

Efficacy of Surgery and Adjuvant Therapy in Older Patients With Colorectal Cancer

A STROBE-compliant article

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Abstract: The present study aimed to assess the efficacy of surgery and adjuvant therapy in older patients (age ≥ 70 years) with colorectal cancer (CRC). Older CRC patients are under-represented in available clinical trials, and therefore their outcomes after receiving surgery and adjuvant therapy are unclear. From two prospective Swedish databases, we assessed a cohort of 1021 patients who underwent curative surgery for stage I, II, or III primary CRC, with or without adjuvant chemotherapy/radiotherapy. Of the patients with colon cancer ($n=467$), 182 (39%) were aged <70 years, 162 (35%) aged 70 to 80 years, and 123 (26%) were aged ≥ 80 years. Of rectal cancer patients ($n=554$), 264 (48%) were aged <70 years, 234 (42%) aged 70 to 80 years, and 56 (10%) aged ≥ 80 years. Older patients with either colon or rectal cancer had higher comorbidity than did younger patients. Older patients with colon cancer had equivalent postoperative morbidity and 30-day mortality to younger patients. Rectal cancer patients aged ≥ 80 years had a higher 30-day mortality than younger patients (odds ratio [OR], 2.37; 95% confidence interval [CI], 1.6–4.55; $P=0.03$). For either colon or rectal cancer, adjuvant chemotherapy compromised the 5-year overall survival (OS) of older patients with stage II disease and had no effect on those with stage III disease. Receiving adjuvant chemotherapy was a poor factor of OS for older patients with either colon (HR 1.88,

95% CI: 1.20–4.35, $P=0.03$) or rectal cancer (HR 1.72, 95% CI: 1.05–2.26, $P=0.004$). Preoperative short-course radiotherapy improved both OS and local control for older patients with stage III rectal cancer and had no effect on those with stage II disease. Radiotherapy was a favorable factor for the OS of the older patients with rectal cancer (HR 0.42, 95% CI: 0.21–3.57, $P=0.01$). In conclusion, Older CRC patients had equal safety of surgery as younger patients, except rectal cancer patients aged ≥ 80 years that had a higher mortality. Adjuvant 5FU-based chemotherapy did not benefit older CRC patient, while neoadjuvant radiotherapy improved the prognosis of older patients with stage III rectal cancer.

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Abbreviations: CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, HR = hazard ratio, OR = odds ratio, OS = overall survival, RT = radiotherapy.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the leading cause of cancer-related death worldwide. Most CRC patients are over 65 years old. Of the old patients, more than half are over 70 years old and one fourth of them are over 80 years old.^{1,2} The probability of developing CRC is around 1.0% to 1.5% in a population aged 60 to 69 years, 4.0% to 5.0% in a population aged ≥ 70 years while.¹ With continued population aging and an increasing life expectancy, oncologists will confront increasing numbers of older CRC patients in the near future.

As older patients may have multiple comorbidities requiring polypharmacy, and have a decreased reserve capacity, treating them is more complicated and as such they are often under-treated compared with younger patients. A large systematic review showed that older CRC patients were less likely to be offered curative surgery or adjuvant therapy than their younger counterparts.³ Chang et al⁴ reported that for rectal cancer patients aged ≥ 70 years, each half-decade increase in age was associated with a decreased receipt of cancer-directed surgery and adjuvant therapy. This under-treatment could be explained by patients' preferences or by surgeons' opinions regarding patients of advanced age. Actually, neither surgeons nor patients could get any clear guidance for the treatment of older CRC patients from available literatures.

Compared with younger patients, fewer older CRC patients were recruited for clinical trials, possibly because of eligibility criteria that specify performance status and comorbidity requirements.^{5,6} Patients older than 65 years only

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accounted for 40% of those enrolled in clinical trials within the United States, while more than 70% of CRC patients surpassed this age limit.⁷ Similar results were reported by other recent studies.^{8,9} As older CRC patients are under-represented in clinical trials, it remains unclear whether surgery and adjuvant therapy are effective in this population. Therefore, we assessed the efficacy of curative surgery, 5-FU/leucovorin regimen, and neoadjuvant short-course radiotherapy in older CRC patient in the present study.

PATIENTS AND METHODS

Patients and Data Acquisition

Between 1990 and 2001, consecutive patients who had undergone curative surgery for stage I, II, or III primary CRC in the Southeast Swedish Health Care region were included in this study, as well as patients who participated in a randomized Swedish rectal cancer trial involving preoperative radiotherapy (RT).¹⁰ Patients received only local excision and patients with a family history of CRC, familial adenomatous polyposis, inflammatory bowel disease, or hereditary nonpolyposis CRC or distant metastasis were excluded. All clinicopathological data were recorded prospectively. TNM stages were classified according to the AJCC Cancer Staging Manual (7th ed).¹¹ Patient comorbidities were scored by Charlson Comorbidity Index.¹² Follow-up was performed by matching all patients against the Swedish Cancer Register and the Cause of Death Register until July 2006. The median follow-up period was 85 months (range, 0–196 months). Three age groups, <70, 70 to 80, and ≥80 years, were compared with regard to clinicopathological features, local/distant recurrence, 5-year overall survival (OS), and disease-free survival (DFS).

Short-course neoadjuvant RT and adjuvant chemotherapy were recommended for patients with stage II or III rectal cancer. Patients with stage II colon cancer at high risk of recurrence (poorly differentiated histology, lymphatic/vascular invasion, bowel obstruction, localized perforation, or positive margins) or stage III disease were recommended for adjuvant chemotherapy. Neoadjuvant RT for rectal cancer was given at a total of 25 Gy in 5 fractions over a median of 6 days (range, 5–12 days), delivered with 6 to 10 MV photons. Surgery was then performed after a median of 3 days (range, 1–13 days) after neoadjuvant RT. Adjuvant chemotherapy with intravenous fluorouracil (370 mg/m²) and with high-dose (175 mg) or low-dose (25 mg) L-folinic acid was delivered within 1 month of surgery as six 5-day courses every 4 weeks. Written informed consent was obtained from all subjects. This study was approved by the institutional review board of Linköping University, Sweden.

Statistical Analysis

All statistical analyses were performed by using the STATA software package (version 10.0; STASOFT Inc, Tulsa, OK). The associations between categorical variables were analyzed by using Pearson's χ^2 test. Comparison of Charlson Comorbidity Index scores was analyzed by Variance test. Correlations of the variables with postoperative 30-day mortality were analyzed by using a logistic regression model. Survival analysis was performed by using the Kaplan–Meier method and a log-rank test followed by a Cox proportional hazards regression model. OS (censored at 5 years) was defined as the period from the date of diagnosis to the date of death from all causes. DFS (censored at 5 years) was defined as the number of years from a curative surgery to the first of either disease

recurrence or death. The test was two-sided, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patient Cohort

A total of 1021 eligible patients with primary colon cancer (*n* = 467) or rectal cancer (*n* = 554) were enrolled in this study. Of colon cancer patients, 182 (39%) were aged <70 years, 162 (35%) aged 70 to 80 years, and 123 (26%) were aged ≥80 years, and 149 (31.9%) received 5-FU-based adjuvant chemotherapy. Of rectal cancer patients, 264 (48%) were aged <70 years, 234 (42%) aged 70 to 80 years, and 56 (10%) aged ≥80 years. Of them, 101 (18.2%) received 5-FU-based adjuvant chemotherapy and 190 (34.3%) received short-course neoadjuvant RT. For either colon or rectal cancer, the proportions of patients receiving adjuvant chemotherapy or radiotherapy seemed lower in patients aged 70 to 80 years or ≥80 years than those aged <70 years, while the differences were not statistically significant (Table 1). The clinico-pathologic features of patients are shown in Table 1. There was no significant difference among age groups regarding the proportions of gender, TNM stages, tumor differentiations, tumor numbers, and tumor growth pattern (*P* > 0.05). According to Charlson Comorbidity Index, the patients aged ≥70 years had higher comorbidity score than the patients aged <70 years, for both colon cancer (*P* = 0.03) and rectal cancer (*P* = 0.02). The most common comorbidities were chronic pulmonary disease, peripheral vascular disease, diabetes, and cerebrovascular disease. There was no statistical difference of postoperative morbidity between age groups in both colon cancer (*P* = 0.73) and rectal cancer patients (*P* = 0.54). Wound infection, pulmonary infection, anastomotic leakage, and bowel obstruction were the most common postoperative complications.

The postoperative 30-day mortality was not statistically different among age groups for colon cancer patients (2.2% in <70 years group, 3.0% in 70–80 years group, and 5.7% in ≥80 years group; *P* = 0.13). For rectal cancer, the patients aged ≥80 years had higher 30-day mortality (4/56; 7.1%) than those aged 70 to 80 years (6/234; 2.6%) and those aged <70 (5/264; 1.9%) (*P* = 0.008). By a multivariate analysis, 30-day mortality was positively related to the age of the rectal cancer patients (≥80 vs <80 years; odds ratio [OR], 2.37; 95% confidence interval [CI], 1.6–4.55; *P* = 0.03), as well as postoperative morbidity for both colon cancer patients (OR, 1.41; 95% CI, 1.30–3.52; *P* < 0.001) and rectal cancer patients (OR, 1.26; 95% CI, 1.03–5.32; *P* = 0.002).

Older Patients Had Comparable Survival to Younger Patients

For colon cancer patients, the OS and DFS rates were 64% and 61%, respectively, for patients aged <70 years; 64% and 59%, respectively, for patients aged 70 to 80 years; and 52% and 46%, respectively, for patients aged ≥80 years. There was no significant difference of either OS or DFS among age groups (*P* = 0.62; 0.14, respectively). For rectal cancer patients, the OS and DFS rates were 67% and 59%, respectively, for patients aged <70 years; 64% and 58%, respectively, for patients aged 70 to 80 years; and 53% and 50%, respectively, for patients aged ≥80 years. The difference of either OS or DFS was not significant among age groups (*P* = 0.11; 0.08, respectively). By multivariate analysis, older age (≥70 years) was not an independent prognostic factor for the OS of the patients with

TABLE 1. Characteristics of Colorectal Cancer Patients and Tumors According to Age Groups

Variables	Colon cancer (n = 467)			P value	Rectal cancer (n = 554)			P value
	<70 years n (%)	70–80 years n (%)	≥80 years n (%)		<70 years n (%)	70–80 years n (%)	≥80 years n (%)	
Total number of patients	182 (38.9)	162 (34.7)	123 (26.4)		264 (47.7)	234 (42.2)	56 (10.1)	
Gender				0.77				0.69
Male	88 (48.4)	80 (69.8)	55 (44.7)		158 (60.8)	137 (58.5)	31 (55.4)	
Female	94 (51.6)	82 (30.2)	68 (55.3)		106 (40.2)	97 (41.5)	25 (44.6)	
TNM stages				0.08				0.12
I	36 (19.7)	30 (18.5)	20 (16.3)		71 (26.9)	83 (35.5)	7 (12.5)	
II	64 (35.2)	50 (30.9)	35 (28.5)		92 (34.8)	70 (29.9)	18 (32.1)	
III	82 (45.1)	82 (50.6)	68 (55.2)		101 (38.3)	81 (34.6)	31 (55.4)	
Tumor differentiation				0.45				0.87
Good + moderate	133 (73.1)	103 (63.6)	81 (65.9)		209 (79.2)	192 (72.1)	46 (82.1)	
Poor	49 (26.9)	59 (36.4)	42 (34.1)		55 (20.8)	42 (17.9)	10 (17.9)	
Tumor numbers				0.16				0.07
Single	168 (92.4)	141 (87.1)	101 (82.1)		248 (93.9)	216 (92.7)	48 (87.5)	
Multiple	14 (7.6)	21 (12.9)	22 (17.9)		16 (6.1)	18 (7.7)	7 (12.5)	
Tumor growth pattern				0.13				0.57
Expansive	104 (57.1)	96 (59.3)	77 (62.6)		135 (51.1)	138 (59.0)	37 (66.1)	
Infiltrative	78 (42.9)	66 (40.7)	46 (37.4)		129 (48.9)	96 (41.0)	19 (33.9)	
Comorbidities				0.003				0.01
None	124 (70.3)	104 (64.2)	69 (56.1)		199 (75.4)	147 (62.8)	37 (66.1)	
One or more	52 (29.7)	58 (35.8)	54 (43.9)		65 (24.6)	87 (37.2)	19 (33.9)	
Charlson comorbidity index (mean ± SD)	3.5 ± 0.5	4.8 ± 0.3	6.2 ± 1.0	0.03	4.0 ± 0.7	5.0 ± 0.4	6.5 ± 0.4	0.02
Surgical type				0.83				0.36
Right hemicolectomy	99 (54.4)	83 (51.2)	69 (56.1)		–	–	–	
Left hemicolectomy	20 (10.9)	18 (11.1)	16 (13.0)		–	–	–	
Transverse colectomy	63 (34.7)	61 (37.7)	38 (30.9)		–	–	–	
Anterior resection	–	–	–		216 (81.8)	178 (76.1)	43 (76.8)	
Abdominoperineal	–	–	–		48 (11.2)	56 (23.9)	13 (23.2)	
Radiotherapy				0.72				0.08
No	182 (100)	162 (100)	123 (100)		169 (64.0)	152 (65.0)	43 (76.9)	
Adjuvant	0 (0)	0 (0)	0 (0)		95 (36.0)	82 (35.0)	13 (23.1)	
Chemotherapy				0.10				0.39
No	118 (94.8)	154 (72.6)	112 (71.5)		213 (80.7)	194 (82.9)	46 (82.1)	
Adjuvant	64 (35.2)	50 (27.4)	35 (28.5)		51 (19.3)	40 (17.1)	10 (17.9)	
Postoperative morbidity				0.73				0.54
No	150 (82.4)	130 (80.2)	98 (79.2)		189 (71.6)	160 (68.4)	36 (64.3)	
Yes	32 (17.6)	32 (19.8)	25 (20.8)		75 (28.4)	74 (31.6)	20 (35.7)	
Postoperative 30-day mortality				0.13				0.008
No	178 (97.8)	157 (96.9)	116 (94.3)		259 (98.1)	228 (97.4)	52 (92.9)	
Yes	4 (2.2)	5 (3.0)	7 (5.7)		5 (1.9)	6 (2.6)	4 (7.1)	

(%) Indicates the proportion of patients with a specific clinical or pathologic feature in each age group. P, Pearson’s χ^2 test or Variance test, SD = standard deviation.

Bold value, the P value with statistical significance.

either colon cancer (HR 1.13, 95% CI: 0.62–2.91, $P=0.18$) or rectal cancer (HR 1.64, 95% CI: 1.02–2.83, $P=0.09$) (Table 2A).

Older Patients Did Not Benefit From Adjuvant Chemotherapy

To further clarify the role of adjuvant chemotherapy, older patients (≥ 70 years) were stratified into two groups of “adjuvant chemotherapy” and “no adjuvant chemotherapy”. As shown in Table 3, the patients that received adjuvant chemotherapy had more poor prognostic factors including more advanced stage (stage III, 70.6% vs 45.0%; $P=0.007$, for colon cancer; 64.0% vs 33.3%; $P<0.001$, for rectal cancer), and more tumors with poor differentiation (52.9% vs 28.0%; $P=0.03$, for

colon cancer; 52.0% vs 25.0%; $P=0.02$, for rectal cancer). There had no other significant differences of patient, tumor, and treatment characteristics between groups.

For older patients with either colon or rectal cancer, those received adjuvant chemotherapy showed worse OS (48.5% vs 61.3%, $P=0.02$; 47.5% vs 68.2%, $P=0.01$, respectively; Figure 1A, B) while similar 5-year DFS (40.5% vs 56.7%, $P=0.11$; 42.3% vs 54.4%, $P=0.22$, respectively), and similar local recurrence rate (4.3% vs 4.5%, $P=0.36$; 4.0% vs 6.0%, $P=0.28$, respectively) and distant recurrence rate (10.6% vs 11.1%, $P=0.94$; 10.0% vs 17.1%, $P=0.19$, respectively), compared with those without chemotherapy. When stratified by TNM stages, patients with stage II colon or rectal cancer who received adjuvant chemotherapy showed worse OS (71.5% vs 85.4%, $P=0.039$; 73.6% vs 89.2%, $P=0.01$, respectively)

TABLE 2. Multivariate Model of Overall Survival for the Patients With Colorectal Cancer

Variables	Hazard ratio (95% CI)	P-value	
(A). Entire patients			
Age, ≥ 70 vs < 70	Colon cancer Rectal cancer	1.13 (0.62–2.91) 1.64 (1.02–2.83)	0.18 0.09
TNM stage, III vs (I + II)	Colon cancer Rectal cancer	3.20 (1.65–8.51) 3.05 (1.25–9.37)	< 0.001 < 0.001
Tumor differentiation, poor vs (good + moderate)	Colon cancer Rectal cancer	1.27 (1.33–5.31) 1.36 (0.46–2.87)	0.01 0.01
Postoperative morbidity, yes vs no	Colon cancer Rectal cancer	1.22 (0.74–2.15) 1.15 (0.38–4.01)	0.02 0.02
Adjuvant chemotherapy, yes vs no	Colon cancer Rectal cancer	0.21 (0.14–0.85) 0.46 (0.28–0.72)	0.03 0.005
Adjuvant radiotherapy, yes vs no	Rectal cancer	0.25 (0.20–0.90)	0.018
(B). Patients aged ≥ 70 years			
TNM stage, III vs (I + II)	Colon cancer Rectal cancer	2.10 (1.26–3.45) 1.84 (1.38–3.03)	0.005 0.01
Postoperative morbidity, yes vs no	Colon cancer Rectal cancer	1.62 (0.74–2.15) 1.47 (1.05–3.44)	0.03 0.01
Adjuvant chemotherapy, yes vs no	Colon cancer Rectal cancer	1.88 (1.20–4.35) 1.72 (1.05–2.26)	0.03 0.004
Adjuvant radiotherapy, yes vs no	Rectal cancer	0.42 (0.21–0.77)	0.018

CI = confidence interval.

while similar 5-year DFS (65.4% vs 70.5%, $P = 0.23$; 67.5% vs 72.8%, $P = 0.14$, respectively), and similar local recurrence rate (2.5% vs 3.6%, $P = 0.68$; 6.8% vs 8.0%, $P = 0.82$, respectively) and distant recurrence rate (7.4% vs 8.1%, $P = 0.24$; 5.6% vs 6.4%, $P = 0.75$, respectively), compared with those without chemotherapy. For patients with stage III colon or rectal cancer, those received adjuvant chemotherapy showed similar OS (52.5% vs 45.0%, $P = 0.11$; 51.4% vs 41.8%, $P = 0.77$, respectively; Figure 1C, D) and DFS (49.6% vs 40.8%, $P = 0.23$; 48.2% vs 43.5%, $P = 0.46$, respectively), and similar local recurrence rate (5.2% vs 4.8%, $P = 0.39$; 9.3% vs 8.5%, $P = 0.20$, respectively) and distant recurrence rate (15.1% vs 14.5%, $P > 0.99$; 12.6% vs 16.4%, $P = 0.32$, respectively), compared with those without chemotherapy. By multivariate analysis, adjuvant chemotherapy was an independent poor prognostic factor for the OS of the older patients with either colon cancer (HR 1.88, 95% CI: 1.20–4.35, $P = 0.03$) or rectal cancer (HR 1.72, 95% CI: 1.05–2.26, $P = 0.004$) (Table 2B).

Older Patients With Stage III Rectal Cancer Benefited From Neoadjuvant RT

The efficacy of neoadjuvant RT was analyzed between two groups of “neoadjuvant RT” and “no neoadjuvant RT” in rectal cancer patients. For patients aged < 70 years, those received neoadjuvant RT ($n = 150$) showed significantly better OS (78.2% vs 67.0%, $P = 0.023$) and DFS (72.0% vs 62.5%, $P = 0.015$), lower local recurrence rate (4.1% vs 5.9%, $P = 0.021$) and similar distant recurrence rate (18.2% vs 17.5%, $P = 0.53$), compared with those without neoadjuvant RT ($n = 114$). When stratified by TNM, patients with either stage II or III disease got the same benefit from neoadjuvant RT (data not shown). By multivariate analysis, neoadjuvant RT was related to a better OS of the patients (HR 0.32, 95% CI: 0.15–2.6, $P = 0.032$).

In patients aged ≥ 70 years, the clinico-pathologic characteristics, such as TNM stages, tumor differentiations, morbidity and mortality, etc, were not significantly different between groups as shown in Table 3. Patients that received neoadjuvant

RT ($n = 95$) showed significantly better OS (74.7% vs 63.0%, $P = 0.01$) and DFS (70.2% vs 60.4%, $P = 0.03$), lower local recurrence rate (3.2% vs 6.7%, $P = 0.02$) and similar distant recurrence rate (16.8% vs 15.4%, $P = 0.64$), compared with those without neoadjuvant RT ($n = 195$) (Table 3).

For older patients with stage II disease, the OS and DFS (Figure 2A, B) as well as local/distant recurrence rate were not significantly different between those received neoadjuvant RT and those without neoadjuvant RT (data not shown). For older patients with stage III disease, those who received neoadjuvant RT showed significantly better OS (77.5% vs 45.6%, $P = 0.003$) and DFS (74.2% vs 42.7%, $P = 0.006$) (Figure 2C, D), lower local recurrence rate (5.2% vs 10.2%, $P = 0.03$) and similar distant recurrence rate (18.2% vs 16.5%, $P = 0.52$), compared with those without neoadjuvant RT. By multivariate analysis, neoadjuvant RT was a favorable factor for the OS of the older patients (HR 0.42, 95% CI: 0.21–3.57, $P = 0.018$) (Table 2B). When analyzing all stage III patients without age classification, neoadjuvant RT was still related to a better OS of the patients (HR 0.45, 95% CI: 0.2–3.1, $P = 0.005$).

DISCUSSION

Older patients may have a higher comorbidity and lower reserve capacity than younger patients. With this concern, older CRC patients are less likely to be offered curative surgery than their younger counterparts, as shown by a large review including more than 34,000 patients.³ However, available studies on this issue yielded inconsistent results, showing either equal or higher morbidity/mortality in older patients than in younger patients.^{3,13,14} The majority of studies did not perform sub-analysis of colon cancer and rectal cancer, nor of emergency surgery and elective surgery.³ In the present study, we found that, compared to younger counterparts, older patients with either colon or rectal cancer had a higher comorbidity but an equivalent morbidity and mortality, except that rectal cancer patients aged ≥ 80 years had a higher risk of postoperative death. This finding indicates that older CRC patients, except rectal cancer patients aged ≥ 80 years, have equivalent safety of

TABLE 3. Comparison Between Adjuvant Therapy Group and No Adjuvant Therapy Group in Older Patients (≥70 years) With Colorectal Cancer

Variables	Older colon cancer patient (n = 285)			Older rectal cancer patient (n = 290)					
	Chemo- Therapy (n = 85) n (%)	No Chemo-therapy (n = 200) n (%)	P value	Chemotherapy (n = 50) n (%)	No Chemotherapy (n = 240) n (%)	P value	Radiotherapy (n = 95) n (%)	No radiotherapy (n = 195) n (%)	P value
Mean age, years	78.9	76.7	0.48	74.1	76.5	0.515	75.1	76.5	0.21
Gender			0.33			0.844			0.48
Male	33 (38.8)	102 (51.0)		18 (36.0)	115 (47.9)		29 (30.5)	104 (53.3)	
Female	52 (61.2)	98 (49.0)		32 (64.0)	125 (52.1)		66 (69.5)	91 (46.7)	
TNM stages			0.007			<0.001			0.18
I	0	50 (25.0)			90 (37.5)		15 (15.8)	75 (38.5)	
II	25 (29.4)	60 (30.0)		18 (36.0)	70 (29.2)		32 (33.7)	56 (28.7)	
III	60 (70.6)	90 (45.0)		32 (64.0)	80 (33.3)		48 (50.5)	64 (32.8)	
Tumor differentiation			0.03			0.02			0.63
Good + moderate	40 (47.1)	144 (72.0)		24 (48.0)	180 (75.0)		45 (47.4)	159 (81.5)	
Poor	45 (52.9)	56 (28.0)		26 (52.0)	60 (25.0)		50 (52.6)	36 (18.5)	
Tumor numbers			0.10			0.43			0.46
Single	85 (89.5)	167 (83.5)		45 (90.0)	204 (85.0)		76 (88.0)	173 (88.7)	
Multiple	10 (10.5)	33 (16.5)		5 (10.0)	36 (15.0)		19 (12.0)	22 (11.3)	
Tumor growth pattern			0.37			0.07			0.38
Expansive	53 (62.4)	120 (60.0)		33 (66.0)	137 (57.1)		62 (65.3)	108 (79.5)	
Infiltrative	32 (37.6)	80 (40.0)		17 (34.0)	103 (42.9)		33 (34.7)	87 (20.5)	
Comorbidities			0.55			0.38			0.73
None	55 (64.8)	118 (59.0)		30 (60.0)	154 (64.2)		61 (64.2)	123 (63.1)	
One or more	30 (35.2)	82 (41.0)		20 (40.0)	86 (35.8)		34 (35.8)	72 (36.9)	
Radiotherapy						0.11			
No	85 (100.0)	200 (0)		28 (56.0)	175 (72.9)		–	–	
Adjuvant	0 (0)	0 (0)		22 (44.0)	65 (27.1)		–	–	
Chemotherapy									0.05
No	–	–		–	–		84 (88.4)	156 (80.0)	
Adjuvant	–	–		–	–		11 (11.6)	39 (20.0)	
Postoperative morbidity			0.31			0.22			0.72
No	76 (89.4)	152 (76.0)		32 (64.0)	165 (68.8)		54 (56.8)	119 (61.1)	
Yes	9 (10.6)	48 (24.0)		18 (36.0)	75 (31.2)		41 (43.2)	76 (38.9)	
Postoperative 30-day mortality			0.39			0.25			0.93
No	81 (95.3)	192 (96.1)		47 (94.0)	228 (95.0)		94 (98.9)	190 (97.4)	
Yes	4 (4.7)	8 (3.9)		3 (6.0)	12 (5.0)		1 (1.1)	5 (2.6)	
Local recurrence			0.36			0.28			0.02
No	48 (95.7)	110 (95.5)		48 (96.0)	226 (94.0)		92 (96.8)	182 (93.3)	
Yes	37 (4.3)	90 (4.5)		2 (4.0)	14 (6.0)		3 (3.2)	13 (6.7)	
Distant recurrence			0.94			0.19			0.64
No	76 (99.4)	178 (88.9)		45 (90.0)	199 (82.9)		49 (83.2)	195 (84.6)	
Yes	9 (10.6)	22 (11.1)		5 (10.0)	41 (17.1)		16 (16.8)	30 (15.4)	
5-year cumulative survival (%)									
Overall survival	48.5	61.3	0.02	47.5	68.2	0.01	74.7	63.0	0.01
Disease-free survival	40.5	56.7	0.11	42.3	54.4	0.22	70.2	60.4	0.03

P indicates the comparison of variables between adjuvant therapy and no adjuvant therapy within each cohort. Bold value, the P value with statistical significance.

a curative surgery to younger patients regardless of a higher comorbidity.

For older CRC patients who underwent curative resection, trends in age-related survival are less clear.^{2,3,4} In available literatures, there were studies reporting either a worse OS but an equivalent cancer-specific survival (CSS), or an equal DFS but a worse CSS in older CRC patients, compared to in younger counterparts.^{5,6,15,16} These studies are either retrospective or mainly included fit older patients with good performance status. Additionally, there is considerable variation in the way in which outcomes are reported, which limits comparison of different series. In the present study, the patient data were drawn from

prospective databases and the older patients showed higher comorbidity than the younger patients. We found that, patients aged 70 to 80 years had equivalent OS and DFS after curative surgery for either colon or rectal cancer, compared to their younger counterparts. Patients aged ≥80 years showed relative lower survival rates than their counterparts in the other two age groups, but it did not reach statistical differences. Age was not an independent prognostic factor for the OS of the patients with either colon or rectal cancer. This finding strongly supports the thought that, patients aged ≥70 years could benefit from a curative surgery for either colon or rectal cancer, regardless of their higher comorbidity.

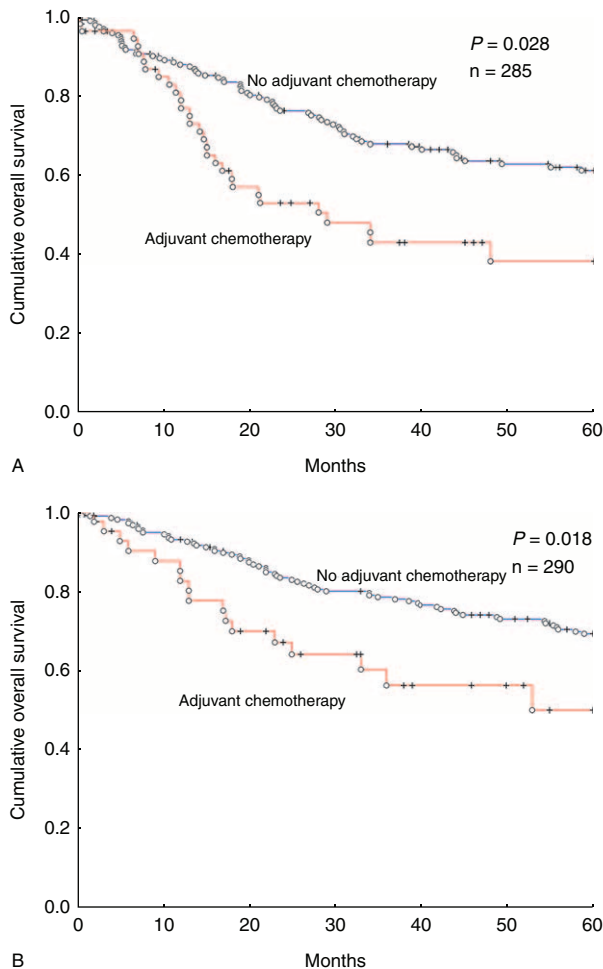


FIGURE 1. Survival curves of patients aged ≥ 70 years with (A) colon cancer or (B) rectal cancer stratified by use of adjuvant chemotherapy.

The risks and benefits of 5-Fu-based adjuvant chemotherapy for CRC have not been clearly defined in older patients. In the present study, we found that, patients aged ≥ 70 years with either colon or rectal cancer had worse OS while similar DFS and local/distant recurrence rates after adjuvant chemotherapy, compared to those without adjuvant chemotherapy. When stratified by stages, this result remained in stage II cases while no difference was seen in those with stage III disease. Adjuvant chemotherapy was an independent poor prognostic factor for the CRC patients aged ≥ 70 years. Consistent with our result, QUASAR (Quick and Simple and Reliable) trial showed a reduced benefit of 5-FU/leucovorin regimen in patients aged ≥ 70 years with stage II colon cancer.¹⁷ In contrast, Sargent et al¹⁸ showed that, CRC patients aged ≥ 70 years had an improved OS after received 5-FU/leucovorin or 5-FU/levamisole regimen. However, the DFS rate and the subgroup of stages were not analyzed in this study. Jessup et al¹⁹ showed that, octogenarians with stage III colon cancer got similar OS to younger counterpart after received 5-FU/leucovorin or 5-FU/levamisole regimen. Nevertheless, the DFS rate and tumor recurrence were not analyzed in this study. In the present study, the effects of adjuvant chemotherapy on OS, as well as DFS and tumor recurrence, were all subanalyzed by stages. Our finding

indicates that, older patients with stage II/III colon or rectal cancer could not benefit from 5-FU/leucovorin regimen.

Oxaliplatin plus 5-FU (FOLFOX) regimen has been recommended as standard adjuvant chemotherapy for stage III CRC in current practice. However, its efficacy in older patients remains controversial. The ACCENT (Adjuvant Colon Cancer Endpoints) database evaluated the benefit of FOLFOX regimen in patients aged >70 years, and found no benefit in DFS or OS of these patients with stage III disease.²⁰ On the contrary, Sanoff et al²¹ recently reported that the addition of oxaliplatin to 5-FU was associated with better survival while led to a modest increase of toxicity relative to single 5-FU regimen among patients aged >65 years. Therefore, the benefit of FOLFOX regimen remains controversial in older CRC patient. In the present study, patients who had poorer histology of tumor after receiving adjuvant chemotherapy may be candidates for FOLFOX regimen. However, they received 5-FU/leucovorin instead of FOLFOX regimen. Therefore, it is likely that the possible sub-optimal treatment, as well as the bias of poorer tumor histology, affected their survival more than the receipt of adjuvant chemotherapy.

Randomized trials have demonstrated that neoadjuvant RT combined with curative surgery improves local control and survival for patients with stage II/III rectal cancer. However, as the median age of patients in these trials is around mid-60s, older patients were underrepresented in these trials. To date, the value of neoadjuvant RT in older patients with rectal cancer is still controversial. Analysis of the Netherlands and the Dutch Trial showed that, not only was there no survival improvement in patients aged 75 years, but also had a higher mortality within 6 months with the introduction of short-course neoadjuvant RT to surgery.²² Similarly, Shahir et al²³ found no survival benefit while higher postoperative complications in rectal cancer patients aged ≥ 70 years after short-course RT and surgery, compared to younger patients. Conversely, Cai et al²⁴ reported that patients aged ≥ 70 years could achieve equal 3-year OS as younger patients after neoadjuvant RT and surgery for rectal cancer. Nevertheless, these studies did not provide the data of DFS and recurrence rate, and had no subgroup analysis of TNM stages. In the present study, we show that neoadjuvant short-course RT did not increase the morbidity and mortality of the patients aged ≥ 70 years with stage II/III rectal cancer, and improved the OS, DFS and local control of them with stage III disease, while had no effect on stage II cases. Neoadjuvant RT was a favorable prognostic factor for the older rectal cancer patients. This finding indicates that, short-course neoadjuvant RT is safe and effective for the older patients with stage III rectal cancer but not for those with stage II disease.

This study had limitations inherent to the databases. We could not evaluate CSS as the related data were incomplete in the databases. By using DFS data, we endeavored to minimize the impact of this limitation. The second limitation of this study is a lack of data regarding the evaluation of performance status for older patients. Patients with a limited performance status may have a lower tolerance to surgery and inferior clinical outcomes, as compared with younger patients. Unfortunately, this study could not determine the impact of performance status on the postoperative mortality and prognosis of older patients. Another limitation is the insufficiency of concordance with current standard therapy. The neoadjuvant RT used in this study was only short-course regimen without concurrent chemotherapy. In addition, the adjuvant chemotherapy for stage III CRC was 5-FU/leucovorin rather than 5-FU/oxaliplatin regimen.

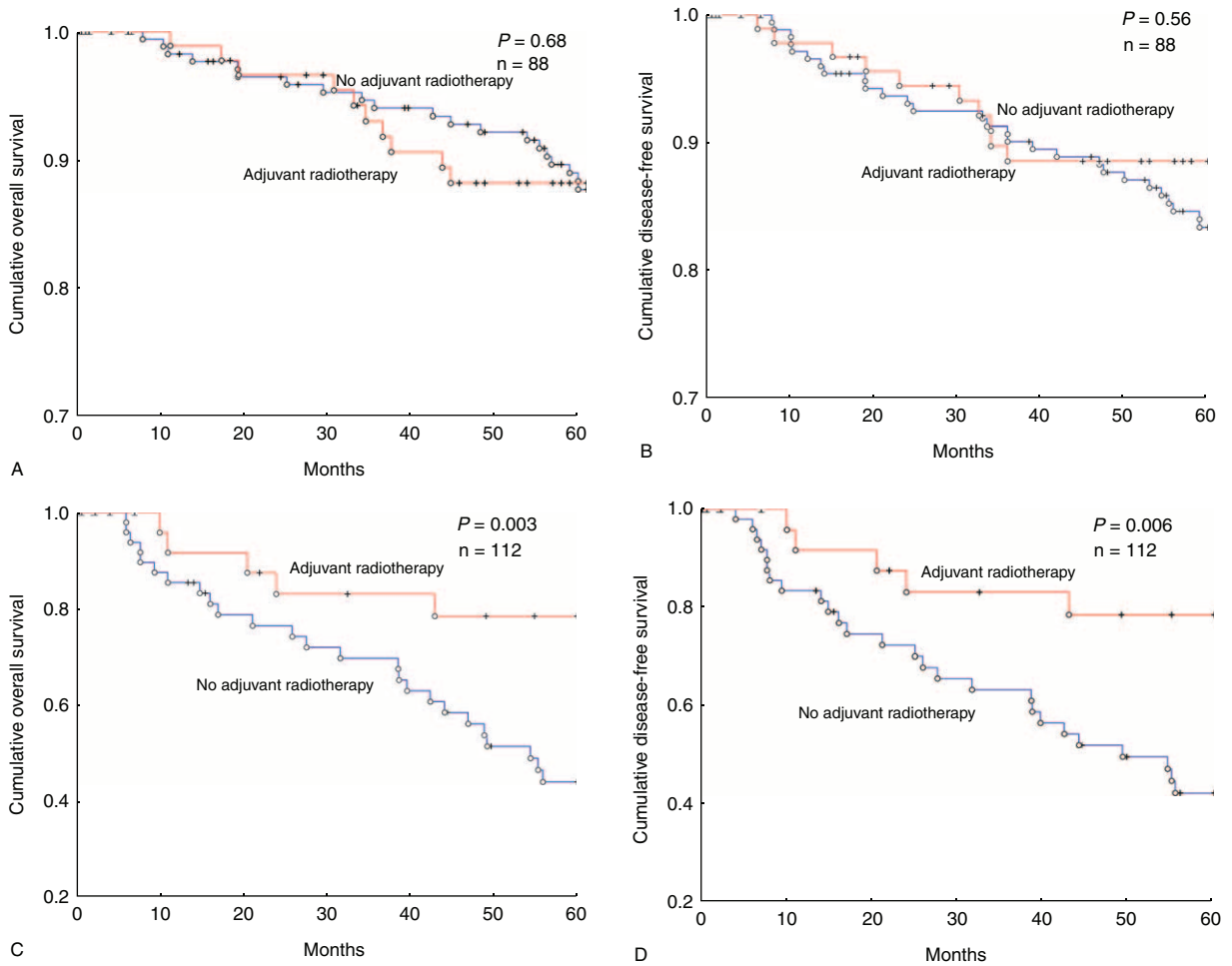


FIGURE 2. Survival curves of patients aged ≥ 70 years with stage II (A, B) or III (C, D) rectal cancer stratified by use of neoadjuvant radiotherapy.

The efficacies of long-course RT and other standard regimens of adjuvant chemotherapy in older CRC patient were not investigated in this study. This limits the role of the present study in influencing current clinical practice.

CONCLUSIONS

In conclusion, patients aged ≥ 70 years had equivalent outcomes to younger patients after curative CRC surgery, except rectal cancer patients aged ≥ 80 years had a higher mortality. Adjuvant chemotherapy with 5-Fu/Leucovorin regimen could not improve the long-term outcomes of older patients with either colon or rectal cancer. Short-course neoadjuvant RT improved both survival and local control for older patients with stage III rectal cancer while had no effect on stage II cases, and it did not increase morbidity and mortality. These findings demonstrate that, curative surgery is safe for older CRC patients except rectal patients aged ≥ 80 years had higher mortality. Older CRC patients could not benefit from single 5-FU-based adjuvant chemotherapy, and short-course neoadjuvant RT is safe and favorable for older patients with stage III rectal cancer.

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