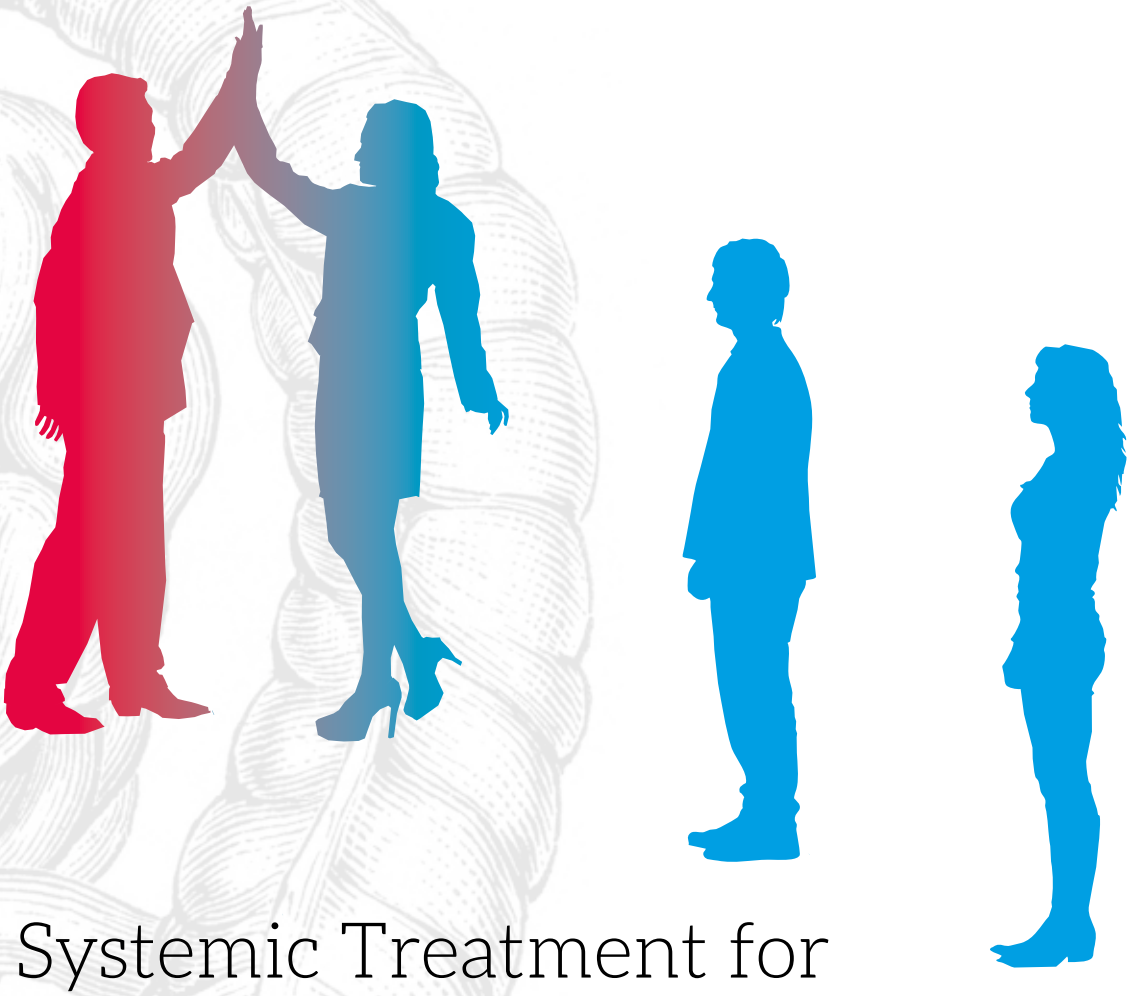

Systemic Treatment for Advanced Colorectal Cancer

Bridging the gap between clinical studies and daily practice

Lieke G.E.M. Razenberg

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De systemische behandeling van gevorderde dikkedarmkanker

De vertaalslag tussen klinische studies en de dagelijkse praktijk

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Chapter 1

General Introduction

Epidemiology of colorectal cancer

Colorectal cancer presents a significant burden of disease throughout the world.[1] In the Netherlands, colorectal cancer currently is the most common cancer.[2] As a result of the introduction of a nationwide screening program, the increasing life expectancy and ageing of the population, the absolute number of colorectal cancer patients increased importantly, from 7,100 in 1990 to 15,549 in 2015 (figure 1). Elderly patients account for the majority of patients presenting with colorectal malignancies (figure 2). Nowadays, approximately one third of the patients is aged ≥75 years.

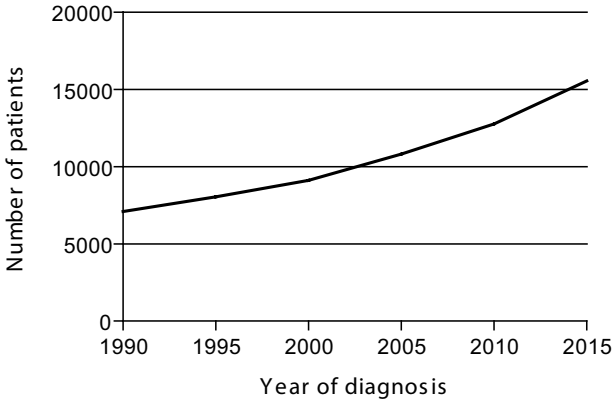

Figure 1 *Incidence of colorectal cancer in the Netherlands, by year of diagnosis.*
Source *Netherlands Cancer Registry*

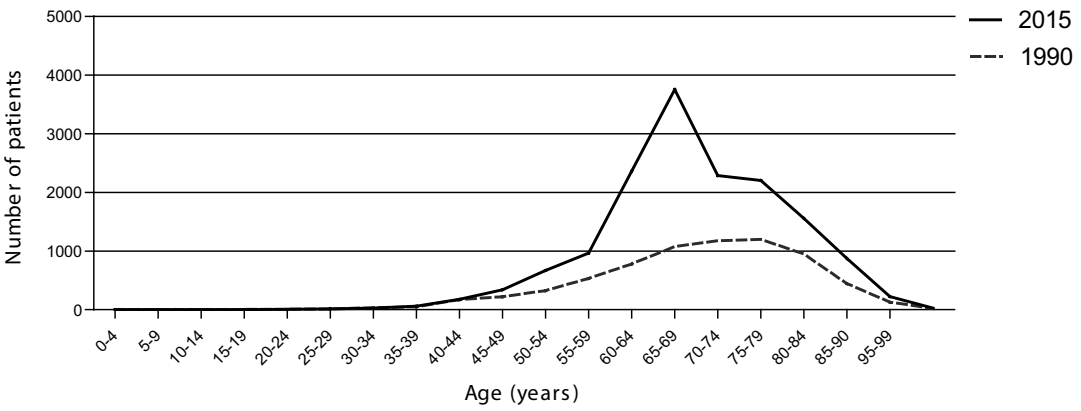

Figure 2 *Incidence of colorectal cancer in the Netherlands, by year of diagnosis and 5-year age group.*
Source *Netherlands Cancer Registry*

Colorectal cancer is classified according to stage at diagnosis, as defined by the tumour-node-metastasis (TNM) staging system.[3] Approximately 80% of the newly diagnosed colorectal cancer patients present with localized disease ($T_{1-4}N_{1-2}M_0$). In the remaining patients, metastases are present at time of diagnosis, typically in the liver, lungs or peritoneal surface.[4,5] In addition, a considerable proportion (40-50%) of patients experience disease recurrence or develop metastatic disease during their course of disease.[6] Until a few decades ago, patients with metastasized disease were treated with palliative intent with disappointing outcome. However, over the past three decades, colorectal cancer treatment has made an enormous leap.

Evolution of systemic therapy in the management of colorectal cancer

Historically, patients with metastasized colorectal cancer were considered incurable and even if patients had localized disease amenable to surgery, cure rates were low.[7] As a result, the concept to treat colorectal cancer with systemic therapy gained interest during the 20th century (figure 3). An overview on key clinical studies in the evolution of modern systemic therapy is depicted in Table 1.

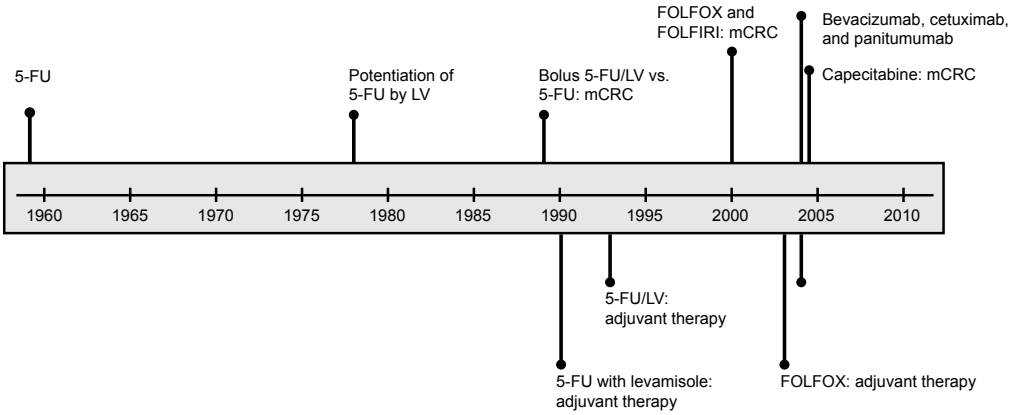

Figure 3 *The evolution of systemic therapy for patients with colorectal cancer.*
Source *Gustavsson et al.*[8]

Chemotherapy

In 1957, systemic treatment of colorectal cancer was initiated by Charles Heidelberger with the discovery of 5-fluorouracil (5-FU)[9], an antimetabolite that interferes with DNA biosynthesis by inhibiting thymidylate synthase. After the detection of 5-FU potentiation by adding leucovorin (LV)[10], 5-FU/LV regimens gained acceptance in the early nineties in both the adjuvant[7,11] and metastatic setting[12]. However, major advances in the evolution of chemotherapy in colorectal cancer were not achieved until the early 2000s when irinotecan (topoisomerase I inhibitor), oxaliplatin (alkylating agent) and the 5-FU prodrug capecitabine were introduced and combination therapies were developed. At first in the USA, irinotecan was combined with bolus 5-FU/LV (IFL).[13] In patients with metastasized colorectal cancer, first-line treatment with IFL resulted in significantly longer progression-free survival (7.0 vs. 4.3 months, p=.004) and overall survival (14.8 vs. 12.6 months, p=.04) in comparison to first-line treatment with 5-FU/LV.[13] However, compared to the European prevailing oxaliplatin-based regimen (FOLFOX: biweekly infusion 5-FU/LV with oxaliplatin) the IFL regimen provided inferior overall survival rates (19.5 vs. 15.0 months, p<.0001).[14] Besides, the FOLFOX regimen was associated with a more favourable toxicity profile than IFL, with less severe nausea, vomiting, diarrhoea and febrile neutropenia. The IFL regimen was abandoned and a combination regimen of irinotecan with continuous 5-FU was developed (FOLFIRI). Several trials showed similar efficacy for the FOLFIRI and FOLFOX regimens in patients with advanced colorectal cancer (table 1).[15,16] Both combination therapies (FOLFOX, FOLFIRI) have become standard cytotoxic combination regimens for the treatment of metastatic colorectal cancer. Treatment choice is based on differences in toxicity profile between these regimens; more gastrointestinal side effects with FOLFIRI and more thrombocytopenia and neurotoxicity with FOLFOX.[16] Combination chemotherapy, however, is not indicated as first-line systemic treatment in all patients. The individual treatment choice between combination or single agent therapy as first-line is dependent on patient and tumour related factors and the ultimate aim of the therapy. Single agent therapy is a reasonable option for patients with metastatic colorectal cancer with never-resectable metastatic disease, or without limiting symptoms and limited risk of rapid deterioration, in whom the aim will rather be prolongation of life than maximal shrinkage of metastases. Combination chemotherapy may not be preferable as it coincides with increased toxicity. Besides, in terms of overall survival, combination chemotherapy has not been shown to be superior to sequential treatment.[17-20] Exposure to all three active cytotoxic agents (fluoropyrimidine, oxaliplatin, irinotecan), rather than the prescribed first-line regimen is associated with the longest survival.[21,22] Therefore, sequential therapy starting with a fluoropyrimidine-derived monotherapy has been considered as a valid option in at least some patients.[23]

Within the adjuvant setting, survival rates improved significantly by the introduction of FOLFOX. In 2004, an interim analysis of the pivotal MOSAIC trial showed significantly improved 3-year disease free survival rates with FOLFOX compared with 5-FU/LV in patients with stage II or stage III

colorectal cancer (78% vs. 73%, p=.002), at the cost of higher toxicity rates.[24] In 2009, these results were updated in the final analysis of the MOSAIC trial, and showed significant improvements in both 5-year disease-free survival (73% vs. 67%, p=.003) and 6-year overall survival (79% vs. 76%, p=.046).[25] This improvement in overall survival was observed only in patients with stage III disease (73% vs. 69%, p=.023).[25] In the PETACC-3 study on the adjuvant treatment of colorectal cancer, no improvements were observed in either disease-free or overall-survival with irinotecan containing chemotherapy.[26] Consequently, FOLFOX is now considered the gold standard in the adjuvant treatment of stage III and high risk stage II CRC.

Another major advance in the treatment of colorectal cancer, both in the adjuvant and metastatic setting, was the introduction of the oral fluoropyrimidine capecitabine, which was shown to be at least equally effective to infusional 5-FU with an improved safety profile, except for more hand-foot syndrome.[27,28] Capecitabine is a patient convenient alternative to treatment regimens requiring intravenous infusion of 5-fluorouracil. Besides, it diminishes the use of medical resources, mainly by avoiding hospital visits for intravenous drug administration and fewer treatment-related hospitalisations during the course of therapy for adverse drug reactions than with conventional intravenous 5-fluorouracil.[29] As a result, a shift has taken place in the Netherlands, with an increasing usage of capecitabine in both monotherapy and combination-chemotherapy.

Targeted therapy

In the early 21st century a new class of agents, usually referred to as targeted therapy, has widened the spectrum of systemic therapy in advanced colorectal cancer. Targeted cancer therapies block the growth and spread of colorectal cancer by interfering with molecular targets that are involved in the growth, progression and spread of cancer. Although the concept of targeting angiogenesis was already raised in the 1960's, when initial attempts were made to characterize tumour blood supply[30], it was not available until the beginning of the 21st century. In 2004, Hurwitz *et al*. were the first to demonstrate that the addition of bevacizumab, a monoclonal antibody directed against the anti-vascular growth factor receptor (VEGF, figure 4a), to first-line IFL resulted in an improved overall survival (20.3 vs. 15.6 months, p<.001).[31] Thereafter, bevacizumab also proved to be effective in combination with multiple backbone chemotherapy regimens[19,32,33] and in different treatment settings.[34,35] The safety profile of bevacizumab is well characterized. Important but rare adverse events are haemorrhage, thromboembolism, proteinuria, bowel perforation and hypertension.[19,31-34,36-38] In 2006, the anti-epidermal growth factor receptor (EGFR) agents cetuximab and panitumumab were introduced and FDA approved (figure 4b). In patients with wild-type KRAS, these agents improved survival.[39,40] Ever since, there has been an ever-increasing number of targeted agents being tested in clinical trials, such as aflibercept and the tyrosine-kinase inhibitor regorafenib. [41,42]

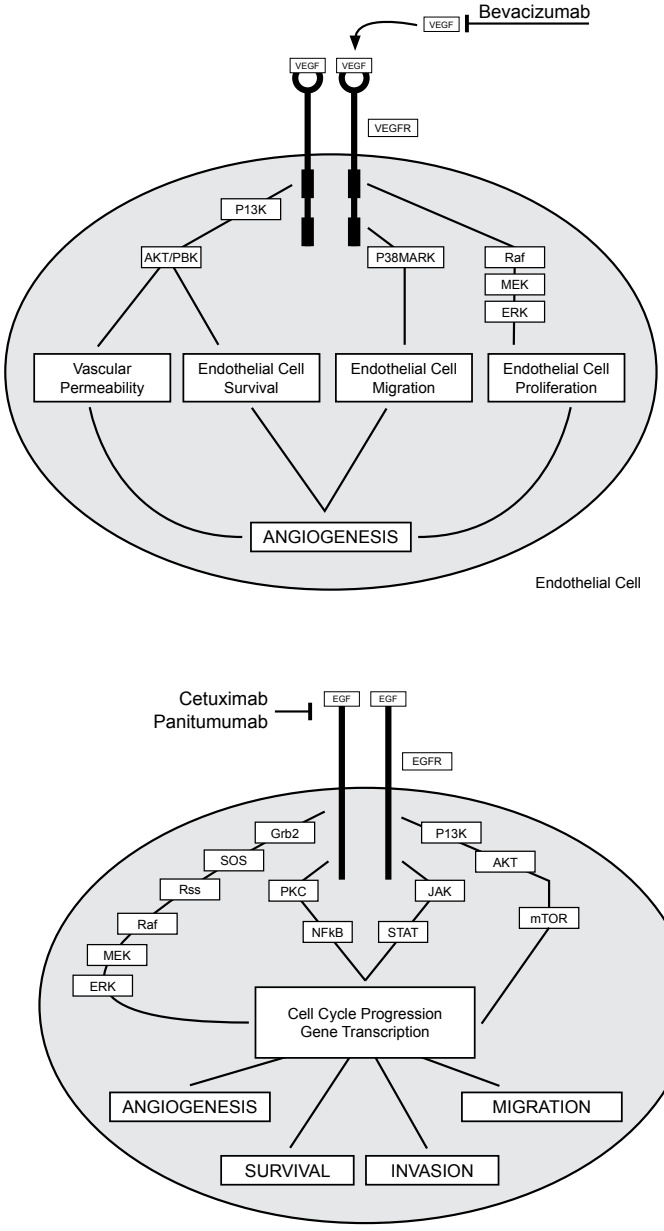

Figure 4 *molecular pathways in targeted therapy for colorectal cancer, A. the vascular endothelial growth factor (VEGF) signalling pathway, B. The endothelial growth factor receptor (EGFR) signalling pathway.*

Source *El Zouhairi et al.* [43]

Table 1 *Randomized phase III trials in the evolution of systemic therapy*

Colorectal cancer a. Metastatic setting		
Author (year)	**Regimens**	**Results**
Chemotherapy		
Poon (1989)	bolus 5-FU/LV vs. bolus 5-FU	OS: 12.2/12.0 (5-FU with high/low dose LV respectively) vs. 7.7 months (p=.05) RR: 26%/37% vs. 10%
Cutsem (2001)	Capecitabine vs. bolus 5-FU/LV	OS 13.2 vs. 12.1 months (p=NS) RR 18.9% vs. 15.0% (p=NS) TTP: 5.2 vs. 4.7 months (p=NS)
Saltz (2000)	IFL vs. bolus 5-FU/LV	OS: 14.8 vs. 12.6 months (p=.04) RR: 39% vs. 21% (p<.001) PFS: 7.0 vs. 4.3 months (p<.01)
Intergroup N9741 (2004)	IFL vs. FOLFOX	OS: 19.5 vs. 15.0 months (p=.04) RR: 45% vs. 31% (p<0.01) TTP: 8.7 vs. 6.9 months (p<0.01)
GERCOR (2004)	FOLFOX vs. FOLFIRI	OS: 21.5 vs. 20.6 months (p=NS) RR: 56% vs. 54% (p=NS) PFS: 8.5 vs. 8.0 months (p=NS)
GOIM (2005)	FOLFOX vs. FOLFIRI	OS 14 vs. 15 months (p=NS) RR: 31% vs. 34% (p=NS) TTP: 7 vs. 7 months (p=NS)
Targeted therapy		
AVF(2004)	IFL ± bevacizumab	OS: 20.3 vs. 15.6 months (p<.001) RR: 44.8% vs. 34.8% p=<.001 PFS: 10.6 vs. 6.2 months (p<.001)
Tebbutt (2010)	Capecitabine ± bevacizumab	OS: 16.4 vs. 18.9 months (NS) RR: 38.1% vs. 30.3% (NS) PFS: 8.5 vs. 5.7% months (p<.001)
Kabbinavar (2005)	bolus 5-FU/LV ± bevacizumab	OS: 16.6 vs. 12.9 months (p=NS) RR: 20.6 vs. 15.2 (p=NS) PFS: 9.2 vs. 5.5 months (p=<.001)
Saltz (2008)	FOLFOX ± bevacizumab	OS: 21.3 vs. 19.9 months (p=NS) RR: 47% vs. 49% (p=NS) PFS: 9.4 vs. 8.0 months (p<0.01)
ECOG 3200 (2007)	FOLFOX ± bevacizumab	OS: 12.9 vs. 10.8 months (p<.001) RR 22.7% vs. 8.6% (p<.001) PFS: 7.3 vs. 4.7 months (p<.001)
ML18147 (2013)	Bevacizumab beyond progression	OS: 11.2 vs. 9.8 (p<.01)
CRYSTAL (2009, 2011)	FOLFIRI ± cetuximab	Wild type KRAS: OS: 23.5 vs. 20.0 months (p<.05) RR: 57.3% vs. 39.7% (p<.01) PFS: 9.9 vs. 8.4 months (p<0.01)
PRIME (2010)	FOLFOX ± panitumumab	Wild type KRAS: OS: 23.9 vs. 19.7 months (p=NS) PFS: 9.6 vs. 8.0 months (p<0.05)
COIN (2011)	FOLFOX ± cetuximab	Wild type KRAS: OS: 17.0 vs. 17.9 months (p=NS) RR: 64% vs. 57% (p=0.05) PFS: 8.6 vs. 8.6 months (p=NS)

Colorectal cancer b. Adjuvant setting		
Chemotherapy		
Moertel (1990)	bolus 5-FU/LV	3-5 year OS: 71% vs. 55%
X-ACT (2005)	Capecitabine	3-year OS: 81% vs. 78% (p=.05) 3-year DFS 64% vs. 61% (p=NS)
MOSAIC (2004, 2009)	FOLFOX vs. 5-FU2/LV	6-year OS: 79% vs. 76% (p<.05) 5-year DFS: 73% vs. 67% (p<.01)
PETACC-3	FOLFIRI vs. 5-FU2/LV	5-year OS: 74% vs 71% (p=NS) 5- year DFS: 57% vs. 54% (p=NS)

5-FU2/LV (de Gramont)=biweekly infusional 5FU/LV

The gap between clinical research and everyday clinical practice

Underrepresentation in clinical trials

With the evolution of systemic therapy and results of large randomized phase III trials, treatment guidelines on colorectal cancer changed. The external validity of clinical trial-based recommendations, however, is limited as clinical trials often use eligibility criteria that often do not represent the patients in every clinical practice.[44] Clinical trials usually select patients with minimal comorbidity and good performance score in order to obtain a homogenous study population and to improve internal validity. Besides, response evaluation is an important feature of the clinical evaluation of cancer therapies and therefore, most clinical trials evaluating systemic therapy exclude patients in whom radiographic imaging is difficult, such as in patients with peritoneal metastases.[45] As a result, several subsets of patients, such as elderly patients, patients with significant co-morbidities and patients with peritoneal metastases, accounting for a significant proportion of colorectal cancer patients, are underrepresented in clinical trials. If elderly patients are included in trials, these are the fit patients without relevant comorbidities and not the frail patients seen in everyday practice. In the absence of randomized data and the lack of evidence-based treatment guidelines for such patients, clinicians are increasingly confronted with the discrepancy between research and clinical practice.[46] As a result, clinicians may offer suboptimal treatment to these patients, or alternatively, expose them to unanticipated risks. Other sources of information are needed to evaluate the effects of modern systemic therapy in the subsets of colorectal cancer patients, in whom evidence-based treatment recommendations are currently lacking.

The need for population-based studies

Population-based studies offer insight into the real-world use, tolerability and effectiveness of the various systemic treatment options among unselected patients. Such studies may help clinicians to bridge the gap of knowledge between selected patients in clinical trials and unselected patients as encountered in everyday clinical practice.[47,48] Concomitant with this awareness, several countries worldwide have created large-scale national cancer registries.[49] Detailed data on systemic therapy, however, are frequently missing in national cancer registries as such data collection is very costly and time consuming, in particular if recurrent disease is taken into account.[50] As a result, there are virtually no real-life data published which can help medical oncologists to discuss the benefits and drawbacks of the various systemic treatment options with patients. Such data are needed, in particular for patients who are currently underrepresented in clinical trials.

Aims and outline of the thesis

This thesis aims to bridge the gap between clinical studies and daily practice, by providing insight into the real-world use, tolerability and effectiveness of the various systemic treatment options among unselected patients, in whom evidence is currently lacking.

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

- To provide insight in the everyday use and tolerability of adjuvant chemotherapy regimens and its impact on the palliative systemic treatment of metastases in patients with colon cancer (part I).
- To assess the daily-based use and impact of age on the palliative systemic treatment of patients with metachronous metastases from primary resected colorectal cancer (part II).
- To evaluate the role of currently available treatment options in colorectal cancer patients with peritoneal metastases (part III).

Part I: Adjuvant treatment and subsequent palliative treatment of metastatic colorectal cancer

In *chapter 2*, we evaluate the intensity and tolerability of adjuvant chemotherapy regimens (CAPOX, CapMono) among elderly stage III colon cancer patients. Detailed insight is provided in the completion of all planned cycles, the received cumulative dosage of the prescribed adjuvant regimens and its association with grade III-IV toxicities. In *chapter* 3, we investigate whether these adjuvant regimens influence the subsequent choice of palliative chemotherapy in patients with metachronous metastases.

Part II: The palliative treatment of recurrent metastatic colorectal cancer
In the next three chapters the use, tolerability and effectiveness of palliative systemic therapy in unselected patients with metachronous metastases from colorectal cancer is evaluated. In *chapter* 4, we focus on bevacizumab in addition to palliative chemotherapy *(chapter 4)*. The intent of this chapter is to provide insight into the actual implementation of bevacizumab in daily practice and to identify its role in the treatment of metachronous metastases. In the following two chapters, we evaluate the impact of age on the daily-based use and effectiveness of palliative systemic therapy. In *chapter 5*, we provide a detailed overview on the age-related use of first-line palliative systemic regimens. Data are presented on the prescribed first-line systemic regimen, initial dosages, the number of received cycles and cumulative dosages. In *chapter 6,* we evaluate the number of patients accessing second and further lines of treatment and evaluated the total number of received systemic agents, in relation to survival.

Part III: The treatment of peritoneal metastases
The third part of this thesis focuses on the subset of colorectal cancer patients presenting with peritoneal metastases and provides evidence for the currently available treatment options. In *chapter 7,* the potential role of bevacizumab in addition to palliative chemotherapy is evaluated in patients with synchronous peritoneal metastases. In *chapter 8,* trends in the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) are evaluated. In *chapter 9*, it was evaluated whether the increasing use of both loco-regional and systemic treatment strategies over time resulted in significantly improved survival rates.

Finally, a summary of the main findings, methodological considerations, and implications of the results presented in this thesis were described in the general discussion (*chapter 10)*.

Data sources

Netherlands Cancer Registry
The Netherlands Cancer Registry (NCR) collects data on all newly diagnosed cancer patients in the Netherlands since 1989, covering the entire Dutch population of approximately 17 million inhabitants. The NCR comprises 9 administrational regions, each covering 7 to 20 hospitals. These regions form a network of health care professionals and institutions for cancer and palliative care in the Netherlands. All pathology laboratories participate in the Dutch Pathology Network (PALGA), which subsequently submits the data to the NCR. Trained registration clerks actively collect data on diagnosis, patient characteristics, staging and detailed information about initial treatment (delivered within 6 months from diagnosis) from the medical records using the registration and coding manual of the NCR. In this registration system, the classification of the primary tumour is determined by the TNM classification system.[3] In case of missing pathologic data, the clinical TNM

stage is used. Anatomical site of the tumour is registered according to the International Classification of Diseases for Oncology (ICD-O).[51] Information on the vital status of the patients is obtained from the nationwide municipal personal records database.

Additional data collection

Thanks to a grant from The Netherlands Organisation for Health Research and Development (grand numbers 113102004,152002012 and 152001022) and an unrestricted grant from Roche, additional data could be collected on adjuvant chemotherapy (chapter 2-3) and the development and treatment of recurrent disease (chapter 4-6). During 2010-2011, additional data were collected on the development and treatment of recurrent disease for patients with colorectal cancer diagnosed between 2003 and 2008 in the Eindhoven area of the NCR. Metachronous metastases were defined as distant metastasis of primary colorectal cancer in other organs, excluding regional lymph nodes, diagnosed at least 3 months after initial diagnosis.

The use of these data sources, reflecting everyday clinical practice, provides us with the opportunity to study the three main objectives as outlined in this introduction.

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Part I

"Adjuvant treatment and subsequent palliative treatment of metastatic colon cancer"

Chapter 2

"Intensity of adjuvant chemotherapy regimens and grade III-V toxicities among elderly stage III colon cancer patients"

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Abstract

Purpose: To provide insight in the use, intensity and toxicity of therapy with capecitabine and oxaliplatin (CAPOX) and capecitabine monotherapy (CapMono) among elderly stage III colon cancer patients treated in everyday clinical practice.

Methods: Data from the Netherlands Cancer Registry were used. All stage III colon cancer patients aged ≥70 years diagnosed in the southeastern part between 2005-2012 and treated with CAPOX or CapMono were included. Differences in completion of all planned cycles, cumulative dosages and toxicity between both regimens were evaluated.

Results: 193 patients received CAPOX and 164 patients received CapMono. 33% (n=63) of the patients receiving CAPOX completed all planned cycles of both agents, whereas 55% (n=90) of the patients receiving CapMono completed all planned cycles ($p<0.0001$). The median cumulative dosage capecitabine was lower for patients treated with CAPOX (163,744mg/m^2, interquartile range [IQR] 83,397-202,858mg/m^2) than for patients treated with CapMono (189,195mg/m^2, IQR 111,667-228,125mg/m^2, $p=0.0003$). 54% (n=105) of the patients treated with CAPOX developed grade III-V toxicity, whereas 38% (n=63) of the patients treated with CapMono developed grade III-V toxicity ($p=0.0026$). After adjustment for patient and tumour characteristics, CapMono was associated with a lower odds of developing grade III-V toxicity than CAPOX (odds ratio 0.54, 95% confidence interval 0.33-0.89). For patients treated with CAPOX, the most common toxicities were gastrointestinal (29%), haematological (14%), neurological (11%) and other toxicity (13%). For patients treated with CapMono, dermatological (17%), gastro-intestinal (13%) and other toxicity (11%) were the most common.

Conclusion: CAPOX is associated with significantly more grade III-V toxicities than CapMono, which had a pronounced impact on the cumulative dosage received and completion of all planned cycles. In this light, CapMono seems preferable over CAPOX.

Introduction

In the Netherlands, approximately 55% of the patients newly diagnosed with colon cancer are aged ≥70 years at the time of colon cancer diagnosis[1]. Due to demographic developments and the introduction of a screening program for colorectal cancer up to 75 years, the number of elderly colon cancer patients will increase even further. Despite colon cancer being a disease of the ageing, patients aged 70-75 years were underrepresented in clinical trials that established the efficacy of adjuvant chemotherapy in stage III colon cancer. Patients aged >75 years may even be excluded as, e.g., in the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, Xeloda [capecitabine] in Adjuvant Colon Cancer Therapy (X-ACT) trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-07 trial[2-4].

In the X-ACT trial, 83% of patients receiving capecitabine completed their treatment course, but 57% required dose modifications. Overall, the toxicity profile of capecitabine was superior to the combination of fluorouracil (FU) and leucovorin (LV) with the exception of a greater frequency of hand-foot syndrome[3]. The NSABP C-07 trial showed that serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin-containing regimens than with a combination of FU and LV alone[5]. Subgroup analyses of these trials showed that patients aged 70-75 years were more likely to discontinue treatment prematurely as compared to younger patients[4,6]. Additionally, dose modifications and reductions were required more often[4] and grade IV-V toxicity was experienced at a higher rate[6]. Since these trials were not specifically designed for elderly patients, the results may not be applicable to unselected elderly patients treated in clinical practice, who are often more vulnerable than elderly patients included in randomised clinical trials. Observational studies have shown that elderly patients are less often treated with adjuvant chemotherapy and less often receive oxaliplatin-containing regimens[7-11]. Additionally, also in population-based studies, dose reductions and treatment discontinuations were more frequent among elderly[7,10]. However, with the exception of the study by Kim et al.[9], no distinction was made between the different single-agent chemotherapies (i.e. capecitabine or FU) and combination therapy (i.e. FULV and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX))[7,8,10]. One population-based study including colon cancer patients from all ages showed a rapid shift from the use of FOLFOX to the use of CAPOX from January 2005 to December 2006[12].

To date, little is known about the extent to which elderly patients in daily practice are treated with CAPOX or capecitabine monotherapy (CapMono). Moreover, there are hardly any population-based studies describing the intensity of and adherence to these adjuvant regimens among elderly stage III colon cancer patients in detail. Furthermore, it is unknown to what degree unselected elderly develop toxicity from the various regimens. Therefore, the aim of the current study is to provide insight in the use, intensity and related toxicity of both CAPOX and CapMono among elderly stage III colon cancer patients treated in everyday clinical practice.

Methods

Data collection

Data from the population-based Netherlands Cancer Registry (NCR), more specifically from the Eindhoven area, were used. This region collects data on all newly diagnosed cancer patients in the southeastern part of the Netherlands. The registry area comprises about 2.4 million inhabitants (~15% of the Dutch population) and encompasses 10 community hospitals. Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators of the cancer registry. Anatomical site of the tumour is registered according to the International Classification of Disease – Oncology. The tumour-node-metastasis (TNM) classification is used for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis. Comorbidities are registered according to a slightly modified version of the Charlson Comorbidity index. The quality of the data is high, due to thorough training of the registration team and computerised consistency checks at regional and national levels.

For the study population, additional data were collected from the medical records by experienced registration administrators. This encompassed detailed information on adjuvant chemotherapy: regimen and agents, number of cycles received and cumulative dosage of each agent. Depending on the hospital in which patients were treated, standard treatment with CAPOX consisted of 6 or 8 cycles. Standard dosage for each cycle is 2000 mg/m^2 capecitabine on days 1-14 and 130 mg/m^2 oxaliplatin on day 1. The next cycle starts at day 21. Standard treatment with CapMono consisted of 6 or 8 cycles with each cycle including a dosage of 2000 or 2500 mg/m^2 capecitabine on days 1-14 and the next cycle starting at day 21. Grade III to V toxicity according to the Common Terminology Criteria (CTC) for Adverse Events version 4.0 that appeared after the start of chemotherapy and within 3 months after the last day of chemotherapy was also documented. For each toxicity, the highest grade that occurred was recorded.

Study population

All stage III ($pT_{1-4}N_{1-2}M_0$) colon cancer patients aged ≥70 years who underwent resection and were diagnosed between 2005-2012 were included. Stage was based on the pathological TNM classification. Tumour localisation was divided into anatomical subsites: proximal colon (C18.0-C18.5), distal colon (C18.6-C18.7) and unknown or overlapping subsites of the colon (C18.8-C18.9).

Statistical analyses

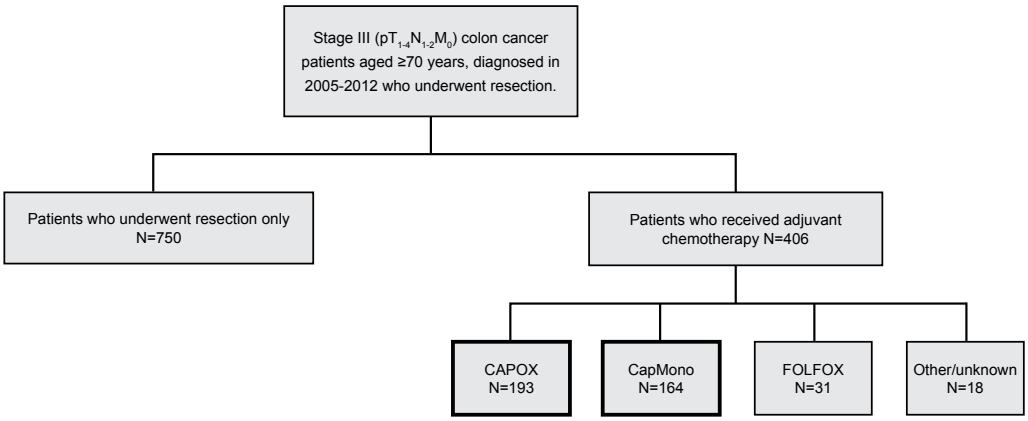
Descriptive statistics were used to provide an overview of the study population by adjuvant chemotherapy regimen, to give insight in the treatment intensity of both regimens, and to present toxicity according to regimen. Multivariable logistic regression analysis was used to assess which variables influenced receipt of CAPOX versus CapMono. Variables included in the model were gender, age, comorbidity, American Society of Anaesthesiologists (ASA) score, pathological T, patho-

logical N, subsite tumour, differentiation grade and period of diagnosis.
Differences in the number of cycles, cumulative dosages received and completion of all planned cycles between both regimens was calculated using Wilcoxon Rank-Sum tests and X^2-tests as appropriate. Multivariable logistic regression was used to assess which variables influenced completion of all planned cycles after stratification by regimen. Included in this model were grade III-V toxicity and the same patient- and tumour characteristics as listed in the model above.
For each grade III-V toxicity that appeared in more than 10% of the patients, the association with treatment characteristics (completion of all planned cycles, number of cycles, cumulative dosage) was investigated after stratification by regimen, using X^2-tests, Fisher's Exact Test and Wilcoxon Rank-Sum tests as appropriate. Multivariable logistic regression was used to assess the independent effect of regimen on grade III-V toxicity after adjustment for gender, age, comorbidity, ASA score, pathological T, pathological N, tumour subsite, differentiation grade and period of diagnosis. *P* values below *0.05* were considered statistically significant. SAS/STAT® statistical software (SAS System 9.4; SAS Institute, Cary, NC) was used for all analyses.

Results

A total of 1156 stage III colon cancer patients aged ≥70 years who underwent resection and were diagnosed in 2005-2012, were identified (figure 1). Over the total study period, 35% of the patients (n=406) received adjuvant chemotherapy. A large majority (88%, n=357) of the patients who were treated with adjuvant chemotherapy received CAPOX or CapMono. The joint proportion of CAPOX and CapMono versus other regimens increased over time from 68% in 2005-2006 to 91% in 2007-2008 to 92% in 2009-2010 and to 98% in 2011-2012 (*P*<0.0001).

Figure 1 *Overview of patients included in the study.*



Use and intensity of CAPOX and CapMono

One hundred ninety-three patients received CAPOX and 164 patients received CapMono. Table 1 shows the association between several patient and tumour characteristics and regimen. Older patients (75-79 years versus 70-74 years: 35% versus 73%, adjusted odds ratio [OR] 0.17, 95% confidence interval 0.10-0.29 and ≥80 years versus 70-74 years: 14% versus 73%, adjusted OR 0.05, 95% CI 0.02-0.17) and patients diagnosed in 2005-2006 (2005-2006 versus 2011-2012: 40% versus 55%, adjusted OR 0.38, 95% CI 0.17-0.87) were less likely to receive CAPOX instead of CapMono.

Table 1 *Crude percentages and adjusted ORs for receipt of CAPOX versus CapMono among elderly patients with stage III colon cancer treated with CAPOX or CapMono (n=357).*

	Total number of patients	Number & percentage receiving CAPOX	OR (95% CI) for receiving CAPOX
Gender			
Male	186	109 (59)	1.00 (reference)
Female	171	84 (49)	0.73 (0.44-1.21)
Age			
70-74 years	194	142 (73)	1.00 (reference)
75-79 years	134	47 (35)	0.17 (0.10-0.29)
≥80 years	29	4 (14)	0.05 (0.02-0.17)
Comorbidity			
0	99	65 (66)	1.00 (reference)
1	100	48 (48)	0.61 (0.31-1.19)
≥2	149	75 (50)	0.64 (0.34-1.21)
Unknown	9		
ASA score			
I-II	230	133 (58)	1.00 (reference)
III-IV	49	21 (43)	0.54 (0.26-1.15)
Unknown	78		
Pathological T			
1-2	46	22 (48)	0.56 (0.26-1.20)
3	255	145 (57)	1.00 (reference)
4	56	26 (46)	0.62 (0.31-1.24)
Pathological N			
1	234	124 (53)	1.00 (reference)
2	123	69 (56)	1.51 (0.88-2.57)
Subsite tumour			
Proximal colon	202	100 (50)	1.00 (reference)
Distal colon	150	90 (60)	1.24 (0.73-2.11)
Other/NOS	5		
Differentiation grade			
Well/moderate	247	140 (57)	1.00 (reference)
Poor/undifferentiated	85	42 (49)	0.73 (0.40-1.34)
Unknown	25		
Period of diagnosis			
2005-2006	63	25 (40)	0.38 (0.17-0.87)
2007-2008	89	56 (63)	1.39 (0.68-2.87)
2009-2010	109	59 (54)	1.07 (0.56-2.03)
2011-2012	96	53 (55)	1.00 (reference)

CI, confidence interval; NOS, not otherwise specified; OR, odds ratio. Adjusted for all variables listed. Included in the analyses but not shown for comorbidity unknown, ASA score unknown, subsite other/NOS and differentation grade unknown.

Table 2 provides an overview of the number of cycles received and the cumulative dosage received according to regimen. Within the CAPOX regimen, the median number of cycles capecitabine received was 7, while the median number of cycles oxaliplatin received was 5. The median cumulative dosage capecitabine received was 163,744 mg/m^2 and the median cumulative dosage for oxaliplatin was 604 mg/m^2. In the CapMono regimen, the median number of cycles received was 8 and the median cumulative dosage was 189,195 mg/m^2. The median number of cycles capecitabine did not differ between both regimens (*P*=0.720), but the median cumulative dosage capecitabine received was lower for patients treated with CAPOX than for patients treated with CapMono (*P*=0.0003).

Table 2 *Treatment intensity of CAPOX and CapMono among elderly patients with stage III colon cancer treated with CAPOX or CapMono.*

	CAPOX (n=193)		**CapMono (n=164)**
	Oxaliplatin	**Capecitabine**	**Capecitabine**
Number of cycles received	n	n	n
Median	5	7	8
Interquartile range	2 - 7	3 - 8	4 - 8
Minimum-maximum	1 - 8	1 - 8	1 - 8
Unknown	1	1	6
Total dosage received	mg/m2	mg/m2	mg/m2
Median	604	163,744	189,195
Interquartile range	261 - 768	83,397 - 202,858	111,667 - 228,125
Minimum-maximum	109 - 1176	1,869 - 253,270	4,980 - 294,329
Unknown	13	13	21

Completion of all planned cycles differed between CAPOX and CapMono (*P*<0.0001); 33% (n=63) of the patients receiving CAPOX completed all planned cycles of both agents, whereas 55% (n=90) of the patients receiving CapMono completed all planned cycles. Among the elderly who discontinued CAPOX prematurely, 63% discontinued both oxaliplatin and capecitabine, 31% discontinued oxaliplatin only and 6% discontinued capecitabine only. In a multivariable logistic regression model, only the presence of any grade III-V toxicity was independently related to early discontinuation of both CAPOX and CapMono (table 3).

Table 3 *Crude percentages and adjusted odds ratios for completing all planned cycles of CAPOX or CapMono among elderly patients with stage III colon cancer.*

	CAPOX (n=193)			CapMono (n=164)		
	total n	**n (%)**	**OR (95% CI)**	**total n**	**n (%)**	**OR (95% CI)**
Gender						
Male	109	41 (38%)	1.00 (reference)	77	47 (61%)	1.00 (reference)
Female	84	22 (26%)	0.58 (0.28-1.19)	87	43 (49%)	0.66 (0.33-1.32)
Age						
70-74 years	142	47 (33%)	1.00 (reference)	52	31 (60%)	1.00 (reference)
75-79 years	47	16 (34%)	1.24 (0.56-2.73)	87	46 (53%)	0.61 (0.27-1.38)
≥80 years	4	0 (0%)	<0.001	25	13 (52%)	0.52 (0.17-1.60)
Comorbidity						
0	65	19 (29%)	1.00 (reference)	34	17 (50%)	1.00 (reference)
1	48	21 (44%)	1.73 (0.71-4.20)	52	31 (60%)	2.38 (0.88-6.45)
≥2	75	20 (27%)	0.74 (0.31-1.78)	74	40 (54%)	1.31 (0.50-3.42)
ASA score						
I-II	133	48 (36%)	1.00 (reference)	97	53 (55%)	1.00 (reference)
III-IV	21	7 (33%)	0.90 (0.28-2.84)	28	17 (61%)	1.33 (0.47-3.73)
Pathological T						
1-2	22	9 (41%)	1.72 (0.57-5.14)	24	16 (67%)	1.60 (0.56-4.54)
3	145	48 (33%)	1.00 (reference)	110	59 (54%)	1.00 (reference)
4	26	6 (23%)	0.48 (0.16-1.43)	30	15 (50%)	0.78 (0.31-1.96)
Pathological N						
1	124	41 (33%)	1.00 (reference)	110	60 (55%)	1.00 (reference)
2	69	22 (32%)	1.27 (0.60-2.69)	54	30 (56%)	1.28 (0.59-2.75)
Subsite tumour						
Proximal colon	100	31 (31%)	1.00 (reference)	102	51 (50%)	1.00 (reference)
Distal colon	90	31 (34%)	1.01 (0.49-2.08)	60	38 (63%)	1.94 (0.88-4.25)
Differentiation grade						
Well/moderate	140	49 (35%)	1.00 (reference)	107	60 (56%)	1.00 (reference)
Poor/undifferentiated	42	10 (24%)	0.62 (0.25-1.55)	43	23 (53%)	0.88 (0.37-2.05)
Period of diagnosis						
2005-2006	25	9 (36%)	0.79 (0.22-2.77)	38	18 (47%)	0.36 (0.12-1.08)
2007-2008	56	19 (34%)	1.23 (0.50-3.01)	33	21 (64%)	1.08 (0.34-3.39)
2009-2010	59	16 (27%)	0.55 (0.22-1.38)	50	26 (52%)	0.85 (0.33-2.19)
2011-2012	53	19 (36%)	1.00 (reference)	43	25 (58%)	1.00 (reference)
Any grade III-V toxicity						
No	88	39 (44%)	1.00 (reference)	101	65 (68%)	1.00 (reference)
Yes	105	24 (23%)	0.34 (0.17-0.68)	63	25 (40%)	0.24 (0.11-0.52)

CI, confidence interval; NOS, not otherwise specified; OR, odds ratio. Adjusted for all variables listed. Included in the analyses but not shown for comorbidity unknown, ASA score unknown, subsite other/NOS and differentation grade unknown.

Grade III-V toxicity

An overview of the number and proportion of patients with grade III-V toxicity that occurred per regimen is presented in table 4. Overall, 54% (n=105) of the patients treated with CAPOX developed any grade III-V toxicity, whereas 38% (n=63) of the patients treated with CapMono developed any grade III-V toxicity (*P*=0.0026). Additionally, among patients receiving CAPOX as compared to patients receiving CapMono, grade III (53% versus 38%, *P*=0.0048) and grade IV toxicity (8% versus 1%, *P*=0.0038) occurred more frequently. Only 1 case of grade V toxicity was reported. Also in a multivariable logistic regression model, adjusted for gender, age, comorbidity, ASA score, pathological T, pathological N, tumour subsite, differentiation grade and period of diagnosis, was CapMono associated with a lower odds of developing any grade III-V toxicity than CAPOX (adjusted OR 0.54, 95% CI 0.33-0.89). The other listed variables were not associated with any grade III-V toxicity (results not shown).

For patients treated with CAPOX, most common toxicities were gastrointestinal (26%, mostly nausea/vomiting and diarrhoea), haematological (14%), neurological (11%) and other toxicity (13%, mostly fatigue). For patients treated with CapMono, dermatological (17%), gastrointestinal (13%, mostly diarrhoea) and other toxicity (11%, mostly fatigue) were most common.

Table 4 *Number and proportion of elderly stage III colon cancer patients with CTC grade III-V toxicities, by chemotherapy regimen.*

	CAPOX (n=193)				**CapMono (n=164)**			
	Grade III	**Grade IV**	**Grade V**	**Total n (%)**	**Grade III**	**Grade IV**	**Grade V**	**Total n (%)**
Haematological toxicity	20	7	0	27 (14%)	3	0	1	4 (2%)
Gastrointestinal toxicity	46	4	0	50 (26%)	22	0	0	22 (13%)
Cardiovascular toxicity	11	1	0	12 (6%)	7	0	0	7 (4%)
Pulmonary toxicity	3	0	0	3 (2%)	2	0	0	2 (1%)
Dermatological toxicity	5	0	0	5 (3%)	28	0	0	28 (17%)
Neurological toxicity	21	0	0	21 (11%)	2	0	0	2 (1%)
Renal/genital/urinary toxicity	5	0	0	5 (3%)	2	0	0	2 (1%)
Other toxicity	22	3	0	25 (13%)	17	1	0	18 (11%)
Any toxicity*	103	15	0	105 (54%)	63	2	1	63 (38%)

**In this row, the number of patients in the columns grade III, IV and V do not add up to the number of patients in the column total, because patients can have more than one toxicity.*

Associations between treatment intensity and toxicity

Table 5 presents the number of cycles and cumulative dosages received for both regimens according to the presence or absence of the most common grade III-V toxicity. For patients treated with CAPOX, the cumulative dosage received of both capecitabine and oxaliplatin was lower for patients with gastro-intestinal toxicity. Additionally, the received cumulative dosage of capecitabine but not of oxaliplatin was higher for patients with neurological toxicity and lower for patients with other toxicity (i.e. fatigue). With regard to the number of cycles received, similar results were found, although the number of cycles of capecitabine did not differ for patients with or without neurological toxicity, while the number of cycles of oxaliplatin received was higher for patients with neurological toxicity. For patients treated with CapMono, both the received cumulative dosage of capecitabine and the number of cycles was significantly lower for patients with diarrhoea or other toxicity (i.e. fatigue).

Table 5 *Number of cycles and total dosage of CAPOX or CapMono received among elderly patients with stage III colon cancer, according to grade III-V toxicity.*

CAPOX (n=193)	**Capecitabine**		**Oxaliplatin**	
	cycles, n (median, IQR)	**dosage, mg/m² (median, IQR)**	**cycles, n (median, IQR)**	**dosage, mg/m² (median, IQR)**
Haematological toxicity				
Yes	5 (2-8)	146,618 (59,484-183,178)	3 (2-8)	495 (253-757)
No	7 (4-8)	164,281 (90,314-204722)	6 (2-6)	605 (263-768)
P	*0.174*	*0.281*	*0.555*	*0.637*
Gastrointestinal toxicity				
Yes	3 (1-8)	59,783 (28,292-159,636)	2 (1-5)	254 (129-633)
No	8 (6-8)	176,232 (135,539-209,184)	6 (3-7)	647 (380-779)
P	<0.0001	*<0.0001*	*<0.0001*	*<0.0001*
Neurological toxicity				
Yes	8 (6 - 8)	181,729 (150,520 - 218,169)	6 (5 - 7)	648 (524 - 803)
No	7 (3 - 8)	163,468 (81,492 - 199,959)	5 (2 - 6)	586 (258 - 763)
P	*0.130*	0.038	*0.045*	*0.068*
Other toxicity				
Yes	4 (2-8)	90,550 (55,197-155,556)	4 (2-7)	540 (256-793)
No	7 (4-8)	166,179 (115,420-202,879)	6 (2-7)	607 (261-767)
P	*0.013*	*0.023*	*0.278*	*0.584*
CapMono (n=164)	**Capecitabine**			
	cycles, n (median, IQR)	dosage, mg/m² (median, IQR)		
Gastrointestinal toxicity				
Yes	4 (2-8)	86,547 (49,018-168,603)		
No	8 (5-8)	197,862 (144,763-232,555)		
P	*0.006*	*0.0002*		
Dermatological toxicity				
Yes	8 (5-8)	187,314 (145,797 - 231,579)		
No	8 (4-8)	189,862 (101,030 - 228,125)		
P	*0.523*	*0.684*		
Other toxicity				
Yes	5 (2-8)	123,190 (61,222-173,205)		
No	8 (5-8)	195,654 (139,026-229,150)		
P	*0.024*	*0.028*		

P value indicates significance of the Wilcoxon rank-sum test. IQR, interquartile range.

Discussion

The aim of this study was to provide insight in the use, intensity and related toxicity of both CAPOX and CapMono among elderly stage III colon cancer patients treated in everyday clinical practice.

This study showed that only 35% of the elderly stage III colon cancer patients received adjuvant chemotherapy, which is in line with previous population-based studies from the Netherlands[8,13] but somewhat lower than the 40-50% reported in other international studies[7,14].

In the years included in this study (2005-2012), adjuvant chemotherapy consisted of CAPOX or CapMono in 87%, while FU-based regimens were prescribed sparsely. In contrast, 87% received FULV in the previous period (1997-2004)[15]. The use of capecitabine instead of FU in the Netherlands is high in comparison to other countries. A population-based study from France including patients from all ages showed that almost 95% of the patients receiving chemotherapy, was treated with either FOLFOX or FULV in 2004-2009[16]. Another French study that only included the year 2009, showed higher proportions of capecitabine, especially among elderly[11]. Additionally, a single-centre retrospective study suggests that in Canada, regardless of age, FOLFOX was prescribed more often than CAPOX in the years 2006-2011[17]. The shift towards capecitabine-based regimens in the Netherlands over the last decade is related to the fact that capecitabine-based regimens are non-inferior to and less toxic than FU-based regimens[3,4], are more convenient for the patient and have a more favourable reimbursement policy for hospitals. On the other hand, especially among elderly cancer patients in which polypharmacy is common, possible drug interactions with capecitabine should be taken into account when deciding on capecitabine administration. For example, interaction with anticoagulant coumarin derivates have been previously shown[18]. However, in practice, oral anticoagulants are often replaced by dalteparin instead of that the use of capecitabine is waived.

Patients aged ≥70 years were less likely to receive CAPOX instead of CapMono, which is in line with previous studies showing that elderly patients were less likely to receive oxaliplatin-containing regimens[7-11]. This most likely reflects the highly debated additional benefit from adding oxaliplatin to fluoropyrimidine chemotherapy in elderly patients[19-21]. One trial in which the effect of the different chemotherapy regimens on 3-year disease-free survival are compared among elderly patients with colon cancer is now ongoing[22].

Elderly patients receiving CAPOX less frequently completed all planned cycles compared to patients receiving CapMono (33% versus 55%, $P<0.0001$). Although the median number of capecitabine cycles did not differ between regimens, the median cumulative dosage of capecitabine was lower for patients who received CAPOX compared to patients who received CapMono. This is probably related to the fact that the standard dosage for capecitabine is lower in the CAPOX regimen compared to the CapMono regimen (2000 versus 25000 mg/m^2). In addition, increased toxicity with the CAPOX regimen can also have impacted the cumulative dosage of capecitabine. The

fact that patients treated with CAPOX received a lower median cumulative dosage capecitabine than patients treated with CapMono seems counterproductive, as it has been suggested that the main benefit from adjuvant treatment is derived from the fluoropyrimidine.

The proportions of patients completing their adjuvant treatment as described in our study are mostly lower compared to currently available studies. Not only in comparison to large phase III trials such as the X-ACT trial[4] in which 74% of the patients aged 70-75 years completed their treatment course but also compared to other population-based studies including elderly. In the study by Kim et al., 51% of patients aged ≥65 years treated with CAPOX or FOLFOX and 23% of the patients aged ≥65 years treated with either CapMono or FU-LV completed less than 75% of their cycles[9]. Results from the study by Laurent et al. showed that among patients aged ≥70 years and treated with FOLFOX, early discontinuation (i.e. <12 cycles) was present in 33% for 5-FU and in 69% for oxaliplatin[23]. In yet another population-based study, 40% of patients aged ≥65 years discontinued chemotherapy[7]. No distinction was made in type of adjuvant chemotherapy. We found that only the presence of any grade III-V toxicity was independently related to early discontinuation of both CAPOX and CapMono. The relationship between toxicity and treatment discontinuation was not often investigated in previous studies, except for the study by Kim et al., in which differences in treatment discontinuation between patients treated with monotherapy (capecitabine + FU) or combination chemotherapy (CAPOX + FOLFOX) according to the presence of non-haematological and haematological toxicity was investigated[9]. A difference was found between both types of chemotherapy in discontinuation due to haematological toxicity (3% versus 17% respectively, *P*=0.0004) but no difference in discontinuation due to non-haematological toxicity (28% versus 34% respectively, *P*=0.20)[9].

Especially for elderly patients with competing causes of death, adjuvant treatment should lead to gains in quality of life, symptom control and preserved functional status beyond survival benefit[24]. In this light, and given the uncertain effect of the addition of oxaliplatin on (overall) survival in elderly patients[19-21], is it important to consider the prevalence of chemotherapy-induced toxicity. Grade III-V toxicity was more evident with CAPOX (54%) than with CapMono (38%). This is in line with previous studies showing higher toxicity rates with oxaliplatin-containing regimens[5,9]. Previous studies have shown that the incidence of severe toxicity is not only determined by the chemotherapeutic agents itself but also by patient characteristics. The study by Extermann et al.[25] showed that the risk of severe toxicity is significant for any older patient receiving chemotherapy. Patient differences in Eastern Cooperative Oncology Group performance status, nutritional status and mental status contributed two to three times more than chemotherapy differences to the risk of non-haematological toxicity[25]. The study by Hurria et al. described the importance of a scoring system dominated by patient characteristics (based upon a geriatric assessment) in predicting chemotherapy toxicity[26]. Other studies have also shown the impact of geriatric factors on patient

selection for (type of) chemotherapy and risk of toxicity. These factors included for example malnutrition and functional and cognitive impairment[27,28].

Among patients treated with CAPOX, mostly oxaliplatin-related toxicity occurred. Especially grade III-IV neurological toxicity, i.e. neuropathy, which occurred in 11%, can have a disabling and prolonged effect with a major influence on quality of life[24,29]. In a previous study we reported that among patients treated with oxaliplatin, neuropathy-related symptoms are still reported 2 to 11 years after diagnosis[30].

Another toxicity of concern in the CAPOX regimen is diarrhoea. In our study the rate of gastrointestinal toxicity was twice as high with CAPOX compared with CapMono. In a trial comparing continuous or intermittent chemotherapy (COIN), which included patients with metastatic colorectal cancer, has shown that the incidence of grade III-IV diarrhoea was also higher among patients receiving CAPOX ± cetuximab compared to patients receiving FOLFOX ± cetuximab[31,32]. Additionally, another trial in the metastatic setting which included exclusively frail and elderly patients (the Fluorouracil, Oxaliplatin, CPT11 [irinotecan]: Use and Sequencing 2 (FOCUS2) trial) reported that the overall risk of grade ≥III toxicity was higher with capecitabine compared to FU, with specifically higher rates of nausea, vomiting, diarrhoea, anorexia and hand-foot syndrome[33]. As studies in the adjuvant setting showed a favourable toxicity profile for capecitabine[3,34], literature data are discordant.

In the X-ACT trial, grade III hand-foot syndrome occurred in 17% of the patients receiving capecitabine[4]. In our study, 17% of the patients receiving CapMono developed dermatological complications such as hand-foot syndrome. In contrast, only 3% of the patients treated with CAPOX developed dermatological complications. This presumably reflects the lower dosage of capecitabine in the CAPOX regimen in comparison with the monotherapy regimen.

The current study also investigated the associations between the most common grade III-V toxicity and the median number of cycles and cumulative dosage received. In general, toxicity that occurred rapidly was associated with a lower median number of cycles and cumulative dosage received, such as gastro-intestinal toxicity (i.e. nausea/vomiting and diarrhoea). Other toxicity was cumulative, appeared in a later stage during the treatment course and did not result in lower median number of cycles and cumulative dosages received, such as haematological toxicity, neuropathy and hand-foot syndrome. It is also possible that, when these toxicities occur and need to be mitigated, cycles are delayed instead of the dosage being reduced or cycles prematurely discontinued.

A limitation of our study is that only grade ≥III toxicity was recorded. Kalsi et al. previously showed that even low grade toxicities can lead to treatment modification and early discontinuation in older patients[35].

In conclusion, still only one third of stage III colon cancer patients aged ≥70 years received adjuvant chemotherapy. CAPOX is associated with more grade III-IV toxicities than CapMono, which had a pronounced impact on treatment intensity as patients receiving CAPOX more often discontinued treatment before all planned cycles were completed and received a lower cumulative dosage capecitabine as compared to patients receiving CapMono. As the main benefit from adjuvant therapy arises from fluoropyrimidine agents, CapMono seems preferable over CAPOX in elderly patients. Of course, effects on recurrence-free survival and quality of life should be taken into account as well. Nonetheless, the current study provides new insights that will help medical oncologists to discuss more adequately the benefits and drawbacks of the regimens with elderly patients.

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Chapter 3

"The impact of adjuvant therapy on the type of palliative chemotherapy in patients with metastatic colon cancer"

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Submitted

Abstract

Background: In the current era of modern adjuvant chemotherapy, treatment of recurrent metastatic colon cancer presents clinicians with significant challenges. There are no clinical studies or population-based data on the impact of adjuvant chemotherapy on subsequent chemotherapy choice in patients with metastatic colon cancer.

Methods: All consecutive patients diagnosed in the Eindhoven area between 2003-2008 with stage I-III colon cancer were extracted from the Netherlands Cancer Registry. Additional data on the development and treatment of metachronous metastases were collected between 2010-2011. We evaluated the influence of prior adjuvant chemotherapy on the subsequent type of palliative chemotherapy.

Results: Of the total number of 224 patients who received palliative systemic therapy for the treatment of metachronous metastases, 50% were previously exposed to adjuvant chemotherapy (n=111). Prior adjuvant therapy was associated with a lower odds for treatment with first-line combination chemotherapy (mostly oxaliplatin-based) if metastases occurred <1 year compared to no prior adjuvant therapy (OR 0.3, 95% CI 0.13-0.89). No such differences were observed if metastases occurred >1 year after primary tumour diagnosis (OR 0.6, 95% CI 0.30-1.14).

Conclusion: Oncologists' choice of palliative chemotherapy is influenced by prior adjuvant therapy. Notably, this trend was observed only if metastases developed <1 year after primary tumour diagnosis, which may indicate the feasibility of oxaliplatin reintroduction if metastases develop later. Continued investigations into the efficacy and tolerability of this approach are needed.

Introduction

Colon cancer (CC) is one of the most common malignancies in the Netherlands with 10,911 new cases in 2015, of who about 3,700 are expected to ultimately die of the disease.[1]

Since the 1990s, adjuvant chemotherapy – initially fluoropyrimidine monotherapy and since 2004 combinations with oxaliplatin – significantly improved the survival rate of patients with resected CC. Despite improved cure rates with adjuvant therapy, still a relatively large proportion (20%) of the patients with early stage (I-III) CC eventually develops metastases.[2] Although some patients have isolated metastases suitable for curative surgery, most patients with metastatic CC are incurable. For the latter group, treatment generally consists of palliative systemic therapy, aiming to prolong overall survival and maintain quality of life.

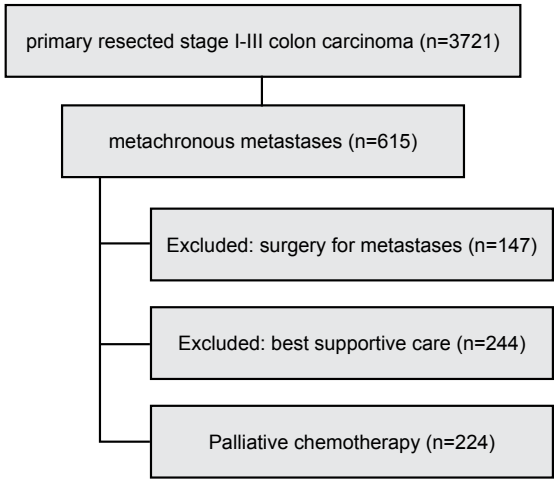
At the moment, little is known about the effect of prior adjuvant chemotherapy on the subsequent use of different types of systemic therapy. The present study aims to provide insight into the impact of prior adjuvant chemotherapy on the subsequent use of different types of palliative chemotherapy in a large consecutive series of non-selected CC patients.

Methods

Patients and data

Data were retrieved from the Eindhoven area of the Netherlands Cancer Registry (NCR), which collects data of all newly diagnosed cancer patients in a large part of the Southern Netherlands. This area comprises approximately 2.4 million inhabitants (~15% of the Dutch population), six pathology departments, ten hospitals and two radiotherapy institutions. Information on patient and tumour characteristics are collected from medical records by specially trained registry staff after notification by pathologists and medical registration offices. The tumour-node-metastasis (TNM) classification is used for stage notification of the primary tumour. Anatomical site of the tumour is registered according to the International Classification of Diseases for Oncology (ICD-O). Due to thorough training of the registration personnel and computerized consistency checks, the quality of the data is high. For the present study, additional data on the development and treatment of metachronous metastases were collected between 2010 and 2011 for patients diagnosed between 2003 and 2008 with stage I-III CC (n=3721). Metachronous metastases were defined as distant metastases of primary CC in other organs, diagnosed at least 3 months after initial diagnosis. Median time from primary diagnosis to data collection was 5.3 years (range 1.5-8.8 years). All consecutive patients with metachronous metastases from primary resected stage I-III CC (C18.0-C18.9) were selected (n=615). Patients undergoing surgery for metastases (n=147) or receiving best supportive care (n=244) were excluded, resulting in a study population of patients receiving palliative systemic therapy (n=224, Figure 1).

Figure 1 *Flowchart*



Statistical analyses

Palliative chemotherapy was classified according to the number (single-agent chemotherapy, combination chemotherapy) and type of prescribed cytotoxic agents (oxaliplatin-based, irinotecan-based, fluoropyrimidine monotherapy). Differences in patient and tumour characteristics were compared and analyzed using a two-sided Chi^2 test or Fisher's exact test if sample sizes were too small. Multivariable logistic regression analyses were used to evaluate the impact of prior adjuvant chemotherapy (yes vs. no, model 1), the impact of prior adjuvant therapy according to disease-free interval (≤1 year vs. > 1 year, model 2) and the impact of the prescribed adjuvant regimen (oxaliplatin-based vs. fluoropyrimidine monotherapy, model 3) on the type of first-line chemotherapy. Adjustments were made for all univariate significant or clinically relevant variables (age, comorbidity, primary tumour localization, time from initial CC diagnosis to metastases). P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

Results

The final study population included 224 patients receiving palliative systemic therapy for metachronous metastases from primary resected stage I-III CC. Mean age was 68 years at time of metachronous metastases diagnosis (SD 9.8), 29% was ≥75 years. Half of the patients (n=111) received prior adjuvant chemotherapy.

Patient and tumour characteristics

In the palliative setting, 120 of the 224 patients received first-line combination chemotherapy (oxaliplatin-based n=110, irinotecan-based n=10) and 104 patients received first-line single agent chemotherapy with either a fluoropyrimidine (n=79) or irinotecan (n=25). An overview on patient and tumour characteristics according to palliative chemotherapy is shown in Table 1.

Type of first-line chemotherapy according to prior adjuvant chemotherapy

Patients who received combination chemotherapy were less often exposed to prior adjuvant chemotherapy than patients who received single-agent chemotherapy (Table 1; 43% vs 57%, $p<0.05$). This was confirmed in a multivariable regression analysis (table 2; model 1), in which the likelihood of combination chemotherapy was significantly lower for patients who received prior adjuvant chemotherapy compared to patients who did not (OR 0.4, 95% CI 0.22-0.78). Patients who received prior adjuvant chemotherapy were less likely to receive oxaliplatin-based chemotherapy than patients who did not receive prior adjuvant chemotherapy (OR 0.4, 95% CI 0.23-0.80). These results were related primarily to patients who developed metastases ≤1 year after primary tumour diagnosis (Table 2; model 2) and who were previously exposed to oxaliplatin (Table 2; model 3).

Table 1 *Patient and tumour characteristics of patients receiving palliative chemotherapy for metachronous metastases from primary resected stage I-III CC (n=224).*

	Palliative chemotherapy (n=224)					**Palliative chemotherapy (n=224)**						
	Single-agent CTx (n=104)		**Combination CTx (n=120)**			**Oxaliplatin based CTx (n=110)**		**Irinotecan based CTx (n=35)**		**FU monotherapy (n=79)**		
	N	**(%)**	**N**	**(%)**	**p-value**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p-value**
Gender												
Male	39	(38)	50	(42)	0.53	46	(42)	10	(43)	28	(35)	0.62
Female	65	(62)	70	(58)		64	(58)	20	(57)	51	(65)	
Age (years)												
<65	27	(26)	43	(36)	<0.01	38	(35)	21	(60)	11	(14)	<0.0001
65-74	36	(35)	52	(43)		47	(43)	13	(37)	28	(35)	
≥ 75	41	(39)	25	(21)		25	(23)	1	(3)	40	(51)	
Comorbidity*												
0	32	(31)	41	(34)	0.33	40	(36)	10	(29)	23	(29)	0.22
1	29	(28)	36	(30)		31	(28)	10	(29)	24	(30)	
≥2	32	(31)	38	(32)		35	(32)	9	(26)	26	(33)	
Unknown	11	(11)	5	(4)		4	(4)	6	(17)	6	(8)	
Primary tumour localization												
Proximal colon	58	(56)	49	(41)	**<0.05**	45	(41)	20	(57)	42	(53)	0.28
Distal colon	41	(39)	67	(56)		61	(55)	13	(37)	34	(43)	
Other/NOS	5	(5)	4	(3)		4	(4)	2	(6)	3	(4)	
Period of primary tumour diagnosis												
2003-2004	20	(19)	26	(22)	0.36	22	(20)	8	(23)	25	(32)	0.69
2005-2006	48	(46)	63	(53)		59	(54)	17	(49)	23	(29)	
2007-2008	36	(35)	31	(26)		29	(26)	10	(29)	31	(39)	
Time to metastases (months)												
≤12	36	(35)	36	(30)	0.75	30	(27)	17	(49)	33	(42)	**<0.05**
12-24	34	(33)	41	(34)		38	(35)	14	(40)	27	(34)	
>24	34	(33)	43	(36)		42	(38)	4	(11)	19	(24)	
Number of organs affected												
1 organ	44	(42)	54	(45)	0.89	48	(44)	17	(49)	33	(42)	0.82
2 organs	34	(33)	36	(30)		35	(32)	8	(23)	27	(34)	
≥3 organs	26	(25)	30	(25)		27	(25)	12	(29)	19	(24)	
Adjuvant chemotherapy												
No	45	(43)	68	(57)	**<0.05**	63	(57)	5	(14)	45	(57)	**<0.0001**
Yes	59	(57)	52	(43)		47	(43)	30	(86)	34	(43)	
Combination	34	(69)	27	(52)	0.83	22	(47)	21	(70)	18	(53)	0.35
Single-agent	21	(43)	21	(40)		21	(45)	7	(23)	14	(41)	
Missing	4	(8)	4	(8)		4	(9)	2	(7)	2	(6)	

**comorbidity at primary diagnosis. CTx: chemotherapy*

Table 2 *An overview on type of first-line palliative chemotherapy according to prior adjuvant therapy, adjusted for all factors listed below.*

	Total	Of which combination CT_x		Of which oxaliplatin-based CT_x	
		N (%)	OR (95%CI)	N (%)	OR (95%CI)
Model 1					
Adjuvant CT_x					
No	113	68 (60)	Ref	63 (56)	Ref
Yes	111	52 (47)	**0.4 (0.22-0.78)**	47 (42)	**0.4 (0.23-0.80)**
Model 2					
Adjuvant CT_x					
No	113	68 (60)	Ref	63 (56)	Ref
Yes, metastases ≤ 12 months	30	11 (37)	**0.3 (0.11-0.88)**	8 (27)	**0.3 (0.10-0.82)**
Yes, metastases > 12 months	81	41 (51)	0.5 (0.23-1.01)	39 (48)	0.5 (0.26-1.09)
Model 3					
Adjuvant CT_x					
Cap/FU	42	21 (50)	Ref	21 (50)	Ref
CAPOX/FOLFOX	61	27 (44)	0.6 (0.24-1.49)	22 (36)	**0.4 (0.14-0.97)**
Metastases ≤ 12 months					
Cap/FU	12	6 (50)	*	6 (50)	*
CAPOX/FOLFOX	16	4 (25)		1 (6)	
Metastases > 12 months					
Cap/FU	30	15 (50)	Ref	15 (50)	Ref
CAPOX/FOLFOX	45	23 (51)	0.7 (0.24-2.23)	21 (47)	0.6 (0.21-1.92)

Adjusted for univariate significant or clinically relevant variables; age, comorbidity, primary tumour localization, time to metastases.
Model 3: results not shown for adjuvant regimen unknown (n=8).
**multivariate analysis not possible due to limited number of patients*
CTx: chemotherapy; N: number of patients; OR: odds ratio; CI: confidence interval; Cap: capecitabine; FU: fluorouracil; CAPOX: capecitabine-oxaliplatin; FOLFOX: fluorouracil-oxaliplatin.

Discussion

To the best of our knowledge, this is the first population-based study providing insight into the impact of adjuvant chemotherapy on subsequent chemotherapy choice in patients with metastatic CC. Prior adjuvant therapy was shown to reduce the probability of receiving first-line combination chemotherapy (in particular oxaliplatin-based chemotherapy) if metastases developed ≤1 year, but not if metastases developed >1 year after primary tumour diagnosis.

The present study reflects a period in which adjuvant therapy has been redefined. The benefit of adjuvant therapy was established already in the early 1990s.[3] In 2004, the addition of oxaliplatin to infusional 5-fluorouracil/leucovorin (FOLFOX) was shown to increase 3-year disease free survival rates from 72.9% to 78.2% (p=0.002).[4-7] National guidelines changed, recommending oxaliplatin-based therapy as the standard adjuvant therapy in stage III and high-risk stage II CC.[8] In 2009, the final analysis of data from the MOSAIC trial confirmed these results, with improvements in 5-year disease-free (73% vs. 67%, p=0.003) and 6-year overall-survival (79% vs 76.0%, p=0.046). This improvement in overall survival was observed only in patients with stage III disease (73% vs. 69%, p=0.23) Consequently, oncologists have been increasingly confronted with metastatic CC patients who were previously treated with adjuvant chemotherapy. In the current study, 50% of the patients with metastatic CC received prior adjuvant therapy, of whom 59% were exposed to oxaliplatin. In line with Dutch practice guidelines, the majority of patients received oxaliplatin-based chemotherapy (mainly CAPOX), whereas fewer patients were treated with single-agent chemotherapy (mostly capecitabine).

In the present population-based study with everyday clinical practice data, oncologists' choice of palliative chemotherapy was significantly influenced by prior adjuvant therapy if metastases occurred ≤1 year after primary tumour diagnosis. In these patients, combination chemotherapy was less frequently prescribed. Patients were less likely to receive oxaliplatin-based chemotherapy, in particular if patients were previously exposed to oxaliplatin. This may be explained by persistent troublesome neuropathy and the consideration of refractory disease as metastases occurred within 6 months after completion of the adjuvant treatment.[9,10] In these cases, irinotecan-based chemotherapy (either single-agent or combination chemotherapy) may be considered a good alternative, especially since there are no significant difference in terms of efficacy between first-line irinotecan and oxaliplatin-based chemotherapy, as long as the patient was exposed to all the drugs.[11,12] Besides, concomitant use of targeted agents may also be considered in the current era of evolving targeted therapy, especially since it has been hypothesized that this may prevent or reverse resistance to oxaliplatin.[13]

Interestingly, we observed equal proportions of combination chemotherapy and oxaliplatin-based chemotherapy if metastases developed more than one year after primary tumour diagnosis, also after stratifying for the prescribed adjuvant regimen. Although these results need to be interpreted with caution due to the limited number of patients and the lack of outcome data, it may implicate the feasibility of re-treatment with oxaliplatin after prior adjuvant therapy. Oxaliplatin reintroduction has been noted also in the OPTIMOX trials, in which patients with metastatic disease were assigned to FOLFOX7 or FOLFOX4 in a stop and go fashion.[14,15] Continued investigations into the efficacy and tolerability of this approach are merited.

The retrospective nature of the data collection presents several limitations to this study. At first, it should be mentioned that CC patients were included between 2003-2008, although oxaliplatin was not considered standard until 2004. Besides, no data could be captured on the reasons (not) to prescribe specific regimens. Whether persistent neuropathy or other toxicity was an obstacle to re-administration of specific cytotoxic agents is unknown. In addition, quality of life issues and overall/disease-free response rates could not be determined. Nevertheless, the present study present real-world data providing insight into everyday clinical practice, which is of utmost importance as it there are currently no randomized data guiding clinicians.

Conclusion

The present consecutive series of primary resected stage I-III CC patients provides insight into actual daily practice and shows that oncologists' choice is significantly influenced by prior adjuvant therapy. Notably, this trend was observed only if metastases developed <1 year, which may indicate the feasibility of oxaliplatin reintroduction if metastases develop later. Continued investigations into the efficacy and tolerability of this approach are needed.

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Part II

"The palliative treatment of recurrent metastatic colorectal cancer"

Chapter 4

"Bevacizumab for metachronous metastatic colorectal cancer: a reflection of community based practice"

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Abstract

Background: Although the efficacy of bevacizumab has been established in patients with metastatic colorectal cancer (mCRC), population-based studies are needed to gain insight into the actual implementation of bevacizumab in daily practice. Since these studies are lacking for patients with metachronous metastases, the aim of this study is to evaluate the current role of bevacizumab in the treatment of metachronous metastases of CRC.

Methods: Data on the use of bevacizumab as palliative treatment of metachronous metastases were collected for patients diagnosed with M0 CRC between 2003 and 2008 in the Eindhoven Cancer Registry (n=361). Median follow up was 5.3 years.

Results: 185 patients received bevacizumab in addition to first-line palliative chemotherapy (51%), ranging from 36% to 80% between hospitals of diagnosis ($p<0.0001$). Combined cytostatic regimens (CAPOX/FOLFOX in 97%) were prescribed in the majority of patients (63%) and were associated with a higher odds for additional treatment with bevacizumab than single-agent cytostatic regimens (OR 9.9, 95% CI 5.51-18.00). Median overall survival (OS) rates were 21.6 and 13.9 months with and without the addition of bevacizumab to palliative systemic treatment respectively ($p<0.0001$). The addition of bevacizumab to palliative chemotherapy was associated with a reduced hazard ratio for death (HR 0.6, 95% CI 0.45-0.73) after adjustment for patient- and tumor characteristics and the prescribed chemotherapeutic regimen.

Conclusion: Bevacizumab is adopted as a therapeutic option for metachronous metastasized CRC mainly in addition to first-line oxaliplatin-based regimens, and was associated with a reduced risk of death. The presence of inter-hospital differences in the prescription of bevacizumab reflected important differences in attitude and policies in clinical practice. Ongoing efforts should be made to further define the position of targeted agents in the treatment of metastatic colorectal cancer.

Introduction

Metastatic disease is a common manifestation in patients with advanced colorectal cancer (CRC). Approximately one fifth of patients presents with metastasized disease at diagnosis[1-3] and 20% of patients with initial M0 disease develops metachronous metastases.[4]

Fluorouracil based palliative chemotherapy has been the mainstay of treatment for many years. Over the past decade, the systemic treatment of metastatic CRC (mCRC) has changed considerably. The availability of the cytostatic drugs irinotecan and oxaliplatin has improved the prognosis of mCRC patients.[5] Moreover, advances in the understanding of molecular oncology have served for the development of targeted agents such as the anti-vascular endothelial growth factor blocking agent (VEGF-a) bevacizumab. Although the efficacy of bevacizumab has been established in patients with mCRC[6], the role of bevacizumab in clinical practice remains a topic of debate. Population-based data are useful in reflecting community based practice. To date, no such population-based figures of patients with metachronous metastases are available. Therefore the aim of this study is to provide population-based data on the use and effect on overall survival of bevacizumab in the palliative treatment of metachronous metastasized CRC in the Netherlands.

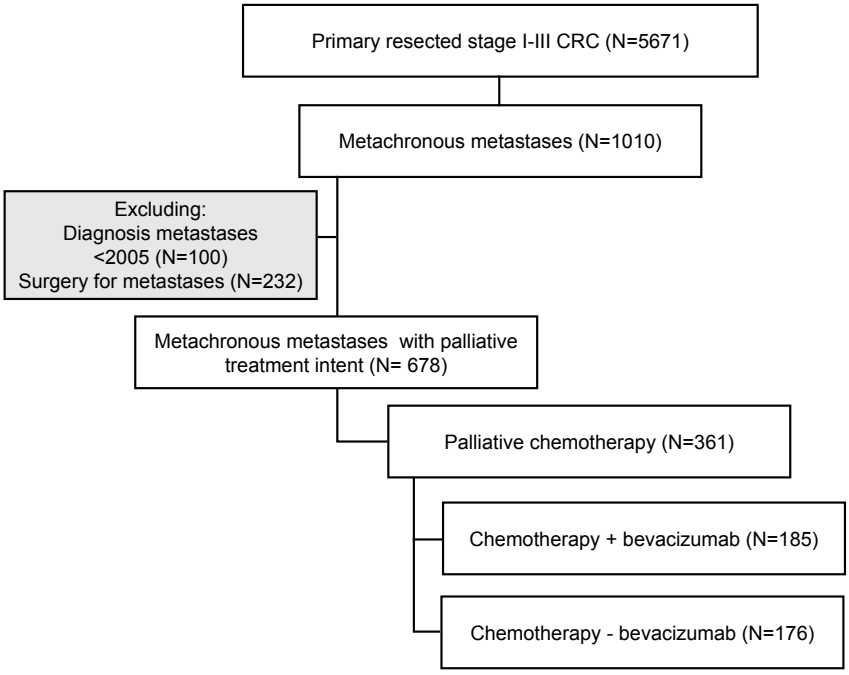
Methods

Patients and data

Data from the population-based Netherlands Cancer Registry (NCR), more specifically from the Eindhoven area, were used. The Eindhoven Cancer Registry (ECR) collects data of all patients with newly diagnosed cancer in a large part of the Southern Netherlands. The ECR covers an area of approximately 2.4 million inhabitants, six pathology departments, ten hospitals and two radiotherapy institutions. Patient and tumor characteristics are collected from medical records by specially trained registry staff after notification by pathologists and medical registration offices, resulting in high quality of the data. The completeness of cancer registration is estimated to exceed 95%. In the ECR, primary tumors are classified according to the TNM classification of Malignant Tumors by the international Union Against Cancer (UICC), 7th edition.[7] Additional data were retrospectively collected on metachronous metastases for patients diagnosed between 2003 and 2008 with stage I-III CRC. Hospitals were asked to participate in the study by giving permission to use their data from the ECR and by giving permission for the retrospective registration of additional data. All hospitals voluntarily participated. Metachronous metastases were defined as distant metastases of primary CRC in other organs, diagnosed at least 3 months after CRC diagnosis. However, the majority of metachronous metastases diagnoses (94%) occurred at least 6 months after CRC diagnosis. Patterns of metastatic disease were determined based on the site of metastasis according to the International Classification of Diseases for Oncology (ICD-O), which could involve multiple localizations. Median time from primary diagnosis to data collection was 5.3 years (range 1.5-8.8 years). All consecutive pa-

tients with metachronous metastases from primary resected CRC were selected (n=1010). Patients diagnosed with metachronous metastases before 2005 (n=100) were excluded as bevacizumab is registered and recommended as a therapeutic option in addition to first-line chemotherapy in the Netherlands since 2005.[8] Subsequently, patients undergoing surgery for metastases were excluded (n=232), resulting in a study population treated with palliative intent (n=678) of whom 361 received palliative chemotherapy (with or without palliative procedures; bypass, anastomosis, stoma). These latter patients were categorized into two treatment groups according to the prescription of bevacizumab in addition to palliative chemotherapy (Figure 1). In the current study, we focused on the first-line palliative treatment as this is the indication for which bevacizumab is registered in the Netherlands.

Figure 1 *An overview on the palliative systemic treatment of metachronous metastases for patients diagnosed between 2003 and 2008 with stage I-III colorectal cancer in the south of the Netherlands.*



Statistical analysis

Variation in the prescription of bevacizumab between hospitals of diagnosis in the ECR-region was assessed using a χ^2 test. Also, differences in patient and tumor characteristics and the prescription of bevacizumab between chemotherapeutic regimens were tested by means of a χ^2 test. To discriminate independent predictors of treatment with bevacizumab, a multivariable logistic regression model was used. Adjustments were made for relevant patient and tumor characteristics: gender, age, comorbidity at time of CRC diagnosis, primary tumor localization, adjuvant chemotherapy, time to metastases, period of metastases diagnosis, number of metastases and the prescribed first-line chemotherapeutic regimen. In order to limit potential endogeneity bias due to the population-based nature of the data, a propensity score matched sample was created. Propensity scores were determined with a logistic regression model in which bevacizumab was the variable of interest and the independent variables were factors potentially associated with the use of bevacizumab (similar to variables taken into account in the multivariable logistic regression analysis). Patients were then matched within tight bounds of the propensity scores (probability could vary by no more than 1%). Overall survival time was defined as the time from diagnosis of the first metachronous metastatic site to death or lost to follow-up. Patients still alive at the end of follow-up (January 1st, 2014) and those who emigrated were censored. Crude survival estimates according to the prescription of bevacizumab were calculated with the Kaplan-Meier method and presented up to 48 months in both the total study population and the propensity score matched sample. Median survival (MS) was presented in months and corresponding 95% confidence intervals (CIs). A log-rank test was carried out to evaluate significant differences between survival curves. Multivariable Cox regression analyses were performed in both the total study population and propensity score matched sample to evaluate the independent effect of additional bevacizumab on the risk of death. Adjustments were made for the clinically relevant variables age, comorbidity, localization of primary tumor, adjuvant chemotherapy, time to metastases, period of metastases diagnosis, number of metastases, prescribed first-line chemotherapeutic regimen and the total number of systemic lines for the treatment of metastases. All analyses were performed with SAS/STAT® statistical software (SAS system 9.3; SAS institute, Cary, NC).

Ethical considerations

In the Netherlands, the NCR and Dutch hospitals have a formal agreement that all cancer patients are informed about registration in the Cancer Registry and the possibility to decline registration. According to the Dutch law, all cancer patients are included in the NCR unless the patient has objected to be registered. Therefore, consent of the patient for this specific study was not applicable.

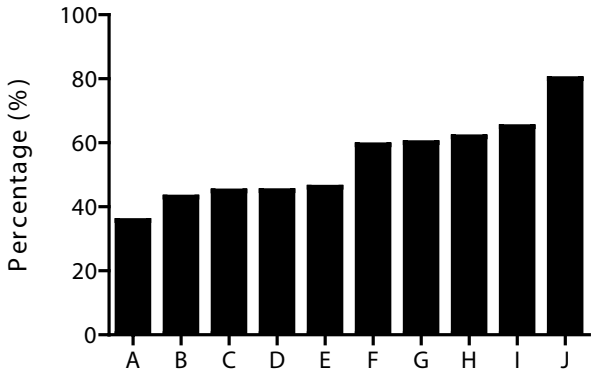
The NCR retrospectively collects data from medical records and is obligated to work according to laws in which the privacy of patients and doctors is fixed in regulations; the law about protection of privacy and the law "Geneeskundige BehandelOvereenkomst". An independent Committee of Privacy reassures that the NCR works compliant to these regulations. In the Netherlands, retro-

spective studies with data collected from medical charts do not fall under the scope of the Medical Research Involving Human Subjects Act ('Wet Medisch-wetenschappelijk Onderzoek") as patient integrity is not violated in these studies. Therefore, this study was exempted from further medical ethics review.

Results

Out of 5671 primary resected stage I-III CRC patients diagnosed between 2003 and 2008, 1010 patients developed metachronous metastases (18%). In total, 361 patients received first-line systemic therapy for the palliative treatment of metachronous colorectal metastases. Palliative procedures including a diverting stoma, bypass or anastomosis were performed in a minority of the patients (n=18,5%). Bevacizumab was prescribed in 51% of the patients (n=185), with proportions varying from 36% to 80% between the 10 hospitals in the ECR region (p<0.0001, Figure 2). An overview of patient and tumor characteristics according to the addition of bevacizumab to first-line systemic therapy is shown in Table 1.

Figure 2 *Proportion of patients receiving first-line palliative chemotherapy plus bevacizumab according to hospital of diagnosis (n=361).*



Patient and tumor characteristics

Of the 361 patients treated with first-line systemic therapy, 219 patients received combination chemotherapy (CAPOX/FOLFOX in 96%) and 142 patients received single-agent chemotherapy (capecitabine 74%, irinotecan 20%). Patient and tumor characteristics of patients treated with these chemotherapeutic regimens are shown in Table 1. Patients receiving combination chemotherapy were younger, had less comorbidities, were more often diagnosed with rectal tumors and less often received prior adjuvant chemotherapeutic treatment than patients receiving single-agent chemotherapy. Moreover, patients treated with combination chemotherapy more frequently received bevacizumab (n=153, 70%) than patients treated with single-agent chemotherapy (n=32, 23%, p<0.0001).

Predictors of treatment with bevacizumab

In multivariable regression analysis including adjustment for the type of prescribed first-line chemotherapeutic regimen, several factors were shown to influence the probability to receive additional first-line bevacizumab (Table 2). It was confirmed that patients treated with combination chemotherapy were more likely to receive bevacizumab than patients treated with single-agent chemotherapy (OR 9.666, 95% CI 5.43-17.05). Moreover, the odds for treatment with bevacizumab was higher for patients diagnosed with metastases in a recent time period than patients diagnosed with metastases shortly after the introduction of bevacizumab in Dutch guidelines (2005-2006). The probability to receive bevacizumab was lower for patients with ≥2 comorbidities than patients without comorbidity (OR 0.4, 95% CI 0.21-0.81) No association was observed between age and the use of bevacizumab. However, elderly patients (≥ 75 years) were less likely to receive combination chemotherapy (OR 0.2, 95% CI 0.11-0.30).

Table 1 *Patient and tumor characteristics according to the addition of bevacizumab to first-line systemic therapy (n=361).*

N=361	Without bevacizumab (n=176)		With bevacizumab (n=185)			Combination CT_x (n=219)		Single-agent CT_x (n=142)		
	N	(%)	N	(%)	P-value	N	(%)	N	(%)	P-value
Gender										
Male	75	(43)	72	(41)	0.69	126	(58)	89	(63)	0.33
Female	101	(57)	113	(59)		93	(42)	53	(37)	
Age (years)										
<60	36	(20)	57	(31)	<0.0001	71	(32)	24	(17)	<0.0001
60-75	91	(52)	111	(60)		128	(59)	72	(51)	
≥75	49	(28)	17	(9)		20	(9)	46	(32)	
Comorbidity										
No	50	(28)	81	(44)	<0.001	38	(28)	91	(42)	<0.01
1 comorbid condition	49	(28)	56	(30)		36	(26)	66	(30)	
≥2 comorbid conditions	63	(36)	33	(18)		52	(36)	44	(20)	
Unknown	14	(8)	15	(8)	0.13	14	(19)	18	(8)	
Primary tumor localization										
Rectum	68	(39)	85	(46)		107	(49)	47	(33)	<0.01
Colon	108	(61)	100	(54)		112	(51)	95	(67)	
Adjuvant CT_x										
No	103	(59)	100	(54)	0.34	137	(63)	67	(47)	<0.01
Yes	73	(41)	85	(46)		82	(37)	75	(53)	
Time to metastases (years)										
< 1 year	57	(32)	43	(23)	0.12	57	(26)	42	(30)	0.59
1-2 years	56	(32)	71	(38)		82	(37)	46	(32)	
≥ 2 years	63	(36)	71	(38)		80	(37)	54	(38)	
Period of diagnosis metastases	70	(40)	41	(22)	<0.01	69	(31)	42	(30)	0.81
2005-2006	57	(32)	78	(42)		83	(38)	52	(37)	
2007-2008	49	(28)	66	(36)		67	(31)	48	(34)	
2009-2011										
Number of organs affected										
1 organ	72	(41)	85	(46)	0.29	92	(42)	65	(46)	0.39
2 organs	69	(39)	59	(32)		83	(38)	44	(31)	
≥ 3 organs	35	(20)	41	(22)		44	(20)	33	(23)	
First-line CT_x										
Single agent CT_x	110	(63)	32	(27)	<0.0001					
Combination CT_x	66	(37)	153	(83)						
Bevacizumab										
Yes						153	(70)	32	(23)	<0.0001
No						66	(30)	110	(77)	

Table 2 *Proportion of patients treated with bevacizumab among patients who received chemotherapy, and predictors of treatment with bevacizumab in first line, adjusted for all factors listed (n=361).*

N=361	N	(%)	OR	95% CI
Gender				
Male	72	(49)	Ref	
Female	113	(53)	1.3	0.79-2.16
Age (years)				
<60	57	(60)	Ref	
60-74	111	(56)	1.1	0.61-2.05
≥75	17	(26)	0.5	0.22-1.27
Comorbidity				
No	81	(62)	Ref	
1 comorbid condition	56	(54)	0.8	0.42-1.45
≥2 comorbid conditions	33	(34)	0.4	**0.21-0.81**
Unknown	15	(48)	0.7	0.27-1.65
Primary tumor localization				
Rectum	85	(55)	Ref	
Colon	100	(48)	0.9	0.37-2.26
Adjuvant chemotherapy				
No	100	(49)	Ref	
Yes	85	(54)	1.7	0.98-2.96
Time to metastases (years)				
< 1 year	43	(43)	Ref	
1-2 years	71	(55)	1.5	0.78-2.82
≥ 2 years	71	(53)	1.2	0.60-2.30
Period of diagnosis metastasis				
2005-2006	41	(37)	Ref	**1.62-5.70**
2007-2008	78	(58)	3.0	**1.67-6.74**
2009-2011	66	(57)	3.3	
Number of organs affected				
1 organ	85	(54)	Ref	**0.29-0.91**
2 organs	59	(46)	0.5	0.46-1.74
≥ 3 organs	41	(53)	0.9	
First-line chemotherapy				
Single agent chemotherapy	32	(23)	Ref	
Combination chemotherapy	153	(70)	9.6	**5.43-17.05**

N; number of patients receiving bevacizumab in the first-line of systemic treatment. %; percentage of patients receiving bevacizumab in the first-line of systemic treatment. OR; odds ratio, CI; confidence interval.

Survival analysis

As shown in Figure 3, the addition of bevacizumab to first-line palliative chemotherapy was associated with an improved median overall survival, from 14 months (95% CI 11-16) to 22 months (95% CI 19-24) (log rank p<0.0001). In the propensity score matched sample, including 60 patients (with bevacizumab n=30, without bevacizumab n=30), comparable results were found with a median overall survival of 13 months (95%CI 7.62-18.92) versus 25 months (95%CI 7.62-18.92) (log rank p<0.05). In multivariable analysis, the addition of bevacizumab to palliative chemotherapy resulted in a reduced hazard ratio on death, in both the total study population (HR 0.6, 95% CI 0.45-0.73) and propensity score matched sample (HR 0.3; 95% CI 0.14-.079, Table 3). After stratification for the prescribed first-line chemotherapeutic regimen, the beneficial effect of the addition of bevacizumab was observed in the subset of patients receiving combination chemotherapy (HR 0.6; 95% CI 0.40-0.81), but not in patients treated with single-agent chemotherapy (HR 0.9, 95% CI 0.60-1.54).

Figure 3 *Overall survival according to the addition of bevacizumab to first-line systemic therapy (n=361).*

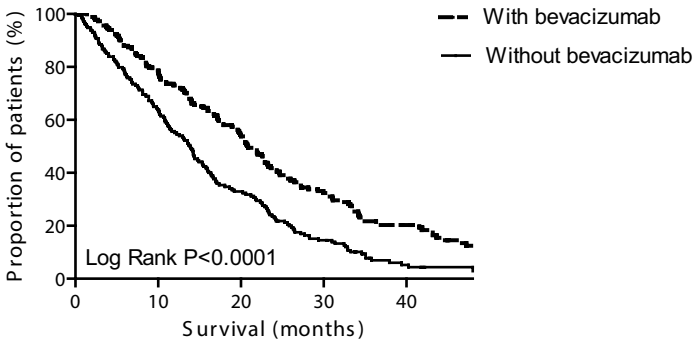


Table 3 *Multivariable Cox regression analysis modelling the independent effect of additional bevacizumab on the risk of death, adjusted for all factors listed.*

	Total study population (N=361)			Propensity score matched sample (N=60)		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age (years)						
<60	Ref			Ref		
60-74	1.0	0.76-1.38	0.86	1.8	1.82-4.13	0.15
≥75	1.3	0.87-1.90	0.21	0.8	0.20-3.53	0.80
Comorbidity						
No	Ref			Ref		
1 comorbid condition	0.9	0.69-1.22	0.56	1.1	0.40-2.86	0.88
≥2 comorbid conditions	0.8	0.54-1.04	0.08	1.0	0.34-3.01	1.07
Unknown	0.7	0.47-1.17	0.19	0.6	0.21-1.98	1.00
Primary tumor localization						
Rectum	Ref			Ref		
Colon	**1.3**	1.01-1.65	<0.05	0.6	0.21-1.98	0.35
Adjuvant CT_x						
No	Ref			Ref		0.97
Yes	1.0	0.82-1.34	0.68	1.0	0.44-2.32	
Time to metastases (years)						
< 1 year	Ref			Ref		
1-2 years	1.1	0.87-1.57	0.28	0.7	0.25-1.87	0.46
≥ 2 years	1.0	0.72-1.31	0.85	0.4	0.16-1.22	0.11
Period of diagnosis metastasis						
2005-2006	Ref	0.81-1.64	0.42	Ref	0.64-8.34	0.20
2007-2008	1.1	0.78-1.71	0.47	2.3	0.67-9.62	0.16
2009-2011	1.1			2.5		
Number of organs affected	Ref	0.96-1.63	0.19	Ref	0.74-4.78	0.18
1 organ	1.2	**1.12-2.21**	**<0.01**	1.8	**1.48-13.00**	**<0.01**
2 organs	**1.6**			**4.3**		
≥ 3 organs						
First-line CT_x						
Single agent chemotherapy	Ref			Ref		
Combination chemotherapy	0.9	0.69-1.27	0.69	**0.2**	**0.07-0.49**	**<0.001**
Additional bevacizumab						
No	Ref	0.49-0.89	<0.01	0.3	**0.14-0.79**	**<0.05**
Yes	**0.6**					
Number of systemic lines						
1 line	Ref	0.44-0.84	<0.01	0.5	0.16-1.74	0.29
2 lines	**0.6**	0.31-0.58	<0.0001	**0.3**	**0.13-0.72**	**<0.01**
≥ 3 lines	**0.4**					

N; number of patients, HR; hazard ratio, CI; confidence interval

Discussion

To our knowledge, this is the first study providing population-based data on the use of bevacizumab in the metachronous setting, which has been suggested to differ from synchronous manifestation of disseminated disease with respect to tumor biology and prognostics.[9-11] Bevacizumab was prescribed in approximately half of the patients with metachronous metastases receiving first-line palliative treatment between 2005 and 2011 in the southern part of the Netherlands, achieving a median overall survival of 22 months. Prescription of bevacizumab varied significantly between hospitals of diagnosis and depended on the prescribed chemotherapeutic regimen.

The inter-hospital variation in the adoption of bevacizumab as observed in our study may reflect differences in policy and attitude towards the use of this anti-angiogenic agent in daily practice.[12] Bevacizumab was FDA-approved following the landmark publication by Hurwitz et al in which a survival benefit was demonstrated in patients treated with irinotecan, bolus fluorouracil and leucovorin (IFL).[6] However, by the time bevacizumab was adopted in clinical practice, a shift towards oxaliplatin-based chemotherapy had taken place in the Netherlands.[13-15] Due to the initial absence of efficacy data in addition to these oxaliplatin containing regimens and the controversial results that were reported later on[16], the role of bevacizumab remained a highly debated topic. Also, the recent introduction of antibodies against epidermal growth factor receptors (EGFR)[17] strengthened the debate, as the question was raised which targeted agent should be preferred in the first-line systemic treatment.[18] In order to prevent an expanding gap between "believers" and "non-believers" in the current era of evolving treatment options for mCRC, ongoing efforts are needed to establish an evidence based opinion on the use of bevacizumab.

In line with the Dutch guidelines, the majority of patients with metachronous metastases received oxaliplatin-based chemotherapy (CAPOX or FOLFOX) whereas fewer patients were treated with single-agent chemotherapy (mostly capecitabine). Elderly patients and patients with multiple comorbidities were less often considered candidates for treatment with oxaliplatin-based chemotherapy, reflecting the generally accepted opinion that individual components of a systemic regimen should be selected on a number of factors, including patient related factors such as age, performance status and comorbidity.[19] Moreover, we observed that adjuvant chemotherapy influenced the choice of chemotherapy for the treatment of metachronous metastases. If adjuvant chemotherapy was prescribed, patients were less likely to receive combination chemotherapy as palliative treatment. This probably reflects the persistence of troublesome oxaliplatin induced polyneuropathy after adjuvant chemotherapy.[20] Since 2004, adjuvant oxaliplatin-based chemotherapy is considered the standard treatment schedule in the Netherlands for high risk stage II and stage III colonic tumors.[21,22] For rectal tumors, however, adjuvant chemotherapy is generally not recommended, which probably explains the relatively higher proportion of oxaliplatin-based regimens

for the treatment of metastases in this subset of patients.
The likelihood of treatment with bevacizumab was shown to depend strongly on the prescribed chemotherapeutic regimen for the metastatic disease. If a patient was considered a candidate for combination-chemotherapy, bevacizumab was prescribed in approximately 70% of the cases. On the opposite, if single-agent chemotherapy was prescribed, only 23% of the patients received bevacizumab. These findings are in line with results from observational cohort studies in the U.S.[13-15] Of course, it could be speculated that bevacizumab was prescribed in combination with further lines of chemotherapy, as the results from the CAIRO III study revealed equal results for combined and sequential treatment chemotherapy strategies.[23] However, very few patients included in the current study received bevacizumab in further lines of treatment (data not shown).
In accordance with observations from the current literature in which age has been identified as one of the most important factors when deciding the type of therapy for patients with mCRC[24,25], we observed that elderly patients (≥ 75 years) were less likely to receive combination-chemotherapy than younger patients. However, advanced age did not influence the probability to receive bevacizumab if adjustments were made for the prescribed chemotherapeutic regimen. Thus, age influenced primarily the choice of cytostatic backbone. This observation reflects the lack of data on the benefit-risk ratio of combination-chemotherapy regimens in older patients. It has been shown that the bevacizumab related adverse events do not increase with age, except for arterial thromboembolic events.[26] However, for this complication other patient related factors appeared to be stronger predictive factors than age.[26] Bevacizumab should therefore be considered a potential therapeutic option for elderly patients with mCRC and age alone should not be considered an absolute contraindication.[27]

The addition of bevacizumab to first-line palliative therapy was associated with a median overall survival of 22 months, which is consistent with reports from observational studies on mCRC from the period 2002-2007.[13-15] Of course, this observed improvement in overall survival with the addition of bevacizumab was biased by the prescription of more potential cytostatic backbone regimens in the presence of bevacizumab, and by patient selection by the treating physician. Nevertheless, after adjustment for important prognostic factors such as the prescribed chemotherapeutic regimen, a reduced hazard of death was observed in patients receiving additional bevacizumab. Moreover, results remained present in the propensity score matched sample, in which an effort is made to limit potential endogeneity bias. After stratification for the type of chemotherapy, the beneficial effect of additional bevacizumab achieved significance only in the subset of patients treated with combination-chemotherapy, probably because patient numbers were too small in the subset of single-agent backbone therapy. Although these non-randomized observational data should be interpreted with caution, together with the demonstrated benefit of bevacizumab across chemotherapy regimens in several RCTs[6,16,28-30] and observational studies[13-15],

they strengthen the suggestion that bevacizumab is likely to add activity to various chemotherapy regimens with which it is combined.
Despite the accurate and concise patient registration, use of the ECR also implies limitations to our data. No data on relevant prognostic factors such as extent of metastatic burden were available. Moreover, data on patient and tumor characteristics such as comorbidity are registered by registration personnel approximately 6-9 months after primary tumor diagnosis. Therefore, it is not possible to provide data on the specific comorbidities present at the time of treatment for metachronous metastases.

In conclusion, in this population-based study it was revealed that addition of bevacizumab to the first line treatment of metachronous metastases of CRC is likely to be an independent beneficial factor for overall survival in patients receiving oxaliplatin containing chemotherapy. Moreover, a significant inter-hospital difference in the prescription of bevacizumab was found, reflecting differences in attitude towards and policies in the use of bevacizumab in clinical practice. Ongoing efforts should be made to further define the position of targeted agents in the treatment of metachronous metastases from CRC.

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Chapter 5

"The impact of age on first-line systemic therapy in patients with metachronous metastases from colorectal cancer"

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Abstract

Objectives: The paucity of evidence for the optimal use of systemic therapy in elderly patients with metastatic colorectal cancer (mCRC) poses significant challenges to cancer specialists. The present population-based study provides insight into the impact of age on palliative systemic therapy in patients with metachronous metastases from CRC, in order to optimize the decision-making process.

Methods: Data on the development and treatment of metachronous metastases were collected for patients with primary resected CRC diagnosed between 2003 and 2008 in the Eindhoven area of the Netherlands Cancer Registry. Patients undergoing surgery for metastases were excluded, resulting in a study population treated with palliative intent, with or without systemic therapy (n=746).

Results: 385 patients received palliative systemic therapy (52%). Patients aged ≥75 years were less likely to receive systemic therapy (31% ≥75 years vs 73% <60 years) and more likely to receive single-agent chemotherapy than combination-chemotherapy. Elderly patients (≥75 years) treated with capecitabine-oxaliplatin (CAPOX) received fewer cycles (51% ≤3 oxaliplatin cycles, 43% ≤3 capecitabine cycles) and lower cumulative dosages compared to patients aged <75 years, although initial dosages were similar. If capecitabine monotherapy (CapMono) was administered, starting dosages were 2,414mg/m^2/d <75 years and 1,992mg/m^2/d ≥75 years ($p<0.05$), but no differences in number of received cycles or cumulative dosages were observed.

Conclusion: Age beginning at 75 years significantly influenced palliative systemic therapy. Even in selected elderly patients, first-line treatment with CAPOX was associated with less cycles and lower cumulative dosages compared to younger patients. With single-agent fluoropyrimidine therapy, however, no such results were observed.

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide and currently the third most common malignancy in the Netherlands.[1] The occurrence of CRC increases with age, with 54% being 70 years or older and over one third being 75 years or older.[1]

Most cancer deaths result from progressive growth of metastases. Metastases are present at the time of diagnosis in approximately one fifth of the patients with CRC [2,3] and another relatively large proportion (14-34%) develops metachronous metastases during the course of disease.[4-6]

Over the past decades, treatment modalities for metastatic CRC (mCRC) have made a substantial leap. Although nowadays an increasing proportion of patients with mCRC receive surgical treatment with curative intent, the majority of patients are still ineligible for curative treatment modalities and remain dependent on palliative treatment. Also, treatment has evolved for these patients. Various systemic regimens, combining cytotoxic agents and targeted agents, have become available. Guidelines on mCRC are based on trials in which the elderly are generally underrepresented.[7] Because ageing is an individual process, treatment recommendations for fit, younger patients cannot automatically be extrapolated to older patients. Due to the paucity of evidence for the feasibility and optimal use of these systemic regimens in elderly patients with mCRC, decisions on optimal management for the growing number of elderly patients with mCRC poses significant challenges to cancer specialists. High quality population-based data, reflecting daily based practice, are needed to further optimize the decision-making process. Such data are currently lacking in the subset of patients with metachronous metastases from CRC, in which data collection is very time consuming and costly. Therefore, the aim of the present population-based study was to provide insight into the impact of age on the palliative treatment of metachronous metastases from CRC in daily practice.

Methods

Data collection

Data from the population-based Netherlands Cancer Registry (NCR), more specifically from the Eindhoven area, were used. This registry collects data of all patients with newly diagnosed cancer in a large part of the Southern Netherlands and comprises approximately 2.4 million inhabitants (~15% of the Dutch population), six pathology departments, ten hospitals and two radiotherapy institutions. Information on patient and tumor characteristics are collected from medical records by specially trained registry staff after notification by pathologists and medical registration offices. In this registry, the tumor-node-metastasis (TNM) classification is used for stage notification of the primary tumor.[8] Anatomical site of the tumor is registered according to the International Classification of Diseases for Oncology (ICD-O).[9] Comorbidity at cancer diagnosis was obtained from the medical records and was registered according to a slightly modified version of the Charlson

Comorbidity index.[10] Data on socioeconomic status were based on individual fiscal data on the economic value of home and household income, which was provided at an aggregated level for each postal code.[11] Due to thorough training of the registration personnel and computerized consistency checks at regional and national levels, the quality of the data is high. Completeness of the data is estimated to be at least 95%.[12]

For the present study, additional data were retrospectively collected between 2010-2011 on metachronous metastases for patients diagnosed between 2003 and 2008 with non-metastatic CRC (stage I-III). Hospitals were asked to participate in the study by giving permission to use their data from the NCR and by giving permission for the retrospective registration of additional data. All hospitals voluntarily participated. Metachronous metastases were defined as distant metastases of primary CRC in other organs, diagnosed at least 3 months after CRC diagnosis. Median time from primary diagnosis to data collection was 5.3 years (range 1.5-8.8 years). The additional data collection encompassed detailed information on fist-line systemic therapy for metachronous metastases, both chemotherapy and targeted therapy; which regimen and agents, dosages, and number of cycles of each agent received. In the Netherlands, all hospitals have multidisciplinary tumor boards. Nowadays, more than 90% of the patients are discussed in these boards.[13] Even though geriatricians are present in every hospital, it is unknown whether they were available for oncologic consultation.

All consecutive patients with metachronous metastases from primary resected stage I-III CRC (C18.0-C18.9, C190, C209) were selected. Patients undergoing surgery for metastases were excluded, resulting in a study population treated with palliative intent, with or without systemic therapy. Patients were divided into categories according to their age at time of metachronous metastases diagnosis and the usage of first-line systemic therapy was assessed.

Statistical analyses

Descriptive statistics were used to provide an overview on patient and tumor characteristics of the total study population (n=746). Variation in the receipt of palliative systemic therapy between age categories and hospital of diagnosis was assessed using a $\chi 2$ test. Multivariable logistic regression analysis was used to assess the independent influence of age on the receipt of palliative systemic therapy. Adjustments were made for relevant patient and tumor characteristics: gender, comorbidity and socioeconomic status at time of CRC diagnosis, primary tumor localization, adjuvant chemotherapy, time to metastases, period of metastases diagnosis, the number of affected organs, and hospital of diagnosis. Differences in the received chemotherapeutic backbones between age categories were assessed and tested using a $\chi 2$ test. Initial dosages (mg/m2/d), cumulative dosages (mg/m2), and the number of received cycles in the first-line of systemic treatment were calculated for the most frequently prescribed cytostatic agents and regimens; capecitabine-oxaliplatin (CAPOX) and capecitabine-monotherapy (CapMono). Univariate linear regression analysis was ap-

plied to investigate the association between age at time of metastases diagnosis and the received initial dosage of cytostatic agents in the most frequently prescribed regimens (CAPOX, CapMono). Differences in cumulative dosages (mg/m2) and total number of received cycles between age categories were tested by means of a Wilcoxon Rank-Sum test. P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

Ethical considerations

In the Netherlands, the NCR and Dutch hospitals have a formal agreement that all patients with cancer are informed about registration in the Cancer Registry and the possibility to decline registration. According to the Dutch law, all patients with cancer are included in the NCR unless the patient has objected to be registered. Therefore, consent of the patient for this specific study was not applicable.

The NCR retrospectively collects data from medical records and is obligated to work according to laws in which the privacy of patients and doctors is fixed in regulations; the law about protection of privacy and the law "Geneeskundige BehandelOvereenkomst". An independent Committee of Privacy reassures that the NCR works compliant to these regulations. In the Netherlands, retrospective studies with data collected from medical charts do not fall under the scope of the Medical Research Involving Human Subjects Act ('Wet Medisch-wetenschappelijk Onderzoek") as patient integrity is not violated in these studies. Therefore, this study was exempted from further medical ethics review.

Results

A total of 1007 patients with metachronous metastases from primary resected stage I-III CRC were identified. Patients undergoing surgery for metastases were excluded (n=261), resulting in a study population of 746 patients treated with palliative intent, with or without systemic therapy (Figure 1). Mean age at time of metachronous metastases diagnosis was 71.0 years (SD 10.7 years) and 42% was 75 years or older (n=315). An overview on patient and tumor characteristics is shown in Table 1.

Figure 1 *Overview of patients included in the study.*

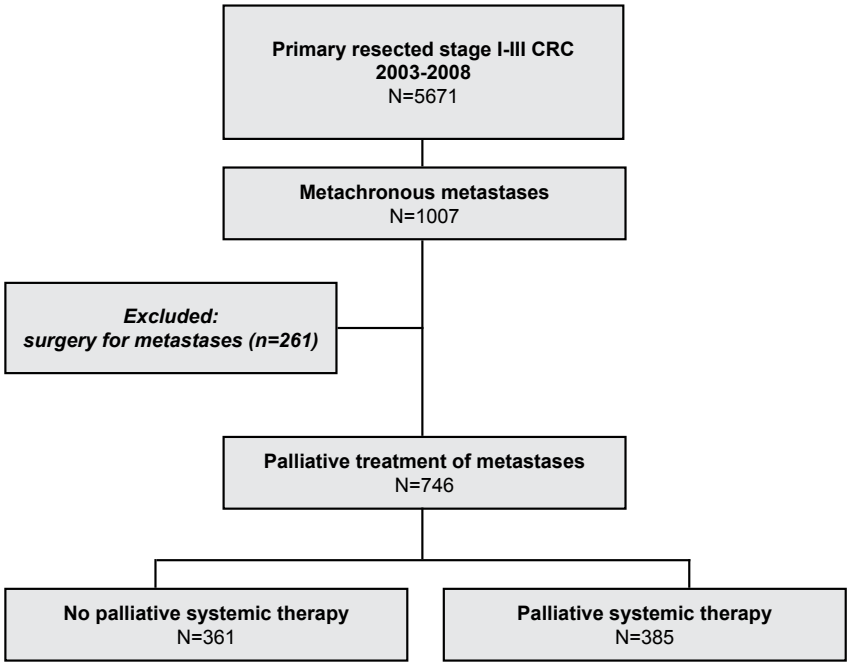


Table 1 *Patient and tumor characteristics of the total study population of patients with metachronous metastases from primary resected stage I-III CRC treated with palliative intent, with or without systemic therapy (n=746).*

	Total		**Palliative systemic therapy**				
	(n=746)		**Yes (n=385)**		**No (n=361)**		
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**p-value**
Gender							
Male	329	(44)	154	(40)	175	(48)	<0.05
Female	417	(56)	231	(60)	186	(52)	
Age (years)*							
<60	113	(15)	83	(22)	30	(8)	<0.0001
60-70	171	(23)	110	(29)	61	(17)	
70-75	147	(20)	92	(24)	55	(15)	
≥ 75	351	(42)	100	(26)	215	(60)	
Comorbidity							
No	219	(29)	141	(37)	78	(22)	<0.0001
1 comorbid condition	216	(29)	112	(29)	104	(29)	
≥ 2 comorbid conditions	260	(25)	104	(27)	156	(43)	
Unknown	51	(7)	28	(7)	23	(6)	
Socioeconomic status							
Low	203	(27)	86	(22)	117	(32)	<0.001
Intermediate	305	(41)	174	(45)	131	(36)	
High	202	(27)	110	(29)	92	(25)	
Institutionalized	25	(3)	7	(2)	18	(5)	
Unknown	11	(1)	8	(2)	3	(1)	
Primary tumor localization							
Rectum	276	(37)	160	(42)	116	(32)	<0.01
Colon	470	(63)	225	(58)	245	(68)	
Adjuvant chemotherapy							
No	499	(67)	226	(59)	273	(76)	<0.0001
Yes	247	(33)	159	(41)	88	(24)	
Time to metastases (years)							
<1 year	247	(33)	119	(31)	128	(35)	0.42
1-2 years	255	(34)	136	(35)	119	(33)	
≥2 years	244	(33)	130	(34)	114	(32)	
Period of diagnosis metastases							
2003-2005	162	(22)	77	(20)	85	(24)	0.42
2006-2008	380	(51)	197	(51)	183	(51)	
2009-2011	204	(27)	111	(29)	93	(26)	
Number of organs affected							
1 organ	388	(52)	168	(44)	220	(61)	<0.0001
2 organs	244	(33)	135	(35)	109	(30)	
≥3 organs	114	(15)	82	(21)	32	(9)	

** at time of metastases diagnosis.*

The use of palliative systemic therapy

Of the total number of 746 patients treated with palliative intent, 385 patients received palliative systemic therapy (51.6%). Proportions varied significantly between hospitals, in particular in patients aged ≥75 years (from 17% to 63%, p<0.05, Figure 2). The probability to receive palliative systemic therapy decreased with age (73% <60 years vs. 31% ≥75 years, p<0.0001). As illustrated in figure 3A, the main decline was observed in patients aged ≥75 years. This was confirmed in a multivariate analysis with adjustment for relevant patient and tumor characteristics (Table 2). The odds for treatment with palliative systemic therapy was significantly lower in patients aged ≥75 years compared to patients <60 years (OR 0.2, 95%CI 0.12-0.38, p<0.0001), but no significance was achieved in patients aged between 70-75 years compared to patients <60 years (OR 0.6, 95%CI 0.36-1.16, p=0.14). Besides, presence of comorbidity at initial diagnosis, the number of affected organs and hospital of diagnosis were shown to influence the likelihood of treatment with palliative systemic therapy.

Figure 2 *Inter-hospital variation in the prescription of palliative systemic therapy according to age at time of metastases diagnosis, A. patients aged <75 years, B. patients aged ≥75 years.*

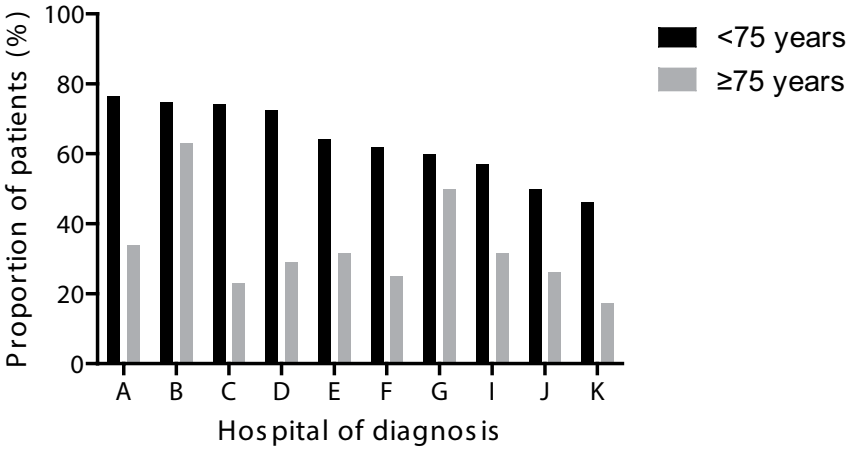


Table 2 *Predictors of treatment with palliative systemic therapy, adjusted for all factors listed (n=746).*

N=746	N	(%)	OR	95%CI	P-value
Gender					
Male	154	(47)	Ref	0.90-1.76	0.17
Female	231	(55)	1.2		
Age (years)*					
<60	83	(73)	Ref	0.40-1.24	0.22
60-70	110	(64)	0.7	0.36-1.16	0.14
70-75	92	(63)	0.6	0.12-0.38	<0.0001
≥ 75	100	(32)	0.2		
Comorbidity					
No	141	(64)	Ref		
1 comorbid condition	112	(52)	0.7	0.48-1.15	0.18
≥ 2 comorbid conditions	104	(40)	0.5	0.33-0.79	<0.01
Unknown	28	(55)	0.6	0.31-1.23	0.17
Socioeconomic status					
Low	86	(42)	0.8	0.53-1.32	0.45
Intermediate	174	(57)	1.1	0.77-1.73	0.46
High	110	(54)	Ref		
Institutionalized	7	(28)	0.5	0.18-1.48	0.22
Unknown	8	(73)	2.8	0.60-13.09	0.18
Primary tumor localization					
Rectum	160	(58)	Ref	0.56-1.14	0.45
Colon	225	(48)	0.8		
Adjuvant chemotherapy	226	(45)	Ref	0.83-1.82	0.29
No	159	(64)	1.2		
Yes					
Time to metastases (years)					
<1 year	119	(48)	Ref	0.74-1.69	0.56
1-2 years	136	(53)	1.1	0.86-2.11	0.18
≥2 years	130	(53)	1.3		
Period of diagnosis metastases					
2003-2005	77	(48)	Ref		
2006-2008	197	(52)	1.1	0.75-1.69	0.39
2009-2011	111	(54)	1.3	0.86-2.11	0.25
Number of organs affected					
1 organ	168	(54)	Ref	1.03-2.11	<0.05
2 organs	135	(55)	1.4	1.52-4.21	<0.001
≥3 organs	82	(72)	2.3		
Hospital of diagnosis					
A	71	(60)	Ref		
B	30	(63)	1.1	0.51-2.42	0.78
C	28	(35)	0.3	0.16-0.63	<0.01
D	75	(56)	0.7	0.43-1.34	0.35
E	41	(53)	0.8	0.42-1.56	0.53
F	33	(50)	0.4	0.24-0.96	<0.05
G	42	(64)	1.1	0.58-2.31	0.66
H	21	(48)	0.6	0.28-1.36	0.23
I	21	(45)	0.5	0.28-1.10	0.08
J	23	(33)	0.3	0.17-0.70	<0.01

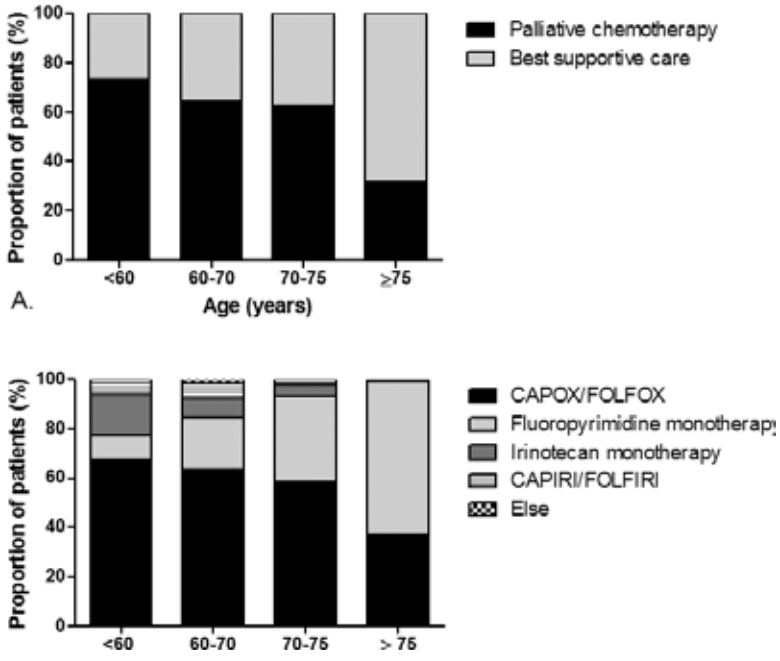
** at time of metastases diagnosis. N; number of patients receiving palliative systemic therapy. %; percentage of patients receiving palliative systemic therapy. OR; odds ratio, CI; confidence interval.*

First-line systemic therapy

Of the total number of 385 patients receiving palliative systemic therapy, 217 patients (56%) received oxaliplatin-combined chemotherapy, with either capecitabine (CAPOX, n=197) or 5-fluorouracil (FOLFOX, n=20). Fluoropyrimidines (capecitabine, 5-fluorouracil) were prescribed as monotherapy in approximately one third of the patients (n=125, mostly capecitabine n=115). Irinotecan was prescribed in 41 patients (10%), as monotherapy (n=27) or in combination with a fluoropyrimidine (CAPIRI or FOLFIRI, n=14). In two patients, only a targeted agent was prescribed. There were significant differences in chemotherapy regimens between age categories, as shown in Figure 3B. In patients aged 75 years or older there was a strong increase in the use of fluoropyrimidine monotherapy (62% ≥75 years versus 9% <60 years) and a decrease in the use of oxaliplatin-containing chemotherapy (37% ≥75 years versus 67% <60 years).

Targeted agents (bevacizumab in 98%) were added to first-line systemic therapy in 45% of the patients (n=174) and were prescribed mainly in addition to combination chemotherapy (n=139, 80%). Only 29% of the elderly patients (≥75 years) received systemic treatment including a targeted agent, compared to 55% in patients aged <60 years (p<0.0001).

Figure 3 *The use of palliative systemic therapy (A, n=746) and the prescribed chemotherapeutic regimen (B, n=385), according to age at time of metastases diagnosis.*



Initial dosages of chemotherapy

Age did not influence the prescribed initial dosage in patients receiving CAPOX (p=0.64). The median initial dosage of oxaliplatin was 129mg/m^2 (IQR 124-131) and the median initial dosage of capecitabine was 1,977mg/m^2/d (IQR 1,902-2,034).

For patients receiving CapMono, the median initial dosage of capecitabine was 2,127mg/m^2/d (IQR 1,901-2,454). The received initial capecitabine dosage decreased with age (p<0.0001). Median initial capecitabine dosage was 1,992mg/m^2/d (IQR 1,753-2,158) in patients ≥75 years compared to 2,414mg/m^2/d (IQR 2,047-2,488) in patients <75 years (p<0.0001).

Cumulative dosages of chemotherapy

Table 3 provides an overview of the cumulative dosage and total number of received cycles according to chemotherapy regimen and age at time of metastases diagnosis. Within the CAPOX-regimen, median cumulative dosages of both oxaliplatin and capecitabine were significantly lower in patients aged ≥75 years compared to patients aged <75 years (p<0.05). For patients receiving CapMono no differences were observed in the received cumulative dosage (p=0.30).

Total number of received chemotherapy cycles

Within the CAPOX regimen, treatment was discontinued significantly earlier in patients ≥75 years compared to patients aged <75 years (p<0.05, Table 3). Approximately half of the elderly patients (≥75 years) received ≤3 oxaliplatin cycles (51%) and 43% received ≤3 capecitabine cycles, compared to respectively 28% and 21% in patients aged <75 years. In patients treated with CapMono, no differences were observed in the received total number of capecitabine cycles between age categories (p=0.16).

Table 3 *Cumulative dosages and total number of received cycles of cytostatic agents in the first line of palliative chemotherapy, according to age at time of metastases diagnosis.*

	CAPOX						**CapMono**		
	Oxaliplatin			**Capecitabine**			**Capecitabine**		
	<75 yrs	**≥75 yrs**		**<75 yrs**	**≥75 yrs**		**<75 yrs**	**≥75 yrs**	
N total	**162**	**35**		**162**	**35**		**59**	**56**	
Cumulative dosage	*mg/m^2*	*mg/m^2*	*P-value*	*mg/m^2*	*mg/m^2*	*P-value*	*mg/m^2*	*mg/m^2*	*P-value*
Median	718	398	0.02	167,741	105,217	0.03	138,403	111,924	0.30
Interquartile range	378-796	130-766		78,161-305,085	26,016-256,442		73,454-199,943	60,277-284,591	
Unknown	29	0		33	1		9	9	
Number of cycles	*N (%)*	*N (%)*	*P-value*	*N (%)*	*N (%)*	*P-value*	*N (%)*	*N (%)*	*P-value*
Median	6.0	3.0	0.05	6.0	6.0	0.10	5.0	5.0	0.36
Interquartile range	3-6	1-6		5-12	1-10		3-8	2-11	
≤3 cycles	44 (28)	18 (51)	0.02	31 (21)	15 (43)	0.02	20 (38)	23 (43)	0.16
3-6 cycles	91 (57)	14 (40)		44 (30)	6 (17)		17 (32)	9 (17)	
>6 cycles	24 (15)	3 (9)		72 (49)	14 (40)		16 (30)	22 (41)	
Unknown	3	0		15	0		6	2	

Discussion

The present population-based study provided insight into the impact of age on palliative systemic therapy in real-life non-trial patients with metachronous metastases from CRC. An age of 75 years or older significantly influenced the receipt of palliative treatment. Patients aged ≥75 years were less likely to receive systemic therapy and more frequently received single-agent chemotherapy than their younger counterparts. If combination chemotherapy (mostly CAPOX) was administered, initial dosages were similar but cycles were discontinued earlier, resulting in lower cumulative dosages.

Although metachronous metastases occur in a substantial proportion of patients with CRC, there are only few population-based studies focusing specifically on this group of patients.[4,6,14] The majority of these studies focused at one particular site of metastases and neither of these studies addressed the use of palliative systemic therapy nor the impact of ageing on systemic treatment.

In both younger and older patients, palliative systemic therapy aims to reduce tumor load and hereby improve or eliminate distressing symptoms.[15,16] In addition, systemic therapy improves overall survival (OS) and time to progression (progression free survival; PFS).[16] The beneficial effect of adjuvant chemotherapy in colon cancer has shown to be independent of age[17] and it is expected that this applies also for palliative chemotherapy in the presence of metastases.[18] Nevertheless, elderly patients are still likely to be less intensively treated in clinical practice[19-21], probably due to concerns on safety, tolerability, and efficacy. In a previous population-based study by Ho and colleagues less than 50% of the elderly patients (>70 years) received palliative systemic chemotherapy.[22] Similar proportions were observed in a French nationwide study. In this study, 48% of the elderly patients with stage IV CRC (≥75 years) received palliative chemotherapy.[20] In our study with a mean age of 71.0 years (SD 10.7), a decrease in the use of palliative systemic therapy was observed with increasing age. The decline was observed mainly in patients aged 75 years or more. This was confirmed in a multivariate analysis, in which the probability to receive systemic therapy was significantly lower for patients aged ≥75 years compared to patients aged <60 years, whereas no significance was observed in patients aged 70-75 years. Only 31% of the patients aged ≥75 years received palliative systemic therapy, which compares dismal to the proportions reported previously by population-based studies[20-22], probably due to differences in patients selection. In the present study, only patients with unresectable metachronous metastases were included, whereas most population-based studies included all patients with stage IV CRC. Our results indicate that, in daily practice, age over 75 years may be appropriate to define the elderly patients with mCRC, which has also been suggested by Kozloff and colleagues.[23] Continued investigations are needed for this group of patients.

Significant inter-hospital variation was observed in the prescription of palliative systemic therapy. In patients aged 75 years or more, there was an even more prominent inter-hospital variation with proportions varying between 17% and 63%, reflecting the paucity of evidence for systemic treatment in the elderly. Clinical trials conducted in adult populations typically included younger patients (<65 years), limiting the available evidence for elderly patients in treatment guidelines.[24] In order to prevent under-usage of chemotherapy in elderly patients, elderly cancer gained more interest over the past decade. It has become clear that enrollment barriers for older patients need to be overcome and that older age should be redefined.[25] Although numerous solutions have been proposed, those that have been implemented have limited success.[26] Still, few elderly patients are enrolled in clinical trials[7] and even if elderly patients are enrolled, they often do not reflect the elderly as seen in everyday clinical practice. Future efforts are needed, especially in the current era with evolving systemic treatment options.

Fluoropyrimidines have long been the only available systemic treatment for advanced CRC. Over time, chemotherapeutic regimens combining fluoropyrimidines with oxaliplatin or irinotecan have emerged as preferable regimens in fit patients with good performance status.[27-29]
In the current population-based study, oxaliplatin-containing regimens (mostly CAPOX) were the most frequently prescribed first-line cytostatic backbone (56%). A significant decline in the use of oxaliplatin-containing chemotherapy was observed in older patients, especially in patients aged ≥75 years (37%). If oxaliplatin-containing regimens were prescribed, similar initial dosages were prescribed in younger and older patients. In line with treatment guidelines[30], oxaliplatin and capecitabine dosages were respectively 130mg/m2 and 2000mg/m^2/d. Cumulative dosages within the CAPOX regimen were significantly lower in patients ≥75 years compared to patients <75 years. Oxaliplatin was discontinued ≤3 cycles in 51% of the patients aged ≥75 years and also capecitabine was discontinued earlier in patients aged ≥75 years compared to patients <75 years. These results align with the highly debated clinical benefit of first-line doublet regimens in elderly patients. Results from trials establishing the evidence for first-line doublet- regimens were not validated in elderly patients, resulting in an initial lack of evidence.[27,28] Ever since, several studies have attempted to further explore the role of first-line doublet regimens in the elderly but still, data remain controversial.[18,31-36]. In the Focus2 trial, the addition of oxaliplatin to capecitabine/5-FU improved response rate but failed to significantly improve PFS in frail or unfit patients.[34] In a recent meta-analysis, doublet-chemotherapy was associated with a modest benefit in terms of PFS, but no benefit in OS.[36] Irinotecan containing regimens (CAPIRI/FOLFIRI) have been associated with increased toxicity in elderly patients[35,36] and according to the French randomized phase III trial (FFCD 2001-02) there are no PFS or OS data justifying this increase in toxicity.[37] Also on a population-based level, the addition of intravenous chemotherapy has been associated with increasing adverse effects in elderly patients with CRC patients.[38]

Within the CapMono regimen, initial prescribed dosages were lower in elderly patients. Median initial capecitabine dosages were 2,414 mg/m2/d in patients <75 years compared to 1,992 mg/m2/d in patients ≥75 years, probably reflecting toxicity concerns. Initial evidence on the efficacy and tolerability of capecitabine compared to conventional 5-FU was established with capecitabine dosages of 1250mg/m^2/bi-daily.[39] In the FOCUS2 study with elderly and frail patients, however, 80% of the standard licensed dosages were prescribed (CapMono 1000mg/m^2/bi-daily, CAPOX 800mg/m^2/bi-daily) and even then, higher toxicity and lower quality of life was observed with capecitabine.[34] Capecitabine was specifically associated with increased rates of nausea, vomiting, diarrhea, anorexia and hand-foot syndrome.[34] Despite the differences in prescribed initial dosages between elderly and younger patients, the current study did not observe differences in either the cumulative capecitabine dosage or the total number of received cycles. Thus, the higher starting dosage (1250mg/m^2/bi-daily) as prescribed in younger patients (<75 years) did not result in higher cumulative dosages. Besides, our data demonstrate that even selected elderly patients (≥75 years) receiving CAPOX often discontinued treatment early, whereas this was not the case if CapMono was administered. Continued investigations are needed to predict toxicity in elderly patients with cancer. Instruments such as geriatric assessments may be helpful to measure independent clinical predictors of morbidity and mortality in older adults[40], such as cognitive function and autonomy.[41] Targeted agents (mostly bevacizumab) were prescribed in 29% of the elderly patients (≥75 years) compared to 51% in patients<75 years. Targeted agents were added primarily to combined-cytostatic regimens, which were administered mainly to younger patients. In 2005 bevacizumab was introduced and recommended for the treatment of stage IV CRC in the Netherlands. At that time, evidence on the use of bevacizumab was derived mainly from studies that recruited primarily younger patients.[42,43] Nowadays, several trials[44] and observational studies[23,45] have shown similar improved PFS and OS rates also in elderly patients (>65 years). Therefore, the addition of bevacizumab has become standard.[45]

The non-randomized nature of this study obviously presents a potential risk of bias. Relevant patient characteristics such as comorbidity and socio-economic status were registered only at initial CRC diagnosis. Moreover, performance score and the reasons (not) to prescribe systemic therapy were often not noted in patient charts and as a result, these data were not useful. Despite these limitations, this large population-based study has the advantage to avoid selection bias by including a long-term series of consecutive patients. Moreover, all data were collected by independent registration clerks which prevents bias that may occur when data collection relies on clinicians.

Conclusion

In daily practice, age beginning at 75 years was shown to influence palliative systemic treatment of metachronous mCRC. In the selected group of elderly patients (≥75 years) receiving combination-chemotherapy (CAPOX), first-line systemic treatment was discontinued earlier compared to younger patients, resulting in lower cumulative dosages of both cytostatic agents. Within the CapMono regimen, however, no differences were observed in either the received number of cycles or the received cumulative dosage, despite lower starting dosages in elderly patients.

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Chapter 6

"Age-related systemic treatment and survival of patients with metachronous metastases from colorectal cancer"

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Abstract

Background: Although the spectrum of systemic treatment for metastatic colorectal cancer (mCRC) has widened, there is a paucity of evidence for the feasibility and optimal use of these systemic agents in elderly patients. The present study provides real-world data on the age-related systemic treatment and survival of CRC patients with non-resectable metachronous metastases.

Methods: All consecutive patients with non-resectable metastases from primary resected CRC were extracted from the Eindhoven area of the Netherlands Cancer Registry (NCR). Patients receiving palliative systemic therapy were enrolled (n=385). Systemic treatment and survival were analyzed according to age at diagnosis of metastases.

Results: Patients aged ≥75 years more often received first-line single-agent chemotherapy than their younger counterparts (63% vs. 32%, p<0.0001). First-line single-agent chemotherapy was often prescribed without additional targeted therapy (78%). Advanced age (≥75 years) was associated with a lower probability of receiving all active cytotoxic agents compared to patients aged <60 years at time of diagnosis of metastases (OR 0.2, 95% CI 0.10-0.77). In a multivariable Cox regression analysis with adjustment for age and other relevant prognostic factors, the total number of received systemic agents was the only predictor of death (HR 0.7, 95% CI 0.61-0.81).

Conclusion: The beneficial effect of treatment with all active systemic agents on survival (simultaneously or sequentially prescribed) should be taken into account when considering systemic therapy in patients with mCRC. In light of our results, future studies are warranted to clarify the role of potential targeted therapy in elderly mCRC patients, who are often not candidates for combination chemotherapy and treatment with all active cytotoxic agents.

Introduction

Colorectal cancer (CRC) is the second most lethal cancer in the Netherlands. Most cancer-related deaths result from the progressive growth of metastases, which are present at time of diagnosis in approximately 20% of the patients[1-3] or occur during the course of disease in another 14-34% of the patients.[4-8]

Since the late 1990's, the spectrum of systemic treatment in metastatic CRC (mCRC) has widened. Various systemic regimens combining fluoropyrimidines, oxaliplatin and irinotecan have become available, and more recently different monoclonal antibodies were introduced including bevacizumab, cetuximab and panitumumab.

The use of targeted therapy in addition to the available cytotoxic agents has been positively associated with survival.[9,10] The feasibility and optimal sequence of the administration of these systemic agents in elderly patients, however, is unclear. With the traditional underrepresentation of elderly patients in clinical trials[11], randomized data are scarce. High quality real-life studies are needed as the increasing proportion of elderly mCRC patients poses significant challenges to cancer specialists. The aim of the current study was to provide insight into the impact of age on the systemic treatment and survival of patients with unresectable metachronous metastases from CRC outside the setting of a randomized clinical trial.

Methods

Data collection

Data from the population-based Netherlands Cancer Registry (NCR), more specifically from the Eindhoven area, were used. This registry records data on all patients with newly diagnosed cancer in the southern part of the Netherlands, an area with approximately 2.4 million inhabitants (~15% of the Dutch population), six pathology departments, ten hospitals and two radiotherapy institutions. Information on patient and tumor characteristics are collected from medical records by specially trained registry staff after notification by pathologists and medical registration offices, resulting in high quality of the data. In the NCR, primary tumors are classified according to the TNM classification of Malignant Tumors by the international Union Against Cancer (UICC), 7th edition.[12] Anatomical site of the tumor is registered according to the International Classification of Diseases for Oncology (ICD-O). A slightly modified version of the Charlson comorbidity index was used to register comorbidities.

For the present study, additional data were retrospectively collected between 2010 and 2011 on metachronous metastases for patients diagnosed between 2003 and 2008 with non-metastatic CRC (stage I-III). Hospitals were asked to participate in the study by giving permission to use their data from the NCR and by giving permission for the retrospective registration of additional data. Metachronous metastases were defined as distant metastases of primary CRC in other organs, diagnosed at least 3 months after CRC diagnosis. Median time from primary diagnosis to data collection was 5.3 years (1.5-8.8 years). The additional data collection encompassed detailed information on systemic therapy, both chemotherapy and targeted therapy.

All consecutive patients with metachronous metastases from primary resected stage I-III CRC (C18.0-C18.9 , C190, C209) were selected (n=1007). Patients undergoing surgery for metastases (n=261) or only supportive care (n=361) were excluded for the present study, resulting in a study population of patients treated with palliative systemic therapy (n=385). Patients were divided into categories according to their age at time of metachronous metastases diagnosis (<60 years, 60-75 years, ≥75 years) and palliative systemic treatment was assessed according to the number of received systemic agents and systemic treatment lines.

Statistical analyses

Descriptive statistics were used to provide an overview on patient and tumor characteristics of the total study population (n=385). First-line systemic regimens were categorized according to the number of prescribed cytotoxic agents (single-agent chemotherapy, combination-chemotherapy) and the additional prescription of targeted therapy. Variation in the use of these systemic regimens between age categories was assessed using a χ^2 test. Duration of first-line treatment was calculated and presented as median duration in months. Differences in first-line duration between age categories were assessed and tested using a Wilcoxon Rank-Sum test. Subsequently, proportions of patients receiving second-line systemic therapy were calculated and a multivariable logistic regression analysis was applied to investigate the independent influence of age on the receipt of second-line therapy. Adjustments were made for relevant patient and tumor characteristics: gender, comorbidity and socioeconomic status at time of CRC diagnosis, primary tumor localization, adjuvant chemotherapy, time to metastases, period of diagnosis of metastases, follow-up time since metastases diagnosis, the number of affected organs and the prescribed first-line regimen. This model was also applied to investigate the influence of age on the odds of exposure to all three active cytotoxic agents.

Overall survival time was defined as the time from diagnosis of the first metachronous metastatic site to death or lost to follow-up. Patients still alive at the end of follow-up (February 1st, 2016) and those who emigrated were censored. Crude survival estimates were calculated for both the total study population and according to age with the Kaplan-Meier method; crude survival rates were presented up to 48 months. A log-rank test was carried out to evaluate differences between survival curves. Median survival (MS) was presented in months and corresponding 95% confidence intervals (CIs). Multivariable Cox regression analyses were used to identify independent prognostic factors. Adjustments were made for clinically relevant variables that were applied in the multivariable logistic regression analysis, also including the total number of received systemic agents. P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

Results

In total, 385 patients received palliative systemic therapy for the treatment of metachronous metastases from primary resected CRC. Mean age at time of metachronous metastases diagnosis was 67.5 years (SD 10, range 26-90 years). An overview of patient and tumor characteristics is shown in Table 1.

Table 1 *Patient and tumor characteristics of the total study population of patients with metachronous metastases from primary resected stage I-III CRC treated with palliative systemic therapy (n=385).*

N=385	N	(%)
Gender		
Male	154	(40)
Female	231	(60)
Age (years) at time of metastases diagnosis		
<60	83	(22)
60-75	202	(52)
≥ 75	100	(26)
Comorbidity at primary CRC diagnosis		
No	141	(37)
1 comorbid condition	112	(29)
≥ 2 comorbid conditions	104	(27)
Unknown	28	(7)
Socioeconomic status at primary CRC diagnosis		
Low	86	(22)
Intermediate	174	(45)
High	110	(29)
Institutionalized	7	(2)
Unknown	8	(2)
Primary tumor localization		
Rectum	160	(42)
Colon	225	(58)
Adjuvant chemotherapy		
No	226	(59)
Yes	159	(41)
Time to metastases (years)		
<1 year	247	(31)
1-2 years	255	(35)
≥2 years	244	(34)
Period of diagnosis of metastases		
2003-2005	77	(20)
2006-2008	197	(51)
2009-2011	111	(29)
Number of organs affected		
1 organ	168	(44)
2 organs	135	(35)
≥3 organs	82	(21)

CRC; colorectal cancer.

First-line systemic therapy

Table 2 provides an overview on the palliative systemic treatment of metachronous metastases from primary resected CRC. Of the total number of 385 patients, 60% received first-line combination chemotherapy (of which 94% oxaliplatin-based) and 40% received single-agent chemotherapy (of which 82% fluoropyrimidines). Targeted agents (mostly bevacizumab) were prescribed in 174 patients (45%), primarily in addition to combination chemotherapy. Significant differences in first-line systemic regimens were observed between age categories; elderly patients (≥75 years) more often received single-agent chemotherapy than their younger counterparts (63% ≥75 years vs 27% <60 years).

Median duration of first-line treatment was 3.6 months (IQR 1.3-8.4). Significant differences in first-line treatment time were observed between age categories, with respectively 4.1 months (IQR 2.06-11.72) in patients <60 years, 3.6 months (IQR 1.57-8.37) in patients aged 60-75 years and 3.4 months (IQR 0.68-7.59) in patients aged ≥75 years.

Table 2 *Palliative systemic treatment of metachronous metastases from primary resected CRC, according to age at diagnosis of metastatic disease (n=385).*

	Total N=385		**<60 yrs N=83**		**60-75 yrs N=202**		**≥75 yrs N=100**		
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p-value**
First-line									
Single-agent CT_x	154	(40)	22	(27)	69	(34)	63	(63)	<0.0001
+ targeted therapy	34	(22)	5	(23)	21	(30)	8	(13)	0.04
- targeted therapy	120	(78)	17	(77)	48	(70)	55	(87)	
Combination CT_x	231	(60)	61	(73)	133	(66)	37	(37)	
+ targeted therapy	140	(61)	41	(67)	78	(59)	21	(57)	0.45
- targeted therapy	91	(39)	20	(33)	55	(41)	16	(43)	
Total treatment									
Cytotoxic agents									
1	117	(30)	17	(21)	46	(23)	54	(54)	<0.0001
2	184	(48)	36	(43)	111	(55)	37	(37)	
3	84	(22)	30	(36)	45	(22)	9	(9)	
Targeted agents									
0	169	(44)	27	(32)	79	(39)	63	(63)	<0.001
1	190	(49)	48	(58)	107	(53)	35	(35)	
2	26	(7)	8	(10)	16	(8)	2	(2)	

CTx=chemotherapy; cytotoxic agents: fluoropyrimidines (fluorouracil/capecitabine), oxaliplatin, irinotecan; Targeted agents: anti-VEGF (bevacizumab), anti-EGFR (cetuximab/panitumumab).

Second and further lines of systemic treatment

Less than half of the patients (40%) received second-line therapy (n=154, Figure 2a). With increasing age, the proportion of patients receiving secondary treatment decreased, from 55% in patients <60 years to 26% in patients aged ≥75 years (p<0.0001, Figure 2b). This was confirmed in a multivariable analysis (Table 3) in which patients aged ≥75 years at time of metachronous metastases diagnosis were less likely to receive second-line treatment than patients aged <60 years (OR 0.3, 95% CI 0.16-0.80).

Figure 1 *First-line chemotherapeutic regimens according to age at time of diagnosis of metachronous metastases (n=385).*

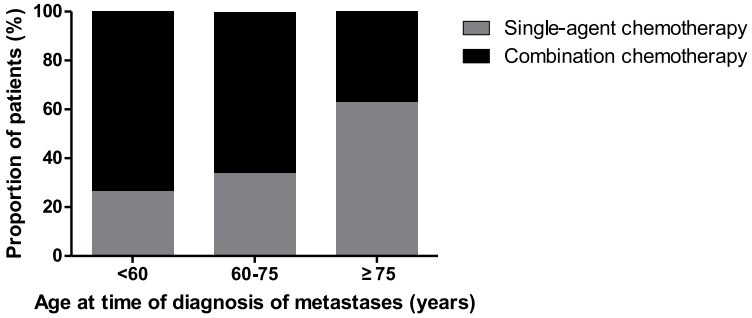
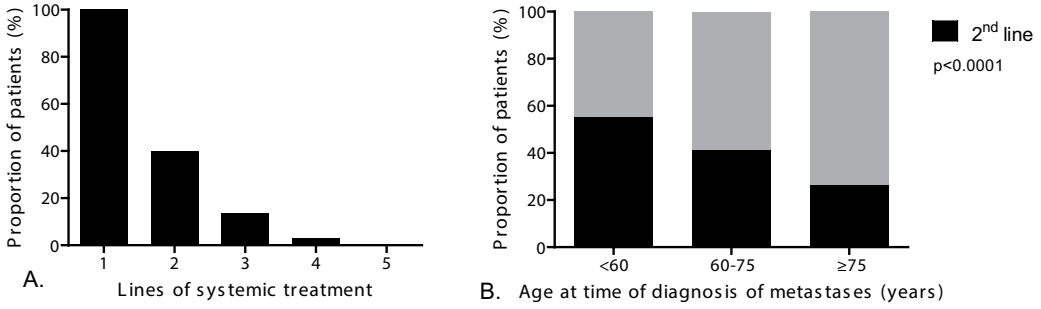


Figure 2 *Proportion of patients receiving second and further lines of systemic treatment (a), according to age at time of diagnosis of metachronous metastases (b) (n=385).*



Total number of received systemic agents during treatment course

-Cytotoxic agents

Fluoropyrimidines were prescribed at any time during treatment course in 93% of the patients (mostly capecitabine), whereas oxaliplatin and irinotecan were prescribed in respectively 61% and 37%. A minority of the patients (22%) were exposed to all three cytotoxic agents (Table 2). Advanced age (≥75 years) was associated with a lower probability to receive all three active cytotoxic agents compared to patients aged<60 years at time of metastases diagnosis (OR 0.2, 95% CI 0.10-0.77, Table 3). Patients receiving first-line combination chemotherapy were more likely to receive all three cytotoxic agents than patients treated with first-line single-agent chemotherapy (OR 7.1, 95% CI 3.16-16.11).

-Targeted agents

In total, 56% of the patients received additional targeted therapy during their course of disease (n=216). Over time, the use of targeted therapy increased from 30% in 2003-2005 to 64% in 2009-2011. This trend was observed regardless of age, although in elderly patients (≥75 years) proportions increased primarily since 2009 whereas the increase in younger patients was observed already since 2005. Overall, proportions were significantly lower in patients aged ≥75 years (37%,Table 2). Bevacizumab was the most frequently prescribed targeted agent (n=207), which was added primarily to first-line systemic therapy (81%). Epidermal growth factor (EGFR) inhibitors (cetuximab/panitumumab) were administered to 35 patients (9%), mainly in addition to second-line treatment(n=23).

Survival and predictors of death

Median overall survival (OS) of the total study population was 16.6 months (95% CI 14.42-19.19). Significant differences in OS time were observed between age categories, with respectively 14.2 months (95% CI 11.33-16.69) in patients ≥75 years and 20.3 months (95% CI 13.96-22.60) in patients <60 years (p<0.01). After adjustment for relevant patient and tumor characteristics and treatment variables (first-line systemic therapy, number of exposed systemic agents) advanced age (≥75 years) was no longer significantly associated with OS (HR 1.3, 95% CI 0.90-1.86, p=0.16). Although significant in univariate analysis (HR 0.7, 95% CI 0.57-0.86, p<0.01), first-line combination chemotherapy also did not achieve significance in multivariate analysis (HR 1.2, 95% CI 0.86-1.56, p=0.33), but the number of exposed systemic agents remained significantly associated with OS (HR 0.7, 95% CI 0.61-0.81, P<0.0001).

Table 3 *Predictors of treatment with second-line treatment and exposure to all three available cytotoxic agents, adjusted for all factors listed (n=385).*

	Second-line treatment				**All three active cytotoxic drugs**			
N=385	**(%)**	**OR**	**95% CI**	**P-value**	**(%)**	**OR**	**95% CI**	**P-value**
Gender								
Male	(40)	Ref	0.54-1.44	0.62	(23)	Ref	0.10-0.70	0.84
Female	(40)	0.9			(21)	0.9		
Age (years) at time of metastases diagnosis								
<60	(55)	Ref	0.32-1.09	0.09	(36)	Ref	0.27-1.05	0.42
60-75	(41)	0.6	**0.16-0.81**	**<0.05**	(22)	0.5	**0.10-0.77**	**<0.01**
≥ 75	(26)	**0.3**			(9)	**0.2**		
Comorbidity at primary CRC diagnosis								
No	(46)	Ref			(26)	Ref		
1 comorbid condition	(36)	0.7	0.40-1.31	0.28	(21)	0.9	0.46-1.81	0.80
≥ 2 comorbid conditions	(34)	0.9	0.49-1.78	0.83	(18)	1.2	0.56-2.58	0.63
Unknown	(50)	1.0	0.38-2.61	0.99	(21)	0.8	0.24-2.40	0.64
Socioeconomic status at primary CRC diagnosis								
Low	(38)	1.2	0.65-2.49	0.48	(20)	1.3	0.59-3.07	0.46
Intermediate	(40)	1.0	0.63-1.89	0.75	(24)	1.4	0.73-2.78	0.29
High	(42)	Ref			(19)	Ref		
Institutionalized	(57)	2.4	0.39-14.98	0.33	(29)	2.8	0.35-22.97	0.32
Primary tumor localization								
Rectum	46)	Ref	0.46-1.24	0.27	(27)	Ref	0.47-1.56	0.62
Colon	(36)	0.8			(18)	0.8		
Adjuvant chemotherapy								
No	(39)	Ref	0.51-1.41	0.90	(24)	Ref	0.47-1.56	
Yes	(42)	1.0			(19)	0.8		0.57
Time to metastases (years)								
<1 year	(40)	Ref	0.85-2.80	0.14	(25)	Ref	0.81-3.12	0.18
1-2 years	(49)	1.5	0.49-1.83	0.87	(29)	1.6	0.32-1.68	0.47
≥2 years	(31)	1.0			(12)	0.7		
Period of diagnosis of metastases								
2003-2005	(47)	Ref			(31)	Ref		
2006-2008	(46)	1.0	0.57-1.97	0.84	(24)	0.6	0.34-1.37	0.25
2009-2011	(25)	0.6	0.28-1.28	0.18	(12)	0.4	0.16-1.09	0.07
Number of organs affected								
1 organ	(38)	Ref	0.55-1.64	0.85	(23)	Ref	0.38-1.36	0.31
2 organs	(39)	0.9	0.67-2.36	0.47	(22)	0.7	0.32-1.45	0.32
≥3 organs	(46)	1.2			(21)	0.6		
First-line systemic therapy								
Single-agent chemotherapy	(33)	Ref	0.64-1.82	0.77	(5)	Ref	3.16-16.11	<0.0001
Combination chemotherapy	(44)	1.0			(33)	7.1		

Ref: reference; OR: Odds Ratio; CI: confidence interval; CRC: colorectal cancer
also adjusted for follow-up time since metastases diagnosis

Discussion

In the present population-based study we provided insight into the age-related systemic treatment and survival of patients with unresectable metachronous metastases from primary resected CRC. We demonstrated that in everyday clinical practice only 26% of the elderly patients started second-line treatment. Since most elderly patients received first-line single-agent chemotherapy without targeted therapy, elderly patients were less likely to receive all active systemic agents during their course of treatment, which was associated negatively with survival.

Overall, more than half (60%) of the mCRC patients received first-line combination chemotherapy with or without a targeted agent. As first-line treatment, combination chemotherapy has been associated with prolonged progression-free survival (PFS) and OS compared with single-agent chemotherapy.[13-16] Nevertheless, only a minority of the elderly patients (≥75 years) received combination chemotherapy (37%), probably due to concerns on tolerability and toxicity. For a subgroup of patients with indolent disease, irrespective of age, there is no indication for combination chemotherapy. In the FOCUS2 trial investigating chemotherapy options in frail and elderly patients with advanced CRC, patients were randomly assigned to either intravenous fluorouracil with levofolinate, capecitabine, oxaliplatin and fluorouracil with levofolinate, or oxaliplatin and capecitabine. Treatment was started at 80% of the standard dose as full-dose regimens are often considered unsuitable in elderly and frail patients. The addition of oxaliplatin did not improve PFS.[17] Besides, the French FFCD2001-02 trial failed to demonstrate improved OS rates with irinotecan combination-chemotherapy versus single-agent fluorouracil with levofolinate although even greater toxicity rates were reported with irinotecan combination-chemotherapy.[18]

Regardless of the sequence of administration, exposure to all active cytotoxic agents during treatment has been associated with prolonged survival.[19] In view of this observation, it has been suggested that the sequential use of active single agents might be preferable to initial combination chemotherapy as this could conceivably reduce overall toxicity. Three European trials directly addressed this issue. In the FOCUS and FFCD 2000-05 trial, initial monotherapy followed by combination chemotherapy was non-inferior to initial combination therapy.[20,21] These results were endorsed by the CAIRO trial in which the sequential treatment strategy (first-line capecitabine, second-line irinotecan, third-line CAPOX) provided a similar benefit to initial combination treatment (first-line CAPIRI, second-line CAPOX).[22]

The sequential treatment strategy, however, has several limitations. At first, it should not be initiated patients with potentially resectable metastases or severe cancer-related symptoms in whom the primary goal is downsizing of the tumor, as response rates are superior with combination chemotherapy.[13,15] Besides, sequential treatment implies that patients are still fit for second and further lines of treatment after progressing, which might not be the case in patients with an aggressive disease or a poor performance status. According to the study by Grothey et al, with data from

seven phase III trials, 50% to 80% of the patients received second-line treatment after failure of first-line treatment.[19] In the present population-based study, higher dropouts rates were observed in everyday clinical practice (60% after first-line) due to the impact of a relatively large number of elderly patients. Only 26% of the elderly patients (≥75 years) received second-line therapy. This percentage is in line with the study by Sorbye et al, in which a poor performance status at start of first-line chemotherapy was identified as a poor predictor for administration of second-line treatment.[23]

In our study, only 22% of the mCRC patients were exposed to all three cytotoxic drugs during their course of treatment. The likelihood of receiving all active cytotoxic agents was significantly lower with the use of first-line single-agent chemotherapy (5%) than with initial combination therapy (33%). These results are in line with data from the FOCUS and CAIRO trial, although proportions of patients receiving all cytotoxic agents in these two trials were higher. With the sequential treatment, 19% of the patients in the FOCUS trial and 36% of the patients in the CAIRO trial received all cytotoxic agents, whereas proportions were respectively 33% and 55% with initial combination treatment.[21,22] The dismal proportions as observed in our study probably arose from the relatively large proportion of elderly patients in daily based practice. In the present study, advanced age (≥75 years) was independently associated with a lower probability to access all three active cytotoxic drugs compared to patients aged <60 years.

During the current study period, elderly patients (≥75 years) were not only less likely to receive all active cytotoxic agents during their course of treatment, but also less frequently received targeted therapy. Initially, evidence on the use of bevacizumab – the first available and registered targeted agent in The Netherlands– was derived from a trial in which a currently outdated chemotherapy regimen (IFL) was used and elderly patients were underrepresented.[9] Nowadays, several studies have suggested that bevacizumab is both safe and effective in combination with multiple chemotherapy backbone regimens[24], also in elderly patients[25-27] and that age itself should no longer be regarded an absolute contraindication. Probably as a result, bevacizumab was prescribed increasingly over time[28], also in elderly mCRC patients. Evidence on the use of other targeted agents such as anti-EGFR therapies (cetuximab, panitumumab) in elderly KRAS-wild type mCRC patients, however, remains scarce and less clear.[29] Recently, it has been suggested that single-agent panitumumab may be a well-tolerated and active therapeutic option for frail elderly patients with wild-type RAS tumors.[30] More studies are needed to clarify the role of anti-EGFR therapies in the population of elderly mCRC patients, especially as targeted agents may sometimes be the only therapeutic option for frail elderly patients who are unable to tolerate chemotherapy.
Several phase III trials[13-15,31,32] and retrospective cohort studies[28,33] have demonstrated survival rates exceeding 21.5 months in mCRC patients treated with modern systemic regimens, which seems

in line with the median OS of 20.2 months in patients <60 years as observed in our study. Inferior results, however, were observed in elderly mCRC patients (≥75 years), with a median OS of 14 months. These results, along with results from a prior Nordic population-based registry[34], raise concerns over our ability to improve treatment options for elderly mCRC patients. In a multivariate analysis with adjustments for available prognostic factors, we found that only the number of exposed systemic agents was associated with OS, which suggests the need of a strategy to make all active agents available to patients with mCRC. Of course, these results need to be interpreted with caution due to the invariable presence of selection bias in this non-randomized study (patients who receive all drugs must live longer, since they need to be in shape for this), which cannot be fully out ruled in a multivariate analysis. Nevertheless, our results indicate that in elderly patients, initial treatment with the highest potential of improving both survival and maintaining quality of life is needed as most of these patients are not candidates for second-line treatment. Further studies are warranted to further define the role of targeted therapy in elderly mCRC patients who often are not candidates for intensive chemotherapy.

To the best of our knowledge, this is the first population-based study describing the whole spectrum of systemic treatment and survival of a long-term series of consecutive CRC patients with non-resectable metachronous metastases. The non-randomized nature of this study also presents a potential risk of (selection) bias. Reasons (not) to prescribe specific systemic regimens were not available. Besides, relevant patient characteristics such as comorbidity and performance score were registered only at initial CRC diagnosis. Moreover, performance score was often not noted in patient charts (missing in >50%) and as a result, these data were not useful. Data on RAS/BRAF mutation status were also not present. Despite these limitations, this large population-based study presents real-world data which are of need in today's developing cancer care.

Conclusion

In daily practice, most elderly patients with non-resectable metachronous metastases from primary resected CRC receive first-line single-agent chemotherapy without a targeted therapy. Only a minority of the elderly mCRC patients receives a second line of treatment. As a consequence, very few elderly patients received all active systemic agents during their course of treatment, shown to be the only independent predictor of death. Future studies are needed to clarify the role of targeted therapy in elderly mCRC patients, who are often not candidates for combination chemotherapy.

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Part III

"The treatment of peritoneal metastases"

Chapter 7

"Bevacizumab in addition to palliative chemotherapy for patients with peritoneal carcinomatosis of colorectal origin: a nationwide population-based study"

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Abstract

Background: The majority of colorectal cancer (CRC) patients presenting with peritoneal carcinomatosis (PC) depends on palliative systemic treatment options. However, data on the use and effect of systemic treatment strategies including targeted agents for the palliative treatment of colorectal PC are lacking. We conducted a nationwide population-based study with data from the period in which the targeted agent bevacizumab was introduced in the Netherlands.

Methods: The study included all patients diagnosed between 2007 and 2014 with synchronous PC from CRC treated with only palliative systemic therapy. We assessed the use of bevacizumab, the standard choice of targeted treatment in addition to first-line chemotherapy. Multivariable logistic regression analyses were performed to calculate predictors for the additional prescription of bevacizumab. Survival estimates were calculated and multivariable Cox analyses were performed to estimate hazard ratios (HR's) of death, according to treatment.

Results: In total, 1235 patients received palliative chemotherapy of whom 436 received bevacizumab (35%). Patients aged 75 years or older and patients with PC from colonic tumors were less likely to receive chemotherapy plus bevacizumab. The addition of bevacizumab to palliative chemotherapy was associated with an improved overall median survival of 7.5 vs. 11 months, in both patients with isolated PC and concomitant extra-peritoneal metastases, also after adjustment for patient and tumor characteristics (HR 0.7; 95% CI 0.64-0.83).

Conclusion:
The results of this nationwide population-based study may support the rationale for bevacizumab in addition to palliative chemotherapy in patients with PC of CRC and underline the need for ongoing efforts to precise the position of targeted therapy in the treatment of PC.

Introduction

At initial diagnosis almost one-fourth of all colorectal cancer (CRC) patients present with disseminated disease, with the liver and peritoneum being the most frequently affected sites.[1,2] In the past two decades substantial progress has been made in the systemic treatment of metastatic CRC. The development of chemotherapeutic regimens combining 5-fluorouracil and oxaliplatin or irinotecan and the introduction of targeted agents such as bevacizumab has improved the prognosis of patients with stage IV CRC remarkably, defining the backbone of current systemic therapy.[3-8]

Nevertheless, very little is known about the efficacy of these systemic regimens including targeted therapy in the subset of CRC patients with peritoneal carcinomatosis (PC), a frequently encountered metastatic site with an invariable fatal prognosis.[9,10] Despite the development of potentially curative loco-regional treatment modalities for a selected group of PC patients, the majority of PC patients remains dependent on palliative systemic treatment options. Therefore the aim of this nationwide population-based study is to provide data on the usage and effect of targeted therapy in addition to chemotherapy for the palliative treatment of patients with synchronous PC of colorectal origin.

Methods

Patients and data

The Netherlands Cancer Registry (NCR) collects data of all patients with newly diagnosed cancer in the Netherlands, covering the entire Dutch population of approximately 16 million inhabitants. The NCR comprises 9 administrational regions, each covering between 7 and 20 hospitals. These regions form a network of health care professionals and institutions for cancer care and palliative care in the Netherlands. Pathologists enter histopathological and cytopathological reports of all diagnosed cancers in the nationwide Dutch Pathology Network (PALGA), which subsequently submits data to the NCR. Specially trained registry staff collects data on patient and tumor characteristics from the medical records using the registration and coding manual of the NCR. In this registration system, classification of the primary tumor is based on the TNM classification.[11] In case of missing pathological data, clinical TNM stage is used. Synchronous metastases were defined as metastases diagnosed within three months after initial CRC diagnosis and were registered according to the International Classification of Disease for Oncology (ICD-O).[12] Data on location of distant metastases were available and complete in approximately 95% of all patients with metastasized disease since 2007 and from 2008 on nearly complete for all patients.

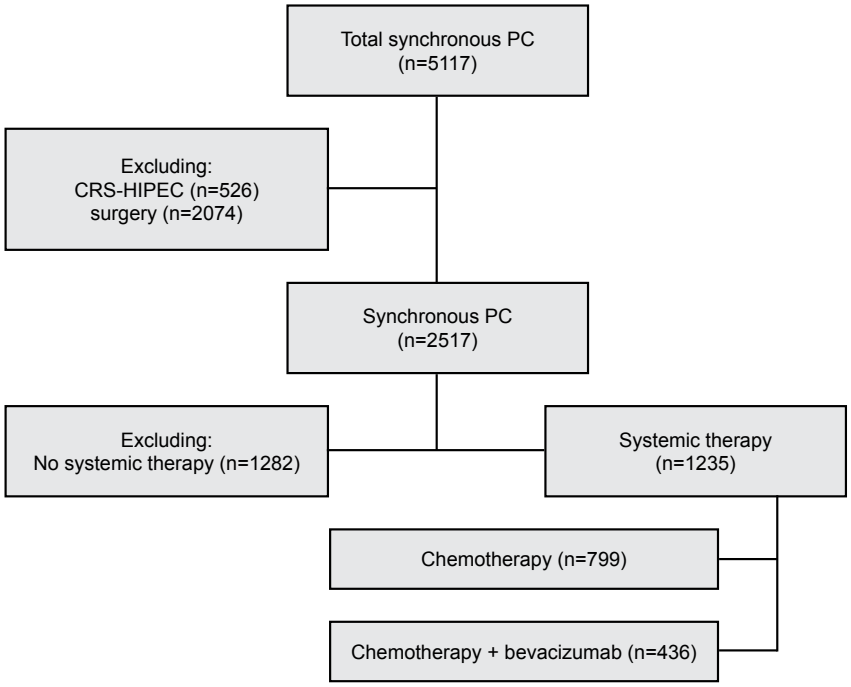
All patients who were diagnosed between 2007 and 2014 with synchronous PC from colorectal cancer were extracted from the nationwide database (n=5117). The current study focused on patients receiving only systemic therapy with palliative intent. Thus, patients treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) were excluded

(CRS-HIPEC, n=526). Moreover, patients primary undergoing surgery (local tumor resection, metastasectomy, debulking n=2074) or palliative treatment without systemic therapy (n=1282) were excluded from the current study, resulting in a study population of 1235 patients with PC receiving only palliative systemic therapy (Figure1).

In accordance with the Dutch national treatment guidelines, oxaliplatin-containing chemotherapy (e.g. CAPOX/FOLFOX) is recommended as the standard combination treatment for patients with stage IV CRC since 2001, whereas historically patients received standard first-line monotherapy with a fluoropyrimidine (5-FU or capecitabine).[13]

Both systemic chemotherapy and targeted therapy were registered (yes versus no) up to 6-9 months after initial diagnosis in the NCR. In the current study period, bevacizumab was the standard targeted therapy in addition to first-line chemotherapy.[14,15]

Figure 1 *An overview on the patients diagnosed with synchronous PC from CRC between 2007 and 2014 in the Netherlands.*



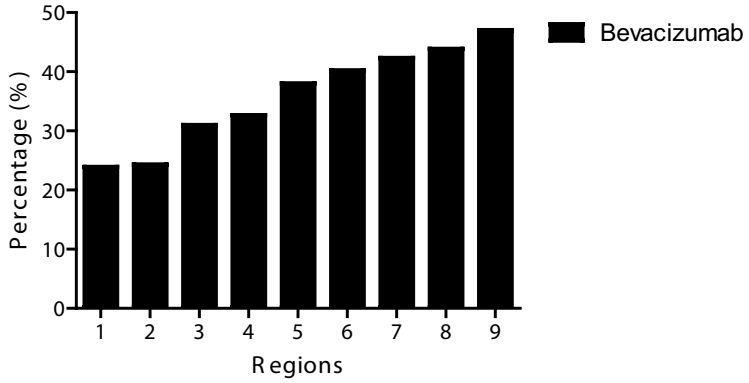
Statistical analyses

The number of colorectal PC patients treated with palliative chemotherapy and the proportion of patients receiving bevacizumab were calculated. Variation in the prescription of bevacizumab between the 9 administrational regions of the NCR was assessed and tested by means of a χ^2-test. Factors associated with the probability of receiving bevacizumab in addition to palliative chemotherapy were investigated by multivariable logistic regression analysis adjusted for age, gender, year of diagnosis, primary tumor localization, histological subtype, differentiation grade, T and N stage and radiotherapy. In addition, survival estimates of PC patients according to treatment (palliative chemotherapy with or without bevacizumab) were calculated using the Kaplan Meier method and proportions were compared using a log-rank test. Survival was defined as the time from diagnosis of CRC until death and patients lost to follow-up or still alive at January 1, 2015 were censored. Median survival (MS) was presented with the 95% confidence intervals (CI). Furthermore, multivariable Cox proportional hazards regression analyses were performed to investigate the independent prognostic impact of additional bevacizumab in patients with PC. Adjustments were made for relevant patient and tumor characteristics. Survival analyses were performed in both the total study population of PC patients and after stratification for the presence of concomitant extraperitoneal metastases. SAS/STAT statistical software® (SAS system 9.3, SAS Institute, Cary, NC) was used for all analyses.

Results

In total, 1235 patients with synchronous PC from CRC treated with palliative systemic therapy were enrolled in the current study. There were 712 men (58%) and 523 women (42%) with a median age of 65 years (min 21 years - max 91 years). Concomitant metastases were present in 69% of the patients (n=851). The majority of concomitant metastases were located in the liver (77%). Pulmonary metastases and lymph node metastases were present in respectively 188 patients (22%) and 159 patients (19%). Liver metastases were the only site of extra-peritoneal disease in 50% of the patients (n=433).

Figure 2 *Prescription of bevacizumab in addition to palliative chemotherapy in the Netherlands, according to region (n=1235).*



Palliative systemic treatment

All 1235 PC patients received palliative chemotherapy. Bevacizumab was added to palliative chemotherapy in 35% of the patients, with interregional variation from 24% to 47% (n=436, Figure 2, p<0.0001). As shown in table 1, patients receiving palliative chemotherapy plus bevacizumab were younger than patients receiving chemotherapy without this anti-vascular agent (p<0.0001). This was confirmed in multivariable logistic regression analysis, as it was shown that the likelihood of being treated with bevacizumab in addition to palliative chemotherapy was influenced by age. Elderly patients (>75 years) were less likely to receive bevacizumab compared to patients aged between 60-75 years (OR 0.4, 95%CI 0.29-0.61). Moreover, patients with a primary signet-ring cell carcinoma were less likely to receive additional bevacizumab than patients with PC from adenocarcinoma (OR 0.5, 95%CI 0.32-0.89), as well as patients with colon cancer as compared with rectal cancer (OR 0.6, 95%CI 0.46-0.93). Within colonic primary tumor localization, no differences were observed between right-sided or left-sided tumors (OR 1.0, 95%CI 0.72-1.52). Finally, it was observed that the likelihood of additional bevacizumab prescription was lower in irradiated PC patients (OR 0.5, 95%CI 0.26-0.98).

Table 1 *Clinicopathological characteristics of patients diagnosed with colorectal PC between 2007-2014 in the Netherlands, according to palliative systemic treatment.*

N=1235	Chemotherapy + bevacizumab (N=436)		Chemotherapy (N=799)		
	N	(%)	N	(%)	P-value
Gender					
Male	255	(58)	457	(57)	0.66
Female	181	(42)	342	(43)	
Age (years)					
<60	139	(32)	190	(24)	<0.0001
60-75	246	(56)	413	(52)	
≥ 75	51	(12)	196	(24)	
Tumor localization					
Rectum	86	(20)	115	(14)	<0.01
Colon	350	(80)	684	(86)	
Histologic subtype					
Adenocarcinoma	329	(75)	564	(71)	0.23
Mucinous carcinoma	71	(16)	144	(18)	
Signet ring cell carcinoma	25	(6)	67	(8)	
Other	11	(3)	24	(3)	
Tumor grade					
Well/moderate	72	(17)	138	(15)	0.73
Poor/undifferentiated	71	(15)	117	(16)	
Unknown	293	(68)	544	(70)	
Extent of metastases					
PC only	121	(28)	263	(33)	0.06
PC other	315	(72)	536	(67)	
Radiotherapy	15	(3)	39	(5)	0.24

Table 2 *Multivariable logistic regression analysis modelling the odds for bevacizumab in addition to palliative chemotherapy.*

	(%)	OR	CI
Gender			
Male	(36)	Ref	
Female	(35)	1.0	0.80-1.32
Age (years)			
<60	(42)	1.2	0.94-1.63
60-75	(37)	Ref	
≥75	(21)	0.4	**0.29-0.61**[a]
Tumor localization			
Rectum	(43)	Ref	
Colon	(34)	0.6	**0.46-0.93**[a]
Histologic subtype			
Adenocarcinoma	(37)	Ref	
Mucinous carcinoma	(33)	0.9	0.62-1.22
Signet cell carcinoma	(27)	0.5	**0.32-0.89**[a]
Other	(31)	0.8	0.37-1.68
Tumor grade			
Well/moderate	(34)	Ref	
Poor/undifferentiated	(38)	1.2	0.77-1.85
Unknown	(35)	1.0	0.74-1.45
Extent of metastases			
PC only	(32)	Ref	
PC other	(37)	1.2	0.94-1.62
Radiotherapy			
No	(36)	Ref	
Yes	(28)	0.5	**0.26-0.98**[a]

Analysis was also adjusted for year of diagnosis and T and N stage.
Abbreviations: CI = confidence interval; OR = odds ratio; PC only = isolated peritoneal carcinomatosis; PC other = peritoneal carcinomatosis with concomitant extraperitoneal metastases.

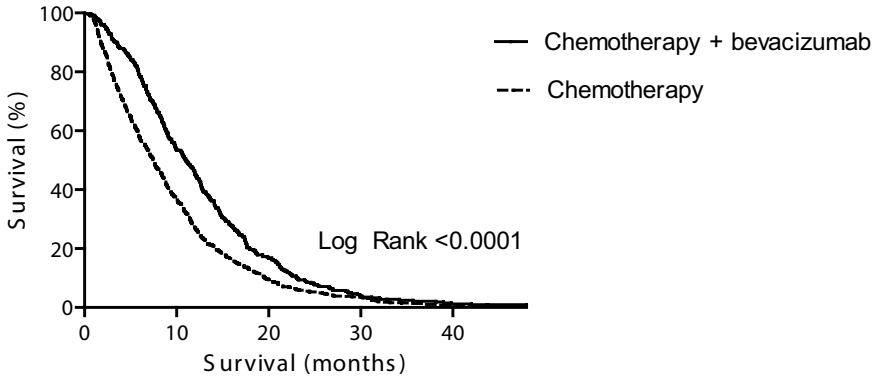
a Statistically significant.

Overall survival

The addition of bevacizumab to palliative chemotherapy was associated with improved median overall survival rates, from 7.4 months (95%CI 6.83-8.24) to 11.0 months (95%CI 9.79-12.09, Figure 3). Similar results were observed after stratification for the presence of extra-peritoneal metastases. Median survival rates improved from approximately 7.5 to 11 months with the additional prescription of targeted therapy in both patients with isolated PC (PC-Only, $p<0.05$) and concomitant extra-peritoneal metastases (PC-Other, $p<0.0001$).

In multivariable Cox regression analysis with adjustment for relevant prognostic factors, the addition of bevacizumab to palliative chemotherapy was associated with a decreased risk of death (HR 0.7; 95% CI 0.64-0.83).

Figure 3 *Overall survival of patients with synchronous PC from colorectal origin according to treatment (n=1235).*



Discussion

In this nationwide population-based study we demonstrate the use and potential effect of bevacizumab in addition to palliative chemotherapy in a selected group of colorectal PC patients who does not meet the criteria for potentially curative treatment procedures.

In the last decade, remarkable progress has been achieved in the systemic treatment of mCRC.[13,14] In 2001, oxaliplatin was registered in the Netherlands and recommended as a first-line cytostatic agent in combination chemotherapy for stage IV CRC. In addition, bevacizumab was registered since 2005 for the first-line treatment in mCRC in the Netherlands. Bevacizumab targets the vascular endothelial growth factor (VEGF), which is the most important angiogenic factor. Metastasis formation and growth depends on the presence of sufficient oxygen which is supplied by the formation of new bloodvessels (angiogenesis). High levels of VEGF have been associated with metastases in CRC. Moreover, VEGF has been shown to play a role in PM and prognosis.[16,17] Blocking VEGF could reduce ascites formation and progression. For patients with peritoneal metastases, however, the effect of systemic regimens including targeted therapy remains uncertain. Radiographic imaging of peritoneal tumor deposits is difficult, limiting the available evidence on this topic. In addition, the hypothesis that PC should be regarded as loco-regional rather than systemic spread of disease caused a shift in clinical attention from systemic towards loco-regional treatment modalities combining CRS and HIPEC. Various large case studies have demonstrated that this treatment may now be offered successfully with 5 year survival rates of over 30%.[18-20] However, only selected PC patients will be likely to benefit from this invasive treatment procedure.[20,21] Thus, the majority of colorectal PC patients depend on palliative systemic treatment strategies.

To the best of our knowledge, this is the first nationwide population-based study describing the

potential role of bevacizumab in the palliative treatment of colorectal PC. In view of the nationwide character, the number of colorectal PC patients receiving this anti-vascular agent was substantial (n=436). Bevacizumab was prescribed as a part of palliative systemic therapy in 35% of the PC patients diagnosed and treated after 2007. Large interregional variation was observed in the prescription of this tumor targeting agent, reflecting differences in policy towards the use of this novel tumor targeting therapy for the treatment of colorectal PC between the administrational regions in the Netherlands. Also, we observed that elderly patients were less likely to receive bevacizumab in addition to palliative chemotherapy. Older age has been described as one of the most important factors in refraining systemic chemotherapy, especially combination chemotherapy.[22-24] However, it has been shown that it is feasible to treat older patients with chemotherapy, even in the presence of widespread peritoneal disease combined with distant metastases.[25-27] In addition, several recent studies have suggested that age itself is not a contraindication for targeted therapy as bevacizumab, the standard recommended target agent in mCRC, is generally well-tolerated.[28-30] Finally, we observed that the prescription of bevacizumab was less likely in patients with colon cancer than rectal cancer. We cannot explain this difference, it might be related to tumor or host factors for which we could not control for in our analyses, such as metastatic tumor load within organs or differences in comorbidity patterns.

In the current study the addition of bevacizumab to palliative chemotherapy was associated with a significant increase in overall median survival of 3.5 months (from 7.5 to 11 months), both in patients with isolated PC and concomitant extra-peritoneal metastases (mostly liver metastases). In patients with stage IV CRC, the addition of bevacizumab has shown to improve median progression free survival with approximately 4 months in the first-line treatment.[7,31-33] However, most of these studies did not show an improvement in overall survival with the additional use of bevacizumab.[7, 29,34] We hypothesize that in these studies, patients who were assigned not to receive bevacizumab in the first-line of treatment, could have received bevacizumab in further lines. However, patients with PC as described in our study, are unlikely to receive multiple lines of systemic treatment due to the notorious prognosis of PC. Therefore, the gain in progression free survival with bevacizumab may be translated into an overall survival benefit in these patients.

Evidence on the potential role of targeting agents in the subset of CRC patients presenting with PC is scarce and still debatable. Data are derived from few small studies, that did not present stratified data according to the presence of concomitant extraperitoneal metastases. In a study by Klaver and colleagues on 22 patients with PC, overall median survival improved from 10.1 months to 18.2 months with the addition of targeted agents.[35] In two other small studies, median survival rates of respectively 15 and 23 months were observed with addition of targeted therapy, mostly bevacizumab.[36,37] In comparison to these survival rates, the outcomes as described in our nationwide

study are dismal, probably reflecting differences in patient selection. In our study, patients eligible for CRS-HIPEC and surgical procedures were excluded which implicates a selection of PC patients with unfavorable prognostic characteristics. Moreover, peritoneal tumor burden is expected to be extensive in our study population as patients were diagnosed in a non-operative setting either clinically and/or by radiographic imaging, which are both inaccurate techniques for the early detection of PC. An extensive peritoneal tumor burden often coincides with physical complaints such as abdominal discomfort, nausea, loss of appetite, diarrhea, constipation and unexplained weight loss or gain, which are invariably associated with a poor outcome.

Due to the nature of this population-based study potential selection bias is inevitable. No data on important prognostic factors such as comorbidity, socio-economic status, functional status and KRAS or BRAF mutational status were present in our database. Data on differentiation grade were missing in 70% of the patients included in the current study, probably due to non- operative setting in which these patients were diagnosed. Detailed information on the prescribed chemotherapeutic regimen was unavailable in the NCR.

Conclusion

The results of the current study may support the rationale for the addition of bevacizumab to palliative treatment with the best available systemic chemotherapy schedules for patients with PC who do not meet the inclusion criteria for CRS and HIPEC or surgery, however, due to the non-randomized nature of this study, results have to interpreted with caution.

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Chapter 8

"Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands"

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Abstract

Background: Population-based data on the percentage of colorectal cancer (CRC) patients with synchronous peritoneal carcinomatosis (PC) being treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are currently lacking. The current population-based study describes trends in the use of CRS-HIPEC in the Netherlands, one of the first countries where CRS and HIPEC was introduced.

Methods: All patients diagnosed with synchronous PC of CRC between 2005-2012 were extracted from the Netherlands Cancer Registry (n=4623). Patients with primary appendiceal cancer were excluded resulting in a study population of 4430 patients. Trends in the use of CRS-HIPEC over time were analyzed by means of a Cochrane Armitage trend test. Survival proportions were calculated as the time between diagnosis and date of death or last follow-up (January 2014).

Results: Of the total 4430 patients with synchronous PC, 297 (6.4%) underwent treatment with CRS-HIPEC. The proportion of colorectal PC patients receiving CRS-HIPEC increased significantly over time from 3.6% in 2005-2006 to 9.7% in 2011-2012 ($p<0.0001$). Overall median survival (MS) for patients treated with CRS- HIPEC was 32.3 months, whereas MS rates were respectively 12.6, 6.1 and 1.5 for months palliative chemotherapy with/without surgery, palliative surgery and best supportive care.

Conclusion: The proportion of patients diagnosed with synchronous PC from CRC treated with CRS-HIPEC has increased significantly over time and currently almost 10% of PC patients are treated with CRS-HIPEC. Median survival in this population based group is 32.3 months.

Introduction

Peritoneal tumor deposits are relatively common in patients with colorectal cancer and have long been considered a terminal condition with an invariable fatal outcome.[1] Palliative treatment with systemic chemotherapy has been the standard of care for these patients for many years. Recently, the understanding that peritoneal carcinomatosis (PC) results from loco-regional rather than systemic spread raised interest in this specific metastatic manifestation resulting in the development of loco-regional treatment modalities combining cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[2] In 2003, this combined technique was shown to be superior to palliative chemotherapy with conventional 5-fluorouracil (5-FU) and leucovorin (LV) or irinotecan in a randomized controlled trial.[3] Based on this evidence, CRS-HIPEC is adopted by an increasing number of centers worldwide. At present, many HIPEC-centers have published their experiences and the procedure is now well characterized. However, population-based studies providing data on the percentage of PC patients being treated with CRS-HIPEC and characterization of these patients are currently completely lacking.

The current population-based study was undertaken in the Netherlands, one of the first countries where CRS- HIPEC was introduced about 20 years ago. The trends in the Netherlands since then may provide important information on the amount of PC-patients being potentially eligible for this treatment in countries where HIPEC was introduced more recently. Therefore the aim of the present study was describe the usage and effect of CRS-HIPEC for the treatment of synchronous PC from CRC in the Netherlands.

Methods

Patients' selection and data

Data were retrieved from the Netherlands Cancer Registry (NCR). The NCR collects data on all patients with newly diagnosed cancer in the Netherlands, covering a population of approximately 16 million inhabitants. Histopathological and cytopathological reports of the diagnosed tumors are entered in the nationwide Dutch Pathology Network (PALGA) by pathologists, which subsequently submits the data to the NCR. Information on patient and tumor characteristics, diagnosis and treatment are extracted from the medical records by trained registry staff using the registration and coding manual of the NCR. The anatomical site of the tumor and metastases are registered according to the International Classification of Diseases for Oncology (ICD-O).[4] Synchronous metastases are defined as metastases of colorectal cancer in other organs within 3 months after primary tumor diagnosis. Primary tumor staging is based on the TNM Classification of Malignant Tumors.[5] In case of missing pathological data, clinical data is used.

As since 2005 data on CRS and HIPEC were available, all consecutive patients diagnosed with synchronous PC of colorectal origin between 2005-2012 were extracted from the NCR database (n=4623). Patients with primary appendiceal cancer were excluded (n=193) as they reflect a dis-

tinct entity with different prognosis. Of the remaining 4430 patients, 1109 were untreated, 1044 patients received only palliative surgery, 1980 patients received palliative chemotherapy (with or without surgery) and 297 patients were treated with CRS-HIPEC. Patients undergoing CRS-HIPEC or palliative chemotherapy were the main focus in this study.

Statistical analysis

Clinicopathological characteristics of patients with synchronous PC of colorectal cancer treated with CRS-HIPEC or palliative chemotherapy were compared using a two-sided χ^2 test. Trends in the use of CRS-HIPEC for the treatment of colorectal PC across the period 2005-2012 were analyzed by means of a Cochran-Armitage trend test. Factors influencing the probability of receiving CRS-HIPEC were evaluated by multivariable logistic regression analysis, providing odd's ratio's (OR) with their 95% confidence intervals (CIs). In order to investigate differences in patient selection over time, patients were divided into two groups according to period of diagnosis (2005-2008 & 2009-2012). Survival time was calculated as the time between diagnosis of colorectal cancer and date of death. Patients still alive at the end of follow-up (January 1, 2014) and those who emigrated were censored. Median survival (MS) was presented in months and corresponding 95% confidence intervals (CIs). Crude survival estimates were calculated with the Kaplan-Meier method and compared using the log-rank test. Finally, it was investigated in a multivariable Cox regression analysis whether period of diagnosis (2009-2012 vs. 2005-2008) was associated with the risk of death in patients receiving CRS-HIPEC. The following important prognostic factors were included in the model; age, period of diagnosis, differentiation grade, histological subtype, primary tumor localization, T- and N-stage and the presence of concomitant liver metastases. All analysis were performed with SAS/STAT® statistical software (SAS system 9.3; SAS institute,Cary,NC).

Results

Patient and tumor characteristics

In the study period 2005-2012, 4430 patients were diagnosed with synchronous PC from colorectal cancer in the Netherlands. In total, 297 patients were treated with CRS-HIPEC (6.7%) whereas palliative chemotherapy was prescribed in 1980 cases (45%). Patient and tumor characteristics are presented in Table 1. Except for gender and primary tumor localization, all general and tumor specific characteristics differed between patients who were treated with CRS-HIPEC and those who received palliative chemotherapy ($p<0.0001$).

Table 1 *General characteristics of patients diagnosed between 2005 and 2012 in the Netherlands with synchronous PC of colorectal origin, treated with CRS-HIPEC or palliative chemotherapy.*

	CRS-HIPEC (N=297)		**Palliative chemotherapy (N=1980)**		
	N	**%**	**N**	**%**	**P value**
Gender					
Male	149	50	958	54	
Female	148	50	794	46	NS
Age (years)					
< 60	143	48	561	31	
60-70	106	36	639	36	
>70	48	16	552	33	<0.0001
Period of diagnosis					
2005-2008	31	10	359	18	
2009-2012	266	90	1621	82	<0.0001
Tumor localization					
Colon	249	84	1451	86	
Rectum	48	16	233	14	NS
Tumor morphology					
Adenocarcinoma	156	63	1162	69	
Mucinous carcinoma	106	36	373	22	
Signet-ring cell carcinoma	32	11	114	7	
Other	3	1	35	2	<0.0001
Differentiation grade					
Well/moderately	134	45	570	34	
Poorly/undifferentiated	74	25	416	25	
Unknown	89	30	698	41	<0.0001
T stage					
0-2	9	3	26	2	
3	99	33	425	25	
4	185	63	772	46	
X	4	1	461	27	<0.0001
N stage					
0	57	19	177	11	
1,2	230	77	1058	62	
X	10	4	449	27	
Liver metastases	27	9	1077	54	<0.0001
Systemic CT_x	213	72	NA	NA	

NA: not applicable

The use of CRS-HIPEC over time

Treatment with CRS-HIPEC in the Netherlands increased significantly from 3.6% of colorectal PC patients in 2005-2006 to 9.7% in 2011-2012 (Figure 1). Several factors influenced the probability of receiving CRS-HIPEC (Table 2). Compared to patients aged between 60-70 years, younger patients (<60 years) were more likely to receive this treatment modality (OR 1.9, 95% CI 1.40-2.64) whereas elderly patients (>70 years) received CRS-HIPEC less often (OR 0.3, 95% CI 0.18-0.39). In addition, patients with poorly or undifferentiated tumors were less likely to undergo CRS-HIPEC, but this effect was shown to be dependent on the period of diagnosis. Patients diagnosed with poorly/undifferentiated tumors between 2005-2008 received CRS-HIPEC less frequently (OR 0.1, CI 0.02-0.52) whereas no significant OR was observed for patients diagnosed with poorly/undifferentiated tumors since 2009 (OR 0.8, CI 0.56-1.16). Most CRS-HIPEC procedures were performed in patients with isolated PC. However, a small group of patients with concomitant liver metastases (n=27), especially since 2008 (n=26), received treatment with CRS-HIPEC.

Figure 1 *Percentage of patients with synchronous PC from colorectal cancer (n=4430) receiving treatment with CRS-HIPEC in the period 2005-2012 in the Netherlands.*

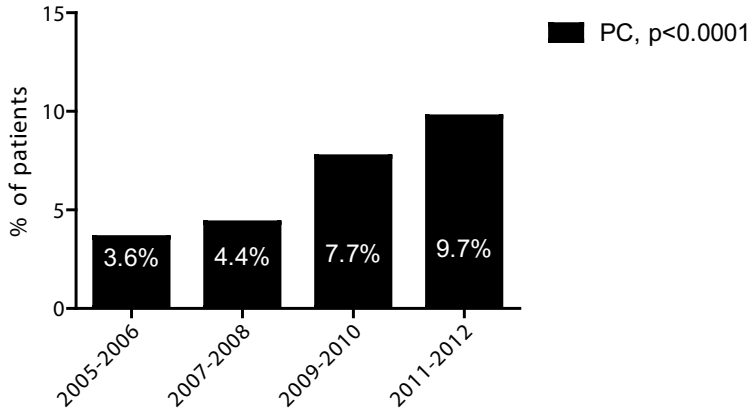


Table 2 *Multivariable logistic regression analysis modeling the chance of treatment with CRS-HIPEC among patients with synchronous PC from colorectal cancer, diagnosed between 2005 and 2012 in the Netherlands.*

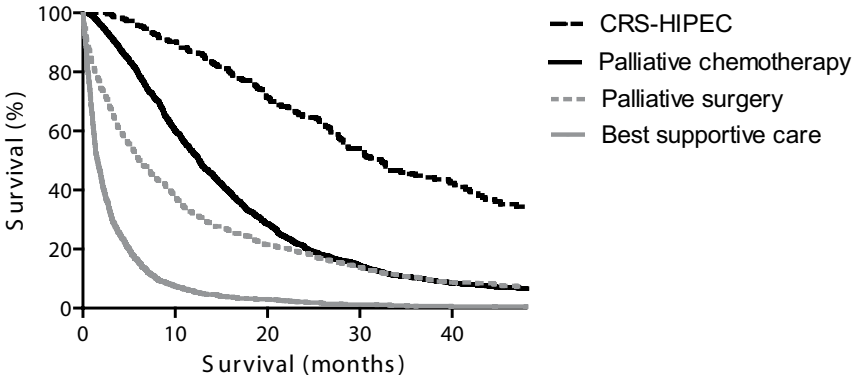
N=4430	%	OR	95% CI
Gender			
Male	7	Ref	
Female	7	1.0	0.77-1.35
Age (years)			
<60	15	1.9	**1.40-2.64**
60-70	8	Ref	
>70	2	0.3	**0.18-0.39**
Period of diagnosis			
2005-2008	4	Ref	
2009-2012	7	3.1	2.06-4.76
Tumor localization			
Colon	6	Ref	
Rectum	8	1.9	**1.21-2.83**
Tumor morphology			
Adenocarcinoma	5	Ref	
Mucinous carcinoma	11	1.6	**1.20-2.25**
Signet-ring cell	10	1.2	0.74-2.04
Other	2	0.4	0.10-1.38
Differentiation grade			
Well/moderately	9	Ref	
Poorly/undifferentiated	6	0.7	**0.46-0.93**
Unknown	5	1.3	0.88-1.86
T stage			
0-2	9	1.4	0.54-3.57
3	9	Ref	
4	9	1.2	0.86-1.58
X	0	0.7	0.24-2.28
N stage			
0	10	1.4	0.94-2.00
1,2	9	Ref	
X	1	0.5	0.21-1.12
Liver metastases			
No	10	Ref	
Yes	1	0.1	**0.06-0.15**
Systemic chemotherapy			
No	4	Ref	
Yes	10	1.9	**1.41-2.61**

Data are adjusted for all variables listed. OR, odds ratio; CI, confidence interval.

Survival

Overall median survival (MS) was 32.3 months for patients with colorectal PC treated with CRS-HIPEC and 12.6 months for patients receiving palliative chemotherapy (Figure 2). In the presence of concomitant liver metastases, MS rates were respectively 23.1 months (CI 13.90-36.07) and 12.5 months (CI 11.3-13.08) for patients treated with CRS-HIPEC or palliative chemotherapy.

Figure 2 *Overall survival of patients with synchronous PC of colorectal origin treated with CRS-HIPEC, systemic chemotherapy, palliative surgery or best supportive care (n=4430).*



Risk of death

In a multivariable proportional hazards regression analysis with adjustment for important patient and tumor characteristics, period of diagnosis (2005-2008 vs 2009-2012) did not influence the risk of dying in patients receiving treatment with CRS-HIPEC (HR 1.0 CI 0.62-1.61).

Discussion

In the Netherlands, CRS-HIPEC was introduced already 20 years ago. Ever since, the number of hospitals offering CRS-HIPEC has increased gradually to the current number of six centers all using an uniform technique.3,6 The long tradition of this treatment in the Netherlands provides an opportunity to study the trends in treatment over the years. This may provide important information to health care providers (e.g. hospital staff and insurance companies) worldwide to anticipate on future developments and requirements. Furthermore, the percentage of PC patients being treated with CRS and HIPEC may serve as benchmark to compare between countries rather than studies reporting absolute numbers only.

This current study demonstrates that the proportion of colorectal cancer patients with PC treated with CRS-HIPEC increased significantly over time. In 2011-2012, 9.7% of all PC patients underwent this procedure. This trend confirms the increase in the absolute number of CRS and HIPEC procedures as described by several centers worldwide.[6,7] The increasing awareness of clinicians in referring hospitals probably attributes to this phenomena and will likely result in a further increase in the future as it was shown that a plateau was not yet reached in the Netherlands.

Accurate patient selection has shown to be a key predictor of CRS-HIPEC outcome. In specialized PC centers, consensus has been established on essential CRS-HIPEC selection criteria.[8] CRS and HIPEC are usually contraindicated in patients with extensive peritoneal tumor burden, concomitant extra-peritoneal metastases, serious comorbidities and a poor performance status.[8,9] With respect to age, some centers considered elderly patients (>70 years) ineligible [10,11], whereas other showed feasibility in these patients. In general, most clinicians agree that age itself should not be considered as an absolute contraindication and that elderly patients should be evaluated on an individual base.[8,9] This study confirmed the presence of stringent patient selection, despite the lack of detailed information on CRS-HIPEC selection criteria due to the nature of this population based study. Younger patients with moderately or well differentiated tumors are more likely to undergo this potentially curative treatment modality compared to patients aged between 60-70 years whereas elderly patients were less likely to receive CRS-HIPEC. Patients with PC from poorly or undifferentiated tumors were less likely to undergo CRS-HIPEC, especially if diagnosed between 2005-2008. Although differentiation grade is not generally taken into account in patient selection for CRS-HIPEC, it is known that a poor differentiation grade generally implies a more aggressive tumor biology [12] which could implicate a more extensive peritoneal tumor burden in these patients.

In this population-based study, median survival (MS) was found to exceed 32 months for patients treated with CRS-HIPEC, which is in line with current literature. In the large multi-institutional study by Glehen et al., including 523 colorectal PC patients treated with this therapeutic approach an overall MS of 30 months was found.

Although patients with concomitant extra-peritoneal metastases are generally not considered candidates for CRS-HIPEC, the results of our study demonstrated that even a small number of colorectal PC patients with limited concomitant liver metastases underwent this procedure, especially since 2008, with a median survival of 23 months. A non-anatomical wedge resection of the liver metastases was performed in the vast majority of these cases. The fact that a small group of PC patients with concomitant liver metastases underwent CRS-HIPEC results from current evidence stating that liver involvement should not be considered an absolute contra-indication if metastases are confined to a maximum of three-well defined lesions.[3,13,14]

Despite the increased proportion of patients treated with CRS-HIPEC over time and perhaps the inclusion of patients with more extensive disease (i.e. poorly/ undifferentiated primary tumor and concomitant liver metastases) in the recent time period (2009-2012), median survival rates of patients treated with CRS-HIPEC did not reduce over time. Moreover, major complication rates and mortality rates remained comparable to the literature according to a recent study by Kuijpers et al.[3] In this study, a major complication rate of 34% and a mortality rate of 3% was observed after CRS and HIPEC.[6] These findings may reflect an increase in surgical experience over time and improved insight in relevant predictors of outcome.
The median survival of patients in our study treated with current palliative systemic treatment modalities consisting of 5-FU based chemotherapy often combined with oxaliplatin or irinotecan and targeted therapies was approximately 13 months. Historically, with fluoropyrimidine based monotherapy (5-FU,capecitabine), MS rates were poor, ranging from approximately 6 months [1,15] up to a maximum of 12.6 months in a positive selection of patients.[16] The effect of modern combined cytostatic regimens is only sparsely studied in the subset of patients with PC, due to the difficulty of evaluating treatment response in these patients.[17] In the few available studies so far, modern systemic regimens were associated with improved survival rates ranging from 10 months to 23 months.[17-20] Thus, the median survival rate of 13 months as described in our study probably reflects the implementation of modern combination systemic therapy in the Netherlands during the last decade.

Due to the inevitable presence of selection bias in our population-based study and the lack of data on important prognostic factors such as performance status, extent of peritoneal disease and comorbidity were not registered in the NCR, conclusions on the effect of CRS-HIPEC compared to chemotherapy cannot be drawn upon these data exclusively. In the only currently available randomized trial, the beneficial effect of CRS-HIPEC compared with conventional chemotherapy (fluorouracil-leucovorin) was established.[3] Unfortunately, no randomized trials have been published ever since. Therefore, evidence on the effectiveness of CRS and HIPEC compared with modern combined systemic regimens arises from few studies with methodological limitations. The only two currently available controlled studies comparing CRS-HIPEC and modern systemic regimens both indicated a trend towards a more beneficial effect in the CRS-HIPEC group.[19,20] Despite the obstacles in interpreting these data, an independent effect of the combined treatment modality CRS-HIPEC is generally accepted. Nevertheless, the independent effect of cytoreduction, hyperthermia and intraperitoneal chemotherapy in this combined treatment modality remains unknown.

Conclusion

The proportion of patients diagnosed with synchronous PC from colorectal origin treated with CRS-HIPEC increased significantly over time and still has not reached a plateau in the Netherlands. Currently almost 10% of PC patients appear to be eligible for CRS-HIPEC. This includes primarily younger patients with well or moderately differentiated tumors and isolated PC resulting in a median survival of 32.3 months.

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Chapter 9

"Challenging the dogma of peritoneal metastases as an untreatable condition: results of a population based study"

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Abstract

Purpose: To determine the impact of the implementation of novel systemic regimens and loco-regional treatment modalities on survival at population level in colorectal cancer (CRC) patients presenting with peritoneal metastases (PM).

Methods: All consecutive CRC patients with synchronous PM (<3 months) between 1995 and 2014 were extracted from the Eindhoven area of the Netherlands Cancer Registry. Trends in treatment and overall survival were assessed in four time periods. Multivariable regression analysis was used to analyze the impact of systemic and loco-regional treatment modalities on survival.

Results: A total of 37,036 patients were diagnosed with primary CRC between 1995 and 2014. Synchronous PM were diagnosed in 1,661 patients, of whom 55% had also metastases at other sites (n=917) and 77% received anticancer therapy (n=1273). Treatment with systemic therapy increased from 23% in 1995-1999 to 56% in 2010-2014 (p<0.0001). Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) was applied since 2005 and increased from 10% in 2005-2009 to 23% in 2010-2014. Surgery for lymphatic or hematogenous metastases increased from 2% to 10% in these periods. Median overall survival of the complete cohort improved from 6.0 months in 1995-2000 to 12.5 months in 2010-2014 (p<0.0001), with a doubling of survival for both PM alone and PM with other involved sites. The influence of year of diagnosis on survival (HR 2010-2014 vs 1995-1999; 0.5, 95%CI 0.43-0.62, p<0.0001) disappeared after including systemic therapy and loco-regional treatment modalities in subsequent multivariable models.

Conclusion: CRC patients presenting with PM are increasingly offered a multi-disciplinary treatment approach, resulting in an increased overall survival for the entire cohort.

Introduction

Peritoneal dissemination is a common manifestation of metastases in patients with colorectal cancer (CRC), affecting approximately 10% of CRC patients.[1-3] Responses to 5-fluorouracil are poor and results after only palliative surgical interventions are disappointing[4], resulting in an invariable fatal prognosis with conventional treatment.[2,3,5] Therefore, patients with peritoneal metastases (PM) are considered to be virtually untreatable by many physicians, often resulting in only best supportive care in a palliative setting. The introduction of novel systemic regimens combing chemotherapy and monoclonal antibodies may offer new treatment possibilities for CRC patients with PM. However, results from randomized studies on the efficacy of these systemic regimens in patients with PM are lacking, as these patients are often excluded from clinical trials given the problems in disease measurability by CT imaging.

The hypothesis that PM may be regarded as loco-regional tumor spread rather than systemically metastasized CRC resulted in the development of a loco-regional treatment strategy combining cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Although promising results have been demonstrated with this treatment, the efficacy of CRS and HIPEC in CRC patients with PM remains a matter of debate with only one RCT supporting its beneficial value.[6]

Due to the grim prognosis and the lack of solid evidence on both the systemic and loco-regional treatment of PM, peritoneal disease still has a reputation of an untreatable condition. In spite of this, patients with PM in The Netherlands are treated with increased frequency and intensity.[7] We performed a population-based analysis to provide insight on the impact of this practice on survival in CRC patients presenting with PM.

Methods

Patients and data

Data from the Eindhoven area of the population-based Netherlands Cancer Registry (NCR) were used. This registry collects data of all patients with newly diagnosed cancer in a large part of the south-eastern Netherlands and covers an area of approximately 2.4 million inhabitants and is notified by six pathology departments, 10 community hospitals at 17 locations and two large radiotherapy institutions. Specially trained administrators of the cancer registry extract data on patient and tumor characteristics from medical records after notification by pathologists and medical registration offices, resulting in high quality of the data. Primary tumors are classified according to the TNM classification of Malignant Tumors. In case of missing pathological data, clinical TNM is used. Subsites of systemic metastasis at the time of diagnosis are registered according to the International Classification of Diseases for Oncology (ICD-O). Synchronous metastases were defined as metastases diagnosed within three months after initial CRC diagnosis. Systemic treatment (yes versus no) was defined as prescription of either cytostatic drugs or targeted agents of any

kind at initial diagnosis. A distinction in surgical procedures was made between primary tumor resection (either open or laparoscopic), surgery for metastases (surgical procedures aiming to remove lymphatic or hematogenous metastases) or CRS-HIPEC. Four periods (1995-2000, 2000-2005, 2005-2010, 2010-2014) were defined based on year of diagnosis to analyze time trends in the application of systemic therapy and loco-regional treatment modalities for metastatic CRC as well as overall survival.

All consecutive patients diagnosed with primary CRC (C18.0-C20.9) between 1995 and 2014 were extracted (n=37,036). Subsequently, all patients presenting with PM at the time of initial CRC diagnosis were included (n=1,661). In all patients, follow-up of vital status was complete until January 2015. This information was obtained from the municipal administrative databases, in which data on all deceased and emigrated persons are collected in The Netherlands.

Statistical analyses

Descriptive statistics were used to provide an overview of the total study population of patients with synchronous PM from CRC. Trends in treatment across the four periods were analyzed by means of a Cochran Armitage trend test. Changes in the use of different treatment modalities (systemic therapy, CRS-HIPEC, surgery for lymphatic or hematogenous metastases) were evaluated by period and according to a number of relevant patient and tumor characteristics. Overall survival time was defined as the time from initial CRC diagnosis to death or lost to follow-up. Patients still alive at the end of follow-up (January 1st, 2015) and those who emigrated were censored. Actuarial survival estimates according to period of diagnosis were calculated with the Kaplan-Meier method and presented up to 48 months in both the total study population of PM patients and according to the sites of metastatic disease (PM only, PM + other). A log-rank test was used to compare survival between relevant subgroups. Median survival (MS) was expressed in months and corresponding 95% confidence intervals (CIs) were calculated. Multivariable Cox regression analyses of overall survival were performed to estimate hazard ratios (HRs) for the various relevant patient and tumor characteristics, including period of diagnosis. The model was first built without adjustment for treatment variables. Subsequently, systemic therapy was included in model 2 and all other treatment modalities (primary tumour resection, surgery for lymphatic or hematogenous metastases, CRS-HIPEC) were included in model 3. It was hypothesized that if adjustment for different treatment modalities attenuated the association between period of diagnosis and the hazard ratio on death, this would suggest that these treatment modalities had contributed to the reduced mortality over time. All analyses were performed with SAS/STAT ® statistical software (SAS system 9.3; SAS institute, Cary, NC).

Results

Between 1995 and 2014, 1,661 patients were diagnosed with synchronous PM from CRC in the Southern part of The Netherlands, representing 4.5% of the total number of CRC diagnoses and 23% of the stage IV CRC diagnoses during this period. Over time, the absolute number of CRC patients diagnosed with PM increased, but the relative proportions remained stable. Patient and tumor characteristics are shown in Table 1.

Table 1 *General characteristics of patients with peritoneal metastases (PM) from colorectal origin, diagnosed between 1995 and 2014 in the south of the Netherlands (n=1661).*

N=1661	N	(%)
Gender		
Male	808	(49)
Female	853	(51)
Age (years)		
<70	917	(55)
≥70	744	(45)
Period of diagnosis		
1995-1999	293	(18)
2000-2004	333	(20)
2005-2009	492	(29)
2010-2014	543	(33)
Comorbidity		
Yes	897	(54)
No	609	(37)
Unknown	155	(9)
Socioeconomic status		
Low	388	(23)
Intermediate	629	(38)
High	518	(31)
Institutionalized	78	(5)
Unknown	48	(3)
Localization of primary tumor		
Caecum	376	(23)
Appendix	59	(4)
Colon	968	(58)
Rectosigmoid	84	(5)
Rectum	174	(10)
T stage of primary tumor		
T1-T2	42	(3)
T3	517	(31)
T4	664	(40)
Tx	438	(26)
N stage of primary tumor		
N0	128	(8)
N1,2	689	(41)
Nx	844	(51)
N=1661	N	(%)
Differentiation grade primary tumor		
Well/moderate	625	(38)
Poor/undifferentiated	480	(29)
Unknown	556	(33)
Sites of metastatic disease		
PM only	744	(45)
PM and other sites	917	(55)

The treatment of PM over time

Over time, the proportion of PM patients receiving any registered treatment modality increased slightly from 73% in the time periods 1995-1999 and 2000-2004 to 78% in 2005-2010 and 79% in the most recent time period 2010-2014 ($p<0.05$). In total, 1,273 PM patients received any anticancer treatment (77%). However, type of treatment changed over time, as shown in Figure 1. Treatment with systemic therapy increased from 23% in 1995-1999 to 56% in 2010-2014 ($p<0.0001$). CRS-HIPEC was applied since 2005 with increasing percentages thereafter (10% 2005-2009; 23% in 2010-2014). The increase in the use of these treatment modalities was observed regardless of age, comorbidity and the involved sites of metastatic disease. Details are shown in Table 2. Surgery for lymphatic or hematogenous metastases significantly increased as well ($p<0.0001$), especially in the most recent time period 2010-2014 (10%). In contrast, there was a decrease in primary tumor resections from 62% in 1995-1999 to 52% in 2010-2014 ($p<0.01$).

Figure 1 *Treatment of colorectal PM, by period of diagnosis.*

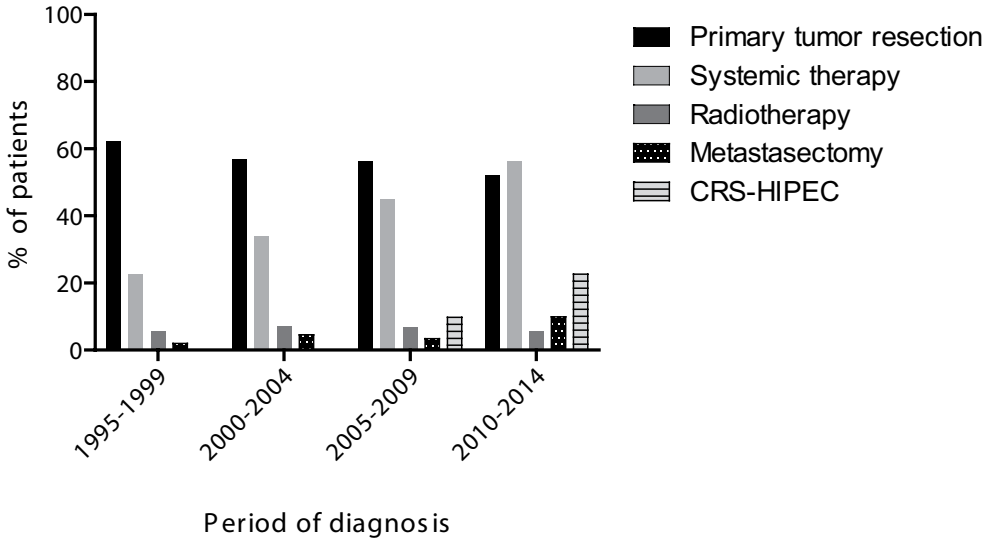

Table 2 *Percentage of patients who received systemic therapy, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and/or surgery for lymphatic or hematogenous metastases, by period and according to a number of relevant patient and tumor characteristics*

	1995-1999			2000-2004			2005-2009			2010-2014			
	Total N	systemic therapy (%)	surgery for metastases (%)	Total N	systemic therapy (%)	surgery for metastases (%)	Total N	systemic therapy (%)	surgery for metastases (%)	CRS+HIPEC (%)	Total N	systemic therapy (%)	surgery for metastases (%)	CRS+HIPEC (%)
Overall	293	(23)	(2)	333	(34)	(5)	492	(45)	(4)	(10)	543	(56)	(10)	(23)
Age (years)														
< 70	168	(33)	(2)	183	(50)	(7)	252	(61)	(6)	(17)	314	(67)	(14)	(31)
≥ 70	125	(9)	(2)	150	(14)	(2)	240	(28)	(1)	(2)	229	(41)	(4)	(11)
Gender														
Male	138	(30)	(3)	167	(40)	(6)	224	(48)	(6)	(9)	279	(61)	(13)	(22)
Female	155	(16)	(1)	166	(28)	(2)	268	(43)	(1)	(10)	264	(51)	(8)	(23)
Comorbidity														
No	150	(27)	(1)	157	(42)	(4)	174	(51)	(4)	(6)	128	(65)	(12)	(23)
Yes	124	(14)	(4)	170	(26)	(5)	274	(39)	(3)	(7)	329	(52)	(9)	(19)
Unknown	19	(47)	(0)	6	(33)	(0)	44	(57)	(7)	(41)	86	(50)	(12)	(35)
Extent of metastatic disease														
PM only	144	(19)	(0)	145	(27)	(0)	210	(37)	(5)	(0)	245	(50)	(0)	(28)
PM + other	149	(26)	(4)	188	(39)	(8)	284	(51)	(6)	(6)	298	(61)	(18)	(18)

Trends in survival

Median overall survival (OS) improved over time in the total population of PM patients, from 6.0 months in 1995-1999 to 12.5 months in 2010-2014 (p<0.0001, Table 3). This increase was observed in both patients with isolated PM (PM Only) and PM plus other sites of metastases (PM + Other), as shown in Figure 2.

Figure 2 *Overall survival of patients with A. PM-Only B. PM-Other, by period of diagnosis (n=1661).*

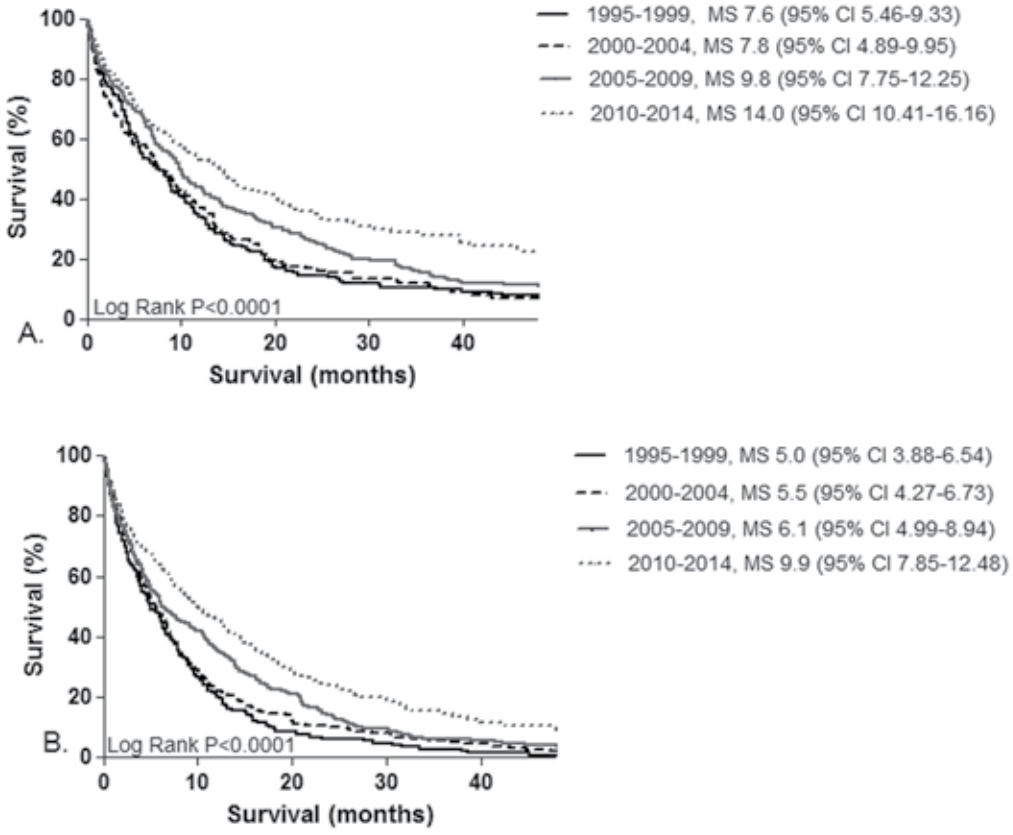

Table 3 *Median overall survival (in months) of patients with peritoneal metastases (PM) from colorectal origin (n=1,661), separated for whether or not other metastatic sites were involved and period of diagnosis.*

	1995-1999		2000-2004		2005-2009		2010-2014	
	MS	**CI**	**MS**	**CI**	**MS**	**CI**	**MS**	**CI**
PM total	6.0	4.96-7.42	6.5	4.96-7.22	8.0	6.76-9.75	12.5	9.56-13.53
PM Only	7.6	5.46-9.33	7.8	4.89-9.95	9.8	7.75-12.25	14.0	10.41-16.16
PM + Other	5.0	3.88-6.54	5.5	4.27-6.73	6.1	4.99-8.94	9.9	7.85-12.48

CI, confidence interval; MS, median survival; PM, peritoneal metastasis.
p- values: overall / PC-Only/PC-Other p<0.0001

Multivariable proportional hazards regression analysis modelling the risk for death for patients with synchronous PM from CRC is shown in Table 4. Patients diagnosed between 2005-2009 and 2010-2014 had a decreased risk of death as compared to patients diagnosed in the two earlier periods of time (model 1). The difference was not observed any more for patients diagnosed in the period 2005-2009 after adjusting for systemic therapy (model 2), but remained for patients diagnosed in the most recent time period (2010-2014) compared to earlier periods of diagnosis. If adjustments were made for all treatment modalities that were applied in the most recent time period (model 3), the lower risk of death disappeared for the period 2010-2014. Other beneficial prognostic factors identified by multivariable analysis were the absence of lymph node metastases and a well or moderate differentiation grade of the primary tumor. Poor prognostic factors were higher age (≥70 years).

Table 4 *Multivariable proportional Cox regression analysis modelling the risk for death for patients with synchronous PM from CRC, diagnosed between 1995-2014 (n=1661).*

	Model 1		Model 2		Model 3	
	HR	**95% CI P-value**	**HR**	**95 % CI P-value**	**HR**	**95% CI P-value**
Gender						
Male	Ref	0.93-1.17 0.40				
Female	1.0					
Age (years)						
<70	Ref	1.52-1.90 <0.0001				
≥70	1.7					
Period of diagnosis						
1995-1999	Ref	0.76-1.06 0.23	Ref	0.88-1.23 0.64	Ref	0.88-1.24 0.59
2000-2004	0.9	0.60-0.83 <0.0001	1.0	0.78-1.09 0.35	1.0	0.87-1.21 0.78
2005-2009	0.7	0.44-0.62 <0.0001	0.9	0.62-0.88 <0.001	1.0	0.74-1.06 0.19
2010-2014	0.5		0.7		0.9	
Comorbidity						
No	Ref	0.95-1.19 0.28				
Yes	1.0					
Socioeconomic status						
Low	**1.2**	**1.01-1.36 <0.05**				
Mid	1.1	0.97-1.26 0.13				
High	Ref					
Institutionalized	**1.8**	**1.40-2.31 <0.0001**				
Localization primary tumor						
Colon	Ref	0.77-1.04 0.16				
Rectum	0.9					
T stage primary tumor						
T1-T2	0.7	0.47-1.10 0.13				
T3	Ref	0.88-1.15 0.88				
T4	1.0	1.11-1.57 <0.01				
Tx	1.3					
N stage primary tumor						
N0	0.5	0.39-0.65 <0.0001				
N1,2	Ref	1.33-1.78 <0.0001				
Nx	1.5					
Differentiation grade primary tumor						
Well/moderate	Ref	1.31-1.72 <0.0001				
Poor/undifferentiated	1.5	1.07-1.41 <0.01				
Unknown	1.2					
Sites of metastatic disease						
PM only	Ref	1.27-1.60 <0.0001				
PM + other	1.4					

**Ref=reference category. Model1; without adjustment for treatment. Model2; with adjustment for systemic chemotherapy. Model 3;with adjustment for all treatment modalities (systemic chemotherapy; primary tumor resection, surgery for lymphatic or hematogenous metastases, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC)*

Discussion

The present population-based study including 1,661 consecutive CRC patients with PM shows that treatment has changed remarkably over the last two decades. Both systemic therapy and loco-regional treatment modalities are increasingly offered to these patients. To the best of our knowledge, this is the first study demonstrating an increased overall survival for the entire cohort of PM patients, compellingly challenging the dogma of PM as an untreatable condition.

In patients with metastatic CRC, the introduction of systemic schedules combining various cytotoxic agents and targeted agents resulted in a substantial improvement in overall survival, with increased median survival rates from approximately 6 months to more than 20 months. [8-12] Promising data from small pooled analyses[13-15] led to the suggestion that, also in the presence of PM, novel systemic regimens could be of use. In France, this resulted in a substantial increase in the proportion of patients receiving chemotherapy over time, from 11% before 1997 to 48% in 2011 for synchronous PM and from 3% to 38% for metachronous PM.[16] Treatment with palliative systemic therapy in the Netherlands increased from 16% in 1995 to 46% in 2008 according to data from a previous-population based study by Klaver and colleagues.[17] As demonstrated in the current study, the application of systemic therapy for PM increased even further over time up to 56% in the most recent time period. During the study period, there was a slight but significant decrease in the proportion of PM patients undergoing primary tumor resection. This might be related to the increasing availability of more effective systemic therapy providing an alternative to palliative surgery in most recent years. This phenomenon was previously described in other gastrointestinal cancers.[18] Although detailed data on the prescribed systemic regimen were not available in the NCR, the increasing use of systemic therapy in daily practice probably implicates treatment intensification not only by an increased proportion of patients being treated, but also by the implementation of more potential systemic regimens.

The two most recent time periods evaluated in this study (2005-2009, 2010-2014) reflect a period in which not only novel systemic regimens but also loco-regional treatment strategies (including surgery for lymphatic or hematogenous metastases and CRS-HIPEC) were implemented in the Netherlands. In 2003, the RCT by Verwaal and colleagues demonstrated an improved overall survival with CRS-HIPEC compared to conventional fluorouracil based-chemotherapy.[6,19] Since then, no new randomized data have become available. Various large case studies have demonstrated that this treatment may now be offered successfully with 5-year survival rates of over 30%,[19-21] also in the current era with modern combination chemotherapy.[22] These results are currently comparable to those obtained with resection of liver metastases only.[23] Opponents of CRS and HIPEC claim that these results may be primarily obtained by selection bias, with treatment being offered to relatively young patients in a good general condition with limited PM. Nevertheless, the intro-

duction of CRS-HIPEC has resulted in the increasing usage of CRS-HIPEC nationwide [15,21] as was also confirmed in the current study. In the most recent time period 2010-2014, 23% of the patients underwent CRS-HIPEC: 28% in PM only and 18% in PM with other metastatic sites involved. Although regarded as peritoneal metastases by some, metastases to the ovary are defined as "systemic metastasis" in the NCR. This explains the relatively high percentage of 18% of PM patients with "other metastases" that received CRS-HPEC in the most recent time period. Besides ovarian metastases, this group also included patients with metastases in the liver or distant lymph nodes. Resection of ovarian metastases also attributes to the high number of patients undergoing surgery for lymphatic or hematogenous metastases (10% in 2010-2014).

In the current study, median overall survival rates of PM patients were 6.0 months in 1995-2000 and 12.5 months in 2010-2014. These survival rates seem in line with current literature. With palliative treatment only, overall survival rates in patients with peritoneal tumor spread typically ranged around 6 months[3,5,24,25], whereas with novel combined systemic regimens and loco-regional procedures (CRS-HIPEC) higher survival rates even exceeding 30 months have been reported.[15,22,26]

The improved survival rates over time remained present after stratifying for other involved metastatic sites. Multivariable analyses were applied to investigate the independent effect of recent diagnosis (and the concomitant availability of more potential systemic/loco-regional treatment modalities) on the risk of death. The observation that the lower risk of death for diagnosis between 2010-2014 disappeared after including all treatment modalities into the multivariable model strongly supports our hypothesis that improved survival rates can be contributed to a multi-disciplinary approach, consisting of both systemic and loco-regional (CRS-HIPEC, surgery for lymphatic or hematogenous metastases) treatment options. Although these non-randomized data need to be interpreted with caution, it might be stated that PM should no longer be regarded as an untreatable condition.

This large population-based study has the advantage of omitting any selection bias by including a long-term series of consecutive patients. The results from this study accurately reflect daily practice. Of course, the population-based nature of this study also presents a potential risk of bias. Data on the extent of peritoneal burden, functional status of patients, BRAF and KRAS mutational status and other prognostic factors were not available in the NCR. Moreover, lead time bias might be expected as one could hypothesize that patients with PM in recent time periods were diagnosed at an earlier stage. However, this seems unlikely as accurate diagnostic tools for PM are still lacking and peritoneal tumor deposits are still difficult to detect with currently available imaging techniques.[27,28]. This is also illustrated by the fact that the relative proportion of patients presenting with PM remained stable in the last two decades.

Conclusion

In this population based study, survival of patients with PM increased significantly over time and this seems to be related to a multi-disciplinary approach in treating these patients incorporating both modern systemic regimens and loco-regional surgical procedures. Therefore, in spite of the lack of data from randomized trials, patients with PM should be considered for multidisciplinary treatment whenever possible.

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Chapter 10

Summary and general discussion

In this chapter, the main findings of the studies performed in this thesis are summarized and subsequently discussed in a broader context. Next, several methodological issues are discussed that should be considered when interpreting findings of the studies presented in this thesis. Future direction and implications for clinical practice and future research are discussed as well.

Summary of results

The research underlying this thesis aimed to bridge the gap between clinical studies and daily practice, by providing insight into the real-world use, tolerability and effectiveness of the various systemic treatment options among unselected colorectal cancer patients.
The main objectives of the studies described in this thesis were:

- To provide insight in the everyday use and tolerability of adjuvant chemotherapy regimens and its impact on the palliative systemic treatment of metastases in patients with colon cancer (part I).
- To assess the daily-based use and impact of age on the palliative systemic treatment of patients with metachronous metastases from primary resected colorectal cancer (part II).
- To evaluate the role of currently available treatment options in colorectal cancer patients with peritoneal metastases (part III).

Part I of this thesis started by evaluating the intensity and tolerability of the most commonly used adjuvant chemotherapy regimens in unselected elderly stage III colon cancer patients (**chapter 2**). For this study, additional data was collected within the Netherlands Cancer Registry for all stage III colon cancer patients aged ≥70 years diagnosed in the ten hospitals in the southeast part of the Netherlands between 2005 and 2012. Of the patients who were treated with adjuvant chemotherapy, a large majority received capecitabine-oxaliplatin (CAPOX) or capecitabine monotherapy (CapMono). In the most recent study period (2011-2012), the proportion of CAPOX and CapMono versus other regimens was as high as 98%. Patients receiving CAPOX less frequently completed all planned cycles (33% vs. 55%) and received a lower median cumulative dosage of capecitabine (163,744mg/m^2 vs. 189,195mg/m^2) compared to patients receiving CapMono. Besides, CAPOX was associated with significantly more grade III-V toxicity than CapMono (54% vs. 38%). With CAPOX, the most common toxicities were gastrointestinal (mainly nausea/vomiting and diarrhoea, 29%), haematological (14%), neurological (i.e. neuropathy, 11%) and other toxicity (mainly fatigue, 13%). With CapMono, dermatological (i.e. hand-foot syndrome, 17%), gastrointestinal (mainly diarrhoea, 13%) and other toxicity (mostly fatigue, 11%) were the most common. In general, toxicity that occurred rapidly (such as gastrointestinal toxicity) was associated with a lower median number of cycles and cumulative dosage received. Other toxicity that appeared in a later stage during the treatment course (such as hand-foot syndrome and neuropathy) was cumulative and did not result in lower median number of cycles and cumulative dosages received.
In **chapter** 3, insight was provided into the impact of prior adjuvant chemotherapy on the subsequent use of different types of palliative chemotherapy for the treatment of metachronous metastases from colon cancer. In the current era of modern adjuvant chemotherapy, treatment of recurrent metastatic colon cancer presents clinicians with significant challenges. In this study with

a consecutive series of 224 colon cancer patients with metachronous metastases, we found that oncologists' choice of first-line palliative chemotherapy was significantly influenced by prior adjuvant therapy. Overall, 111 patients (50%) were previously exposed to adjuvant chemotherapy. Prior adjuvant therapy was associated with a lower odds for treatment with first-line combination chemotherapy (mostly oxaliplatin-based) if metastases occurred <1 year compared to no prior adjuvant therapy (OR 0.3, 95% CI 0.13-0.89), but no such differences were observed if metastases developed > 1 year after primary tumour diagnosis (OR 0.6, 95% CI 0.30-1.14).

In **Part II** of this thesis we studied the everyday use, tolerability and efficacy of palliative systemic therapy in unselected patients with metachronous metastases from colorectal cancer, an underreported topic in population based studies as data collection on recurrences is very time consuming and costly. Additional data on the development and treatment of recurrences was collected within the Netherlands Cancer Registry for all stage I-III colorectal cancer patients diagnosed between 2003-2008 in the ten hospitals in the southeast part of the Netherlands (n=5,671).
In **chapter 4**, we provided a reflection on the everyday use of bevacizumab over the period in which this targeted agent was adopted as standard first-line therapy in the Netherlands. The study demonstrated significant inter-hospital differences in the prescription of bevacizumab, with proportions varying from 36% to 80%. Overall, approximately half of the patients (51%) received additional bevacizumab. In a multivariable regression analysis, several factors were shown to influence the probability to receive additional first-line bevacizumab. Patients who received first-line combination chemotherapy (CAPOX/FOLFOX in 97%) were more likely to receive bevacizumab than patients who received single-agent chemotherapy (OR 9.9, 95 % CI 5.51-18.00). Besides, the odds for treatment with bevacizumab was higher for patients diagnosed with metastases in a recent time period than patients diagnosed with metastases shortly after the introduction of bevacizumab in Dutch guidelines (2005-2006). The probability to receive bevacizumab was lower for patients with ≥2 comorbidities than patients without comorbidity (OR 0.4, 95 % CI 0.21–0.81), but no association was observed between age and the use of bevacizumab. However, elderly patients (≥75 years) were less likely to receive combination chemotherapy (OR 0.2, 95 % CI 0.11–0.30) and therefore indirectly less susceptible for treatment with bevacizumab. Besides reflecting on usage patterns, the study investigated survival outcomes with the use of bevacizumab in everyday clinical practice and demonstrated that the addition of bevacizumab to palliative chemotherapy was associated with an improved median overall survival, from 14 months to 22 months. This effect remained present after adjustment for patients- and tumour characteristics and the prescribed chemotherapeutic regimen (HR 0.6, 95 % CI 0.45-0.73), also when additional efforts were made to limit potential endogeneity bias (propensity score matched analysis, HR 0.3; 95% CI 0.14-0.79).
Decisions on the optimal management for the growing number of elderly metastatic colorectal patients poses significant challenges to cancer specialists. In **chapter 5**, we provided insight into

the impact of age on palliative systemic therapy in patients with metachronous metastases from colorectal cancer, in order to optimize the decision-making process. The study showed a clear decline in the use of palliative systemic therapy with increasing age, in particular after the age of 75 years. Especially in these patients (≥75 years), there was a remarkable variation in the use of palliative systemic therapy between hospitals (17%-63%, p<.05). Overall, patients aged ≥75 years were less likely to receive combination-chemotherapy than single-agent chemotherapy. Even in selected elderly patients, first-line treatment with CAPOX was associated with less cycles (51% ≤3 oxaliplatin cycles, 43% ≤3 capecitabine cycles) and lower cumulative dosages of both cytostatic agents compared to younger patients, although initial dosages were similar. With single-agent fluoropyrimidine therapy (CapMono), however, no differences were observed in either the number of received cycles or the cumulative dosage, despite even lower starting dosages in elderly patients (2,414 mg/m^2/d <75 years, 1,992 mg/m^2/d ≥75 years).
With an ongoing view of metastatic colorectal cancer as a continuum of care, we were interested to evaluate the impact of age on further lines of treatment as well. In **chapter 6**, the age-related systemic treatment and survival of patients with metachronous metastases from colorectal cancer was evaluated. Elderly patients mostly received first-line single-agent chemotherapy (often without additional targeted therapy) and only 26% of the patients aged ≥75 years received second-line treatment. In a multivariable logistic regression analysis, advanced age (≥75 years) was associated with a lower probability of receiving all active cytotoxic agents compared to patients aged <60 years at time of diagnosis of metastases (OR 0.2, 95% CI 0.10-0.77), which was the only predictor of death in a multivariable Cox regression analysis with adjustment for age and other relevant prognostic factors (HR 0.7, 95% CI 0.61-0.81).

In part **III** of this thesis, special focus was directed to the subset of colorectal cancer patients with peritoneal metastases (PM). Even though a relevant proportion of colorectal cancer patients develops PM, patients with PM are not frequently studied. In clinical trials, they are underrepresented or not included at all due to the difficulty of evaluating response to treatment. Compared to other metastatic sites, such as the liver, patients with PM are believed to benefit less from conventional chemotherapy. The role of novel systemic regimens including targeted therapy, is largely unknown.
In **chapter 7** of this thesis, the potential role of bevacizumab- the standard choice of targeted therapy in addition to first-line chemotherapy in metastatic patients- was evaluated in this particular subset of patients. All colorectal cancer patients with synchronous PM (stage IV) diagnosed between 2007 -2014 in the Netherlands were extracted from the Netherlands Cancer Registry. Only patients treated with palliative systemic therapy were included in the study (n=1,235). In total, 436 of the patients received additional bevacizumab (35%). Elderly patients and patients with PM from colonic tumours were less likely to receive additional bevacizumab. The addition of bevacizumab

to palliative chemotherapy was associated with an improved overall median survival of 11 versus 7.5 months (p<.0001), in both patients with isolated PM and those with concomitant extra-peritoneal metastases The improvement remained present after adjustment for patient and tumour characteristics (HR 0.7, 95% CI 0.64-0.83).

In **chapter 8,** we evaluated the use of another, potentially even curative, treatment modality for PM being cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Population-based studies providing data on the percentage of PM patients being treated with CRS-HIPEC and characterization of these patients have been lacking. Therefore, the aim of this study was to evaluate trends in the use of CRS-HIPEC in the Netherlands where CRS-HIPEC was introduced about 20 years ago. The trends in the Netherlands since then may provide important information on the amount of PM patients being potentially eligibly for this treatment modality in countries where HIPEC was introduced more recently. Between 2005 and 2012, all patients diagnosed with synchronous PM of colorectal cancer were extracted from the Netherlands Cancer Registry. Of the total number of 4,430 patients, 6.4% underwent treatment with CRS-HIPEC. There was a significant increase over time, from 3.6% in 2005-2006 to 9.7% in 2011-2012. The study confirmed the presence of stringent patient selection, despite the lack of detailed information on CRS-HIPEC criteria due to the nature of the population-based study. Several factors, including age, period of diagnosis, differentiation grade and the presence of liver metastases were shown to influence the probability of treatment with CRS-HIPEC. Overall, CRS-HIPEC was associated with an overall median survival exceeding 32 months.

Despite the ongoing improvements in treatment modalities for PM, the dogma of PM as an untreatable disease remains. In **chapter 9**, we intended to challenge this dogma of PM as an untreatable disease, by evaluating trends in treatment and survival of PM patients diagnosed in the southeast part of the Netherlands over the past 2 decades. In this study, we included 1,661 patients and demonstrated that the overall median survival of PM patients more than doubled over time, from 6.0 months in 1995-2000 to 12.5 months in 2010-2014. We revealed a strong correlation between this improved survival over time and the increasing use of a multidisciplinary treatment, including both loco-regional surgery (CRS-HIPEC) and systemic therapy (chemotherapy +/- targeted therapy).

General discussion

As a result of the introduction of the national screening program on colorectal cancer and demographic developments, the absolute number of colorectal cancer patients is increasing rapidly.[1] With the evolution of systemic therapy and results of large randomized phase III trials, treatment guidelines on colorectal cancer changed, even though patients as seen in everyday clinical practice are often underrepresented or even excluded from these trials. In the current era of personalized cancer medicine, it is of utmost importance to bridge the gap between knowledge that is currently present between clinical studies and daily practice. Therefore, this thesis aimed to provide insight into the real-world use, tolerability and effectiveness of the various systemic treatment options among unselected colorectal cancer patients in whom there is a current lack of evidence.

Adjuvant chemotherapy for advanced (stage III) colon cancer

Even though adjuvant chemotherapy has been the standard of care for stage III colon cancer patients since 1990[2,3], there are still many uncertainties regarding its use in elderly patients due to the insufficient number of patients over 75 years participating in clinical trials.[11,12]

The probability to receive adjuvant chemotherapy following complete surgical resection has shown to decline with increasing age.[4-10] Reasons for non-treatment vary between hospitals, but mostly include the presence of comorbidities, frailty/poor performance score, patient refusal or surgical complications.[11,12] In case an elderly patient is treated with adjuvant chemotherapy, they are less often treated with oxaliplatin-containing regimens than their younger counterparts as the optimal regimen for elderly patients is still uncertain.[13-15] In the elderly, questions remain with respect to toxicity and the survival benefit of adding oxaliplatin to a 5-FU based adjuvant chemotherapy regimen. The available data are conflicting. Some studies have shown a potential benefit of oxaliplatin across all age groups[16,17], although results from the MOSAIC trial (biweekly infusional 5-FU/LV with and without oxaliplatin)[18] and the NSABP C-07 trial (bolus weekly FU and LV with and without oxaliplatin)[19] doubt the benefit of oxaliplatin in the elderly. In subgroup analysis of both trials, the significant disease-free survival benefit of adding oxaliplatin was present only in patients under the age of 70. This thesis with unselected elderly patients (aged ≥70 years) as seen in everyday clinical practice, demonstrates that if elderly stage III colon cancer patients receive an oxaliplatin-based regimen (CAPOX), they less frequently completed all planned cycles compared to patients receiving single-agent chemotherapy (CapMono) with respectively 33% vs. 55% ($p<.0001$). Although the median number of capecitabine cycles did not differ between these regimens, the median cumulative dosages of capecitabine was lower for patients who received CAPOX (163,744 mg/m^2) compared to patients who received CapMono (189,195mg/m^2, $p<.001$). This might be counterproductive, since the main benefit of adjuvant treatment is derived from the fluoropyrimidine. Besides, our research shows that the incidence of severe toxicity (grade III-V) was significantly higher with CAPOX (54%) than with CapMono (38%, $p<.01$). Toxicity that occurred

rapidly – nausea, vomiting and diarrhoea – was associated with a lower median number of cycles and cumulative dosage derived. Other toxicity that occurred in a later stage during the treatment course (polyneuropathy, hand-foot syndrome) did not result in lower median number of cycles and cumulative dosages received, but may have influenced quality of life later on.[20,21] Chemotherapy-induced peripheral neuropathy (CIPN) is frequently encountered if oxaliplatin is used and previous studies demonstrated that it may persist even until 11 years after cessation of therapy.[22] According to our results, it may even influence the subsequent use of palliative chemotherapy if patients develop metachronous metastases. Prior adjuvant therapy was associated with a lower probability of subsequent combination-chemotherapy (mostly oxaliplatin-based) if metastases developed within 1 year after primary tumour diagnosis, which probably indicates the presence of troublesome neuropathy and the consideration of refractory disease in these patients.[23,24] All together, these results question the standard of oxaliplatin-containing adjuvant therapy in stage III elderly patients and indicate the need for the refinement of patient selection in elderly patients. Nowadays, evaluation of mismatch repair enzymes (MMR) should be considered, as tumours with microsatellite instability (MSI, the biologic footprint of MMR enzyme deficiency) have a favourable prognosis and appear to be resistant to fluoropyrimidines[25-27], but not to oxaliplatin-containing regimens[28]. In case of stage III MSI tumours, only oxaliplatin-containing chemotherapy should be offered.[29] In elderly patients, the MSI or MMR detection could be used as a tool in the decision of adjuvant therapy. In addition, a comprehensive geriatric assessment (CGA) may be useful to determine whether or not an individual elderly patient is a candidate for adjuvant therapy and to derive all patients with the appropriate adjuvant regimen, by balancing potential benefits and side effects of therapy.[30]

Palliative systemic therapy for metachronous metastatic colorectal cancer

Despite technologic advances in the surgical treatment of colorectal cancer and the implementation of (neo)adjuvant therapy, recurrence rates for initially non-metastasized colorectal cancer patients are still relatively high (20-75%)[31], depending on numerous factors such as tumour grade and the number of lymph nodes involved.[24] In the present thesis, the proportion of patients developing metachronous metastases after primary tumour resection for stage I-III colorectal cancer was as high as 18%. Even though curation may be achieved in some patients with localized metastatic disease[35,36], the majority of these patients (74%) had metastatic disease that was not considered suitable for potentially curative therapy. In these patients, palliative systemic therapy may be considered in an attempt to improve the quality and quantity of life. Nowadays, oncologists have a wide range of cytotoxic agents and regimens to chose for the treatment of advanced colorectal cancer. However, their optimal use and sequence in real-life practice remains unclear. Trials establishing the evidence for the various available systemic regimens generally do not include patients as seen in everyday clinical practice.

Since 2004, several targeted agents (bevacizumab, cetuximab and panitumumab) have been ap-

proved for the treatment of metastatic colorectal cancer following randomized clinical trials that established improvements in patient outcome.[32-34] Bevacizumab was FDA-approved and adopted as the standard of care in addition to first-line chemotherapy following the landmark publication by Hurwitz *et al* in which a survival benefit was demonstrated with irinotecan, bolus fluorouracil and leucovorin (IFL).[33] As a result, a rapid increase has been observed in the use of first-line bevacizumab.[35,36] This thesis with data from everyday clinical practice demonstrates bevacizumab as the most commonly used targeted agent in first-line treatment, representing approximately half of all first-line treatment initiations. However, the presence of a large variation between hospitals in the southern part of the Netherlands with regard to the use of bevacizumab indicates important differences in attitude and policy towards the use of this anti-vascular agent in clinical practice.

By the time of regulatory approval of bevacizumab, IFL was no longer considered the preferred first-line backbone regimen. Other regimens, including FOLFIRI and the European prevailing oxaliplatin-based regimen (FOLFOX), gradually replaced the IFL regimen. Even though several clinical trials[37-43] and large non-randomized prospective cohort studies[44-47] evaluated bevacizumab in combination with other chemotherapy regimens, they provided less convincing results compared with the AVF trial.[33] In the NO16966 trial, there was only a modestly longer progression free survival with the addition of bevacizumab to an oxaliplatin-based regimen (CAPOX or FOLFOX4, 9.4 vs. 8.0 months, p=.002) and no statistically significant improvement in overall survival (21.3 vs. 19.9 months, p=.077).[37] As a result, a gap between "believers" and "non believers" was created, resulting in differences in the use of bevacizumab. According to our thesis, the likelihood of bevacizumab was shown to depend strongly on the prescribed chemotherapeutic regimen. If a patient was considered a candidate for combination-chemotherapy (according to Dutch guidelines mostly oxaliplatin-based), bevacizumab was prescribed in approximately 70% of the cases. On the opposite, if single-agent chemotherapy was prescribed (mostly capecitabine), only 23% of the patients received bevacizumab, which is in line with results from observational cohort studies. [44,45,47] Consequently, advanced age was indirectly associated with a lower probability of treatment with bevacizumab. This observation reflects the lack of conclusive data on the risk/benefit ratio of bevacizumab in older patients. Even though two randomized trials demonstrated improved progression-free survival rates with the addition of bevacizumab to first-line single-agent chemotherapy (5-FU/LV or capecitabine), they failed to demonstrate a statistically significant survival benefit.[42,43] However, results of recent non-randomized studies suggest a significant benefit from the addition of bevacizumab to standard chemotherapy for elderly patients, comparable with that observed in younger patients.[48,49] Therefore, it is now believed that age alone should not be considered an absolute contraindication for the use of bevacizumab.

Patients aged ≥75 years represented more than 40% of the cases with non-resectable metachronous metastases. In line with prior population-based studies[13,48-52], we demonstrated a decrease in the likelihood of palliative systemic therapy with increasing age. The main decline was observed in

patients aged 75 years or more. In these patients, there was a significant inter-hospital variation in the prescription of palliative systemic therapy, which indicates the complexity of systemic therapy in the elderly. Clinical trials conducted in adult populations typically included younger patients, limiting the available evidence for elderly patients in treatment guidelines.[53] Therefore, most of the currently available evidence for elderly patients is derived from subgroup or pooled analyses of prospective clinical trials. However, these analyses are potentially biased by the relatively small sample size and the variable age criteria used to defined the elderly population. In particular in the heterogeneous subset of elderly patients, efforts should be made to help clinicians balancing potential side effects, tolerability and toxicity against the primary aim of treatment and its benefits. Even though first-line combination chemotherapy (±targeted therapy) has been associated with prolonged progression-free survival and overall survival in the general population[37,54-56], it should be questioned whether this derives the preferred option in elderly patients. In elderly patients, there is an increased incidence of physiological changes and comorbidities, which are risk factors for altered pharmacokinetics and pharmacodynamics, potentially leading to increased treatment-related toxicity.[13] Up to date, the results of clinical trials have been controversial. In the FOCUS2 trial, the addition of oxaliplatin to capecitabine/5-FU improved the overall response rate but failed to significantly improve progression-free survival in frail or not fit patients.[57] Besides, a more recent meta-analysis showed that combination-chemotherapy was associated only with a modest benefit in terms of progression-free survival, but no benefit in overall survival[58], even though the addition of intravenous chemotherapy has been associated with increasing adverse events.[59,60] As a result, this thesis showed that only a minority of the elderly patients as seen in everyday clinical practice received first-line combination chemotherapy (37%). More importantly, our thesis demonstrates that even if selected elderly patients were considered candidates for combination-chemotherapy (CAPOX), first-line treatment was discontinued earlier compared to younger patients, resulting in lower cumulative dosages of both cytostatic agents. With single-agent chemotherapy (CapMono), however, no such differences were observed in either the received number of cycles or the received cumulative dosage, despite lower starting dosages in elderly patients. Altogether, these results question the definition as first-line combination chemotherapy as the standard of care in elderly patients.

With an ongoing view as metastatic colorectal cancer treatment as a continuum of care, it has been hypothesized that, at least in a subset of metastatic colorectal cancer patients, the sequential use of active single agents might be preferable to initial combination chemotherapy. This could conceivably reduce overall toxicity, while providing a similar benefit to initial combination treatment.[61,62] In the present thesis, we indicate the complexity of such an approach in everyday clinical practice, with a large proportion of elderly patients, who often do not receive second-line treatment. Dropout rates as presented in this thesis were even higher than dropout rates reported in

prior research[63], reflecting the relatively large number of elderly patients as seen in everyday clinical care.[64] Besides, we demonstrated the total number of received cytotoxic agents to be the only factor associated with survival outcome. In the light of these results, attempts should be made to individually tailor treatment. In elderly patients (≥75 years), initial treatment with the highest potential of improving both survival and maintaining quality of life may be indicated, as most of these patients are not candidates for second-line treatment. Targeted therapy should be considered and not be out-ruled based on advanced age itself[51,65-67], especially since many elderly patients may not be candidates for intensive (combination)chemotherapy. In order to derive all elderly patients with an optimal treatment strategy, an individual evaluation of the benefit/risk ratio should be performed. Factors such as life expectancy, presence of comorbidities, performance status/frailty and patient's choice should be taken into account. Instruments such as geriatric assessments may be helpful to measure independent clinical predictors of morbidity and mortality.[30] Besides, when deciding on the dosage of fluoropyrimidine, an important consideration is the presence of dihydropyrimidine dehydrogenase (DPD) deficiency, encoded by the gene DPYD. DPD deficiency, expressed by the variants DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3, has been associated with increased risk for severe and life-threatening fluoropyrimidine-associated (haematological and gastrointestinal) toxicity[68,69]. Therefore, dose reductions of 50% for the first two variants and 25% for the latter variant are now recommended[69,70].

Treating peritoneal metastases from colorectal cancer

Peritoneal dissemination is a common and debilitating manifestation in patients with CRC.[71-73] The disease is characterized by the spread of tumour deposits throughout the peritoneal surface, which can ultimately invade any abdominal organ and lead to blockage of the lymphatic drainage system. Due to the fact that peritoneal metastases (PM) were thought to be relatively resistant to systemic chemotherapy[74] and results with palliative interventions were disappointing[75], patients with PM were considered to be virtually untreatable by many physicians. The present thesis, however, challenges the dogma of PM as an untreatable condition. Over the past 20 years, median overall survival rates for patients with PM doubled (from 6.0 to 12.5 months). This increase in overall survival was shown to be related to the increasing use of a multidisciplinary treatment, incorporating both modern systemic regimens and loco-regional surgical procedures (CRS-HIPEC).

Although the notion of PM as loco-regional tumour spread was raised already in the early nineties[76], aggressive loco-regional treatment modalities were not available until the beginning of the twentieth century. In 2003, a phase III randomized trial comparing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with standard palliative care provided beneficial survival rates with CRS-HIPEC (22.4 months vs. 12.6 months). [77,78] Since then, no new randomized data have become available. Nevertheless, the introduction of CRS-HIPEC has resulted in the increasing usage of CRS-HIPEC nationwide.[15,79] In the Netherlands – one of the first countries where

CRS-HIPEC was introduced about 20 years ago – we demonstrated an increase in the use of CRS-HIPEC from 3.6% in 2005-2006 to 9.7% in 2011-2012. Even higher rates may be expected nowadays, as proportions were even higher in 2010-2014 in the southeastern of the Netherlands (23%). In line with previous large case-studies demonstrating 5-year survival rates of over 30%[77,79,80], our thesis demonstrated median overall survival rates exceeding 32 months. Opponents, however, claim that these results may be primarily obtained by selection bias, with treatment being offered to relatively young patients in a good general condition with limited PM. Our thesis confirms the presence of stringent patient selection for CRS-HIPEC, which is of utmost importance to select patients who will benefit the most from this extensive treatment along with acceptable morbidity and mortality. However, we also showed that the survival in the entire population - regardless of treatment – doubled over the last two decades, a result being highly dependent on the intensified treatment with CRS and HIPEC together with systemic therapy. Over time, several attempts have been made to develop tools to assist clinicians in the decision about performing CRS and HIPEC, such as the Peritoneal Cancer Index (PCI), Peritoneal Surface Disease Severity Score (PSDSS)[81] and Colorectal Peritoneal Metastases Prognostic Surgical Score (COMPASS).[82] These tools, including previously identified prognostic factors such as the extent of PM, the presence of clinical symptoms and histopathological features of the primary tumour, may aid in predicting postoperative survival outcomes.[82-84]

Even though a substantial proportion of PM patients is receiving potentially curative treatment, the majority of PM patients will still not be considered candidates for extensive treatment and remain dependent on palliative systemic therapy. Prior research has shown that even with effective chemotherapy the prognosis of patients with PM remains worse compared to patients with metastases elsewhere.[85,86] Nevertheless, this thesis demonstrated an increasing use of palliative systemic therapy over time, also in patients with PM. The role of targeted therapy, however, still seems a topic of much debate as there were large inter-regional variations in the prescription of bevacizumab, the standard choice of targeted therapy in addition to first-line chemotherapy. This seems counterproductive, since in particular these patients may benefit from additional targeted therapy as there is an susceptibility of increased chemotherapy resistance in patients with PM. Besides, the present thesis demonstrated a potential survival benefit with the addition of bevacizumab, which is in line with previous literature.[87-89]

Methodological considerations

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

Strengths and limitations of the data sources

Netherlands Cancer Registry

The studies that are described in this thesis are based on data from the Netherlands Cancer Registry (NCR), or the southeast part of the NCR (formerly known as the Eindhoven Cancer Registry). The NCR routinely collects data on all newly diagnosed cancer patients in the Netherlands. Detailed information regarding patient and tumour characteristics, cancer diagnosis, stage and primary treatment are routinely available. Since 1995, the southeast of the Netherlands registers comorbidity at cancer diagnosis, which is unique as compared to other cancer registries worldwide.
Although data on systemic primary cancer therapy were obtained, no details were available on the type of agent, dosage and treatment regimen used. Besides, data on the development and treatment of recurrences was also not yet collected. These data were additionally collected for several studies included in this thesis (*chapter 1-6)*. A limitation is that information on the performance status of the patients was frequently missing from the medical files and could not be included. Besides, data regarding mutational status (KRAS/BRAF), MSI, the extensiveness of disease (tumour load) and reasons (not) too prescribe systemic therapy were also lacking.

Study design

All studies in this thesis had an observational design. The interval validity of population-based studies compared to randomized clinical trials (RCTs) is inferior, but the generalizability is better as it provides the opportunity of evaluating a large consecutive series of non-selected patients, as seen in everyday clinical practice. Therefore, the observational nature of population-based studies has the ability to provide an unique insight into the use, safety and effects of treatments in everyday clinical practice. Especially for subsets of patients who do not meet the eligibility criteria from RCTs, as addressed in this thesis, observational studies are of utmost importance. Nevertheless, several biases are inherent to population-based observational studies and should be considered when interpreting the results of the studies included in this thesis.

Bias and confounding

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

Selection bias

Selection bias may refer to either the selective recruitment of patients into the study who are not a representative of the population intended to be analysed, or to systematic differences between baseline characteristics of the groups that are compared in the study.

Attempts were made to limit the first type of selection bias by including a long-term series of consecutive patients in all studies. Data were extracted from the NCR, which collects data on all newly diagnosed cancer patients. Therefore, the NCR data will be a representative of the population as seen in everyday clinical practice. In several studies (*chapters 2-6,9)*, data were derived from the southeast area of the Netherlands (Eindhoven area), which comprises an area of 2.4 million inhabitants served by 10 community hospitals. Although no academic hospitals are included in this region, the data from the Eindhoven are believed to be representative for the total population of colorectal cancer patients. For part I and part II of this thesis (*chapters 2-6)*, additional data were collected for two subsets of patients in the Eindhoven area; all stage III colon cancer patients aged ≥70 years who underwent resection and were diagnosed between 2005 and 2012, and all primary resected stage I-III colorectal cancer patients who were diagnosed between 2003 and 2008. For the latter, data on the development and treatment of metachronous metastases were collected between 2010-2011, resulting a median time from primary diagnosis to data collection of 5.3 years (range 1.5-8.8 years). Prior research has shown that almost 90% of the metastases arises within 3 years after primary tumour diagnosis.[90-93] In both additional data collections, data were collected for all consecutive series of patients.

The second type of selection bias is present in all studies included in this thesis as patients were grouped according to (systemic) therapy receipt. There were significant differences on several patients and tumour characteristics such as age and comorbidity between treatment groups. In order to limit this potential form of selection bias, we used statistical techniques to adjust for these imbalances between treatment groups. Statistical regression models were used to produce estimates of treatment effects adjusted for relevant patient and tumour characteristics (covariates). Of course, we could only adjust for the patient and tumour characteristics that were available in the NCR. Due to the lack of information on other prognostic factors, this analysis alone cannot fully out rule selection bias. Therefore, we also used propensity score matching if possible (*chapter 4)*. In this study, the propensity score was estimated using logistic regression model in which bevacizumab was the variable of interest and the independent variables were factors potentially associated with the use of bevacizumab (similar to variables taken into account in the multivariable logistic regression analysis). Patients were matched within tight bounds of the propensity scores (probability could vary by no more than 1%), to create two groups comparable on baseline characteristics. Crude survival estimates were calculated and multivariable Cox regression analysis were performed in both the total study population and propensity score matched sample to evaluate the independent effect of additional bevacizumab on the risk of death.

Immortal time bias

Some studies presented in the present thesis may have been exposed to immortal time bias, since time between cancer diagnosis (primary cancer diagnosis, metachronous metastases diagnosis) and treatment initiation was taken into account in survival analyses (*chapters 4&6)*. In this period, death could not occur, since patients must have been alive to receive treatment. Therefore, a period of 'immortal time' was present. This bias may result in an overestimation of the effect of a treatment. To minimize this immortal time bias, the starting points for survival analyses were chosen as adequately as possible. For studies on metachronous metastases (*chapter 4-6)*, the date of first metachronous metastases diagnosis was used to evaluate overall survival according to treatment modality. Unfortunately, no data were available on the date of the receipt of specific therapy, and therefore a more appropriate time-dependent Cox regression analysis was not possible.

Stage migration

When interpreting trends in treatment and survival (*chapter 9)*, one should take potential stage migration and related forms of bias (lead time bias) into account. Hypothetically, improved diagnostic techniques in a later period may lead to detection of disease that would have been missed in an earlier period. The result is that a person with extensive disease is counted in a "more extensive stage" in the later period, whereas in the earlier period such a person would have been counted in a "less extensive" stage. The effect is an apparent improved survival within each stage over time, even though no actual improvement has taken place. In *chapter 9,* however, this seems unlikely as accurate diagnostic tools for PM are still lacking and peritoneal tumour deposits are still difficult to detect with currently available imaging techniques. This was also illustrated by the fact that the relative proportion of patients presenting with PM remained stable in the last two decades.

Implications of the main findings and directions for the future

Implications for clinical practice

In the current era of evolving systemic therapy and the shift towards personalized cancer therapy, medical specialists will be increasingly challenged with the gap of knowledge between clinical studies and daily practice. Based on the findings of this thesis, a number of recommendations on the use of the various available systemic regimens among unselected colorectal cancer patients are formulated.

Part I: Adjuvant treatment and the treatment of metastases
When deciding on adjuvant treatment in elderly stage III colon cancer patients (aged ≥ 75 years), an oxaliplatin-based regimen should not be considered the standard regimen. The choice to prescribe an oxaliplatin-based regimen should be made on an individual level, including patient and tumour related prognostic factors. Tumour related prognostic factors include the number of involved lymph nodes and the mismatch repair status (MMR). Patient related factors – including performance score, comorbidities, polypharmacy, activity of daily living, nutritional status and patients preference (i.e. with regard to preservation of independence or functional status) – should be taken into account to balance potential benefits and side effects of therapy.

Part II: The palliative systemic treatment of metachronous metastases
In patients with unresectable metachronous metastases, palliative systemic therapy including both chemotherapy and targeted therapy should be considered. Advanced age itself should not be regarded an absolute contra-indication for palliative systemic therapy. First-line combination-chemotherapy, however, does not derive the preferred first-line treatment for elderly patients (≥75 years). In particular in elderly patients, decisions regarding the prescribed (first-line) regimen should be individually tailored and discussed as most of the elderly patients are not candidates for second line treatment. In the case of extensive disease and the risk of rapid deterioration, attempts should be made to derive individual patients with initial treatment with the highest potential of improving both survival and maintaining quality of life. In particular in elderly patients, a combination of single agent chemotherapy with the addition of targeted therapy should be considered, since most patients will not be candidates for intensive combination-chemotherapy (with or without targeted therapy).

Part III: The treatment of peritoneal metastases
Colorectal cancer patients with peritoneal metastases should no longer be regarded as untreatable. In selected patients with isolated peritoneal metastases (or with limited liver metastases), CRS-HIPEC should be considered. Attempts should be made to predict which patients will benefit the most from this extensive treatment, along with acceptable morbidity and mortality. Additional tools may be helpful. In the remaining subset of patients with peritoneal metastases who are not deemed candidates for CRS-HIPEC, one should consider palliative systemic treatment whenever possible, including both chemotherapy and targeted therapy.

Implications for further research
Unselected colorectal cancer patients need to become the focus of future colorectal cancer research as the gap of knowledge between clinical studies and everyday practice needs to be

bridged in order to realize personalized cancer therapy for all advanced colorectal cancer patients. Efforts should be made to design clinical trials and prospective observational studies for the frail and elderly patients. In these studies, patient characteristics should be described extensively (i.e. performance score, comorbidity) and appropriate outcomes should be evaluated, including quality of life. Future efforts are needed to discover predictors of individual response, prognosis and tolerability. A focus should be derived on the potential role of targeted therapy in elderly patients, who are often not candidates for intensive combination-chemotherapy or multiple lines of chemotherapy. For patients with peritoneal metastases, future efforts are needed to establish the role of the various available systemic regimens in addition to loco-regional treatment modalities (CRS-HIPEC) and to derive insight into the potential role of palliative systemic therapy in these patients.

Concluding remarks

There is a current gap between clinical studies and everyday clinical practice, which will expand even further in the near future due to demographic developments and the ongoing evolution of systemic therapy. This thesis provides accurate insight into the actual state of care of advanced colorectal cancer patients in real-life practice and provides evidence on the use, tolerability and effectiveness of the various systemic treatment options. It was shown that oxaliplatin-based regimens should not be considered the standard (adjuvant and first-line) regimen for elderly patients. An individual evaluation of the benefit/risk ratio should be performed, both in the adjuvant and metastatic setting. In particular in elderly patients, who often are not candidates for intensive chemotherapy, consideration of additional targeted therapy is warranted. If metastases are defined to the peritoneum, patients should no longer be regarded as untreatable. Treatment modalities including CRS-HIPEC and systemic therapy (chemotherapy + targeted therapy) should be considered if possible.

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Nederlandse samenvatting

Dutch summary

Inleiding

Door de vergrijzing van de bevolking, de verhoogde levensverwachting en de invoer van het landelijke bevolkingsonderzoek neemt het aantal mensen dat dikkedarmkanker heeft sterk toe, van maar liefst 7,100 in 1990 naar 15,549 in 2015. Oudere patiënten vormen een groot deel van de dikkedarmkanker patiënten; een derde van de patiënten is 75 jaar of ouder.

Ondanks dat een groot deel van de patiënten ten tijde van de diagnose dikkedarmkanker nog geen uitzaaiingen heeft (80%), zal een aanzienlijk deel van de patiënten deze alsnog later ontwikkelen ("metachrone uitzaaiingen"). Voorheen impliceerde de aanwezigheid van uitzaaiingen dat genezing niet meer mogelijk was. Omdat palliatieve behandelopties gering waren, was de algehele prognose beperkt.

Gelukkig zijn er de afgelopen decennia aanzienlijke vorderingen gemaakt in de behandeling van uitgezaaide dikkedarmkanker. Waar we voorheen maar één soort chemotherapie voor handen hadden, hebben we nu meerdere chemotherapie middelen welke we kunnen combineren of achtereenvolgens kunnen geven. Tevens heeft de opkomst van "doelgerichte middelen" (ook wel "targeted agents" genoemd) voor een nog breder scala aan "systemische" behandelopties gezorgd. Van deze middelen is de werkzaamheid onderzocht in verschillende klinische studies, op grond waarvan ze inmiddels worden ingezet bij de alledaagse behandeling van uitgezaaide en gevorderde dikkedarmkanker.

Echter, klinische studies omvatten veelal niet de patiënten zoals deze in de alledaagse praktijk worden gezien. Oudere patiënten, patiënten die in een beperkte conditie verkeren en patiënten met uitzaaiingen die moeilijk te vervolgen zijn (bv. buikvliesuitzaaiingen), zijn ondervertegenwoordigd of zelfs geheel ontbrekend in klinische studies. Derhalve beschikken we over weinig informatie omtrent het gebruik, de verdraagzaamheid en effectiviteit van de verschillende systemische behandelopties bij juist deze groep patiënten.

Doel van dit proefschrift

Het doel van dit proefschrift is om de vertaalslag te leggen tussen klinische studies en de dagelijkse praktijk. Het verschaft inzicht in het alledaagse gebruik, de verdraagbaarheid en effectiviteit van de diverse systemische behandelopties bij ongeselecteerde patiënten met uitgezaaide dikkedarmkanker, zoals deze in de dagelijkse praktijk worden gezien.
De belangrijkste doelstellingen van dit proefschrift zijn als volgt:

- Inzicht verschaffen in het alledaagse gebruik en de verdraagbaarheid van adjuvante chemotherapie en de invloed daarvan op de behandeling van metachrone uitzaaiingen van dikkedarmkanker (deel I)

- Het alledaagse gebruik en de invloed van leeftijd op het gebruik van palliatieve systemische therapie onderzoeken bij patiënten met metachrone uitzaaiingen van dikkedarmkanker (deel II).
- De rol evalueren van huidige behandelingsmethoden voor dikkedarmkanker patiënten met buikvlies uitzaaiingen (deel III).

Belangrijkste bevindingen

In **deel I** van dit proefschrift is bekeken hoe de meest gebruikte adjuvante chemotherapie schema's worden verdragen door oudere dikkedarmkanker patiënten met lymfeklieruitzaaiingen (stadium III, **hoofdstuk 2**). Voor deze studie werden alle 70+ patiënten meegenomen die tussen 2005 en 2012 de diagnose stadium III dikkedarmkanker kregen in zuidoost Nederland. Het overgrote deel van de patiënten dat werd na behandeld met chemotherapie bleek een behandeling te hebben gehad met capecitabine alleen (CapMono), of met capecitabine in combinatie met oxaliplatin (CAPOX). Het gebruik van CAPOX bleek geassocieerd te zijn met meer bijwerkingen dan CapMono. Daarnaast bleken patiënten die CAPOX kregen minder vaak de gehele behandeling te voltooien dan patiënten die CapMono kregen. Bijwerkingen die vroeg optraden (zoals diarree, misselijkheid/braken) bleek geassocieerd te zijn met een kortere duur en lagere dosering, terwijl andere bijwerkingen die later optraden (hand-voet syndroom, neuropathie) niet leken te zorgen voor een lagere dosering of kortere duur.

In **hoofdstuk 3**, werd vervolgens bekeken wat de invloed was van een eerdere behandeling met adjuvante chemotherapie op de keuze van palliatieve chemotherapie wanneer er later uitzaaiingen optraden (metachrone uitzaaiingen). In deze studie met 224 dikkedarmkanker patiënten bleek dat maar liefst de helft eerder adjuvante chemotherapie had gehad. De keuze van palliatieve systemische therapie bleek te worden beïnvloed door eerdere nabehandeling met chemotherapie (adjuvante chemotherapie). Deze patiënten bleken een kleinere kans te hebben om te worden behandeld met combinatie-chemotherapie (meestal oxaliplatin-bevattend), maar alleen wanneer uitzaaiingen optraden binnen 1 jaar na de oorspronkelijke diagnose. Wanneer uitzaaiingen later (na 1 jaar) waren ontstaan, werd dit effect niet gezien.

In **deel II** van dit proefschrift onderzochten we het alledaagse gebruik, de verdraagzaamheid en de effectiviteit van de verschillende palliatieve systemische behandelopties bij dikkedarmkanker patiënten met metachrone uitzaaiingen. Tot op heden is dit een veelal onderbelicht onderwerp, aangezien het vastleggen van gegevens over metachrone uitzaaiingen erg tijdrovend is. Voor deze studie werden additionele gegevens verzameld over de ontwikkeling en behandeling van metachrone uitzaaiingen, voor patiënten die tussen 2003-2008 werden gediagnosticeerd met dikkedarmkanker in zuidoost Nederland (n=5,671).

In **hoofdstuk 4**, verschaften we een reflectie van het alledaagse gebruik van bevacizumab (een doelgericht middel dat vaatgroei tegen gaat) in de periode waarin dit middel werd aangenomen als de standaard behandeling voor uitgezaaide dikkedarmkanker in Nederland. Deze studie toonde aanzienlijke verschillen in het gebruik van bevacizumab tussen ziekenhuizen in de regio zuidoost Nederland, met percentages variërend tussen de 36% en 80%. Over het geheel kreeg ongeveer de helft (51%) van de patiënten bevacizumab. Met name patiënten die geschikt werden geacht voor combinatie-chemotherapie (meerdere middelen chemotherapie) bleken bevacizumab te krijgen. Alhoewel oudere patiënten niet direct minder vaak bevacizumab kregen, bleken zij wel indirect minder waarschijnlijk om bevacizumab te krijgen aangezien zij minder vaak een kandidaat waren voor combinatie-chemotherapie. De studie toonde ook dat, zelfs na correctie voor vertekenende factoren, patiënten die zowel chemotherapie als bevacizumab kregen langer leefden dan patiënten die geen bevacizumab kregen.

Juist de behandeling van oudere patiënten met uitgezaaide dikke darmkanker is in de praktijk lastig en stelt de medisch specialist voor een dilemma. In **hoofdstuk 5**, onderzochten we daarom de invloed van leeftijd op de keuze van palliatieve chemotherapie voor de behandeling van metachrone uitzaaiingen van dikkedarmkanker. We vonden een evidente afname in het gebruik van palliatieve systemische therapie met het stijgen van de leeftijd, waarbij de grootste afname leek plaats te vinden vanaf een leeftijd van 75 jaar. Vooral bij deze patiënten groep (75+) zagen we een aanzienlijke variatie in het gebruik van palliatieve systemische therapie tussen de ziekenhuizen, variërend van 17% tot 63%. Oudere patiënten bleken niet alleen minder vaak palliatieve systemische therapie te krijgen, maar kregen ook minder vaak combinatie-chemotherapie (meerdere middelen) dan monotherapie (1 middel). Zelfs bij de zorgvuldig geselecteerde groep oudere patiënten die wel combinatie-chemotherapie kregen, zagen we dat er minder kuren en lagere doseringen werden gegeven van beide middelen. Wanneer één middel werd gegeven (CapMono), zagen we geen verschil in het aantal kuren of de dosering, terwijl startdoseringen wel lager waren bij oudere patiënten dan bij jongere patiënten.

In **hoofdstuk 6**, werd de impact van leeftijd op de totale behandeling en overleving onderzocht. Oudere patiënten bleken niet alleen vaker te starten met monotherapie - vaak zonder doelgerichte middelen - maar bleken ook vaak niet toe te komen aan een vervolg behandeling (tweede lijn). Een gevorderde leeftijd bleek geassocieerd met een kleinere kans op het ontvangen van alle middelen tijdens het beloop van de ziekte, terwijl dit de enige voorspeller bleek te zijn van overleving.

In **deel III** werd een speciale focus gelegd op de groep dikkedarmkanker patiënten met uitzaaiingen naar het buikvlies (peritoneale metastasen; PM). Ondanks dat een groot deel van de patiënten met dikkedarmkanker buikvlies uitzaaiingen ontwikkelt, zijn er maar weinig studies naar deze groep patiënten omdat het moeilijk is om te evalueren wat het effect van een behandeling is.

Met beeldvorming zijn buikvliesuitzaaiingen namelijk moeilijk te zien. Vergeleken met andere uitzaaiingen, zoals lever uitzaaiingen, lijken buikvliesuitzaaiingen minder baat te hebben bij een behandeling met conventionele chemotherapie. De rol van nieuwe behandelschema's, waarin doelgerichte middelen zijn opgenomen, is veelal onbekend.

In **hoofdstuk 7** van dit proefschrift onderzochten wij de rol van bevacizumab (de standaard 1e keus) in toevoeging aan chemotherapie bij deze specifieke patiënten groep. Voor deze studie namen wij alle dikkedarmkanker patiënten mee die tussen 2007 en 2014 in Nederland werden gediagnosticeerd met naar het buikvlies uitgezaaide dikkedarmkanker (1,235). In totaal kreeg ongeveer een derde van de patiënten bevacizumab. Oudere patiënte bleken minder vaak bevacizumab te krijgen. De toevoeging van bevacizumab aan chemotherapie bleek te zorgen voor een verbeterde overleving, van 7.5 maand naar 11.0 maanden, bij zowel patiënten met alleen buikvliesuitzaaiingen als bij patiënten met zowel buikvliesuitzaaiingen als andere uitzaaiingen.

In **hoofdstuk 8**, werd een andere – potentieel curatieve - behandelingsoptie voor buikvliesuitzaaiingen geëvalueerd. Dit betreft een behandeling waarbij een operatie wordt verricht om alle zichtbare tumor te verwijderen ("cytoreductive surgery"; CRS) en waarna de buik wordt gespoeld met een verwarmde chemotherapie-vloeistof (HIPEC). Deze behandeling (CRS-HIPEC) bleek in toenemende mate te zijn gebruikt in Nederland over de afgelopen 20 jaar. Tussen 2005-2006 kreeg 3.6% van de patiënten met buikvliesuitzaaiingen deze behandeling, terwijl het percentage in 2011-2012 al 9.7% was. Alleen strikt geselecteerde patiënten ondergingen de behandeling. Verschillende factoren zoals leeftijd, periode van diagnose, de aanwezigheid van lever uitzaaiingen beïnvloedde de kans op het ondergaan van CRS-HIPEC. Bij deze groep patiënten resulteerde een behandeling met CRS-HIPEC in een overlevingsduur van meer dan 32 maanden.

Ondanks dat er de afgelopen decennia allerlei behandelingen voor buikvliesuitzaaiingen zijn verschenen, blijft veelal het dogma bestaan dat buikvliesuitzaaiingen onbehandelbaar zijn. In **hoofdstuk 9**, trachtten wij dit dogma te doorbreken. In deze studie evalueerden wij de behandeling en overleving van patiënten met buikvliesuitzaaiingen van dikkedarmkanker over de afgelopen 2 decennia. We namen de gegevens van 1,661 patiënten mee en zagen dat de overleving meer dan verdubbelde (van 6.0 maanden in 1995-2000 naar 12.5 maand in 2010-2014). Daarnaast bleek deze verbeterde overleving sterk samen te hangen met de invoer van een multidisciplinaire aanpak, waarbij zowel CRS-HIPEC als systemische therapie (chemotherapie en doelgerichte middelen) een rol lijken te spelen.

Concluderende opmerkingen

In de huidige tijd met continue ontwikkelingen in behandelmogelijkheden en de behoefte aan geïndividualiseerde zorg, worden medisch specialisten steeds meer geconfronteerd met het gebrek aan kennis tussen klinische studies en de dagelijkse praktijk. Dit proefschrift verschaft inzicht in het alledaagse gebruik, de verdraagzaamheid en effectiviteit van diverse sys-

temische behandelmethoden bij uitgezaaide dikkedarmkanker patiënten, zoals deze in de dagelijkse praktijk worden gezien. Het toont dat oxaliplatin-bevattende schema's niet de standaard zouden moeten zijn bij oudere stadium III dikkedarmkanker patiënten. Daarnaast toont het dat men bij oudere patiënten met metachrone uitzaaiingen van dikkedarmkanker, die vaak geen kandidaat zijn voor intensieve combinatie-chemotherapie of tweedelijns behandeling, ook de potentiele rol van doelgerichte middelen in acht zou moeten nemen. Tenslotte laat het onderzoek uit dit proefschrift zien dat patiënten met uitzaaiingen naar het buikvlies niet als onbehandelbaar beschouwd moeten worden. Behandelopties zoals CRS-HIPEC, systemische therapie (chemotherapie, doelgerichte middelen) zouden overwogen moeten worden.

List of publications

Publications included in this thesis

1 van Erning FN, Razenberg LG, Lemmens VE, et al. Intensity of adjuvant chemotherapy regimens and grade III-V toxicities among elderly stage III colon cancer patients. *Eur J Cancer*. 2016; **61**: 1-10.

2 Razenberg LG, van Erning FN, Pruijt HF, et al. The impact of age on first-line systemic therapy in patients with metachronous metastases from colorectal cancer. *J Geriatr Oncol*. 2016 [Epub ahead of print].

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Curriculum vitae auctoris

Lieke G.E.M. Razenberg was born on the 12th of July 1990 in Breda, the Netherlands. In 2008, she finished secondary education at the Jacob Roeland Lyceum in Boxtel (cum laude). Subsequently, she started medical school at Maastricht University. In 2009, during her Bachelor, she enriched her scientific skills by participating in the Honours Programme Research. For the study year 2009/2010 she received a Top 3% Award. After receiving her Bachelor's degree in Medicine in 2011 and finishing her regular internships, she conducted her scientific internship. This internship focused on the treatment of peritoneal metastases from colorectal origin, under supervision of dr. Geert-Jan Creemers and Ignace H.J.T. de Hingh and was provided with data from the Netherlands Comprehensive Cancer Organisation (IKNL). In 2014, after receiving the Master's degree in Medicine, she started her PhD project at the Netherlands Comprehensive Cancer Organization, location Eindhoven, on the gap of knowledge that is currently present between clinical studies an the everyday systemic treatment of advanced colorectal cancer patients. After three months of fulltime research, she started working as a resident (ANIOS) in Internal Medicine – Oncology at the Catharina Hospital for 3 days a week. By combining both medical practice and her PhD project, she was able to derive a better insight into her research. After completing her PhD, she started her specialty training in the Catharina Hospital on November 1st 2016 (head: dr. C.J.A.M. Konings).

PhD Portfolio

Name PhD student: Lieke G.E.M. Razenberg
Erasmus MC department: Public Health / Netherlands Comprehensive Cancer Organisation
PhD period: July 2014 – November 2016
Promotor: Prof.dr. V.E.P.P. Lemmens
Supervisor: Dr. G.J. Creemers
Dr. I.H.J.T. de Hingh

	Year	Workload Hours/ ECTS
Courses		
'Cursus Statistiek', Catharina Ziekenhuis	2013	20
'Wetenschappelijke Integriteit', Erasmus MC	2016	8
Seminars and workshops		
't Wasven 'colorectaal carcinoom', Catharina Ziekenhuis	2013	4
'Het colorectaal carcinoom nieuwe stijl', MMC	2014	4
Wetenschapsavond, Catharina Ziekenhuis	2014	4
't Wasven 'ins and outs of the anorectum', Catharina Ziekenhuis	2014	4
GI symposium, IKNL	2014	4
Wetenschapsavond, Catharina Ziekenhuis	2015	4
't Wasven 'ulcuslijden', Catharina Ziekenhuis	2015	4
Wetenschapsavond, Catharina Ziekenhuis	2016	4
Presentations and teaching		
2 Poster presentations, 9th International Congress on Peritoneal Surface Malignancies (PSOGI)	2014	64
1 Poster presentation, ESMO	2014	32
1 Oral presentation, Co-creatie voor Medisch Oncologen	2014	64
1 Oral presentation, Colorectaal scholing IKNL datamanagers	2015	32
1 Oral presentation, Roche	2016	32
1 Poster presentation, 10th International Congress on peritoneal Surface malignancies (PSOGI)	2016	32
Conferences		
6th International symposium on Abdominal Metastatic Cancer	2014	24
ESSO	2014	24
9th International Congress on Peritoneal Surface Malignancies (PSOGI)	2014	24
ESMO	2014	24
Other		
GI werkgroep, IKNL	2014-2016	40
ANIOS oncologie, Catharina ziekenhuis	2014-2016	2300
Total		2752