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Advanced Age Is a Risk Factor for Recurrence After Resection in Stage II Colorectal Cancer

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Abstract. *Background/Aim: The number of older patients with colorectal cancer (CRC) is increasing. Stage II CRC is a heterogeneous group of cancers with different prognoses. We aimed to examine older patients in relation to clinical outcome following curative resection in stage II CRC. Patients and Methods: We analyzed data for 329 consecutive patients with stage II CRC following curative resection. Recurrence-free survival (RFS) and overall survival (OS) were compared between older patients ≥75 years of age and those <75 years. Cox proportional hazards model was used to compute hazard ratios (HRs) controlling for potential confounders. Results: In the multivariable analyses, patients ≥75 years were independently associated with shorter RFS (multivariable HR=2.56, 95% confidence interval (CI)=1.55-4.31, p<0.001) and OS (multivariable HR=4.36, 95%CI=2.08-9.97, p<0.001) in stage II CRC. Conclusion: Older patients were independently associated with shorter RFS and OS following curative resection in stage II CRC.*

Colorectal cancer is the most common cancer in Japan and the third most common cancer worldwide (1, 2). Surgery with complete resection represents a potentially curative treatment for most patients with stage I or II colorectal cancer (3, 4). Although the current standard treatment for stage III colorectal cancer is curative surgery and adjuvant chemotherapy, the benefit of adjuvant chemotherapy in patients with stage II colorectal cancer remains controversial (5).

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Stage II colorectal cancer is a heterogeneous group of cancers with differing biology (6). Large-scale studies demonstrate that patients with stage II colorectal cancer have widely different prognoses (7-9). Western clinical guidelines indicate: i) T4 stage, ii) fewer than 12 examined lymph nodes, iii) bowel perforation and obstruction, iv) lymphatic and venous invasion, and v) poorly differentiated tumors as poor prognostic factors in stage II colorectal cancer and recommend adjuvant chemotherapy for patients presenting these 'high-risk' features (10, 11). Unfortunately, the benefit of adjuvant chemotherapy for such patients has not been confirmed yet (5, 12). Hence, identifying predictive biomarkers for the selection of patients with stage II colorectal cancer who benefit from adjuvant chemotherapy are important.

Due to low birth and high longevity rates many populations around the world are aging rapidly, resulting in an increasing requirement for surgery to treat gastrointestinal cancer in older patients (13-16). Because many clinical trials for colorectal cancer have not included patients with colorectal cancer ≥75 years of age (17-19), there is a lack of evidence-based guidelines for older patients with colorectal cancer, who usually have age-related compromised organ function and host immunity (20, 21). Here we tested the hypothesis that older patients may suffer worse clinical outcomes following curative resection in stage II colorectal cancer.

Patients and Methods

Patients. We retrospectively analyzed data for consecutive patients with pathological stage II colorectal cancer who underwent D3 lymph node dissection at the National Hospital Organization Kumamoto Medical Center between January 2009 and December 2016. The main inclusion criteria were as follows: i) histologically confirmed stage II colorectal adenocarcinoma following curative resection, ii) no prior chemotherapy or radiotherapy for colorectal cancer, and iii) no other active malignancy.

Recurrence-free survival (RFS) was defined as the time to recurrence or death. Overall survival (OS) was calculated from

Table I. *Patient characteristics according to age group.*

Characteristics*	All patients (n=329)	<75 years (n=158)	≥75 years (n=171)	*p*-Value†
Gender				0.009
Men	167 (51%)	92 (58%)	75 (44%)	
Women	162 (49%)	66 (42%)	96 (56%)	
Body mass index (kg/m^2)				0.11
<25	268 (81%)	123 (78%)	145 (85%)	
≥25	61 (19%)	35 (22%)	26 (15%)	
ASA-PS				0.048
1 or 2	244 (74%)	125 (79%)	119 (70%)	
3 or 4	85 (26%)	33 (21%)	52 (30%)	
Obstruction or perforation				0.16
Absent	284 (86%)	132 (84%)	152 (89%)	
Present	45 (14%)	26 (16%)	19 (11%)	
Emergency operation				0.48
Absent	316 (96%)	153 (97%)	163 (95%)	
Present	13 (4.0%)	5 (3.2%)	8 (4.7%)	
Tumor location				0.003
Appendix, caecum, ascending colon, transverse colon	133 (40%)	49 (31%)	84 (49%)	
Descending colon, sigmoid colon, rectosigmoid junction	143 (43%)	77 (49%)	66 (39%)	
Rectum	53 (16%)	32 (20%)	21 (12%)	
CEA				0.37
<5	173 (53%)	79 (50%)	94 (55%)	
≥5	156 (47%)	79 (50%)	77 (45%)	
CA19-9				0.66
<37	284 (86%)	135 (85%)	149 (87%)	
≥37	45 (14%)	23 (15%)	22 (13%)	
Prognostic Nutritional Index				<0.001
Median (IQR)	57 (46-71)	62 (49-79)	54 (43-63)	

ASA: The American Society of Anesthesiologists; ASA-PS: ASA physical status classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9, IQR: interquartile range. *Categorical variables are presented as proportions. Non-normally distributed variables are reported as medians with interquartile ranges. †Categorical data were compared using the chi-square test or Fisher's exact test. Non-normally distributed data were compared using the Mann-Whitney *U*-test.

surgery to death from any cause. A single institutional pathologist diagnosed the i) depth of wall invasion, ii) status of lymph node metastasis, iii) histopathological differentiation, and iv) the degree of lymphatic and venous invasion, based on the Japanese Classification of Colorectal Carcinoma (1, 22). Postoperative complications were recorded and graded as defined by the Clavien-Dindo classification system (23, 24). Preoperative blood samples were obtained within two weeks before resection for colorectal cancer. The prognostic nutritional status was calculated on the basis of admission data as follows: 10× serum albumin (g/dl)+0.005× total lymphocyte count (per mm^3) (25). The definition of anastomotic leakage was used as previously reported in clinical trials (26, 27); peritonitis from any staple line, and pelvic abscess without radiologically proven leakage mechanism were included. Leakage was verified by i) clinical (inspection of drain contents), ii) endoscopic (flexible sigmoidoscopy), or iii) radiologic (rectal contrast study, computed tomography scan) interventions.

This study was approved by the Human Ethics Review Committee of the National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan (institutional ethical committee number: 907).

Statistical analysis. All statistical analyses were conducted using JMP (version 12.2, SAS Institute, Cary, NC, USA) and all *p*-Values were two-sided. All statistical tests were two-sided at an α level of 0.005, considering multiple comparisons and consequent false positives (28).

The Kaplan-Meier method was used to describe the distribution of RFS and OS, and the log-rank test was performed. A Cox proportional hazards model was used to compute the hazard ratios (HRs) and the confidence intervals (95%CIs). Multivariable Cox proportional hazards regression models were used to identify independent risk factors for RFS and OS. The multivariable models included variables showing a univariable association ($p<0.10$) with RFS or OS.

Categorical variables are presented as proportions. Non-normally distributed variables were reported as medians with interquartile ranges. Categorical data were compared using the chi-square test or Fisher's exact test, and non-normally distributed data were compared using the Mann-Whitney *U*-test.

Results

Clinicopathological features and surgical outcomes according to age group. A total of 329 patients with stage II colorectal cancer were included in this retrospective study. Of the 329

Table II. *Perioperative and pathological outcomes according to age group.*

Characteristics*	All patients (n=329)	<75 years (n=158)	≥75 years (n=171)	*p*-Value†
Surgical approach				0.34
Open	231 (70%)	107 (68%)	124 (73%)	
Laparoscopy	98 (30%)	51 (32%)	47 (27%)	
Operating time (minutes)				0.047
<240	179 (54%)	77 (49%)	102 (60%)	
≥240	150 (46%)	81 (51%)	69 (40%)	
Intraoperative bleeding (ml)				0.67
<180	208 (63%)	98 (62%)	110 (64%)	
≥180	121 (37%)	60 (38%)	61 (36%)	
90-day mortality				0.022
No	325 (99%)	158 (100%)	167 (98%)	
Yes	4 (1.2%)	0	4 (2.3%)	
Anastomotic leakage				0.67
Absent	316 (96%)	151 (96%)	165 (96%)	
Present	13 (4.0%)	7 (4.4%)	6 (3.5%)	
Postoperative complications				
≥Grade III Clavien-Dindo classification				0.68
No	302 (92%)	144 (91%)	158 (92%)	
Yes	27 (8.2%)	14 (8.9%)	13 (7.6%)	
pT stage (depth of tumor invasion)				0.54
pT3	277 (84%)	131 (83%)	146 (85%)	
p T4	52 (16%)	27 (17%)	25 (15%)	
Tumor differentiation				0.85
Well	307 (93%)	147 (93%)	160 (94%)	
Poor or mucinous	22 (6.7%)	11 (7.0%)	11 (6.4%)	
Lymphatic invasion				0.010
Negative	72 (22%)	25 (16%)	47 (27%)	
Positive	257 (78%)	133 (84%)	124 (73%)	
Venous invasion				0.08
Negative	122 (37%)	51 (32%)	71 (42%)	
Positive	207 (63%)	107 (68%)	100 (58%)	
No. of analyzed lymph nodes				<0.001
≥12	266 (81%)	140 (89%)	126 (74%)	
<12	63 (19%)	18 (11%)	45 (26%)	
Adjuvant chemotherapy				<0.001
No	250 (76%)	99 (63%)	151 (88%)	
Capecitabine, UFT, or TS-1	67 (20%)	48 (30%)	19 (11%)	
XELOX or FOLFOX	12 (3.7%)	11 (7.0%)	1 (0.6%)	

UFT: Tegafur-uracil; TS-1: tegafur, gimeracil, and oteracil potassium; XELOX: capecitabine and oxaliplatin; FOLFOX: bolus and infused fluorouracil with oxaliplatin. *Categorical variables are presented as proportions. †Categorical data were compared using the chi-square test or Fisher's exact test.

patients, 171 (52%) were ≥75 years and 158 (48%) were <75 years. Tables I and II summarize the clinicopathological features and surgical outcomes according to age group. Advanced age in stage II colorectal cancer was associated with i) a low preoperative prognostic nutritional index, ii) right-sided colon cancer, iii) analysis of fewer than 12 lymph nodes, and iv) the absence of adjuvant chemotherapy ($p<0.001$, with an α level of 0.005).

Associations of advanced age with recurrence-free and overall survival in stage II colorectal cancer. We examined the associations of advanced age with RFS and OS in stage II colorectal cancer after excluding four patients with in-hospital mortality. The median follow-up was 3.1 years (interquartile range=2.5 to 4.9 years). Using Kaplan-Meier analysis we found that older patients ≥75 years with stage II colorectal cancer were associated with shorter RFS ($p<0.001$ by the log-rank test) and OS ($p<0.001$ by the log-rank test; Figure 1).

Among the high-risk features in stage II colorectal cancer that have been described in major guidelines (10, 11), lymphatic invasion tended to be associated with shorter RFS in univariable analysis ($p=0.026$; Table III). Associations of other high-risk factors, including i) T4 stage, ii) fewer than 12 examined lymph nodes, iii) bowel perforation and obstruction,

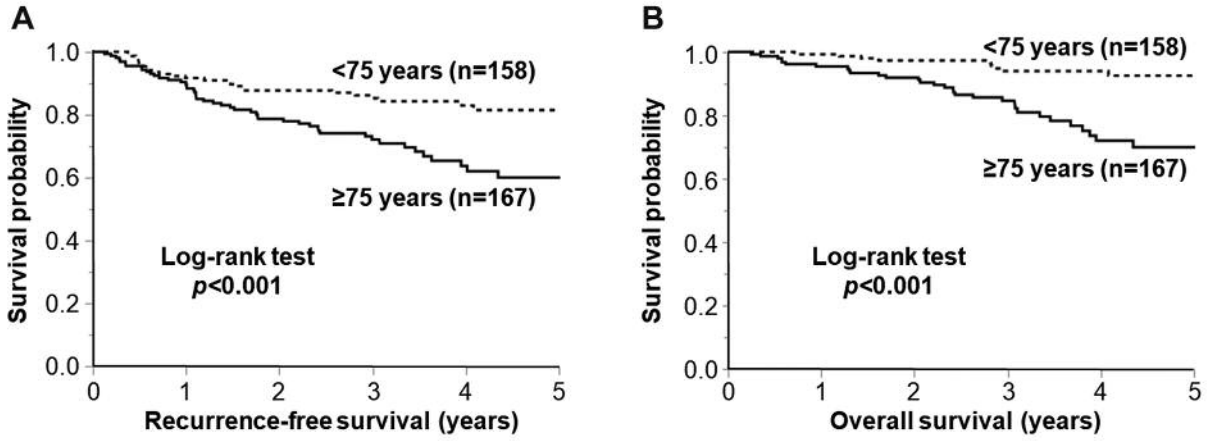

Figure 1. *Kaplan-Meier curves for recurrence-free survival (A) and overall survival (B), according to age group. The p-Value was calculated using the log-rank test (two-sided).*

and iv) poorly differentiated tumors, with RFS or OS were not statistically significant in univariable analyses ($p>0.05$).

Multivariable Cox regression analyses revealed that older age of patients (≥75 years) remained as a factor showing significant association with shorter RFS ($p<0.001$) and OS ($p<0.001$; Table III). Compared to patients <75 years of age, multivariable HRs (95%CI) for RFS and OS in those aged ≥75 years were 2.56 (1.55 to 4.31) and 4.36 (2.08 to 9.97), respectively.

We also performed multivariable Cox regression analyses after excluding patients who received adjuvant chemotherapy and observed significant associations of age ≥75 years with shorter RFS ($p=0.001$) and OS ($p<0.001$; Table IV) in colorectal cancer patients treated with surgery alone.

Discussion

We conducted this study to test the hypothesis that advanced age might be associated with worse clinical outcome following curative resection in patients with stage II colorectal cancer. In the 329 stage II colorectal carcinoma cases after curative resection, we found that age ≥75 years was independently associated with a shorter RFS and OS after controlling for the high-risk features that have been described in the major guidelines. In the 246 stage II colorectal cancer patients treated with surgery alone, age ≥75 years remained as an independent risk factor showing associations with a shorter RFS and OS.

Approximately 60% of colorectal cancer cases are diagnosed in people aged ≥65years, with a median age at diagnosis of 68 years (29, 30). Hence, further clinical trials are needed to establish evidence-based guidelines for older patients with colorectal cancer. Older patients have been shown to have decline in age-related immune function (31). Experimental and clinical evidence in old mice or older patients has demonstrated that dendritic cells exhibit i) impaired maturation and lower antigen uptake in the aged environment (32, 33), ii) impaired T-cell expansion and differentiation, iii) impaired induction of effector molecules, such as INF-γ and granzyme B, and iv) increased production of PGE2 and IL10 (34-36). The preoperative nutritional status has been associated with the host immune response against cancers and their clinical outcome (25, 37-40). In 843 colorectal cancer patients, the number of analyzed lymph nodes was associated with lymphocytic reactions against colorectal cancer, which have been associated with longer survival (41). In the current study, older patients with stage II colorectal cancer were associated with low a preoperative prognostic nutritional index and an analysis of fewer than 12 lymph nodes. Collectively, the data from our current study support the hypothesis that advanced age might represent a risk factor for worse clinical outcomes following curative resection of stage II colorectal cancer, partly due to the downregulation of the antitumor immune response. Further studies are needed to clarify the exact mechanism.

Perioperative nutrition support has been shown to reduce postoperative complications and enhance host immunity in patients with gastrointestinal cancers (42-45). A systematic review has demonstrated that older patients with colorectal cancer are less likely to receive adjuvant chemotherapy compared to younger patients (46), consistent with the current study. Enteral nutrition support has been shown to reduce the incidence of chemotherapy-related toxicities in patients with gastrointestinal cancers (47, 48). Hence, perioperative nutrition support may improve prognosis in older patients with colorectal cancer.

Table III. *Associations of advanced age with recurrence-free and overall survival following curative resection in 325 patients with stage II colorectal cancer.*

	Univariable HR (95%CI)	*p*-Value	Multivariable HR (95%CI)*	*p*-Value
Recurrence-free survival				
Age in years				
≥75 (*vs*. <75)	2.15 (1.36-3.46)	<0.001	2.56 (1.55-4.31)	<0.001
CEA level				
≥5 ng/ml (*vs*. <5 ng/ml)	1.78 (1.14-2.81)	0.012	1.48 (0.91-2.43)	0.12
CA19-9 level				
≥37 U/ml (*vs*. <37 U/ml)	2.70 (1.56-4.44)	<0.001	2.11 (1.18-3.66)	0.013
Lymphatic invasion				
Present (*vs*. negative)	1.93 (1.08-3.76)	0.026	1.76 (0.88-3.71)	0.11
Venous invasion				
Present (*vs*. negative)	1.61 (0.99-2.68)	0.051	1.40 (0.81-2.53)	0.24
Anastomotic leakage				
Present (*vs*. absent)	2.57 (1.07-5.23)	0.037	2.20 (0.88-4.70)	0.09
Adjuvant chemotherapy				
Present (*vs*. absent)	0.40 (0.19-0.76)	0.004	0.53 (0.24-1.03)	0.06
Overall survival				
Age in years				
≥75 (*vs*. <75)	3.56 (1.88-7.19)	<0.001	4.36 (2.08-9.97)	<0.001
ASA-PS				
3 or 4 (*vs*. 1 or 2)	2.12 (1.14-3.83)	0.017	1.52 (0.82-2.79)	0.18
CEA level				
≥5 ng/ml (*vs*. <5 ng/ml)	2.26 (1.24-4.25)	0.007	2.25 (1.14-4.54)	0.019
CA19-9 level				
≥37 U/ml (*vs*. <37 U/ml)	2.55 (1.23-4.88)	0.013	2.22 (1.02-4.53)	0.044
No. of analyzed lymph nodes				
<12 (*vs*. ≥12)	1.95 (0.99-3.63)	0.054	1.92 (0.93-3.77)	0.08
Anastomotic leakage				
Present (*vs*. absent)	3.05 (1.04-7.12)	0.043	4.55 (1.42-12.28)	0.013
Adjuvant chemotherapy				
Present (*vs*. absent)	0.15 (0.02-0.49)	<0.001	0.36 (0.06-1.23)	0.11

CI: Confidence interval; HR: hazard ratio; ASA: The American Society of Anesthesiologists; ASA-PS: ASA physical status classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. *Multivariable Cox proportional hazards regression models included variables showing a univariable association (*p*-Value<0.10) with recurrence-free survival or overall survival.

In the current study, preoperative serum levels of CEA and CA19-9 and the incidence of anastomotic leakage were independently associated with worse RFS or OS following surgery for stage II colorectal cancer; consistent with the findings of previous studies (49-51). Identifying predictive biomarkers for the selection of patients with stage II colorectal cancer who could benefit from adjuvant chemotherapy are important. Hence, further clinical trials are needed to identify predictive biomarkers for the selection of patients with stage II colorectal cancer who could benefit from adjuvant chemotherapy.

We acknowledge that there are several limitations of our study such as, i) its retrospective nature and single-center design, and ii) the lack of data assessing tumor molecular features or immune cells in colorectal cancer tissue. Thus, further investigations are needed to examine the potential influence of aging on tumor molecular features and antitumor immunity in colorectal cancer.

A major strength of this study was that it included a relatively large number of older patients, which enabled us to assess the prognostic significance of advanced age in stage II colorectal cancer after controlling for potential confounders.

In conclusion, advanced age was associated with a shorter RFS and OS in stage II colorectal cancer following curative resection. Further clinical trials are needed to identify the robust risk factors for recurrence in stage II colorectal cancer, and to establish evidence-based guidelines for older patients with stage II colorectal cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Table IV. *Associations of advanced age with recurrence-free and overall survival following curative resection in 246 stage II colorectal cancer patients treated with surgery alone.*

	Univariable HR (95%CI)	*p*-Value	Multivariable HR (95%CI)*	*p*-Value
Recurrence-free survival				
Age in years				
≥75 (*vs.* <75)	1.77 (1.08-2.98)	0.022	2.40 (1.42-4.20)	0.001
CA19-9 level				
≥37 U/ml (*vs.* <37 U/ml)	3.00 (1.70-5.06)	<0.001	2.71 (1.51-4.65)	0.001
Lymphatic invasion				
Present (*vs.* negative)	1.99 (1.10-3.90)	0.021	1.62 (0.80-3.47)	0.18
Venous invasion				
Present (*vs.* negative)	1.80 (1.09-3.06)	0.021	1.38 (0.77-2.57)	0.28
Anastomotic leakage				
Present (*vs.* absent)	2.32 (0.96-4.77)	0.06	2.34 (0.94-5.07)	0.07
Overall survival				
Age in years				
≥75 (*vs.* <75)	2.80 (1.45-5.84)	0.002	5.48 (2.52-13.18)	<0.001
CEA level				
≥5 ng/ml (*vs.* <5 ng/ml)	1.81 (0.98-3.43)	0.06	1.88 (0.95-3.76)	0.07
CA19-9 level				
≥37 U/ml (*vs.* <37 U/ml)	2.77 (1.33-5.35)	0.008	2.39 (1.10-4.91)	0.029
Lymphatic invasion				
Present (*vs.* negative)	1.89 (0.92-4.39)	0.09	2.28 (1.08-5.44)	0.030
Anastomotic leakage				
Present (*vs.* absent)	2.52 (0.86-5.91)	0.09	3.64 (1.14-9.78)	0.031

CI: Confidence interval; HR: hazard ratio; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. *Multivariable Cox proportional hazards regression models included variables showing a univariable association ($p<0.10$) with recurrence-free survival or overall survival.

Authors' Contributions

KM, NM, and HB contributed to the study conception and design. Data collection was performed by KM, JK, AM, SY, TM, KK, MI, TM, TK, NM, and HB. Analysis and interpretation of data were performed by KM and NM. The first draft of the manuscript was written by KM and all authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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