Decreasing Use of Chemotherapy in Older Patients With Stage III Colon Cancer Irrespective of Comorbidities

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ABSTRACT

Background: Chemotherapy underuse in elderly patients (aged ≥ 75 years) with colon cancer has been reported in previous studies. However, these studies were mostly registry-based and limited in their potential to consider underlying reasons of such undertreatment. This study aimed to evaluate patient and hospital determinants of chemotherapeutic treatment in patients with stage III colon cancer, with a particular focus on age and underlying reasons for nontreatment of elderly patients. **Methods:** A total of 629 patients with stage III colon cancer who were diagnosed in 2003 through 2012 and recruited into a population-based study in the Rhine-Neckar region of Germany were included. Information on sociodemographic and lifestyle factors, comorbidities, and treatment was collected from patient interviews and physicians. Patient (with an emphasis on age) and hospital factors were evaluated for their associations with administration of adjuvant chemotherapy overall and of oxaliplatin specifically using multivariable logistic regression. **Results:** Administration of chemotherapy decreased from 94% in patients aged 30 to 64 years to 51% in those aged ≥ 75 years. A very strong decline in chemotherapy use with age persisted even after comprehensive adjustment for multiple patient factors—including comorbidities—and hospital factors and was also seen among patients without any major comorbidities. Between 2005 and 2008, and 2009 and 2012, chemotherapy administration in patients aged ≥ 75 years decreased from 60% to 41%. Among chemotherapy recipients, old age was also strongly associated with higher odds of nonadministration of oxaliplatin. The 2 most commonly reported reasons for chemotherapy nonreceipt among the study population were patient refusal (30%) and old age (24%). **Conclusions:** Age was the strongest predictor of chemotherapy underuse, irrespective of comorbidities and even in patients without comorbidities. Such underuse due just to older age in otherwise healthy patients deserves increased attention in clinical practice to ensure that elderly patients also get the best possible care. Patients' refusal as the most frequent reason for chemotherapy nonreceipt also warrants further investigation to exclude misinformation as underlying cause.

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Background

Colorectal cancer (CRC) incidence is particularly high in Western countries.¹ In Germany, $>60,000$ people are diagnosed with CRC each year, and approximately two-thirds of the tumors are located in the colon.² Colon cancers are primarily treated by surgery, followed by adjuvant chemotherapy under certain conditions. Adjuvant treatment of stage II colon cancer is controversial³ and mostly restricted to high-risk patients.^{4–7} However, adjuvant chemotherapy has been widely recommended for patients with stage III colon cancer, beginning in the 1990s. In 2004, results from the MOSAIC trial showed that a combination of oxaliplatin with conventional 5-FU/leucovorin (LV) chemotherapy significantly improved 3-year disease-free survival by 24% and nonsignificantly reduced 3-year all-cause mortality by 14% compared with 5-FU/LV therapy alone.⁸ Subsequently, treatment recommendations for stage III colon cancer changed to combination therapy, also known as the FOLFOX regimen (5-FU, LV, oxaliplatin).^{9,10}

5-FU/LV alone has been shown to prolong survival throughout age groups,^{11,12} even in patients aged >75 years.^{13,14} However, the benefit of oxaliplatin-based therapy in elderly patients is viewed more skeptically,^{15–18} although Haller et al¹⁹ suggested that the addition of oxaliplatin be considered in patients of all age groups and in those with comorbidities due to its disease-free survival benefit compared with 5-FU/LV alone. Nevertheless, registry-based studies have shown chemotherapy underuse among older patients in several countries.^{20–25} However, given the limited information included in cancer registries, little is known about the determinants of potential underuse of adjuvant chemotherapy.

This study evaluated the factors associated with chemotherapy administration in patients with stage III

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colon cancer in a population-based study from Germany, in which both patient and hospital characteristics were ascertained in great detail.

Methods

Study Design and Population

This study was based on secondary analyses of data from patients with colon cancer who were diagnosed in 2003 through 2012 and recruited into the Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study, an ongoing population-based case-control study performed in the southwest of Germany, with regular follow-up of participants. All patients with a first, histologically confirmed diagnosis of CRC (ICD-10 codes C18–C20) and aged ≥ 30 years were eligible, and all had to be physically and mentally able to participate in an interview lasting for approximately 1 hour. Further details of the DACHS study have been described elsewhere.^{26–28} In the 22 recruiting clinics, eligible patients were informed about the study by their physicians and recruited during or shortly after their hospital stay. Data from cancer registries indicate that approximately 50% of eligible patients in the study region of approximately 2 million inhabitants were recruited. Recruitment rates were largely dependent on the clinicians in charge of recruitment in the hospitals and were slightly higher for younger versus older patients, but unlike previous studies, our study had no upper age limit. All participants provided written informed consent, and the study was approved by the ethics committees of the Medical Faculty of Heidelberg University and the state medical boards of Baden-Wuerttemberg and Rhineland-Palatinate.

Sociodemographic information, medical history, and lifestyle factors were obtained at baseline by trained interviewers. Details of the data collection process have been described elsewhere.^{29–32} Approximately 3 years after diagnosis, treatment information was obtained from general practitioner (GPs) and oncologist reports (through a standardized questionnaire and both inpatient and outpatient reports, which were extracted from the patient charts in the computer system). In case of missing information, the attending GPs/oncologists were contacted for clarification. Discharge letters were also obtained from hospitals where patients underwent colon cancer surgery, and pathology reports were obtained.

Inclusion/Exclusion Criteria

Inclusion criteria comprised a colon cancer diagnosis (ICD-10 code C18), UICC stage III disease, an R0 tumor resection, and availability of information on chemotherapy and other covariates of interest (Figure 1). Patients were included in the analysis regardless of whether

Figure 1. Flow diagram of inclusion and exclusion criteria.

they died before ascertainment of therapy information from physicians.

Ascertainment of Therapeutic Information

Information on adjuvant chemotherapy (hereafter referred to as *chemotherapy*) and the administered regimens and specific compounds was extracted from physician medical reports. Reasons for chemotherapy nonadministration were also extracted.

Statistical Analysis

The distribution of patient and hospital factors according to chemotherapy use was evaluated in descriptive analyses. Associations were tested for significance using chi-square tests. Factors associated with chemotherapy nonreceipt (yes/no) were investigated with multivariable logistic regression and in 2 adjustment settings: (1) adjustment for age and hospitals where patients were

Table 1. Receipt of Adjuvant Chemotherapy Based on Patient and Hospital Factors (N=629)

	n (%)	P Value
Total	488 (77.6)	
Sex		.6325 ^a
Female	234 (78.5)	
Male	254 (76.7)	
Age at diagnosis, y		<.0001
30–64	182 (94.3)	
65–74	193 (89.8)	
≥75	113 (51.1)	
BMI, ^b kg/m ²		.0511
<25.0	189 (74.1)	
25.0–29.9	199 (77.4)	
≥30.0	100 (85.5)	
Tumor grade		.3664 ^a
1/2	323 (78.8)	
3/4	165 (75.3)	
T stage		.4398
T1–2	57 (74.0)	
T3	359 (78.9)	
T4	72 (74.2)	
N stage		.1937 ^a
N1	308 (75.9)	
N2	180 (80.7)	
Number of comorbidities ^c		<.0001
0	201 (86.3)	
1	171 (78.8)	
≥2	116 (64.8)	
Smoking status		.0695
Never-smoker	258 (77.9)	
Former smoker	173 (74.2)	
Current smoker	57 (87.7)	
Education level ^d		.0035
Low (<9 y)	94 (67.6)	
Medium (9–10 y)	281 (79.2)	
High (>10 y)	113 (83.7)	
Living with a partner		<.0001 ^a
Yes	385 (81.7)	
No	103 (65.2)	

(continued)

Abbreviation: BMI, body mass index; CoC, Commission on Cancer.

^aCalculated using Fisher exact test.^b16 patients (2.5%) were underweight (BMI <18.5 kg/m²).^cIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.^dYears of school education.^eNumber of colon cancer surgeries performed per year.**Table 1. Receipt of Adjuvant Chemotherapy Based on Patient and Hospital Factors (N=629) (cont.)**

	n (%)	P Value
Period of diagnosis		.0037
2003–2004	115 (81.0)	
2005–2008	206 (82.4)	
2009–2012	167 (70.5)	
Surgical volume ^e		.0285
Low (<70)	109 (70.8)	
Medium (70–149)	163 (82.7)	
High (≥150)	216 (77.7)	
CoC-certified center status (at diagnosis/in 2017)		.0054
No/No	229 (76.3)	
No/Yes	152 (85.4)	
Yes/Yes	107 (70.9)	

Abbreviation: BMI, body mass index; CoC, Commission on Cancer.

^aCalculated using Fisher exact test.^b16 patients (2.5%) were underweight (BMI <18.5 kg/m²).^cIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.^dYears of school education.^eNumber of colon cancer surgeries performed per year.

treated, and (2) further adjustment for sex, body mass index (BMI), tumor grade, T stage, N stage, comorbidities (absolute number assessed at the time of colon cancer diagnosis, including diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders), smoking status, education level, living with a partner, year of diagnosis, surgical volume (number of CRC surgeries performed per year, with low defined as <70, medium as 70–149, and high as ≥150), and treatment at a Commission on Cancer (CoC)–certified CRC center.

We adjusted for individual hospitals to account for potentially differing chemotherapy administration rates between hospitals. We further examined factors associated with oxaliplatin nonuse (yes/no) using multivariable logistic regression, excluding patients diagnosed in 2003 through 2004 because oxaliplatin was rarely administered during this period. In the sensitivity analysis, hierarchical logistic regression was used to account for the potential within-hospital clustering of patients and the potential between-hospital differences in chemotherapy administration.

To investigate the extent of undertreatment in elderly patients, we examined the joint effect of age and comorbidity on chemotherapy nonreceipt using multivariable logistic regression. Potential variation in the association of age with chemotherapy administration by comorbidity was examined by adding interaction terms to the model. In chemotherapy nonrecipients, reasons for chemotherapy

nonadministration were further investigated. Data analyses were performed using SAS 9.4 (SAS Institute Inc.). Figures showing treatment patterns were created with R 3.3.2 (R Foundation for Statistical Computing). Statistical tests were 2-sided, with an alpha level of .05.

Results

Of 4,040 patients with CRC diagnosed in 2003–2012, those with rectal/rectosigmoidal cancer, stage I–II and IV colon cancer, no information regarding adjuvant chemotherapy, non-R0 resection, and missing covariate information were excluded (n=3,411; Figure 1).

The analytic sample comprised 629 patients, of whom 488 (78%) received chemotherapy (Table 1). Administration of chemotherapy decreased with age and increasing number of comorbidities. In patients aged <75 years, nearly 90% received chemotherapy compared with only 51% of those aged ≥75 years. In patients with ≥2 comorbidities, 65% received chemotherapy compared with >75% of those with fewer comorbidities. Moreover, chemotherapy was most frequently administered in hospitals with medium surgical volume. A summary of the hospital characteristics is shown in eTable 1 (available with this article at JNCCN.org).

Chemotherapeutic Regimens and Compounds

Administered chemotherapeutic regimens and compounds are summarized in Figure 2. FOLFOX was the most frequently administered regimen (51.4%). Among the compounds, 5-FU (mostly in combination with LV) was the most frequently applied compound (80%), followed by oxaliplatin (54%). Oxaliplatin use increased significantly after 2004. We also observed an increase in capecitabine use, which was especially administered in

patients aged ≥75 years, with 42% receiving it, compared with 9% of those aged <65 years and 18% of those aged 65 to 74 years (data not shown).

Factors Associated With Chemotherapy Nonreceipt

In the multivariable model (Table 2), patients aged ≥75 years had >13-fold higher odds of chemotherapy nonreceipt compared with those aged 30 to 64 years (odds ratio [OR], 13.2; 95% CI, 6.04–28.80), even after comprehensive adjustment for multiple factors. Patients with ≥2 comorbidities had significantly higher odds of chemotherapy nonreceipt than those with no comorbidities (OR, 2.55; 95% CI, 1.36–4.78).

Compared with patients with BMI <25 kg/m², chemotherapy nonreceipt was much less common in those with BMI ≥30.0 kg/m² (OR, 0.48; 95% CI, 0.23–0.98). Patients not living with a partner and those diagnosed in 2009–2012 had approximately 80% and 110% higher odds of not receiving chemotherapy, respectively. Patients treated in medium-volume hospitals had lower odds of chemotherapy nonreceipt compared with low-volume hospitals (OR, 0.44; 95% CI, 0.24–0.82). Patients with a higher educational level and those who received treatment in hospitals that received CoC certification for CRC care after patients' diagnosis had nonsignificant lower odds of chemotherapy nonreceipt.

Factors Associated With Oxaliplatin Nonuse

Table 3 shows the determinants of oxaliplatin nonuse in chemotherapy recipients. Old age was strongly associated with oxaliplatin nonuse, with adjusted ORs of 7.00 (95% CI, 2.87–17.1) for patients aged 65 to 74 years and 80.4 (95% CI, 28.3–228.6) for those aged ≥75 years

Figure 2. Administered chemotherapy (A) regimens and (B) compounds in patients with stage III colon cancer, overall and by period of diagnosis. Abbreviations: AIO, 5-FU/leucovorin; Ardan, 5-FU/leucovorin; Cap, capecitabine monotherapy; CAPOX, capecitabine/oxaliplatin; FOLFOX, 5-FU/leucovorin/oxaliplatin; FUFOX, 5-FU/leucovorin/oxaliplatin; Mayo, 5-FU/leucovorin; Roswell Park, 5-FU/leucovorin.

Table 2. Factors Associated With Nonadministration of Adjuvant Chemotherapy

	Patients n	Events n	No Chemotherapy vs Chemotherapy	
			OR ^a (95% CI)	OR ^b (95% CI)
Sex				
Female	298	64	Ref	Ref
Male	331	77	1.26 (0.81–1.97)	1.59 (0.86–2.94)
Age at diagnosis, y				
30–64	193	11	Ref	Ref
65–74	215	22	1.98 (0.92–4.27)	1.67 (0.73–3.83)
≥75	221	108	16.7 (8.35–33.3)	13.2 (6.04–28.80)
BMI, kg/m ²				
<25.0	255	66	Ref	Ref
25.0–29.9	257	58	0.77 (0.47–1.24)	0.75 (0.44–1.28)
≥30.0	117	17	0.57 (0.29–1.11)	0.48 (0.23–0.98)
Tumor grade				
1/2	410	87	Ref	Ref
3/4	219	54	1.17 (0.74–1.85)	1.31 (0.79–2.16)
T stage				
T1–2	77	20	Ref	Ref
T3	455	96	0.73 (0.38–1.43)	0.72 (0.35–1.47)
T4	97	25	1.02 (0.44–2.35)	1.02 (0.40–2.58)
N stage				
N1	406	98	Ref	Ref
N2	223	43	0.66 (0.41–1.07)	0.65 (0.39–1.09)
Number of comorbidities ^c				
0	233	32	Ref	Ref
1	217	46	1.22 (0.68–2.20)	1.18 (0.64–2.19)
≥2	179	63	2.37 (1.32–4.26)	2.55 (1.36–4.78)
Smoking status				
Never-smoker	331	73	Ref	Ref
Former smoker	233	60	1.60 (1.00–2.56)	1.54 (0.88–2.70)
Current smoker	65	8	1.24 (0.49–3.13)	1.04 (0.39–2.77)
Education level ^d				
Low (<9 y)	139	45	Ref	Ref
Medium (9–10 y)	355	74	0.97 (0.58–1.64)	0.95 (0.53–1.71)
High (>10 y)	135	22	0.58 (0.29–1.13)	0.47 (0.21–1.04)
Living with a partner				
Yes	471	86	Ref	Ref
No	158	55	1.50 (0.92–2.42)	1.77 (1.00–3.12)

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Abbreviations: BMI, body mass index; CoC, Commission on Cancer; OR, odds ratio.

^aAdjusted for age and hospital where patients were treated.^bAdditional adjustment for sex, BMI, T stage, N stage, number of comorbidities, smoking status, education level, living with a partner, and period of diagnosis.^cIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.^dYears of school education.^eHospital where patients received treatment was removed from the model.

Table 2. Factors Associated With Nonadministration of Adjuvant Chemotherapy (cont.)

	Patients n	Events n	No Chemotherapy vs Chemotherapy	
			OR ^a (95% CI)	OR ^b (95% CI)
Period of diagnosis				
2003–2004	142	27	Ref	Ref
2005–2008	250	44	0.96 (0.51–1.80)	0.86 (0.44–1.67)
2009–2012	237	70	2.10 (1.15–3.85)	2.07 (1.09–3.93)
Surgical volume ^a				
Low	154	45	Ref	Ref
Medium	197	34	0.56 (0.31–0.98)	0.44 (0.24–0.82)
High	278	62	0.75 (0.45–1.25)	0.67 (0.39–1.14)
CoC-certified center status (at diagnosis/in 2017) ^c				
No/No	300	71	Ref	Ref
No/Yes	178	26	0.54 (0.31–0.93)	0.59 (0.33–1.05)
Yes/Yes	151	44	1.14 (0.69–1.89)	0.88 (0.49–1.61)

Abbreviations: BMI, body mass index; CoC, Commission on Cancer; OR, odds ratio.

^aAdjusted for age and hospital where patients were treated.

^bAdditional adjustment for sex, BMI, T stage, N stage, number of comorbidities, smoking status, education level, living with a partner, and period of diagnosis.

^cIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.

^dYears of school education.

^eHospital where patients received treatment was removed from the model.

compared with younger patients. Patients without a partner had 2.3-fold increased odds of oxaliplatin nonuse, and those treated in medium-volume versus low-volume hospitals and hospitals that received CoC certification for CRC care after patients' diagnosis versus no certification had 56% and 58% lower odds of oxaliplatin nonuse, respectively. Results from hierarchical logistic models for the determinants of chemotherapy nonreceipt and oxaliplatin nonuse were comparable to those from logistic regression models.

Joint Effect of Age and Comorbidity on Chemotherapy Administration

Table 4 shows the frequency of chemotherapy use according to age and comorbidity. Patients aged ≥ 75 years received chemotherapy much less often than younger patients, even when none of the assessed comorbidities were present. Multivariable logistic regression analysis of the joint effect of age and comorbidity on chemotherapy nonreceipt showed similar results (Table 5). Among patients aged < 75 years, comorbidities were not associated with chemotherapy nonreceipt, whereas age ≥ 75 was strongly associated with chemotherapy nonreceipt even in the absence of comorbidities, but the interaction test showed no significant result ($P = .5452$).

Trend of Chemotherapy Use

Chemotherapy administration decreased over time from 81% in 2003–2004 to 71% in 2009–2012 ($P_{\text{Cochran-Armitage trend}} = .0069$;

Table 6). In patients aged < 75 years, the decrease was more moderate ($P_{\text{Cochran-Armitage trend}} = .1885$), whereas in those aged ≥ 75 years, administration decreased from 60% in 2005–2008 to 41% in 2009–2012 ($P_{\text{Cochran-Armitage trend}} = .0149$).

Reasons for Chemotherapy Nonreceipt

Reasons for not administering chemotherapy to some patients, as reported by physicians, are shown in eTable 2. The 3 most commonly reported reasons were patient refusal (30%), old age (24%), and poor health (17%). No strong associations were observed between patient and hospital characteristics and patient refusal, but refusal seemed to be more common in recent versus earlier years (eTable 3). Sensitivity analysis of factors associated with chemotherapy nonadministration excluded patients who refused chemotherapy ($n = 42$). The associations for old age, comorbidity, and year of diagnosis were slightly attenuated but remained highly significant, whereas those for living with a partner and treatment in a medium-volume hospital became stronger (eTable 4). The association for higher education level also became stronger and reached statistical significance.

Discussion

In this multicenter cohort of patients from Germany with stage III colon cancer, older age was strongly associated with chemotherapy nonreceipt, irrespective of comorbidities and other potential determinants.

Table 3. Associations of Patient and Hospital Factors With Nonadministration of Oxaliplatin

Variable	Total (N=372) ^a	Did Not Receive Oxaliplatin (n=120)	No Oxaliplatin vs Oxaliplatin	
	N	n (%)	OR ^b (95% CI)	OR ^c (95% CI)
Sex				
Female	173	57 (33.0)	Ref	Ref
Male	199	63 (31.7)	0.94 (0.52–1.70)	1.20 (0.57–2.54)
Age at diagnosis, y				
30–64	136	9 (6.6)	Ref	Ref
65–74	149	44 (29.5)	7.05 (3.14–15.8)	7.00 (2.87–17.1)
≥75	87	67 (77.0)	81.3 (30.8–214.3)	80.4 (28.3–228.6)
BMI, kg/m ²				
<25.0	153	44 (28.8)	Ref	Ref
25.0–29.9	153	49 (32.0)	1.14 (0.59–2.20)	1.11 (0.55–2.26)
≥30.0	66	27 (40.9)	2.17 (0.93–5.09)	2.21 (0.88–5.55)
Tumor grade				
1/2	252	83 (32.9)	Ref	Ref
3/4	120	37 (30.8)	0.86 (0.45–1.61)	0.80 (0.40–1.60)
T stage				
T1–2	43	14 (32.6)	Ref	Ref
T3	271	89 (32.8)	1.21 (0.49–3.01)	1.30 (0.47–3.58)
T4	58	17 (29.3)	1.20 (0.39–3.74)	2.01 (0.55–7.32)
N stage				
N1	236	84 (35.6)	Ref	Ref
N2	136	36 (26.5)	0.71 (0.38–1.32)	0.64 (0.33–1.25)
Number of comorbidities ^d				
0	150	37 (24.7)	Ref	Ref
1	136	42 (30.9)	0.75 (0.37–1.51)	0.63 (0.30–1.34)
≥2	86	41 (47.7)	1.56 (0.73–3.37)	1.38 (0.60–3.20)
Smoking status				
Never-smoker	178	66 (37.1)	Ref	Ref
Former smoker	145	45 (31.0)	0.98 (0.52–1.84)	1.07 (0.51–2.22)
Current smoker	49	9 (18.4)	0.81 (0.30–2.20)	0.74 (0.25–2.19)
Education level ^e				
Low (<9 y)	69	33 (47.8)	Ref	Ref
Medium (9–10 y)	210	63 (30.0)	0.68 (0.33–1.41)	0.77 (0.34–1.73)
High (>10 y)	93	24 (25.8)	0.56 (0.23–1.37)	0.63 (0.23–1.76)
Living with a partner				
Yes	292	84 (28.8)	Ref	Ref
No	80	36 (45.0)	1.95 (0.95–4.08)	2.30 (1.03–5.15)
Period of diagnosis				
2005–2008	206	64 (31.0)	Ref	Ref
2009–2012	166	56 (33.7)	1.43 (0.78–2.59)	1.48 (0.78–2.79)

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Abbreviations: BMI, body mass index; CoC, Commission on Cancer; OR, odds ratio.

^aPatients diagnosed in 2003–2004 were excluded (n=116).^bAdjusted for age and treating hospital.^cAdditional adjustment for sex, BMI, T stage, N stage, number of comorbidities, smoking status, education level, living with a partner, and period of diagnosis.^dIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorder.^eYears of school education.^fHospital where patients received treatment was removed from the model.

Table 3. Associations of Patient and Hospital Factors With Nonadministration of Oxaliplatin (cont.)

Variable	Total (N=372) ^a	Did Not Receive Oxaliplatin (n=120)	No Oxaliplatin vs Oxaliplatin	
	N	n (%)	OR ^b (95% CI)	OR ^c (95% CI)
Surgical volume ^f				
Low	75	33 (44.0)	Ref	Ref
Medium	124	32 (25.8)	0.51 (0.25–1.06)	0.44 (0.20–0.96)
High	173	55 (31.8)	0.63 (0.32–1.25)	0.60 (0.29–1.22)
CoC-certified center status (at diagnosis/in 2017) ^e				
No/No	163	55 (33.7)	Ref	Ref
No/Yes	103	23 (22.3)	0.44 (0.22–0.88)	0.42 (0.20–0.87)
Yes/Yes	106	42 (39.6)	1.28 (0.68–2.39)	1.16 (0.59–2.32)

Abbreviations: BMI, body mass index; CoC, Commission on Cancer; OR, odds ratio.

^aPatients diagnosed in 2003–2004 were excluded (n=116).

^bAdjusted for age and treating hospital.

^cAdditional adjustment for sex, BMI, T stage, N stage, number of comorbidities, smoking status, education level, living with a partner, and period of diagnosis.

^dIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorder.

^eYears of school education.

^fHospital where patients received treatment was removed from the model.

In particular, age ≥ 75 years was strongly associated with chemotherapy nonreceipt, even when no major comorbidity was present, and chemotherapy administration in this age group furthermore decreased over time.

Potential underuse of chemotherapy in elderly patients with colon cancer has been reported in previous studies.^{20–25,33} However, these studies were mostly registry-based^{20–24,33} and therefore largely limited in terms of other potentially influential factors associated with chemotherapy use that they could have considered. This population-based study aimed to provide important and comprehensive insight into possible patient- and hospital-based determinants of chemotherapy administration. It also examined chemotherapeutic under-treatment in elderly patients in detail and, as one of few studies, reported potential underlying reasons for non-treatment³⁴ and further assessed the joint effect of age and comorbidity.³⁵

A review of US patients with stage III colon cancer diagnosed in 1991 through 2001 found that older age, female sex, diagnosis in recent years, being unmarried, and presence of comorbidities were associated with lower likelihood of receiving chemotherapy.²¹ Looking at patient factors, our analysis showed similar results, but further broadened the investigative spectrum to healthcare settings outside the United States and to a more recent time period. The associations for age indicate a potential under-treatment in older patients, despite the reported survival benefits from chemotherapy.^{11–14,24} We found that the frequency of chemotherapy administration was significantly lower in patients with ≥ 2 comorbidities, which agrees with findings from previous studies.^{20,21,23,25}

However, strong associations between age and chemotherapy nonreceipt persisted even after comprehensive adjustment for this important covariate. Chemotherapy use at older age was even substantially lower in recent years than in earlier time periods. The reasons for this trend are unclear and warrant further investigation.

Previous studies rarely investigated reasons for and the joint effect of age and comorbidity on chemotherapy nonreceipt. We observed that even in the absence of comorbidities, patients aged ≥ 75 years were much less likely to receive chemotherapy than younger patients; for instance, of 18 patients in this category who did not receive chemotherapy, 6 were explicitly reported not to have received chemotherapy due to old age. Nevertheless, frailty, poor functional status, or contraindications to chemotherapy may have influenced whether a patient received chemotherapy, irrespective of the comorbidities evaluated in our study. In a previous study, Ko et al³⁴ reported comorbidities (60%), old age (45%), and patient choice (32%) as the most frequent reasons for chemotherapy nonreceipt in patients aged ≥ 70 years, whereas the most commonly reported reasons in our study were patient choice (30%), old age (24%), and poor health (17%). However, the association for old age and chemotherapy nonreceipt was only attenuated slightly when patients who refused chemotherapy were excluded from the analysis.

Reasons for refusal of treatment are unknown, but patients are likely to be influenced by recommendations from their oncologist.³⁶ Our analysis also showed higher refusal rates in patients diagnosed in more recent

Table 4. Relative Frequency of Chemotherapy Administration According to Age and Number of Comorbidities

Age at Diagnosis	Number of Comorbid Conditions ^a		
	0	1	≥2
	% (n Treated/n Total)	% (n Treated/n Total)	% (n Treated/n Total)
30–64 y	94.6% (106/112)	94.7% (54/57)	91.7% (22/24)
65–74 y	88.7% (63/71)	91.1% (72/79)	89.2% (58/65)
≥75 y	64.0% (32/50)	55.6% (45/81)	40.0% (36/90)

^aIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.

years. Patient choice as one of the most important influential factors for not receiving chemotherapy should be investigated more closely to exclude misinformation as an underlying cause. The potential undertreatment of elderly patients without comorbidities should also be investigated more closely.

Regarding hospital factors, previous studies have investigated volume and type,^{22,33,37,38} but have reported heterogeneous results. No significant associations have been reported for hospital volume, but lower odds of chemotherapy administration in patients treated at teaching hospitals have been previously noted.^{22,37} Daly et al³³ found that low surgical volume was associated with undertreatment of patients with stage III colon cancer, and that these patients were more likely to receive chemotherapy in academic/research institutions. In another study,³⁸ patients with stage III colon cancer treated in hospitals with a CoC–certified cancer program were more likely to receive chemotherapy. Our analysis found treatment at medium-volume hospitals to be significantly associated with higher odds of chemotherapy administration.

Oxaliplatin is administered in most patients with stage III colon cancer. Haller et al¹⁹ even suggested

consideration of oxaliplatin in all age groups, considering its disease-free survival benefit compared with 5-FU/LV therapy alone. No previous study has investigated the determinants of oxaliplatin administration, although advanced age was the strongest predictor of its nonuse in our analysis. In addition, patients living without a partner and those treated in low-volume hospitals and in hospitals without a certified CRC program had higher odds of oxaliplatin nonuse.

Reasons for the trend in decreasing chemotherapy use overall and in older adults are unclear. However, one explanation could be the observed increase in patient refusal rates. Additionally, the frequency of comorbidities seems to be increasing,³⁹ as observed in our study, possibly due to enhanced comorbidity assessments. Finally, due to the small amount of evidence showing the benefits of oxaliplatin-based therapy in older patients⁴⁰ coupled with the potentially high risk/benefit ratio of chemotherapy in older patients, it is possible that eligibility criteria for chemotherapy have become more stringent in recent years.

Major strengths of our study include its use of a population-based sample and inclusion of a thorough ascertainment of therapy data. We evaluated and

Table 5. Joint Association of Age and Comorbidity With Odds of Not Receiving Adjuvant Chemotherapy

Age at Diagnosis + Comorbidities ^a	Patients, n	Events, n	No Chemotherapy vs Chemotherapy	
			OR ^b (95% CI)	OR ^c (95% CI)
<75 y + 0 comorbidities	183	14	Ref	Ref
<75 y + 1 comorbidity	136	10	0.93 (0.40–2.18)	0.94 (0.38–2.32)
<75 y + >1 comorbidity	89	9	1.47 (0.60–3.58)	1.84 (0.71–4.75)
≥75 y + 0 comorbidities	50	18	5.89 (2.59–13.35)	6.54 (2.73–16.65)
≥75 y + 1 comorbidity	81	36	10.11 (4.91–20.83)	10.14 (4.64–22.17)
≥75 y + >1 comorbidity	90	54	22.79 (10.90–47.62)	23.23 (10.34–52.23)
			<i>P</i> _{interaction} = .2602 ^d	<i>P</i> _{interaction} = .5452 ^d

^aIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.

^bAdjusted for hospitals where patients were treated.

^cAdditional adjustment for body mass index, tumor grade, T stage, N stage, smoking status, education status, living with a partner, and period of diagnosis.

^d*P*_{interaction} assesses the multiplicative effect of age and comorbidity on chemotherapy administration.

Table 6. Probability of Receiving Chemotherapy

Period of Diagnosis	Overall (Proportion)	Age at Diagnosis	
		<75 y (Proportion)	≥75 y (Proportion)
2003–2004	81.0% (115/142)	93.7% (89/95)	55.3% (26/47)
2005–2008	82.4% (206/250)	93.4% (156/167)	60.2% (50/83)
2009–2012	70.5% (167/237)	89.0% (130/146)	40.7% (37/91)

adjusted for several clinically relevant variables related to chemotherapy administration, including factors not previously covered. Data collection by trained interviewers and a thorough follow-up led to a very low proportion of missing values in these data. The clustering of patients within hospitals was adequately addressed by adjusting for individual hospitals where patients were treated. We also explored the determinants of oxaliplatin-based therapy and assessed physician reasons for not administering chemotherapy to some patients in order to identify potential starting points for increasing rates of chemotherapy acceptance and use.

However, our study also had limitations. We were unable to consider dosage or duration of chemotherapy in these analyses. Because most of the hospitals included were teaching hospitals, the study sample may have received a higher standard of treatment than patients in other studies. Despite comprehensive adjustment for potential confounders, we cannot exclude the possibility of residual confounding by factors potentially associated with chemotherapy administration but not adjusted for, such as functional status, microsatellite instability, enrollment in clinical trials, or postoperative complications. In particular, contraindications to chemotherapy, such as reduced renal clearance, are more common at older age. However, it seems unlikely that residual confounding by such factors could explain the strong association between old age and chemotherapy underuse persisting even in the fully adjusted models. Finally, although comorbidity seemed to have a substantial impact on chemotherapy administration in older but not younger patients, the interaction tests showed no significant results. This may be because of the small sample size or the assessment of interaction on a multiplicative scale only.

Conclusions

In this population-based sample of patients with stage III colon cancer in the Rhine-Neckar region of Germany, age was the strongest predictor of chemotherapy non-administration, irrespective of comorbidity and other potential determinants. In particular, old age was a strong predictor of chemotherapy undertreatment, even in patients with no major comorbidities. This finding

corroborates the still apparent issue of undertreatment in healthy older patients, although several studies have shown that the elderly could benefit well from chemotherapy. Further investigation is required to identify the underlying reasons for non-adherence to recommended adjuvant therapy in elderly patients whose health and preferences would allow for treatment.

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Decreasing Use of Chemotherapy in Older Patients With Stage III Colon Cancer Irrespective of Comorbidities

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eTable 1: Overview of Hospital Characteristics

eTable 2: Reasons for Not Administering Adjuvant Chemotherapy According to Physicians

eTable 3: Characteristics of Patients Who Refused Chemotherapy

eTable 4: Factors Associated With Nonadministration of Adjuvant Chemotherapy

eTable 1. Overview of Hospital Characteristics

Clinic	Clinic Size, Beds	Surgical Volume ^a	Certification Status ^b
1	<250	70–149	Never certified
2	<250	0–69	Never certified
3	250–749	0–69	Never certified
4	<250	0–69	Never certified
5	250–749	70–149	Certified before 2017
6	750–999	≥150	Certified before 2017
7	<250	0–69	Never certified
8	<250	0–69	Never certified
9	<250	0–69	Never certified
10	750–999	≥150	Certified before 2017
11	≥1,000	≥150	Certified before 2017
12	250–749	70–149	Never certified
13	<250	0–69	Never certified
14	<250	70–149	Never certified
15	250–749	0–69	Never certified
16	250–749	0–69	Never certified
17	<250	0–69	Never certified
18	250–749	70–149	Certified before 2017
19	≥1,000	≥150	Never certified

^aNumber of colon cancer surgeries performed per year.^bCommission on Cancer–certified.**eTable 2. Reasons for Not Administering Adjuvant Chemotherapy According to Physicians**

	n (%)	Mean Age at Diagnosis (SD), y
Total	141 (100)	79.2 (9.1)
Patient refusal	42 (29.8)	78.5 (8.1)
Old age	34 (24.1)	85.5 (4.1)
Poor health	24 (17.0)	81.0 (8.3)
Severe secondary diagnosis	17 (12.1)	76.4 (10.8)
Long disease course	6 (4.3)	71.7 (14.2)
Death	4 (2.8)	79.0 (14.9)
Wound healing disorder	2 (1.4)	67.0 (2.8)
Only follow-up care recommended	1 (0.7)	86.0 (0)
Postoperative sepsis	1 (0.7)	69.0 (0)
No reason given	39 (27.7)	77.3 (9.4)
Several of the above	25 (17.7)	81.1 (8.2)

eTable 3. Characteristics of Patients Who Refused Chemotherapy (N=42)

Variable	Chemotherapy Nonrecipients, n	Refused Chemotherapy, n	Row %
Sex			
Female	64	20	31.3
Male	77	22	28.6
Age, y			
30–64	11	3	27.3
65–74	22	7	31.8
≥75	108	32	29.6
Number of comorbidities ^a			
0	32	8	25.0
1	46	14	20.4
≥2	63	20	31.8
Period of diagnosis			
2003–2004	27	6	22.2
2005–2008	44	15	34.1
2009–2012	70	21	30.0
Surgical volume			
Low	45	14	31.1
Medium	34	12	35.3
High	62	16	25.8
CoC-certified center status (at diagnosis/in 2017)			
No/No	71	23	32.3
No/Yes	26	5	19.2
Yes/Yes	14	14	31.8

Abbreviation: CoC, Commission on Cancer.

^aIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.

eTable 4. Factors Associated With Nonadministration of Adjuvant Chemotherapy^a

	Patients, n	Events, n	No Chemotherapy vs Chemotherapy	
			OR ^b (95% CI)	OR ^c (95% CI)
Sex				
Female	278	44	Ref	Ref
Male	309	55	1.34 (0.81–2.22)	1.95 (0.97–3.93)
Age at diagnosis, y				
30–64	190	8	Ref	Ref
65–74	208	15	1.73 (0.71–4.24)	1.54 (0.59–4.05)
≥75	189	76	15.5 (7.12–33.9)	12.5 (5.19–30.3)
BMI, kg/m ²				
<25.0	235	46	Ref	Ref
25.0–29.9	241	42	0.82 (0.48–1.41)	0.82 (0.45–1.49)
≥30.0	111	11	0.54 (0.25–1.18)	0.48 (0.21–1.11)
Number of comorbidities ^d				
0	225	24	Ref	Ref
1	203	32	1.17 (0.61–2.25)	1.12 (0.56–2.22)
≥2	159	43	2.17 (1.13–4.17)	2.09 (1.03–4.21)
Smoking status				
Never-smoker	309	51	Ref	Ref
Former smoker	215	42	1.59 (0.94–2.69)	1.55 (0.82–2.92)
Current smoker	63	6	1.35 (0.48–3.78)	1.25 (0.42–3.73)
Education level ^e				
Low (<9 y)	127	33	Ref	Ref
Medium (9–10 y)	332	51	0.82 (0.46–1.47)	0.71 (0.37–1.39)
High (>10 y)	128	15	0.51 (0.24–1.09)	0.40 (0.16–0.99)
Living with a partner				
Yes	444	59	Ref	Ref
No	143	40	1.61 (0.94–2.75)	1.96 (1.04–3.69)
Period of diagnosis				
2003–2004	136	21	Ref	Ref
2005–2008	235	29	0.75 (0.38–1.50)	0.62 (0.30–1.29)
2009–2012	216	49	1.82 (0.94–3.50)	1.67 (0.83–3.37)
Surgical volume ^f				
Low	140	31	Ref	Ref
Medium	185	22	0.52 (0.27–1.00)	0.40 (0.19–0.83)
High	262	46	0.73 (0.41–1.30)	0.65 (0.35–1.20)
CoC–certified center status (at diagnosis/in 2017) ^g				
No/No	277	48	Ref	Ref
No/Yes	173	21	0.61 (0.33–1.12)	0.70 (0.36–1.34)
Yes/Yes	137	30	1.13 (0.64–2.00)	0.83 (0.41–1.66)

Abbreviations: BMI, body mass index; CoC, Commission on Cancer; OR, odds ratio.

^aExcluding patients who refused chemotherapy (n=42).

^bAdjusted for age and hospitals where patients were treated.

^cAdditional adjustment for sex, BMI, T stage, N stage, number of comorbid conditions, smoking status, education level, living with a partner, and period of diagnosis.

^dIncluding diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, stroke, and cerebrovascular disorders.

^eYears of school education.

^fHospital where patients were treated was removed from the model.