Age-Specific Administration of Chemotherapy and Long-Term Quality of Life in Stage II and III Colorectal Cancer Patients: A Population-Based Prospective Cohort

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Critically appraise the current pattern of administration of chemotherapy in older patients with colorectal cancer.
2. Describe the survival benefits associated with chemotherapy as well as its long-term effects on quality of life in stage II/III colorectal cancer patients.

CME

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ABSTRACT

Purpose. To investigate the age-specific pattern of administration of chemotherapy and its association with long-term survival and quality of life (QoL) in stage II and III colorectal cancer patients.

Methods. Chemotherapy allocation according to disease and patient characteristics was investigated in a population-based cohort of 562 stage II and III colorectal cancer patients. Five years after diagnosis, survival was determined and QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items and a tumor specific module. The association among chemotherapy, survival,

and QoL was examined while controlling for potential confounders.

Results. Chemotherapy was administered in 71% of patients aged <60 years and in only 20% of patients aged ≥80 years. A significant association between chemotherapy and longer survival time was found for stage III cancer only. Chemotherapy was associated with higher symptom levels for trouble with taste, anxiety, and hair loss. In age-specific analyses, younger survivors (<70 years at time of follow-up) with a history of chemotherapy reported significantly lower physical, role, and cognitive functioning and higher pain, appetite loss, hair loss, and trouble with taste symptom levels. In con-

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trast, for older survivors (≥ 70 years), only two (hair loss and dry mouth) out of 38 QoL scores were significantly associated with chemotherapy.

Discussion. Chemotherapy is associated with lower long-

term QoL, especially in younger survivors. In cases of uncertain survival benefits of chemotherapy, consideration of its long-term effects on QoL should be incorporated into final decisions on treatment. *The Oncologist* 2011;16:1741–1751

INTRODUCTION

With >1.2 million new incident cases, colorectal cancer is one of the most common malignant diseases worldwide [1]. Surgery is the primary treatment for colorectal cancer, but, depending on the tumor location and stage, it may be complemented by adjuvant or neoadjuvant treatments. Chemotherapy is mainly administered for stage III and IV colon cancer, whereas radiotherapy and radiochemotherapy are primarily administered for stage II–IV rectal cancer [2]. For stage II colon cancer, there is no agreement on the administration of chemotherapy [3].

The outcome of treatment is usually assessed by its effect on survival time, but because of continuous improvements in survival outcomes, an additional assessment of late adverse effects of treatments becomes increasingly important. Late effects of radiotherapy in rectal cancer survivors have been extensively investigated, and long-term effects like bowel dysfunction and sexual functioning problems have been demonstrated [4]. However, few studies have addressed the late effects of chemotherapy in colorectal cancer survivors, and results are conflicting. Whereas one study reported worse role and social functioning 1–3 years after diagnosis in patients who received chemotherapy [5], other studies did not find an association between past chemotherapy and quality of life (QoL) [6, 7]. To our knowledge, no study directly investigated the effect of chemotherapy on long-term (≥ 5 years past diagnosis) QoL of colorectal cancer survivors, although studies in long-term breast cancer survivors have shown that past adjuvant chemotherapy may lead to detriments in QoL that may be clinically apparent only years after treatment [8, 9]. Such information on late effects might aid in treatment decisions and help to better inform patients about potential consequences of treatment. The aim of this paper was to investigate the pattern of care in colorectal cancer patients with stage II and III disease with respect to chemotherapy and whether past chemotherapy is associated with changes in long-term QoL. Because earlier research indicated that both the administration of chemotherapy in colorectal cancer and its outcomes might be related to patient age [10, 11], specific attention was paid to age- and stage-specific patterns.

PATIENTS AND METHODS

Study Design and Study Population

This analysis is based on patients with a colorectal cancer diagnosis in 2003 or 2004 from a population-based case–control study carried out in southwest Germany (Rhine-Neckar-Odenwald region) including patients with a first histologically confirmed diagnosis of colorectal cancer [Darmkrebs–Chancen der Verhütung durch Screening (DACHS)]. Further details of the original study have been described elsewhere [12, 13].

Eligible patients who were mentally and physically able to participate in a personal interview of ~1 hour were informed about the study by their clinicians, usually a few days after sur-

gery, and the study center was notified upon receipt of informed consent. Additionally, patients who could not be recruited during their in-patient stay were contacted by mail after discharge by clinicians and clinical cancer registries. All participants gave written informed consent. The study was approved by the ethics committees of the University of Heidelberg and the state medical boards of Baden-Wuerttemberg and Rhineland-Palatinate.

After an average of 3 years since diagnosis, detailed information on colorectal cancer treatment was collected from attending physicians in a standardized questionnaire. The 5-year follow-up was conducted in 2009. After ascertainment of vital status and dates of death through population registries, a QoL questionnaire was sent to all patients alive who had not refused further contact. Nonresponders were mailed up to two reminder letters, which were followed by one reminder phone call in cases of nonresponse to mailings. Patients who did not return the QoL questionnaire were offered a phone interview on the basis of a shortened version of the QoL questionnaire (referred to as short questionnaire; for details, see below). Both questionnaires entailed questions concerning new concomitant diseases or recurrences after the colorectal cancer diagnosis. In cases of reported new diagnoses, including cancer recurrence, attending physicians were contacted to validate the diagnoses. Attending physicians were also contacted when information on recurrence within 5 years after diagnosis was lacking or uncertain.

QoL Questionnaire

QoL was assessed with the Quality of Life Questionnaire Core 30 Items (QLQ-C30) [14] and the tumor specific module QLQ-CR29 [15, 16], both developed by the European Organization for Research and Treatment of Cancer (EORTC). The short questionnaire, which was used in cases when a patient was not willing to complete the full questionnaire, was restricted to the global QLQ-C30 item as the sole QoL measure.

Assessment of Treatment

Information on treatment was collected during the 3-year follow-up and during the 5-year follow-up. For the 3-year follow-up, attending physicians were asked for information on initial treatment of the tumor and, separately, for information on treatment of any local recurrence or distant metastasis after diagnosis. Only information on the initial treatment of the tumor was used to define whether or not a patient received chemotherapy, because the aim of our study was to investigate associations between primary chemotherapy treatment and long-term survival and QoL. For the 5-year follow-up, information on recurrence after diagnosis and, in cases of recurrence, information on treatment was requested from the attending phy-

sician. This information was only used to assess how much time had elapsed between the last chemotherapy and the reply to the questionnaire during the 5-year follow-up.

Statistical Methods

The distributions of patient and disease characteristics were compared among responders, nonresponders, short-questionnaire responders, and deceased patients to assess the potential impact of nonrandom missing data. The allocation of chemotherapy with respect to gender, age (≤ 59 years, 60–69 years, 70–79 years, and ≥ 80 years), stage, cancer site (colon and rectum), and self-reported medical conditions (myocardial infarction, coronary heart disease, heart failure, stroke, and diabetes) at baseline was descriptively compared. This analysis was done in the cohort of all patients with a diagnosis in 2003 or 2004 to avoid survival bias. In addition, the association between chemotherapy allocation and each of the aforementioned factors was tested in a logistic regression model with adjustment for all other factors.

Cox proportional-hazards regression was employed to estimate the hazard ratio (HR) for chemotherapy-associated survival adjusting for sex, age at follow-up, stage at diagnosis, cancer site, radiotherapy, and presence (yes/no) of any self-reported comorbidities (myocardial infarction, coronary heart disease, heart failure, stroke, and diabetes) at baseline. The same analysis was done in the subgroups of stage II and stage III patients.

For the QoL analysis, scoring of the EORTC QLQ-C30 and EORTC QLQ-CR29 was performed according to the EORTC scoring manual [16, 17]. All scores were linearly transformed to a 0–100 scale. In cases of missing items, multi-item scores were calculated as the mean of the nonmissing items if at least half of the items from the corresponding scale had been completed. Differences in mean QoL scores > 10 points were considered clinically meaningful [18].

The QoL of patients with and without chemotherapy was compared using mean values and standard errors. Analyses of covariance with the factors sex, age at follow-up, stage at diagnosis, cancer site, radiotherapy, chemotherapy, and presence of any self-reported comorbidities at baseline were carried out to test for an independent effect of chemotherapy on QoL. In sensitivity analyses, additional separate adjustments for living with a partner, highest level of education (three levels), recurrence, second cancer, physical activity (assessed by a modified version of the international physical activity questionnaire [19] with the categories low, moderate, and high), and body mass index at follow-up were conducted, but results are not reported because no substantial deviations were found. The same QoL analysis was performed separately for two age groups, using the median age at follow-up (71 years) as the cutoff, and for stage II and stage III patients.

All analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined by $p < .05$. No multiple comparison corrections were made.

RESULTS

Overall, 562 patients with a diagnosis of stage II (52%) or stage III (48%) colorectal cancer in 2003 or 2004 were recruited (Table 1). The mean age at diagnosis was 68.4 years (standard deviation, 10.5 years). Sixty-six percent of the patients had colon cancer and 50% received chemotherapy. All patients underwent surgical treatment and 23% received radiotherapy.

Administration of Chemotherapy

The pattern of chemotherapy administration according to sex, age at diagnosis, stage, cancer type, and comorbidities is shown in Table 2. Adjuvant or neoadjuvant chemotherapy was more often administered for stage III cancer at diagnosis (77%, compared with 25% of stage II patients). The three most frequently administered cytostatics were 5-fluorouracil ($n = 257$, 93%), folinic acid ($n = 214$, 77%), and oxaliplatin ($n = 36$, 13%). Chemotherapy was administered in 71% of patients aged < 60 years but in only 20% of patients aged ≥ 80 years. For both stage II and stage III patients, chemotherapy administration was strongly associated with age, even after adjustment for sex, cancer site, stage, and baseline comorbidities ($p = .0007$, $p < .0001$). For stage II patients, the odds of receiving chemotherapy was 4.92 times higher for rectal cancer patients than for colon cancer patients, whereas for stage III cancer, the odds of receiving chemotherapy was 2.50 times higher for colon cancer patients. Sample sizes for the analysis of the association between chemotherapy and comorbidities were small and no significant associations were found. However, the odds for chemotherapy administration were generally lower for patients who had heart failure, stroke, and diabetes but higher for patients with a previous myocardial infarction or prevalent coronary heart disease.

Primary chemotherapy was started, on average, 2 months after diagnosis (standard deviation, 3 months) and was stopped after an average of 6 months (standard deviation, 4 months). Chemotherapeutic treatment was started after > 12 month for six patients. Among the patients who provided information during the 5-year follow-up, only one patient with stage II disease and three patients with stage III disease were reported to have received chemotherapy during the last 12 months. In the previous 2 years, two and five responders had received chemotherapy, respectively.

Association Between Survival and Chemotherapy

The vital status could be determined for all except one patient who moved abroad. Of the 561 patients with a known vital status, 178 (32%) patients died prior to or during the 5-year follow-up. After adjustment for confounders, chemotherapy was nonsignificantly associated with a longer overall survival time (HR, 0.80; 95% confidence interval [CI], 0.55–1.17). This trend resulted from a significant survival benefit for stage III patients (HR=0.63, 95% CI: 0.39–0.99) and lack of survival benefit for stage II patients (HR, 1.22; 95% CI, 0.62–2.40). Exclusion of six patients who received chemotherapy in the second year after diagnosis or later did not materially alter the findings.

Table 1. Characteristics of study population at baseline and follow-up according to response status

	According to responder status at the 5-year follow-up						
	Total (n = 562)	Responder (n = 312)	Short-questionnaire responder (n = 15)	Nonresponder ^a (n = 57)	Deceased (n = 178)	χ ² test, all groups ^b	χ ² test, responders versus nonresponders ^b
Sex							
Female	260 (46%)	133 (43%)	11 (73%)	30 (53%)	86 (48%)		
Male	302 (54%)	179 (57%)	4 (27%)	27 (47%)	92 (52%)	.0719	.0278
Age at diagnosis							
≤59 yrs	111 (20%)	75 (24%)	0 (0%)	9 (16%)	27 (15%)		
60–69 yrs	193 (34%)	127 (41%)	3 (20%)	15 (26%)	48 (27%)		
70–79 yrs	164 (29%)	91 (29%)	6 (40%)	16 (28%)	51 (29%)		
≥80 yrs	94 (17%)	19 (6%)	6 (40%)	17 (30%)	52 (29%)		
Mean (standard deviation), yrs	68.4 (10.5)	65.7 (9.5)	75.9 (7.5)	71.7 (10.8)	71.4 (10.9)	<.0001	<.0001
Location							
Colon	370 (66%)	193 (62%)	14 (93%)	43 (75%)	120 (67%)		
Rectum	192 (34%)	119 (38%)	1 (7%)	14 (25%)	58 (33%)	.0176	.0055
Stage							
II	293 (52%)	169 (54%)	13 (87%)	36 (63%)	75 (42%)		
III	269 (48%)	143 (46%)	2 (13%)	21 (37%)	103 (58%)	.0006	.0320
Therapy ^c							
Surgery	561 (100%)	312 (100%)	15 (100%)	57 (100%)	177 (99%)	–	–
Chemotherapy	277 (50%)	172 (55%)	2 (13%)	19 (34%)	84 (48%)	.0005	.0001
Neoadjuvant	27 (5%)	17 (6%)	0 (0%)	1 (2%)	9 (5%)		
Adjuvant	259 (46%)	161 (52%)	2 (13%)	18 (32%)	78 (44%)		
Radiotherapy	126 (23%)	78 (25%)	0 (0%)	7 (13%)	41 (24%)	.0212	.0056
Neoadjuvant	61 (11%)	36 (12%)	0 (0%)	4 (7%)	21 (12%)		
Adjuvant	65 (12%)	42 (14%)	0 (0%)	3 (5%)	20 (11%)		
Recurrence ^d							
Yes	117 (21%)	24 (8%)	2 (13%)	5 (9%)	86 (48%)		
No	436 (78%)	288 (92%)	13 (87%)	45 (79%)	90 (51%)		
Missing	9 (2%)	0 (0%)	0 (0%)	7 (12%)	2 (1%)	<.0001	<.0001

^aIncluding 20 patients who were not eligible for the 5-year follow-up because they were physically or mentally too ill to participate.

^bShort-questionnaire responders are counted as nonresponders.

^cInformation on therapy was collected during the 3-year follow-up.

^dInformation on recurrence was collected during the 3-year follow-up and updated after 5 years.

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^bShort-questionnaire responders are counted as nonresponders.

^cInformation on therapy was collected during the 3-year follow-up.

^dInformation on recurrence was collected during the 3-year follow-up and updated after 5 years.

Follow-up with Respect to QoL After 5 Years

Of the 383 patients who were alive through the 5-year follow-up, 20 were excluded from the survey because they were physically or mentally not able to participate (e.g., because of dementia or hospitalization), 12 patients did not respond to mailings and could not be contacted by phone, eight agreed to participate but did not return the questionnaire, and 16 actively refused to participate. The remaining patients returned a full ($n = 312$) or short ($n = 15$) questionnaire, resulting in a response rate of 90%. Full responders were significantly more often male, were younger, were more likely to have had rectal cancer or stage III cancer, were more likely to have received chemotherapy and radiotherapy, and were less likely to have had a recurrence than nonresponders, including short-questionnaire responders (Table 1). The overall QoL of re-

sponders who completed a full questionnaire was higher than the QoL of short-questionnaire responders ($\Delta = 11.06$), but after adjustment for age and sex the difference was no longer significant ($p = .13$).

Association Between QoL and Chemotherapy

Table 3 presents the raw QLQ-C30 and QLQ-CR29 QoL mean scores of survivors stratified by chemotherapy and the difference between the adjusted mean scores of survivors who did and did not receive chemotherapy. After adjustment for age at follow-up, sex, cancer site, stage, radiotherapy, and comorbidities, all functioning scores except the global QoL score were lower and all QLQ-C30 symptom scores except diarrhea were higher in survivors who received chemotherapy, but none

Table 2. Allocation of chemotherapy according to disease and patient characteristics for the baseline population of stage II and stage III colorectal cancer patients

	Stage II and III (n = 277 of 557, 50%) ^a			Stage II (n = 73 of 291, 25%) ^a			Stage III (n = 204 of 266, 77%) ^a		
	Chemotherapy			Chemotherapy			Chemotherapy		
	Yes, n (%)	No, n (%)	OR (95% CI) ^b	Yes, n (%)	No, n (%)	OR (95% CI) ^b	Yes, n (%)	No, n (%)	OR (95% CI) ^b
Age at baseline									
≤59 yrs	77 (71%)	32 (29%)	Reference	24 (49%)	25 (51%)	Reference	53 (88%)	7 (12%)	Reference
60–69	116 (60%)	76 (40%)	0.66 (0.36–1.22)	29 (31%)	65 (69%)	0.48 (0.22–1.07)	87 (89%)	11 (11%)	1.02 (0.36–2.86)
70–79	66 (40%)	98 (60%)	0.31 (0.16–0.59)	17 (17%)	80 (83%)	0.26 (0.11–0.63)	49 (73%)	18 (27%)	0.34 (0.12–0.96)
80+	18 (20%)	74 (80%)	0.08 (0.04–0.20)	3 (6%)	48 (94%)	0.05 (0.01–0.26)	15 (37%)	26 (63%)	0.08 (0.02–0.25)
			<i>P</i> _{Trend} < .0001			<i>P</i> _{Trend} = .0007			<i>P</i> _{Trend} < .0001
Sex									
Female	116 (45%)	140 (55%)	Reference	26 (20%)	107 (80%)	Reference	90 (73%)	33 (27%)	Reference
Male	161 (53%)	140 (47%)	1.05 (0.67–1.65)	47 (30%)	111 (70%)	1.20 (0.63,2.29)	114 (80%)	29 (20%)	1.21 (0.59–2.48)
Cancer site									
Colon	157 (43%)	210 (57%)	Reference	31 (15%)	172 (85%)	Reference	126 (77%)	38 (23%)	Reference
Rectum	120 (63%)	70 (37%)	1.82 (1.14–2.90)	42 (48%)	46 (52%)	4.92 (2.66–9.12)	78 (76%)	24 (24%)	0.40 (0.19–0.86)
Myocardial infarction ^c									
No	257 (50%)	254 (50%)	Reference	68 (26%)	199 (74%)	Reference	189 (77%)	55 (23%)	Reference
Yes	18 (41%)	26 (59%)	1.34 (0.54–3.32)	5 (21%)	19 (79%)	1.19 (0.30–4.64)	13 (65%)	7 (35%)	1.29 (0.32–5.16)
Coronary heart disease ^c									
No	248 (52%)	234 (48%)	Reference	64 (26%)	184 (74%)	Reference	184 (79%)	50 (21%)	Reference
Yes	27 (43%)	36 (57%)	1.42 (0.68–2.97)	9 (24%)	29 (76%)	1.41 (0.52–3.88)	18 (72%)	7 (28%)	1.78 (0.49–6.47)
Heart failure ^c									
No	259 (53%)	226 (47%)	Reference	68 (27%)	180 (73%)	Reference	191 (81%)	46 (19%)	Reference
Yes	16 (27%)	43 (73%)	0.53 (0.24–1.17)	4 (12%)	30 (88%)	0.54 (0.16–1.85)	12 (48%)	13 (52%)	0.55 (0.18,1.70)
Stroke									
No	268 (51%)	257 (49%)	Reference	68 (25%)	203 (75%)	Reference	200 (79%)	54 (21%)	Reference
Yes	9 (28%)	23 (72%)	0.53 (0.19–1.46)	5 (25%)	15 (75%)	1.58 (0.45–5.52)	4 (33%)	8 (67%)	0.10 (0.02–0.50)
Diabetes ^c									
No	235 (52%)	215 (48%)	Reference	64 (27%)	171 (73%)	Reference	171 (80%)	44 (20%)	Reference
Yes	41 (40%)	62 (60%)	0.76 (0.42–1.40)	9 (17%)	45 (83%)	0.78 (0.31–1.98)	32 (65%)	17 (35%)	0.67 (0.28–1.58)

^aInformation on chemotherapy was missing for two patients with stage II disease at diagnosis and three patients with stage III disease at diagnosis.

^bOR and 95% CI adjusted for sex, age at baseline, cancer site (colon, rectum), myocardial infarction, coronary heart disease, heart failure, stroke, diabetes (and stage for the stage II and III analysis).

^cBecause of missing values, numbers do not add up to the overall number of survivors.
Abbreviations: CI, confidence interval; OR, odds ratio.

of these associations was significant. Of the QLQ-CR29 scores, anxiety, hair loss, and trouble with taste symptom levels were significantly and meaningfully higher in survivors who received chemotherapy.

Results from an age-stratified analysis are presented in Table 4. Survivors who were aged ≤70 years at the 5-year follow-up and received chemotherapy reported significantly lower adjusted physical, role, and cognitive functioning and significantly higher pain, appetite loss, hair loss, and trouble with taste symptom levels than survivors of the same age group who did not receive chemotherapy. Differences were clinically meaningful for all these scales except appetite loss. Differences in QoL according to chemother-

apy status were much smaller for survivors who were >70 years old. Among the elderly, only hair loss and dry mouth were significantly and meaningfully associated with chemotherapy.

Results from a stage-stratified analysis suggest that chemotherapy was associated with better QoL in stage III colorectal cancer patients, whereas an opposite association was observed for stage II patients (Table 5). For example, concern about weight was significantly stronger in stage II patients who received chemotherapy, whereas stage III patients who received chemotherapy had tentatively fewer concerns than patients who did not receive chemotherapy. This pattern (i.e., higher QoL for stage III patients who underwent chemotherapy but

Table 3. Quality of life scores of survivors with respect to chemotherapy

	Scale type ^a	Mean (SE)		Chemotherapy (n = 172)	No chemotherapy (n = 140)
		Adjusted difference ^b	GLM (p) ^c		
QLQ-C30 score ^d					
Physical functioning	F	77.1 (1.7)	73.9 (2.0)	−3.6	.28
Role functioning	F	72.9 (2.3)	72.3 (2.7)	−4.1	.39
Emotional functioning	F	71.0 (2.1)	75.5 (2.0)	−6.8	.08
Cognitive functioning	F	79.0 (1.8)	77.8 (2.1)	−2.8	.46
Social functioning	F	70.4 (2.3)	79.4 (2.6)	−6.5	.16
Global health/QoL	F	64.2 (1.8)	62.1 (2.2)	0.2	.96
Fatigue	S	32.2 (2.1)	34.9 (2.4)	3.3	.42
Nausea/vomiting	S	5.1 (1.0)	4.6 (1.1)	2.1	.26
Pain	S	28.7 (2.5)	26.9 (2.7)	7.6	.12
Dyspnea	S	22.6 (2.2)	24.7 (2.8)	3.4	.46
Insomnia	S	32.9 (2.6)	29.2 (2.7)	7.1	.16
Appetite loss	S	13.3 (1.9)	10.8 (2.1)	6.4	.09
Constipation	S	17.7 (2.2)	15.6 (2.4)	1.4	.75
Diarrhea	S	24.9 (2.4)	22.6 (2.7)	−1.1	.81
Financial difficulties	S	21.4 (2.3)	15.4 (2.3)	0.9	.83
QLQ-CR29 score ^d					
Gastrointestinal					
Urinary frequency	S	43.7 (2.0)	49.2 (2.2)	1.2	.76
Stool frequency	S	31.3 (2.1)	20.7 (2.1)	2.8	.45
Urinary incontinence	S	15.1 (2.0)	14.6 (2.2)	3.7	.36
Flatulence	S	35.6 (2.6)	29.6 (2.8)	2.2	.66
Bloated feeling	S	30.2 (2.4)	27.0 (2.6)	0.9	.86
Blood or mucus in stool	S	4.8 (1.0)	3.9 (0.8)	0.5	.83
Fecal incontinence	S	19.8 (2.3)	15.6 (2.3)	1.6	.72
Embarrassed by bowel movement	S	20.8 (2.7)	16.0 (2.7)	−3.5	.47
Stoma care problems	S	22.2 (6.2)	23.3 (10.0)	−10.1	.63
Sore skin	S	19.7 (2.4)	16.2 (2.3)	0.1	.98
Pain					
Dysuria	S	4.3 (1.2)	3.6 (1.1)	2.1	.34
Abdominal pain	S	14.6 (2.0)	12.7 (1.9)	2.5	.50
Buttock pain	S	16.1 (2.1)	13.5 (2.3)	2.7	.51
Worries about					
Body image	F	75.6 (2.1)	80.6 (2.2)	1.1	.79
Anxiety	F	57.4 (2.7)	66.4 (2.7)	−12.4	.0181
Weight	F	72.3 (2.4)	75.8 (2.6)	−5.0	.29
Sexuality					
Sexual interest (men)	F	49.5 (3.5)	51.1 (3.8)	6.0	.35
Sexual interest (women)	F	72.8 (4.0)	77.3 (4.2)	−6.3	.37
Impotence	S	60.7 (4.4)	57.1 (4.1)	4.3	.56
Dyspareunia	S	18.0 (5.4)	10.4 (3.8)	2.1	.84
Systemic therapy					
Dry mouth	S	25.7 (2.4)	22.2 (2.3)	8.8	.06
Hair loss	S	15.9 (2.1)	5.6 (1.4)	15.9	<.0001
Trouble with taste	S	16.3 (2.2)	8.0 (1.8)	13.0	.0009

^aF: higher scores reflect better functioning and fewer worries; S: higher scores reflect higher symptom levels. Functional scales are shown in bold to enhance discrimination from inversely orientated symptom scales.

^bDifference is score in patients with chemotherapy minus score in patients without chemotherapy adjusted for all independent variables in the analysis of covariance except chemotherapy.

^cAssociation of chemotherapy (yes/no) with QoL scores adjusted for sex (male/female), age at follow-up, stage (II/III), cancer site (colon, rectum), radiotherapy, and presence of self-reported comorbidities prior to diagnosis (yes/no).

^dNumber of missing QoL scores was <5% except for three sexuality scores that had 9% (impotence), 30% (female sexual functioning), and 48% (dyspareunia) missing values, respectively. Older survivors were more reluctant to provide information on these intimate items.

Abbreviations: F, functioning scale; GLM, general linear model; QLQ-C30, Quality of Life Questionnaire Core 30 Items; QLQ-CR29, Quality of Life Questionnaire Colorectal Cancer specific module; QoL, quality of life; S, symptom scale; SE, standard error.

Table 4. QoL scores of survivors with respect to chemotherapy for the subgroups of young and old survivors

		≤70 yrs (n = 144)		>70 yrs (n = 168)	
	Scale type ^a	Adjusted difference ^b	GLM (p) ^c	Adjusted difference ^b	GLM (p) ^c
QLQ-C30 score ^c					
Physical functioning	F	−12.8	.0070	2.5	.60
Role functioning	F	−12.9	.0432	2.8	.68
Emotional functioning	F	−11.4	.07	−2.3	.65
Cognitive functioning	F	−14.0	.0112	5.7	.26
Social functioning	F	−9.3	.17	−5.1	.44
Global health/QoL	F	−0.5	.92	0.4	.95
Fatigue	S	11.0	.09	−2.9	.59
Nausea/vomiting	S	0.0	.98	3.6	.18
Pain	S	15.3	.0421	0.8	.90
Dyspnea	S	11.4	.08	−1.6	.81
Insomnia	S	1.1	.88	8.8	.20
Appetite loss	S	9.9	.0476	2.0	.71
Constipation	S	5.0	.46	−1.7	.77
Diarrhea	S	−0.7	.93	−3.0	.63
Financial difficulties	S	2.0	.80	2.0	.71
QLQ-CR29 score ^c					
Gastrointestinal					
Urinary frequency	S	3.8	.55	−2.1	.68
Stool frequency	S	−1.4	.82	5.7	.22
Urinary incontinence	S	8.5	.17	−0.8	.89
Flatulence	S	6.7	.41	−1.0	.88
Bloated feeling	S	−1.3	.85	2.2	.73
Blood or mucus in stool	S	5.0	.13	−2.6	.22
Fecal incontinence	S	7.6	.26	−3.5	.52
Embarrassed by bowel movement	S	−2.4	.76	−4.7	.48
Stoma care problems	S	— ^d	— ^d	−12.1	.67
Sore skin	S	−3.3	.64	2.0	.73
Pain					
Dysuria	S	7.0	.07	−1.7	.50
Abdominal pain	S	1.4	.79	2.8	.59
Buttock pain	S	4.0	.57	2.8	.58
Worries about					
Body image	F	3.8	.56	−0.8	.88
Anxiety	F	−15.6	.06	−10.3	.14
Weight	F	−4.7	.54	−5.4	.38
Sexuality					
Sexual interest (men)	F	2.0	.84	7.0	.44
Sexual interest (women)	F	−18.8	.12	6.2	.47
Impotence	S	3.9	.76	3.6	.71
Dyspareunia	S	8.4	.66	−6.9	.60
Systemic therapy					
Dry mouth	S	2.2	.74	13.1	.0408
Hair loss	S	20.3	.0001	13.6	.0054
Trouble with taste	S	16.1	.0061	10.1	.0634

^aF: higher scores reflect better functioning and fewer worries; S: higher scores reflect higher symptom levels. Functional scales are shown in bold to enhance discrimination from inversely orientated symptom scales.

^bDifference is score in patients with chemotherapy minus score in patients without chemotherapy adjusted for all independent variables in the analysis of covariance except chemotherapy.

^cAssociation of chemotherapy (yes/no) with QoL scores adjusted for sex (male/female), age at follow-up, stage (II/III), cancer site (colon, rectum), radiotherapy, and presence of self-reported comorbidities prior to diagnosis (yes/no).

^dTest and adjusted means could not be computed because of insufficient number of colorectal cancer survivors with stoma (n = 24).

^eNumber of missing QoL scores was <5% except for three sexuality scores that had 9% (impotence), 30% (female sexual functioning), and 48% (dyspareunia) missing values, respectively. Older survivors were more reluctant to provide information on these intimate items.

Abbreviations: F, functioning scale; GLM, general linear model; QLQ-C30, Quality of Life Questionnaire Core 30 Items; QLQ-CR29, Quality of Life Questionnaire Colorectal Cancer specific module; QoL, quality of life; S, symptom scale.

Table 5. QoL scores of survivors with respect to chemotherapy for the subgroups of survivors with stage II and III at diagnosis

		Stage II (n = 169)		Stage III (n = 143)	
		Adjusted difference ^b	GLM (p) ^c	Adjusted difference ^b	GLM (p) ^c
Scale type ^a					
QLQ-C30 score ^c					
Physical functioning	F	−6.4	.20	6.3	.21
Role functioning	F	−7.6	.27	7.0	.36
Emotional functioning	F	−7.8	.16	−0.3	.96
Cognitive functioning	F	−4.4	.42	3.0	.61
Social functioning	F	−10.4	.09	6.0	.47
Global health/QoL	F	−5.5	.29	9.5	.12
Fatigue	S	7.4	.19	−8.3	.22
Nausea/vomiting	S	2.2	.44	3.8	.19
Pain	S	9.9	.17	0.5	.95
Dyspnea	S	8.5	.20	−5.6	.45
Insomnia	S	8.7	.21	−0.9	.92
Appetite loss	S	10.3	.06	−7.7	.17
Constipation	S	4.9	.39	−6.2	.42
Diarrhea	S	3.0	.67	−3.1	.69
Financial difficulties	S	6.0	.31	−9.6	.21
QLQ-CR29 score ^c					
Gastrointestinal					
Urinary frequency	S	2.6	.62	−5.0	.46
Stool frequency	S	7.0	.20	−1.2	.84
Urinary incontinence	S	5.1	.38	1.0	.88
Flatulence	S	8.7	.22	−5.8	.47
Bloated feeling	S	10.0	.11	−8.1	.33
Blood or mucus in stool	S	−0.3	.92	0.5	.88
Fecal incontinence	S	8.4	.17	−5.3	.43
Embarrassed by bowel movement	S	−0.5	.95	−4.6	.57
Stoma care problems	S	−5.4	.81	−105.6 ^d	.0197
Sore skin	S	−0.6	.92	−1.7	.81
Pain					
Dysuria	S	3.2	.33	−1.4	.68
Abdominal pain	S	0.2	.97	2.5	.70
Buttock pain	S	1.8	.78	1.9	.76
Worries about					
Body image	F	−1.4	.80	6.6	.37
Anxiety	F	−13.2	.06	−10.2	.27
Weight	F	−17.3	.0071	11.2	.16
Sexuality					
Sexual interest (men)	F	9.0	.31	5.3	.60
Sexual interest (women)	F	−5.4	.62	−13.2	.21
Impotence	S	5.3	.55	5.8	.69
Dyspareunia	S	−13.1	.36	−1.9	.92
Systemic therapy					
Dry mouth	S	7.8	.18	5.7	.49
Hair loss	S	13.4	.0011	14.5	.0311
Trouble with taste	S	10.1	.0327	17.4	.0191

^aF: higher scores reflect better functioning and fewer worries; S: higher scores reflect higher symptom levels. Functional scales are shown in bold to enhance discrimination from inversely orientated symptom scales.

^bDifference is score in patients with chemotherapy minus score in patients without chemotherapy adjusted for all independent variables in the analysis of covariance except chemotherapy.

^cAssociation of chemotherapy (yes/no) with QoL scores adjusted for sex (male/female), age at follow-up, cancer site (colon, rectum), radiotherapy, and presence of self-reported comorbidities prior to diagnosis (yes/no).

^dAdjusted difference is out of range because of small sample size and ceiling effects of the scale.

^eNumber of missing QoL scores was <5% except for three sexuality scores that had 9% (impotence), 30% (female sexual functioning), and 48% (dyspareunia) missing values, respectively. Older survivors were more reluctant to provide information on these intimate items.

Abbreviations: F, functioning scale; GLM, general linear model; QLQ-C30, Quality of Life Questionnaire Core 30 Items; QLQ-CR29, Quality of Life Questionnaire Colorectal Cancer specific module; QoL, quality of life; S, symptom scale.

higher QoL for stage II patients who did not) was stronger for younger patients, patients with colon cancer, and patients not undergoing radiotherapy (data not shown). In contrast, little or no difference in QoL outcomes between stage II and stage III patients with and without chemotherapy administration was observed for older patients, patients with rectal cancer, and patients undergoing radiotherapy (data not shown). However, because of small sample sizes, results of this subgroup analysis must be interpreted with caution.

DISCUSSION

Adjuvant treatment is highly recommended for stage II and stage III rectal cancer and stage III colon cancer patients, but recommendations for stage II colon cancer are inconclusive. Our results support the positive association between survival and chemotherapy for stage III colorectal cancer patients. For stage II patients, no significant association was found, but these results should be interpreted cautiously because of the small number of events and the differences in treatment for rectal and colon cancer patients. Recommendations for adjuvant treatment of colorectal cancer patients are given irrespective of age at diagnosis, because studies indicate that older individuals may benefit from chemotherapy to the same extent as younger individuals as long as the dose intensity is adapted [2, 20]. Nonetheless, patients with an advanced age receive intensive cancer therapy less often than younger patients, even if the patients are highly functional and lack comorbidities [21]. As a consequence, older patients are often undertreated [10, 22, 23]. Our results support this finding, because the proportion of patients treated with chemotherapy decreased with increasing age, even after adjustment for potential confounders. Reasons for this potential undertreatment of the elderly may be based on misinformation by the attending physician, because the median life expectancy of older patients is often underestimated [10], or based on a lack of detailed information on safety and efficacy of cancer treatment in the elderly, because older patients have often been excluded from clinical trials [24] and are more vulnerable to the complications of cytotoxic chemotherapy [20, 25].

Our results suggest that chemotherapy is not associated with changes in the long-term QoL of elderly (≥ 70 years) colorectal cancer patients. Only the hair loss and dry mouth symptom levels were significantly higher for survivors who received chemotherapy. This finding is in agreement with the results of Bouvier et al. [7], who reported that chemotherapy was not associated with restrictions in QoL within 1 year postdiagnosis for elderly (≥ 75 years) stage III colon cancer survivors.

For survivors aged < 70 years at the 5-year follow-up, chemotherapy was associated with lower physical, role, and cognitive functioning and higher pain, appetite loss, hair loss, and trouble with taste symptom levels. Results from studies including breast cancer survivors show comparable restrictions in QoL [8, 9] and acute and delayed cognitive dysfunction [26] that are associated with chemotherapy. However, comparisons between breast and colorectal cancer survivors should be made with caution because breast cancer patients are, on average, younger, almost exclusively female, and receive different chemotherapeutic agents than those used in colorectal cancer.

It was previously reported that the overall impact of having

cancer is higher in younger colorectal cancer survivors [5]. A possible explanation for this finding might be that younger survivors may have fewer coping strategies and resources that are needed to manage a life-threatening disease like colorectal cancer [27]. For older survivors, cancer often occurs in the presence of other diseases [28]. These potential different coping strategies and resources and different experiences with severe diseases might also explain the difference in the associations between QoL and chemotherapy between younger and older survivors. However, further studies are needed to investigate this interaction in detail.

Our results suggest that chemotherapy might be negatively associated with QoL for stage II patients but positively associated with QoL for stage III patients. This finding is particularly important because the chemotherapy-associated survival benefit is also generally lower or even absent in stage II patients. However, our results must be interpreted with caution because our sample size was neither sufficient to detect small to moderate stage-specific chemotherapy-associated differences nor sufficient to test for an interaction between chemotherapy and stage. Thus, this potential interaction should be evaluated in future studies.

In our study, survivors treated with chemotherapy had high levels of hair loss and trouble with taste symptoms. Although the reference frame for the evaluation of the hair loss and trouble with taste symptoms was within the last week, the wording of the item for hair loss specifically addresses hair loss as a result of treatment. Thus, we cannot exclude that, at least for this item, survivors referred to the situation during treatment instead of evaluating their current situation. To decide whether these symptoms are still relevant for long-term survivors, the validity of this item must be further evaluated in detail for long-term survivors.

We cannot exclude the possibility that patients who received chemotherapy had different baseline QoL from those who did not. The decision for chemotherapeutic treatment depends on the health status of the patient at diagnosis [2] and, thus, probably also on QoL at baseline. We report adjusted mean values of the association between QoL and chemotherapy to account for differences between the patient groups, but we cannot exclude residual confounding. Unfortunately, the QoL of patients was not assessed at baseline. Because chemotherapy is usually administered to healthier patients, the reported differences for younger survivors may be underestimated and there might be an undetected detrimental effect of chemotherapy in the elderly. Because it is not necessarily standard practice to administer chemotherapy for stage II colon cancer, this potential bias by health status may be even stronger. Furthermore, the decision for chemotherapeutic treatment may depend on disease characteristics other than stage that are linked to the progression or aggressiveness of the tumor. Thus, stage II colon cancer patients who received chemotherapy might have had more severe disease and, therefore, worse QoL at baseline. We cannot exclude the possibility that this potential difference in QoL between patients who did and did not receive chemotherapy was still present at baseline and we cannot adjust for this potential effect. However, stage was not found to be associated with long-term QoL [4]. Thus, it is unlikely that differences in baseline QoL resulting from differences in disease progression have a strong effect on long-term QoL. An assessment of and ad-

justment for baseline QoL would have reduced confounding and corroborated our findings. The gold standard design to assess chemotherapy-related differences in long-term QoL is a randomized clinical trial, but such a trial could only be performed for stage II colon cancer nowadays because a survival benefit linked to chemotherapy has already been established for rectal cancer [29] and stage III colon cancer [30].

A further caveat is that our results are based on patients with a cancer diagnosis and treatment in 2003 and 2004. Since then, treatment for colorectal cancer has changed, especially with the introduction of oxaliplatin as a chemotherapeutic agent. Only 13% of the patients who received chemotherapy in our study received oxaliplatin. Thus, results cannot be directly applied to patients who are currently receiving treatment.

In our study, the characteristics of responders and nonresponders were different. In addition, full responders had a higher QoL than short-questionnaire responders. These findings indicate that nonresponders may have a worse QoL, which could be a reason that they did not respond. Such a nonresponder bias would lead to an overestimation of the QoL of survivors in our study. However, the impact of this potential selection bias on our overall findings may be small given the response rate of 90% and the small differences in response according to stage and history of chemotherapy.

Further limitations of our study are the sample size, which was too small to do further subgroup analyses, and the combined analysis of colon and rectal cancer survivors. Strengths are the population-based design, high response rate, and almost complete stage and therapy information.

The chemotherapy-associated survival benefit for stage III colon and rectal cancer patients is very high and, thus, the reported association between QoL and chemotherapy in younger survivors does not directly influence any treatment decision. However, our

results describe long-term effects on QoL and provide important implications for treatment decisions in cases of uncertain chemotherapy survival benefits, like in stage II colon cancer patients. In these cases, the potential detrimental effects should be incorporated for a final decision on treatment. In addition, clinicians should inform patients about the potential consequences of treatment.

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