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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.

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

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What's new?
With adjuvant chemotherapy the standard treatment option for stage III colon cancer patients, great effort has been made to identify combinations of drugs that effectively reduce the risk of cancer recurrence in this setting. Here, for elderly stage III colon cancer patients treated in everyday clinical practice, receipt of adjuvant chemotherapy consisting of capecitabine with oxaliplatin or capecitabine alone was associated with improved recurrence-free and overall survival. Improved outcome depended more on completion of treatment cycles than regimen, suggesting that the addition of oxaliplatin may not be necessary.

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% *vs.* 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.

Material and 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 ($pT_{1\text{-}4}N_{1\text{-}2}M_0$) 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

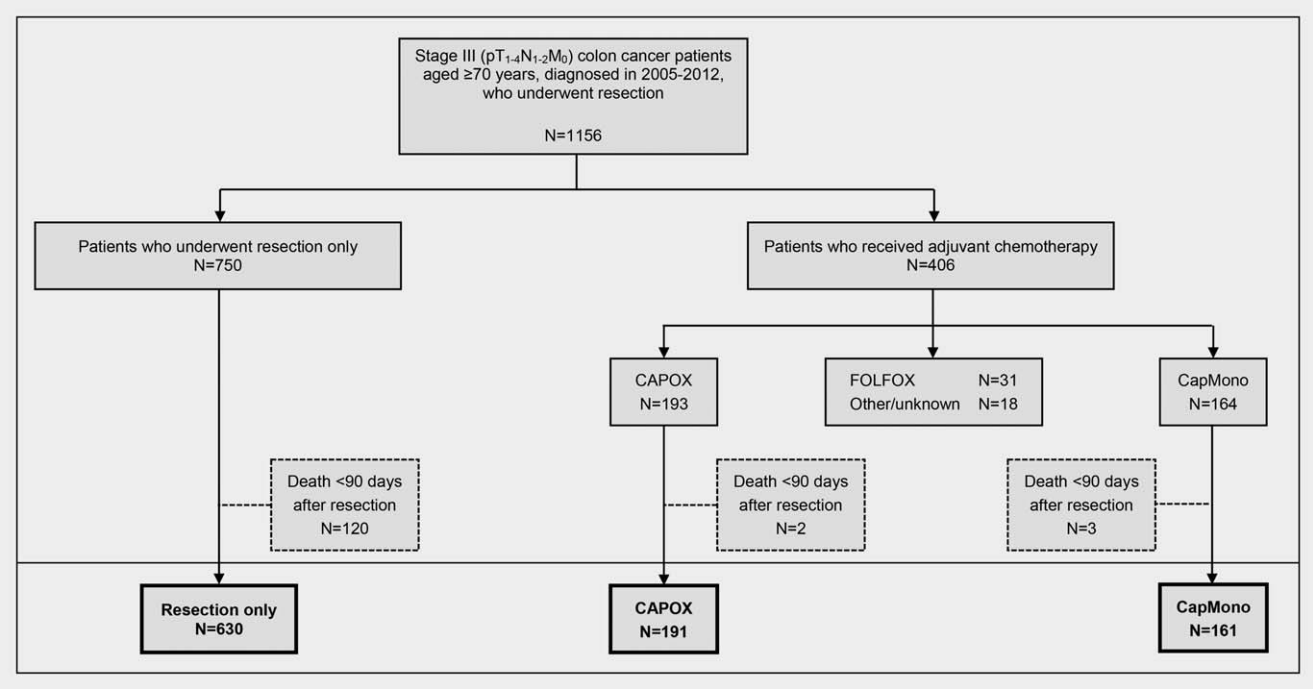

Figure 1. Overview of patients included in the study.

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 χ^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 χ^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 (Fig. 1). Table 1 provides an overview of

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

	Resection only *n* (%)	Resection + CAPOX *n* (%)	Resection + CapMono *n* (%)	*p* values[1]	*p* values[2]
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					
Proximal colon	393 (62)	98 (51)	99 (62)		
Distal colon	230 (37)	90 (47)	60 (37)	0.08	0.16
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)		

[1] *p* values indicate significance of the χ^2 test or Fisher's Exact test between all groups.
[2] *p* values indicate significance of the χ^2 test or Fisher's Exact test between patients receiving CAPOX and patients receiving CapMono.

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).

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* values[1]	CapMono, complete *n* (%)	CapMono, incomplete *n* (%)	*p* values[1]
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)	

[1] *p* values indicate significance of the χ^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).

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

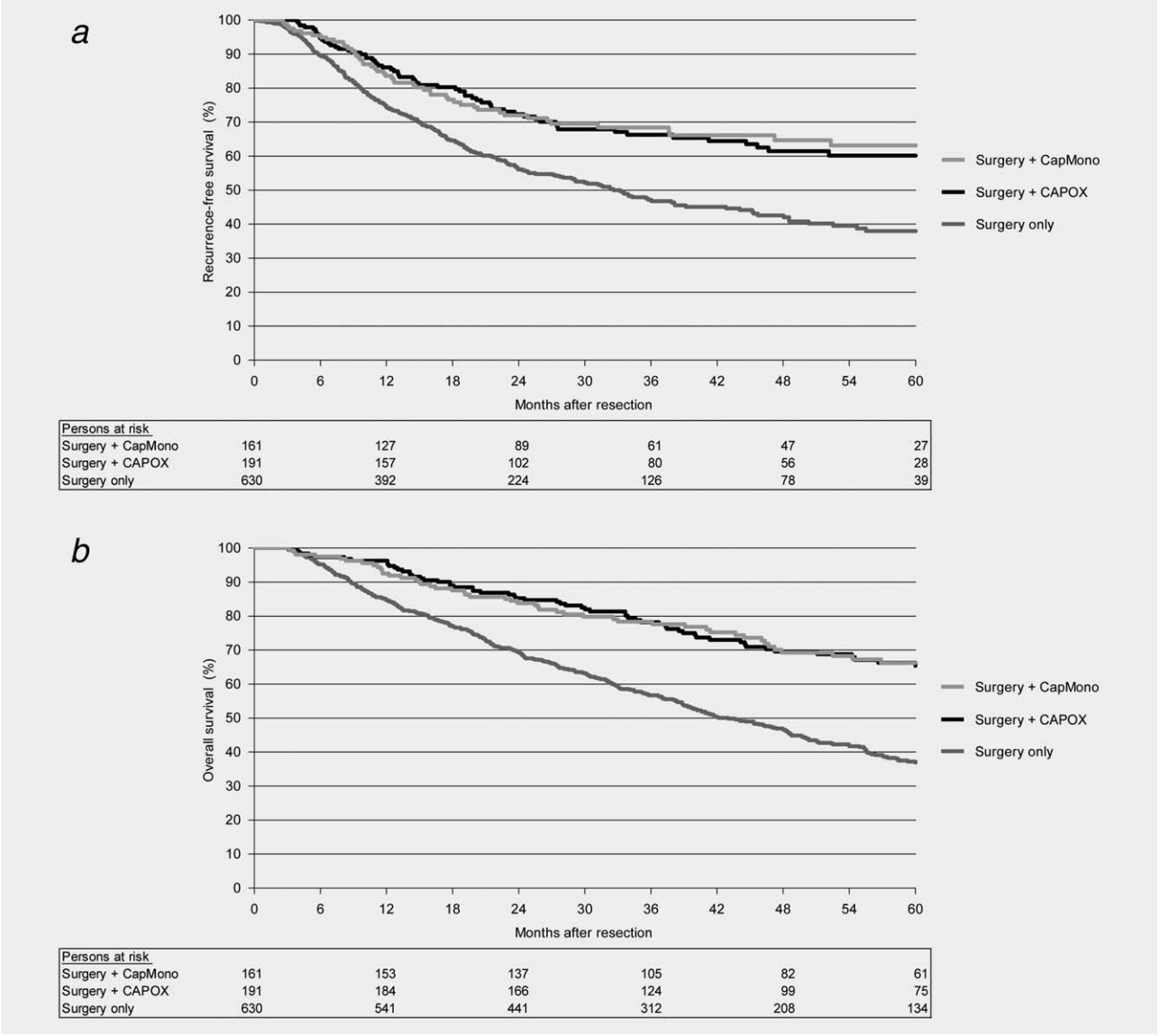

Figure 2. Recurrence-free survival (*a*) and overall survival (*b*) according to treatment modality among elderly stage III colon cancer patients.

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 completion rate was higher with 109 (68%) patients completing all planned cycles ($p < 0.0001$). 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 six 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.

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

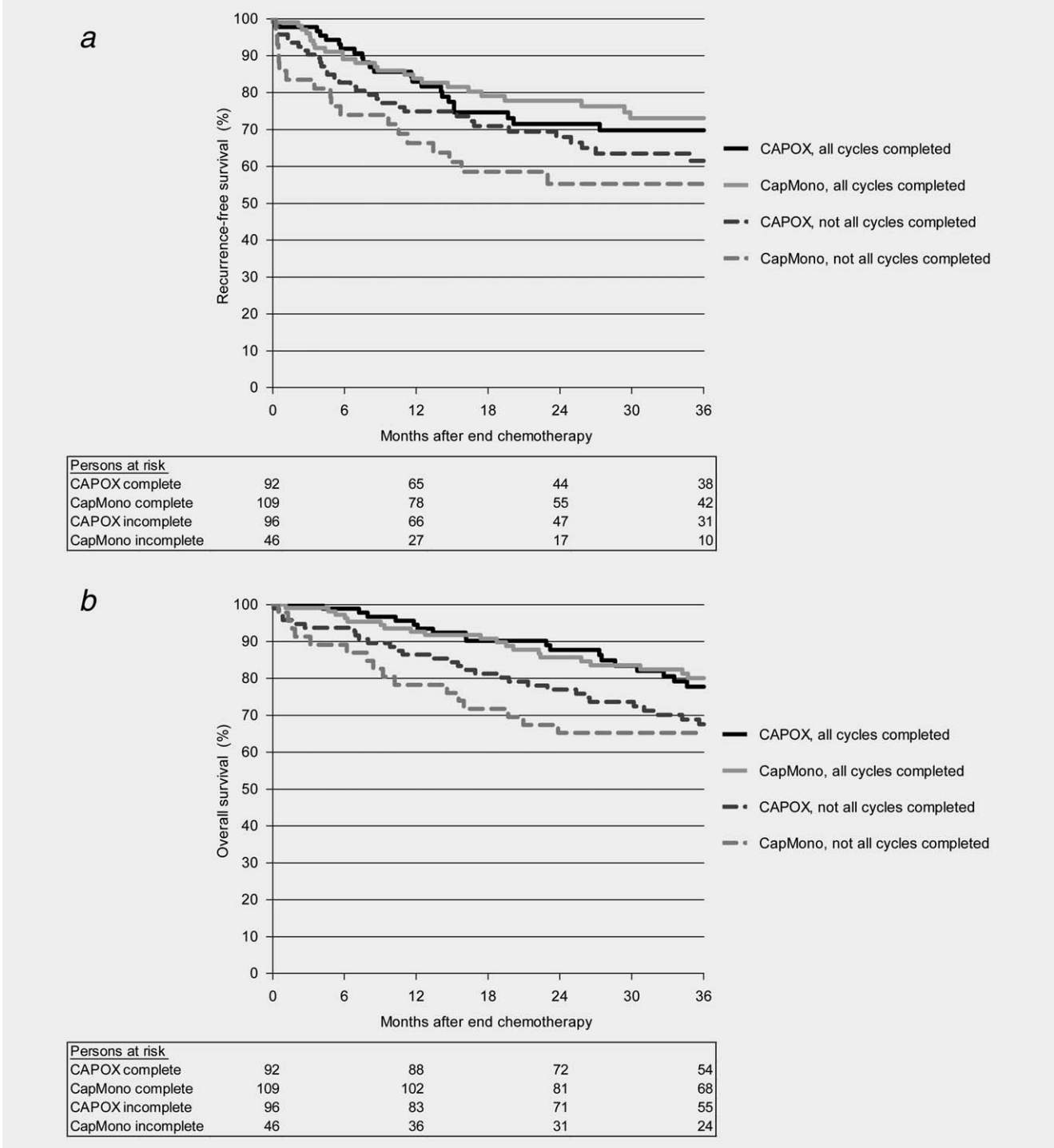

Figure 3. Recurrence-free survival (*a*) and overall survival (*b*) according to adjuvant chemotherapy regimen and completion of all planned cycles among elderly stage III colon cancer patients. Excluded from the analyses were patients for whom completion of all planned cycles was unknown (CAPOX: 3 patients,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

($p = 0.47$) 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% (Fig. 2). As shown in Figure 4, both the risk of 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)).

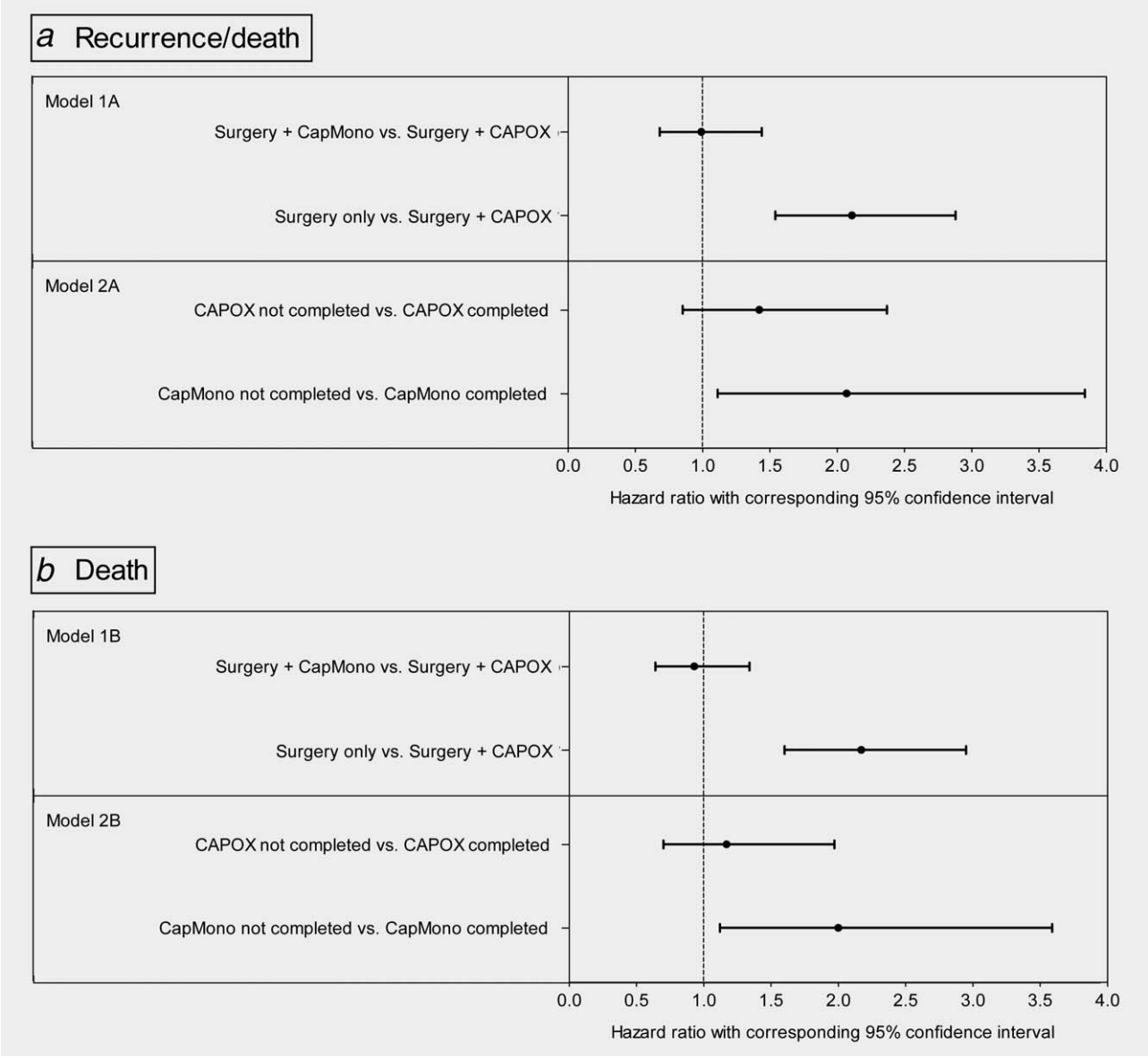

Figure 4. Adjusted hazard ratios for recurrence or death (*a*) or death alone (*b*) according to treatment modality (models 1, $n = 982$) or adjuvant chemotherapy regimen and completion of all planned cycles (models 2, $n = 343$) among elderly stage III colon cancer patients. Hazard ratios adjusted for 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).

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 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% ($p = 0.01$)) (Fig. 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)).

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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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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