Adjuvant Chemotherapy Among Elderly Colon Cancer Patients

from gut feeling towards evidence-based use in clinical practice

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IKNL Netherlands comprehensive cancer organisation

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from gut feeling towards evidence-based use in clinical practice

Adjuvante chemotherapie bij oudere patiënten met dikkedarmkanker

van onderbuikgevoel naar wetenschappelijk bewijs voor gebruik in de klinische praktijk

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General introduction

Changes in the age structure of the Dutch population

Elderly form the fastest growing segment of the population. The post-war baby boom, which lasted from 1946 until approximately 1970, brought on a demographic shift leading to a rapid increase in the population of elderly in the Netherlands (figure 1). On top of that, life expectancy is also increasing: the remaining life expectancy for a 70-year old man increased from 12 years in 1990 to 16 years in 2015. Similarly, for a 70-year old female, remaining life expectancy increased from 16 years in 1990 to 18 years in 2015[1]. Both factors contribute to an increase in the proportion of elderly over time. In the year 1990, the proportion of persons aged 70 years or older was 9%. This proportion has increased to 12% in 2015 and is projected to rise further to a peak of 21% by the year 2040[1].

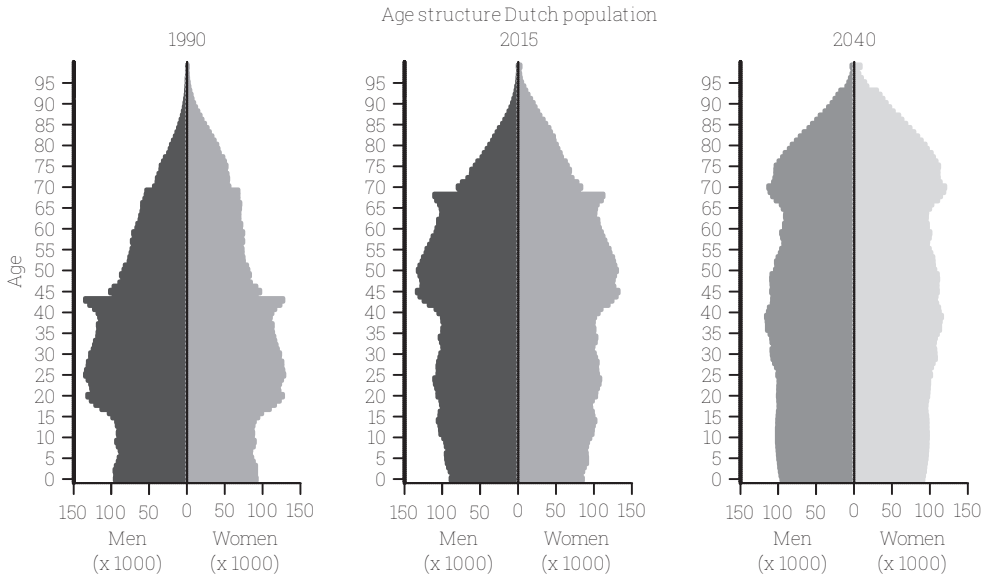

Figure 1 Age structure of the Dutch population in 1990, 2015 and as projected for 2040
Source: Statistics Netherlands (CBS)

Ageing and colon cancer

Due to the ageing of the population, but also due to the introduction of a screening program and unfavourable lifestyle changes, the incidence of colorectal cancer is increasing[2,3]. Colorectal cancer is currently the most common cancer in terms of newly diagnosed patients per year in the Netherlands[4]. Approximately two third of the colorectal cancers is located in the colon.

The European age-standardized incidence rate of colon cancer has increased substantially over the past 25 years: from 29 per 100,000 persons in 1990 to 44 per 100,000 persons in 2015. The absolute number of colon cancer patients in the Netherlands has more than doubled

(figure 2); from 4,600 in 1990 to 10,900 in 2015[4], and is expected to rise further. Nowadays, mean age at time of colon cancer diagnosis is 69 years and approximately one third of the patients is aged ≥75 years.

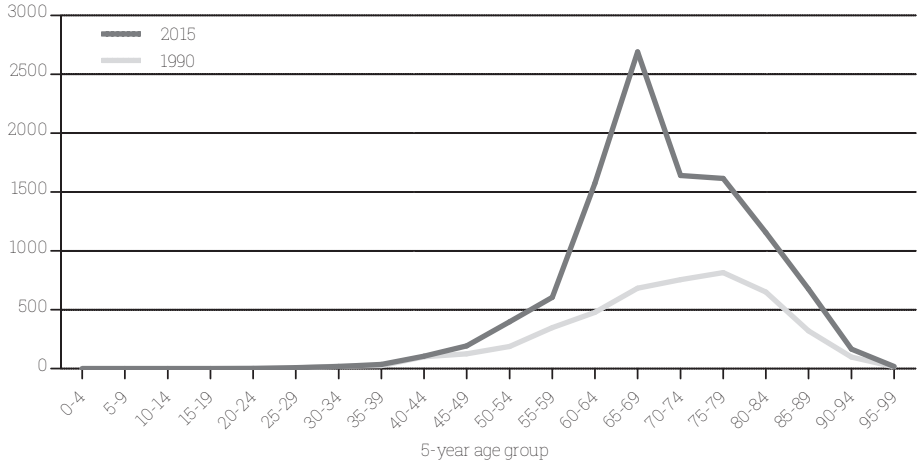

Figure 2 Incidence of colon cancer in the Netherlands, by year of diagnosis and 5-year age group
Source: Netherlands Cancer Registry

Comorbidity and polypharmacy

Due to the high mean age at colon cancer diagnosis, a large proportion of the patients also suffer from other chronic medical conditions (comorbidity)[5-7]. A previous study among unselected colorectal cancer patients showed that in 55% of the patients at least one comorbid condition was present and that 29% of the patients suffered from two or more comorbid conditions. The most common concomitant diseases were hypertension (22%), cardiac disease (19%), other malignancies (15%) and diabetes (11%). In general, the prevalence of comorbidity increased with age until the age of 80-89 years, with 30% of the colorectal cancer patients aged <60 years suffering from comorbidity compared to 71% of the patients aged ≥80 years. In the oldest patients (i.e. ≥90 years) a slight decrease was observed[7]. It is well established that colorectal cancer patients with comorbidity are treated less aggressively and that the presence of comorbidity is associated with worse short- and long-term outcomes[6,8-11].

As a consequence of multimorbidity, polypharmacy is also prevalent among elderly[12]. Polypharmacy can be problematic when decreased drug compliance, wrong intakes and drug interactions lead to adverse drug reactions, toxicity and therapeutic failure[13]. Subsequent cancer treatments with antineoplastic and supportive care agents lead to even greater complexity and might have impact on the tolerance and effect of the treatments[14].

Adjuvant chemotherapy for stage III colon cancer

To classify the extensiveness of colon cancer, the tumour-node-metastasis (TNM) staging system is used[15]. The TNM system consists of four stages. Approximately a quarter of all colon cancer patients presents with stage III disease ($T_{1-4}N_{1-2}M_0$), in which the cancer is not confined to the bowel but has spread to at least one regional lymph node, but not to other, distant organs or tissues.

Treatment for stage III colon cancer consists of oncologic resection of the primary tumour and regional lymph nodes, followed by adjuvant chemotherapy. Adjuvant chemotherapy is used with the intention to eradicate any residual micrometastatic disease[16].

The positive effect of adjuvant chemotherapy on disease-free and overall survival for patients with stage III colon cancer has been established in clinical trials and is standard treatment since the nineties[17-20]. Treatment with 5-fluorouracil and leucovorin (5-FU/LV) was the only effective option until 2005. At that time, the oral fluoropyrimidine capecitabine became available. The X-ACT trial demonstrated that capecitabine was at least equivalent to 5-FU/LV with regard to five-year disease-free (61% vs. 57%) and overall survival (71% vs. 68%) with an improved safety profile except for more hand-foot syndrome[21,22]. Another development was the introduction of the chemotherapeutic oxaliplatin. The MOSAIC and NSABP C-07 study showed that the addition of oxaliplatin to 5-FU/LV (FOLFOX) provided an additional survival gain, but at the cost of higher toxicity rates, especially significant neurotoxicity[23-26]. In the MOSAIC trial, the absolute gain in five-year disease-free survival was 7% (66% vs. 59%) and in six-year overall survival 4% (73% vs. 69%), corresponding to relative risk reductions of 22% and 20% respectively[23]. The XELOXA trial showed a comparable survival gain from the combination of oxaliplatin with capecitabine (CAPOX) compared to 5-FU/LV with an absolute gain in five-year disease-free survival of 6% (67% vs. 61%, relative risk reduction 20%) and in six-year overall survival of 5% (76% vs. 71%, relative risk reduction 17%)[27] and provided an alternative treatment option. However, the rates of grade III-IV neurotoxicity and grade III hand-foot syndrome were higher[28].

Underrepresentation and exclusion of elderly in trials

Despite colon cancer being a disease of the elderly, patients aged 70-75 years were underrepresented in the aforementioned trials and patients aged >75 years were even excluded[21,23,29]. Clinical trials often use eligibility criteria that do not take into account the patient characteristics as seen in real life. As a consequence, the elderly patients who participate in trials, are usually the relatively healthy with minimal comorbidity and good performance status to fulfil the eligibility criteria[30]. They do not represent the typical older patient seen in everyday clinical practice.

Subgroup analyses by age group and pooled data from trials are used to evaluate the effects for the elderly patients. It was shown by one subgroup analysis that selected elderly received the same benefit from 5-FU-based adjuvant chemotherapy as their younger counterparts without a significant increase in toxic effects[31]. Similarly, oral capecitabine also maintained its effectiveness in older patients and the prevalence of grade III-V chemotherapy-related toxicity did not differ by age (<65 versus ≥65 years)[21,22]. However, patients aged 70-75 years

were more likely to discontinue treatment prematurely as compared to younger patients and dose modifications and reductions were required more often[21]. Regarding the beneficial survival effect of adding oxaliplatin to 5-FU-based regimens, inconsistent results were found[32,33]. One study that used pooled data from trials found that the efficacy of FOLFOX was similar for patients aged <70 years and patients aged ≥70 years with regard to disease-free and overall survival[34]. Furthermore, although results were inconclusive, differences in toxicity suggested that older patients may be more prone to develop oxaliplatin-related toxicity[32]. In the NSABP C-07 trial, patients aged 70-75 years were more likely to discontinue treatment prematurely as compared to younger patients and grade IV-V toxicity was experienced at a higher rate[32]. The XELOXA trial showed an overall higher rate of grade III-IV toxicity with CAPOX for patients aged ≥65 years versus younger patients (65% versus 57% respectively)[28].

However, the limitation remains that the results of these studies may not be applicable to unselected elderly patients treated in every clinical practice[30]. Oncological medical specialists have to deal with elderly patients who are very heterogeneous with respect to their underlying health status. As a result, clinicians have to extrapolate the data to help them make a meaningful decision, which can result in both undertreatment and excessive toxicity[35]. Therefore, besides clinical trials other sources of information are needed to evaluate the effects of adjuvant chemotherapy in elderly stage III colon cancer patients[30].

Population-based studies

Population-based studies are needed to bridge the gap of knowledge between clinical trials in selected patients and unselected patients treated in everyday clinical practice[30,36]. Population-based studies can offer additional insight in the use and effectiveness of the various adjuvant chemotherapy options among unselected elderly patients. These studies can therefore provide new insights that will help oncological medical specialists to discuss more adequately the benefits and drawbacks of the various treatment options with elderly patients.

In 2012, a research grant from the Netherlands Organisation for Health Research and Development (ZonMw) enabled the Netherlands Comprehensive Cancer Organisation (IKNL) to perform the research included in this thesis. At that time, observational studies had already shown that elderly patients were less often treated with adjuvant chemotherapy and less often receive oxaliplatin-containing regimens[37-45]. Additionally, dose reductions and treatment discontinuations were more frequent among elderly[37,38]. However, a distinction between the different single agent chemotherapies (i.e. 5-FU or capecitabine) and combination therapies (i.e. FOLFOX or CAPOX) was hardly made. There were also hardly any data available on factors playing a role in the decision-making on adjuvant chemotherapy in daily practice among elderly patients with stage III colon cancer. Furthermore, it was unknown to what degree unselected elderly patients tolerate the various adjuvant chemotherapy options and develop toxicity, and what the differences are in recurrence-free and overall survival between the various treatment modalities in the real world.

Aim and outline of the thesis

This thesis intends to realise a more evidence-based use of the existing adjuvant treatment options for elderly patients with stage III colon cancer. The main objectives of this thesis were:

- To provide insight in the administration of the different adjuvant chemotherapy options (part I).
- To investigate the dose intensity and related toxicity of the different adjuvant chemotherapy options (part II).
- To evaluate the associations between adjuvant chemotherapy and the risk of recurrence, and to evaluate the associations between adjuvant chemotherapy and recurrence-free and overall survival (part III).

First, an overview of drugs dispensed to elderly colon cancer patients in the year before colon cancer diagnosis is provided and compared to an age- and gender-matched control group without cancer (*chapter 2*). The intent of this chapter is to create awareness among (oncology) health care providers as to which drugs are commonly dispensed to their patients.

The next two chapters cover part I of the thesis. In *chapter 3*, subjective, doctor-related factors influencing the decision-making on adjuvant chemotherapy are identified. More specifically, motives for non-referral or non-treatment, the consultation of geriatricians, the choice for monotherapy or combination therapy, and the (grade of) toxicity deemed acceptable is investigated. For this study, surgeons and medical oncologists were invited to complete a short questionnaire. Subsequently, *chapter 4* evaluates which patient and tumour characteristics influence the administration of oxaliplatin-based chemotherapy as compared to non-oxaliplatin-based chemotherapy and presents variation in both types of chemotherapy between hospitals.

For part II of this thesis, *chapter 5* provides a detailed insight in the completion of all planned cycles and received cumulative dosage of the regimens CAPOX and CapMono and investigates the association with grade III-V toxicity. Additionally, *chapter 6* focuses on differences in the course of neuropathic symptoms between patients who are treated with either CAPOX or capecitabine and patients who are not treated with adjuvant chemotherapy. For this study, patients were invited to complete a questionnaire after resection and subsequently six and twelve months later.

The next three chapters comprise part III of the thesis. In *chapter 7*, the association between adjuvant chemotherapy and the risk of distant recurrence is investigated. Additionally, we investigate whether the association is comparable for patients aged ≥75 years and their younger counterparts. In *chapter 8*, the associations of the regimens CAPOX and CapMono with recurrence-free and overall survival are investigated and it is assessed whether oxaliplatin provides additional benefit. This chapter also investigates the effects of (non-)completion of both regimens on recurrence-free and overall survival. *Chapter 9* investigates which demographic and clinical variables are associated with the timing of adjuvant chemotherapy and how this timing is associated with overall survival.

In *chapter 10*, the main findings and methodological considerations are discussed. Additionally, implications for clinical practice and future research are outlined.

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Drug dispensings among elderly in the year before colon cancer diagnosis versus matched cancer-free controls

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Abstract

What is known and objective: The concomitant use of multiple drugs is common among the general population of elderly. The aim of this study was to provide an overview of which drugs are dispensed to elderly in the year before colon cancer diagnosis and to compare this with cancer-free controls.

Methods: Data from the Eindhoven Cancer Registry were linked to the PHARMO Database Network. Colon cancer patients aged ≥70 years were included and matched with controls on gender, birthyear and postal code. Proportions of cases and controls with ≥1 dispensing of each WHO-ATC 2nd-level drug during the total year and during each quarter of the year were calculated and differences between cases and controls tested.

Results and discussion: Proportion of cases with ≥1 drug dispensing was highest for drugs for constipation (cases vs. controls 58% vs. 10%), antithrombotics (42% vs. 33%), drugs for acid related disorders (35% vs. 22%), antibacterials (34% vs. 24%), agents acting on the renin-angiotensin system (33% vs. 27%), beta blockers (33% vs. 23%), lipid modifying agents (29% vs. 22%), diuretics (29% vs. 21%), psycholeptics (25% vs. 18%) and antianemics (23% vs. 6%). The proportion of cases with ≥1 drug dispensing increased from the first to the last quarter of the year for drugs for constipation (7% to 53%), drugs for acid related disorders (16% to 27%), antibacterials (12% to 16%), beta blockers (26% to 28%), psycholeptics (15% to 19%) and antianemics (6% to 18%). Elevated proportions of cases with ≥1 drug dispensing for several drugs is mostly related to comorbidity, although increasing proportions of cases with ≥1 drug dispensing for certain drugs during the year can be attributed to the incidence of colon cancer.

What is new and conclusion: We have provided insight into which drugs are commonly used in the year preceding colon cancer diagnosis. This may trigger general practitioners and medical specialists to further evaluate the patient.

What is known and objective

In the Netherlands, more than 9000 patients were newly diagnosed with colon cancer in 2013, and 55% of these patients was aged 70 years or older[1]. Due to the aging of the population and the rising incidence rates of colon cancer with age, the age of patients with colon cancer will increase[2].

Among elderly colon cancer patients, comorbidities such as cardiovascular diseases, diabetes and other malignancies all occur relatively frequent[3]. Patients often also receive drugs for these diseases. Polypharmacy, defined as the use of several drugs for the treatment of coexisting diseases, can be problematic. Polypharmacy can lead to decreased drug compliance, wrong intakes and drug interactions, thereby increasing the risk of adverse drug reactions, toxicity and therapeutic failure[4,5]. Additionally, among elderly, age dependent changes in organ function can alter pharmacokinetics and pharmacodynamics of drugs, which also increases the risk of toxicity and therapeutic failure[5,6]. On the other side, polypharmacy can potentially also lead to more frequent medical consultations which may lead to earlier recognition of symptoms and diagnosis. Subsequent cancer treatments with antineoplastic and supportive care agents will lead to an even greater complexity and might have an impact on tolerance to and effect of the treatments[7].

It has already been shown that the concomitant use of multiple drugs is common among the general population of elderly[8]. However, information related to drug use among elderly cancer patients is limited[9,10]. So far, studies usually focused on the prevalence of polypharmacy, but lacked a detailed specification of which drugs were commonly used[8]. A mere quantification of the number of drugs used has been proven to be an indicator of limited value[4]. Therefore, knowing which drugs are commonly dispensed is important when deciding on prescribing anticancer drugs.

The aim of the current study is to provide an overview of drugs dispensed to elderly colon cancer patients in the year before colon cancer diagnosis and to compare this with an age- and gender-matched control group without cancer, with the primary intent to create awareness among (oncology) health care providers (i.e. medical oncologists, geriatricians and general practitioners) as to which drugs are commonly dispensed to their patients. The secondary objective is to obtain more insight into associations between commonly dispensed drugs and patient and tumor characteristics.

Methods

Data were obtained from the Eindhoven Cancer Registry (ECR) and linked on a patient-level to the PHARMO Database Network, covering an overlapping demographic region in the southeastern part of the Netherlands of approximately 1.2 million inhabitants. The construct and validity of the ECR-PHARMO cohort are described elsewhere[11].

The ECR, maintained by the Netherlands Comprehensive Cancer Organisation (IKNL), is a population-based registry that collects data on all newly diagnosed cancer patients in the southern part of the Netherlands. Information on patient and tumor characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators.

Anatomical site of the tumor is registered according to the International Classification of Disease – Oncology (ICD-O). The tumor-node-metastasis (TNM) classification is used for stage notification of the primary tumor, according to the edition valid at time of diagnosis. Comorbidities present at time of cancer diagnosis are registered according to a slightly modified version of the Charlson comorbidity index. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, is provided at an aggregated level for each postal code.

The PHARMO Database Network is a large patient-centric data network including multiple linked observational databases designed for drug safety and outcomes research. The database used for this study includes complete longitudinal data obtained from out-patient pharmacies in which drugs are classified according to the WHO Anatomic Therapeutic Chemical (ATC) coding. Additionally, the Chronic Disease Score (CDS) was assessed based on drug prescriptions in the year prior to cohort entry date. The CDS is defined as a set of scoring rules that assigns "chronic disease" weights based on single or combinations of used drugs. Higher scores signify more comorbid conditions. Scores were classified into four categories (0-5, 6-8, 9-11, ≥12).

In the Netherlands, studies with anonymized patient records do not fall under the scope of the Medical Research Involving Human Subjects Act. This study is therefore exempt from medical ethics review.

Study population

All stage I-IV colon cancer patients aged 70 years or older diagnosed between 2000 and 2011 and registered in the ECR-PHARMO cohort were included. Cancer-free controls were identified and included by selecting patients living in the overlapping ECR-PHARMO region who were included in the PHARMO Database Network but not in the ECR. Cancer patients were matched with controls –1 control per case– on gender, year of birth and postal code. For each control, the colon cancer incidence date of the matched patient was assigned as cohort entry date.

Drugs were classified according to the WHO ATC coding and grouped on ATC-2 level (i.e. ATC A01). Non-therapeutic products (ATC V07) were excluded from the analyses. ATC-2 level drugs were counted for cases and controls if there was at least 1 dispensing during the year before colon cancer diagnosis or cohort entry date. The number of different drugs on ATC-2 level dispensed to cases and controls during the year before colon cancer diagnosis or cohort entry date was divided into the following categories: 0, 1-6 or ≥7 drugs.

Statistical analyses

Differences between cases and controls in the proportion with at least 1 dispensing of each drug during the year before colon cancer diagnosis or cohort entry date were calculated using Chi^2-test or Fisher's Exact test.

For the 10 drugs with the highest proportions of colon cancer patients with at least 1

dispensing in the total year before colon cancer diagnosis, additional analyses were performed: after dividing the study year into quarters, we calculated differences in the proportion of cases and controls with at least 1 dispensing during each quarter of the year before colon cancer diagnosis or cohort entry date using Chi^2-tests. To investigate changes over time, differences in the proportions with at least 1 dispensing in the first quarter as compared to the last quarter were also calculated, for cases and controls separately.

Differences in patient and tumor characteristics between patients with and patients without a dispensing of each of the 10 drugs were also analyzed using Chi^2-tests. Multivariable logistic regression was used to assess the independent effect of each patient and tumor characteristic on the dispensing of each of these 10 drugs. All odds ratios were adjusted for gender, age, socioeconomic status, comorbidity, TNM stage, subsite of the tumor and period of cancer diagnosis, but only variables with statistically significant odds ratios were reported. For SES and comorbidity, there were 79 (2.9%) and 192 (7.0%) missing values. These were included in the analyses as separate categories, but results not shown.

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 and discussion

The total study population consisted of 2735 elderly colon cancer patients and 2735 matched cancer-free controls. As a result of the matching procedure, gender, age and period distributions for the cases and controls were equal (table 1). Half of the population was male. Mean age was 77.8 ± 5.3 years. For 18%, period of diagnosis or cohort entry was 2000-2003, for 33% 2004-2007 and for 49% 2008-2011. Increasing entrance of patients during the study periods was partly related to the increasing incidence of colon cancer, but mostly due to the expansion of the PHARMO Database Network within the ECR region.

Drug dispensings and CDS differed between cases and controls (table 1). Drug dispensings were higher among cases than among controls ($p<0.0001$). Among cases, 10% had no drug dispensings, 41% had 1-6 drugs with ≥1 dispensing and 49% had ≥7 drugs with ≥1 dispensing. For controls, these percentages were 31%, 40% and 29% respectively (table 1). The CDS was also higher for cases than for controls ($p<0.0001$). 18% of cases had a CDS of 0-5 while 31% of controls had a CDS of 0-5. Among cases, 45% had a CDS of ≥12 while this was 33% among controls.

For each drug, the number and proportion of cases and controls with ≥1 dispensing in the year before colon cancer diagnosis or cohort entry date are presented in appendix A. For 36 drugs, the proportion of cases with ≥1 dispensing was significantly higher than for controls. For the other 44 drugs, there was no difference in the proportion of cases and controls with ≥1 dispensing. There were no drugs for which the proportion of controls with ≥1 dispensing was higher as compared to cases.

The 10 drugs with the highest proportions of cases with ≥1 dispensing, were drugs for constipation (cases vs. controls 58% vs. 10%), antithrombotics (42% vs. 33%), drugs for acid related disorders (35% vs. 22%), antibacterials (34% vs. 24%), renin-angiotensin system (RAS)

Table 1 Demographic characteristics, dispensed drugs and chronic disease score for the total study population (n=5470)

	Cases n (%)	Controls n (%)
Gender		
Male	1377 (50)	1377 (50)
Female	1358 (50)	1358 (50)
Age		
70-74	896 (33)	896 (33)
75-79	892 (33)	892 (33)
80-84	615 (22)	615 (22)
≥85	332 (12)	332 (12)
Cohort entry		
2000-2003	498 (18)	498 (18)
2004-2007	900 (33)	900 (33)
2008-2011	1337 (49)	1337 (49)
Dispensed drugs in the year prior to cohort entry		
No drugs	269 (10)	848 (31)
1-6 drugs	1124 (41)	1082 (40)
≥7 drugs	1342 (49)	805 (29)
Chronic Disease Score		
0-5	491 (18)	850 (31)
6-8	450 (17)	425 (16)
9-11	553 (20)	548 (20)
≥12	1241 (45)	912 (33)

related agents (33% vs. 27%), beta blockers (33% vs. 23%), lipid modifying agents (29% vs. 22%), diuretics (29% vs. 21%), psycholeptics (25% vs. 18%) and antianemics (23% vs. 6%) ($p<0.0001$ for all).

Figure 1 presents for each of the top 10 drugs the proportion of cases and controls with ≥1 dispensing in each quarter of the year before colon cancer diagnosis or cohort entry date. In each quarter, the proportion of cases with ≥1 dispensing was higher as compared to the controls for all 10 drugs. Furthermore, the proportion of cases with ≥1 dispensing increased from the first to the last quarter of the year, i.e. the last three months before colon cancer diagnosis, with regard to drugs for acid related disorders (from 16% to 27%, $p<0.0001$), drugs for constipation (from 7% to 53%, $p<0.0001$), antianemics (from 6% to 18%, $p<0.0001$), beta blockers (from 26% to 28%, $p=0.048$), antibacterials (from 12% to 16%, $p<0.0001$) and psycholeptics (from 15% to 19%, $p=0.0002$). The proportion of cases with ≥1 dispensing did not significantly increase from the first to the last quarter of the year with regard to antithrombotics, diuretics, RAS related agents and lipid modifying agents. The proportion of controls with ≥1 dispensing did not increase from the first to the last quarter of the year for any of the 10 drugs.

Table 2 provides an overview of the crude percentages of elderly colon cancer patients with ≥1 dispensing for each of the 10 drugs according to several demographic and clinical characteristics. In addition, figure 2 presents the adjusted odds ratios that remained significant in multivariable analysis. Drugs for constipation, antithrombotics and lipid modifying agents were more often dispensed to male patients than to female patients,

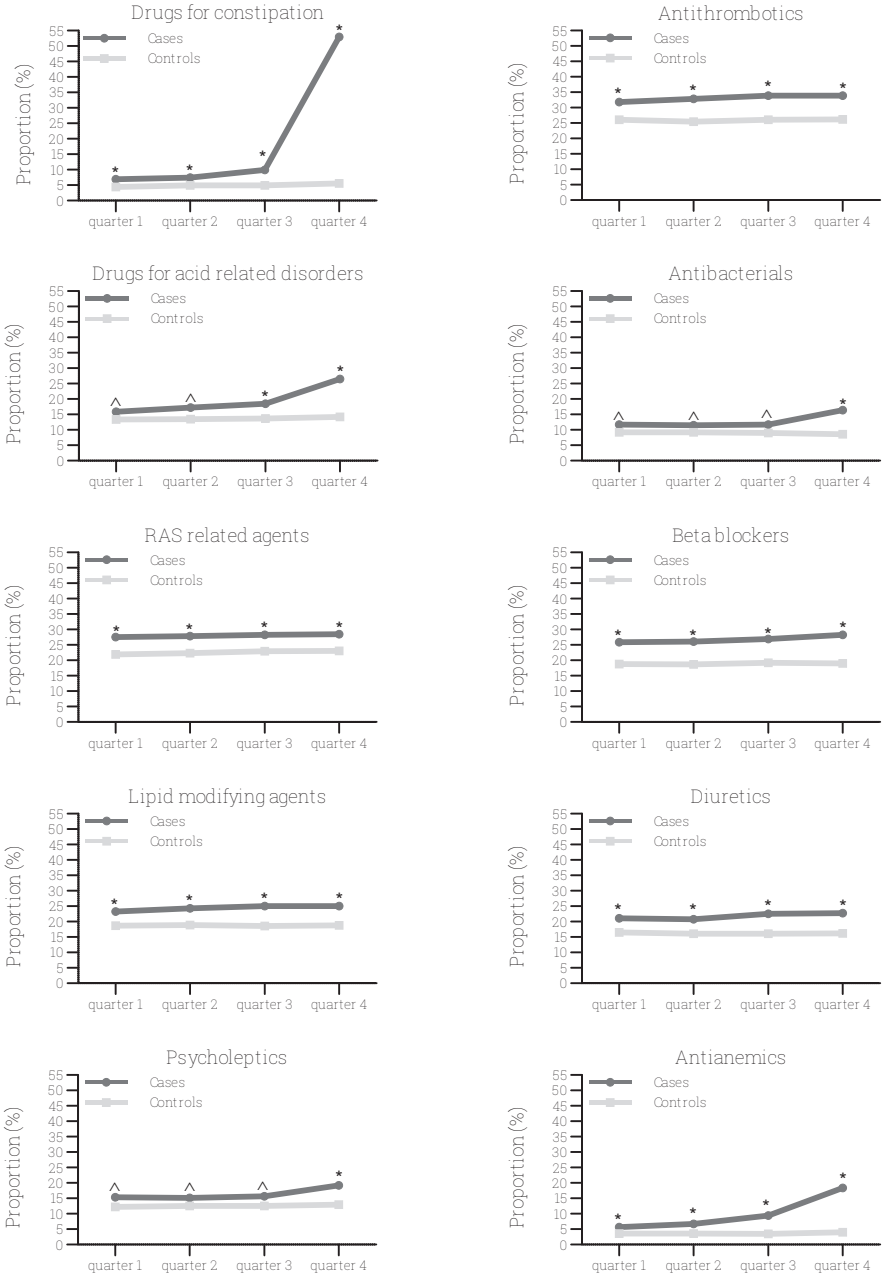

Figure 1 Proportion of cases and controls with at least one dispensing of 10 drugs in each quarter of the year before colon cancer diagnosis or cohort entry date (n=5470)
RAS: renin-angiotensin system
^ P value Chi²-test cases vs. controls <0.05
* P value Chi²-test cases vs. controls <0.0001

Table 2 Demographic and clinical characteristics of elderly colon cancer patients (cases), according to the 10 drugs with the highest proportion of cases with ≥1 dispensing in the year before diagnosis (n=2735)

		Drugs for constipation	Anti-thrombotics	Drugs for acid related disorders	Anti-bacterials	RAS related agents	Beta blockers	Lipid modifying agents	Diuretics	Psycho-leptics	Anti-anemics
	n	%	%	%	%	%	%	%	%	%	%
Gender		^	**				^	**	**	**	^
Male	1377	61	49	35	33	35	34	33	25	18	21
Female	1358	55	34	35	35	31	31	25	32	32	26
Age		^	**		^	^	^	**	**	^	^
70-74	896	60	35	34	32	29	29	31	21	21	19
75-79	892	59	40	35	34	33	33	32	26	25	23
80-84	615	58	49	36	32	37	35	28	35	28	27
≥85	332	49	52	36	40	36	36	17	47	31	30
Socioeconomic status			^	^			^	^	**	^	
Low	841	55	45	35	38	34	34	31	33	27	25
Intermediate	983	59	42	36	32	33	34	31	26	23	22
High	676	60	37	31	32	32	27	26	25	22	22
Institutions	156	57	44	40	35	32	35	22	40	33	26
Unknown	79	54	34	43	33	32	34	33	27	29	27
Comorbidity			**	^	^	**	**	**	**		**
0	477	60	14	29	27	6	8	9	8	24	16
1	731	57	31	33	34	27	26	20	23	24	20
≥2	1335	58	58	38	36	47	45	42	39	25	28
Unknown	192	59	38	37	31	26	32	25	32	26	26
TNM stage		^	^								^
I	490	60	46	34	35	34	33	29	28	23	22
II	1085	61	42	35	35	32	33	29	31	24	27
III	669	56	42	34	32	33	32	30	28	26	23
IV	491	53	37	36	33	32	31	29	26	26	18
Subsite of tumor		**		**		^			^		**
Proximal colon	1600	55	41	40	34	31	32	28	31	25	31
Distal colon	1135	63	43	29	33	36	33	31	26	24	12
Period cancer diagnosis			^	^		**	**	**		**	
2000-2003	498	58	36	30	37	24	24	12	29	30	25
2004-2007	900	58	46	33	35	32	34	28	30	28	24
2008-2011	1337	58	41	38	32	37	34	36	28	21	22

RAS: renin-angiotensin system

^ P<0.05

** P<0.0001

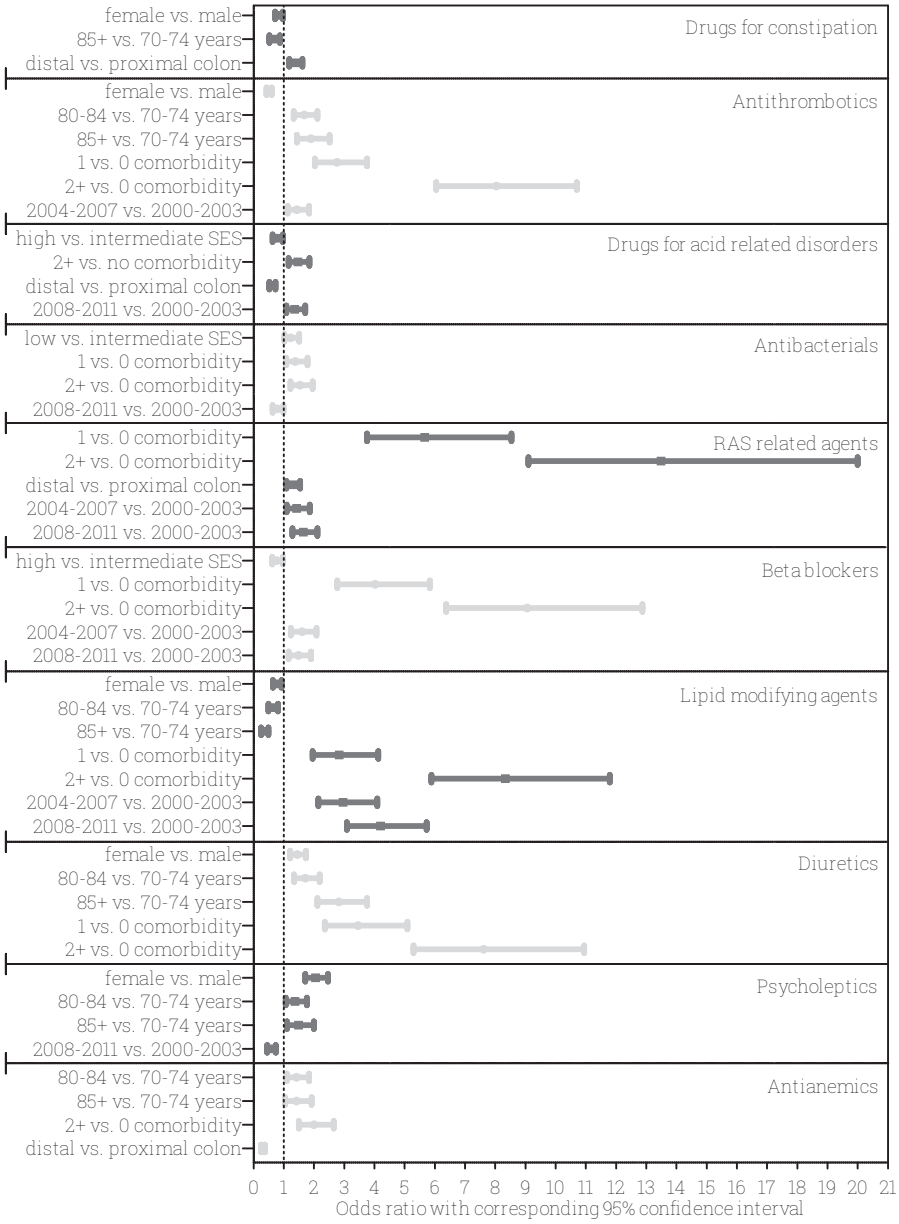

Figure 2 Odds ratios[a] of receiving each of the 10 listed drugs according to patient and tumour characteristics among cases (n=2735)

[a]All odds ratios are adjusted for gender, age, socioeconomic status (SES), comorbidity, TNM stage, subsite of the tumor and period of cancer diagnosis

RAS: renin-angiotensin system

Only variables with statistically significant odds ratios are reported

while diuretics and psycholeptics were less often dispensed to male patients as compared to female patients. Older patients more often had at least 1 dispensing of antithrombotics, antianemics, diuretics and psycholeptics but less often had one or more dispensings of drugs for constipation and lipid modifying agents. Socioeconomic status was associated with dispensing of drugs for acid related disorders, beta blockers and antibacterials. With increasing comorbidity, the dispensing of drugs also increased, with the exception of drugs for constipation and psycholeptics. In multivariable analysis, TNM stage was not associated with any of the drugs. Patients with a tumor located in the distal colon more often had at least 1 dispensing of drugs for constipation and RAS related agents, but less often for drugs for acid related disorders and antianemics as compared to patients with a tumor located in the proximal colon. During the study period, the dispensing of drugs for acid related disorders, beta blockers, RAS related agents and lipid modifying agents increased, while the dispensing of antibacterials and psycholeptics decreased. The dispensing of antithrombotics was higher in 2004-2007 as compared to 2000-2003.

What is new and conclusion

Our study demonstrates a higher proportion of drug dispensing from out-patient pharmacies to elderly colon cancer patients during the total year before diagnosis as compared to a matched cancer-free control group, which increased even more during the last three months before diagnosis.

Increasing drug dispensing in the months preceding cancer diagnosis is in line with previous research[12]. In our study, drugs for constipation, drugs for acid related disorders, antianemics, beta blockers, antibacterials and psycholeptics were dispensed to an increasing proportion of cases in the last quarter of the year. Drugs for constipation are probably increasingly dispensed for symptom management and as colon preparation agent before a diagnostic colonoscopy can take place. Drugs for acid related disorders, especially antacids (i.e. magnesium, calcium and aluminium compounds), are often concomitantly prescribed with drugs for constipation. Additionally, tumors in the proximal colon may mimic symptoms of higher gastrointestinal diseases and this can lead to unjustifiable but explainable prescription of acid lowering drugs. The increasing dispensing of antianemics might be related to iron deficiency due to blood loss as a symptom of the colon cancer[13]. Antacids can also be described as a pragmatic drug for iron deficiency, during the waiting time of diagnostics, when a gastric ulcer is still considered a possible explanation. Antibacterials, especially antibiotics, might be increasingly dispensed because an infection is suspected. Although our explanation for the increasing dispensing of psycholeptics is very uncertain, we hypothesize that for some patients it may perhaps reflect fear and anxiety during the diagnostic procedures or in reaction to symptoms. Additionally, it could also suggest that patients are anxious or experience delirium due to their colon cancer without being diagnosed yet. Although psycholeptics do not interact with colon cancer related chemotherapeutics, their use does deserve attention, because of the risk of interactions with other drugs, such as for benzodiazepine derivates[14]. Long-acting benzodiazepines increase the risk of falls and fractures with as much as 60%[15] and can be found among the inappropriate drugs according to the Beers criteria[16-18].

As stated before, drug dispensing was higher among cases than among controls for the total year before diagnosis or cohort entry date. This could be caused by a higher level of comorbidity, which was reflected in a higher proportion of cases than controls with a CDS ≥12. Beta blockers, RAS related agents and diuretics are prescribed for cardiovascular diseases such as hypertension. Lipid modifying agents are used in the treatment of diabetes. However, higher drug dispensing and especially the underlying symptoms or diseases for which the drugs are prescribed could also serve as a warning signal for general practitioners to further evaluate the patient. Higher dispensing of laxatives could partly reflect a misinterpretation of symptoms in cancer patients[12]. The elevated dispensing of antithrombotics among cases might be explained by the association between venous thromboembolism and cancer[19] and in some cases by the first cancer symptoms. Moreover, the use of antithrombotics might also lead to an earlier notice of blood loss and colon cancer diagnosis. Among colon cancer patients receiving (adjuvant) chemotherapy with fluorouracil or its oral analogous capecitabine, one should be attentive for a potential interaction with antithrombotic agent warfarin, which can lead to an increased risk of bleeding[20-22].

In general, the elevated dispensing of drugs among cases as compared to controls during the total study year is mostly related to comorbidity, as is reflected in our results, which show associations between almost all 10 drugs and the presence of comorbidity among the colon cancer patients. This association with comorbidity is in part because the elderly who develop colon cancer probably have certain risk factors (i.e. overweight, smoking and physical inactivity) which make them also more vulnerable for other comorbidities that share the same risk factors, but also because patients with comorbidities are under more intense medical surveillance. Vice versa, patients who seek medical attention for (cancer) symptoms could also be diagnosed with other chronic diseases during the diagnostic process. Because only comorbidity present at time of colon cancer diagnosis was registered, the exact influence remains uncertain.

The increasing proportion of cases with a dispensing of certain drugs during the year will probably be mostly related to the colon cancer, especially drugs for constipation, which were not related to comorbidity.

Some of the odds ratios in our study were accompanied by wide confidence intervals. The width of the confidence interval depends on the sample size and risk of the event. Although these confidence intervals were not centered around 1 (i.e. no effect) and it is therefore improbable that there was no effect, it should be acknowledged that the exact strength of the effect remains fairly uncertain. Future large scale studies are needed to provide more precise estimates of the strength of the effects.

A limitation of our study is that we cannot be certain whether dispensed drugs were actually taken. However, because this applies to both cases and controls, possible misclassification will be non-differential. Additionally, prescription length was not taken into account, but again no difference between cases and controls is expected. Finally, no data from in-hospital pharmacies was included.

We acknowledge that it is hard to draw clinical conclusions from our manuscript. As expected, drug use is frequent in the time leading up to a colon cancer diagnosis among

elderly patients and many patients use multiple drugs. However, we have also provided insight into which drugs are commonly used in the year preceding colon cancer diagnosis. This may trigger general practitioners and medical specialists to further evaluate the patient. Additionally, our study provides starting points for future research, for example, for the most frequently used drugs, in-depth analyses can investigate whether distinct drug combinations or patterns of drugs use predict subsequent cancer diagnosis.

In conclusion, our study demonstrates that to a substantial proportion of elderly, multiple drugs are dispensed in the year before colon cancer diagnosis and, usually, this reflects multimorbidity. For drugs that are dispensed to an increasing proportion of cases in the months before colon cancer diagnosis, this seems related to symptom management of the colon cancer itself. Subsequent cancer treatments with antineoplastic and supportive care agents will lead to an even greater complexity and might have an impact on tolerance to and effect of these treatments. The effect of specific drugs on cancer treatment (i.e. receiving surgery, undergoing adjuvant or palliative chemotherapy, deviations from guidelines) and outcome (i.e. complications, toxicity, survival) should be subject of further study.

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Appendix

Appendix A Number and proportion of elderly using ATC-2 level drugs in the year before colon cancer diagnosis (cases) or cohort entry date (cancer-free controls) (n=5470)

ATC-2 level code	Cases n (%)	Controls n (%)	P value*
A Alimentary tract and metabolism			
A01 Stomatological preparations	37 (1.4)	37 (1.4)	NS
A02 Drugs for acid related disorders	959 (35.1)	597 (21.8)	<0.0001
A03 Drugs for functional gastrointestinal disorder	293 (10.7)	80 (2.9)	<0.0001
A04 Antiemetics and antinauseants	6 (0.2)	2 (0.1)	NS
A05 Bile and liver therapy	1 (0.1)	2 (0.1)	NS
A06 Drugs for constipation	1589 (58.1)	284 (10.4)	<0.0001
A07 Antidiarrheals, intestinal anti-inflammatory/anti-infective	161 (5.9)	53 (1.9)	<0.0001
A08 Antiobesity preparations, excluding diet products	2 (0.1)	2 (0.1)	NS
A09 Digestives, including enzymes	1 (0.1)	2 (0.1)	NS
A10 Drugs used in diabetes	426 (15.6)	365 (13.4)	0.019
A11 Vitamins	76 (2.8)	69 (2.5)	NS
A12 Mineral supplements	171 (6.3)	158 (5.8)	NS
A14 Anabolic agents for systemic use	1 (0.1)	1 (0.1)	NS
B Blood and blood forming organs			
B01 Antithrombotic agents	1142 (41.8)	891 (32.6)	<0.0001
B02 Antihemorrhagics	41 (1.5)	16 (0.6)	0.0009
B03 Antianemic preparations	640 (23.4)	174 (6.4)	<0.0001
B05 Blood substitutes and perfusion solutions	4 (0.2)	8 (0.3)	NS
C Cardiovascular system			
C01 Cardiac therapy	472 (17.3)	361 (13.2)	<0.0001
C02 Antihypertensives	45 (1.7)	24 (0.9)	0.011
C03 Diuretics	783 (28.6)	574 (21.0)	<0.0001
C04 Peripheral vasodilators	640 (23.4)	174 (6.4)	<0.0001
C05 Vasoprotectives	124 (4.5)	59 (2.2)	<0.0001
C07 Beta blocking agents	888 (32.5)	625 (22.9)	<0.0001
C08 Calcium channel blockers	451 (16.5)	324 (11.9)	<0.0001
C09 Agents acting on the renin-angiotensin system	902 (33.0)	730 (26.7)	<0.0001
C10 Lipid modifying agents	796 (29.1)	604 (22.1)	<0.0001
D Dermatologicals			
D01 Antifungals for dermatological use	310 (11.3)	230 (8.4)	0.0003
D02 Emollients and protective	256 (9.4)	208 (7.6)	0.020
D03 Preparations for treatment of wounds and ulcers	3 (0.1)	3 (0.1)	NS
D04 Antipruritics, including antihistamines, anesthetics, etc.	7 (0.3)	6 (0.2)	NS
D05 Antipsoriatics	32 (1.2)	19 (0.7)	NS
D06 Antibiotics and chemotherapeutics for dermatological use	121 (4.4)	95 (3.5)	NS
D07 Corticosteroids, dermatological preparations	530 (19.4)	375 (13.7)	<0.0001
D08 Antiseptics and disinfectants	20 (0.7)	14 (0.5)	NS
D09 Medicated dressings	1 (0.1)	0 (0.0)	NS
D10 Anti-acne preparations	11 (0.4)	8 (0.3)	NS
D11 Other dermatological preparations	23 (0.8)	37 (1.4)	NS
G Genito-urinary system and sex hormones			
G01 Gynecological anti-infectives and antiseptics	12 (0.4)	17 (0.6)	NS
G02 Other gynecologicals	1 (0.1)	1 (0.1)	NS
G03 Sex hormones and modulator of the genital system	65 (2.4)	62 (2.3)	NS
G04 Urologicals	265 (9.7)	235 (8.6)	NS
H Systemic hormonal preparations, excluding sex hormones and insulins			
H01 Pituitary and hypothalamic hormones and analogues	5 (0.2)	9 (0.3)	NS
H02 Corticosteroids for systemic use	262 (9.6)	212 (7.8)	0.016
H03 Thyroid therapy	105 (3.8)	78 (2.9)	0.042
H04 Pancreatic hormones	4 (0.2)	2 (0.1)	NS
H05 Calcium homeostasis	65 (2.4)	62 (2.3)	NS

Appendix A continued

ATC-2 level code	Cases n (%)	Controls n (%)	P value*
J Anti-infectives for systemic use			
J01 Antibacterials for systemic use	924 (33.8)	650 (23.8)	<0.0001
J02 Antimycotics for systemic use	18 (0.7)	13 (0.5)	NS
J04 Antimycobacterials	0 (0.0)	2 (0.1)	NS
J05 Antivirals for systemic use	29 (1.1)	12 (0.4)	0.008
J06 Immune sera and immunoglobulins	15 (0.6)	9 (0.3)	NS
J07 Vaccines	26 (1.0)	31 (1.1)	NS
L Antineoplastic and immunomodulating agents			
L01 Antineoplastic agents	25 (0.9)	16 (0.6)	NS
L02 Endocrine therapy	53 (1.9)	16 (0.6)	<0.0001
L03 Immunostimulants	0 (0.0)	1 (0.1)	NS
L04 Immunosuppressants	21 (0.8)	17 (0.6)	NS
M Musculo-skeletal system			
M01 Anti-inflammatory and antirheumatic products	577 (21.1)	483 (17.7)	0.001
M02 Topical products for joint and muscular pain	13 (0.5)	10 (0.4)	NS
M03 Muscle relaxants	6 (0.2)	2 (0.1)	NS
M04 Antigout preparations	83 (3.0)	64 (2.3)	NS
M05 Drugs for treatment of bone diseases	180 (6.6)	148 (5.4)	NS
M09 Other drugs for disorders of the musculo-skeletal system	52 (1.9)	43 (1.6)	NS
N Nervous system			
N01 Anesthetics	38 (1.4)	25 (0.9)	NS
N02 Analgesics	459 (16.8)	374 (13.7)	0.001
N03 Antiepileptics	103 (3.8)	56 (2.1)	0.0002
N04 Anti-parkinson drugs	50 (1.8)	46 (1.7)	NS
N05 Psycholeptics	679 (24.8)	493 (18.0)	<0.0001
N06 Psychoanaleptics	202 (7.4)	186 (6.8)	NS
N07 Other nervous system drugs	137 (5.0)	96 (3.5)	0.006
P Antiparasitic products, insecticides and repellents			
P01 Antiprotozoals	30 (1.1)	17 (0.6)	NS
P02 Anthelmintics	103 (3.8)	56 (2.1)	0.0002
P03 Ectoparasiticides, including scabicides, insecticides and repellents	1 (0.1)	0 (0.0)	NS
R Respiratory system			
R01 Nasal preparations	181 (6.6)	134 (4.9)	0.006
R02 Throat preparations	1 (0.1)	5 (0.2)	NS
R03 Drugs for obstructive airway diseases	425 (15.5)	361 (13.2)	0.014
R05 Cough and cold preparations	306 (11.2)	233 (8.5)	0.0009
R06 Antihistamines for systemic use	139 (5.1)	130 (4.8)	NS
S Sensory organs			
S01 Ophthalmologicals	582 (21.3)	440 (16.1)	<0.0001
S02 Otologicals	102 (3.7)	75 (2.7)	0.039
V Various			
V03 All other therapeutic products	7 (0.3)	4 (0.2)	NS

NS: not significant

* P value indicates significance of the Chi^2-test or Fisher's Exact test where appropriate

Deciding on adjuvant chemotherapy for elderly stage III colon cancer patients: a qualitative insight into the perspectives of surgeons and medical oncologists

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Abstract

Objective: The aim of this study is to identify doctor-related factors determining the decision-making for adjuvant chemotherapy for stage III colon cancer patients aged ≥75 years.

Materials and methods: 21 surgeons and 15 medical oncologists from 10 community hospitals were asked to complete a short questionnaire including tick-box questions regarding motives for non-referral/non-treatment, consultation of geriatricians, chemotherapy schemes prescribed and an open question regarding tolerability of chemotherapy.

Results: 29 medical specialists returned a completed questionnaire (response 81%). The motives for non-referral/non-treatment reported most often were comorbidity/bad general health condition of the patient; surgical complications; and treatment offered but refused by patient/family. 39% of the surgeons and 55% of the medical oncologists reported consultation of a geriatrician in 2-30% of their decisions. CAPOX and capecitabine were reported by medical oncologists as the most frequently prescribed regimens. Factors that influenced the decision for monotherapy or combination therapy were comorbidity; general health condition of the patient; and toxicity profile of the chemotherapeutics. In general, medical oncologists defined grade ≤2 toxicities as tolerable, with the exception of neuropathy, for which grade ≤1 toxicity was accepted.

Conclusions: In case medical oncologists prescribe adjuvant chemotherapy to elderly stage III colon cancer patients, the chemotherapy schemes used are in line with clinical guidelines and they agree on acceptable levels of toxicity. However, the variation among surgeons and medical oncologists in motives for non-referral, non-treatment and consultation of geriatricians when deciding on adjuvant chemotherapy for elderly stage III colon cancer patients, shows the complexity and need for specific knowledge.

Introduction

In previous studies, we showed that only a small proportion of elderly patients with stage III colon cancer receives adjuvant chemotherapy[1] and that there is a large variation between hospitals in the southern part of the Netherlands with regard to adjuvant chemotherapy administration among these patients, which could not be explained by casemix. Additionally, type of prescribed chemotherapy varied, broadly distinguishing between oxaliplatin-containing chemotherapy and non-oxaliplatin-containing chemotherapy[2].

The objective of the current study was to identify subjective, doctor-related factors in the decision-making on adjuvant chemotherapy in elderly stage III colon cancer patients. More specifically, the aim of the study was fourfold. The first goal was to identify which motives surgeons and medical oncologists have for non-referral for, or non-treatment with, adjuvant chemotherapy of stage III colon cancer patients aged 75 years or older. Secondly, we evaluated whether surgeons and medical oncologists consult geriatricians in the decision-making process. Thirdly, we investigated which chemotherapy schemes medical oncologists prescribe to patients and what motives they have for prescribing monotherapy or combination therapy. Finally, we assessed the (grade of) toxicity caused by the adjuvant chemotherapy deemed acceptable by medical oncologists.

Materials and methods

36 medical specialists with colorectal cancer as their area of interest and who are directly involved in the treatment of colon cancer patients (21 surgeons and 15 medical oncologists) were asked to complete a short questionnaire between December 2013 and January 2014.

The medical specialists represent all 10 community hospitals in the southern part of the Netherlands. Eight of these hospitals are also teaching hospitals (seven for surgery, eight for internal medicine and four for clinical geriatrics). In 2013, between 75 and 200 colon cancer patients were diagnosed in each hospital, of whom 2-15% was 75 years or older and diagnosed with stage III disease. Furthermore, all hospitals have multidisciplinary tumour boards. More than 90% of the patients are discussed in these multidisciplinary tumour boards[3]. Geriatricians are present in each hospital, but it is unknown whether they are available for oncological consultation.

Self-administered questionnaires were developed and discussed with a medical oncologist involved in the study for content and relevance. Two slightly different versions (one for surgeons and one for medical oncologists) of the questionnaire with room for remarks were created. The questionnaire addressed to surgeons included tick-box questions regarding motives for non-referral of stage III colon cancer patients aged 75 years or older for adjuvant chemotherapy and consultation of a geriatrician in the decision for (non-)referral (appendix A). The questionnaire addressed to medical oncologists included tick-box questions regarding motives for omitting adjuvant chemotherapy in stage III colon cancer patients aged 75 years or older, consultation of a geriatrician in their treatment decision, type of chemotherapy schemes the medical oncologists prescribed to these patients, and an open question regarding the (grade of) toxicities deemed (un)acceptable

(appendix B). Demographic characteristics of the respondent (gender, age) were also included in both questionnaires. To increase the number of respondents, the final versions of the questionnaires were intentionally kept to a three page maximum, which could be completed within 10 minutes.

The medical specialists were requested to return the questionnaire to the Netherlands Comprehensive Cancer Organisation (IKNL) in a provided envelope. Returned questionnaires contained a study number only. If the questionnaire was not returned within 4 weeks, a reminder letter and questionnaire were sent. A second digital reminder and online questionnaire were sent 2 weeks after the first reminder.

Results

29 medical specialists from 10 hospitals returned a completed questionnaire (response 81%). More specifically, 18 surgeons (response 86%) and 11 medical oncologists (response 73%) participated. All hospitals were represented by at least one surgeon (range 1-3) and one medical oncologist (range 1-2). A large majority of the respondents was male (25/29, 86%) and were in the age groups 40-49 years (10/29, 34%) or 50-59 years (10/29, 34%). In contrast, among the non-respondents (3 surgeons, 4 medical oncologists), the majority was female (4/7, 57%). Age of the non-respondents was unknown.

Motives for non-referral and non-treatment

Figure 1 presents the proportions of surgeons and medical oncologists reporting each listed reason as motive that they have for non-referral or non-treatment with adjuvant chemotherapy of patients with stage III colon cancer aged 75 years or older. The motives that most surgeons had were comorbidity or bad general health condition of the patient (100% of the surgeons); presence of surgical complications (89%); and refusal of adjuvant therapy by the patient and/or family (61%). These motives were also reported by most of the medical oncologists (91%, 63% and 91% of the medical oncologists, respectively). Medical oncologists also frequently reported that they had the motive that expected side effects were too severe (63%). Age per se was only an issue in a minority of the surgeons and medical oncologists. Two medical oncologists (18%) reported a motive for non-treatment which was not in the predefined list, namely non-referral of the patient by the surgeon.

Involvement of geriatricians

When surgeons were asked whether they sometimes consulted a geriatrician in their decisions for (non-)referral of elderly patients for adjuvant chemotherapy, less than half of them (n=7, 39%) reported to do so, whereas more than half of the medical oncologists (n=6, 55%) reported to consult a geriatrician in some of their decisions for (non-)treatment. The consultation of geriatricians seemed to be related to the hospital where the medical specialists worked; the surgeons reporting consultation of geriatricians originated from five hospitals and the medical oncologists reporting consultation of geriatricians originated from these same

five hospitals and one additional hospital. Amongst them were three of the four teaching hospitals for clinical geriatrics.

The percentage of patients for whom those 7 surgeons reported to consult a geriatrician in their decision for (non-)referral varied between 2% and 30%, with an outlier of 100%. The latter was accompanied by the explanation that all patients are discussed in a multidisciplinary team that includes a geriatrician. The percentage of patients for whom the 6 medical oncologists reported to consult a geriatrician in their decision for (non-)treatment varied from 5% to 25%.

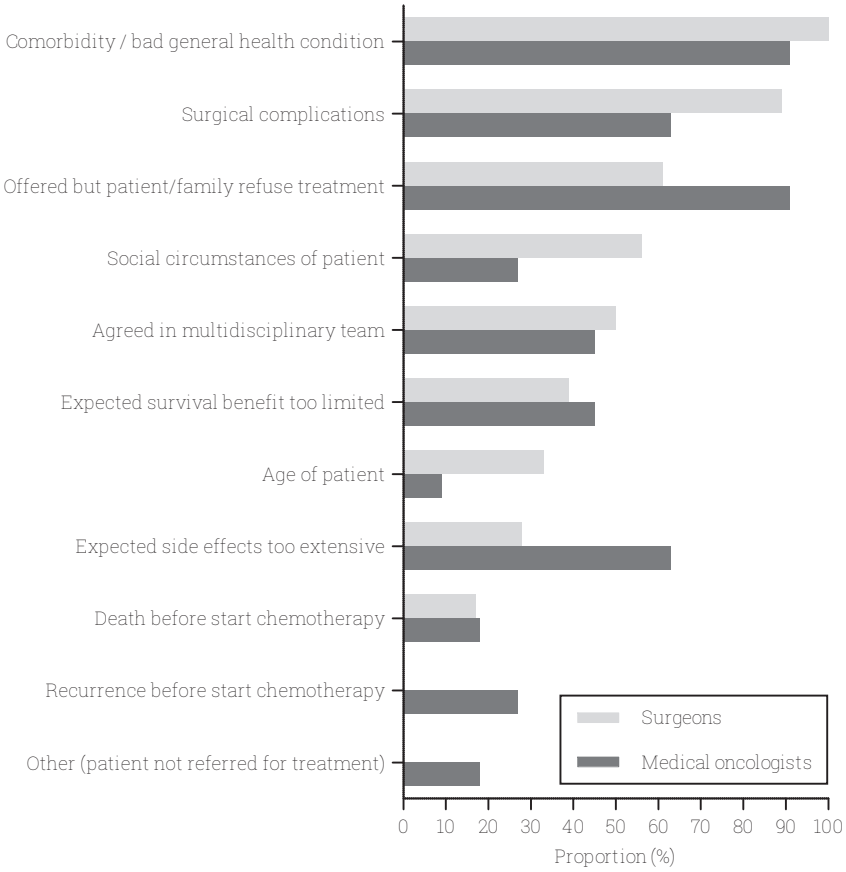

Figure 1 Proportions of surgeons and medical oncologists reporting each listed reason as motive that they have for non-referral or non-treatment with adjuvant chemotherapy of patients with stage III colon cancer aged 75 years or older (n=29)

(Choice for) chemotherapy schemes

Capecitabine combined with oxaliplatin (CAPOX) and capecitabine monotherapy were both reported by 10 out of 11 medical oncologists as chemotherapy schemes that they prescribe to elderly patients with stage III colon cancer. Furthermore, 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) was prescribed by three medical oncologists and 5-fluoracil and leucovorin (5-FU/LV) by one. No other schemes were reported.

Medical oncologists' decision for monotherapy versus combination therapy was mostly based on comorbid disease(s) (i.e. neurological complaints), general health condition of the patient (i.e. poor performance) and toxicity profile of the chemotherapeutics (i.e. risk of neuropathy in case of oxaliplatin administration). Other factors, such as quality of life and patient preference, were mentioned less often.

(Un)acceptable toxicities

In general, medical oncologists defined grade ≤2 toxicities as acceptable. The one exception was neuropathy, which was only deemed acceptable if grade 1, without dysfunction. Grade ≤2 diarrhea, hand foot syndrome and fatigue were mentioned most often as acceptable toxicities. Other acceptable (mild) side effects reported by medical oncologists were hair loss, temporary change of taste, anorexia, anaemia, kidney disorders, asthenia and bone marrow toxicity.

As unacceptable toxicities, grade ≥3 diarrhoea and hand foot syndrome, and grade ≥2 neuropathy were listed most often. Other unacceptable toxicities mentioned less often were cardiovascular side effects, neutropenia, and leukopenia, if grade ≥3, with a hospitalization indication.

Discussion

Our study showed that comorbidity/bad general health condition of the patient, surgical complications, and refusal of adjuvant chemotherapy by the patient and/or family, were the most frequently reported motives for non-referral and/or non-treatment with adjuvant chemotherapy of stage III colon cancer patients aged 75 years or older. Less than half of the surgeons and little over half of the medical oncologists consulted a geriatrician for a minority of the patients. In case adjuvant chemotherapy was prescribed by medical oncologists, the chemotherapy schemes used were according to the clinical guidelines. Comorbidity, patients general health condition and toxicity profile were the most frequently reported factors on the decision for monotherapy instead of combination therapy. Finally, medical oncologists defined grade ≤2 toxicities as acceptable, with the exception of neuropathy, which was only deemed acceptable if grade ≤1.

The motives that were most frequently reported in our study for non-referral and non-treatment of elderly colon cancer patients are in line with previous research[4,5]. In a Canadian study, comorbidity was also the most common reason for not recommending adjuvant chemotherapy based on a chart review. Interestingly, they found that 22% of the

patients for whom comorbidity was listed as the motive for non-treatment actually had a comorbidity score of 0 based on administrative data.

Patient or family refusal was another frequently reported motive for non-referral and non-treatment. A further elucidation of which reason(s) patients or family had for refusing adjuvant chemotherapy was not part of our questionnaire. Therefore, it is unknown whether their reasons were justly and based on adequate background information.

The reason of medical oncologists to not treat patients because of non-referral by the surgeon has been studied previously. In that study, approximately 20% of the variability in whether a stage III colon cancer patient is referred to a medical oncologist is attributable to the surgeon. Surgeons with fewer years since graduation, surgeons who practice in a teaching hospital and surgeons with a higher volume of colon cancer patients, are more likely to refer patients to a medical oncologist[6]. It is questionable whether surgeons should decide not to refer certain patients to the medical oncologist and, additionally, whether patients and/or family should refuse adjuvant chemotherapy before consulting a medical oncologist. Non-consultation withholds patients from explicit information about chemotherapy treatment and from an assessment of their physiological and functional status 6 to 12 weeks after surgery. This assessment is usually undertaken before administering chemotherapy and is complex among elderly due to their aging process[7]. Every stage III colon cancer patient, regardless of age, should be referred to the medical oncologist, who should weigh the risk for recurrence or death against the risk for toxicity of the treatment. In addition, the International Society of Geriatric Oncology (SIOG) recommends that for patients with physical or psychological comorbidities, a geriatrician should be involved in patient management[8]. A recent study showed both the need for geriatric screening and assessment -revealing problems for more than half of older cancer patients, which led to geriatric interventions in a quarter of these patients- and the feasibility of including geriatrics in oncology care[9]. Another study showed that the influence of geriatric assessment on treatment decisions is most prominent for chemotherapy[10].

In the adjuvant treatment of elderly patients with colon cancer, medical oncologists generally agree that grade ≤2 toxicities are acceptable, except for neuropathy (only acceptable if grade ≤1). Recent studies show that chemotherapy-induced peripheral neuropathy is negatively associated with quality of life[11] and may continue years after diagnosis among patients treated with oxaliplatin[12].

Toxicity of the chemotherapeutics was also one of the most reported factors influencing the decision for monotherapy instead of combination therapy. For elderly patients, the use of combination regimens and more specifically of oxaliplatin-based chemotherapy should also depend on the individual patient's remaining life expectancy (without recurrence) as the gains from oxaliplatin are uncertain in comparison to monotherapy with fluoropyrimidine[8]. On the other hand, the recently published Dutch practice guideline states that for patients with a microsatellite instable tumour, only oxaliplatin-containing chemotherapy should be offered as the effectiveness of fluoropyrimidine monotherapy is questionable for these patients.

Variation among surgeons and medical oncologists in deciding on referral for and treatment with adjuvant chemotherapy for elderly stage III colon cancer patients can be related to the lack of evidence-based guidelines for elderly cancer patients. Although in general adjuvant chemotherapy is recommended as the efficacy has been established in clinical trials[8], it is questionable whether this also applies to elderly cancer patients. Elderly cancer patients are often excluded from clinical trials and trial populations may therefore not always be representative for elderly patients seen in clinical practice. Furthermore, observational studies focusing on overall survival are prone to selection bias. The realization of clinical trials especially for elderly cancer patients and of prospective observational studies including an extensive description of elderly patient characteristics and with appropriate outcome parameters is important to expand the evidence base for the treatment of elderly cancer patients.

A limitation of our study is that the study population was relatively small. However, the response rate was high and we were able to include medical specialists from 10 different hospitals. Additionally, to keep our questionnaire short, we limited the amount of predefined motives for (non-)treatment.

In conclusion, in case adjuvant chemotherapy is prescribed to elderly stage III colon cancer patients by medical oncologists, chemotherapy schemes used are in line with clinical guidelines and medical oncologists agree on acceptable levels of toxicity. However, variation among surgeons and medical oncologists in motives for non-referral, non-treatment and consultation of geriatricians when deciding on adjuvant chemotherapy for elderly, shows the complexity and need for specific knowledge. We believe that every elderly patient with or without comorbidity should be referred to the medical oncologist to receive sufficient information and to assess the benefits and risks of adjuvant chemotherapy. In our opinion, in case of doubt on vitality or goal setting for individual patients, it is preferable that consultation by a geriatrician and geriatric assessment are part of the care pathway.

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Appendices

Appendix A Questions related to (non-)referral posed to surgeons (translated from the original questionnaire)

Which motives do you have for not referring a patient aged 75 years or older with stage III colon cancer for adjuvant chemotherapy? (multiple answers possible)

- o Comorbidity/bad general health condition
- o Social circumstances of patient
- o Age of patient
- o Agreed in multidisciplinary team
- o Surgical complications
- o Expected survival benefit too limited
- o Expected side effects too extensive
- o Offered but patient/family refuse treatment
- o Recurrence before start chemotherapy
- o Death before start chemotherapy
- o Other, namely: .....

Do you sometimes involve a geriatrician in your decision to not refer a patient aged 75 years or older with stage III colon cancer for adjuvant chemotherapy? If yes; can you give an estimate on how often you involve a geriatrician in your decision?

- o No
- o Yes, for approximately .....% of the patients

Appendix B Questions related to (non-)treatment posed to medical oncologists (translated from the original questionnaire)

Which motives do you have for not treating a patient aged 75 years or older with stage III colon cancer with adjuvant chemotherapy? (multiple answers possible)
- o Comorbidity/bad general health condition
- o Social circumstances of patient
- o Age of patient
- o Agreed in multidisciplinary team
- o Surgical complications
- o Expected survival benefit too limited
- o Expected side effects too extensive
- o Offered but patient/family refuse treatment
- o Recurrence before start chemotherapy
- o Death before start chemotherapy
- o Other, namely: .....

Do you sometimes involve a geriatrician in your decision to not treat a patient aged 75 years or older with stage III colon cancer with adjuvant chemotherapy? If yes; can you give an estimate on how often you involve a geriatrician in your decision?
- o No
- o Yes, for approximately .....% of the patients

With which chemotherapy scheme(s) do you treat patients aged 75 years or older with stage III colon cancer? (multiple answers possible)
- o 5-FU/LV
- o FOLFOX (5-FU, leucovorin and oxaliplatin)
- o Capecitabine
- o CAPOX / XELOX
- o Uracil / tegafur
- o Other, namely: .....

Which factors play a role in your decision to treat certain patients aged 75 years or older with stage III colon cancer with monotherapy and others with combination therapy?
.....(multiple answers possible)

What are, in your opinion, acceptable side effects that are to be expected from treatment with (a certain type of) adjuvant chemotherapy for patients aged 75 years or older with stage III colon cancer?
.....(multiple answers possible)

What are, in your opinion, unacceptable side effects that can arise from treatment with (a certain type of) adjuvant chemotherapy for patients aged 75 years or older with stage III colon cancer?
.....(multiple answers possible)

Administration of adjuvant oxaliplatin to patients with stage III colon cancer is affected by age and hospital

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To the editor

According to the Dutch clinical practice guideline, the standard adjuvant treatment for patients with stage III colon cancer is a combination of fluorouracil, leucovorin and oxaliplatin (FOLFOX). Fluorouracil can be replaced by its oral analogue capecitabine, which provides similar overall survival, and is more convenient for the patient. The guideline also states that an adjuvant regimen without oxaliplatin, i.e. capecitabine monotherapy, can be considered in cases of advanced age or concomitant comorbidity. The efficacy of these chemotherapy schemes has been established in clinical trials, which showed improved disease-free and overall survival[1-3].

Population-based studies have shown that the administration of chemotherapy declines with increasing age[4-6]. For individual patients, there may be valid reasons to deviate from standard treatment, however, variations in treatment between hospitals or geographic regions after adjustment for patient casemix indicate that arguments for deviating from clinical guidelines are interpreted differently across hospitals[5-8].

To date, the type of chemotherapy has often been ignored in population-based studies. Therefore, the current study evaluates which factors influence the administration of oxaliplatin-based chemotherapy as compared to non-oxaliplatin-based chemotherapy for patients with stage III colon cancer treated in daily clinical practice.

Patients and methods

Data from the Eindhoven Cancer Registry (ECR) were used. The ECR is a population-based registry that collects data on all newly diagnosed cancer patients in the southern Netherlands. The registry area comprises about 2.4 million inhabitants and encompasses six pathology departments, 10 community hospitals, and two radiotherapy institutions. Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators. The anatomical site of the tumour is registered according to the International Classification of Disease – Oncology (ICD-O). The tumour-node-metastasis (TNM) classification is used for stage notification of the primary tumour, according to the edition valid at the time of cancer diagnosis. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, is provided at an aggregated level for each postal code. Comorbidities are registered according to a slightly modified version of the Charlson Comorbidity index.

For the present study, patients who underwent resection only or who underwent resection and received adjuvant chemotherapy for primary colon cancer stage III ($T_{any}N_{1-2}M_0$) diagnosed between 2008 and 2011 were included. Patients were excluded if they had received radiotherapy (n=20), neo-adjuvant chemotherapy (n=6), local chemotherapy (n=3) or targeted therapy (n=7). Stage was based on the pathological TNM classification. Tumour localisation was categorised into three subsites: proximal colon (C18.0–C18.5), distal colon (C18.6–C18.7) and colon other/not otherwise specified (C18.8–C18.9). Patients were divided into age groups: <70, 70–74 and ≥75 years.

Statistical analyses

Differences in patient and tumour characteristics between patients receiving oxaliplatin-based chemotherapy, non-oxaliplatin-based chemotherapy and no chemotherapy were analysed using Chi^2-tests. Differences in casemix between the hospitals were also analysed using Chi^2-tests. Patients with unknown SES, comorbidity, T stage, subsite or differentiation grade were not excluded from the study population, but were not taken into account in the respective Chi^2 calculations.

After stratification by age group, the observed proportions of patients receiving oxaliplatin and non-oxaliplatin-based chemotherapy were calculated for each hospital. The expected proportions of patients receiving oxaliplatin and non-oxaliplatin-based chemotherapy were also calculated after stratification by age group: a multivariable logistic regression model was used to calculate the chance of an individual patient receiving oxaliplatin and non-oxaliplatin-based chemotherapy, adjusted for gender, age, SES, comorbidity, T stage, N stage, subsite, differentiation grade and period of diagnosis. Based on these individual chances, the chance of receiving oxaliplatin and non-oxaliplatin-based chemotherapy was calculated for each hospital by taking the mean of all chances of the individual patients of each hospital.

After exclusion of patients who did not receive adjuvant chemotherapy, multivariable logistic regression analysis was conducted to assess the influence of several patient and tumour characteristics and hospital on the probability of the administration of oxaliplatin.

P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.3, SAS Institute, Cary, NC) was used for all analyses.

Results

The study population consisted of 1140 patients. Overall, 47% of the patients received oxaliplatin-based chemotherapy, 13% received non-oxaliplatin-based chemotherapy and 40% received no chemotherapy. Table 1 shows the general characteristics of the study population by adjuvant treatment.

With regard to casemix in the hospitals, SES and N stage differed significantly between the hospitals (p=0.007 and p=0.048, respectively). Gender, age, comorbidity, subsite, differentiation grade and period of diagnosis did not differ significantly between hospitals.

Figure 1 shows the observed and expected proportions of patients receiving oxaliplatin and non-oxaliplatin-based chemotherapy by hospital of treatment and stratified according to age group.

For patients aged <70 years, the observed proportions of patients receiving oxaliplatin varied from 63% to 87% between the different hospitals (Δ=24%), whereas the expected proportions of patients receiving oxaliplatin ranged from 76% to 79% (Δ=3%). Similarly, the observed proportions of patients receiving non-oxaliplatin varied between 3% and 20% (Δ=17%), whereas the expected proportions ranged from 9% to 10% (Δ=1%).

Table 1 Characteristics of patients with resected stage III colon cancer, by adjuvant treatment (n=1140)

	OX (n=533) n (%)	nOX (n=145) n (%)	NoCT (n=462) n (%)	P value*
Gender				0.070
Male	302 (57)	77 (53)	228 (49)	
Female	231 (43)	68 (47)	234 (51)	
Age				<0.0001
<70	413 (77)	49 (34)	69 (15)	
70-74	84 (16)	29 (20)	62 (13)	
≥75	36 (7)	67 (46)	331 (72)	
SES				<0.0001
Low	83 (16)	33 (23)	142 (31)	
Intermediate	226 (43)	59 (40)	151 (32)	
High	194 (36)	39 (27)	119 (26)	
Institutions	13 (2)	4 (3)	27 (6)	
Unknown	17 (3)	10 (7)	23 (5)	
Comorbidity				<0.0001
0	231 (43)	43 (30)	84 (18)	
1	144 (27)	40 (27)	98 (21)	
≥2	150 (28)	61 (42)	269 (58)	
Unknown	8 (2)	1 (1)	11 (3)	
T stage				0.013
1	7 (1)	9 (6)	7 (2)	
2	56 (11)	14 (10)	37 (8)	
3	395 (74)	104 (72)	332 (72)	
4	41 (8)	12 (8)	42 (9)	
Unknown	34 (6)	6 (4)	44 (9)	
N stage				0.045
1	345 (65)	100 (69)	333 (72)	
2	188 (35)	45 (31)	129 (28)	
Subsite				0.002
Proximal colon	266 (50)	89 (61)	277 (60)	
Distal colon	258 (48)	55 (38)	177 (38)	
Other/NOS	9 (2)	1 (1)	8 (2)	
Differentiation grade				0.010
Well/moderate	399 (75)	105 (72)	301 (65)	
Poor/undifferentiated	105 (20)	32 (22)	125 (27)	
Unknown	29 (5)	8 (6)	36 (8)	
Period of diagnosis				0.004
2008–2009	263 (49)	88 (61)	207 (45)	
2010–2011	270 (51)	57 (39)	255 (55)	

NoCT, no chemotherapy; nOX, non-oxaliplatin-based chemotherapy; OX, oxaliplatin-based chemotherapy.
* P value indicates significance of the Chi^2-test.

In patients aged 70–74 years, the observed proportions receiving oxaliplatin varied from 15% to 100% between hospitals (Δ=85%), whereas the expected proportions ranged between 41% and 61% (Δ=20%). Observed proportions receiving non-oxaliplatin ranged from 0% to 29% (Δ=29%), whereas expected proportions varied between 14% and 18% (Δ=4%).

For patients aged ≥75 years, observed proportions of patients receiving oxaliplatin ranged from 0% to 19% (Δ=19%), whereas the expected proportions varied between 7% and 10% (Δ=3%).

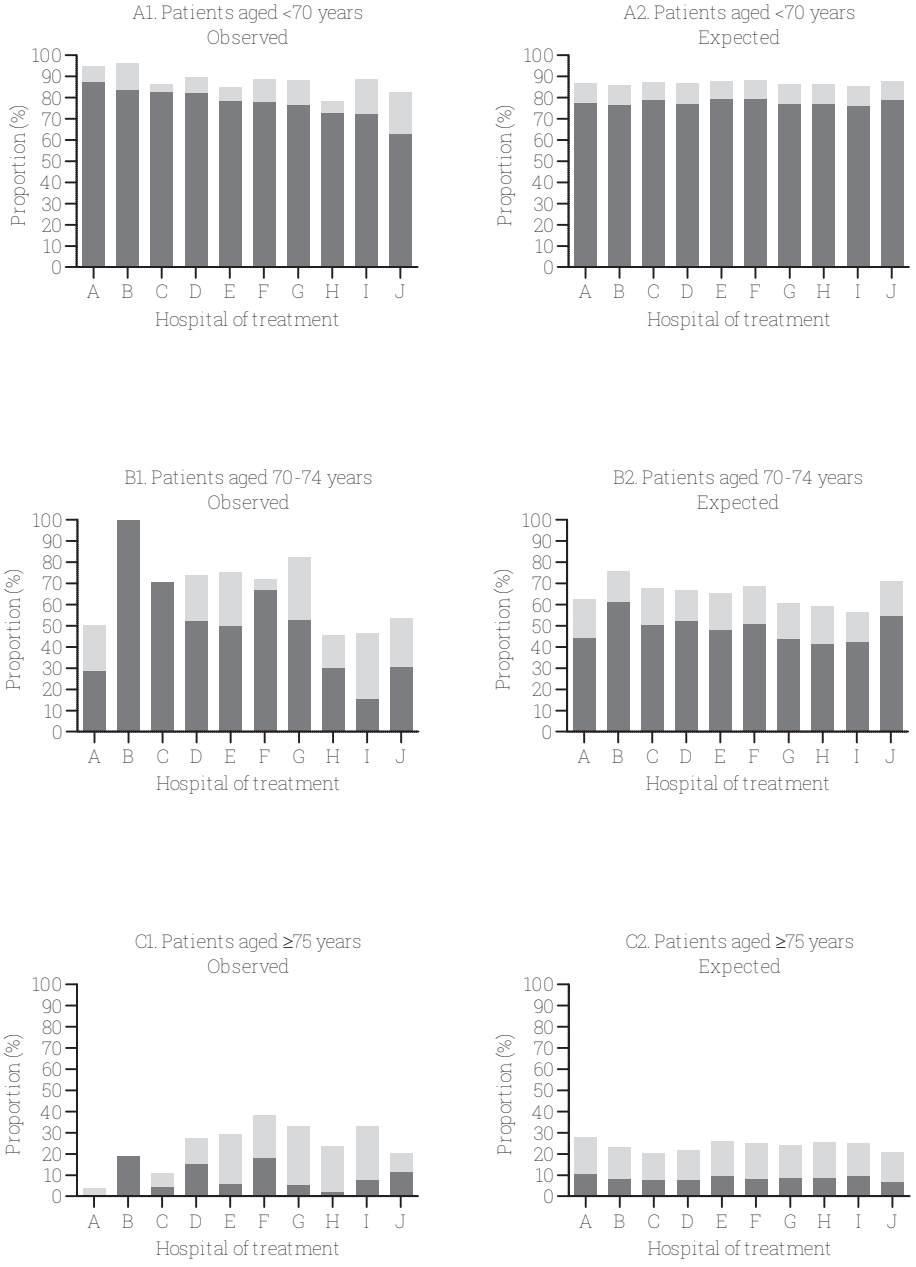

Figure 1 Observed and expected proportions of patients receiving oxaliplatin-based chemotherapy (dark grey) and non-oxaliplatin-based chemotherapy (light grey) among patients with resected stage III colon cancer, by hospital of treatment and age group; expected proportions based on casemix adjustment for gender, age, SES, comorbidity, T stage, N stage, subsite, differentiation grade and period of diagnosis (A: n=531; B: n=175; C: n=434)

Table 2 Crude percentages and odds ratios[a] for receipt of oxaliplatin-based adjuvant chemotherapy among patients with stage III colon cancer treated with adjuvant chemotherapy (n=678)

	Crude %	Odds ratio (95% CI)
Gender		
Male	80	1.00 (reference)
Female	77	1.08 (0.69–1.72)
Age		
<70	89	1.00 (reference)
70-74	74	0.37 (0.21–0.64)
≥75	35	0.06 (0.03–0.11)
SES		
Low	72	1.00 (reference)
Intermediate	79	1.24 (0.68–2.29)
High	83	1.47 (0.76–2.83)
Institutions	76	0.43 (0.11–1.62)
Unknown	63	0.82 (0.27–2.45)
Comorbidity		
0	84	1.00 (reference)
1	78	0.91 (0.51–1.61)
≥2	71	0.86 (0.49–1.49)
Unknown	89	0.95 (0.11–8.48)
T stage		
1	44	0.15 (0.04–0.50)
2	80	1.08 (0.50–2.36)
3	79	1.00 (reference)
4	77	1.79 (0.74–4.33)
Unknown	85	1.68 (0.54–5.16)
N stage		
1	78	1.00 (reference)
2	81	1.18 (0.72–1.93)
Subsite		
Proximal colon	75	1.00 (reference)
Distal colon	82	1.40 (0.87–2.26)
Other/NOS	90	2.07 (0.22–19.06)
Differentiation grade		
Well/moderate	79	1.00 (reference)
Poor/undifferentiated	77	0.90 (0.51–1.60)
Unknown	78	1.14 (0.42–3.09)
Period of diagnosis		
2008–2009	75	1.00 (reference)
2010–2011	83	2.08 (1.26–3.44)
Hospital of treatment		
A	84	0.59 (0.20–1.75)
B	90	1.82 (0.50–6.59)
C	92	1.95 (0.70–5.47)
D	82	1.00 (reference)
E	75	0.54 (0.22–1.31)
F	81	0.93 (0.37–2.33)
G	67	0.35 (0.14–0.85)
H	74	0.53 (0.22–1.26)
I	64	0.26 (0.10–0.69)
J	69	0.39 (0.15–1.04)

[a] Adjusted for all variables listed.

With respect to patients receiving non-oxaliplatin, observed proportions ranged between 0% and 28% (Δ=28%), whereas the expected proportions varied from 13% to 18% (Δ=5%).

In the subgroup of patients treated in the adjuvant setting, large inter-hospital variation in the addition of oxaliplatin was noted, ranging from 76–96% for patients aged <70 years, from 33–100% for patients aged 70–74 years, and from 0–100% for patients aged ≥75 years.

Table 2 presents the crude percentages and adjusted odds ratios for receipt of oxaliplatin among patients treated with adjuvant chemotherapy. Patients treated in hospital G and I were less likely to receive oxaliplatin than patients treated in hospital C (adjusted OR for G vs. C 0.35, 95% CI 0.14–0.85; adjusted OR for I vs. C 0.26, 95% CI 0.10–0.69). Furthermore, older patients, patients with a T1 stage and patients diagnosed in 2008-2009 were also less likely to receive oxaliplatin.

Discussion

The current study showed that although the casemix was similar in all hospitals and the expected proportions of patients receiving oxaliplatin therefore varied little between hospitals, the observed proportions of patients receiving oxaliplatin varied greatly between hospitals. In the multivariate analysis, patients from two hospitals had decreased odds of receiving oxaliplatin. Although the addition of oxaliplatin improves disease-free and overall survival, this improvement is rather limited[2,9]. Additionally, the administration of oxaliplatin is associated with more toxicity and more inconvenience due to the need for intravenous administration[3]. These factors are likely taken into account by medical oncologists. A study recently found that physician and hospital characteristics had little influence on the receipt of adjuvant oxaliplatin among patients aged ≥65 years[10]. However, another study found that patients in rural regions were less likely to receive oxaliplatin-containing chemotherapy than patients from large metropolitan regions[8]. The wide variation among hospitals in chemotherapy administration and type of chemotherapy demonstrated in the present study underscores the influence of institutional factors and local practice patterns in determining the administration and type of adjuvant chemotherapy. Data on the influence of physicians and practice settings on the prescription of adjuvant systemic treatment in general are scarce. In 2009, a population-based study showed that elderly women with breast cancer treated by oncologists in a private practice were more likely to receive adjuvant chemotherapy. This was presumed to be related to patient volume; oncologists in private practices generally had a higher patient volume, translating into a greater comfort level in treating patients[11]. Other factors hypothesized by the authors to play a role in daily practice are clinical tradition, age of the medical specialists, multidisciplinary team meetings, involvement of medical specialists in scientific research and the teaching status of the hospital.

The range of observed proportions of patients receiving oxaliplatin among hospitals was found to vary more for patients aged ≥75 years than for patients aged <70 years. Despite the significant proportion of elderly patients with colon cancer in clinical practice, the elderly are often excluded from clinical trials. Approximately 50% of patients with colon

cancer are aged ≥70 years, but only 16% of patients enrolled in trials were ≥70 years[12]. Since data on the effects of adjuvant chemotherapy in patients aged ≥75 years is scarce, it is impossible for guidelines to advise on adjuvant chemotherapy for patients over 75 years of age and even more complicated to indicate who is eligible for platinum-based regimens, leaving this decision up to the physicians' judgement. However, a pooled analysis using data from randomized trials compared the efficacy of adjuvant chemotherapy for elderly and non-elderly patients and found that the efficacy of FOLFOX with regard to disease-free and overall survival was similar for patients aged less than 70 years and patients aged 70 years or older[12]. This confirms that older patients fit enough to meet clinical trial eligibility criteria derive the same benefit from adjuvant chemotherapy as younger trial participants. However, whether the addition of oxaliplatin offers additional benefit to patients aged ≥75 years remains unclear, as the available data are conflicting[9,12-15]. A previous study suggested that physicians consider the eligibility criteria of the MOSAIC trial (i.e. age <75 years, Karnofsky performance score ≥60, and adequate blood counts and liver and kidney function) when deciding on the prescription of oxaliplatin[16]. Uncertainty remains over whether the lower rates of oxaliplatin observed in elderly patients represent justified clinical judgement or undertreatment. Moreover, this observational study cannot answer to what degree the older patients not treated adjuvantly might also have tolerated and benefited from the administration of adjuvant chemotherapy.

A limitation of our study is that detailed information on patients' health status and nutritional status is lacking. ECOG performance status, for example, has previously been demonstrated to influence the administration of oxaliplatin[17]. However, the results of our study indicate that casemix did not differ between hospitals so this cannot explain the large variation in adjuvant (oxaliplatin-based) chemotherapy administration found between hospitals. Another limitation of our study is that for those patients receiving adjuvant chemotherapy, additional information on the number of (oxaliplatin-based) cycles administered, dose schedules used and dose modifications were not available. Previous research showed that approximately 30% of stage III colon cancer patients discontinued adjuvant therapy after less than three months despite recommendations to continue for six months[17]. Additionally, older patients are more likely than their younger counterparts to discontinue oxaliplatin early[18].

In conclusion, the decision to administer oxaliplatin does not only depend on predictable factors such as age and T stage, but also on hospital. The impact of hospital variation in type of adjuvant chemotherapy on outcomes such as toxicity, disease-free survival and quality of life needs to be further elucidated in population-based studies.

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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 (163,744 mg/m^2, interquartile range [IQR] 83,397-202,858 mg/m^2) than for patients treated with CapMono (189,195 mg/m^2, IQR 111,667-228,125 mg/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%), gastrointestinal (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, pathological 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 Chi^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 Chi^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).

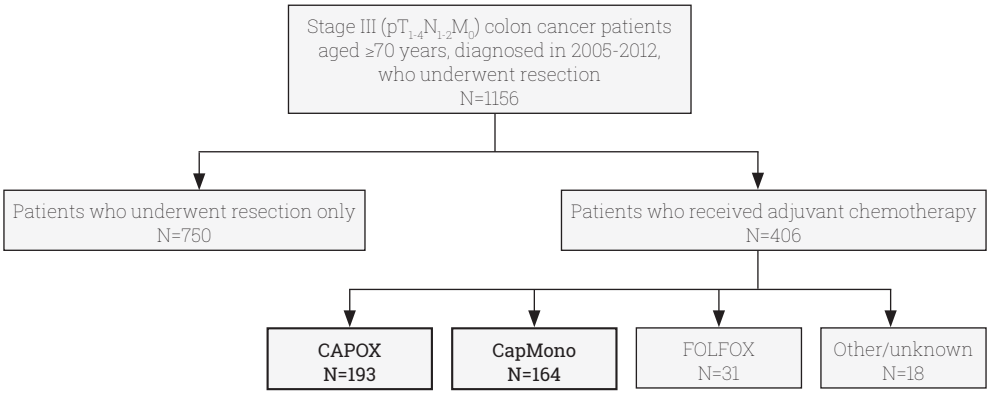

Figure 1 Overview of patients included in the study

Table 1 Crude percentages and adjusted ORs[a] 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.
Included in the analyses but results not shown for comorbidity unknown, ASA score unknown, subsite other/NOS and differentiation grade unknown.
[a] Adjusted for all variables listed.

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 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).

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 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/m^2*	*mg/m^2*	*mg/m^2*
Median	604	163,744	189,195
Interquartile range	261 - 768	83,397 - 202,858	111,667 - 228,125
Minimum-maximum	109 - 1,176	1,869 - 253,270	4,980 - 294,329
Unknown	13	13	21

Table 3 Crude percentages and adjusted odds ratios[a] 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; OR, odds ratio.
Included in the analyses but results not shown for comorbidity unknown, ASA score unknown, subsite other/not otherwise specified and differentiation grade unknown.
[a] Adjusted for all variables listed.

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 gastrointestinal 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 (90,314-204,722)	6 (2-6)	605 (263-768)
P value	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 value	<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 value	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 value	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 value	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 value	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 value	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 2500 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 gastrointestinal 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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The course of neuropathic symptoms in relation to adjuvant chemotherapy among elderly patients with stage III colon cancer: a longitudinal study

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Abstract

Introduction: Among the elderly, the impairment of functional capacities due to neuropathy can have a significant impact. The aim of the present study was to investigate the course of neuropathic symptoms among elderly patients with stage III colon cancer treated with CAPOX, capecitabine monotherapy or no adjuvant chemotherapy.

Materials and methods: The Netherlands Cancer Registry was used to select patients with stage III colon cancer and aged ≥70years. Questionnaires were sent after resection (T1) and six (T2) and twelve months (T3) later. Neuropathy was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20. Logistic generalized estimating equations analyses were used to evaluate the effect of chemotherapy on the course of neuropathic symptoms.

Results: Of 155 eligible patients, 117 (76%) completed the T1 questionnaire, and 69 and 59 completed the T2 and T3 questionnaires, respectively. The course of the sensory symptoms tingling fingers or hands; tingling toes or feet; numbness in fingers or hands; and numbness in toes or feet was significantly unfavorable for patients treated with adjuvant chemotherapy (CAPOX or capecitabine) compared with that for patients who had not received adjuvant chemotherapy. The course of numbness in toes or feet also differed significantly between patients treated with CAPOX (T1, 7%; T2, 50%; T3, 42%) and patients treated with capecitabine (T1, 17%; T2, 31%; T3, 8%). Additionally, patients treated with capecitabine reported significantly less tingling toes or feet (T1, 6%; T2, 25%; T3, 7%) compared with patients treated with CAPOX (T1, 0%; T2, 50%; T3, 58%).

Conclusion: The course of several sensory symptoms over time was less favorable for elderly patients with colon cancer treated with chemotherapy. Moreover, CAPOX was associated with more symptoms in toes and feet compared with capecitabine. It is important to inform patients of these risks to enable informed decision-making.

Introduction

The adjuvant treatment for patients with pathological stage III colon cancer after resection of the primary tumor is chemotherapy (CTx). Oxaliplatin combined with a fluoropyrimidine (i.e. capecitabine or 5-fluorouracil/leucovorin) is the standard regimen for these patients, although the benefit of oxaliplatin on recurrence-free and overall survival is uncertain in elderly patients[1-5]. In the case of contraindications for oxaliplatin, adjuvant treatment should consist of capecitabine monotherapy (CapMono)[6].

CTx-induced peripheral neuropathy (CIPN) is increasingly recognized as an important toxicity which compromises treatment plans. Although peripheral neuropathy is a very rare complication of capecitabine[7], it is a common adverse effect of oxaliplatin. Oxaliplatin can cause both an acute, mainly cold-triggered neuropathy and a chronic neuropathy[8,9]. Symptoms can differ: most symptoms are sensory, although motor and autonomic dysfunction can also occur[10,11]. In general, acute neuropathy is characterized by paresthesia and dysesthesia of the hands and feet and reverses within a week, while chronic neuropathy mainly consists of symptoms of hypoesthesia and is only partly reversible[9,12,13]. Acute neuropathy occurs in 80 to 90% of patients treated with oxaliplatin[10,14-16] and chronic neuropathy affects 30 to 60% of patients[10,15].

The prevention and treatment of CIPN remain difficult[17]. Because CIPN interferes with many aspects of daily life and is negatively associated with health-related quality of life, this is of major concern[18,19]. Particularly for the growing population of elderly patients, the impairment of functional capacities can have a significant effect on their lives. Having information about the effects of different CTx regimens on neuropathic symptoms can help patients and clinicians in deciding on a suitable treatment course.

The aim of the present study was to gain insight into differences in the course of neuropathic symptoms among elderly patients with stage III colon cancer subsequently treated with a combination of capecitabine and oxaliplatin (CAPOX), CapMono or no adjuvant CTx in daily clinical practice. First, the interaction between treatment and time was investigated. Subsequently, the main effect of treatment on neuropathic symptoms was investigated. We expected that patients treated with CAPOX would experience neuropathic symptoms more often and that the course of their symptoms would be less favorable than that of patients treated with CapMono or no CTx.

Materials and methods

Data collection and study population

Data were collected within the PROFILES database (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship)[20]. PROFILES is linked to clinical data from the population-based Netherlands Cancer Registry (NCR). The NCR records the data for all patients with newly diagnosed cancer in the Netherlands. Information on patients and tumor characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators of the NCR. The anatomic tumor site is registered according to the International Classification of Diseases – Oncology. The pathologic TNM

classification is used for staging of the primary tumor, according to the edition valid at the cancer diagnosis. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, is provided at an aggregated level for each postal code. The number of comorbid conditions at time of cancer diagnosis is registered using a slightly modified version of the Charlson comorbidity index.

The NCR was used to identify patients with stage III ($pT_{1-4}N_{1-2}M_0$) colon cancer aged ≥70 years who had undergone resection. Questionnaire data were collected for patients diagnosed in nine hospitals in the southeastern part of the Netherlands between March 2013 to October 2014. The treating physicians verified the status of each eligible patient before the patient was approached for study participation (e.g. patients with serious cognitive impairment were excluded). All eligible patients received an invitation letter from their attending surgeon and both a paper questionnaire and a login account and password to complete the survey online. After two weeks, reminders were sent to patients who had not responded to the survey. The first questionnaire was sent after resection (T1) and the respondents received subsequent questionnaires six months (T2) and twelve months (T3) later.

A certified medical ethics committee approved the present study, and all patients provided written informed consent for participation in the study and agreed to the linkage of the questionnaire data with the sociodemographic and clinical information in the NCR.

Study measures

Peripheral neuropathy was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20)[21], which contains 20 items assessing sensory, motor and autonomic symptoms. All items are measured on a four point Likert scale ranging from 1 (not at all) to 4 (very much).

Diabetes, osteoarthritis or rheumatoid arthritis are comorbid conditions that are known to be associated with neuropathy-like symptoms. The presence of these conditions at completion of the first questionnaire was self-reported by the patients and assessed using the adapted Self-Administered Comorbidity Questionnaire[22].

Statistical analyses

Differences in the characteristics between the respondents and non-respondents were assessed using Chi^2-tests and Fisher's Exact tests as appropriate. Differences between respondents completing 1 questionnaire and respondents completing ≥2 questionnaires and differences between respondents treated with CAPOX, CapMono or no CTx were analyzed similarly.

For the group of respondents subsequently treated with CAPOX, CapMono or no CTx, the number and percentages of patients who experienced mild to severe neuropathic symptoms at T1 were reported per individual item of the EORTC QLQ-CIPN20. The severity of neuropathic symptoms was dichotomized as in a previous report[23] as follows: the response

categories 'a little', 'quite a bit' and 'very much' were grouped as mild to severe neuropathic symptoms and the response category 'not at all' as no neuropathic symptoms. Multivariable logistic regression analyses were performed to evaluate differences between treatment groups in the proportion of patients reporting mild to severe neuropathy symptoms at T1. Adjustments were made for age category (70-74, 75-79 and ≥80 years), and the presence of osteoarthritis and diabetes.

For the subgroup of patients completing ≥2 questionnaires and treated with CAPOX, CapMono or no CTx, the number and percentages of patients who experienced mild to severe neuropathic symptoms at T1, T2 and T3 were reported per individual item of the EORTC QLQ-CIPN20. Because neuropathic symptoms were repeatedly measured in the same patients and observations of one patient were not independent of each other, logistic Generalized Estimating Equations (GEE) analyses with an exchangeable correlation structure were used. Both the interaction between treatment and time (i.e. T1 to T2 to T3) and the main effect of treatment on neuropathic symptoms were evaluated. First, the interaction between receipt of CTx (yes vs. no, regardless of regimen) and time was evaluated. Second, the interaction between the CTx regimen received and time was assessed. In all logistic GEE-analyses, adjustments were also made for time, age category, osteoarthritis and diabetes.

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

Study population

Of the 155 elderly patients with stage III colon cancer eligible for participation, 117 completed the first questionnaire (T1), resulting in a response rate of 76%. Subsequently, 69 patients completed the second questionnaire (T2) and 59 patients the third questionnaire (T3) (figure 1).

No significant differences between the respondents and non-respondents were present, except for older age at the cancer diagnosis among the non-respondents (table 1). For the respondents, the mean interval between the date of resection of the primary tumor and the date of completing the first questionnaire was 40 ± 18 days. Additionally, among the respondents treated with adjuvant CTx, 88% completed the first questionnaire before or during cycle 1 and 12% during cycle 2. The patients receiving CAPOX were younger than those receiving CapMono or no CTx, and the patients treated without CTx more often had osteoarthritis compared with those receiving CAPOX or CapMono (table 2).

Analyses between the respondents who completed one and those who completed ≥2 questionnaires showed no significant differences in gender, age, SES, number of comorbid conditions, diabetes or adjuvant treatment (data not shown). Osteoarthritis was less common among respondents completing ≥2 questionnaires than among respondents completing 1 questionnaire (19% vs. 35%, p=0.0434).

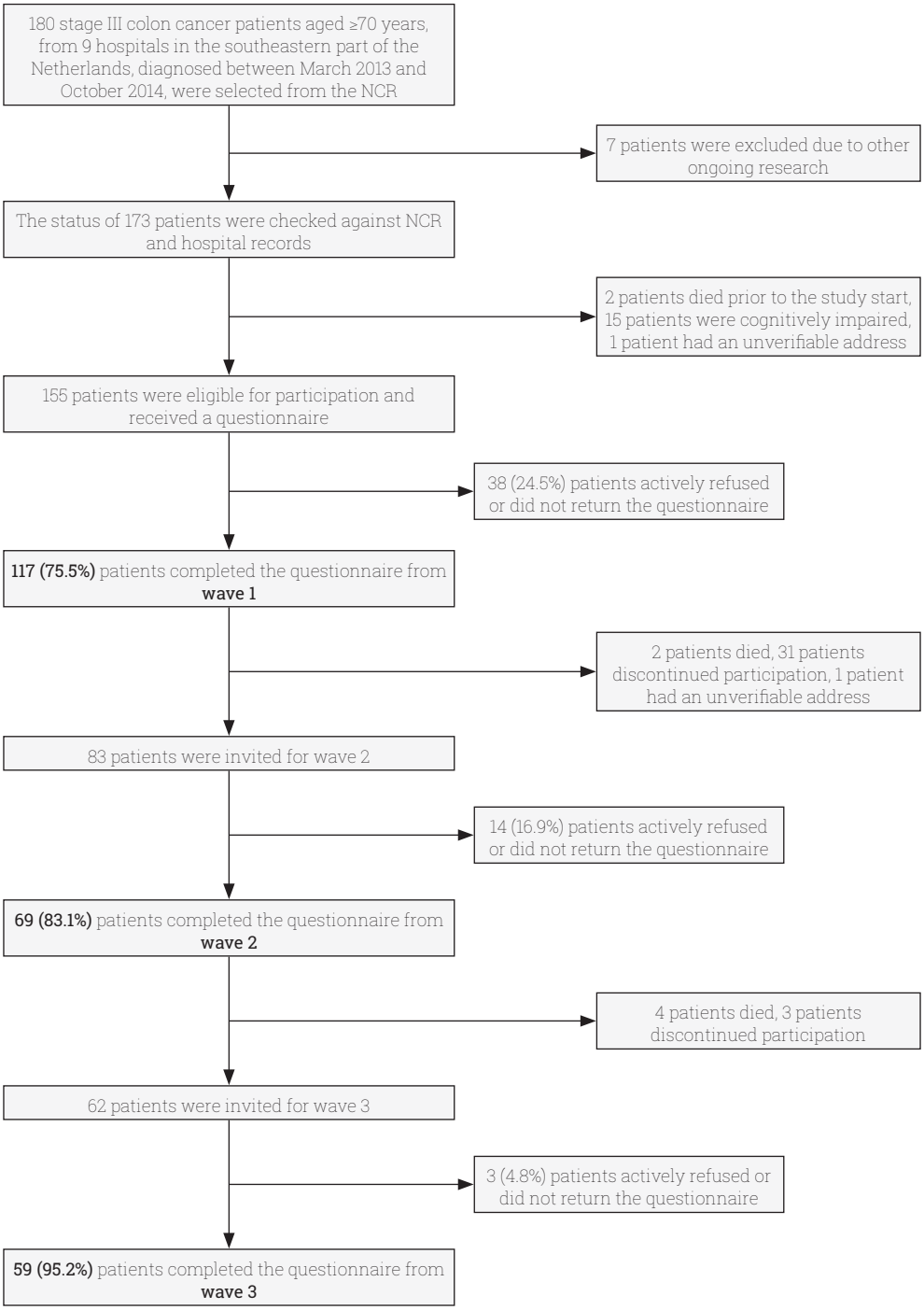

Figure 1 Flowchart of the data collection process

Table 1 Characteristics of respondents (completing ≥1 questionnaire) and non-respondents

	Respondents n=117 (76%) n (%)	Non-respondents n=38 (24%) n (%)	P value[b]
Gender			0.6043
Male	58 (50)	17 (45)	
Female	59 (50)	21 (55)	
Age[a]			0.0417
70-74 years	32 (27)	13 (34)	
75-79 years	44 (38)	6 (16)	
≥80 years	41 (35)	19 (50)	
Socioeconomic status			0.4562
Low	29 (25)	11 (29)	
Intermediate	41 (35)	14 (36)	
High	28 (24)	11 (29)	
Institutions	4 (3)	1 (3)	
Unknown	15 (13)	1 (3)	
Number of comorbid conditions[a]			0.1278
0	18 (15)	5 (13)	
1	37 (32)	7 (18)	
≥2	62 (53)	25 (66)	
Unknown	0 (0)	1 (3)	
Adjuvant chemotherapy			0.5290
None	58 (50)	18 (47)	
Capecitabine + oxaliplatin	27 (23)	7 (18)	
Capecitabine monotherapy	28 (24)	13 (34)	
Other regimen	4 (3)	0 (0)	

[a] At time of cancer diagnosis
[b] P value indicates significance of the Chi²-test or Fisher's exact test as appropriate

Neuropathic symptoms at baseline (T1)

Among the group of T1 respondents subsequently treated with CAPOX, CapMono or no CTx, the neuropathy symptoms that bothered >20% of the patients at baseline included trouble getting or maintaining an erection (80% of men), trouble opening a jar or bottle due to loss of strength in hands (36%), trouble walking stairs or standing up from a chair due to weakness in legs (29%), trouble handling small objects (e.g. buttoning a blouse, 27%), trouble hearing (25%), dizziness after standing up (25%) and tingling fingers or hands (24%).

After adjustment for age category, osteoarthritis and diabetes, patients (subsequently) treated with CAPOX less often reported trouble walking stairs or standing up from a chair due to weakness in legs compared with patients (subsequently) treated with CapMono (crude percentages 7% vs. 36%, adjusted p=0.0266) and compared with patients who did not receive adjuvant CTx (crude percentages 7% vs. 36%, adjusted p=0.0418) (table 3). No other differences were found among the groups.

Table 2 Characteristics of respondents completing ≥1 questionnaire and treated with capecitabine + oxaliplatin (CAPOX), capecitabine monotherapy (CapMono) or no adjuvant chemotherapy (no CTx)

	CAPOX n=27 (24%) n (%)	CapMono n=28 (25%) n (%)	No CTx n=58 (51%) n (%)	P value[c]
Gender				0.4315
Male	16 (59)	15 (54)	26 (45)	
Female	11 (41)	13 (46)	32 (55)	
Age[a]				<0.0001
70-74 years	16 (59)	6 (22)	6 (10)	
75-79 years	9 (33)	11 (39)	24 (42)	
≥80 years	2 (8)	11 (39)	28 (48)	
Socioeconomic status				0.7329
Low	7 (26)	10 (36)	12 (21)	
Intermediate	10 (37)	10 (36)	18 (31)	
High	7 (26)	5 (18)	16 (27)	
Institutions	0 (0)	0 (0)	4 (7)	
Unknown	3 (11)	3 (10)	8 (14)	
Number of comorbid conditions[a]				0.0606
0	7 (26)	2 (7)	8 (14)	
1	10 (37)	5 (18)	20 (34)	
≥2	10 (37)	21 (75)	30 (52)	
Diabetes[b]				0.3763
No	24 (89)	21 (75)	48 (83)	
Yes	3 (11)	7 (25)	10 (17)	
Osteoarthritis[b]				0.0148
No	24 (89)	24 (86)	37 (64)	
Yes	3 (11)	4 (14)	21 (36)	

[a] At time of cancer diagnosis
[b] At time of first questionnaire
[c] P value indicates significance of the Chi^2-test or Fisher's exact test as appropriate

Course of neuropathic symptoms by adjuvant treatment (T1-T2-T3)

The data from patients who completed ≥2 questionnaires are listed in table 4, which includes an overview of the number and percentages of patients who reported mild to severe neuropathic symptoms at T1, T2 and T3 by adjuvant treatment.

Logistic GEE analyses showed a significant interaction between the receipt of CTx (yes vs. no) and time (T1, T2, T3) for the items tingling fingers or hands (p=0.0017); tingling toes or feet (p=0.0060); numbness in fingers or hands (p=0.0118); and numbness in toes or feet (p=0.0073). This indicates that the course of these neuropathic symptoms differed between patients treated with and without CTx. Additionally, for the item numbness in toes or feet, a significant interaction was also present between CTx regimen and time (p=0.0152), indicating that the course of this symptom differed between patients receiving CAPOX and patients receiving CapMono. A graph of these four sensory neuropathic symptoms is depicted in figure 2.

In the subgroup of patients receiving CTx, a main effect of CTx regimen was found for the item tingling toes or feet (p=0.0199): patients receiving CapMono had a lower odds of

reporting tingling toes or feet compared with patients receiving CAPOX (odds ratio 0.18, 95% confidence interval 0.04-0.76).

For all other neuropathic symptoms, no significant interaction between adjuvant treatment and time was found, indicating that the course of these neuropathic symptoms over time was similar among the treatment groups.

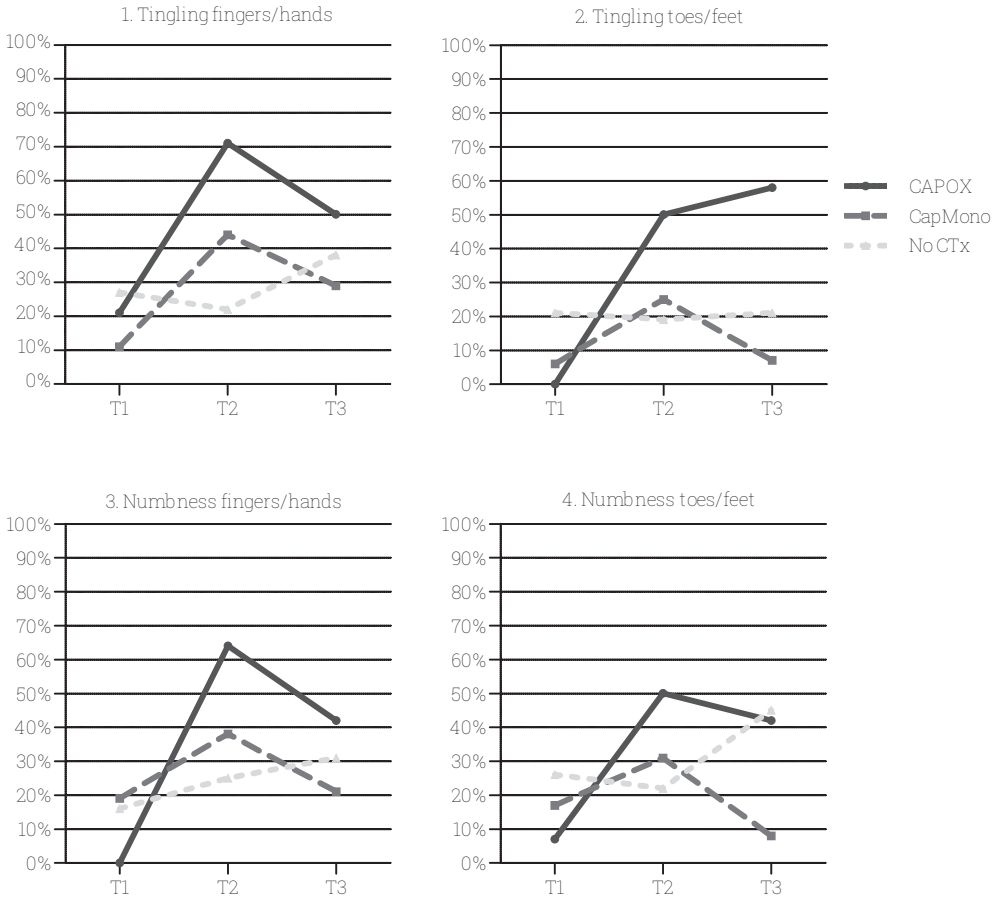

Figure 2 Graphical representation of the course of percentages of patients who experienced mild to severe neuropathic symptoms[a] over time among respondents[b] treated with capecitabine + oxaliplatin, capecitabine monotherapy or no adjuvant chemotherapy

[a] Mild to severe symptoms reflect the response categories: 'a little', 'quite a bit' and 'very much'

[b] Only respondents completing ≥2 questionnaires were included

Table 3 Number and percentages of patients who experience mild to severe neuropathic symptoms[a] at T1 among respondents (subsequently) treated with capecitabine + oxaliplatin (CAPOX), capecitabine monotherapy (CapMono) or no adjuvant chemotherapy (no CTx)

	CAPOX n (%)	CapMono n (%)	No CTx n (%)	P value* CAPOX vs. CapMono	P value* CAPOX vs. no CTx
Sensory symptoms and problems					
1. Tingling fingers or hands	9 (33)	3 (11)	15 (26)	0.2056	0.4392
2. Tingling toes or feet	5 (19)	2 (7)	8 (14)	0.5159	0.5188
3. Numbness in fingers or hands	1 (4)	4 (15)	11 (20)	0.0784	0.0527
4. Numbness in toes or feet	3 (11)	5 (18)	12 (21)	0.2827	0.1398
5. Aching or burning pain in finger or hands	1 (4)	2 (7)	3 (5)	0.7081	0.9969
6. Aching or burning pain in toes or feet	2 (7)	2 (7)	3 (5)	0.6855	0.3989
9. Trouble standing or walking	2 (7)	4 (15)	12 (21)	0.8127	0.3712
10. Trouble distinguishing hot and cold water	0 (0)	0 (0)	5 (9)	#	#
18. Trouble hearing	4 (15)	7 (26)	17 (30)	0.3760	0.2338
Motor scale					
7. Cramps in hands	3 (11)	4 (15)	10 (18)	0.5002	0.4186
8. Cramps in feet	1 (4)	4 (15)	13 (22)	0.3300	0.2555
11. Trouble holding a pen making writing difficult	2 (7)	1 (4)	11 (19)	0.6188	0.1180
12. Trouble handling small objects (e.g. buttoning a blouse)	5 (19)	7 (25)	18 (31)	0.6450	0.3934
13. Trouble opening jar/bottle due to loss of strength in hands	7 (26)	11 (39)	22 (39)	0.2026	0.2994
14. Trouble walking because your feet come down too hard	0 (0)	1 (4)	8 (14)	#	#
15. Trouble walking stairs or standing up from a chair due to weakness in legs	2 (7)	10 (36)	20 (36)	0.0266	0.0418
19. Only for those driving cars: trouble driving due to use of pedals	1 (7)	2 (13)	2 (8)	0.4504	0.5762
Autonomic scale					
16. Dizziness after standing up	5 (19)	5 (18)	18 (32)	0.8791	0.3273
17. Blurry vision	4 (15)	4 (14)	11 (19)	0.7814	0.4828
20. Only for males: trouble getting or maintaining an erection	5 (83)	8 (89)	11 (73)	0.7240	0.7263

[a] Mild to severe symptoms reflect the response categories: 'a little', 'quite a bit' and 'very much'.

* P values based on logistic regression analyses showing differences adjusted for age category, osteoarthritis and diabetes.

Numbers are too small to calculate P value.

Table 4 Number and percentages of patients who experience mild to severe neuropathic symptoms[a] over time among respondents who completed ≥2 questionnaires and were treated with capecitabine + oxaliplatin (CAPOX), capecitabine monotherapy (CapMono) or no adjuvant chemotherapy (no CTx)

	CAPOX			CapMono			No CTx		
	T1 *n (%)*	*T2* *n (%)*	*T3* *n (%)*	*T1* *n (%)*	*T2* *n (%)*	*T3* *n (%)*	*T1* *n (%)*	*T2* *n (%)*	*T3* *n (%)*
Sensory symptoms and problems									
1. Tingling fingers or hands	3 (21)	10 (71)	6 (50)	2 (11)	7 (44)	4 (29)	9 (27)	7 (22)	11 (38)
2. Tingling toes or feet	0 (0)	7 (50)	7 (58)	1 (6)	4 (25)	1 (7)	7 (21)	6 (19)	6 (21)
3. Numbness in fingers or hands	0 (0)	9 (64)	5 (42)	3 (19)	6 (38)	3 (21)	5 (16)	8 (25)	9 (31)
4. Numbness in toes or feet	1 (7)	7 (50)	5 (42)	3 (17)	5 (31)	1 (8)	9 (26)	7 (22)	13 (45)
5. Aching or burning pain in finger or hands	1 (7)	1 (7)	1 (8)	1 (6)	3 (19)	2 (14)	2 (6)	2 (6)	4 (14)
6. Aching or burning pain in toes or feet	1 (7)	3 (21)	2 (17)	1 (6)	4 (25)	3 (21)	2 (6)	6 (19)	5 (17)
9. Trouble standing or walking	0 (0)	6 (43)	3 (25)	2 (11)	4 (25)	2 (14)	6 (18)	8 (24)	7 (24)
10. Trouble distinguishing hot and cold water	0 (0)	4 (29)	4 (33)	0 (0)	1 (6)	1 (7)	3 (9)	1 (3)	2 (7)
18. Trouble hearing	0 (0)	1 (7)	1 (8)	4 (24)	8 (47)	3 (21)	9 (27)	13 (39)	11 (37)
Motor scale									
7. Cramps in hands	0 (0)	0 (0)	3 (25)	3 (17)	4 (24)	4 (29)	5 (16)	9 (28)	9 (31)
8. Cramps in feet	0 (0)	0 (0)	3 (25)	2 (12)	4 (24)	6 (43)	8 (24)	15 (47)	11 (37)
11. Trouble holding a pen making writing difficult	0 (0)	5 (36)	5 (42)	1 (6)	2 (12)	1 (7)	7 (21)	6 (19)	5 (17)
12. Trouble handling small objects (e.g. buttoning a blouse)	2 (14)	8 (57)	7 (58)	4 (22)	7 (41)	5 (36)	11 (32)	12 (36)	13 (43)
13. Trouble opening jar/bottle due to loss of strength in hands	3 (21)	7 (50)	4 (33)	7 (39)	10 (59)	6 (43)	11 (33)	10 (30)	12 (40)
14. Trouble walking because your feet come down too hard	0 (0)	1 (7)	0 (0)	0 (0)	2 (13)	1 (7)	6 (18)	7 (22)	6 (20)
15. Trouble walking stairs or standing up from a chair due to weakness in legs	1 (7)	4 (29)	5 (42)	6 (33)	7 (41)	5 (36)	11 (33)	13 (39)	13 (43)
19. Only for those driving cars: trouble driving due to use of pedals	0 (0)	1 (11)	0 (0)	1 (9)	0 (0)	0 (0)	1 (6)	2 (10)	1 (5)
Autonomic scale									
16. Dizziness after standing up	2 (14)	2 (14)	2 (17)	3 (17)	2 (13)	3 (21)	10 (30)	11 (34)	9 (30)
17. Blurry vision	1 (7)	5 (36)	1 (8)	3 (17)	6 (35)	3 (21)	7 (21)	7 (22)	6 (21)
20. Only for males: trouble getting or maintaining an erection	2 (67)	4 (67)	3 (100)	7 (100)	7 (100)	6 (86)	8 (67)	10 (91)	10 (100)

[a] Mild to severe symptoms reflect the response categories: 'a little', 'quite a bit' and 'very much'.

Discussion

The present longitudinal study of real world elderly patients with stage III colon cancer provided insight into the course of neuropathic symptoms of patients receiving treatment with CAPOX, CapMono or no CTx.

Because peripheral neuropathy is a very rare complication of capecitabine[7], we were surprised that the course of some sensory symptoms was less favorable for all patients receiving adjuvant CTx, regardless of whether the patients had received CAPOX or CapMono. A possible explanation might be found in another toxicity often caused by capecitabine: palmar-plantar erythrodysesthesia or 'hand-foot syndrome' (HFS)[24]. Initial symptoms of HFS are dysesthesia and tingling in the palms, fingers and soles of the feet. These symptoms can progress in a few days to burning pain with erythema and swelling[25-28]. The symptoms caused by HFS are therefore partly comparable to the symptoms caused by neuropathy. We expect that patients treated with CapMono scored these complaints on the questionnaires.

The finding that patients treated with CAPOX more often reported tingling toes or feet than patients treated with CapMono could have been because in HFS, the palms of the hands are more frequently affected than the soles of the feet[25,26,28]. Additionally, another study that used the EORTC QLQ-CIPN20 sensory subscale to measure CIPN reported more numbness, tingling and burning pain in toes or feet than in fingers or hands[29].

Studies on patient-reported neuropathic symptoms are limited. In both the XELOXA trial and MOSAIC trial, neuropathic symptoms were monitored and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events[30,31]. In the XELOXA trial, all grade neurosensory toxicity was common (78%) but mild to moderate in severity (i.e. 10-12% grade III-IV) among patients treated with CAPOX[30]. In the MOSAIC trial, 92% of the patients treated with FOLFOX developed peripheral sensory neuropathy (PSN) of any grade during treatment and respectively 41%, 30% and 15% had residual PSN six months, one year and four years after treatment[31]. The frequency of grade III PSN at these time points was 13%, 2%, 1% and <1% respectively. For patients treated with FULV, grade III PSN during treatment was reported for <1%[31]. In the NSABP C-07 trial, self-reported neurotoxicity was included for a subgroup of the trial population and measured using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Oxaliplatin-specific Neurotoxicity questionnaire[32]. Among patients without symptoms at baseline, the most often reported symptoms during the second cycle of treatment with oxaliplatin were cold-induced pain in the hands and feet (severity 'quite a bit' or 'very much' for 26%) and hand numbness/tingling (20%). By 6 months after the start of CTx, cold-induced hand/foot pain had diminished (8%), but hand numbness/tingling remained high (17%), and foot numbness/tingling (17%) and foot discomfort (10%) increased. Foot numbness/tingling remained high (14%) after 18 months[32]. Of note, both in this trial and the previously mentioned MOSAIC trial, oxaliplatin was administered in a regimen with 5-fluorouracil instead of the oral analogue capecitabine. Another study showed that although the incidence of acute neuropathy seemed comparable between CAPOX and FOLFOX, chronic peripheral neuropathy appeared to be more common with CAPOX[15].

In contrast to previous studies on patient reported neuropathic symptoms, only patients

aged ≥70 years were included in the present study. A comparison of the neuropathic symptoms as reported in our study with a younger patient population would be valuable to establish whether elderly experience neuropathic symptoms to a smaller, similar or greater extent. Unfortunately data for a direct comparison are not available. However, the symptoms reported in our study were similar to those reported in earlier studies, suggesting that the elderly experience neuropathic symptoms comparable to that of their younger counterparts, although comparisons are difficult because these studies included patients 2 to 11 years after diagnosis and the data were not longitudinal[33,34].

The present study also showed that at baseline several neuropathic symptoms were already present and bothered more than 20% of the patients. These symptoms were in the sensory, motor and autonomic domains. Previous research has shown that subclinical peripheral neuropathy is a common finding in patients with colorectal cancer prior to CTx, indicating that the cancer itself is a contributing factor[35]. Moreover, many symptoms could also be related to the aging process instead of to the cancer or its treatment[36]. With the exception of weakness in legs, which was less often reported by patients treated with CAPOX, no differences in symptoms were found at T1 among the treatment groups. That the patients treated with CAPOX were younger and less often had osteoarthritis suggests that confounding by indication might have played a role.

Previous studies have shown that the benefit of oxaliplatin on recurrence-free and overall survival is uncertain in elderly patients with stage III colon cancer[1-5]. To help clinicians and patients decide on a desirable course of treatment, not only information on the survival benefit associated with different treatment regimens is important, but also information on the possible short- and long-term side-effects. CIPN might impair functional capacities and affect health-related quality of life, both during and after adjuvant treatment[18,19]. Neuropathy is only partly reversible and, as also shown in previous research, chronic neuropathy is still present in many patients ≥1 year after the termination of therapy[12]. Even as long as 11 years after diagnosis, neuropathic symptoms have still been reported by colorectal cancer patients, especially sensory symptoms in the toes and feet among those treated with oxaliplatin[33]. As the effect of oxaliplatin on survival is uncertain among elderly and the results of the present study indicate that the elderly treated with CAPOX compared with CapMono reported more sensory symptoms in toes/feet that are known to persist long term, the addition of oxaliplatin might not be justified. At the very least, the present results do not provide support for the addition of oxaliplatin to adjuvant CTx for elderly patients with stage III colon cancer.

Previous studies have shown that a higher cumulative dose of oxaliplatin seems to be a predictive factor for the development of chronic peripheral neuropathy[12,34]. This chronic peripheral neuropathy occurs after a cumulative dose of ~750-800 mg/m^2 of oxaliplatin[16]. Unfortunately, the number of patients in our study was too small to perform analyses according to the cumulative dose received. The present study also had some other limitations. Although we achieved a high response rate at T1 despite the timing shortly after major cancer surgery, the sample size at T2 and T3 was relatively small. At T1, in addition to informed consent, patients were able to indicate that they discontinued participation for the next 2 questionnaires. It is conceivable that patients would have decided differently if

asked after six months. Additionally, not all patients receiving adjuvant CTx had completed the first questionnaire before the start of adjuvant CTx. However, a large majority had completed the questionnaire before the start of the second cycle, during which the first toxicity might occur[16,37]. It is possible that the differences were underestimated as a result. Furthermore, the scores for each item were dichotomized, thereby impeding the possibility to investigate differences in the severity of symptoms among the treatment groups. Previous research has shown that even low grade toxicities can lead to treatment alterations in older patients[38]. Another limitation was that it was unknown why non-respondents declined participation. This could be caused by neuropathic symptoms or other problems. However, we were able to compare respondents and non-respondents on sociodemographic and clinical characteristics and only found differences in age at the time of cancer diagnosis.

Despite these limitations, the current study provides an important contribution to the limited data available on self-reported neuropathic symptoms according to CTx regimen among elderly patients with stage III colon cancer. The strong points of the present study include the longitudinal design with a baseline measurement and the adjustment for comorbid conditions (i.e. osteoarthritis and diabetes) also associated with neuropathic symptoms. Although rheumatoid arthritis is also associated with neuropathy-like complaints, only 3 patients in our study had rheumatoid arthritis; therefore, no adjustments were made for this comorbid condition.

Conclusions

Our results have shown that the course of some sensory symptoms over time is less favorable for all patients undergoing adjuvant chemotherapy, regardless of the regimen. Additionally, patients treated with CAPOX more often reported symptoms in toes and feet than patients treated with CapMono. While improving survival is important, evaluating the harms of treatment will determine the functional effectiveness of the treatment. It is of paramount importance to inform patients on the risk of developing CIPN to enable patients to make an informed decision.

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7

Reduced risk of distant recurrence after adjuvant chemotherapy in patients with stage III colon cancer aged 75 years or older

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Abstract

Background: Little is known about the effects of adjuvant chemotherapy on the risk of distant recurrence in elderly with stage III colon cancer, treated in daily practice.

Patients and methods: One thousand two hundred and ninety-one stage III colon cancer patients diagnosed in the southern Netherlands between 2003 and 2008 were included. Propensity score matching was applied to create a subsample to reduce bias caused by differences between patients receiving adjuvant chemotherapy and patients not receiving adjuvant chemotherapy. For both the total study population and the propensity score matched sample, Cox regression analysis was used to discriminate independent risk factors for distant recurrence.

Results: Adjuvant chemotherapy (CT) was correlated with a reduced risk of distant recurrence in both the total study population [hazard ratio (HR) CT versus nCT 0.55, 95% confidence interval (CI) 0.42-0.70] and in the propensity score matched sample (HR CT versus nCT 0.46, 95% CI 0.33-0.63). In separate analyses for patients aged <75 years and ≥75 years, the effect of adjuvant chemotherapy on the risk of distant recurrence remained comparable for both age groups (HR CT versus nCT 0.50, 95% CI 0.37-0.68 and 0.57, 95% CI 0.36-0.90 respectively).

Conclusion: Distant recurrence risks at higher age definitely warrant consideration of adjuvant chemotherapy for elderly stage III colon cancer patients. This decision should be based on a multidisciplinary and functional assessment of the patient, not on age.

Introduction

The primary treatment for stage III colon cancer is surgery, followed by adjuvant chemotherapy consisting of 5-fluorouracil (5-FU) often in combination with oxaliplatin[1,2].

The efficacy of adjuvant chemotherapy has been established in clinical trials, which showed improved disease-free and overall survival[3-8]. However, despite the significant proportion of elderly patients in clinical practice, elderly are often excluded in clinical trials. Approximately half of the patients with colon cancer is aged ≥70 years, but only 16% of patients enrolled in trials was ≥70 years[9].

More recently, studies have compared the efficacy of adjuvant chemotherapy for elderly and nonelderly patients using pooled data from randomized trials. One study found that for selected elderly, adjuvant treatment (5-FU plus leucovorin or levamisole) had the same significant positive effect on overall survival and time to recurrence as for their younger counterparts[10]. In another pooled analysis, the efficacy of FOLFOX was similar for patients aged <70 years and patients aged ≥70 years with regard to disease-free and overall survival[9]. These pooled analyses confirm that older patients fit enough to meet clinical trial eligibility criteria derive the same benefit from adjuvant therapy as younger trial participants.

Population-based studies have shown that despite its apparent efficacy in older patients, chemotherapy usage declines rapidly with age[2,11-18]. As a result, it is difficult to determine whether the efficacy realized in trials applies for elderly in daily practice. Therefore, population-based studies should offer additional insight in the effectiveness of adjuvant chemotherapy in elderly patients.

To date, most population-based studies focused on overall survival, which is prone to selection bias (e.g. the fittest patients receiving adjuvant chemotherapy thereby by definition exhibiting better survival). Little is known about the risk of distant recurrence in daily clinical practice. Therefore, the aim of this study is to gain more insight in the effect of adjuvant chemotherapy on the risk of distant recurrence in patients with stage III colon cancer, using population-based data from clinical practice. Furthermore, it is investigated whether patients aged ≥75 years treated in clinical practice derive comparable benefit from adjuvant chemotherapy as their younger counterparts.

Methods

Data collection

Data from the Eindhoven Cancer Registry (ECR) were used. The ECR is a population-based registry which collects data on all newly diagnosed cancer patients in the southern Netherlands. The registry area comprises about 2.4 million inhabitants and encompasses 6 pathology departments, 10 community hospitals, and 2 radiotherapy institutions. 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 (ICD-O). The TNM (tumour-node-metastasis) classification is used

for stage notification of the primary tumour, according to the edition valid at time of cancer diagnosis. Comorbidities are registered according to a slightly modified version of the Charlson Comorbidity index. Socioeconomic status, based on individual fiscal data on the economic value of the home and household income, is provided at an aggregated level for each postal code. The quality of the data is high, due to thorough training of the registration team and computerized consistency checks at regional and national levels.

Additional data on the development of distant recurrences and the date of diagnosis of distant recurrences was collected from the medical records by experienced registration administrators, encompassing all patients with stage I-III ($T_{any}N_{any}M_0$) colorectal cancer diagnosed between 2003 and 2008. In the present study, distant recurrence is defined as a distant metastasis of primary colon cancer in other organs, regional lymph nodes not included, after a primary diagnosis of M_0 disease.

Study population

For the present study, all patients with resected stage III ($T_{any}N_{1-2}M_0$) primary colon cancer diagnosed in the south of the Netherlands in the period 2003-2008 were included. Stage was based on the pathological TNM classification. If pathological stage was unknown, clinical stage was used (n=4). Tumour localization 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). The study period was divided into categories: 2003-2005 and 2006-2008. Patients were divided into age groups (<75/≥75 years).

Propensity score matched sample

Due to the population-based nature of the data, comparing patients who received adjuvant chemotherapy with non-recipients, raises the question of potential endogeneity bias caused by differences between both groups. Therefore, a subsample was created through the application of propensity score matching. Propensity scores were determined on the basis of a logistic regression model in which the dependent variable was the variable of interest (adjuvant chemotherapy receipt) and the independent variables were factors potentially associated with the variable of interest (sex, age, socioeconomic status, comorbidity, T stage, N stage, differentiation grade, subsite and period of diagnosis). The propensity score represented the probability that a patient would not receive adjuvant chemotherapy. On the basis of propensity scores, patients who did not receive adjuvant chemotherapy were then matched to patients who did receive adjuvant chemotherapy using the nearest available pair matching method. Individuals were matched within tight bounds of the propensity scores; predicted probability could vary by no more than 0.01 (1%) on a scale of 0 to 1.

Statistical analyses

For both the total study population and the propensity score matched sample, differences between age groups and differences between patients receiving versus not receiving

adjuvant chemotherapy were analysed by means of Chi^2-tests. Furthermore, crude 5-year percentages for distant recurrence were calculated based on Kaplan-Meier curves to correct for differences in follow-up time and Cox regression analyses were used to discriminate independent risk factors for distant recurrence. Time to distant recurrence was defined as the time from first diagnosis to distant recurrence. Patients without a distant recurrence were censored at time of death or last follow-up date, whichever occurred first.

P values below 0.05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.3, SAS Institute, Cary, NC) was used for all analyses.

Results

One thousand two hundred ninety-one patients were included in the study of whom 56% received adjuvant chemotherapy and 31% developed a distant recurrence. 37% of the study population was aged ≥75 years. Median follow-up time was 32 months. In the propensity score matched sample, 466 patients (36%) of the original study population could be included, with an equal proportion of patients receiving and not receiving adjuvant chemotherapy. 32% was aged ≥75 years and 34% developed a distant recurrence. Median follow-up time was 29 months.

Table 1 shows the demographic distribution and the proportion of patients receiving adjuvant chemotherapy according to age group, for both the total study population and the propensity score matched sample. In the total study population, patients aged ≥75 years received significantly less adjuvant chemotherapy than patients aged <75 years (p<0.0001). Furthermore, patients aged ≥75 years were more often female (p<0.0001) and had more comorbidities (p<0.0001) than patients aged <75 years. Patients aged ≥75 years also had more poor or undifferentiated tumours (p=0.020) and more proximal located tumours (p<0.0001) in comparison to patients aged <75 years. Finally, patients aged ≥75 years and patients aged <75 years differed with regard to socioeconomic status (p<0.0001). Within the group of patients aged <75 years, patients receiving adjuvant chemotherapy were younger (p<0.0001), had less comorbidities (p<0.0001) and had higher socioeconomic status (p=0.004) than non-recipients. Among patients aged ≥75 years, patients receiving adjuvant chemotherapy were less often female (p=0.028), were younger (p<0.0001), had higher socioeconomic status (p=0.034) and had more N2 stage (p=0.048) than non-recipients.

In the propensity score matched sample, patients aged ≥75 years had more comorbidities (p=0.015) than patients aged <75 years. Both in the group of patients aged <75 years as in the group of patients aged ≥75 years, patients receiving adjuvant chemotherapy did not differ from non-recipients.

Table 2 shows the crude 5-year percentages and adjusted hazard ratios (HRs) for distant recurrence. For the total study population, multivariate analysis showed that after adjustment for relevant patient and tumour characteristics, the risk of recurrence was correlated with adjuvant chemotherapy receipt [HR CT versus nCT 0.55, 95% confidence interval (CI) 0.42-0.70]. In addition, lower T stage, lower N stage and a well or moderate differentiation grade all reduced the recurrence risk. Age did not significantly influence the recurrence risk. When

Table 1 Demographic distribution and proportion of patients receiving adjuvant chemotherapy by age group, for the total study population (n=1291) and for the propensity score matched sample (n=466)

	Total study population				Propensity score matched sample			
	<75 years		*≥75 years*		*<75 years*		*≥75 years*	
	n	*% CT*	*n*	*% CT*	*n*	*% CT*	*n*	*% CT*
Total	816	78	475	17	317	50	149	51
Sex								
Male	434	78	195	22	166	45	72	53
Female	382	79	280	14	151	54	77	49
Age (years)								
<65	401	87			110	52		
65-69	191	77			79	46		
70-74	224	64			128	50		
75-79			220	32			123	51
≥80			255	5			26	50
Comorbidity								
0	319	87	83	18	87	51	29	48
1	223	77	121	22	93	45	45	51
≥2	212	68	241	17	110	51	70	54
Unknown	62	77	30	3	27	56	5	20
Socioeconomic status								
Low	188	74	162	13	83	51	44	48
Intermediate	338	82	136	21	119	52	47	53
High	254	80	118	22	98	51	49	45
Institutions	21	57	48	8	10	20	4	100
Unknown	15	53	11	36	7	14	5	80
T stage								
1-2	68	75	37	19	28	46	14	50
3	603	80	360	16	231	51	109	48
4	145	75	78	24	58	45	26	65
N stage								
1	572	77	345	15	236	51	101	49
2	244	81	130	23	81	46	48	56
Differentiation grade								
Well/moderate	574	79	304	18	211	48	95	52
Poor/undifferentiated	196	76	148	15	84	51	45	49
Unknown	46	76	23	26	22	55	9	56
Subsite								
Proximal	419	79	306	15	165	50	83	53
Distal	380	79	166	21	144	50	63	49
Other/NOS	17	65	3	33	8	25	3	33
Distant recurrence								
Yes	264	77	142	20	107	45	50	48
No	552	79	333	16	210	52	99	53
Period of diagnosis								
2003-2005	358	79	220	15	137	52	66	47
2006-2008	458	78	255	20	180	48	83	54

CT, adjuvant chemotherapy; n, number of patients.

Table 2 Crude 5 year percentages and hazard ratios[a] of developing a distant recurrence after resection for stage III colon cancer for the total study population (n=1291), and for the propensity score matched sample (n=466)

	Total study population		Propensity score matched sample	
	Crude 5-year %	*Hazard ratio (95% CI)*	*Crude 5-year %*	*Hazard ratio (95% CI)*
Sex				
Male	40	1.00 (reference)	44	1.00 (reference)
Female	37	0.91 (0.75-1.12)	39	0.87 (0.62-1.22)
Age (years)				
<65	37	1.00 (reference)	44	1.00 (reference)
65-69	40	1.04 (0.76-1.41)	35	0.79 (0.47-1.33)
70-74	39	1.10 (0.81-1.48)	39	1.08 (0.69-1.71)
75-79	41	1.02 (0.74-1.41)	44	0.89 (0.57-1.39)
≥80	38	0.81 (0.56-1.17)	37	0.53 (0.22-1.28)
SES				
Low	38	0.80 (0.61-1.05)	40	0.78 (0.50-1.21)
Intermediate	42	1.05 (0.82-1.33)	41	0.97 (0.66-1.44)
High	37	1.00 (reference)	41	1.00 (reference)
Comorbidity				
0	37	1.00 (reference)	39	1.00 (reference)
1	39	1.07 (0.82-1.39)	40	0.98 (0.62-1.54)
≥2	38	1.06 (0.82-1.38)	41	1.11 (0.71-1.72)
Unknown	46	1.36 (0.94-1.98)	58	1.70 (0.93-3.09)
T stage				
1-2	22	0.56 (0.35-0.90)	20	0.40 (0.17-0.91)
3	38	1.00 (reference)	41	1.00 (reference)
4	51	1.63 (1.28-2.08)	55	1.57 (1.06-2.32)
N stage				
1	34	1.00 (reference)	38	1.00 (reference)
2	52	1.96 (1.59-2.42)	51	1.53 (1.06-2.21)
Subsite				
Proximal colon	38	1.00 (reference)	43	1.00 (reference)
Distal colon	38	1.09 (0.89-1.34)	39	1.15 (0.81-1.63)
Other/NOS	65	1.80 (0.96-3.35)	38	0.78 (0.24-2.57)
Differentiation grade				
Well/moderate	35	1.00 (reference)	35	1.00 (reference)
Poor/undifferentiated	46	1.43 (1.14-1.79)	54	2.02 (1.40-2.91)
Unknown	48	1.52 (1.01-2.28)	51	1.59 (0.85-2.97)
Period of diagnosis				
2003-2005	41	1.00 (reference)	41	1.00 (reference)
2006-2008	35	0.87 (0.71-1.06)	41	1.10 (0.79-1.54)
Adjuvant chemotherapy				
No	42	1.00 (reference)	50	1.00 (reference)
Yes	36	0.55 (0.42-0.70)	34	0.46 (0.33-0.63)

[a] Adjusted for all variables listed.
CI, confidence interval; NOS, not otherwise specified.

the analysis was repeated for patients aged <75 years and ≥75 years separately, the effect of adjuvant chemotherapy on the recurrence risk remained comparable for both age groups (HR CT versus nCT 0.50, 95% CI 0.37-0.68 and 0.57, 95% CI 0.36-0.90, respectively).

For the propensity score matched sample, comparable results were found. The strength of the effect of adjuvant chemotherapy on the development of distant recurrence even increased (HR 0.46, 95% CI 0.33-0.63).

Discussion

Given the increasing life expectancy, the number of elderly patients in oncologic practice will increase substantially in the near future[19].

In line with previous research[2,11-18], the current study shows older patients are less likely to receive adjuvant chemotherapy. The use of chemotherapy declines with age due to, e.g. comorbidity, frailty, lack of a supportive care system or decreased acceptance of side effects leading to more patient refusal[15]. Additionally, medical specialists (surgeons, medical oncologists) might not consider older patients suitable candidates[11].

Our study suggests older patients derive comparable benefits from adjuvant chemotherapy as their younger counterparts with regard to risk of recurrence[20,21]. Another study with a follow-up of 8 years found that adjuvant chemotherapy reduces the risk of recurrence within the first 2 years, suggesting adjuvant chemotherapy eradicates micrometastases[21]. Moreover, a recent pooled analysis of trials demonstrated that adjuvant chemotherapy did not have an effect on post-relapse survival, indicating that improved disease-free and overall survival after adjuvant chemotherapy are not endangered by deteriorated post-relapse survival[22].

The present study also shows the risk of recurrence is influenced to a large extent by the tumour characteristics T stage, N stage and differentiation grade, in line with results from previous studies[6,20,23].

Besides the analyses carried out for the total study population, which provide externally valid analyses, a propensity score matched sample was used to provide more internally valid analyses by reducing presence of heterogeneity between treatment groups. The results of the matched sample are comparable with the overall results, further supporting the equally beneficial effect of adjuvant chemotherapy on risk of recurrence for patients aged <75 years and patients aged ≥75 years. Moreover, the effects found in the current study are even stronger than the effects found in pooled analyses of trials, in which HRs for recurrence and recurrence-free survival for patients treated with adjuvant chemotherapy versus non-recipients were around 0.65-0.70, regardless of age[9,10].

It is acknowledged that, due to the observational character, this study has limitations and bias in treatment selection factors cannot be completely ruled out. It is unknown to what extent the positive effect of adjuvant treatment was caused by selection of the 'fitter' patients for adjuvant chemotherapy or other factors not included in the analysis.

Another limitation of this study is that it is unknown which chemotherapy scheme patients

received. Previous studies have shown that usage of especially oxaliplatin-based schemes decrease with rising age[18,24], making it likely that also in this study the chemotherapy schemes that were received by patients aged <75 years and patients aged ≥75 years are different. Whether the addition of oxaliplatin offers additional benefit to patients aged ≥75 years is unclear, as data has been conflicting[9,18,19,25]. However, one pooled analysis of trial data found that the benefit of oxaliplatin was modestly diminished in patients aged ≥70 years, but a significant effect was found regardless of age[26].

Furthermore, chemotherapy schemes have also changed over time. During the first half of the study period (2003-2005), patients mostly received a combination of 5-FU and leucovorin. Since the second half of the study period (2006-2008), oxaliplatin has become the standard adjuvant chemotherapy in combination with 5-FU or capecitabine.

An important factor contributing to the risk-benefit ratio with respect to adjuvant chemotherapy are treatment-related side-effects. In pooled analyses of randomized trials, it was found that no significant increase in toxic effects was found in elderly patients as compared to their younger counterparts from both fluorouracil-based and FOLFOX adjuvant therapy[9,10]. For the present study, no data on toxicity was available.

Future prospective studies should investigate how adjuvant chemotherapy affects the quality of life of elderly patients, which is of paramount importance in treatment decisions among elderly patients. To date, few studies have specifically addressed the effect of chemotherapy on quality of life in elderly patients. However, it seems likely that a substantial degree of undertreatment exists which reflects assumptions about age which might not be in line with current evidence on effectiveness of adjuvant chemotherapy[11].

Overall, the results of the present study underline that consideration of adjuvant chemotherapy is definitely warranted for all patients aged ≥75 years with resected stage III colon cancer, as they derive comparable benefit from adjuvant chemotherapy as their younger counterparts. However, it remains important to realize that in certain circumstances, withholding adjuvant chemotherapy from elderly may be appropriate, for example in case of short life expectancy (<1-2 years) or increased risk of serious side-effects. The assessment of older patients is complex and should include considerations of comorbidities, activities of daily living, socioeconomic conditions, clinical geriatric assessment, polypharmacy and nutritional status.

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Recurrence-free and overall survival among elderly stage III colon cancer patients treated with CAPOX or capecitabine monotherapy

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Abstract

The aim of this study is to investigate the effects of CAPOX and capecitabine on recurrence-free survival (RFS) and overall survival (OS) among elderly stage III colon cancer patients and to evaluate the effect of (non-)completion. Patients aged ≥70 years who underwent resection only or who were subsequently treated with CAPOX or capecitabine in 10 large non-academic hospitals were included. RFS and OS were analyzed with Kaplan-Meier curves and multivariable Cox regression adjusted for patient and tumor characteristics. 982 patients were included: 630 underwent surgery only, 191 received CAPOX and 161 received capecitabine. Five-year RFS and OS did not differ between capecitabine and CAPOX (RFS: 63% vs. 60% (p=0.91), adjusted HR=0.99 (95% CI 0.68-1.44); OS: 66% vs. 66% (p=0.76), adjusted HR=0.93 (95% CI 0.64-1.34)). After resection only, RFS was 38% and OS 37%. Completion rates were 48% for CAPOX and 68% for capecitabine. Three-year RFS and OS did not differ between patients who discontinued CAPOX early and patients who completed treatment with CAPOX (RFS: 61% vs. 69% (p=0.21), adjusted HR=1.42 (95% CI 0.85-2.37); OS: 68% vs. 78% (p=0.41), adjusted HR=1.17 (95% CI 0.70-1.97)). Three-year RFS and OS differed between patients who discontinued capecitabine early and patients who completed treatment with capecitabine (RFS: 54% vs. 72% (p=0.01), adjusted HR=2.07 (95% CI 1.11-3.84); OS: 65% vs. 80% (p=0.01), adjusted HR=2.00 (95% CI 1.12-3.59)). Receipt of CAPOX or capecitabine is associated with improved RFS and OS. The advantage does not differ by regimen. The addition of oxaliplatin might not be justified in elderly stage III colon cancer patients.

Introduction

Adjuvant chemotherapy is standard care for patients with stage III colon cancer. Several randomized controlled trials have been performed to compare the effectiveness of a number of agents in this setting. In the X-ACT trial, oral capecitabine demonstrated to be as effective as 5FU/LV, with an improved safety profile except for more hand-foot syndrome[1,2]. The MOSAIC trial and NSABP C-07 study showed that oxaliplatin in combination with 5-flourouracil/leucovorin (FOLFOX) provided an additional ~4% survival gain compared to 5FU/LV alone, but at the cost of higher toxicity rates, especially significant neurotoxicity[3-6]. In the XELOXA trial, the combination of oxaliplatin with capecitabine (CAPOX) also improved disease-free and overall survival compared with bolus fluorouracil/folinic acid (FU/FA) and was shown to provide an alternative treatment option, but with higher rates of grade III-IV neurotoxicity and grade III hand-foot syndrome[7-9]. Up to date, no randomized controlled trial compared FOLFOX and CAPOX head to head in the adjuvant setting and therefore both are considered standard care.

Despite the fact that patients aged ≥70 years account for more than half of the patients with colon cancer[10], only a small part of this group is included in clinical trials. Subgroup analyses of trials by age group have shown that oral capecitabine maintained its effectiveness in older patients and that the prevalence of grade ≥3 chemotherapy-related toxicities did not differ by age (<65 vs. ≥65 years)[2,11]. However, regarding the beneficial survival effect of adding oxaliplatin to 5FU-based regimens, inconsistent results were found[12,13]. Furthermore, although results were inconclusive, differences in toxicity suggested that older patients may be more prone to develop oxaliplatin-related toxicity[12]. The XELOXA trial showed an overall higher rate of grade III-IV toxicity with CAPOX for patients aged ≥65 years versus younger patients (65% versus 57% respectively)[9].

One pooled analysis found that FOLFOX was equally efficient in selected elderly as compared to younger patients[14], while other pooled analyses reported that elderly experienced reduced benefit from adding oxaliplatin to FU/LV or capecitabine[15,16]. Oxaliplatin-related grade III-IV toxicity was not elevated among elderly[16]. However, these subgroup and pooled analyses can only provide information on elderly who are fit enough to meet clinical trial eligibility criteria. Whether unselected elderly patients in daily clinical practice derive benefit is unclear. So far, population-based studies among elderly mostly included 5FU/LV and FOLFOX and provided inconsistent results regarding the additional benefit provided by the addition of oxaliplatin to chemotherapy[17-20].

Nowadays, in the Netherlands CAPOX and capecitabine monotherapy (CapMono) are the mostly prescribed regimens for elderly stage III colon cancer patients treated in daily clinical practice. A significant part of the elderly treated with adjuvant chemotherapy however do not complete all planned cycles[21]. Previous studies have shown that patients who failed to complete chemotherapy treatment with FU/LV exhibited a worse cancer-specific survival than those who completed treatment[22-24], while early discontinuation of FOLFOX did not affect disease-free and overall survival[25].

Therefore, the aim of the current study is twofold. The first aim is to investigate the effects of the regimens CAPOX and CapMono on recurrence-free and overall survival and to assess

whether oxaliplatin provides additional benefit among elderly stage III colon cancer patients treated in clinical practice. The second aim is to investigate the effects of (non-)completion of both regimens on recurrence-free and overall survival.

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 tumor characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators of the cancer registry. Anatomical site of the tumor is registered according to the International Classification of Disease – Oncology (ICD-O). The TNM (tumor-node-metastasis) classification is used for stage notification of the primary tumor, 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 computerized consistency checks at regional and national levels.

For the present study, additional data were collected from the medical records by experienced registration administrators in 2013 and 2014. This encompassed more detailed information on which adjuvant chemotherapy regimen patients received, whether all planned cycles were completed and on the development and diagnosis of recurrences. Depending on the hospital in which patients were treated with adjuvant chemotherapy, 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. Recurrence as defined for this study encompasses local and/or regional recurrence and/or distant metastases of colon cancer, after a primary diagnosis of stage III disease.

In the Netherlands, studies with anonymized patient records do not fall under the scope of the Medical Research Involving Human Subjects Act. This study is therefore exempt from medical ethics review.

Study population

For the present study, patients with primary stage III ($pT_{1-4}N_{1-2}M_0$) colon cancer aged ≥70 years who were diagnosed between 2005 and 2012 and who underwent resection only or who were subsequently treated with adjuvant chemotherapy consisting of CAPOX or CapMono were included. Surgery consisted of an oncologic resection of the primary tumor and regional lymph nodes. Stage was based on the pathological TNM classification. Tumor

localization 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).

Patients who did not survive the first 90 days after surgery were excluded (N=125), since deaths within 90 days after surgery were expected to limit the feasibility and gains of adjuvant chemotherapy administration and to overcome the effect of postoperative mortality on long-term survival.

Patients who received 6-8 cycles of adjuvant chemotherapy were categorized as patients who completed all planned cycles. Patients who received 1-5 cycles were categorized as patients who discontinued treatment before all planned cycles were completed.

Statistical analyses

Descriptive statistics were used to provide an overview of the study population by treatment modality. Differences in patient and tumor characteristics between treatment modalities were calculated using Chi^2-test or Fisher's Exact test as appropriate. After stratification by regimen, differences in patient and tumor characteristics between patients who completed all planned cycles and patients who discontinued treatment prematurely were also calculated using Chi^2-test or Fisher's Exact test, while differences in median total dosage received were calculated using Wilcoxon Rank-Sum test.

Differences in recurrence-free survival (RFS) and overall survival (OS) according to treatment modality and according to chemotherapy regimen and completion of all planned cycles were visualized by means of Kaplan-Meier curves and tested with Log-Rank tests and multivariable Cox regression analyses. To minimize immortal time bias, different starting points were used in these comparisons. In the comparison of RFS according to treatment modality, RFS time was defined as the time between the date of resection of the primary tumor to the date of diagnosis of recurrence or date of death. In the comparison of RFS according to chemotherapy regimen and completion of all planned cycles, RFS time was defined as the time between the last date of chemotherapy to the date of diagnosis of recurrence or date of death. In both comparisons, patients without a recurrence or death were censored at time of last follow-up date. Last follow-up date for recurrence differed between patients and was dependent on last patient contact and ascertainment of recurrence status. For OS, the same starting points were used. Date of death was completed until 31 December 2014. Variables included in the multivariable analysis were gender, age, comorbidity, ASA score, pathological T, pathological N, tumor subsite, differentiation grade and period of diagnosis.

To investigate whether the effects of the treatment modalities on RFS and OS differed according to patient characteristics, interaction tests were performed between treatment modality and respectively age, gender and comorbidity, using multivariable Cox regression.

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 consisted of 982 elderly colon cancer patients: 630 patients (64%) underwent surgery only, 191 patients (20%) received CAPOX and 161 patients (16%) received CapMono (figure 1). Table 1 provides an overview of the patient and tumor characteristics of the study population by treatment modality. Mean age of the patients who underwent resection only was 79.8 years, while this was 73.2 years and 75.9 years respectively for patients treated with CAPOX and CapMono. On average, patients who underwent resection only had the highest number of comorbid conditions and the highest ASA score. The proportion pathological N2 was higher among the patients treated with adjuvant chemotherapy. In 2005-2006, the proportion of patients treated with CAPOX was still relatively low, but increased in the next periods. In separate analyses comparing patients who received CAPOX to patients who received CapMono, differences were found with regard to age, comorbidity and period of diagnosis (table 1).

Among patients receiving CAPOX, 92 patients (48%) completed all planned cycles. For these patients, the median cumulative dosage received per patient was 191,894 mg/m^2 for capecitabine and 765 mg/m^2 for oxaliplatin. 96 patients (50%) did not complete all planned cycles of CAPOX. For this group, the median number of cycles was 4 (range 1-8) for capecitabine and 2 (range 1-8) for oxaliplatin. The median cumulative dosages received for capecitabine and oxaliplatin were therefore significantly lower: 88,004 mg/m^2 and 263 mg/m^2 respectively (p<0.0001 for both). For the remaining 3 patients (2%) who received CAPOX, the number of cycles was unknown. Among patients receiving CapMono, the

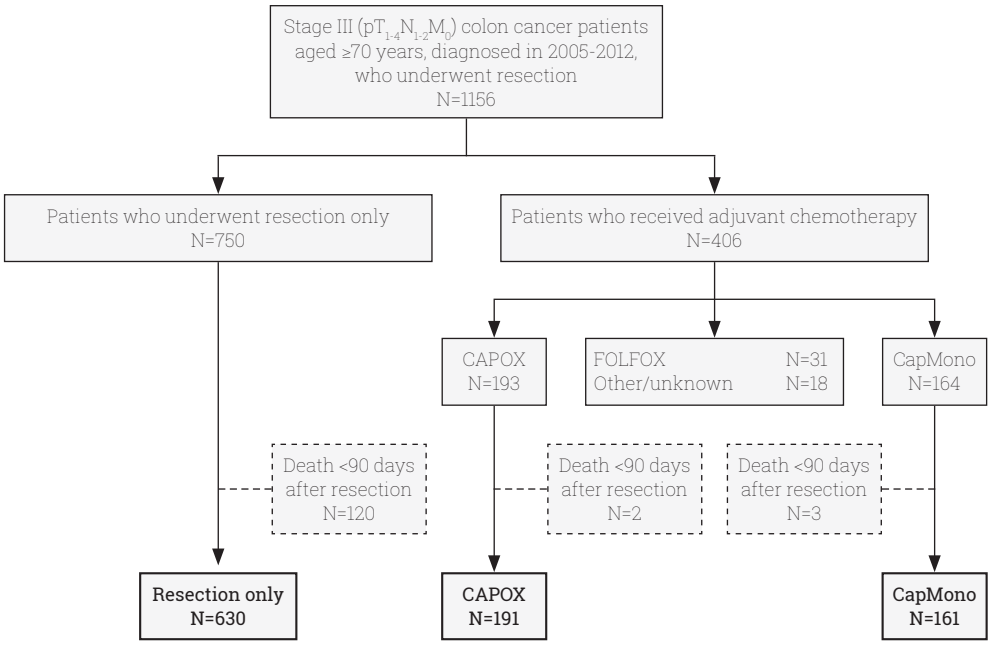

Figure 1 Overview of patients included in the study

Table 1 Patient and tumor characteristics of the study population, according to treatment modality

	Resection only n (%)	Resection + CAPOX n (%)	Resection + CapMono n (%)	P value*	P value#
Gender				0.02	0.06
Male	284 (45)	108 (57)	75 (47)		
Female	346 (55)	83 (43)	86 (53)		
Age				<.0001	<.0001
70-74 years	108 (17)	140 (73)	52 (32)		
75-79 years	197 (31)	47 (25)	84 (52)		
≥80 years	325 (52)	4 (2)	25 (16)		
Comorbidity				<.0001	0.04
0	97 (15)	65 (34)	33 (21)		
1	135 (22)	48 (25)	52 (32)		
≥2	377 (60)	74 (39)	72 (45)		
Unknown	21 (3)	4 (2)	4 (2)		
ASA score				<.0001	0.14
I-II	257 (41)	131 (69)	95 (59)		
III-IV	224 (35)	21 (11)	27 (17)		
Unknown	149 (24)	39 (20)	39 (24)		
Pathological T				0.14	0.18
1-2	61 (10)	22 (12)	24 (15)		
3	452 (72)	144 (75)	107 (66)		
4	117 (18)	25 (13)	30 (19)		
Pathological N				0.0026	0.76
1	478 (76)	124 (65)	107 (66)		
2	152 (24)	67 (35)	54 (34)		
Subsite tumor				0.08	0.16
Proximal colon	393 (62)	98 (51)	99 (62)		
Distal colon	230 (37)	90 (47)	60 (37)		
Other/NOS	7 (1)	3 (2)	2 (1)		
Differentiation grade				0.48	0.28
Well/moderate	428 (68)	139 (73)	105 (65)		
Poor/undifferentiated	163 (26)	41 (21)	42 (26)		
Unknown	39 (6)	11 (6)	14 (9)		
Period of diagnosis				0.03	0.03
2005-2006	139 (22)	24 (13)	38 (24)		
2007-2008	153 (24)	56 (29)	33 (21)		
2009-2010	154 (25)	59 (31)	49 (30)		
2011-2012	184 (29)	52 (27)	41 (25)		

* P value indicates significance of the Chi^2-test or Fisher's Exact test between all groups
# P value indicates significance of the Chi^2-test or Fisher's Exact test between patients receiving CAPOX and patients receiving CapMono

completion rate was higher with 109 (68%) patients completing all planned cycles (p<.0001). The median cumulative dosage received was 212,029 mg/m^2 for these patients. 46 patients (28%) did not complete all planned cycles. The median number of cycles among patients who discontinued treatment early was 2 (range 1-5) and the median cumulative dosage received was significantly lower (63,580 mg/m^2) than for patients who completed treatment (p<0.0001). For 6 patients (4%), the number of capecitabine cycles was unknown. Table 2 provides an overview of the patient and tumor characteristics of the patients treated with

adjuvant chemotherapy by completion of all planned cycles, after stratification by regimen. Male patients more often completed all planned cycles of CAPOX than female patients.

Table 2 Patient and tumor characteristics of the patients who received adjuvant chemotherapy, according to regimen and completion of all planned cycles

	CAPOX, complete n (%)	CAPOX, incomplete n (%)	P value*	CapMono, complete n (%)	CapMono, incomplete n (%)	P value*
Gender			0.01			0.56
Male	61 (66)	46 (48)		53 (49)	20 (43)	
Female	31 (34)	50 (52)		56 (51)	26 (57)	
Age			0.75			0.09
70-74 years	70 (76)	69 (72)		40 (37)	9 (19)	
75-79 years	21 (23)	25 (26)		54 (49)	27 (59)	
≥80 years	1 (1)	2 (2)		15 (14)	10 (22)	
Comorbidity			0.43			0.37
0	30 (33)	34 (35)		21 (19)	10 (22)	
1	27 (29)	21 (22)		39 (36)	12 (26)	
≥2	32 (35)	40 (42)		45 (41)	24 (52)	
Unknown	3 (3)	1 (1)		4 (4)	0 (0)	
ASA score			0.07			0.47
I-II	70 (76)	59 (61)		62 (57)	30 (65)	
III-IV	9 (10)	11 (11)		20 (18)	5 (11)	
Unknown	13 (14)	26 (27)		27 (25)	11 (24)	
Pathological T			0.84			0.30
1-2	11 (12)	10 (10)		17 (16)	7 (15)	
3	70 (76)	72 (75)		75 (68)	27 (59)	
4	11 (12)	14 (15)		17 (16)	12 (26)	
Pathological N			0.69			0.40
1	61 (66)	61 (64)		74 (68)	28 (61)	
2	31 (34)	35 (36)		35 (32)	18 (39)	
Subsite tumor			0.67			0.47
Proximal colon	45 (49)	51 (53)		65 (60)	30 (65)	
Distal colon	46 (50)	43 (45)		43 (39)	15 (33)	
Other/NOS	1 (1)	2 (2)		1 (1)	1 (2)	
Differentiation grade			0.32			0.14
Well/moderate	72 (78)	66 (69)		74 (68)	25 (54)	
Poor/undifferentiated	16 (18)	23 (24)		28 (26)	14 (30)	
Unknown	4 (4)	7 (7)		7 (6)	7 (15)	
Period of diagnosis			0.39			0.59
2005-2006	10 (11)	13 (14)		23 (21)	10 (22)	
2007-2008	31 (34)	24 (25)		26 (24)	7 (15)	
2009-2010	24 (26)	34 (35)		31 (28)	17 (37)	
2011-2012	27 (29)	25 (26)		29 (27)	12 (26)	

* P value indicates significance of the Chi^2-test or Fisher's Exact test
Excluded from the analyses were patients for whom completion of all planned cycles was unknown (CAPOX: 3 patients, CapMono: 6 patients)

Median follow-up time for all patients treated with CAPOX or CapMono was 35 months for RFS and 65 months for OS, while median follow-up time for the patients treated with CAPOX or CapMono and for whom it was known whether all planned cycles were completed was 39 months for RFS and 59 months for OS. Because the number of patients at risk after 36 months was <10 in the group of patients that did not complete CapMono, survival

curves were limited to 3 years in the analyses of survival by chemotherapy regimen and completion of all planned cycles. The interaction tests between treatment modality and age for RFS and OS were not significant (p=0.73 and p=0.73 respectively). Similarly, no significant interaction was found between treatment and gender for RFS (p=0.74) and OS (p=0.47) and between treatment and comorbidity for RFS (p=0.45) and OS (p=0.11).

In the analyses regarding survival according to treatment modality, crude 5-year RFS and OS did not differ between patients treated with CapMono and patients treated with CAPOX (RFS: 63% vs. 60% (p=0.91); OS: 66% vs. 66% (p=0.76)). For patients who underwent resection only, RFS was 38% and OS was 37% (figure 2). As shown in figure 4, both the risk of

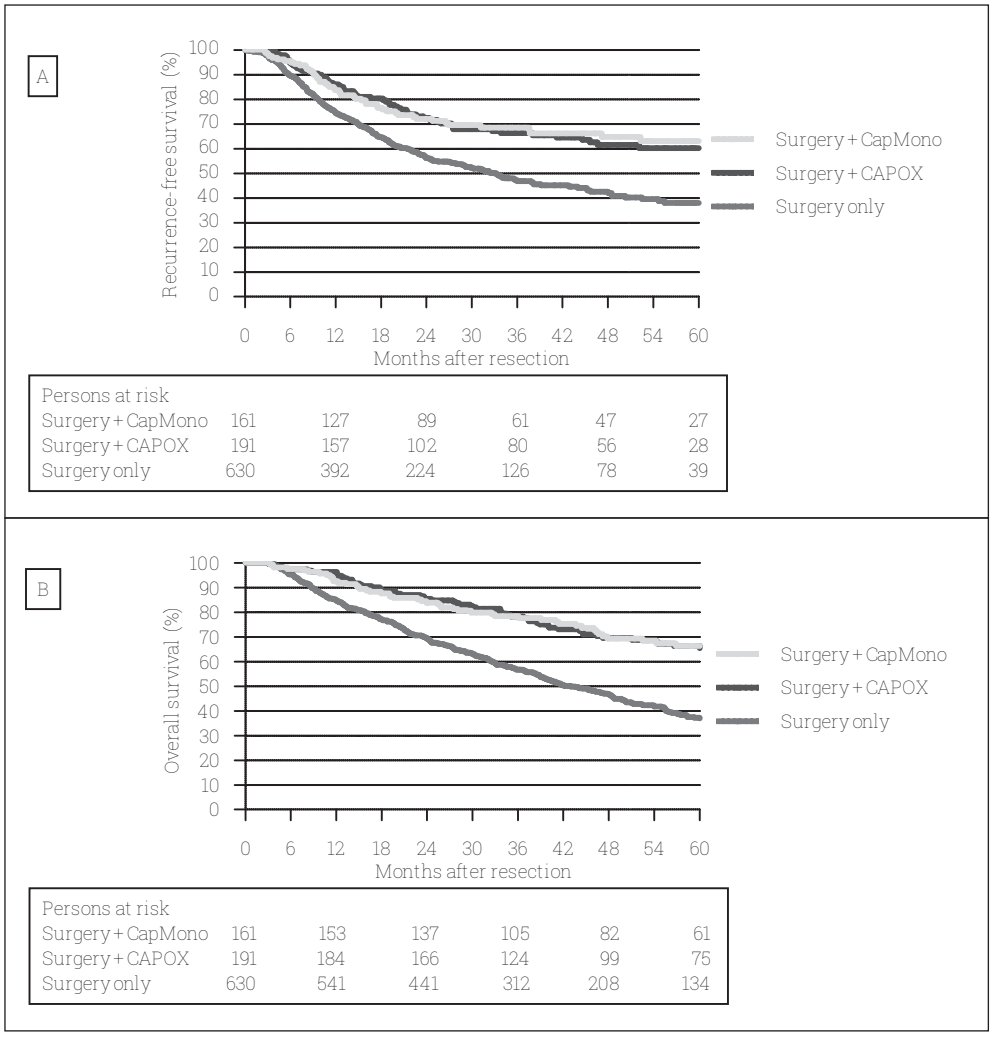

Figure 2 Recurrence-free survival (A) and overall survival (B) according to treatment modality among elderly stage III colon cancer patients

recurrence/death (model 1A) and the risk of death alone (model 1B) were similar for patients treated with CapMono as compared to patients treated with CAPOX after adjustment for casemix (RFS: HR=0.99 (95% CI 0.68-1.44); OS: HR=0.93 (95% CI 0.64-1.34)).

In the analyses regarding survival according to chemotherapy regimen and completion of all planned cycles, crude 3-year RFS and OS did not differ between patients who did not complete all planned cycles of CAPOX and patients who did complete all planned cycles of

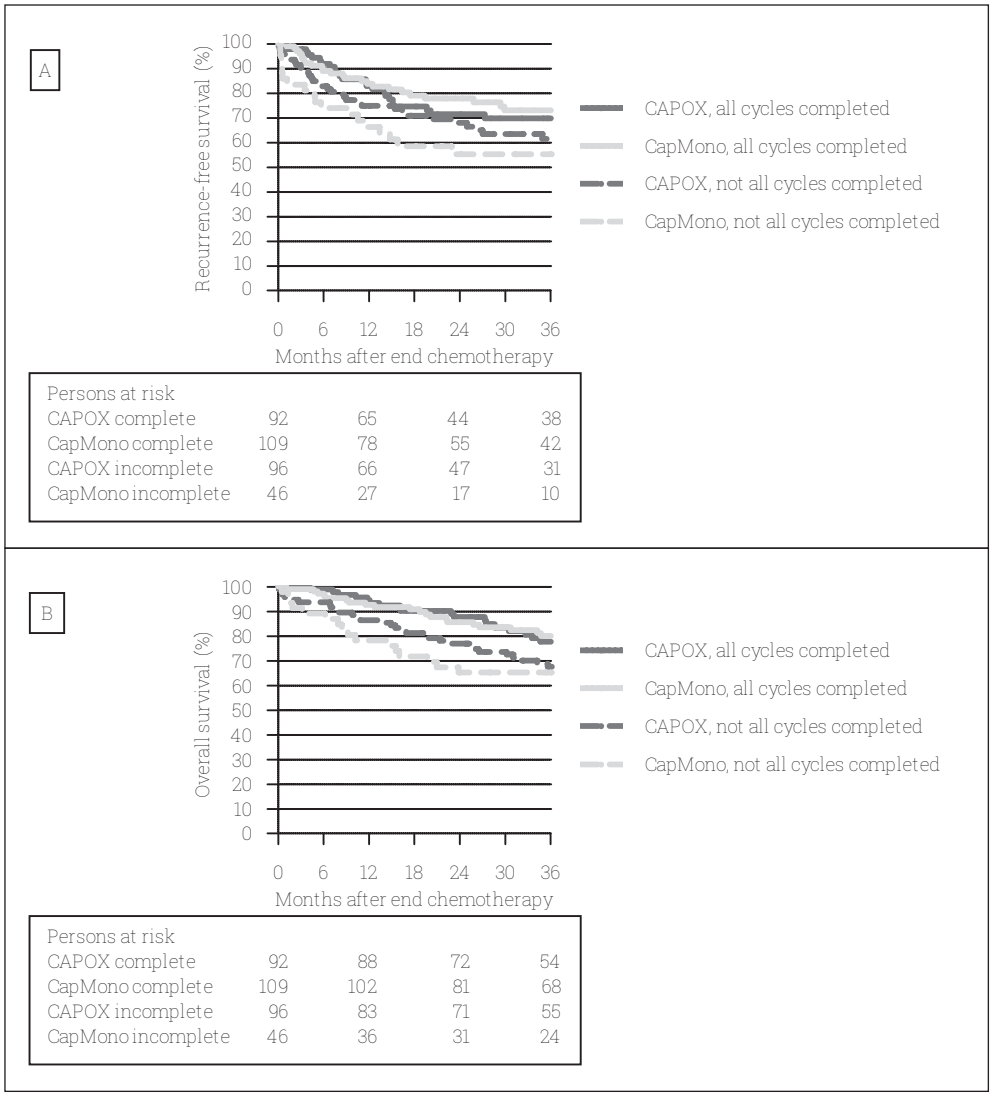

Figure 3 Recurrence-free survival (A) and overall survival (B) according to adjuvant chemotherapy regimen and completion of all planned cycles among elderly stage III colon cancer patients
Excluded from the analyses were patients for whom completion of all planned cycles was unknown (CAPOX: 3 patients, CapMono: 6 patients)

CAPOX (RFS: 61% vs. 69% (p=0.21); OS: 68% vs. 78% (p=0.41)). However, for patients who did not complete all planned cycles of CapMono, crude 3-year RFS and OS was lower than for patients who completed all planned cycles of CapMono (RFS: 54% vs. 72% (p=0.01); OS: 65% vs. 80% (p=0.01)) (figure 3). As shown in figure 4, both the risk of recurrence/death (model 2A) and the risk of death alone (model 2B) were similar for patients who did not complete all planned cycles of CAPOX as compared to patients who did complete all planned cycles of CAPOX in multivariable analysis (RFS: HR=1.42 (95% CI 0.85-2.37); OS: HR=1.17 (95% CI 0.70-1.97)). Among patients treated with CapMono, both the risk of recurrence/death (model 2A) and the risk of death alone (model 2B) were higher for patients who did not complete all planned cycles as compared to patients who did complete all planned cycles (RFS: HR=2.07 (95% CI 1.11-3.84); OS: HR=2.00 (95% CI 1.12-3.59)).

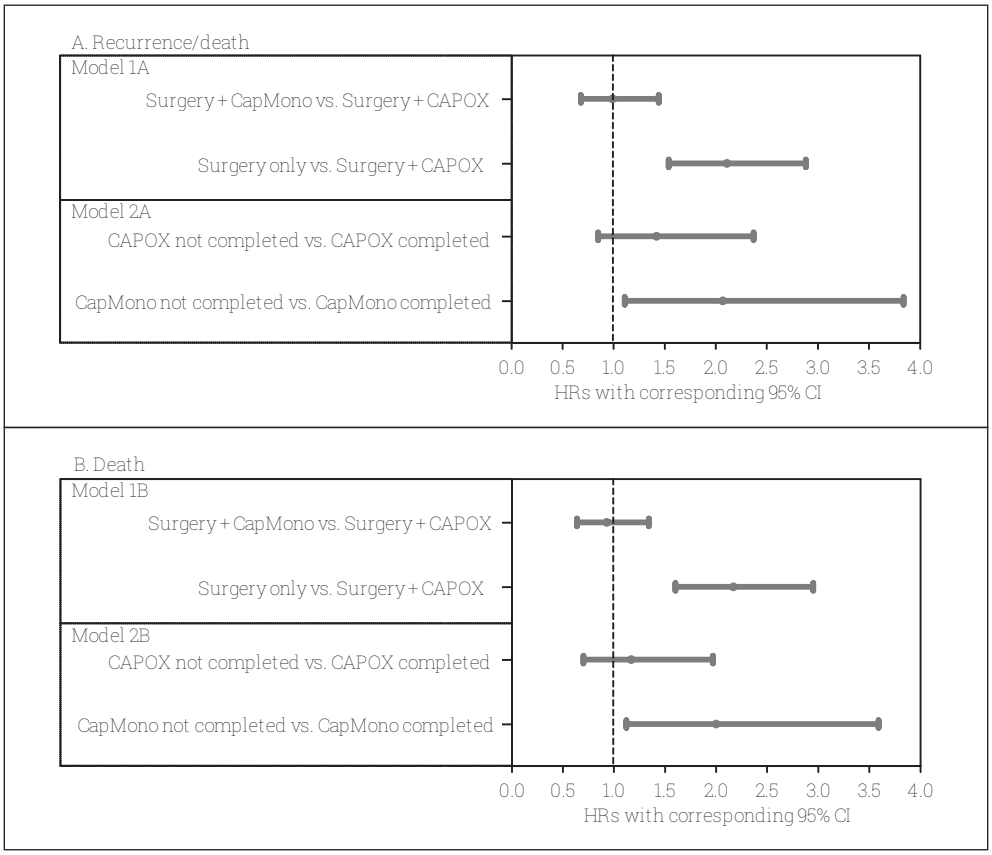

Figure 4 Adjusted hazard ratios for recurrence or death (A) or death alone (B) according to treatment modality (models 1, n=982) or adjuvant chemotherapy regimen and completion of all planned cycles (models 2, n=343) among elderly stage III colon cancer patients
Hazard ratios adjusted for gender, age, comorbidity, ASA score, pathological T, pathological N, tumor subsite, differentiation grade and period of diagnosis
Excluded from models 2 were patients for whom completion of all planned cycles was unknown (CAPOX: 3 patients, CapMono: 6 patients)

Discussion

In this population-based study, we investigated the effects of the chemotherapy regimens CAPOX and CapMono on recurrence-free and overall survival among elderly stage III colon cancer patients. Additionally, we evaluated the effect of (non-)completion of both regimens on survival. We found a 5-year RFS of 60% for patients treated with CAPOX and 63% for patients treated with CapMono. In subgroup analysis of the NSABP C-07 trial with patients aged ≥70 years and treated with either FU/LV or bolus FU and oxaliplatin (FLOX), a 5-year disease-free survival rate of approximately 55% was reported for both groups[12]. The difference is in part related to differences in the definition of disease-free survival versus recurrence-free survival. In the NSABP C-07 trial, besides recurrence and death, also second primary cancers were taken into account[12]. Additionally, patients in trials are monitored more closely for recurrences. Similarly, among patients aged 70-75 years included in the X-ACT trial and treated with CapMono, 5-year disease-free survival was 58%[11]. In line with the current study, no benefit was found with the addition of oxaliplatin in the NSABP C-07 subgroup analysis[12]. Also in the subgroup of patients aged 70-75 years from the MOSAIC trial did treatment with FOLFOX not improve disease-free survival compared to treatment with FU/LV[13]. The 5-year disease-free survival rates in that study were 69% and 66% respectively[13], probably somewhat higher compared to our study because patients with stage II disease were also included and patients over the age of 75 years were not. In contrast, the 5-year OS rates of 66% for both patients treated with CAPOX and patients treated with CapMono as found in the present study were lower than the 5-year OS rates of ~76% as reported in the MOSAIC and NSABP C-07 subgroup analyses[12,13]. However, also in these trials, no difference in OS was found with the addition of oxaliplatin. Importantly, it should be acknowledged that the MOSAIC trial was underpowered for subgroup analyses[13]. In fact, in both the NSABP C-07 trial and the MOSAIC trial, the subgroup analyses by age group were exploratory only[12,13].

Our study suggests that optimal treatment with adjuvant chemotherapy comprises not merely the administration of chemotherapy, but also the completion of all planned cycles. In the current study, the cut-off for treatment completion was set at ≥6 cycles, irrespective of treatment protocol, which could also be 8 cycles. Less than half of the patients treated with CAPOX and approximately two third of the patients treated with CapMono completed all planned cycles. Except for the finding that male patients more often completed all planned cycles of CAPOX than female patients, no other differences in patient and tumor characteristics were found between patients who completed all planned cycles and patients who did not complete all planned cycles, for both CAPOX and CapMono. In a previous study from our group, we found that only the presence of any grade III-V toxicity was related to early treatment discontinuation for both CAPOX and CapMono[21]. The completion rates are lower than those found in other studies. The population-based study by Kumar et al. showed that 69% of the patients aged ≥70 years completed at least 10 cycles of the FOLFOX regimen[25]. In the subgroup of patients aged 70-75 included in the X-ACT trial, 74% completed the planned course of treatment with CapMono[11].

Especially for patients treated with CapMono, recurrence-free and overall survival were worse when patients did not complete all planned cycles. This is in line with previous

studies that showed that patients who failed to complete 5FU-based chemotherapy had worse cancer-specific survival than those who completed treatment. In line with a previous study on FOLFOX, for patients treated with CAPOX, no statistical significant differences were found in RFS and OS according to completion of all planned cycles. Our results however did suggest a trend towards lower crude 3-year recurrence-free and overall survival among the patients who did not complete all planned cycles of CAPOX as compared to their counterparts. The lack of statistical significance could just be the result of an underpowered analysis. Due to the relatively small number of patients in our study, we were only able to report 3-year recurrence-free survival rates in the strata according to both regimen and completion of all planned cycles. We acknowledge that this is relatively short follow-up period. However, previous studies showed that most recurrences occur within this time period[26,27].

A limitation of the current study is the observational design. In general, randomized controlled trials (RCTs) are considered the gold standard in evaluating the efficacy of treatments. As participants are randomly assigned to a treatment or control group -thereby equalizing both groups with respect to all features except the treatment-, RCTs have superior internal validity and enable establishment of causality[28]. As this observational study includes patients treated in everyday clinical practice, it is likely that the fitter patients were selected for adjuvant chemotherapy. This is also reflected in the differences in ASA scores and in the number of comorbid conditions between the patients who underwent surgery only and the patients who received adjuvant chemotherapy. We cannot rule out that residual confounding is partly responsible for the positive effect of adjuvant chemotherapy. Importantly, we did not find a recurrence-free and overall survival benefit for the patients treated with CAPOX as compared to the patients treated with CapMono, despite the fact that the patients receiving CAPOX were younger and had less comorbid conditions than the patients receiving CapMono. This strengthens the conclusion that oxaliplatin might not provide an additional benefit in this study population. However, as the observational nature of the current study limits in establishing causality, the results should be interpreted with caution. The realization of RCTs designed for elderly patients remains important to expand the evidence-base. A trial in which the effect of the different chemotherapy regimens on 3-year disease-free survival is compared among elderly colon cancer patients is now ongoing[29].

On the other hand, RCTs also have disadvantages as these are often restricted to relatively healthy patients, thereby limiting the generalizability of results[28]. Especially for patient groups who do not meet the eligibility criteria from RCTs, such as a large part of the elderly treated in everyday clinical practice, observational studies are important to provide information on outcomes in the real world.

In conclusion, among elderly stage III colon cancer patients treated in clinical practice, receipt of adjuvant chemotherapy consisting of CAPOX or CapMono is associated with improved RFS and OS. Since completion of all planned cycles was of more importance than the regimen used, the addition of oxaliplatin might not be justified, although interpretation should be cautious due to the observational nature of the study.

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

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Abstract

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

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

Results: 6620 patients received adjuvant chemotherapy, 14% commenced after 8 weeks. Factors associated with starting treatment after 8 weeks were older age (Odds ratio (OR) 65-74 versus <65 years 1.3 (95% confidence interval (CI): 1.14-1.58); OR ≥75 versus <65 years 1.6 (1.25-1.94)), emergency resection (OR 1.8 (1.41-2.32)), anastomotic leakage (OR 8.1 (6.14-10.62)), referral to another hospital for adjuvant chemotherapy (OR 1.9 (1.36-2.57)) and prolonged postoperative hospital admission (OR 4.7 (3.30-6.68)). Starting 5-8 weeks post-surgery showed no decrease in OS compared to initiation within 4 weeks (Hazard ratio (HR) 5-6 weeks 0.9 (0.79-1.11); HR 7-8 weeks 1.1 (0.91-1.30)). However, commencing beyond 8 weeks was associated with decreased OS compared to initiation within 8 weeks (HR 9-10 weeks 1.4 (1.21-1.68); HR 11-12 weeks 1.3 (1.06-1.59); HR 13-16 weeks 1.7 (1.23-2.23)).

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

Introduction

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

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

Several population-based studies have shown that a delayed initiation of adjuvant chemotherapy is associated with an unfavourable long-term OS, cancer-specific survival and disease-free survival[12-17]. Results from a meta-analysis has indicated that the relative OS decreased by every 4-week delay in the administration of adjuvant chemotherapy[18]. However, in this meta-analysis there was heterogeneity among the different studies in the cut-off points for the timing of adjuvant chemotherapy, ranging from 8 weeks to more than 12 weeks, as well as in the primary location (colon versus rectum) and stage of disease (2 versus 3).

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

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

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

Patients and methods

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

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

Study population

We selected all patients with colon cancer and lymph node metastases, but without distant metastases at presentation (stage III), diagnosed in The Netherlands in 2008-2013 who underwent surgical resection and received adjuvant chemotherapy (figure 1). Patients were excluded if they had received local chemotherapy (n=4) or neo-adjuvant chemotherapy (n=31). In addition, patients were excluded if the date of chemotherapy initiation was missing (n=1051) or if chemotherapy was started more than 16 weeks after the surgical resection to ensure that treatment was for adjuvant therapy (n=49). The timing to adjuvant chemotherapy was calculated from the date of surgical resection to the date of initiation of adjuvant chemotherapy. The timing of adjuvant chemotherapy was subdivided into six categories: within 4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks and 13-16 weeks from surgical resection. Information on type of adjuvant chemotherapy was available for a subgroup of patients (n=725) who were included in a subgroup analysis. Patients of whom information on prolonged postoperative hospital admission was available (n=2584) were included in a subgroup analysis. Additionally, patients who underwent surgical resection without receiving adjuvant chemotherapy were included in the crude survival analyses to show OS of this group (n=4899; total n=11,519).

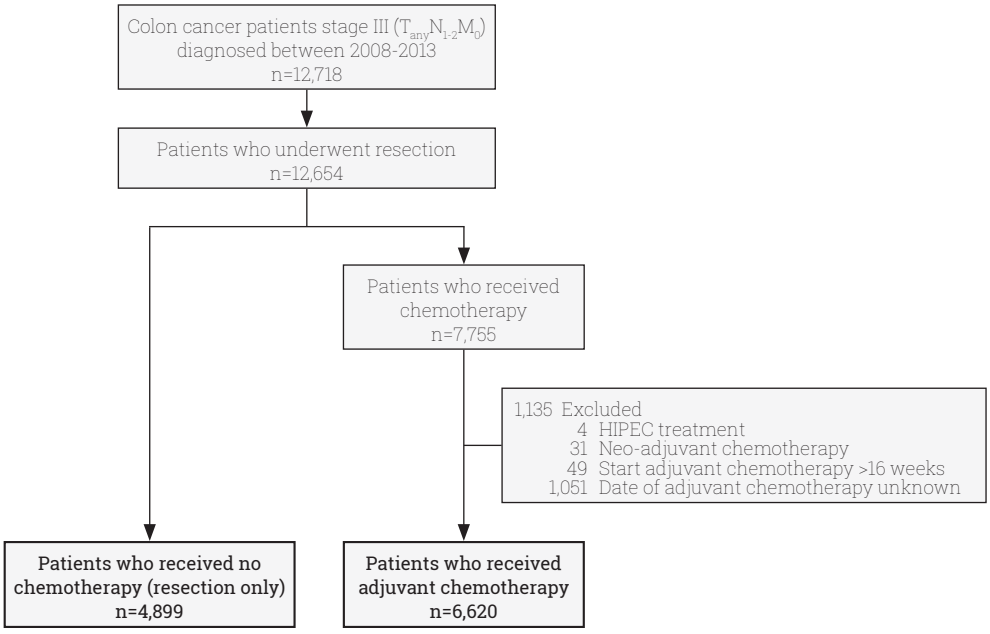

Figure 1 Consort diagram of patient selection

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

Statistical analyses

Differences in clinical, pathological and treatment-related characteristics across the different timings of adjuvant chemotherapy were evaluated using Chi^2-tests. Multivariable logistic regression analysis was conducted to assess the independent influence of several patient and clinical characteristics on the probability of starting adjuvant chemotherapy beyond 8 weeks post-surgery. Similar methods were used in a subgroup analysis to evaluate differences in type of chemotherapy across the different timings of adjuvant chemotherapy.

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

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

Results

Over the period 2008-2013, 6620 patients underwent surgical resection for stage III ($T_{any}N_{1-2}M_0$) colon cancer, and received adjuvant chemotherapy. Mean age of the population was 70 (standard deviation 7.8) years, 14% was ≥75 years of age and 53% was male. The median timing of adjuvant chemotherapy was 5.6 weeks post-surgery. A total of 1106 patients (17%) commenced treatment within 4 weeks after resection. The majority of the patients (n=4512, 69%) started chemotherapy between 5 and 8 weeks after resection. A total of 1002 patients (14%) started treatment after 8 weeks, of whom 165 patients (16%, 2% of total) started treatment between 13 and 16 weeks after resection. Figure 2 presents the distribution of timing of adjuvant chemotherapy in weeks.

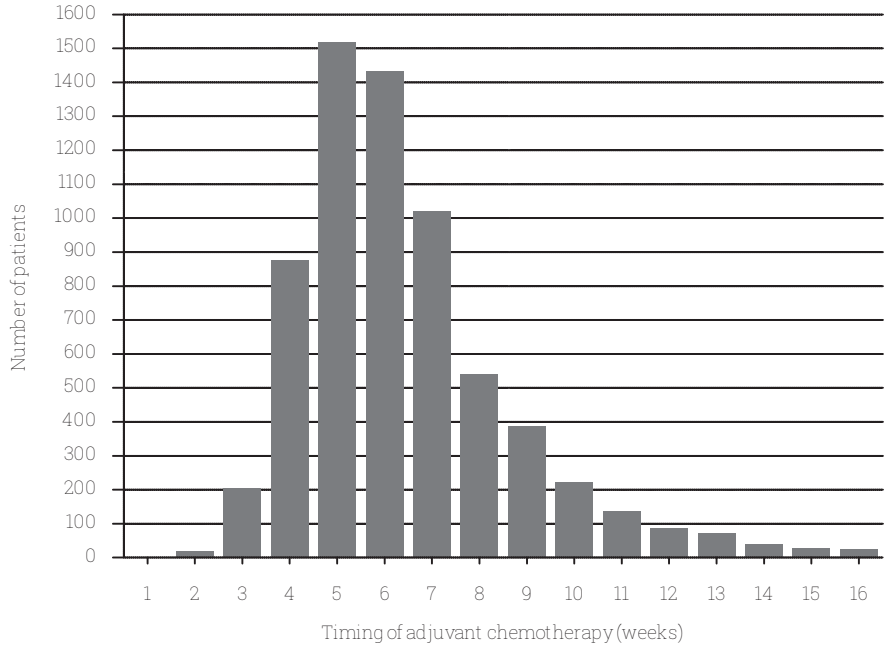

Figure 2 Distribution of the time (in weeks) after surgical resection to the start of adjuvant chemotherapy, for patients diagnosed with stage III colon cancer in the Netherlands, 2008-2013 (n=6620)

Factors associated with timing of adjuvant chemotherapy

In univariable analyses, age, period of diagnosis, T-stage, tumour location, surgical procedure, urgency of resection, presence of an anastomotic leakage and being referred to another hospital for adjuvant chemotherapy all had a significant impact on the timing of adjuvant chemotherapy. In addition, in the subgroup of patients (diagnosed in 2012-2013), a higher proportion of patients with prolonged postoperative hospital admission was found when adjuvant chemotherapy was started beyond 6 weeks (table 1) ($p<0.0001$). Gender, N stage, differentiation grade and histology of the primary tumour were not associated with timing of adjuvant chemotherapy (table 1). Type of chemotherapy was not associated with timing of adjuvant chemotherapy in the subgroup of patients for whom information on type of chemotherapy was available ($p=0.918$).

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

Timing of adjuvant chemotherapy and survival

Median follow-up time was 60 months. Figure 3 shows the crude 5-year OS rates according to the initiation of adjuvant chemotherapy within 4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks or 13-16 weeks. The crude observed 5-year OS rates were 75%, 76%, 72%, 64%, 61% and 54%, respectively, while the proportion of 5-year OS among patients who underwent surgery only (n=4899) was 39%. To overcome immortal time bias between patients who received adjuvant chemotherapy and patients who underwent resection only; only patients who survived the first 16 weeks after the date of resection were included in a subgroup analysis. Similar results for OS were found (data not shown).

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

Table 1 Demographic and clinical variables according to timing of adjuvant chemotherapy for patients diagnosed with stage III colon cancer in the Netherlands, 2008-2013 (n=6620)

	Timing of adjuvant chemotherapy						P value
	≤4 weeks 1106 (17%) n (%)	5-6 weeks 2950 (45%) n (%)	7-8 weeks 1562 (24%) n (%)	9-10 weeks 611 (9%) n (%)	11-12 weeks 226 (3%) n (%)	13-16 weeks 165 (2%) n (%)	
Gender							0.979
Male	587 (53)	1564 (53)	841 (54)	327 (53)	125 (55)	86 (52)	
Female	519 (47)	1386 (47)	721 (46)	284 (47)	101 (45)	79 (48)	
Age							0.001
<65 years	493 (45)	1449 (49)	682 (44)	264 (43)	88 (39)	72 (43)	
65-74 years	432 (39)	1139 (39)	657 (42)	254 (42)	94 (42)	70 (43)	
≥75 years	181 (16)	362 (12)	223 (14)	93 (15)	44 (19)	23 (14)	
Period of diagnosis							0.001
2008-2009	261 (24)	697 (24)	454 (29)	168 (28)	62 (28)	46 (28)	
2010-2011	371 (33)	1075 (36)	558 (36)	199 (33)	80 (35)	65 (40)	
2012-2013	474 (43)	1178 (40)	550 (35)	244 (39)	84 (37)	54 (32)	
T stage							0.022
T1	16 (2)	62 (2)	36 (2)	8 (1)	3 (1)	2 (1)	
T2	103 (9)	256 (9)	123 (8)	46 (8)	18 (8)	12 (7)	
T3	788 (71)	2083 (70)	1070 (69)	423 (69)	145 (64)	105 (63)	
T4	199 (18)	549 (19)	333 (21)	134 (22)	60 (27)	46 (29)	
N stage							0.440
N1	686 (62)	1894 (64)	976 (62)	381 (62)	135 (60)	111 (67)	
N2	420 (38)	1056 (36)	586 (38)	230 (38)	91 (40)	54 (33)	
Tumour location							0.011
Proximal colon	541 (49)	1499 (51)	847 (54)	313 (51)	130 (58)	86 (52)	
Distal colon	548 (49)	1398 (47)	685 (44)	286 (47)	86 (38)	75 (46)	
Other/NOS	17 (2)	53 (2)	30 (2)	12 (2)	10 (4)	4 (2)	
Differentiation grade							0.218
Well/moderated	807 (73)	2153 (73)	1101 (70)	417 (68)	156 (69)	109 (66)	
Poor /undifferentiated	208 (19)	585 (20)	336 (22)	143 (24)	51 (23)	40 (24)	
Unknown	91 (8)	212 (7)	125 (8)	51 (8)	19 (8)	16 (10)	

Table 1 continued

	Timing of adjuvant chemotherapy						P value
	≤4 weeks 1106 (17%) n (%)	5-6 weeks 2950 (45%) n (%)	7-8 weeks 1562 (24%) n (%)	9-10 weeks 611 (9%) n (%)	11-12 weeks 226 (3%) n (%)	13-16 weeks 165 (2%) n (%)	
Histology of primary tumour							0.696
Non-mucinous adenocarcinoma	940 (85)	2495 (85)	1316 (84)	500 (82)	188 (83)	137 (83)	
Mucinous adenocarcinoma	139 (13)	396 (13)	206 (13)	97 (16)	35 (16)	24 (15)	
Unknown	27 (2)	59 (2)	40 (3)	14 (2)	3 (1)	4 (2)	
Surgical procedure							<0.0001
Open resection	585 (53)	1714 (58)	1014 (65)	452 (74)	171 (76)	132 (80)	
Laparoscopic resection	521 (47)	1236 (42)	548 (35)	159 (16)	55 (24)	33 (20)	
Urgency of resection‡							<0.0001
Elective	1040 (93)	2708 (92)	1395 (89)	513 (84)	191 (84)	140 (84)	
Emergency	59 (5)	228 (7)	154 (9)	92 (14)	32 (14)	23 (12)	
Unknown	7 (1)	14 (0.5)	13 (1)	6 (1)	3 (2)	2 (2)	
Anastomotic leak‡							<0.0001
No	1068 (96)	2803 (95)	1391 (90)	494 (81)	182 (80)	120 (73)	
Yes	8 (1)	39 (1)	80 (5)	65 (11)	33 (15)	30 (18)	
Unknown	30 (3)	108 (4)	91 (5)	52 (8)	11 (5)	15 (9)	
Hospital AC equal to hospital resection							<0.0001
No	1075 (97)	2839 (96)	1491 (96)	576 (95)	208 (93)	148 (90)	
Yes	31 (3)	111 (4)	71 (4)	35 (5)	18 (7)	17 (10)	
Prolonged hospital admission (>14 days)∞							<0.0001
No	467 (98)	1141 (97)	459 (83)	172 (71)	56 (67)	36 (66)	
Yes	7 (2)	37 (3)	91 (17)	72 (29)	28 (33)	18 (34)	

AC, adjuvant chemotherapy.
‡ Not included in the analysis: urgency of resection unknown and anastomotic leak unknown.
∞ Included patients diagnosed in 2012-2013 (n=2584).

Table 2 Crude percentages and adjusted odds ratios[a] for timing of adjuvant chemotherapy beyond 8 weeks post-surgery among resected stage III colon cancer patients receiving adjuvant chemotherapy (n=6620)

	Timing of AC >8 weeks Crude %	Multivariable analysis OR (95% CI)
Gender		
Male	15	1.0 (reference)
Female	15	1.0 (0.87-1.18)
Age		
<65 years	14	1.0 (reference)
65-74 years	16	1.3 (1.14-1.58)
≥75 years	17	1.6 (1.25-1.94)
Period of diagnosis		
2008-2009	16	1.0 (reference)
2010-2011	15	0.9 (0.78-1.15)
2012-2013	15	0.9 (0.71-1.04)
T stage		
T1	10	1.0 (reference)
T2	14	1.2 (0.65-3.52)
T3	14	1.1 (0.65-3.23)
T4	16	1.2 (0.62-3.23)
N stage		
N1	15	1.0 (reference)
N2	15	0.9 (0.78-1.08)
Tumour location		
Proximal colon	15	1.0 (reference)
Distal colon	15	1.0 (0.83-1.14)
Other/NOS	20	1.5 (0.94-2.44)
Differentiation grade*		
Well/moderated	14	1.0 (reference)
Poor /undifferentiated	17	1.2 (0.98-1.44)
Histology of primary tumour*		
Non-mucinous adenocarcinoma	15	1.0 (reference)
Mucinous adenocarcinoma	17	1.2 (0.91-1.62)
Surgical procedure		
Open resection	18	1.0 (reference)
Laparoscopic resection	10	0.5 (0.43-0.61)
Urgency of resection*		
Elective	14	1.0 (reference)
Emergency	26	1.8 (1.41-2.32)
Anastomotic leak*		
No	13	1.0 (reference)
Yes	50	8.1 (6.14-10.62)
Hospital AC equal to hospital resection		
No	15	1.0 (reference)
Yes	25	1.9 (1.36-2.57)
Prolonged hospital admission (>14 days)†		
No	11	1.0 (reference)
Yes	47	4.7 (3.30-6.68)

AC, adjuvant chemotherapy; CI, confidence interval; OR, odds ratio.
[a] Adjusted for all variables listed.
* Included in the analysis but results not shown tumour grade unknown, histology of primary tumour unknown, urgency of resection unknown and anastomotic leak unknown.
† Included patients diagnosed in 2012-2013 (n=2584).

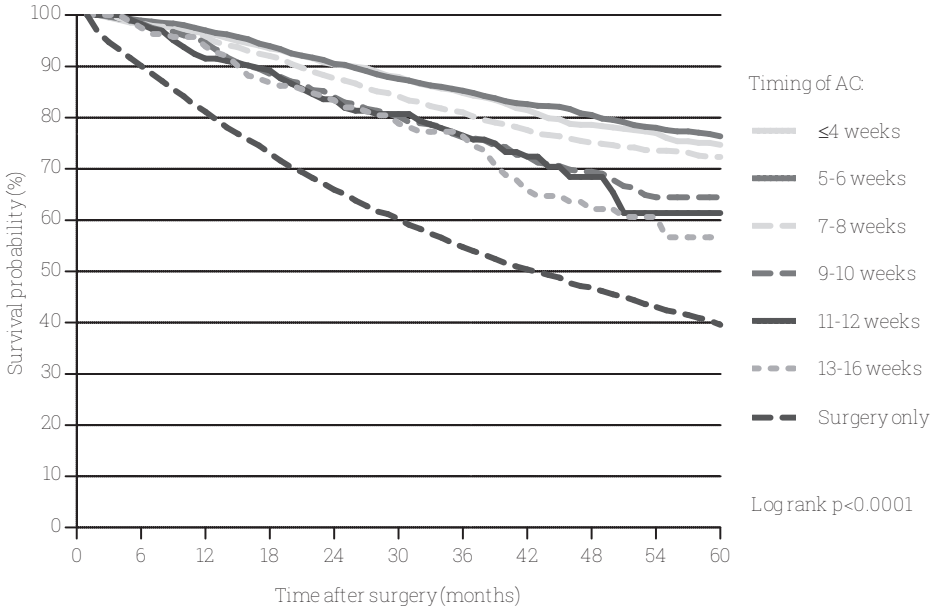

Figure 3 Crude overall survival according to whether adjuvant chemotherapy was initiated within 4 weeks, 5-6 weeks, 7-8 weeks, 9-10 weeks, 11-12 weeks, 13-16 weeks (n=6620) or patients undergoing surgery only (n=4899) AC, adjuvant chemotherapy.

Table 3 Crude 5-year overall survival and adjusted hazard ratios[a] for death among stage III resected colon cancer patients receiving adjuvant chemotherapy (n=6620)

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

AC, adjuvant chemotherapy; CI, confidence interval; HR, hazard ratio.
[a] Adjusted for gender, age, period of diagnosis, T stage, N stage, tumour location, differentiation grade, histology of tumour, surgical procedure, urgency of resection, anastomotic leak, hospital AC equal to hospital resection.

Discussion

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

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

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

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

Previous studies have shown similar results using population-based data on a regional and/or hospital level. This is the first large nationwide observational study to describe the effect of timing of adjuvant chemotherapy in resected stage III colon cancer patients on long-term survival. An important limitation of this study however is its observational nature. The effects observed may be highly susceptible to selection bias, e.g. less fragile patients receiving adjuvant chemotherapy first. Although we adjusted for several patient and

tumour characteristics, data about functional status, specific postoperative complications other than anastomotic leakage and comorbidity were not available. Therefore an analysis of the effect of timing of adjuvant chemotherapy on long-term outcomes may be subject to residual confounding. We hypothesise that patients starting chemotherapy beyond 8 weeks post-surgery were in worse general health, have had more surgical complications and had an inherently worse prognosis, which may have influenced the results. Another limitation of our study is that for 1051 patients date of chemotherapy initiation was missing and were therefore excluded. However, results of our study indicate that casemix did not differ between this group and included patients.

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

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

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

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10

General discussion

In this chapter, the main findings of the studies included in this thesis will be summarized and subsequently discussed in a broader context. Next, several methodological considerations are highlighted that should be taken into account when interpreting the results of the studies. Implications for clinical practice and future research are discussed as well.

Summary of the main findings

This thesis started with an overview of drugs dispensed to elderly colon cancer patients in the year before colon cancer diagnosis in comparison with an age- and gender-matched control group without cancer *(chapter 2)*. The study demonstrated a higher proportion of drug dispensing from out-patient pharmacies to elderly colon cancer patients during the year before diagnosis as compared to a matched cancer-free control group, which increased even more during the last three months before diagnosis. In general, the elevated dispensing of drugs among cases as compared to controls during the total study year was mostly related to comorbidity, while the drugs that were dispensed to an increasing proportion of cases in the months before colon cancer diagnosis were probably mostly related to (symptom management of) the colon cancer. Insight into which drugs are commonly used in the year preceding colon cancer diagnosis may trigger general practitioners and medical specialists to further evaluate the patient's medication and should be considered in subsequent cancer treatment planning as this might impact on the tolerance and effect of these treatments.

The objective of the next study was to identify subjective, doctor-related factors in the decision-making on adjuvant chemotherapy in elderly stage III colon cancer patients *(chapter 3)*. Short questionnaires were sent to surgeons and medical oncologists. Surgeons most often reported the following motives for non-referral: comorbidity or bad general health condition of the patient; presence of surgical complications and refusal of adjuvant chemotherapy by the patient. Medical oncologists also reported these motives for non-treatment, and additionally reported that expected side effects were too severe. Less than half of the surgeons and little over half of the medical oncologists reported to consult a geriatrician for a minority of the patients. The decision of medical oncologists for monotherapy or combination therapy is based on the presence of comorbidity, the general health condition of the patient and the toxicity profile of the chemotherapeutic agents. Medical oncologists agree on acceptable levels of toxicity: in general, grade ≤II toxicity was defined as acceptable, with the exception of neuropathy, which was only deemed acceptable if grade I. The variation among surgeons and medical oncologists in motives for non-referral, non-treatment and consultation of geriatricians when deciding on adjuvant chemotherapy for elderly stage III colon cancer patients might be related to the lack of evidence-based guidelines for, and complexity of, these patients.

Subsequently, patient and tumour characteristics influencing the administration of oxaliplatin-based chemotherapy (FOLFOX and CAPOX) as compared to non-oxaliplatin-based chemotherapy (5-fluorouracil/leucovorin or capecitabine) and variation in the administration of both types between hospitals *(chapter 4)* were evaluated. For this study, 1140 patients originating from 10 community hospitals in the southeast part of the Netherlands and diagnosed between 2008 and 2011 were included. The median age of the patients receiving

oxaliplatin was 64 years, and the median ages of patients receiving non-oxaliplatin-based chemotherapy or no chemotherapy were 74 and 79 years respectively. A large inter-hospital variation in the administration of oxaliplatin-based and non-oxaliplatin-based chemotherapy was noted, which could not be entirely explained by patient casemix. Oxaliplatin-based chemotherapy administration ranged from 63% to 87% for patients aged <70 years, from 15% to 100% for patients aged 70-74 years, and from 0% to 19% for patients aged 75 years or older. For non-oxaliplatin-based chemotherapy, these proportions ranged from 3% to 20%, from 0% to 29% and from 0% to 28% for the respective age groups. In an analysis including only patients receiving adjuvant chemotherapy, the addition of oxaliplatin was affected by age, T stage, period of diagnosis and hospital of treatment.

Hardly any previous population-based studies among elderly stage III colon cancer patients described the exact regimens used in daily practice; the intensity of and adherence to these regimens; and the degree unselected elderly develop toxicity from these regimens. The aim of *chapter 5* was therefore to provide insight in the completion of all planned cycles and received cumulative dosages for the most commonly used regimens in everyday clinical practice and to investigate the association with grade III-V toxicity. 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. The study showed that a large majority (88%) of the patients who were treated with adjuvant chemotherapy received CAPOX or capecitabine monotherapy (CapMono). The joint proportion of CAPOX and CapMono versus other regimens was as high as 98% in the most recent study period (2011-2012). The proportion of patients completing all planned cycles was lower for patients receiving CAPOX (33%) than for patients receiving CapMono (55%). The median cumulative dosage of capecitabine received was also lower for patients treated with CAPOX (163,744mg/m^2) than for patients treated with CapMono (189,195mg/m^2). Additionally, CAPOX was associated with significantly more grade III-V toxicity than CapMono (54% versus 38%), also after adjustment for patient and tumour characteristics. For patients treated with CAPOX, the most common toxicities were gastrointestinal (mainly diarrhoea and nausea/vomiting, 29%), haematological (14%), neurological (i.e. neuropathy, 11%) and other toxicity (mainly fatigue, 13%). For patients treated with CapMono, dermatological (i.e. hand-foot syndrome, 17%), gastrointestinal (mainly diarrhoea, 13%) and other toxicity (mostly fatigue, 11%) were the most common. The 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 gastrointestinal toxicity. 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 neuropathy and hand-foot syndrome.

Chemotherapy-induced peripheral neuropathy (CIPN) is increasingly recognized as an important toxicity which compromises treatment plans. The next study focused on differences in the course of neuropathic symptoms between patients who were treated with CAPOX, CapMono, or no adjuvant chemotherapy *(chapter 6)*. For this longitudinal study, patients were invited to complete the first questionnaire after resection and

subsequent questionnaires six and twelve months later. The number and percentages of patients who experienced mild to severe neuropathic symptoms were measured using the EORTC QLQ-CIPN20. A total of 117 patients completed T1 (response rate 76%), and 69 and 59 patients completed T2 and T3 respectively. Over time, the course of several sensory symptoms was less favourable for the patients treated with adjuvant chemotherapy. Additionally, the course of numbness in toes/feet differed significantly between patients treated with CAPOX (T1 7%, T2 50%, T3 42%) and patients treated with CapMono (T1 17%, T2 31%, T3 8%). Furthermore, patients treated with CapMono reported significantly less tingling toes/feet (T1 6%, T2 25%, T3 7%) than patients treated with CAPOX (T1 0%, T2 50%, T3 58%). As neuropathic symptoms may impair functional capacities and are negatively associated with health-related quality of life during and after treatment, it is of paramount importance to inform elderly on these risks to enable them to make an informed decision on a suitable course of treatment.

In *chapter 7*, the association between adjuvant chemotherapy and the risk of distant recurrence was investigated. It was also evaluated whether the association was similar for patients aged ≥75 years and their younger counterparts. Patients diagnosed with stage III colon cancer between 2003 and 2008 in the southeast of the Netherlands were included as data on the development of metachronous distant recurrences was available for these years. Propensity score matching was applied to create a subsample to reduce bias caused by differences between patients receiving adjuvant chemotherapy and patients not receiving adjuvant chemotherapy. Adjuvant chemotherapy (CTx) was correlated with a reduced risk of distance recurrence in both the total study population (crude five-year percentages for CTx versus no CTx 36% vs. 42%, adjusted HR 0.55, 95% CI 0.42-0.70) and in the propensity score matched sample (34% vs. 50%, adjusted HR 0.46, 95% CI 0.33-0.63). In separate analyses for patients aged <75 years and ≥75 years, the effect of adjuvant chemotherapy on the risk of distant recurrence remained comparable for both age groups (adjusted HR 0.50, 95% CI 0.37-0.68 and adjusted HR 0.57, 95% CI 0.36-0.90 respectively). These results suggest that older patients derive comparable benefit from adjuvant chemotherapy as their younger counterparts with regard to the risk of distant recurrence. Consideration of adjuvant chemotherapy is therefore warranted.

In the next study, the associations of the adjuvant chemotherapy regimens CAPOX and CapMono with recurrence-free survival (RFS) and overall survival (OS) among elderly stage III colon cancer patients were investigated *(chapter 8)*. Moreover, this study also evaluated the effects of (non-)completion of both regimens on RFS and OS. Recurrence as defined for this study encompassed local and/or regional and/or distant recurrence(s). Five-year RFS and five-year OS did not differ between CapMono and CAPOX (RFS: 63% vs. 60%, adjusted HR 0.99, 95% CI 0.68-1.44; OS: 66% vs. 66%, adjusted HR 0.93, 95% CI 0.64-1.34). After resection only, five-year RFS was 38% and five-year OS 37%. Completion of treatment (defined as ≥6 cycles) was achieved for 48% among patients treated with CAPOX and for 68% among patients treated with CapMono. Three-year RFS and OS did not differ between patients who discontinued CAPOX early and patients who completed treatment with CAPOX (RFS: 61% vs. 69%, adjusted HR 1.42, 95% CI 0.85-2.37; OS: 68% vs. 78%, adjusted HR 1.17, 95% CI 0.70-1.97). Three-year RFS and OS differed between patients who discontinued CapMono early and patients who completed treatment with CapMono (RFS: 54% vs. 72%,

adjusted HR 2.07, 95% CI 1.11-3.84; OS: 65% vs. 80%, adjusted HR 2.00, 95% CI 1.12-3.59). In other words, administration of CAPOX or CapMono is associated with improved RFS and OS. Since the advantage does not differ by regimen, the addition of oxaliplatin might not be justified in elderly stage III colon cancer patients treated in everyday clinical practice.

The last study included in this thesis investigated which demographic and clinical variables were associated with the timing of adjuvant chemotherapy and how this timing was associated with overall survival *(chapter 9)*. In this nationwide study, data from the Netherlands Cancer Registry for all stage III colon cancer patients who underwent resection and received adjuvant chemotherapy between 2008 and 2013 was included. The median timing of adjuvant chemotherapy was 5.6 weeks post-surgery. Fourteen percent of the patients commenced adjuvant chemotherapy more than 8 weeks after surgery. Factors associated with starting treatment after 8 weeks post-surgery were older age (65-74 years vs. <65 years: adjusted OR 1.3, 95% CI 1.14-1.58; ≥75 years vs. <65 years: adjusted OR 1.6, 95% CI 1.25-1.94), emergent surgery, anastomotic leakage, referral to another hospital for adjuvant chemotherapy and prolonged postoperative hospital admission. The crude five-year overall survival rates according to initiation of adjuvant chemotherapy within 4, 5-6, 7-8, 9-10, 11-12 or 13-16 weeks were 75%, 76%, 72%, 64%, 61% and 54% respectively. After adjustment for casemix, starting 5-8 weeks post-surgery showed no decrease in overall survival compared to initiation within 4 weeks after surgery. However, commencing beyond 8 weeks post-surgery was associated with decreased overall survival compared to initiation within 8 weeks. These results support initiation of adjuvant chemotherapy in stage III colon cancer within 8 weeks post-surgery, while also providing a time window in which patients can recover from surgery.

General discussion

Elderly represent a substantial part of the colon cancer patients and this will increase even further in the near future due to demographic developments[1]. This provides a significant challenge to cancer specialists, as many uncertainties still remain regarding the optimal treatment for this heterogeneous patient population. This thesis intended to realise a more evidence-based use of the existing adjuvant treatment options for elderly patients with stage III colon cancer.

The administration of adjuvant chemotherapy declines with increasing age[2-10]. Approximately one third of the elderly stage III colon cancer patients receives adjuvant chemotherapy. Several reasons were identified for this low treatment rate. The most frequently reported motives by surgeons for non-referral and by medical oncologists for non-treatment were comorbidity/bad general health condition of the patient, surgical complications, and refusal by the patient and/or family. In line with the first reported motive, patients who received adjuvant chemotherapy had less comorbid conditions and a lower ASA score than patients who underwent resection alone[11-16]. The use of biological age as opposed to chronological age is desirable in deciding on (contra-)indications for adjuvant chemotherapy.

The variation among surgeons and medical oncologists in motives for non-referral, non-treatment and consultation of geriatricians, as well as the variation in treatment

between hospitals after adjustment for patient casemix, show the complexity of an adequate selection of patients that will benefit from adjuvant chemotherapy. As this thesis showed that the older patients who were treated with adjuvant chemotherapy derived comparable benefits from adjuvant chemotherapy as their younger counterparts with regard to the risk of recurrence, a further investigation and refinement of this selection is of paramount importance. Some promising advances have been made, such as the exploration of immunological criteria that could be included in tumour staging. Tumour infiltration by specific types of immune cells has been associated with tumour dissemination, recurrence and survival[17-22]. Additionally, several other markers have been identified that can be used for prognostic stratification of patients and which might help select patients for adjuvant chemotherapy[23]. These markers include for example perineural invasion and lymphovascular invasion[24], microsatellite instability (MSI)[25,26], BRAF mutations[27,28] and KRAS mutations[29,30]. Mutations in BRAF and KRAS have been independently associated with reduced disease-free and overall survival. Especially interpreted in the context of MSI status and tumour location are they of great value. The highest risk of recurrence is found in BRAF-mutated microsatellite stable (MSS) left-sided tumours[23,31]. These advances will challenge researchers and clinicians to develop even more complex and individualized treatment strategies.

For elderly, the inclusion of geriatrics and geriatric assessments provides additional opportunities for further refinement of the selection of elderly who could benefit from adjuvant chemotherapy. The International Society of Geriatric Oncology (SIOG) recommends that for patients with physical or psychological comorbidities, a geriatrician should be involved in patient management[32]. The need for geriatric screening and assessment and the feasibility of including geriatrics in oncology care was previously shown[33]. Problems were revealed for more than half of older cancer patients, which led to geriatric interventions in a quarter of these patients[33]. Recently, psychological stress, neuropsychological problems and the number of prescriptive drugs taken were found to be predictive for the feasibility of chemotherapy[34].

For a patient to receive sufficient information about the treatment with adjuvant chemotherapy and for an assessment of a patient's functional status and possible risks and benefits of treatment with adjuvant chemotherapy, every elderly stage III colon cancer patient should have a consultation with a medical oncologist. On the other hand, it should also be acknowledged that adjuvant chemotherapy may not be desirable for every elderly stage III colon cancer patient, for example in case of a short remaining life expectancy. In case of doubt on vitality or goal setting for individual patients, it is preferable that consultation by a geriatrician and geriatric assessment are part of the care pathway.

In case an elderly patient is treated with adjuvant chemotherapy, another challenge is to select an appropriate regimen for each individual patient. Current guidelines recommend oxaliplatin-containing chemotherapy as the standard of care, with exceptions in which a fluoropyrimidine monotherapy is preferable[32,35]. In clinical practice, elderly patients are less often treated with oxaliplatin-containing regimens than their younger counterparts[5,36-38]. Comorbidity, patients general health condition and toxicity profile were the most frequently reported factors on the decision for monotherapy instead of combination therapy. Again,

there was a large variation between hospitals in the southern part of the Netherlands with regard to the type of adjuvant chemotherapy (that is, combination therapy versus monotherapy) administered to these patients, which could not be explained by casemix.

Nowadays, CAPOX and capecitabine monotherapy (CapMono) are the mostly prescribed regimens for elderly stage III colon cancer patients treated in daily clinical practice. In the included years (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)[16]. A 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[39]. The use of capecitabine instead of FU in the Netherlands is high in comparison to other countries. 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[40,41], are more convenient for the patient and have a more favourable reimbursement policy for hospitals.

This thesis showed that elderly patients receiving CAPOX less frequently completed all planned cycles compared to patients receiving CapMono (33% versus 55%). 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 2500 mg/m^2). In addition, increased toxicity with the CAPOX regimen can also have impacted the cumulative dosage of capecitabine. However, 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.

When deciding on the dosage of fluoropyrimidine, an important consideration is the presence of dihydropyrimidine dehydrogenase (DPD) deficiency, encoded by the gene DPYD. DPYD variants DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 have been shown to be predictive for severe and life-threatening fluoropyrimidine-associated (haematological and gastrointestinal) toxicity[42,43]. Dose reductions of 50% for the first two variants and 25% for the latter variant are now recommended[43,44]. For one of the most well established DPYD variants, DPYD*2A, genotype-guided dosing has been shown to significantly improve safety. Additionally, prospective screening for DPYD*2A was proven to be feasible and cost saving in daily clinical practice[45].

The 5-year recurrence-free and overall survival rates for patients treated with CAPOX (60% and 66% respectively) and for patients treated with CapMono (63% and 66% respectively) were comparable, despite the fact that the patients receiving CAPOX were younger and had less comorbid conditions than the patients receiving CapMono. In other words, oxaliplatin did not provide benefit.

Additionally, 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[36,46]. Other research has 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.[47] showed that the risk of severe toxicity is significant for any older patient receiving chemotherapy. Patient differences in Eastern Cooperative Oncology Group (ECOG) performance status, nutritional status and mental status contributed two to three times more than chemotherapy differences to the risk of non-haematological toxicity[47]. 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[48,49]. Additionally, declining food intake, the number of prescription drugs taken and dependence in shopping were predictive for a higher mortality risk[34]. Unfortunately, these geriatric factors were not available in the studies included in this thesis and only the presence of any grade III-V toxicity was found to be independently related to early discontinuation of both CAPOX and CapMono. It was previously shown that even low grade toxicities (i.e. grade I-II) can lead to treatment modification and early discontinuation in older patients[50].

Especially for elderly, the impairment of functional capacities can have a significant impact on their (quality of) life. Chemotherapy-induced peripheral neuropathy (CIPN) is increasingly recognized as an important adverse effect of oxaliplatin. CIPN interferes with many aspects of daily life and is negatively associated with health-related quality of life, while its prevention and treatment remain difficult[51-55]. CIPN is only partly reversible, with chronic neuropathy still present in many patients more than one year after the termination of therapy[56]. Even as long as 11 years after diagnosis, neuropathic symptoms are still reported by colorectal cancer patients, especially sensory symptoms in the toes and feet among those treated with oxaliplatin[57]. A higher cumulative dose of oxaliplatin seems to be a predictive factor for the development of chronic peripheral neuropathy[56,58,59]. In this light, the results of The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) study in which disease-free survival is compared between standard six months of adjuvant treatment with oxaliplatin versus three months of adjuvant treatment with oxaliplatin will be of great value[60].

As CapMono is better tolerated and less toxic without limiting the recurrence-free and overall survival benefit, a shift towards fluoropyrimidine monotherapy as the standard of care with exceptions in which oxaliplatin-containing chemotherapy is preferable, is indicated. One such exception is the presence of microsatellite instability (MSI). MSI is present in approximately 15% of the patients with colon cancer[61]. Although MSI tumours have a favourable prognosis, they appear to be resistant for fluoropyrimidines[25]. For oxaliplatin-containing regimens, no difference in benefit was found between MSI tumours and microsatellite stable tumours[26]. Therefore, a combination regimen with oxaliplatin is the first choice of treatment in case of MSI tumours. This also implies that evaluation of the mismatch repair status should become standard of care.

With regard to the timing of adjuvant chemotherapy after surgery, this thesis showed that initiating adjuvant chemotherapy beyond 8 weeks was associated with a decrease in overall survival, even when relevant prognostic factors were taken into account. However, a negative effect on survival of initiating adjuvant chemotherapy between 5 and 8 weeks

post-surgery compared to initiation within 4 weeks was not present. A time window seems present in which patients can recover from surgery and prepare for the next step in the treatment process.

Methodological considerations

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

Data sources

NETHERLANDS CANCER REGISTRY

The main data source for most of the studies included in this thesis was the Netherlands Cancer Registry (NCR). More specifically, most studies focused on patients diagnosed and treated in the southeast of the Netherlands (the area formerly covered by the Eindhoven Cancer Registry), which comprises about 2.4 million inhabitants (~15% of the Dutch population) and encompasses 10 community hospitals. No academic or specialized cancer hospitals are included in the region. Information on patient and tumour characteristics and primary treatment are routinely collected within the NCR. Additionally, in the southeast of the Netherlands, comorbid conditions present at time of cancer diagnosis are also registered[62,63]. This is unique as compared to other cancer registries worldwide and provides essential information for studies among elderly cancer patients. However, no detailed information on the systemic treatment such as regimen, number of cycles and dosage were standardly available in the NCR. Data on the development of recurrences was also not yet collected. These data were additionally collected for several studies included in this thesis. A limitation is that information on the performance status of the patients was frequently missing from the medical files and could not be included.

PHARMO

Data on drug dispensings as used for *chapter 2* were retrieved from the out-patient pharmacy database from the PHARMO Database Network and linked to clinical data from the NCR, covering an overlapping demographic region in the southeast of the Netherlands of approximately 1.2 million inhabitants[64]. The PHARMO Database Network is a large patient-centric data network including multiple linked observational databases designed for drug safety and outcomes research. Strengths are that we were able to include a matched control group without cancer and that the sample size for this study was large (i.e. 2735 elderly colon cancer patients and 2735 matched cancer-free controls). Limitations are that it remains unknown whether dispensed drugs are actually ingested by the patients, although possible misclassification will be non-differential; that details regarding prescription length and dosages were not taken into account; and that no data from in-hospital pharmacies was included, which may have resulted in an underestimation of drug dispensings.

QUESTIONNAIRES

For the study in *chapter 3*, in which we investigated subjective, doctor-related factors influencing the decision-making on adjuvant chemotherapy, we developed a short questionnaire for surgeons and medical oncologists. A limitation of this approach is that the questionnaire was not validated. However, we discussed the questionnaire with a medical oncologist for content and relevance. Another limitation was the small sample size, but strengths were the high response rate (i.e. 81%) and the inclusion of medical specialists from 10 different hospitals.

In *chapter 6*, we investigated differences in the course of patient-reported neuropathic symptoms between treatment modalities. In this study, we used the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy 20 (EORTC QLQ-CPIN20) to measure peripheral neuropathy[65]. Other strengths of this study included the use of longitudinal data with a baseline measurement and the adjustment for comorbid conditions that are also associated with neuropathic symptoms. Furthermore, the initial response rate was relatively high (i.e. 76%) and comparable to other surveys[66]. The invitation for the study was sent by the attending surgeon, which may have resulted in this high response rate. A limitation is the relatively small sample size, especially during the second and third wave as many patients discontinued participation after the first measurement. This might have been a consequence of surveying patients shortly after major cancer surgery. The data from the questionnaires was collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship)[67], which is linked to clinical data from the NCR. This linkage enabled us to compare sociodemographic and clinical characteristics between respondents and non-respondents.

Study design

The studies included in this thesis had an observational design and the following advantages and disadvantages of this approach should be considered. In general, randomized clinical trials (RCTs) are considered the gold standard in evaluating the efficacy of treatments. In RCTs, participants are randomly assigned to a treatment or control group, thereby equalizing the treatment and control groups with respect to all features except the treatment assignment. RCTs have a superior internal validity compared to observational studies, but the generalizability of RCTs is limited as RCTs are often restricted to relatively healthy patients with minimal comorbidity and good performance status. Therefore, RCTs cannot establish treatment effectiveness and the knowledge gained from RCTs should be complemented with data from population-based observational studies. The observational nature of population-based studies limits in establishing causality but has the ability to provide a unique insight into the effects of treatments in everyday clinical practice[68-70]. The Netherlands Cancer Registry allows the evaluation of outcomes in the general patient population and provides information regarding the use, safety and outcomes in the real

world. Especially for patient groups who do not meet the eligibility criteria from RCTs, such as a large part of the elderly patient population who were the subject of the studies included in this thesis, observational studies are of paramount importance.

Several biases are inherent to population-based observational studies and should be considered when interpreting the results of the studies included in this thesis. Here, the most important biases and how these biases were dealt with are discussed.

SELECTION BIAS AND ATTRITION BIAS

Selection bias can either refer to the selective recruitment of patients into the study who are not representative for the source population or to systematic differences between baseline characteristics of the groups that are compared in the study.

The proportion of patients reporting neuropathic symptoms *(chapter 6)* may have been influenced by the first type of selection bias even though participants were selected from a population-based sample and initial response rate was relatively high (i.e. 76%). To explore the representativeness of the data, sociodemographic and clinical characteristics of the respondents and non-respondents were compared. We found that respondents were relatively younger at time of cancer diagnosis compared to non-respondents, but both groups did not differ with regard to gender, socioeconomic status, number of comorbid conditions and type of adjuvant chemotherapy. It is possible that non-respondents had more postoperative complications or a poorer performance status.

The findings of this study may also have been affected by attrition bias as a result of loss to follow-up. Of the 117 patients completing the first questionnaire, respectively 69 and 59 patients completed the second and third questionnaire. Comparison of patients who completed 1 versus 2 or 3 questionnaires indicated that those patients who completed 2 or 3 questionnaires represented a selection of the 'fitter' patients compared to those patients who completed 1 questionnaire.

The second type of selection bias is present in all studies included in this thesis in which patients were grouped according to (type of) adjuvant chemotherapy receipt *(chapters 4-9)*. Patients treated with an oxaliplatin-based regimen, monotherapy or no adjuvant chemotherapy differed on several patient and tumour characteristics such as age and comorbidity. We used statistical techniques to adjust for imbalances between treatment groups. First, we used methods involving covariance adjustment in all studies. These methods produce estimates of treatment effects adjusted for patient and tumour characteristics (covariates) which are explicitly included in the statistical regression models. We were able to adjust for a large number of patient and tumour characteristics, including comorbidity.

Second, in one study we also used propensity score matching *(chapter 7)*. The propensity score was estimated using logistic regression and represented the probability that a patient would not receive adjuvant chemotherapy, conditional on the patient's background characteristics (i.e. gender, age, socioeconomic status, comorbidity, T stage, N stage, differentiation grade, subsite and period of diagnosis). Patients who did not receive adjuvant chemotherapy were then matched to patients who did receive adjuvant chemotherapy on the basis of propensity scores, which could vary by no more than 1%, to create two groups comparable on baseline characteristics.

Besides the choice for certain statistical techniques, we also contemplated on adequate outcomes. In addition to overall survival, we included the risk of recurrence and recurrence-free survival *(chapters 7-8)* whenever possible. These outcomes might be less prone to selection bias than overall survival.

IMMORTAL TIME BIAS

In the studies included in this thesis, immortal time bias occurred in case the time between cancer diagnosis and treatment was taken into account in survival analyses *(chapters 8-9)*. In this period death could not occur, in other words, a period of 'immortal time' was present as the patient must have been alive to receive the treatment. This bias results in an overestimation of the effect of a treatment.

To minimize immortal time bias, we differed the starting points for the survival analyses. For recurrence-free and overall survival according to treatment modality (i.e. resection only, CAPOX or capecitabine), the date of resection of the primary tumour was used. For recurrence-free and overall survival according the chemotherapy regimen and completion of all planned cycles, the last date of chemotherapy was taken.

RESIDUAL CONFOUNDING

The lack of randomization in the studies included in this thesis may not only have resulted in differences between treatment groups on observed characteristics, but also on unobserved characteristics[69]. We were only able to adjust for known and observed characteristics in our statistical analyses, while other unobserved characteristics might also have influenced outcomes. For example, no information on ECOG performance status, nutritional status and mental status were available.

Implications for clinical practice

Medical specialists will encounter an increasing number of elderly colon cancer patients. Based on the findings of this thesis, a number of recommendations on adjuvant chemotherapy among elderly patients with stage III colon cancer are formulated.

- Consideration of adjuvant chemotherapy is warranted for all elderly stage III colon cancer patients. Elderly patients derive comparable benefit from adjuvant chemotherapy with regard to the risk of recurrence compared to their younger counterparts.
- Every elderly patient, with or without comorbidity, should have a consultation with the medical oncologist after resection of the primary tumour for an assessment of their physiological and functional status after surgery and to receive sufficient information about the treatment with adjuvant chemotherapy. In certain circumstances, withholding adjuvant chemotherapy may be appropriate, i.e. in case of a short remaining life expectancy (<1-2 years).
- In deciding on the administration of adjuvant chemotherapy, a careful weighing of the expected benefits and drawbacks of adjuvant chemotherapy should be performed. The potential reduction in recurrence risk must be weighed against the potential risk of toxicity and competing causes of death. The assessment of older patients is complex and should also include considerations of comorbidities, polypharmacy, activities of daily living, nutritional status and psychosocial and cognitive functioning. Additionally, remaining life expectancy and patient preference (i.e. with regard to preservation of independence or functional status) are of paramount importance.
- For selected cases, for example in case of doubt on vitality or goal setting for individual patients, consultation with a geriatrician and possibly geriatric assessment is preferable.
- In case adjuvant chemotherapy is administered, fluoropyrimidine monotherapy is the preferred regimen of choice. Capecitabine monotherapy seems preferable over CAPOX for the majority of the patients as capecitabine monotherapy is better tolerated and less toxic, without limiting the recurrence-free and overall survival benefit. When deciding on the dosage, upfront screening for DPYD*2A is recommended to reduce the risk of fluoropyrimidine-associated toxicity. In certain circumstances, oxaliplatin-containing chemotherapy is indicated, for example in patients with a microsatellite instable (MSI) tumour. Therefore, analysis of the mismatch repair status should become standard of care.
- The risk of toxicity from adjuvant chemotherapy should explicitly be discussed with patients. Elderly patients often value quality of life including independent life expectancy above life expectancy itself. Therefore, especially the risk of oxaliplatin-induced neuropathy deserves attention because of the risk of long term disabling effects.
- Adjuvant chemotherapy should be initiated within 8 weeks post-surgery, while providing a time window in which patients can recover from surgery.

Implications for future research

Elderly need to become the focus of future colon cancer research, as they represent a large part of the patient population. Although challenging, the realization of clinical trials designed for elderly cancer patients as well as prospective observational studies including an extensive description of elderly patient characteristics and with appropriate outcomes (i.e. preservation of independence, functional status and quality of life) is important to expand the evidence-base for the treatment of elderly colon cancer patients. For example, the almost exclusive use of capecitabine-based regimens in our study population disabled a direct comparison of the effectiveness of 5-fluorouracil-based therapy with capecitabine-based therapy among elderly stage III colon cancer patients. A 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[71].

The Netherlands Cancer Registry underwent a large scale extension of its dataset for all colorectal cancer patients diagnosed from 2015 onwards and now encompasses more detailed information regarding systemic therapies, prognostic markers and long-term follow-up regarding tumour progression and recurrence. This offers unique opportunities for evaluating the use and effects of treatments in real life patients, especially in a patient group which is often excluded from trials.

Of interest, the national screening program for colorectal cancer will have considerable impact on future (epidemiological) colorectal cancer research and clinical practice. The screening program started in 2014 and is further introduced in phases until in 2019 all persons aged 55-75 years will be invited to participate every 2 years. The primary aim of the screening program is to reduce mortality from colorectal cancer through earlier diagnosis, which will result in less invasive treatments and in less adjuvant treatments. Furthermore, after an initial sharp increase in the number of newly diagnosed colorectal cancer patients, the incidence will decrease[72,73].

Concluding remarks

Elderly represent a substantial part of the colon cancer patients and this will increase even further in the near future due to demographic developments. This thesis provides a substantial contribution to the limited available evidence on the use and effectiveness of adjuvant chemotherapy among unselected elderly patients with stage III colon cancer treated in everyday clinical practice. It was shown that elderly derive comparable benefit from adjuvant chemotherapy as their younger counterparts, indicating that consideration of adjuvant chemotherapy is warranted for all patients. It was also shown that capecitabine monotherapy is better tolerated and less toxic, without limiting the recurrence-free and overall survival benefit, compared to a combination of capecitabine and oxaliplatin. Therefore, the addition of oxaliplatin should not be standard care for the majority of elderly stage III colon cancer patients treated in daily clinical practice.

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Nederlandse samenvatting

(Dutch summary)

Inleiding

Vergrijzing en dikkedarmkanker

De naoorlogse geboortegolf en de stijgende levensverwachting hebben geresulteerd in een toename van het aantal ouderen in Nederland. Door deze vergrijzing, maar ook door ongezonde leefstijlveranderingen en introductie van het bevolkingsonderzoek, neemt het aantal nieuw gediagnosticeerde patiënten met dikkedarmkanker toe. Tussen 1990 en 2015 steeg het aantal patiënten met dikkedarmkanker van 4.600 tot 10.900. Ook de komende jaren zal het aantal patiënten naar verwachting verder stijgen.

De gemiddelde leeftijd ten tijde van de diagnose dikkedarmkanker is 69 jaar; ongeveer een derde van de patiënten is 75 jaar of ouder. Door de hoge gemiddelde leeftijd op het moment van de diagnose, heeft een groot deel van de patiënten ook te maken met andere chronische ziekten (zogeheten comorbiditeiten). Meer dan de helft van de patiënten met dikkedarmkanker heeft één bijkomende ziekte en bijna een derde van deze patiënten heeft twee of meer bijkomende ziekten. De meest voorkomende comorbiditeiten zijn hoge bloeddruk, hart- en vaatziekten, andere vormen van kanker en diabetes. Als gevolg van comorbiditeit, gebruiken patiënten vaak meerdere medicijnen. Dit kan problematisch zijn wanneer interacties tussen medicijnen of verkeerde innames leiden tot toxiciteit en afname van de werkzaamheid van de medicijnen.

Adjuvante chemotherapie voor stadium III dikkedarmkanker

Ongeveer een kwart van alle patiënten met dikkedarmkanker heeft stadium III ten tijde van de diagnose. Dat houdt in dat de kanker niet beperkt is tot de dikke darm, maar dat de ziekte naar tenminste één regionale lymfeklier is verspreid, maar niet naar andere organen. De behandeling bestaat uit het chirurgisch verwijderen van de tumor en regionale lymfeklieren, gevolgd door chemotherapie (zogenaamde adjuvante chemotherapie). Adjuvante chemotherapie wordt gebruikt met de intentie om eventuele achtergebleven tumorcellen uit te roeien.

Het positieve effect van adjuvante chemotherapie op de overleving van patiënten met stadium III dikkedarmkanker is vastgesteld in klinische trials en is sinds de jaren negentig de standaardbehandeling. Tot 2005 was behandeling met de middelen 5-fluorouracil en leucovorin (5-FU/LV) de enige effectieve optie. Op dat moment kwam het middel capecitabine beschikbaar. In een trial werd aangetoond dat capecitabine gelijkwaardig is aan 5-FU/LV met betrekking tot de overleving. Een andere ontwikkeling was de introductie van het middel oxaliplatin. Verschillende trials lieten zien dat de toevoeging van oxaliplatin aan 5-FU/LV (genaamd FOLFOX) voorzag in extra overlevingswinst, maar dit leidde wel tot meer bijwerkingen. In weer een andere trial werd aangetoond dat de combinatie van oxaliplatin met capecitabine (genaamd CAPOX) voor een vergelijkbare overlevingswinst zorgde waardoor een alternatieve behandelingsoptie beschikbaar kwam.

Ondervertegenwoordiging en exclusie van ouderen in trials

Ondanks het feit dat dikkedarmkanker vooral voorkomt bij ouderen, waren patiënten in de leeftijd van 70 tot en met 75 jaar ondervertegenwoordigd in de hiervoor genoemde trials. Patiënten ouder dan 75 jaar werden zelfs volledig uitgesloten. Klinische trials gebruiken dus inclusiecriteria die geen rekening houden met patiëntkarakteristieken zoals deze in de dagelijkse klinische praktijk voorkomen. Het gevolg is dat oudere patiënten die wél deelnemen aan klinische trials vaak relatief vitaal zijn met weinig comorbiditeit. Deze patiëntengroepen zijn niet representatief voor de oudere patiënt in de dagelijkse klinische praktijk.

Om de effecten voor oudere patiënten toch te kunnen evalueren, werden subgroep analyses en analyses op gecombineerde data van trials uitgevoerd. Daaruit bleek dat geselecteerde ouderen hetzelfde voordeel hebben van 5-FU/LV en capecitabine als jongere patiënten. Patiënten in de leeftijd van 70 tot en met 75 jaar stopten wel vaker voortijdig met de behandeling in vergelijking met jongere patiënten. Ook waren er vaker dosisaanpassingen en dosisreducties nodig. Met betrekking tot een overlevingseffect werden inconsistente resultaten gevonden bij de toevoeging van oxaliplatin. Daarnaast braken ouderen behandeling met oxaliplatin vaker voortijdig af en trad er meer toxiciteit op.

Een beperking blijft dat de resultaten van deze studies mogelijk niet van toepassing zijn op ongeselecteerde, oudere patiënten in de dagelijkse klinische praktijk. Medisch specialisten worden steeds vaker geconfronteerd met oudere patiënten die zeer heterogeen zijn met betrekking tot hun onderliggende gezondheidsstatus. Clinici moeten de data extrapoleren om samen met de patiënt betekenisvolle beslissingen te kunnen nemen. Dat kan leiden tot onderbehandeling of overbehandeling al dan niet gepaard gaande met excessieve bijwerkingen. Daarom zijn er naast klinische trials andere bronnen van informatie nodig om de effecten van adjuvante chemotherapie bij oudere patiënten met stadium III dikkedarmkanker te evalueren.

Observationele studies

Observationele studies met data van patiënten uit de dagelijkse klinische praktijk kunnen inzicht geven in het gebruik en de effecten van de verschillende opties voor adjuvante chemotherapie bij ongeselecteerde, oudere patiënten. In 2012 stelde ZonMw een onderzoekssubsidie beschikbaar aan Integraal Kankercentrum Nederland (IKNL) om hier onderzoek naar te doen, wat resulteerde in dit proefschrift. Op dat moment hadden eerdere observationele studies reeds aangetoond dat oudere patiënten minder vaak met adjuvante chemotherapie worden behandeld en dat zij tevens minder vaak oxaliplatin-bevattende chemotherapie ontvangen. Daarnaast kwamen dosisreducties en het voortijdig afbreken van de behandeling vaker voor bij ouderen. Er werd echter zelden onderscheid gemaakt tussen de verschillende monotherapieën (5-FU/LV of capecitabine) en

combinatietherapieën (FOLFOX of CAPOX). Ook was er weinig bekend over de factoren die een rol spelen in de besluitvorming rondom het verstrekken van adjuvante chemotherapie bij oudere patiënten met stadium III dikkedarmkanker. Verder ontbrak inzicht in welke mate ongeselecteerde, oudere patiënten de verschillende adjuvante chemotherapieën verdragen, welke bijwerkingen zij ontwikkelen, en wat de verschillen in recidiefvrije en algemene overleving zijn tussen de diverse behandelingen in de dagelijkse, klinische praktijk.

Doel van dit proefschrift

Het doel van dit proefschrift is om meer bewijs te verzamelen waarop het gebruik van de bestaande adjuvante chemotherapieën voor oudere patiënten met stadium III dikkedarmkanker gebaseerd kan worden. De belangrijkste doelstellingen van dit proefschrift zijn:

- Inzicht geven in het gebruik van de verschillende opties voor adjuvante chemotherapie (deel I).
- Onderzoeken van de dosisintensiteit en gerelateerde toxiciteit van de verschillende adjuvante chemotherapieën (deel II).
- Evalueren van de samenhang tussen adjuvante chemotherapie en het risico op een recidief, en de samenhang tussen adjuvante chemotherapie en de recidiefvrije en algemene overleving (deel III).

Belangrijkste bevindingen

Dit proefschrift begint met een overzicht van medicatie-uitgiftes van de openbare apotheek aan oudere patiënten met dikkedarmkanker in het jaar vóór de kankerdiagnose in vergelijking met een controlegroep zonder kanker die qua leeftijd en geslacht vergelijkbaar is *(hoofdstuk 2)*. Gedurende dit hele jaar was het medicatiegebruik hoger bij deze 'toekomstige' patiënten in vergelijking met de kankervrije controlegroep. Dit aandeel nam verder toe gedurende de laatste drie maanden voorafgaand aan de kankerdiagnose. Het verhoogde aantal medicatie-uitgiftes bij patiënten in vergelijking met de controlegroep gedurende het totale jaar was voornamelijk gerelateerd aan comorbiditeit, terwijl de medicatie-uitgiftes in de laatste maanden voor de diagnose dikkedarmkanker waarschijnlijk voornamelijk aan (symptoombestrijding van) de dikkedarmkanker waren gerelateerd. Inzicht in medicatiegebruik in de periode voor de diagnose dikkedarmkanker kan huisartsen en medisch specialisten aanknopingspunten bieden om patiënten uit te nodigen voor verder onderzoek. Daarnaast is het van belang om rekening te houden met bestaand medicijngebruik bij het bepalen van een passende kankerbehandeling.

Gebruik van adjuvante chemotherapie

In *hoofdstuk 3* zijn subjectieve, arts-gerelateerde factoren onderzocht die mee kunnen spelen in de besluitvorming rondom adjuvante chemotherapie voor oudere patiënten met stadium III dikkedarmkanker. Hiervoor zijn korte vragenlijsten opgesteld en naar chirurgen en medisch oncologen verstuurd. De door chirurgen het vaakst gerapporteerde

motieven voor niet doorverwijzen waren: comorbiditeit of slechte algemene conditie van de patiënt, chirurgische complicaties en weigering van adjuvante chemotherapie door de patiënt. Medisch oncologen rapporteerden deze motieven ook voor niet-behandelen, maar rapporteerden daarnaast dat de verwachte bijwerkingen naar hun idee te ernstig waren. Verder rapporteerden minder dan de helft van de chirurgen en iets meer dan de helft van de medisch oncologen een geriater te consulteren voor een minderheid van de patiënten. Wat betreft de beslissing van medisch oncologen voor behandeling met monotherapie of combinatietherapie, gaven zij aan dit te baseren op de aanwezigheid van comorbiditeit, de algemene conditie van de patiënt en het bijwerkingenprofiel van de middelen. Medisch oncologen waren het eens over acceptabele niveaus van bijwerkingen.

Vervolgens zijn in *hoofdstuk 4* patiënt- en tumorkarakteristieken geëvalueerd die de toediening van oxaliplatin-bevattende chemotherapie (FOLFOX en CAPOX) in vergelijking met non-oxaliplatin-bevattende chemotherapie (5FU/LV en capecitabine) beïnvloedden en is de variatie in de toediening van beide typen tussen ziekenhuizen geëvalueerd. In deze studie zijn 1.140 patiënten geïncludeerd afkomstig uit tien ziekenhuizen in Zuidoost-Nederland en gediagnosticeerd tussen 2008 en 2011. De mediane leeftijd van de patiënten die oxaliplatin ontvingen was 64 jaar, en de mediane leeftijden van patiënten die chemotherapie zónder oxaliplatin of géén chemotherapie ontvingen waren respectievelijk 74 en 79 jaar. Er was grote ziekenhuisvariatie in de toediening van oxaliplatin-bevattende en non-oxaliplatin-bevattende chemotherapie, die niet volledig verklaard kon worden door verschillen in patiëntenpopulaties. De toediening van oxaliplatin-bevattende chemotherapie varieerde van 63% tot 87% voor patiënten jonger dan 70 jaar, van 15% tot 100% voor patiënten van 70 tot 75 jaar, en van 0% tot 19% voor patiënten van 75 jaar of ouder. Voor chemotherapie zonder oxaliplatin liepen deze proporties uiteen van 3% tot 20%, van 0% tot 29% en van 0% tot 28% in de respectievelijke leeftijdsgroepen. In een analyse waarbij alleen de patiënten die adjuvante chemotherapie ontvingen waren geïncludeerd, hing de toevoeging van oxaliplatin samen met leeftijd, de uitgebreidheid van de tumor, de periode van diagnose en het ziekenhuis van behandeling.

Intensiteit en toxiciteit van adjuvante chemotherapie

In *hoofdstuk 5* is inzicht gegeven in het afmaken van alle geplande kuren en de totaal ontvangen cumulatieve dosering voor de in de dagelijkse klinische praktijk meest gebruikte chemotherapie schema's en is het verband met toxiciteit onderzocht. Hiervoor zijn aanvullende data verzameld in de Nederlandse Kankerregistratie voor alle patiënten met stadium III dikkedarmkanker van 70 jaar of ouder, gediagnosticeerd in een van de tien ziekenhuizen in Zuidoost-Nederland tussen 2005 en 2012. Deze studie laat zien dat een grote meerderheid (88%) van de patiënten die een behandeling kregen met adjuvante chemotherapie CAPOX of capecitabine ontvingen. Het aandeel patiënten dat alle geplande kuren afmaakte, was lager voor patiënten behandeld met CAPOX (33%) dan voor patiënten behandeld met capecitabine (55%). De ontvangen cumulatieve dosering van capecitabine was ook lager voor patiënten behandeld met CAPOX (163.744 mg/m^2) dan voor patiënten behandeld met capecitabine (189.195 mg/m^2). Daarnaast was CAPOX geassocieerd met significant meer toxiciteit dan capecitabine (54% versus 38%), ook na

correctie voor patiënt- en tumorkarakteristieken. Voor patiënten behandeld met CAPOX waren de meest voorkomende bijwerkingen gastro-intestinaal (voornamelijk diarree en misselijkheid/overgeven, 29%), hematologisch (14%), neurologisch (voornamelijk neuropathie, 11%) en overig (voornamelijk vermoeidheid, 13%). Voor patiënten behandeld met capecitabine waren dermatologische (hand-voetsyndroom, 17%), gastro-intestinale (voornamelijk diarree, 13%) en overige (voornamelijk vermoeidheid, 11%) bijwerkingen het meest voorkomend.

Neuropathie (zenuwbeschadiging) wordt steeds vaker erkend als een belangrijke bijwerking van oxaliplatin. De volgende studie evalueerde daarom verschillen in het beloop van neuropathie klachten tussen patiënten behandeld met CAPOX, capecitabine of geen adjuvante chemotherapie *(hoofdstuk 6)*. Voor deze studie zijn patiënten uitgenodigd om een eerste vragenlijst na de operatie in te vullen en vervolgens zes en twaalf maanden later nog eens. Het aantal en het percentage patiënten dat milde tot ernstige neuropathie symptomen rapporteerde is gemeten. In totaal vulden 117 patiënten de eerste vragenlijst in (respons 76%), en respectievelijk 69 en 59 patiënten vulden de volgende twee metingen in. Het beloop van verschillende sensorische symptomen was minder gunstig voor de patiënten die behandeld zijn met adjuvante chemotherapie. Daarnaast was het beloop van doofheid in tenen of voeten ongunstiger voor patiënten behandeld met CAPOX en rapporteerden zij vaker tintelende tenen of voeten dan patiënten behandeld met capecitabine. Omdat neuropathie symptomen de functionele capaciteiten kunnen aantasten en negatief geassocieerd zijn met gezondheid-gerelateerde kwaliteit van leven gedurende en na de behandeling, is het van groot belang ouderen te informeren over deze risico's om hen in staat te stellen een weloverwogen besluit te nemen over een gepaste behandeling.

Adjuvante chemotherapie en recidiefvrije en algemene overleving

In *hoofdstuk 7* is de samenhang tussen adjuvante chemotherapie en het risico op een afstandsrecidief (een uitzaaiing naar een ander orgaan) onderzocht. Ook is onderzocht of de samenhang hetzelfde was voor patiënten van 75 jaar of ouder als voor jongere patiënten. Patiënten gediagnosticeerd met stadium III dikkedarmkanker in Zuidoost-Nederland tussen 2003 en 2008 zijn geïncludeerd. Adjuvante chemotherapie was gecorreleerd met een verminderd risico op een afstandsrecidief (ruwe percentages over vijf jaar bij wel versus geen adjuvante chemotherapie: 36% versus 42%). In aparte analyses voor patiënten jonger dan 75 jaar en patiënten van 75 jaar of ouder, bleef de samenhang tussen adjuvante chemotherapie en het risico op een afstandsrecidief vergelijkbaar voor beide leeftijdsgroepen. Deze resultaten suggereren dat oudere patiënten hetzelfde voordeel genieten van adjuvante chemotherapie als jongere patiënten met betrekking tot het risico op een afstandsrecidief. Adjuvante chemotherapie moet daarom zeker overwogen worden.

In de volgende studie is de samenhang tussen de adjuvante chemotherapie schema's CAPOX en capecitabine en de recidiefvrije en algemene overleving bij oudere patiënten met stadium III dikkedarmkanker onderzocht *(hoofdstuk 8)*. De recidiefvrije en algemene vijfjaarsoverleving verschilden niet tussen patiënten behandeld met capecitabine en patiënten behandeld met CAPOX (recidiefvrije vijfjaarsoverleving: 63% versus 60%; algemene vijfjaarsoverleving: 66% versus 66%). Voor patiënten die geen adjuvante chemotherapie

ontvingen, waren de recidiefvrije en algemene vijfjaarsoverleving respectievelijk 38% en 37%. Met andere woorden, de behandeling met CAPOX of capecitabine is geassocieerd met een verbeterde recidiefvrije en algemene overleving. Omdat de overlevingswinst niet verschilt tussen de schema's, is de toevoeging van oxaliplatin wellicht niet gerechtvaardigd bij oudere patiënten met stadium III dikkedarmkanker behandeld in de dagelijkse klinische praktijk.

In de laatste studie van dit proefschrift is onderzocht welke demografische en klinische variabelen geassocieerd waren met de timing van adjuvante chemotherapie en hoe deze timing geassocieerd was met algemene overleving *(hoofdstuk 9)*. In deze studie zijn landelijke data van de Nederlandse Kankerregistratie gebruikt van alle patiënten met stadium III dikkedarmkanker die een operatie hadden ondergaan en adjuvante chemotherapie ontvingen tussen 2008 en 2013. De mediane tijd tussen operatie en adjuvante chemotherapie was 5 tot 6 weken. Veertien procent van de patiënten startte meer dan 8 weken na de operatie met adjuvante chemotherapie. Factoren geassocieerd met het starten van de chemotherapie meer dan 8 weken na de operatie waren een hogere leeftijd van de patiënt, een spoedoperatie, naadlekkage, verwijzing naar een ander ziekenhuis voor de adjuvante chemotherapie en een verlengde postoperatieve ziekenhuisopname. De ruwe algemene vijfjaarsoverleving bij start van adjuvante chemotherapie binnen 4, 5-6, 7-8, 9-10, 11-12 of 13-16 weken na operatie waren respectievelijk 75%, 76%, 72%, 64%, 61% en 54%. Na correctie voor verschillen in casemix, liet een start 5-8 weken postoperatief geen vermindering van de algemene overleving zien ten opzichte van een start binnen 4 weken na operatie. Later dan 8 weken na operatie starten was echter wel geassocieerd met een verminderde algemene overleving ten opzichte van een start binnen 8 weken postoperatief. Deze resultaten ondersteunen het beeld dat bij patiënten met stadium III dikkedarmkanker adjuvante chemotherapie binnen 8 weken na de operatie gestart dient te worden, maar dat daarbij ruimte is om patiënten eerst te laten herstellen van de operatie.

Concluderende opmerkingen

Ouderen vertegenwoordigen een aanzienlijk deel van de patiënten met dikkedarmkanker en dit zal naar verwachting in de toekomst nog verder toenemen. Daarom is het van groot belang om de kennis over deze patiëntengroep te vergroten. Dit proefschrift draagt bij aan meer inzicht in het gebruik en de effecten van bestaande, adjuvante chemotherapieën bij oudere patiënten met stadium III dikkedarmkanker, behandeld in de dagelijkse klinische praktijk. Dit proefschrift laat zien dat adjuvante chemotherapie overwogen dient te worden voor oudere patiënten, omdat zij eenzelfde voordeel genieten van adjuvante chemotherapie met betrekking tot het verkleinen van het risico op een afstandsrecidief. Ook laat dit proefschrift zien dat capecitabine monotherapie over het algemeen de voorkeur geniet boven combinatietherapie met capecitabine en oxaliplatin, omdat monotherapie beter verdragen wordt, minder bijwerkingen geeft en de recidiefvrije en algemene overlevingswinst daarbij niet worden beperkt. De toevoeging van oxaliplatin zou om die reden in de klinische praktijk niet de standaard mogen zijn voor het merendeel van de oudere patiënten met stadium III dikkedarmkanker.

Dankwoord

(Acknowledgements)

Dankwoord

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Felice

Oktober 2016

About the author

Felice N. van Erning was born on April 28, 1989 in Nijmegen, the Netherlands. She finished secondary education at the Stedelijk Gymnasium Nijmegen in 2007. In 2010, she obtained her Bachelor's degree in General Health Sciences cum laude (major: care sciences; minors: mental health and health law) at Maastricht University. Subsequently, she started her Master in Public Health (specialization Health Care Policy, Innovation and Management) at the same institution. During her master she conducted her scientific internship at the Oncology Centre of Maastricht University Medical Centre+. In 2011, she completed her Master's degree in Public Health cum laude. Subsequently, she started her PhD research at the Netherlands Comprehensive Cancer Organisation (IKNL) in 2012. Her research focused on population-based use and effects of adjuvant chemotherapy among elderly colon cancer patients. During her PhD training she followed several epidemiological courses. Currently, she is working as a post-doctoral researcher at IKNL.

List of publications

Publications included in this thesis

1. **van Erning FN**, Janssen-Heijnen MLG, Wegdam J, Slooter GD, Wijsman JH, Vreugdenhil A, van de Poll-Franse LV & Lemmens VEPP. The course of neuropathy in relation to adjuvant chemotherapy among elderly stage III colon cancer patients: a longitudinal study. Clinical Colorectal Cancer, 2016; Epub ahead of print.
2. **van Erning FN**, Janssen-Heijnen MLG, Creemers GJ, Pruijt JFM, Maas HAAM & Lemmens VEPP. Recurrence-free and overall survival among elderly stage III colon cancer patients treated with CAPOX or capecitabine monotherapy. International Journal of Cancer, 2016; Epub ahead of print.
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4. **van Erning FN**, Razenberg LGEM, Lemmens VEPP, Creemers GJ, Pruijt JFM, Maas HAAM & Janssen-Heijnen MLG. Intensity of adjuvant chemotherapy regimens and grade III-IV toxicities among elderly stage III colon cancer patients. European Journal of Cancer, 2016; 61: 1-10.
5. Bos ACRK, **van Erning FN**, van Gestel YRBM, Creemers GJM, Punt CJA, van Oijen MGH & Lemmens VEPP. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. European Journal of Cancer, 2015; 51(17): 2553-61.
6. **van Erning FN**, Janssen-Heijnen ML, Creemers GJ, Pruijt HF, Maas HA & Lemmens VE. Deciding on adjuvant chemotherapy for elderly stage III colon cancer patients: a qualitative insight into the perspectives of surgeons and medical oncologists. Journal of Geriatric Oncology, 2015: 6(3): 219-24.
7. **van Erning FN**, Bernards N, Creemers GJ, Vreugdenhil A, Lensen CJ & Lemmens VEPP. Administration of adjuvant oxaliplatin to patients with stage III colon cancer is affected by age and hospital. Acta Oncologica, 2014; 53(7): 975-80.
8. **van Erning FN**, Creemers GJ, de Hingh IHJT, Loosveld OJL, Goey SH & Lemmens VEPP. Reduced risk of distant recurrence after adjuvant chemotherapy in patients with stage III colon cancer aged 75 years or older. Annals of Oncology, 2013; 24(11): 2839-44.

Other publications

1. Razenberg LGEM, **van Erning FN**, Pruijt JFM, ten Tije AJ, van Riel JMGH, Creemers GJ & Lemmens VEPP. The impact of age on first-line systemic therapy in patients with metachronous metastases from colorectal cancer. Journal of Geriatric Oncology, 2016; Epub ahead of print.
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3. Bos ACRK, **van Erning FN**, Elferink MAG, Rutten HJ, van Oijen MGH, de Wilt, JHW & Lemmens VEPP. No difference in overall survival between hospital volumes for colorectal cancer patients in The Netherlands. Diseases of the Colon & Rectum, 2016; 59(10): 943-53.
4. **van Erning FN**, Vissers PAJ, Punt CJA & Lemmens VEPP. RE: Effects of adjuvant chemotherapy on recurrence, survival and quality of life in stage II colon cancer patients: a 24-month follow-up. Supportive Care in Cancer, 2016; 24(10): 4079-80.
5. Knijn N, **van Erning FN**, Overbeek LIH, Punt CJA, Lemmens VEPP, Hugen N & Nagtegaal ID. Limited effect of lymph node status on the metastatic pattern in colorectal cancer. Oncotarget, 2016; 7(22): 31699-707.
6. Verhoeff SR, **van Erning FN**, Lemmens VEPP, de Wilt JHW & Pruijt JFM. Adjuvant chemotherapy is not associated with improved survival for all high-risk factors in stage II colon cancer. International Journal of Cancer, 2016; 139(1): 187-93.
7. **van Erning FN** & Lemmens VE. Adequacy of lymph node yield and staging in rectal cancer should not be determined based on a minimum number of lymph nodes evaluated. International Journal of Colorectal Diseases, 2016; 31(1): 149.
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13. **van Erning FN**, Crolla RM, Rutten HJ, Beerepoot LV, van Krieken JH & Lemmens VE. No change in lymph node positivity rate despite increased lymph node yield and improved survival in colon cancer. European Journal of Cancer, 2014: 50(18): 3221-9.

14. van Gestel YR, de Hingh IH, van Herk-Sukel MP, **van Erning FN**, Beerepoot LV, Wijsman JH, Slooter GD, Rutten HJ, Creemers GJ & Lemmens VE. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiology, 2014: 38(4): 448-54.

15. **van Erning FN**, van Steenbergen LN, Lemmens VE, Rutten HJ, Martijn H, van Spronsen DJ & Janssen-Heijnen ML. Conditional survival for long-term colorectal cancer survivors in the Netherlands: who do best? European Journal of Cancer, 2014; 50(10): 1731-9.

16. **van Erning FN**, van Steenbergen LN, van den Broek WT, Rutten HJT & Lemmens VEPP. No difference between lowest and highest volume hospitals in outcome after colorectal cancer surgery in the southern Netherlands. European Journal of Surgical Oncology, 2013; 39(11): 1199-206.

PhD portfolio

Summary of PhD training

Name PhD student: F.N. van Erning
Erasmus MC Department: Public Health / Netherlands Comprehensive Cancer Organisation
PhD period: 2012-2016
Promotor: prof. dr. V.E.P.P. Lemmens
Copromotors: dr. M.L.G. Janssen-Heijnen & dr. G.J. Creemers

	Year	Workload hours (ECTS)
Courses		
Introductie tot de klinische en fundamentele oncologie, NVvO	2013	40 (1.4)
Principes van epidemiologische data-analyse, EpidM, VUmc	2013	30 (1.1)
Regressietechnieken, EpidM, VUmc	2013	35 (1.3)
Longitudinale data-analyse, EpidM, VUmc	2014	25 (0.9)
Wetenschappelijke Integriteit, Erasmus MC	2016	8 (0.3)
Oral presentations		
IKZ-KLIMOP symposium	2013	32 (1.1)
IKZ Werkgroep Medische Oncologie	2013	16 (0.6)
IACR conference	2013	32 (1.1)
Department of Pathology, Radboud UMC Nijmegen	2014	32 (1.1)
Department of Public Health, Erasmus MC Rotterdam	2014	32 (1.1)
IKNL symposium 'NKR in beweging'	2015	32 (1.1)
IKNL 9e GI symposium	2015	16 (0.6)
Poster presentations		
5 posters ECCO	2013	62 (2.2)
2 posters SIOG	2013	32 (1.1)
3 posters IACR	2013	32 (1.1)
1 poster SIOG	2014	32 (1.1)
1 poster ESSO	2014	32 (1.1)
3 posters ESMO	2015	96 (3.4)
1 poster ICPE	2015	16 (0.6)
1 poster ISPOR	2015	16 (0.6)
International conferences		
ESSO, Valencia, Spain	2012	24 (0.9)
ECCO, Amsterdam, the Netherlands	2013	32 (1.1)
IACR, Buenos Aires, Argentina	2013	24 (0.9)
SIOG, Lisbon, Portugal	2014	24 (0.9)
ESMO GI, Barcelona, Spain	2015	32 (1.1)
Dutch seminars and conferences		
IKZ 5e GI symposium	2012	3 (0.1)
IKZ-KLIMOP symposium	2013	5 (0.2)
Tilburg University-IKZ symposium en oratie prof. dr. L.V. van de Poll-Franse	2013	6 (0.2)
IKZ thema-avond longkanker	2013	2 (0.1)
IKZ minisymposium colorectale tumoren	2013	3 (0.1)
DICA	2013	16 (0.6)
IKZ 7e GI symposium	2013	3 (0.1)
IKZ symposium hoofdhuidkoeling	2014	4 (0.1)
Erasmus MC-IKNL afscheidssymposium prof. dr. J.W.W. Coebergh	2014	8 (0.3)
IKNL 8e GI symposium	2015	3 (0.1)
IKNL symposium 'NKR in beweging'	2015	8 (0.3)
Erasmus MC-IKNL symposium en oratie prof. dr. V.E.P.P. Lemmens	2015	6 (0.2)
IKNL 9e GI symposium	2015	3 (0.1)
Gerionne 7e nationale symposium	2016	8 (0.3)
IKNL symposium 'NKR in beeld'	2016	8 (0.3)

PhD portfolio continued

	Year	Workload hours (ECTS)
Other tasks		
Factsheets colorectal cancer	2012-2013	144 (5.1)
Factsheet lung cancer	2012	72 (2.6)
Conducting analyses and answering questions for medical specialists	2012-2016	144 (5.1)
Conducting cause of death analyses at Statistics Netherlands (CBS)	2013	72 (2.6)
Newsletters research IKNL	2013-2016	32 (1.1)
Database design for NKR+ CRC	2015-2016	72 (2.6)
Total		**1406 (50.2 ECTS)**