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Patient Age and Long-term Survival in Colorectal Cancer Patients Who Undergo Emergency Surgery

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Abstract. *Background/Aim: Emergency surgery for colorectal cancer (CRC) is a high-risk procedure with high morbidity and mortality rates, especially for older patients. The relationship between patient age status and long-term outcomes is unclear. We hypothesize that patient age might be associated with long-term outcomes in patients with CRC who undergo emergency surgery. Patients and Methods: Utilizing a database of CRC patients who received emergency surgery, we examined the prognostic association of patient age. Results: The ≥80-years group was significantly associated with American Society of Anesthesiologists (ASA) physical status, bowel obstruction, N stage, shorter operating time, and less adjuvant chemotherapy (all p<0.03); and also, with shorter recurrence-free survival [multivariable hazard ratio, 2.79; 95% confidence interval, 1.13-7.21; p=0.026]. ASA status and adjuvant chemotherapy were significantly associated with recurrence-free survival (all p<0.03). Conclusion: Advanced age is associated with shorter recurrence-free survival in CRC patients who undergo emergency surgery.*

Colorectal cancer (CRC) is the third most common cancer for both males and females worldwide (1). Despite remarkable advances in screening systems, up to 30% of patients with CRC will develop a complication, such as bowel obstruction, perforation, or hemorrhage, which will require emergency surgery (2). Accumulating evidence indicates that emergency CRC resection remains a high-risk procedure with high morbidity and mortality rates, especially for older patients, despite the advances in surgical technology and postoperative treatment (3). Considering the fact that emergency surgery has greater morbidity and mortality rates than does elective surgery, improved strategies for complicated CRC are aggressively needed (4-6).

Because of low birth and high longevity rates, many populations around the world are aging rapidly, leading to higher percentage of older patients who require surgery for gastrointestinal cancers, including colorectal cancer. In fact, more than 70% of CRCs is diagnosed in patients older than 65 years. Approximately a third of patients with CRC initially present as an emergency (7). The number of older patients with CRC who require emergency surgery is expected to increase greatly over the coming decades. Emerging evidence suggests that advanced age might be an independent risk factor for shorter survival among patients with CRC (8, 9). However, risk factors for long-term outcomes among patients with CRC in the emergency setting are unclear because their heterogeneity requires a tailored approach that considers individual frailty, especially in this setting.

Based on the line of evidence on CRC, we hypothesize here that patient age might be associated with long-term outcomes in patients with CRC who undergo emergency surgery. To test this hypothesis, we utilized a non-biased consecutive database of CRC cases.

Patients and Methods

Study population. A total of 75 patients with colorectal cancer, who consecutively underwent emergency operation at the National Hospital Organization Kumamoto Medical Center between July 2013 and June 2019, were included in this study. The main inclusion criteria were as follows: (i) patients aged over 18 years; (ii) histologically confirmed colorectal adenocarcinoma before or after operation; (iii) no other active malignancy; and (iv) patients who undergo emergency surgery. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) tumor, node, and metastases (TNM) classification (7th edition). Postoperative complications were recorded and graded as defined by the Clavien–Dindo classification system.

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Key Words: Advanced age, colorectal neoplasms, emergency, lymph node dissection, prognosis, urgent.

Table I. *Clinical and pathological features of colorectal cancer cases according to patient age.*

Characteristic[a]	All cases (N=75)	Age		*p*-Value[b]
		Younger (<80) (N=51)	Older (≥80) (N=24)	
Gender				0.28
Female	37 (49%)	23 (45%)	14 (58%)	
Male	38 (51%)	28 (55%)	10 (42%)	
Age, mean±SD (years)c	73.5±12.3	67.1±9.1	87.0±4.6	<0.0001
Body mass index, mean±SD (kg/m^2)[c]	20.8±4.2	21.5±4.6	19.5±2.8	0.13
American Society of Anesthesiologists physical status				0.027
0	3 (4.0%)	3 (5.9%)	-	
1	6 (8.0%)	6 (12%)	-	
2	36 (48%)	26 (51%)	10 (42%)	
3	26 (35%)	13 (25%)	13 (54%)	
4	4 (5.3%)	3 (5.9%)	1 (4.2%)	
Clinical presentation				0.023
Perforation	37 (49%)	30 (59%)	7 (29%)	
Obstruction	37 (49%)	21 (41%)	16 (67%)	
Necrosis	1 (1.3%)	-	1 (4.2%)	
Tumor location				0.081
Cecum to transverse colon	28 (37%)	15 (29%)	13 (54%)	
Descending to sigmoid colon	31 (41%)	25 (49%)	6 (25%)	
Rectum	16 (21%)	11 (22%)	5 (21%)	
Tumor size, mean±SD (mm)[c]	51.2±17.8	50.3±17.9	53.0±17.8	0.70
Histological type				0.28
Well to moderate	64 (95%)	46 (96%)	18 (95%)	
Poor	1 (1.5%)	1 (2.1%)	-	
Mucinous	1 (1.5%)	-	1 (5.3%)	
Other	1 (1.5%)	1 (2.1%)	-	
T stage (depth of tumor invasion)				0.33
T1 (submucosa)	-	-	-	
T2 (muscularis propria)	5 (6.8%)	2 (4.0%)	3 (13%)	
T3 (subserosa)	44 (60%)	30 (60%)	14 (61%)	
T4 (serosa or other organs)	24 (33%)	18 (36%)	6 (26%)	
N stage (number of positive lymph nodes)			0.0089	
N0 (0)	35 (55%)	25 (54%)	10 (56%)	
N1 (1-3)	18 (28%)	10 (22%)	8 (44%)	
N2 (4-)	11 (17%)	11 (24%)	-	
M stage				0.13
M0	49 (66%)	31 (61%)	18 (78%)	
M1	25 (34%)	20 (39%)	5 (22%)	
AJCC disease stage				0.46
I	4 (5.4%)	2 (3.9%)	2 (8.7%)	
II	26 (35%)	17 (33%)	9 (39%)	
III	19 (26%)	12 (24%)	7 (30%)	
IV	25 (34%)	20 (39%)	5 (22%)	

[a]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of patient age. [b]We used the chi-square test to compare categorical variables and an analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05. [c]Non-normally distributed data were compared using the Mann-Whitney *U*-test. AJCC: American Joint Committee on Cancer; SD: standard deviation.

Recurrence-free survival (RFS) was defined as the time to recurrence or death. Overall survival (OS) was calculated from surgery to death from any cause. The term "prognostic marker" is used throughout this article according to the REMARK Guidelines (10).

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); the requirement for written informed consent was waived in view of the retrospective nature of the study.

Statistical analysis. All statistical analyses were conducted using the JMP program (version 10, SAS Institute, Cary, NC, USA). All *p*-values were two-sided, and the two-sided α level of 0.05 was used for all testing.

Table II. *Perioperative features of colorectal cancer cases according to patient age status.*

Characteristic[a]	All cases (N=75)	Age		*p*-Value[b]
		Younger (<80) (N=51)	Elderly (≥80) (N=24)	
First surgical procedure				0.14
Colectomy	30 (40%)	17 (33%)	13 (54%)	
Hartmann	28 (37%)	23 (45%)	5 (21%)	
Colostomy	16 (21%)	10 (20%)	6 (25%)	
Debridement	1 (1.3%)	1 (2.0%)	-	
Additional surgical procedures				0.095
Absent	61 (81%)	39 (76%)	22 (92%)	
Present	14 (19%)	12 (24%)	2 (8.3%)	
Total resection rate of primary tumor	91%	94%	83%	0.15
Curability				0.68
Curative	38 (51%)	25 (49%)	13 (54%)	
Palliative	37 (49%)	26 (51%)	11 (46%)	
Lymph node dissection				0.19
D0	10 (13%)	5 (9.8%)	5 (21%)	
D1	8 (11%)	5 (9.8)	3 (13%)	
D2	11 (15%)	10 (20%)	1 (4.2%)	
D3	46 (61%)	31 (61%)	15 (63%)	
Number of lymph nodes harvested, mean±SD[c]	18.1±12.8	18.4±13.4	17.4±11.5	0.95
Operating time, mean±SD (minutes)[c]	158±91	175±100	123±54	0.012
Intraoperative bleeding, mean±SD (g)[c]	301±495	385±568	120±197	0.060
Clavien-Dindo classification				0.92
0	39 (52%)	25 (49%)	14 (58%)	
1	9 (12%)	6 (12%)	3 (13%)	
2	19 (25%)	14 (27%)	5 (21%)	
3	4 (5.3%)	3 (5.9%)	1 (4.2%)	
4	1 (1.3%)	1 (2.0%)	-	
5	3 (4.0%)	2 (3.9%)	1 (4.2%)	
Hospital stay, mean±SD (days)[c]	21.4±11.3	21.8±11.3	20.7±11.5	0.77
Mortality at 30 days	4 (5.3%)	2 (3.9%)	2 (8.3%)	0.44
Adjuvant chemotherapy	26 (35%)	22 (43%)	4 (17%)	0.020

[a]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of patient age. [b]We used the chi-square test to compare categorical variables and an analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05. [c]Non-normally distributed data were compared using the Mann-Whitney *U*-test. SD: Standard deviation.

The primary aim was to examine the association between patient age (<80 years *vs*. ≥80 years; as a category variable) and clinical outcomes, including RFS and OS. The Kaplan–Meier method was used to describe the distribution of RFS and OS, and then the log-rank test was performed. A Cox proportional hazards model was used to compute hazard ratios (HRs) and 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 ($p<0.05$) with RFS or OS. All other analyses represented secondary analyses.

To compare characteristics across strata of patient age, we used the chi-square test for categorical variables, and the Student's t test or the Mann–Whitney *U*-test for continuous variables. To assess the interaction between the variables, patient age was cross-correlated with another variable of interest in the univariable Cox proportional hazards regression model for RFS or OS, and the interaction was evaluated by the Wald test.

Results

We included 75 patients with CRC who underwent emergency surgery from a non-biased independent database. The median age was 73.5 years, and 49% of the patients were female; the most frequent clinical presentations were perforation (37 cases, 49%) and obstruction (37 cases, 49%). Table I summarizes the clinical and pathological features of patients with CRC stratified according to patient age. The older group was significantly associated with American Society of Anesthesiologists (ASA) physical status, bowel obstruction, and early N stage (all $p<0.03$). The older group was possibly associated with right-side tumors ($p=0.081$), but not with the other examined features (all $p>0.12$).

Table II summarizes the perioperative features of patients with CRC stratified according to patient age. The older

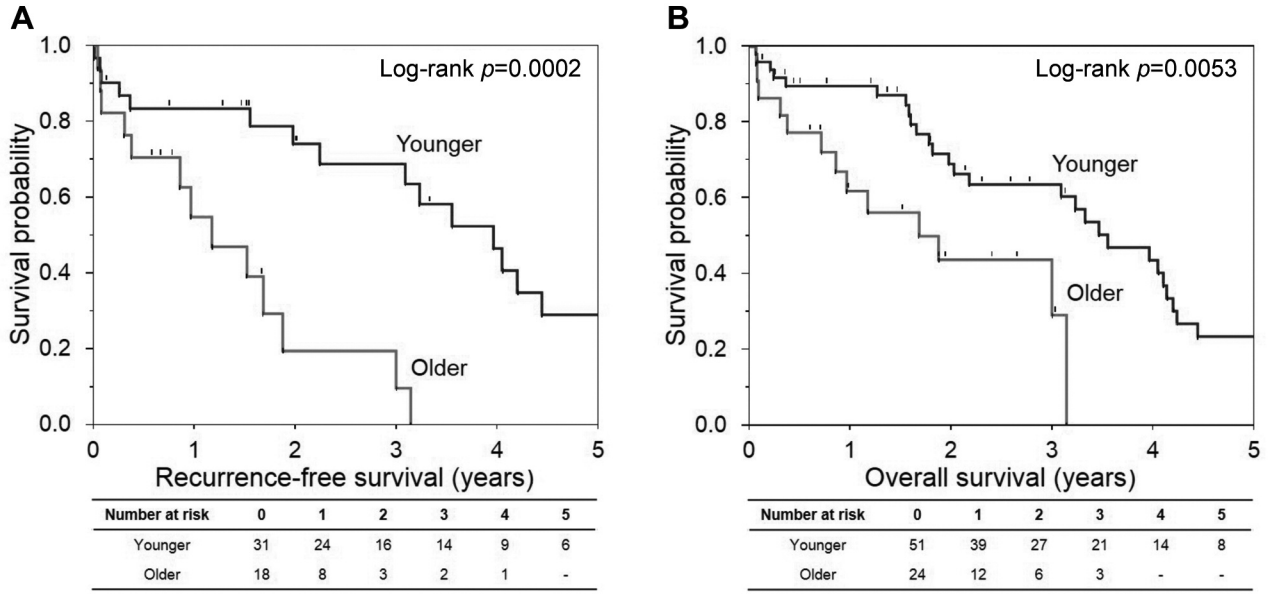

Figure 1. *Kaplan–Meier survival analyses of colorectal cancer patients according to patient age (<80 vs. ≥80). The p-values were calculated using the weighted log-rank test (two sided). A: Recurrence-free survival. B: Overall survival. The number of patients who remained alive and at risk of death at each time point after the diagnosis of colorectal cancer.*

group was significantly associated with shorter operating time and less adjuvant chemotherapy (all $p<0.03$). The older group was possibly associated with less chance of additional surgical procedures ($p=0.095$) and less intraoperative bleeding ($p=0.060$), but was not associated with any of the other features examined, including hospital stay and mortality at 30 days (all $p>0.13$).

During the median follow-up time of 21 months (interquartile range=6.0-37.7 months) for all censored patients, there were 28 all-cause deaths and 16 recurrences. A Kaplan–Meier analysis and Cox proportional hazards regression analysis were conducted to assess the prognostic role of advanced patient age. In Kaplan–Meier survival analyses, the older group was associated with shorter RFS and OS (all $p<0.006$, Figure 1A, B). Using univariable Cox regression analyses, we observed a statistically significant association of the older group with shorter RFS (univariable HR=4.81; 95%CI=1.99-12.2; $p=0.0005$; Table III). After adjustment for potential prognostic factors including disease stage, the older group was significantly associated with shorter RFS (multivariable HR=2.79; 95%CI=1.13-7.21; $p=0.026$; Table III). ASA physical status and adjuvant chemotherapy were also significantly associated with recurrence-free survival [multivariable HR=3.00; 95%CI=1.22-8.00; $p=0.016$ (for ASA physical status) and multivariable HR=0.31; 95%CI=0.09-0.87; $p=0.025$ (for adjuvant chemotherapy)]. Advanced age was possibly associated with longer OS (multivariable HR=1.90; 95%CI=0.88-3.97; $p=0.098$) as well as adjuvant chemotherapy (multivariable HR=0.51; 95%CI=0.24-1.03; $p=0.061$).

As exploratory analyses, we next determined whether the influence of lymph node dissection or adjuvant chemotherapy on patient survival was affected by patient age (Table IV). We did not observe a modifying effect of patient age. Adjuvant chemotherapy was significantly associated with longer RFS in the younger group (univariable HR=0.36; 95%CI=0.11-1.00; $p=0.049$), but not in the older group ($p=0.40$).

Discussion

Emergency surgery for patients with complicated CRC has been considered as a high-risk procedure, especially for older patients. However, risk factors for long-term outcomes among patients who received emergency surgery for complicated CRC remains to be elucidated. To test our hypothesis that patient age might be associated with long-term outcomes among patients with CRC who undergo emergency surgery, we conducted this study, using a non-biased database of CRC cases. We found that the older group is independently associated with shorter RFS in this setting. Moreover, ASA status and adjuvant chemotherapy were significantly associated with recurrence-free survival. Better treatment strategies for patients with complicated CRC, especially older patients, are eagerly demanded.

Evidence suggests that older patients with complicated CRC who undergo emergency surgery have high morbidity

Table III. *Patient age status and patient survival*.

		Recurrence-free survival		Overall survival	
		Univariable HR (95% CI)	Multivariable HR (95%CI)[a]	Univariable HR (95%CI)	Multivariable HR (95%CI)[a]
Age	<80	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	≥80	4.81 (1.99-12.2)	2.79 (1.13-7.21)	2.26 (1.08-4.60)	1.90 (0.88-3.97)
	p-Value	0.0005	0.026	0.032	0.098
Gender	Female	1 (reference)		1 (reference)	
	Male	0.93 (0.45-1.99)		1.21 (0.66-2.27)	
	p-Value	0.84		0.55	
Body mass index	(for 1-kg/m^2 increment)	0.99 (0.90-1.07)		0.98 (0.90-1.05)	
	p-Value	0.80		0.90	
American Society of Anesthesiologists physical status	0-2	1 (reference)	1 (reference)	1 (reference)	
	3, 4	3.95 (1.74-9.60)	3.00 (1.22-8.00)	1.70 (0.89-3.21)	
	p-Value	0.0009	0.016	0.11	
Perforation	Absent	1 (reference)		1 (reference)	
	Present	0.81 (0.40-1.68)		1.09 (0.60-2.00)	
	p-Value	0.57		0.79	
Tumor location	Cecum to transverse colon	1 (reference)		1 (reference)	
	Descending to sigmoid colon	0.87 (0.41-1.81)		1.18 (0.61-2.32)	
	Rectum	0.35 (0.08-1.08)		0.53 (0.22-1.20)	
	p-Value	0.18		0.11	
Primary resection	Absent	-		1 (reference)	
	Present	-		1.35 (0.41-8.31)	
	p-Value	-		0.67	
Lymph node dissection	D0/1	1 (reference)		1 (reference)	
	D2/3	0.56 (0.26-1.35)		0.66 (0.33-1.46)	
	p-Value	0.19		0.28	
Operating time	(for 1-hour increment)	0.80 (0.58-1.06)		0.95 (0.80-1.10)	
	p-Value	0.12		0.51	
Intraoperative bleeding	(for 100-g increment)	0.93 (0.83-1.02)		0.99 (0.92-1.05)	
	p-Value	0.13		0.73	
Clavien-Dindo classification	0-2	1 (reference)		1 (reference)	
	3-5	2.08 (0.60-5.52)		1.61 (0.48-4.05)	
	p-Value	0.22		0.40	
AJCC disease stage	I	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	II	0.37 (0.13-1.33)	0.70 (0.23-2.67)	0.56 (0.18-2.41)	0.76 (0.24-3.32)
	III	0.41 (0.13-1.52)	0.81 (0.25-3.17)	0.48 (0.15-2.14)	0.63 (0.20-2.81)
	IV	-	-	0.33 (0.10-1.49)	0.54 (0.15-2.53)
	p-Value	0.29	0.84	0.36	0.76
Adjuvant chemotherapy	Absent	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Present	0.26 (0.08-.065)	0.31 (0.09-0.87)	0.42 (0.20-0.80)	0.51 (0.24-1.03)
	p-Value	0.0029	0.025	0.0083	0.061

[a]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 ($p<0.05$) with recurrence-free survival or overall survival. AJCC: American Joint Committee on Cancer; CI: confidence interval; HR: hazard ratio.

and mortality rates (11). Menegozzo *et al*. reported a considerable mortality risk (10.4%) during the first 30 postoperative days (11), compared with 8.3% in the ≥80-years group in the current study, which supports feasibility of emergency surgery even for older patients with complicated CRC. The main emergencies from CRC include obstruction, perforation, and hemorrhage. Of these, obstruction is reportedly the most common in approximately 80% (3, 12); it accounted for about 50% in the current study. A growing body of evidence highlights the clinical significance of metallic stent for obstruction by colorectal cancer (13). Further development of colonic stenting and decompression tube for obstructing colorectal cancer might alter the proportion of oncologic emergencies by colorectal cancer (14). Although primary tumor location might be a risk factor of long-term survival for colorectal liver metastases (15), we observed no

Table IV. *Lymph node dissection, adjuvant chemotherapy, and patient survival according to patient age status.*

		Recurrence-free survival	Overall survival
		Univariable HR (95%CI)	Univariable HR (95%CI)
Younger group			
Lymph node dissection	D0/1	1 (reference)	1 (reference)
	D2/3	0.68 (0.24-2.43)	0.83 (0.34-2.47)
	p-Value	0.52	0.71
Elderly group			
Lymph node dissection	D0/1	1 (reference)	1 (reference)
	D2/3	0.77 (0.22-3.61)	0.43 (0.13-1.62)
	p-Value	0.71	0.19
	$P_{interaction}$	0.99	0.39
Younger group			
Adjuvant chemotherapy	Absent	1 (reference)	1 (reference)
	Present	0.36 (0.11-1.00)	0.50 (0.23-1.06)
	p-Value	0.049	0.071
Elderly group			
Adjuvant chemotherapy	Absent	1 (reference)	1 (reference)
	Present	6.50	0.27 (0.01-1.41)
	p-Value	0.40	0.14
	$P_{interaction}$	0.55	0.57

CI: Confidence interval; HR: hazard ratio.

relationship between tumor location and long-term survival. Studies have also reported the large proportion of advanced stages among CRC patients who undergo emergency surgery (2, 16). Despite the current recommendations for CRC screening, patients still present with some complications from advanced stage. In the current study, 60% presented with AJCC stage III or IV. Collectively, further treatments, such as extended lymph node dissection and adjuvant chemotherapy, might improve long-term outcomes.

Patients with CRC who undergo surgery require curative intent. Also, the operative decision depends on clinical presentation, patient's condition, and comorbidities, especially in the emergency setting. Surgeons must generally comply with the oncological principles of en-bloc resection, free margins, and adequate lymphadenectomy (17). Although D2/3 lymph node dissection might be more invasive than D0/1 lymph node dissection, accumulating evidence indicates the prognostic significance of extended (D2/3) lymph node dissection for older patients with CRC; (2, 18-21) and that harvesting 12 or more lymph nodes provides a survival benefit for patients with CRC, including older patients (2, 11, 12, 16, 20). In the current study, we did not observe a significant association of D2/3 lymph node dissection with longer RFS in the ≥80-years group. However, we observed no association of D2/3 lymph node dissection with increased mortality at 30 days or longer hospital stay (data not shown). Considering the differing rates of adjuvant chemotherapy between older and younger patients, the influence of extended lymph node dissection on long-term survival might differ by patient age status. Although our study did not show the aggravations of short-term clinical outcomes by extended lymph node dissection, surgeons should carefully conduct adequate lymphadenectomy based on the patient's condition. A better understanding of the prognostic significance and risks of extended lymph node dissection for older CRC patients who require emergency surgery should be elucidated for promoting individualized treatment strategies for this age group.

Advanced age might be associated with discontinuance of postoperative chemotherapy (22, 23). One retrospective multicenter study utilizing 4,600 CRC cases demonstrated that only 35% of patients with colon cancer and 21% with rectal cancer received adjuvant therapy among patients aged ≥75 years; these percentages were much lower than those for younger patients (24). However, adjuvant chemotherapy might not improve survival among older patients with locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery (25). Advanced age should not be the only criterion to preclude chemotherapy in older patients with CRC. For older patients with frailty or vulnerability, monotherapy or a stop-and-go strategy might be desirable. Targeted therapies might offer better efficacy and lower toxicity for older patients with CRC. Moreover, the success of cancer immunotherapy targeting PDCD1 (programmed death 1, PD-1) has led to a major paradigm shift in the field of cancer treatments for CRC patients (26). Treatments

should be individualized based on the nature of CRC, the status of patient age, physiology, and function (27). Further research is warranted to investigate the therapeutic roles of chemotherapy, including immune checkpoint inhibitors, in older patients with CRC.

We acknowledge limitations in our study. First, the sample size is small, and this study is a retrospective observational study at a single center. As emergency surgery for older patients with complicated CRC, especially older than 80 years, is not popular, our findings should be verified with a larger cohort in a multi-institutional joint study. Second, as all of four patients ≥80 years old who underwent adjuvant chemotherapy died or experienced recurrence, we cannot investigate the significance of adjuvant chemotherapy for older patients. Third, we did not consider the molecular characteristics in CRC tissue. Future studies are needed to confirm our findings and to examine the association of patient age with long-term survival in patients with complicated CRC who undergo emergency surgery.

A major strength of our study is that we focused on patients who are older (≥80 years old) than those in previous studies, and examined the prognostic association of this age group by multivariable Cox proportional hazards regression models after controlling for potential confounders, including disease stage. We also assessed the prognostic significance of extended lymph node dissection or adjuvant chemotherapy in the strata of patient age.

In conclusion, we show here that the older group is independently associated with shorter RFS in patients with CRC who undergo emergency surgery. We also found the prognostic significance of ASA physical status and adjuvant chemotherapy. These findings must provide stimuli for further investigations on strategies for complicated CRC cases, especially for older patients.

Conflicts of Interest

No conflicts of interest exist in relation to this study.

Authors' Contributions

KK, KM, NM, and HB participated in study conception and design. All authors participated in data acquisition. KK, and KM performed the statistical analyses. KK, and KM analyzed the data. NM and HB supervised the work. KK, KM, NM, and HB were the major contributors to manuscript preparation. All Authors contributed to the manuscript, critically revised it, and approved the final version.

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