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

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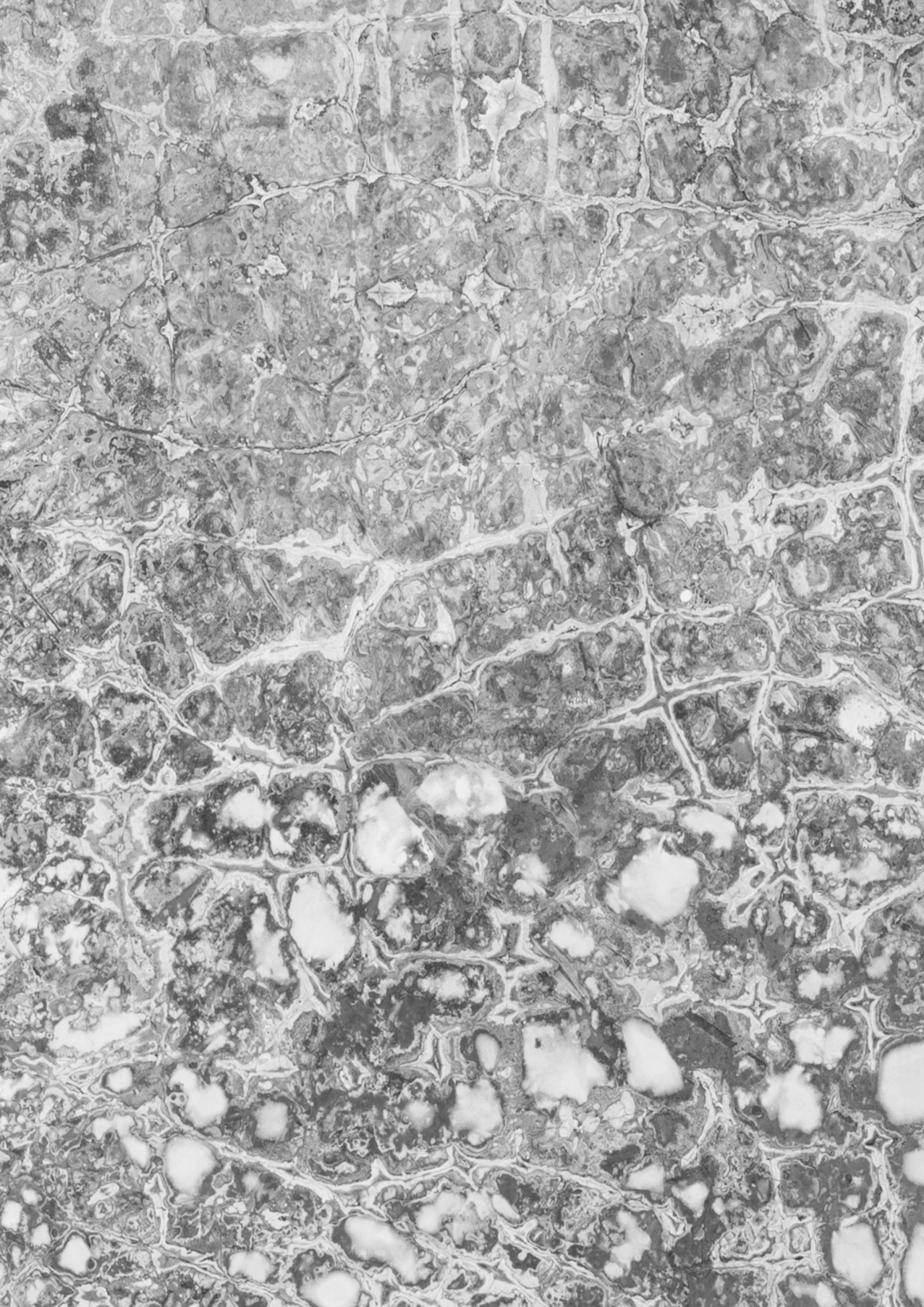

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General introduction and outline of this thesis

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.