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

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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 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.

Key words: adjuvant chemotherapy, colon cancer, elderly, population-based, risk of recurrence

introduction

The primary treatment of 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

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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 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 the 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 M0 disease.

study population

For the present study, all patients with resected stage III ($T_{any}N_{1\text{-}2}M_0$) 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 ($n = 4$). 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). 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 nonrecipients, 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 analyzed by means of χ^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 the 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. The 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 tumors ($P = 0.020$) and more proximal located tumors ($P < 0.0001$) 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 nonrecipients. 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 nonrecipients.

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 nonrecipients.

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 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 tumor 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 the analysis was repeated for patients aged <75 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).

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 (ref)	44	1.00 (ref)
Female	37	0.91 (0.75–1.12)	39	0.87 (0.62–1.22)
Age (years)				
<65	37	1.00 (ref)	44	1.00 (ref)
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 (ref)	41	1.00 (ref)
Comorbidity				
0	37	1.00 (ref)	39	1.00 (ref)
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 (ref)	41	1.00 (ref)
4	51	1.63 (1.28–2.08)	55	1.57 (1.06–2.32)
N stage				
1	34	1.00 (ref)	38	1.00 (ref)
2	52	1.96 (1.59–2.42)	51	1.53 (1.06–2.21)
Subsite				
Proximal colon	38	1.00 (ref)	43	1.00 (ref)
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 (ref)	35	1.00 (ref)
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 (ref)	41	1.00 (ref)
2006–2008	35	0.87 (0.71–1.06)	41	1.10 (0.79–1.54)
Adjuvant chemotherapy				
No	42	1.00 (ref)	50	1.00 (ref)
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.

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 tumor 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 nonrecipients 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 have 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 when compared with their younger counterparts from both fluorouracil-based and FOLFOX adjuvant therapy [9, 10]. For the present study, no data on toxicity were 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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disclosure

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A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer

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Background: The contribution of induction chemotherapy (IC) before preoperative chemoradiation for esophageal cancer (EC) is not known. We hypothesized that IC would increase the rate of pathologic complete response (pathCR).
Methods: Trimodality-eligibile patients were randomized to receive no IC (Arm A) or IC (oxaliplatin/FU; Arm B) before oxaliplatin/FU/radiation. Surgery was attempted ~5–6 weeks after chemoradiation. The pathCR rate, post-surgery 30-day mortality, overall survival (OS), and toxic effects were assessed. Bayesian methods and Fisher's exact test were used.
Results: One hundred twenty-six patients were randomized dynamically to balance the two arms for histology, baseline stage, gender, race, and age. Fifty-five patients in Arm A and 54 in Arm B underwent surgery. The median actuarial OS

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