiotherapy. Besides the fact that there is large variation in adjuvant chemotherapy between these neighbouring countries, it is an interesting finding that still almost ten percent of patients in the Netherlands were not treated according to guideline recommendations.

Although we observed large differences in preoperative and postoperative treatment strategies, we found no differences in relative survival between neighbouring countries. Information on clinical TNM stage would have been very useful in this study. Unfortunately this was not available or missing in a large amount of patients. As a result, analyses could not be performed by substage, because differences in preoperative treatment would have resulted in incomparable data when analysing (y)pTNM substages separately.

Moreover, there might be unknown differences in data registration, there still could be residual confounding although we adjusted the analyses for potential confounders, and data on treatment was recorded as unknown in England if a patient had surgery and no record of receiving preoperative or postoperative treatment. Other details on treatment and for example comorbidity were not available.

This study gives insight in the enormous variation in preoperative and postoperative oncologic treatment strategies. However, we found no clear relation between preoperative and postoperative treatment strategies and adjusted relative survival.

Treatment strategies for patients with incurable metastatic colorectal cancer

Over the past years, survival of patients with incurable metastatic colorectal cancer improved significantly with fluoropyrimidine-based chemotherapy with oxaliplatin or irinotecan often combined with bevacizumab, or EGFR inhibitors (cetuximab or panitumumab).[41-46] Moreover, there is no doubt that obstruction, perforation, or severe bleeding of the primary tumour requires emergency surgery. However, there is ongoing debate about the potential benefit of surgery of the primary tumour in patients with incurable metastatic colorectal cancer with an asymptomatic primary tumour.[47] Several trials have failed to reach a sufficient number of patients and closed prematurely, while results from other trials are still awaited.[48-52] Meanwhile, attempts have been made to study the effect of surgery of the primary tumour in patients with asymptomatic metastatic colorectal cancer with observational data. Retrospective studies demonstrated a benefit of resection of the primary tumour, but these studies are at high risk of confounding by indication as surgery of the primary tumour was not randomised. Patients who did not have surgery of the primary tumour had more extensive metastatic disease, poorer performance status, more comorbidity, and higher alkaline phosphatase and carcinoembryonic antigen (CEA) levels.[53] It is likely that these patients had a worse prognosis on beforehand. For this reason, we need to be cautious to conclude from these data that surgery of the primary tumour results in better survival of patients with incurable metastatic colorectal cancer.

Because it is difficult to directly compare surgery of the primary tumour and survival using retrospective data, we compared treatment strategies and overall survival of patients with incurable metastatic colorectal cancer on country level in **Chapter 9**. We also assessed the effect of different treatment strategies on mortality within the first year using country as an instrumental variable to mimic randomisation. For this EURECCA international comparison, we collected national, population-based data from the Netherlands and Norway. Our results demonstrate that patients from Norway underwent surgery of the primary tumour more often than patients from the Netherlands. Moreover, it may be that patients from the Netherlands received more

chemotherapy than patients from Norway, especially in older patients. However, data on chemotherapy are not complete in the Norwegian Colorectal Cancer Registry and these results should therefore be interpreted with caution. Radiotherapy of the primary tumour in patients with rectal cancer was given less frequent in Norway compared with the Netherlands. Overall, there were no differences observed in crude overall survival between the Netherlands and Norway for patients with incurable metastatic colorectal cancer, though a small survival benefit was observed for Norway compared with the Netherlands after adjustment for potential confounders. Also patients <75 years from Norway had a slightly better crude and adjusted overall survival than patients from the Netherland. On the contrary, patients ≥75 years from Norway had a worse crude and adjusted overall survival compared with the Netherlands. Using instrumental variable analysis, no benefit in one-year mortality was found for a treatment strategy with a higher proportion of surgery of the primary tumour.

Unfortunately, data on chemotherapy was not complete in the Norwegian Colorectal Cancer Registry. Also no information is available in both cancer registries on for example emergency surgery, symptoms of the primary tumour, chemotherapy regimen, toxicity, chemotherapy compliance, comorbidity, and ASA classification. Moreover, especially in this patient group with palliative care, it would be of relevance to have information on quality of life and patient preferences. Still there could be residual confounding as a result of the retrospective design of the study.

From this study, it can be concluded that although there is considerable variation in treatment strategy with especially more surgery and less radiotherapy in Norway compared with the Netherlands, there are only very small differences in overall survival between these two countries and the clinical relevance of the small survival differences could be questioned. Furthermore, different treatment strategies had no effect on one-year mortality using instrumental variable analysis. Comparing treatment strategies and survival on country level prevents the problem of confounding by indication as happened in retrospective studies directly comparing surgery of the primary tumour with observation in patients with asymptomatic incurable metastatic colorectal. Small survival differences between the Netherlands and Norway that we observed may be partly the result of differences in treatment strategies, but there may be other factors as well that impact on survival. Although we can conclude from this study that there are large differences in treatment strategy and only very small differences in overall survival, we cannot define which patient subgroups to select for various treatment options, in particular who will or will not benefit from surgery of the primary tumour. This still remains subject of debate, although the current evidence does not support routine surgery of the primary tumour in patients with asymptomatic incurable metastatic colorectal cancer.

FUTURE PERSPECTIVES

A paradigm shift is occurring in gastrointestinal cancer care from a one-size-fits-all therapy based on TNM stage to that of individually tailored therapy. Furthermore, in gastrointestinal cancer care including rectal cancer care, there is an important shift towards intensified neoadjuvant therapy in order to improve outcomes and even omission of surgery seems to be possible in a selected group of patients.

Given the high rate of complications after surgery for non-metastasised colorectal cancer and its negative impact on short-term and long-term outcomes, a prehabilitation and rehabilitation programme may contribute to reduce complications in older patients who are fit enough for surgery.[54] Although we observed high 30-day and one-year mortality rates especially among patients ≥75 years, a more recent study showed that the difference between older and younger patients in terms of one-year relative postoperative survival became smaller.[55] Geriatric consultation can contribute in final multidisciplinary treatment decision-making. Moreover, strict protocolised Enhanced Recovery After Surgery care improvement processes, resulting in shorter length of hospital stay and less complications, could very well have contributed in reducing the gap in outcomes between older and younger patients.

We found no evidence for the routine use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and total mesorectal excision for patients with rectal cancer. Older research comparing preoperative versus postoperative chemoradiotherapy demonstrated that preoperative treatment leads to better adherence to chemotherapy and less toxicity.[56] A shift towards intensified neoadjuvant therapy for locally advanced rectal cancer is going on. In the meantime, the results of the RAPIDO trial show a lower disease-related treatment failure, as a result of less distant metastases, in patients with high-risk locally advanced rectal cancer after preoperative short-course radiotherapy, followed by chemotherapy and total mesorectal excision compared with conventional chemoradiotherapy.[57] Moreover, since neoadjuvant chemoradiotherapy can result in a complete clinical response, this can result in less extensive surgery, and even in a "watch-and-wait" strategy to spare patients from surgical treatment has been approached in a selected group of patients.[58,59]

An initiative such as EURECCA creates a platform to reflect on cancer care and improve cancer outcomes. Population-based database analyses can result in evidence-based and tailor-made treatment. As shown in this thesis, comparing data from cancer registries gives valuable insight in treatment strategies and outcomes between European countries. However, a core unified dataset in Europe, ideally prospectively collected, including detailed data on patient characteristics such as comorbidity and functional status, on

tumour characteristics, on treatment and its related toxicity and complications, and on outcomes including oncologic outcomes as well as quality of life, would be essential to further use epidemiological data to optimise and improve colorectal cancer care.

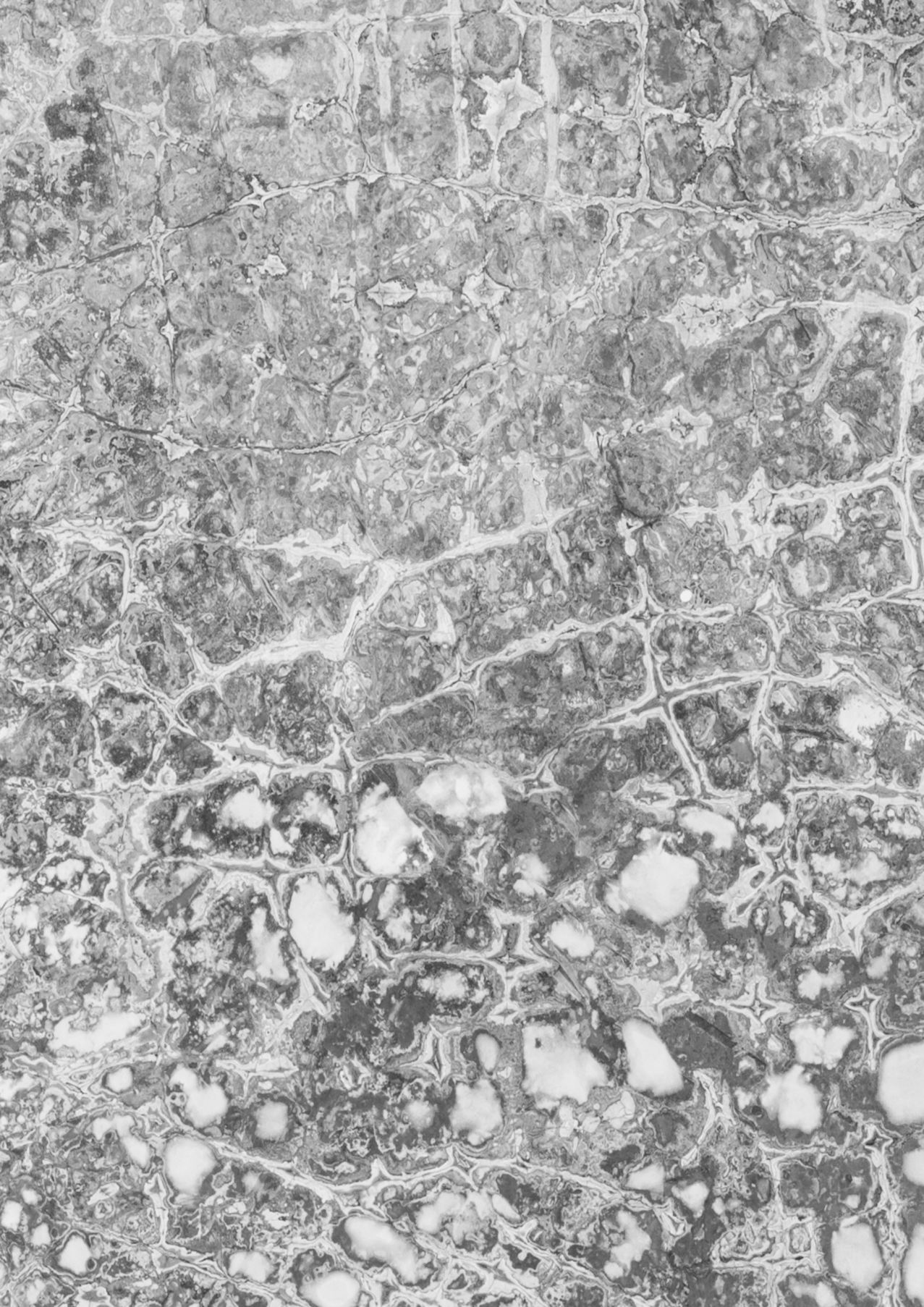
In the era of multidisciplinary management and shared-decision making, analyses from a unified European population-based dataset, of course combined with results from trials as well as the search for additional biomarkers will be the challenge for the future to better select subgroups of patients for treatment. More importantly, intensified neoadjuvant (chemo)radiotherapy addresses the need to monitor patients carefully with intense radiological follow-up to only intervene in case of tumour recurrence. In some patients, this can even avoid surgery in case of long-lasting complete response.

REFERENCES

1. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer* 2015; **51**(15): 2158-68.
2. Shah MA, Renfro LA, Allegra CJ, et al. Impact of Patient Factors on Recurrence Risk and Time Dependency of Oxaliplatin Benefit in Patients With Colon Cancer: Analysis From Modern-Era Adjuvant Studies in the Adjuvant Colon Cancer End Points (ACCENT) Database. *J Clin Oncol* 2016; **34**(8): 843-53.
3. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**(8843): 457-60.
4. 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**(6): 575-82.
5. Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther* 2017; **17**(12): 1131-46.
6. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 2015; **30**(2): 205-12.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**(1): 5-29.
8. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
9. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**(10): 1638-44.
10. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**(6): 352-8.
11. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010; **21**(9): 1743-50.
12. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. *Cochrane Database Syst Rev* 2008; (3): CD005390.
13. Anwar S, Peter MB, Dent J, Scott NA. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. *Colorectal Dis* 2012; **14**(8): 920-30.
14. Gooiker GA, Dekker JW, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* 2012; **19**(8): 2428-34.
15. Odermatt M, Miskovic D, Flashman K, et al. Major postoperative complications following elective resection for colorectal cancer decrease long-term survival but not the time to recurrence. *Colorectal Dis* 2015; **17**(2): 141-9.
16. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**(6): 1533-9.
17. https://www.oncoline.nl/colorectaalcarcinoom. *Accessed September* 2019.
18. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. *Accessed September* 2019.
19. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; (3): CD004078.
20. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**(2): 184-90.
21. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25**(7): 1356-62.
22. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**(2): 223-9.
23. Quasar Collaborative G, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**(9604): 2020-9.

24. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al. Definition of the Rectum: An International, Expert-based Delphi Consensus. *Ann Surg* 2019.
25. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004; **363**(9422): 1728-31.
26. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000; **321**(7256): 255-6.
27. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; **19**(6): 537-54.
28. Boef AG, le Cessie S, Dekkers OM. [Instrumental variable analysis]. *Ned Tijdschr Geneeskd* 2013; **157**(4): A5481.
29. Siesling S, Louwman WJ, Kwast A, et al. Uses of cancer registries for public health and clinical research in Europe: Results of the European Network of Cancer Registries survey among 161 population-based cancer registries during 2010-2012. *Eur J Cancer* 2015; **51**(9): 1039-49.
30. Quah HM, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. *Dis Colon Rectum* 2008; **51**(5): 503-7.
31. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi64-72.
32. Andre T, de Gramont A, Vernerey D, et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. *J Clin Oncol* 2015; **33**(35): 4176-87.
33. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003; **349**(3): 247-57.
34. 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**(23): 2343-51.
35. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011; **29**(11): 1465-71.
36. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
37. Iveson TJ, Kerr RS, Saunders MP, et al. 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. *Lancet Oncol* 2018; **19**(4): 562-78.
38. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11**(9): 835-44.
39. Wiltink LM, Marijnen CA, Meershoek-Klein Kranenbarg E, van de Velde CJ, Nout RA. A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial. *Acta Oncol* 2016; **55**(4): 502-8.
40. Loos M, Quentmeier P, Schuster T, et al. Effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013; **20**(6): 1816-28.
41. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Bmj* 1993; **306**(6880): 752-5.
42. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**(16): 2938-47.
43. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; **343**(13): 905-14.
44. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**(9582): 135-42.
45. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**(23): 2335-42.
46. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. *Cancer treatment reviews* 2012; **38**(6): 618-25.
47. Patel S, Chang GJ. Primary Tumor Resection in Metastatic Colorectal Cancer: Please Pass the Salt. *JAMA Oncol* 2015; **1**(9): 1213-4.

48. Kim CW, Baek JH, Choi GS, et al. The role of primary tumor resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial. *Trials* 2016; **17**: 34.
49. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012; **12**: 142.
50. Biondo S, Frago R, Kreisler E, Espin-Basany E, Spanish CRG. Impact of resection versus no resection of the primary tumor on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4). *Int J Colorectal Dis* 2017; **32**(7): 1085-90.
51. t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014; **14**: 741.
52. Cotte E, Villeneuve L, Passot G, et al. GRECCAR 8: impact on survival of the primary tumor resection in rectal cancer with unresectable synchronous metastasis: a randomized multicentre study. *BMC Cancer* 2015; **15**: 47.
53. Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Ann Surg Oncol* 2014; **21**(12): 3900-8.
54. Souwer ETD, Bastiaannet E, de Bruijn S, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence". *Eur J Surg Oncol* 2018; **44**(12): 1894-900.
55. Brouwer NPM, Heil TC, Olde Rikkert MGM, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. *Eur J Cancer* 2019; **116**: 1-9.
56. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**(17): 1731-40.
57. Bahadoer RR, Dijkstra EA, van Betten E, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial *Lancet Oncol. 2021* Jan;22(1):29-42.
58. Habr-Gama A, de Souza PM, Ribeiro U, Jr., et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis Colon Rectum* 1998; **41**(9): 1087-96.
59. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018; **391**(10139): 2537-45.



&

APPENDICES
Nederlandse samenvatting
List of publications
Curriculum vitae
Dankwoord

NEDERLANDSE SAMENVATTING

Algemeen

Overleving van patiënten met colorectaal carcinoom is de afgelopen decennia aanzienlijk verbeterd als gevolg van ontwikkelingen in screening, stadiëring, behandeling en follow-up.[1-5] Van alle patiënten met colorectaal carcinoom ontwikkelt uiteindelijk echter ongeveer 20% metastasen en 20% van de patiënten blijkt gemetastaseerde ziekte te hebben ten tijde van diagnose.[6,7] Eerdere studies hebben een verbetering van oncologische uitkomsten aangetoond van bijvoorbeeld totale mesorectale excisie (TME) en preoperatieve (chemo)radiotherapie bij rectumcarcinoom en adjuvante chemotherapie bij stadium III coloncarcinoom.[3,4,8-10] Aan de andere kant staat de effectiviteit van andere behandelmodaliteiten, zoals adjuvante chemotherapie bij rectumcarcinoom en stadium II coloncarcinoom en chirurgie van de primaire tumor bij gemetastaseerd colorectaal carcinoom in de asymptomatische fase met permanent irresectabele metastasen, ter discussie. Daarnaast brengen (chemo)radiotherapie en chirurgie aanzienlijke morbiditeit met zich mee, zowel op de korte als de lange termijn. Het verder definiëren van optimale behandelstrategieën is daarom van belang. Dit proefschrift had tot doel het bewijs voor behandelingen voor colorectaal carcinoom die momenteel onderwerp van discussie zijn, te vergroten. Hiervoor werd gebruikt gemaakt van zowel data van gerandomiseerde studies, als data van kankerregistraties.

Deel I van dit proefschrift focust zich op behandeling, bijkomende complicaties en uitkomsten van patiënten met stadium I-III colorectaal carcinoom.

In deel II van dit proefschrift worden behandelstrategieën en overleving tussen verschillende Europese landen vergeleken voor patiënten met stadium II colon carcinoom, stadium I-III rectum carcinoom en asymptomatisch gemetastaseerd colorectaal carcinoom met irresectabele metastasen.

DEEL I: EVALUATIE VAN BEHANDELING VAN PATIËNTEN MET STADIUM I-III COLORECTAAL CARCINOOM

Perioperatieve zorg

Dertig dagen mortaliteit is een geaccepteerde uitkomstmaat om voor- en nadelen van chirurgische behandeling in kaart te brengen. De dertig dagen mortaliteit blijkt echter een onderschatting te zijn van het risico op overlijden binnen een jaar na operatie. Risicofactoren voor oversterfte in het eerste jaar na operatie zijn comorbiditeit, stadium III tumoren, spoedoperaties en postoperatieve complicaties.[11] Behalve het negatieve effect van complicaties op de korte termijn, is in eerder onderzoek de suggestie gewekt dat ernstige postoperatieve complicaties ook een negatief effect kunnen

hebben op de overleving op lange termijn.[12] Een andere interessante bevinding is dat leeftijdsgerelateerde verschillen in kankerspecifieke overleving vooral het gevolg zijn van verschillen in sterfte in het eerste jaar na operatie; patiënten ≥75 jaar die het eerste jaar na operatie overleefden, bleken dezelfde kankerspecifieke overleving te hebben als jongere patiënten.[13]

In **Hoofdstuk 2** werden de meest voorkomende postoperatieve complicaties voor stadium I-III coloncarcinoom in kaart gebracht en werd de associatie tussen complicaties en overleving en recidieven onderzocht. Totaal kreeg meer dan 40% van de patiënten één of meerdere complicaties. Patiënten met postoperatieve complicaties bleken een slechtere eenjaars- en vijfjaarsoverleving te hebben, ook vijf jaar na het overleven van het eerste postoperatieve jaar. De meest voorkomende complicaties waren het optreden van ileus, naadlekkage, pneumonie, overmatig bloedverlies, elektrolytstoornissen, hartritmestoornissen, delier, abces, urineweginfecties en (abdominale) sepsis. Naadlekkage, overmatig bloedverlies, (abdominale) sepsis, delier en het ontwikkelen van een abces waren geassocieerd met een slechtere lange termijn overleving en het vaker optreden van recidieven. Deze studie toont aan dat complicaties niet alleen een effect hebben op de overleving op de korte termijn, maar ook op de lange termijn. Focussen op het verminderen van complicaties kan uiteindelijk leiden tot betere oncologische uitkomsten.

Het analyseren van tijdtrends van oncologische uitkomsten kan onder andere inzicht geven in de relatie tussen kankersterfte en veranderingen in blootstelling aan risicofactoren of tussen kankersterfte en veranderingen in oncologische zorg. In **Hoofdstuk 3** werden tijdtrends in dertig dagen mortaliteit en eenjaarsmortaliteit onderzocht voor patiënten met stadium I-III colorectaal carcinoom. Hierbij werd een afname in dertig dagen mortaliteit en eenjaarsmortaliteit gevonden bij patiënten met stadium I-III coloncarcinoom, alhoewel de absolute afname klein was. Oudere patiënten met colorectaal carcinoom hebben nog steeds een hoge postoperatieve mortaliteit. Dit suggereert dat de aandacht uit zou moeten gaan naar oudere patiënten met colorectaal carcinoom om de juiste patiënten voor de juiste behandeling te selecteren en hiermee de oncologische uitkomsten te kunnen verbeteren.

Adjuvante chemotherapie voor patiënten met rectumcarcinoom

Het doel van adjuvante chemotherapie is om het optreden van metastasen te voorkomen. Het gebruik van adjuvante chemotherapie na preoperatieve (chemo)radiotherapie en totale mesorectale excisie bij patiënten met rectumcarcinoom wordt echter uitgebreid bediscussieerd gezien gebrek aan bewijs. Dit is tevens terug te zien in uiteenlopende aanbevelingen in verschillende behandelrichtlijnen.

Het advies om adjuvante chemotherapie toe te dienen aan patiënten met stadium II of III rectumcarcinoom is lange tijd gebaseerd geweest op resultaten van studies naar adjuvante chemotherapie bij coloncarcinoom en op resultaten van studies die een voordeel van adjuvante chemotherapie na chirurgie voor rectumcarcinoom lieten zien voordat gestandaardiseerde chirurgie werd geïntroduceerd en zonder preoperatieve (chemo)radiotherapie.[10,14]

Hoofdstuk 4 beschrijft de resultaten van de PROCTOR-SCRIPT studie, een gerandomiseerde studie waarin, bij patiënten met (y)pTNM stadium II of III rectumcarcinoom, adjuvante chemotherapie met 5-FU/LV of capecitabine na (chemo)radiatie en totale mesorectale excisie vergeleken werd met observatie. Na bijna dertien jaar werd de studie gesloten zonder de beoogde inclusie te behalen. In deze studie hebben we geen significant effect van adjuvante chemotherapie kunnen aantonen ten aanzien van algehele overleving, ziektevrije overleving en recidieven, alhoewel het gebrek aan statistische power er voor zou kunnen hebben gezorgd dat kleine verschillen niet konden worden aangetoond. Drie andere studies, de I-CNR-RT studie, de EORTC 22921 studie en de CHRONICLE studie hebben eveneens het effect van adjuvante chemotherapie ten opzichte van observatie onderzocht na preoperatieve (chemo)radiotherapie en chirurgie en geen effect van adjuvante chemotherapie aangetoond.[15-17] Aan de andere kant heeft de QUASAR studie wel een klein overlevingsvoordeel voor adjuvante chemotherapie laten zien voor patiënten met rectumcarcinoom, echter slechts 21% van deze patiënten had preoperatieve radiotherapie ondergaan.[18]

Gezien geen van deze individuele studies een eind aan de discussie over de rol van adjuvante chemotherapie heeft gemaakt, werd in **Hoofdstuk 5** een individuele patiënt data meta-analyse verricht om de effectiviteit van fluorouracil-gebaseerde adjuvante chemotherapie na preoperatieve (chemo)radiatie en chirurgie te onderzoeken. Hiervoor kon data van de PROCTOR-SCRIPT studie, de I-CNR-RT studie, de EORTC 22921 studie en de CHRONICLE studie worden verkregen. Bij patiënten met een (y)pTNM stadium II of III rectumcarcinoom, met een R0 resectie en een tumor niet verder dan 15cm vanaf de anus, werd geen verschil in algehele overleving, ziektevrije overleving en metastasen gevonden tussen patiënten die adjuvante chemotherapie kregen vergeleken met observatie. Ook al hebben alle individuele studies die werden geïncludeerd in deze meta-analyse beperkingen, geeft deze meta-analyse op dit moment het best mogelijke bewijs waarin adjuvante chemotherapie met observatie werd vergeleken na preoperatieve (chemo)radiotherapie voor patiënten met rectumcarcinoom en is er op basis hiervan geen indicatie voor het gebruik van adjuvante chemotherapie na preoperatieve (chemo) radiotherapie en chirurgie.

Een eenduidige definitie van het rectum is belangrijk voor het onderscheiden en daarmee

optimaal behandelen van een hoog rectumcarcinoom versus een laag sigmoïdcarcinoom. Er bestaan echter verschillende definities in studies en richtlijnen om het rectum van het sigmoïd te onderscheiden. De meest gebruikte pragmatische definitie van het rectum is een tumor ≤15cm vanaf de anus. In de meta-analyse in **Hoofdstuk 5** hebben we een subgroep analyse verricht naar het effect van adjuvante chemotherapie gestratificeerd naar afstand van de tumor vanaf de anus. Hierbij kwam naar voren dat patiënten met tumoren op 10-15cm vanaf de anus een betere ziektevrije overleving en minder frequent metastasen hadden. Gezien er geen significante interactie was tussen afstand vanaf de anus en behandelgroep zijn deze resultaten echter niet definitief. Desalniettemin roepen deze resultaten de vraag op of tumoren op 10-15cm vanaf de anus beschouwd zouden moeten worden als coloncarcinomen.

Het volbrengen van alle geplande kuren adjuvante chemotherapie is suboptimaal na preoperatieve (chemo)radiotherapie en chirurgie. In de EORTC 22921 studie betrof dit 43% van de patiënten, in de CHRONICLE studie was dit 48% en 55% van de patiënten in de I-CNR-RT studie had drie tot zes kuren chemotherapie afgerond.[15-17] In de PROCTOR-SCRIPT studie was dit 73.6%. Een mogelijke verklaring voor dit hogere percentage is dat patiënten in de PROCTOR-SCRIPT postoperatief werden gerandomiseerd en in de CHRONICLE studie, waar patiënten wel ook postoperatief werden gerandomiseerd, kregen patiënten combinatiechemotherapie en geen 5-FU monotherapie.
Concluderend is er op basis van de resultaten die in dit proefschrift zijn getoond geen bewijs voor het toedienen van adjuvante chemotherapie na preoperatieve (chemo) radiotherapie en chirurgie bij patiënten met stadium II en III rectumcarcinoom. De suggestie is gewekt dat patiënten met een tumor 10-15cm vanaf de anus mogelijk wel baat hebben van chemotherapie, echter deze resultaten zijn niet conclusief.

DEEL II: INTERNATIONAAL VERGELIJKENDE STUDIES NAAR BEHANDELING EN UITKOMSTEN BIJ PATIËNTEN MET COLORECTAAL CARCINOOM

Populatie-gebaseerde observationele studies
'Evidence-based medicine' is het gebruikmaken van de best beschikbare onderzoeken als hulp bij klinische besluitvorming en heeft tot doel om het klinisch oordeel aan te vullen. Gerandomiseerde klinische studies worden gezien als de gouden standaard om het effect van oncologische behandeling te evalueren. Gerandomiseerde studies hebben echter strikte inclusie- en exclusiecriteria en zijn daarom lastig te extrapoleren naar de algehele populatie.[19] Aan de andere kant is het vergelijken van behandelingen in observationele studies discutabel, gezien de geobserveerde uitkomsten ook het effect kunnen zijn van verschillen tussen patiënten in de beide behandelgroepen. Daarnaast kan sprake zijn van residuele confounding.[20]

Er zijn verschillende situaties denkbaar waarin gerandomiseerde studies niet mogelijk zijn. Daarom worden er pogingen gedaan om met behulp van observationele data uitspraken te kunnen doen over behandeleffectiviteit. Een middel dat hiervoor gebruikt kan worden is instrumentele variabele analyse, waarbij een instrumentele variabele is gedefinieerd als een factor die gerelateerd is aan behandeling, maar niet aan de studie-uitkomsten.[21,22]

In **Hoofdstuk 6** werd het EURECCA (European Registration of Cancer Care) project beschreven. EURECCA is een 'quality assurance' project met als doel een multidisciplinaire Europese registratie te creëren met daarin patiënt-, tumor-, en behandelkarakteristieken in relatie tot oncologische uitkomsten om de kwaliteit van oncologische zorg te verbeteren en variatie in uitkomsten te verminderen. Ondanks dat verschillende aspecten van oncologische zorg uitgebreid onderzocht zijn en de effectiviteit van bepaalde behandelingen bewezen is, is er nog steeds aanzienlijke variatie in uitkomsten tussen Europese landen waar niet een eenduidige verklaring voor is.[1]

Om inzicht te krijgen in behandelstrategieën en uitkomsten tussen Europese landen bij patiënten met stadium II coloncarcinoom, stadium I-III rectumcarcinoom en gemetastaseerd colorectaal carcinoom met irresectabele metastasen (**Hoofdstuk 7, 8, 9)**, hebben we binnen het EURECCA project data verzameld van nationale, populatie-gebaseerde kankerregistraties. Momenteel zijn er meer dan twintig Europese landen met een nationale kankerregistratie waarbij de gehele populatie wordt gedekt. Andere Europese landen hebben geen complete dekking, of hebben geen nationale kankerregistratie. Totaal dekken kankerregistraties in Europa ongeveer 60% van de oncologische populatie, waarbij dit over de jaren heen wel toegenomen is.[23]

Verschillende overeenkomstige variabelen werden verzameld vanuit de nationale kankerregistraties, wat resulteerde in waardevolle inzichten in behandelstrategieën en uitkomsten. Er zijn echter ook uitdagingen als het om het vergelijken van data tussen Europese landen gaat. Als gevolg van privacy wetgeving is het voor sommige landen onmogelijk een nationale kankerregistratie op te zetten, of is het niet toegestaan om data te delen voor een project zoals EURECCA. Daarnaast verzamelen niet alle kankerregistraties dezelfde gegevens en verzamelen deze niet op exact dezelfde manier. Ook kunnen verschillen in toegang tot de gezondheidszorg en verschillen in gezondheidszorgsystemen het vergelijken van data bemoeilijken.

Adjuvante chemotherapie voor patiënten met stadium II coloncarcinoom

Gezien eerdere studies geen verbetering in algehele overleving, maar alleen in ziektevrije overleving hebben aangetoond, blijft er discussie bestaan over het effect van adjuvante chemotherapie bij stadium II coloncarcinoom.

Clinicopathologische karakteristieken die zijn geassocieerd met een slechtere prognose bij patiënten met stadium II coloncarcinoom zijn een pT4 stadium, slecht gedifferentieerde tumoren, lymfovasculaire of perineurale invasie, obstructie of perforatie, inadequate hoeveelheid lymfklieren verkregen bij operatie (<12) en een hoog carcino-embryonaal antigen (CEA).[24] Volgens de Europese ESMO richtlijn wordt geadviseerd om adjuvante chemotherapie te overwegen bij patiënten met de aanwezigheid van ten minste één van bovengenoemde risicofactoren.[25]

Binnen het EURECCA project hebben we data van zeven Europese landen kunnen verkrijgen om het gebruik van adjuvante chemotherapie en de relatieve overleving te vergelijken. De resultaten van dit internationaal vergelijk worden beschreven in **Hoofdstuk 7**.

In deze studie observeerden we grote verschillen in het gebruik van adjuvante chemotherapie tussen de verschillende Europese landen. Het percentage patiënten dat adjuvante chemotherapie kreeg varieerde van 4.7% in Nederland tot 25.1% in België bij patiënten met stadium IIA coloncarcinoom en van 22.4% tot 49.4% bij patiënten met stadium IIB coloncarcinoom. Ondanks dat er grote variatie bestond in het percentage patiënten dat adjuvante chemotherapie kreeg toegediend, vonden we geen duidelijk patroon tussen het percentage adjuvante chemotherapie en gecorrigeerde relatieve overleving. Wel werd een betere gecorrigeerde overleving gezien in Zweden en België vergeleken met Nederland. Ook werd een betere overleving gezien in Ierland vergeleken met Nederland in patiënten met stadium IIA coloncarcinoom.

Het is een interessante bevinding dat het percentage patiënten dat behandeld wordt met adjuvante chemotherapie zoveel verschilt binnen Europa, met het grootste verschil tussen Nederland en België. Alhoewel verschillende factoren die geassocieerd zijn met een slechtere prognose zijn geïdentificeerd en adjuvante chemotherapie alleen gegeven wordt aan hoog-risico groepen, is er geen internationale consensus over de exacte definitie van hoog-risico stadium II coloncarcinoom. In de MOSAIC studie bijvoorbeeld, wordt hoog-risico stadium II coloncarcinoom gedefinieerd als de aanwezigheid van ten minste één van de volgende criteria: pT4 stadium, perforatie, of minder dan tien onderzochte lymfklieren.[26] Het zou interessant geweest zijn als we in de huidige studie informatie zouden hebben over andere van deze risicofactoren dan alleen stadium IIA/IIB om te achterhalen waarin de verschillen zitten in het gebruik van adjuvante chemotherapie tussen Europese landen. Daarnaast is bekend dat patiënten met stadium II coloncarcinoom en microsatelliet instabiliteit geen baat hebben bij adjuvante chemotherapie.[27] Echter, informatie over microsatelliet instabiliteit is niet beschikbaar in de kankerregistraties. Patiëntkarakteristieken zoals comorbiditeit en fysiek functioneren zouden ook bij kunnen dragen in het geven van inzicht waarom deze verschillen bestaan.

Adjuvante chemotherapie voor patiënten met coloncarcinoom bestaat standaard uit fluoropyrimidine (oraal capecitabine of infusie van 5-FU/LV) gecombineerd met oxaliplatin. Indien er een contra-indicatie voor oxaliplatin bestaat kan fluoropyrimidine monotherapie worden overwogen.[28-30] Resultaten van de MOSAIC studie toonden slechts een kleine, niet-significante verbetering van 3.7% in algehele overleving en een niet-significante verbetering van 5.7% in ziektevrije overleving voor combinatiechemotherapie vergeleken met fluoropyrimidine monotherapie bij patiënten met hoog-risico stadium II coloncarcinoom.[26] Bovendien is de optimale duur van de chemotherapie niet compleet duidelijk, alhoewel drie maanden adjuvante chemotherapie non-inferieur lijkt ten opzichte van zes maanden.[31]

Het huidige internationaal vergelijk waarin adjuvante chemotherapie en relatieve overleving bij patiënten met stadium II coloncarcinoom werd onderzocht, laat grote variatie zien tussen Europese landen in het gebruik van adjuvante chemotherapie. Echter werd geen duidelijk patroon aangetoond tussen het percentage adjuvante chemotherapie en relatieve overleving. Dit ondersteunt de gedachte dat er geen indicatie is voor het standaard toedienen van adjuvante chemotherapie. Het verder definiëren van selectiecriteria voor adjuvante chemotherapie kan uiteindelijk leiden tot optimale behandeling voor subgroepen van patiënten met stadium II coloncarcinoom. Het registreren van gedetailleerde informatie in kankerregistraties over patiënt- en tumorkarakteristieken, alsook over behandeling, zou van nut zijn om inzicht te verkrijgen in of bepaalde subgroepen patiënten wel baat hebben bij adjuvante chemotherapie.

Behandelstrategieën voor patiënten met stadium I-III rectumcarcinoom

Richtlijnen ten aanzien van preoperatieve en postoperatieve behandeling voor patiënten met stadium I-III rectumcarcinoom verschillen tussen landen. Uit eerdere studies is duidelijk naar voren gekomen dat preoperatieve radiotherapie gevolgd door totale mesorectale excisie effectief is in het verminderen van lokale recidieven en dat er een voordeel is in kankerspecifieke overleving ten opzichte van alleen totale mesorectale excisie.[4] Daarnaast kan bij patiënten met een 'locally advanced' rectumcarcinoom preoperatieve chemoradiatie tot tumorvrije circumferentiële resectiemarges leiden en kan een complete pathologische respons (pCR) bereikt worden in bijna 30% van de patiënten met een cT2 tumor en in meer dan 15% van patiënten met een cT3 tumor.[32] Echter moeten de voordelen van preoperatieve (chemo)radiotherapie afgewogen worden tegen de morbiditeit die hiermee geassocieerd is, zoals fecale incontinentie, blaasdysfunctie, en seksuele dysfunctie.[33,34] Het is daarom een uitdaging om zowel onderbehandeling als overbehandeling te vermijden. Zoals reeds eerder beschreven is adjuvante chemotherapie na preoperatieve (chemo)radiotherapie en chirurgie onderwerp van discussie.

In **Hoofdstuk 8** hebben we een internationaal vergelijk uitgevoerd waarin oncologische behandelstrategieën en relatieve overleving van patiënten met (y)pTNM stadium I-III rectumcarcinoom werden vergeleken. Nationale, populatie-gebaseerde data van zeven Europese landen en data van een ziekenhuis van één Europees land werden verkregen. Er bleken grote verschillen te bestaan in zowel preoperatieve als postoperatieve behandelstrategieën voor patiënten met stadium I-III rectumcarcinoom tussen buurlanden. Er werd meer preoperatieve radiotherapie en minder preoperatieve chemoradiatie gegeven in Nederland vergeleken met België, in Zweden vergeleken met Denemarken en in Engeland vergeleken met Ierland. Data vanuit één ziekenhuis in Litouwen toonde dat meer dan 80% van de patiënten geen preoperatieve behandeling had ondergaan. Patiënten uit België vergeleken met Nederland, uit Denemarken vergeleken met Zweden en uit Engeland vergeleken met Ierland kregen vaker adjuvante chemotherapie. In Spanje kreeg meer dan de helft van de patiënten preoperatieve chemoradiatie en ongeveer 60% adjuvante chemotherapie. Bij het vergelijken van bijvoorbeeld Nederland en België kreeg 9.6% van de patiënten in Nederland adjuvante chemotherapie, terwijl dit 39.1% van de patiënten in België betrof waar adjuvante chemotherapie wordt geadviseerd in patiënten zonder preoperatieve (chemo) radiotherapie en geadviseerd wordt te overwegen in patiënten met stadium II of III na preoperatieve (chemo)radiotherapie. Naast het feit dat er grote variatie is in adjuvante chemotherapie tussen deze twee buurlanden, is het een interessante bevinding dat nog steeds bijna tien procent van de patiënten in Nederland niet volgens de aanbevelingen uit de richtlijn worden behandeld.

Alhoewel we grote verschillen in preoperatieve en postoperatieve behandelstrategieën hebben geobserveerd, vonden we geen verschillen in relatieve overleving tussen buurlanden.

Informatie over klinisch TNM stadium zou in deze studie zeer nuttig zijn geweest. Helaas was deze informatie niet beschikbaar of miste deze informatie in een grote hoeveelheid patiënten. Als gevolg hiervan konden de analyses niet per stadium worden uitgevoerd, aangezien verschillen in preoperatieve behandeling zou leiden tot onvergelijkbare data als de analyses per (y)pTNM stadium zouden worden geanalyseerd. Daarnaast kunnen er verschillen in dataregistratie zijn, er kan nog steeds sprake zijn van residuele confounding en data over behandeling was geregistreerd als onbekend in Engeland als een patiënt chirurgie had gehad en er geen registratie was van het krijgen van preoperatieve dan wel postoperatieve behandeling. Andere details over behandeling en bijvoorbeeld comorbiditeit waren ook niet beschikbaar.

Deze studie geeft inzicht in de enorme variatie in preoperatieve en postoperatieve oncologische behandelstrategieën. Echter hebben we geen duidelijke relatie tussen

preoperatieve en postoperatieve behandelstrategieën en gecorrigeerde relatieve overleving aangetoond.

Behandelstrategieën voor patiënten met asymptomatisch gemetastaseerd colorectaal carcinoom met irresectabele metastasen

De afgelopen jaren is de overleving van patiënten met gemetastaseerd colorectaal carcinoom met irresectabele metastasen aanzienlijk verbeterd met fluoropyrimidine chemotherapie gecombineerd met oxaliplatin of irinotecan vaak gecombineerd met bevacizumab, of EGFR remmers (cetuximab or panitumumab).[35-40] Daarnaast bestaat er geen discussie dat patiënten met obstructie, perforatie of ernstige bloeding van de primaire tumor een spoedoperatie zullen moeten ondergaan. Er is echter wel discussie gaande over het nut van chirurgie van de primaire tumor in patiënten met gemetastaseerd colorectaal carcinoom met irresectabele metastasen en een asymptomatische primaire tumor.[41] Verschillende gerandomiseerde studies hebben niet de beoogde inclusie weten te halen en zijn vroegtijdig gesloten, terwijl resultaten van enkele andere gerandomiseerde studies nog op zich laten wachten.[42-46] In de tussentijd zijn er pogingen gedaan om het effect van chirurgie van de primaire tumor bij patiënten met asymptomatisch gemetastaseerd colorectaal carcinoom te onderzoeken met behulp van observationele data. Retrospectieve studies hebben een overlevingsvoordeel laten zien voor resectie van de primaire tumor, echter kan in deze studies goed sprake zijn van 'confounding by indication' gezien de behandeling, operatie van de primaire tumor, niet is gerandomiseerd. Patiënten die geen chirurgie ondergingen blijken vaker uitgebreidere metastasering te hebben, een slechtere performance status, meer comorbiditeit, en hogere waardes van alkalisch fosfatase en CEA.[47] Het is daarom aannemelijk dat deze patiënten vooraf al een slechtere prognose hebben. Om deze reden moet men voorzichtig zijn conclusies te trekken op basis van deze resultaten.

Aangezien het lastig is overleving tussen patiënten die wel of geen chirurgie van de primaire tumor ondergingen direct te vergelijken, hebben we behandelstrategieën en algehele overleving van patiënten met gemetastaseerd colorectaal carcinoom met irresectabele metastasen vergeleken tussen twee landen in **Hoofdstuk 9**. Ook hebben we het effect van verschillende behandelstrategieën op sterfte in het eerste jaar met land als instrumentele variabele onderzocht om randomisatie na te bootsen. Voor dit EURECCA internationaal vergelijk hebben we nationale, populatie-gebaseerde data uit Nederland en Noorwegen verzameld. Onze resultaten laten zien dat patiënten uit Noorwegen vaker chirurgie van de primaire tumor ondergingen dan patiënten uit Nederland. Daarnaast kan het mogelijk zo zijn dat patiënten uit Nederland vaker chemotherapie ondergingen dan patiënten uit Noorwegen, met name oudere patiënten. Data over chemotherapie is echter niet compleet in de kankerregistratie data uit Noorwegen en dit moet daarom dan ook voorzichtig worden geïnterpreteerd. Radiotherapie van de primaire tumor bij patiënten

met rectumcarcinoom werd minder vaak gegeven in Noorwegen dan in Nederland.

Over het geheel genomen waren er geen verschillen in ongecorrigeerde algehele overleving tussen Nederland en Noorwegen, echter was sprake van een klein overlevingsvoordeel voor Noorwegen ten opzichte van Nederland na corrigeren voor mogelijke confounders. Ook patiënten <75 jaar uit Noorwegen hadden een iets betere overleving dan patiënten uit Nederland, terwijl patiënten ≥75 jaar uit Noorwegen een iets slechtere overleving hadden dan patiënten uit Nederland. Met het gebruik van instrumentele variabele analyse werd geen verschil in eenjaarsmortaliteit gezien tussen de verschillende behandelstrategieën.

Helaas was data betreft chemotherapie niet compleet in de Noorse kankerregistratie. Ook was er in beide kankerregistraties geen informatie beschikbaar ten aanzien van spoedoperatie, klachten door de primaire tumor, chemotherapie schema, toxiciteit, het aantal kuren chemotherapie dat volbracht werd, comorbiditeit en ASA classificatie. Daarnaast zou, met name in deze groep patiënten in de palliatieve fase, het van belang zijn om informatie te hebben over kwaliteit van leven en patiëntvoorkeuren. Ook in deze studie zou sprake kunnen zijn van residuele confounding gezien de retrospectieve opzet van de studie.

Naar aanleiding van deze studie kunnen we concluderen dat er aanzienlijke verschillen zijn in behandelstrategieën tussen Noorwegen en Nederland, met vooral meer chirurgie en minder radiotherapie in Noorwegen, maar dat er slechts kleine verschillen zijn in algehele overleving tussen de twee landen waarvan de klinische relevantie ter discussie gesteld kan worden. Bovendien hadden de verschillende behandelstrategieën geen effect op de eenjaarsmortaliteit bij instrumentele variabele analyse. Het vergelijken van behandelstrategieën en uitkomsten tussen landen kan het probleem van confounding by indication verminderen zoals in eerdere studies waarin de behandelingen direct met elkaar werden vergeleken. Kleine overlevingsverschillen tussen Nederland en Noorwegen kunnen zeker deels het gevolg zijn van verschillen in behandelstrategieën, maar er kunnen nog steeds andere factoren meespelen die ook invloed hebben op overleving. Alhoewel we uit deze studie kunnen concluderen dat er grote verschillen in behandelstrategieën zijn en slechts kleine verschillen in algehele overleving, kunnen we niet definiëren welke subgroepen patiënten te selecteren voor welke behandeling, met name wie wel of geen baat heeft van chirurgie van de primaire tumor. Dit onderwerp blijft daarom nog onderwerp van discussie, alhoewel er momenteel geen bewijsvoering is voor het routinematig opereren van de primaire tumor in patiënten met asymptomatisch gemetastaseerd colorectaal carcinoom met irresectabele metastasen.

Toekomstperspectieven

Binnen de gastro-intestinale oncologische zorg is er een verschuiving gaande van één behandelstrategie op basis van TNM stadium naar behandeling van de individuele patiënt. Bovendien is er binnen de gastro-intestinale oncologische zorg, waaronder behandeling voor rectumcarcinomen, een belangrijke verschuiving in de behandeling naar intensieve neoadjuvante behandeling met als doel uitkomsten te verbeteren en zelfs het weglaten van chirurgie lijkt mogelijk in een geselecteerde groep patiënten.

Gezien de hoge aantallen complicaties na chirurgie voor niet-gemetastaseerd colorectaal carcinoom en de negatieve effecten van complicaties op korte- en langetermijnuitkomsten, kan een prehabilitatie en revalidatieprogramma bijdragen aan het verminderen van complicaties in oudere patiënten die fit genoeg zijn voor chirurgie.[48] Alhoewel in dit proefschrift een hoge 30-dagen en eenjaarsmortaliteit werd gezien met name bij patiënten ≥75 jaar, laat een recentere studie zien dat de verschillen tussen oudere en jongere patiënten kleiner zijn geworden wanneer gekeken wordt naar de relatieve eenjaarsoverleving.[49] Het consulteren van een klinisch geriater of internist-ouderengeneeskunde kan bijdragen in uiteindelijke beslissingen in een multidisciplinair overleg betreft de behandeling. Daarnaast is het goed mogelijk dat strikte, geprotocolleerde 'Enhanced Recovery After Surgery' processen hebben bijgedragen om de kloof in uitkomsten tussen oudere en jongere patiënten te verminderen.

In dit proefschrift wordt geen bewijs gevonden voor het standaard toedienen van adjuvante chemotherapie na preoperatieve (chemo)radiotherapie en totale mesorectale excisie. Oudere studies hebben aangetoond dat preoperatieve chemoradiatie leidt tot het beter kunnen volbrengen van de chemotherapie en minder toxiciteit geeft vergeleken met postoperatieve chemoradiatie.[50] De verschuiving naar een intensiever neoadjuvant schema voor 'locally advanced' rectumcarcinomen is gaande. Inmiddels laten de resultaten van de RAPIDO studie een lagere 'disease-related treatment failure' zien, als gevolg van minder metastasen bij patiënten met een hoog-risico 'locally advanced' rectumcarcinoom na preoperatieve short-course radiotherapie, gevolgd door chemotherapie en totale mesorectale excisie vergeleken met conventionele chemoradiatie.[51] Daarnaast kan neoadjuvante chemoradiatie leiden tot een complete klinische respons, waardoor minder uitgebreide chirurgie mogelijk is en zelfs een 'watch-and-wait' strategie binnen de mogelijkheden ligt om een geselecteerde groep patiënten chirurgie te kunnen besparen.[52,53]

Een initiatief zoals EURECCA creëert een platform om te reflecteren op oncologische zorg en kan op deze manier uitkomsten verbeteren. Populatie-gebaseerde database analyses kunnen leiden tot 'evidence-based' en op maat gemaakte behandeling. Zoals aangetoond in dit proefschrift, geeft het vergelijken van data van kankerregistraties

waardevolle inzichten in behandelstrategieën en uitkomsten tussen Europese landen. Echter, een op elkaar afgestemde dataset in Europa, idealiter prospectief verzameld, met daarin data over patiëntkarakteristieken zoals comorbiditeit en functionele status, tumorkarakteristieken, behandeling en daarbij horende toxiciteit en complicaties, en uitkomsten waaronder oncologische uitkomsten maar ook kwaliteit van leven, zouden essentieel zijn om epidemiologische data verder te kunnen gebruiken om oncologische behandeling te optimaliseren en te verbeteren.

In het tijdperk van multidisciplinaire behandeling en 'shared-decision making', zouden analyses vanuit een Europese populatie-gebaseerde dataset, uiteraard gecombineerd met resultaten uit trials en de zoektocht naar aanvullende biomarkers, de uitdaging zijn voor de toekomst om subgroepen patiënten beter te kunnen selecteren voor bepaalde behandelingen. Daarnaast zal het met intensievere neoadjuvante (chemo)radiotherapie noodzakelijk zijn om patiënten nauwkeurig te vervolgen met behulp van beeldvorming om alleen te hoeven ingrijpen bij het optreden van tumorrecidief na een complete respons. In een geselecteerde groep patiënten kan in het geval van een aanhoudende complete respons chirurgie zelfs vermeden worden.

REFERENTIES

1. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer* 2015; **51**(15): 2158-68.
2. Shah MA, Renfro LA, Allegra CJ, et al. Impact of Patient Factors on Recurrence Risk and Time Dependency of Oxaliplatin Benefit in Patients With Colon Cancer: Analysis From Modern-Era Adjuvant Studies in the Adjuvant Colon Cancer End Points (ACCENT) Database. *J Clin Oncol* 2016; **34**(8): 843-53.
3. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**(8843): 457-60.
4. 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**(6): 575-82.
5. Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther* 2017; **17**(12): 1131-46.
6. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 2015; **30**(2): 205-12.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**(1): 5-29.
8. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
9. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**(10): 1638-44.
10. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**(6): 352-8.
11. Gooiker GA, Dekker JW, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* 2012; **19**(8): 2428-34.
12. Odermatt M, Miskovic D, Flashman K, et al. Major postoperative complications following elective resection for colorectal cancer decrease long-term survival but not the time to recurrence. *Colorectal Dis* 2015; **17**(2): 141-9.
13. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**(6): 1533-9.
14. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; (3): CD004078.
15. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**(2): 184-90.
16. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25**(7): 1356-62.
17. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**(2): 223-9.
18. Quasar Collaborative G, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**(9604): 2020-9.
19. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004; **363**(9422): 1728-31.
20. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000; **321**(7256): 255-6.
21. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; **19**(6): 537-54.
22. Boef AG, le Cessie S, Dekkers OM. [Instrumental variable analysis]. *Ned Tijdschr Geneeskd* 2013; **157**(4): A5481.
23. Siesling S, Louwman WJ, Kwast A, et al. Uses of cancer registries for public health and clinical research in Europe: Results of the European Network of Cancer Registries survey among 161 population-based cancer

registries during 2010-2012. *Eur J Cancer* 2015; **51**(9): 1039-49.
24. Quah HM, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. *Dis Colon Rectum* 2008; **51**(5): 503-7.
25. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi64-72.
26. Andre T, de Gramont A, Vernerey D, et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. *J Clin Oncol* 2015; **33**(35): 4176-87.
27. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003; **349**(3): 247-57.
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**(23): 2343-51.
29. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011; **29**(11): 1465-71.
30. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**(26): 2696-704.
31. Iveson TJ, Kerr RS, Saunders MP, et al. 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. *Lancet Oncol* 2018; **19**(4): 562-78.
32. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11**(9): 835-44.
33. Wiltink LM, Marijnen CA, Meershoek-Klein Kranenbarg E, van de Velde CJ, Nout RA. A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial. *Acta Oncol* 2016; **55**(4): 502-8.
34. Loos M, Quentmeier P, Schuster T, et al. Effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013; **20**(6): 1816-28.
35. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Bmj* 1993; **306**(6880): 752-5.
36. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**(16): 2938-47.
37. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; **343**(13): 905-14.
38. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**(9582): 135-42.
39. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**(23): 2335-42.
40. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. *Cancer treatment reviews* 2012; **38**(6): 618-25.
41. Patel S, Chang GJ. Primary Tumor Resection in Metastatic Colorectal Cancer: Please Pass the Salt. *JAMA Oncol* 2015; **1**(9): 1213-4.
42. Kim CW, Baek JH, Choi GS, et al. The role of primary tumor resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial. *Trials* 2016; **17**: 34.
43. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012; **12**: 142.
44. Biondo S, Frago R, Kreisler E, Espin-Basany E, Spanish CRG. Impact of resection versus no resection of the primary tumor on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4). *Int J Colorectal Dis* 2017; **32**(7): 1085-90.
45. t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014; **14**: 741.

46. Cotte E, Villeneuve L, Passot G, et al. GRECCAR 8: impact on survival of the primary tumor resection in rectal cancer with unresectable synchronous metastasis: a randomized multicentre study. *BMC Cancer* 2015; **15**: 47.
47. Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Ann Surg Oncol* 2014; **21**(12): 3900-8.
48. Souwer ETD, Bastiaannet E, de Bruijn S, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence". *Eur J Surg Oncol* 2018; **44**(12): 1894-900.
49. Brouwer NPM, Heil TC, Olde Rikkert MGM, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. *Eur J Cancer* 2019; **116**: 1-9.
50. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**(17): 1731-40.
51. Bahadoer RR, Dijkstra EA, van Betten E, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial *Lancet Oncol. 2021* Jan;22(1):29-42.
52. Habr-Gama A, de Souza PM, Ribeiro U, Jr., et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis Colon Rectum* 1998; **41**(9): 1087-96.
53. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018; **391**(10139): 2537-45.

LIST OF PUBLICATIONS

A.J. Breugom, E. Bastiaannet, M.G. Guren, H. Kørner, P.G. Boelens, F.W. Dekker, E. Kapiteijn, H. Gelderblom, I.K. Larsen, G.J. Liefers, C.J.H. van de Velde. Treatment strategies and overall survival for incurable metastatic colorectal cancer – a EURECCA international comparison including 21,196 patients from the Netherlands and Norway. European Journal of Surgical Oncology. 2020 Jun;46(6):1167-1173

Y.H. Claassen, M.J. van der Valk, A.J. Breugom, M.A. Frouws, E. Bastiaannet, G.J. Liefers, C.J.H. van de Velde, E. Kapiteijn. Survival differences with immediate versus delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer. Cochrane Database of Systematic Reviews. 2018 Nov 21;11:CD012326.

E.T.D. Souwer, E. Bastiaannet, S. de Bruijn, A.J. Breugom, F. van den Bos, J.E.A. Portielje, J.W.T. Dekker. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence". European Journal of Surgical Oncology. 2018 Dec;44(12):1894-1900.

A.J. Breugom, E. Bastiaannet, J.W.T. Dekker, M.W.J.M. Wouters, C.J.H. van de Velde, G.J. Liefers. Decrease in 30-day and one-year mortality over time in patients aged ≥75 years with stage I-III colon cancer: A population-based study. European Journal of Surgical Oncology. 2018 Dec;44(12):1889-1893.

A.J. Breugom, E. Bastiaannet, P.G. Boelens, E. Van Eycken, L.H. Iversen, A. Martling, R. Johansson, T. Evans, S. Lawton, K.M. O'Brien, H. Ortiz, R. Janciauskiene, O.M. Dekkers, H.J.T. Rutten, G.J. Liefers, V.E.P.P. Lemmens, C.J.H. van de Velde. Oncologic treatment strategies and relative survival of patients with stage I-III rectal cancer - A EURECCA international comparison between the Netherlands, Belgium, Denmark, Sweden, England, Ireland, Spain, and Lithuania. European Journal of Surgical Oncology. 2018 Sep;44(9):1338-1343.

C.B.M. van den Broek, C.C.E.M. Puylaert, A.J. Breugom, E. Bastiaannet, A.J.M. de Craen, C.J.H. van de Velde. Administration of adjuvant chemotherapy in older patients with stage III colon cancer: an observational study. Colorectal Disease. 2017 Oct;19(10):O358-O364.

M. Swets, A.J. Breugom, H. Gelderblom, C.J.H. van de Velde. Should rectal cancer located 10-15 cm from the anal verge be defined as colon cancer. Annals of Oncology. 2017 Mar 1;28(3):664-665.

M.P. van der Sijp, E. Bastiaannet, W.E. Mesker, L.G. van der Geest, A.J. Breugom, W.H. Steup, A.W. Marinelli, L.N. Tseng, R.A. Tollenaar, C.J.H. van de Velde, J.W.T. Dekker. Differences between colon and rectal cancer in complications, short-term survival and recurrences. International Journal of Colorectal Disease. 2016 Oct;31(10):1683-91.

A.J. Breugom, E. Bastiaannet, P.G. Boelens, L.H. Iversen, A. Martling, R. Johansson, T. Evans, S. Lawton, K.M. O'Brien, E. Van Eycken, R. Janciauskiene, G.J. Liefers, A. Cervantes, V.E.P.P. Lemmens, C.J.H. van de Velde. Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - A EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. European Journal of Cancer. 2016 Aug;63:110-7.

A.J. Breugom, D.T. van Dongen, E. Bastiaannet, F.W. Dekker, L.G.M. van der Geest, G.J. Liefers, A.W.K.S. Marinelli, W.E. Mesker, J.E.A. Portielje, W.H. Steup, L.N.L. Tseng, C.J.H. van de Velde, J.W.T. Dekker. Association between the most frequent complications after surgery for stage I-III colon cancer and short-term survival, long-term survival, and recurrences. Annals of Surgical Oncology. 2016 Sep;23(9):2858-65.

A.J. Breugom, C.J.H. van de Velde. Is it time for watchful waiting for rectal cancer? The Lancet Oncology. 2015 Aug;16(8):875-6.

A.J. Breugom, T.A. Vermeer, C.B.M. van den Broek, T. Vuong, E. Bastiaannet, L. Azoulay, O.M. Dekkers, T. Niazi, H.A. van den Berg. H.J. Rutten, C.J.H. van de Velde. Effect of preoperative treatment strategies on the outcome of patients with clinical T3, non-metastasized rectal cancer: A comparison between Dutch and Canadian expert centers. European Journal of Surgical Oncology. 2015 Aug;41(8):1039-44.

A.J. Breugom, M. Swets, C.J.H. van de Velde. Adjuvant chemotherapy for rectal cancer - authors' reply. The Lancet Oncology. 2015 Apr;16(4):e155.

A.J. Breugom*, M. Swets*, J.F. Bosset, L. Collette, A. Sainato, L. Cionini, R. Glynne-Jones, N. Counsell, E. Bastiaannet, C.B.M. van den Broek, G.J. Liefers, H. Putter, C.J.H. van de Velde. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. The Lancet Oncology. 2015 Feb;16(2):200-7.

A.J. Breugom, W. van Gijn, E.W. Muller, Å. Berglund, C.B.M. van den Broek, T. Fokstuen, H. Gelderblom, E. Kapiteijn, J.W.H. Leer, C.A.M. Marijnen, H. Martijn, E. Meershoek-Klein Kranenbarg, I.D. Nagtegaal, L. Påhlman, C.J.A. Punt, H. Putter, A.G.H. Roodvoets, H.J.T. Rutten, W.H. Steup, B. Glimelius, C.J.H. van de Velde, Cooperative Investigators of the

Dutch Colorectal Cancer Group and the Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Annals of Oncology. 2015 Apr;26(4):696-701.

A.J. Breugom, C.J.H. van de Velde. Adjuvant chemotherapy for patients with rectal cancer? The Lancet Oncology. 2014 Oct;15(11):1185-6.

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. Annals of Oncology. 2014 Aug;25(8):1485-92.

C.J.H. van de Velde, P.G. Boelens, P.J. Tanis, E. Espin, P. Mroczkowski, P. Naredi, L. Påhlman. H. Ortiz, H.J. Rutten, A.J. Breugom, J.J. Smith, A. Wibe, T. Wiggers, V. Valentini. Experts reviews of the multidisciplinary consensus conference colon and rectal cancer 2012: science, opinions and experiences from the experts of surgery. European Journal of Surgical Oncology. 2014 Apr;40(4):454-68.

* Authors contributed equally to the work.

CURRICULUM VITAE

Anne was born on May 10th, 1988 in The Hague, the Netherlands. After graduating from the Christelijk Gymnasium Sorghvliet in The Hague, she started medical school at Leiden University in 2006.

After completing her preclinical training, she started her clinical rotations in 2010. In her final year, she did her elective internship at the department of Internal Medicine and Gastroenterology and Hepatology at the HagaZiekenhuis. She did her scientific internship in 2012 at the department of Surgical Oncology at the Leiden University Medical Centre under the supervision of Dr. Bastiaannet and Dr. Liefers. After obtaining her medical degree in January 2013, she started her PhD at the department of Surgical Oncology at the Leiden University Medical Centre under the supervision of Prof.Dr. van de Velde and Dr. Bastiaannet. This resulted in the current thesis. During her PhD research period she followed a post-master educational programme at the department of Clinical Epidemiology, from which she graduates as clinical epidemiologist simultaneously with her PhD defence. In 2016, she started as a resident (AIOS) Internal Medicine at the Leiden University Medical Centre and the Alrijne Ziekenhuis in Leiderdorp under the supervision of Prof.Dr. de Fijter and Dr. Anten. After her internship at the department of Pulmonology at the Alrijne Ziekenhuis under the supervision of Dr. Dik, she decided to change her career path. In 2019, she started as a resident (AIOS) Pulmonology under the supervision of Dr. Ninaber and Dr. Willems.

DANKWOORD

Hierbij wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift.

Prof.dr. van de Velde, beste professor, het was een eer om onderdeel te zijn van uw onderzoeksgroep. Ik heb de afgelopen jaren veel van u geleerd en heb enorme bewondering voor uw werk en uw kennis op oncologisch gebied. Ik wil u bedanken voor het vertrouwen, de betrokkenheid en de mogelijkheden die u mij heeft gegeven om me te ontwikkelen op wetenschappelijk gebied.

Dr. Bastiaannet, beste Esther, vanaf mijn wetenschapsstage ben je voor mij heel belangrijk geweest. Ik heb ontzettend veel van je geleerd en jij bent degene die mij enthousiast heeft gemaakt voor epidemiologisch onderzoek. Dank je voor de fantastische begeleiding tijdens mijn promotietraject.

Dr. Liefers, beste Gerrit-Jan, jouw wetenschappelijke kennis en het maken van de vertaalslag naar de klinische relevantie maakten dat na een overleg met jou alles ineens weer overzichtelijk werd. Heel erg bedankt hiervoor.

Prof.dr. Portielje, beste Johanneke, dankzij jou ben ik in contact gekomen met Esther voor het doen van mijn wetenschapsstage en heb ik binnen dezelfde afdeling uiteindelijk mijn promotietraject kunnen doen. Ik heb enorme bewondering voor je enthousiasme, bevlogenheid en de manier waarop je klinisch werk en wetenschap combineert. Dank je voor alle hulp bij de laatste loodjes van mijn proefschrift.

Dr. Boelens, beste Petra, dankzij de samenwerking met jou hebben we heel wat kunnen bereiken met EURECCA.

Lieve kamergenoten, Esther, Nienke, Mandy, Willemien, Victoria, Xandra en Marloes (Derks), naast de vele nuttige inhoudelijke overlegmomenten tussendoor, hebben jullie ervoor gezorgd dat ik elke dag met zoveel plezier naar mijn werk toe ging door al jullie gezelligheid, ons dagelijkse koffieritueel en niet te vergeten de lunch om stipt 11.50 uur. Collega-onderzoekers en collega's van het datacenter Heelkunde, heel erg bedankt voor de fijne samenwerking en leuke momenten samen.

Dr. Ninaber, beste Maarten, ik wil je bedanken voor de mogelijkheden die je me hebt gegeven om mijn proefschrift af te ronden en mijn opleiding bij de Longziekten te vervolgen.

Lieve collega's uit het Alrijne ziekenhuis en het LUMC, jullie dragen zoveel bij aan mijn werkplezier en ik ben dankbaar voor de vriendschappen die zijn ontstaan.

Mijn vriendinnen wil ik bedanken voor alle leuke momenten die voor de nodige ontspanning zorgen. In het bijzonder wil ik Lieke en Marloes noemen. Lieke, de laatste jaren hebben we lief en leed gedeeld. Je staat altijd voor me klaar en ik ben enorm dankbaar voor onze vriendschap. Nu op naar jouw promotie! Marloes, we hebben samen gestudeerd, we waren huisgenootjes en we hebben samen onderzoek gedaan. Aan een half woord hebben we genoeg elkaar te begrijpen. Ik ben heel blij met jou als vriendin.

Mijn paranimfen Bernadette en Wim, jullie maken allebei een belangrijk deel uit van mijn leven. Bernadette, vanaf ons eerste jaar bij Augustinus is een heel bijzondere vriendschap ontstaan. We hebben al zoveel mooie momenten samen meegemaakt. Ik bewonder jouw eerlijkheid en doorzettingsvermogen. Dank je dat je mijn paranimf wilt zijn. Lieve Wim, jij maakt mij een hele trotse zus. Ondanks je drukke baan ben je er altijd voor mij. Jouw scherpzinnigheid, je relativeringsvermogen, je vrolijke karakter en de rust die je uitstraalt maken dat ik me geen betere broer kan wensen. Dank je dat je naast me staat vandaag.

Lieve papa en mama, jullie onvoorwaardelijke liefde en steun hebben ervoor gezorgd dat ik hier sta. Papa, jouw enorme hoeveelheid energie en doorzettingsvermogen afgewisseld met de nodige momenten 'gek doen' zijn een groot voorbeeld voor mij. Mama, ik heb zoveel bewondering voor jou: je staat altijd voor anderen klaar, straalt zoveel warmte uit en ondanks verschillende medische tegenslagen heb ik je hier nog nooit over horen klagen. Samen zijn jullie de basis waar ik altijd weer op kan terugvallen. Heel erg bedankt hiervoor. Francesca, I am so happy you are part of our family! I admire your positivity and the way you founded your own company. Elizabeth, dank je voor je hulp en goede adviezen als ik deze nodig heb, ik waardeer dit heel erg!

Lieve Sjoerd, je haalt het beste in mij naar boven en hebt mij enorm gesteund en gemotiveerd om mijn proefschrift af te ronden. Hiervoor wil ik je heel erg bedanken. Ik kijk uit naar een toekomst met heel veel mooie momenten met jou samen!