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ORIGINAL ARTICLE

Long-term outcomes of colorectal cancer surgery for elderly patients: a propensity score-matched analysis

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Abstract

Purpose To investigate the effect of old age on the perioperative, short-term, and long-term surgical outcomes of elderly patients undergoing curative surgery for colorectal cancer (CRC).

Methods The subjects of this retrospective study were 526 patients who underwent curative resections for stage I–III CRC between March 2005 and March 2016. We divided the patients into a young group (< 75 years old, $n = 361$) and an elderly group (≥ 75 years old, $n = 165$) and compared the clinicopathological factors and prognoses of the two groups. We performed a propensity score-matched (PSM) analysis with inverse probability of treatment weighting (IPTW) to avoid confounding bias.

Results The elderly group had more right-sided tumors and more comorbidities than the young group. After PSM, there were 148 patients in each group. Although the elderly group had significantly shorter overall survival than the young group, the two groups did not differ significantly in cancer-specific survival (CSS; $P = 0.136$) or recurrence rate (RR; $P = 0.317$). Multivariate analysis with IPTW also revealed no significant difference in CSS ($P = 0.171$) or RR ($P = 0.284$) between the young and elderly groups. Our findings were limited by the study's retrospective single-institute conditions, and the inclusion of only patients who underwent radical resections.

Conclusion Primary tumor resection is appropriate for elderly patients with CRC.

Keywords Colorectal surgery · Elderly people · Propensity score analysis

Background

Colorectal cancer (CRC) is the third most common cancer worldwide [1]. In Japan, more than 130,000 cases of CRC are diagnosed every year and it is the second-leading cause of cancer-related deaths [2].

Low birth rate and extended longevity are also global trends. Persons aged 65 years or older constituted 8.3% of the worldwide population in 2015 and are expected to constitute 17.8% of the population by 2060. However, in Japan, people aged 65 years or older made up 27.7% of the population in 2017 and this number is growing [3]. Thus, the number of elderly people with a diagnosis of CRC is expected to increase significantly in coming years, which will affect the treatment policy. Surgery for elderly patients with CRC has higher mortality and postoperative complication rates than surgery for younger patients [4, 5]. Although age is not an independent limiting factor, caring for elderly patients is often difficult because of comorbidities and poor overall health status [6, 7]. However, the outcomes of CRC surgery for elderly people have not been widely investigated. In this study, we evaluated the clinicopathological and prognostic outcomes of elderly patients who underwent curative surgery for CRC to elucidate the effect of old age on perioperative, short-term, and long-term surgical outcomes.

Patients and methods

The subjects of this retrospective study were 526 patients who underwent radical resections for CRC between March 2005 and March 2016 at Kumamoto University (Kumamoto,

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Japan). The eligibility criteria included, histologically confirmed CRC in patients who underwent radical resection for Stage I–III CRC (UICC Cancer Staging Manual for Colorectal Cancer, 8th edition). We excluded patients who had histologically diagnosed Stage 0 or Stage IV disease. The use of clinical data in this study was approved by the human ethics review committee of the Graduate School of Medicine, Kumamoto University and the Helsinki Declaration of 1964.

We collected the following data from inpatient and outpatient records: age, sex, comorbidities, tumor location (right side, left side, recto-sigmoid [Rs], and lower rectum [Ra and Rb]), histological type (Tub1/Tub2 and others [Por, Muc, Pap]), carcinoembryonic antigen (CEA) levels (ng/mL), tumor factors (pathological T factor, N factor, clinical M factor, and pathological stage), and surgical data (operative method, curability, and postoperative complications). All patients were evaluated for overall survival (OS), cancer-specific survival (CSS), and recurrence rate (RR). We divided the patients into two groups according to their age: the young group (under 75 years old) and the elderly group (75 years or older). We then compared clinicopathological factors and prognoses between these groups.

Statistical analyses

All statistical analyses were performed using JMP (version 10; SAS Institute, Cary, NC, USA) and R (version 3. 4. 4; R Development Core Team, Vienna, Austria). Patients' characteristics, tumor factors and surgical factors were compared between the groups using *t* tests, Mann–Whitney *U* tests and Chi-square tests as appropriate. To assess long-term outcomes, we performed propensity score analysis to minimize the bias arising from the patients' tumor backgrounds. Possible variables associated with tumor factors of the CRC patients, including sex, primary tumor location, histological type, T factor, N factor and CEA levels, were selected comprehensively for one-to-one propensity score matching (PSM) analysis. To perform PSM, stabilized inverse probability of treatment weights (IPTW) was calculated. We applied the IPTW to the Kaplan–Meier method and Cox models to adjust for potential imbalances in the assessment of survival outcomes [8]. Cox proportional hazard analysis was performed to identify prognostic factors. $P < 0.05$ was considered significant. Univariate and multivariate analyses were performed to investigate the correlations between OS and clinicopathological factors. The Kaplan–Meier method and log-rank test were used for survival analysis. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

Patients' characteristics

Table 1 summarizes the patients' baseline characteristics. Among the 526 CRC patients included in this study, 361 were under 75 years and 165 were over 75 years. As expected, the American Society of Anesthesiologists' Physical Status (ASA-PS) was significantly higher in the elderly group. Right-side colon cancers were significantly more prevalent in the elderly group than in the young group ($P < 0.01$). Tumor factors did not differ significantly between the two groups. Among the surgical factors, the young group had a significantly higher rate of invasive surgery, such as pelvic evisceration, than the elderly group; and right hemicolectomies were more common in the elderly group because of the primary tumor location ($P < 0.01$; Table 1). As expected, the elderly group had significantly more comorbidities, such as hypertension and cardiovascular, respiratory, and cerebral/psychiatric diseases ($P < 0.01$; Table 2).

The incidences of postoperative complications did not differ significantly between the groups. The incidence of postoperative complications above Clavien–Dindo classification (CDc) grade II was 24% in the young group and 25% in the elderly group ($P = 0.635$; Table 3). The incidence of postoperative complications above CDc grade III was 12% in both the groups ($P = 0.582$; Table 3).

PSM analysis of survival outcomes

We performed PSM analysis to account for potential imbalances in the patients' characteristics and tumor factors (age, tumor location, histological type, histological depth, lymph node metastasis, and CEA levels) and created propensity scores (Table 4). To assess the prognostic impact of age, age-related comorbidities were unmatched. Figure 1 shows the Kaplan–Meier analyses for OS, CSS, and RR in the two PSM groups. The median follow-up time was 45.7 months for all the patients (47.2 months for the young group and 42.1 months for the elderly group). The 5-year OS rates differed significantly between the two age groups (young: 88.0%, elderly: 69.7%, $P < 0.001$), but their 5-year CSS rates did not differ significantly (young: 96.1%, elderly: 88.9%, $P = 0.136$) nor did their cumulative RR ($P = 0.317$). Multivariate analysis with IPTW also revealed no difference in CSS ($P = 0.171$) and RR ($P = 0.284$) between the two age groups.

Table 1 Baseline characteristics

Variables	Young group (< 75 y/o) (*N* = 361)		Elderly group (≥ 75 y/o) (*N* = 165)		*P* value
	N	(%)	*N*	(%)	
Age (years) (SD)	61.8	(9.3)	80.8	(4.5)	< 0.0001
Gender					
Male	236	(65)	100	(61)	0.292
Female	125	(35)	65	(39)	
ASA-PS					
Grade 1	123	(34)	27	(16)	< 0.0001
Grade 2	185	(51)	102	(62)	
Grade 3	53	(15)	36	(22)	
Primary tumor location					
Right	103	(29)	70	(42)	0.00130
Left	123	(34)	58	(35)	
Rs	40	(11)	15	(9.1)	
Ra and Rb	95	(26)	22	(13)	
Histological type					
Tub1 or Tub2	336	(93)	154	(93)	0.913
Others	25	(6.9)	11	(6.7)	
CEA					
≤ 3.4 U/dL	231	(64)	95	(58)	0.243
> 3.4 U/dL	129 (Lack 1)	(36)	70	(42)	
T factor					
T1/T2	167	(46)	67	(41)	0.356
T3	153	(42)	81	(49)	
T4	41	(11)	17	(10)	
N factor					
N0	261	(72)	123	(75)	0.629
N1	76	(21)	32	(19)	
N2	22	(6.0)	10	(6.1)	
N3	2	(0.6)	0	(0)	
Stage					
I	148	(41)	56	(34)	0.073
II	114	(32)	69	(42)	
III	99	(27)	40	(24)	
Ileocecal resection	34	(9.4)	19	(12)	< 0.0001
Right hemicolectomy	32	(8.9)	35	(21)	
Left hemicolectomy	4	(1.1)	6	(3.6)	
Sigmoidectomy	82	(23)	35	(21)	
High or low anterior resection	131	(36)	31	(19)	
Segmental colon resection	45	(12)	25	(15)	
Rectal excision without anastomosis	6	(1.7)	4	(2.4)	
Abdominoperineal resection of rectum	14	(3.9)	9	(5.5)	
Others	13	(3.6)	1	(0.6)	
Surgical approach					
Open	120	(33)	61	(37)	0.405
Laparoscopic	241	(67)	104	(63)	

ASA-PS American Society of Anesthesiologists' Physical Status, *CEA* carcinoembryonic antigen

Table 2 Comorbidities

	Young group (≤ 5 y/o) (*N* = 361)		Elderly group (≥ 75 y/o) (*N* = 165)		*P* value
	N	(%)	*N*	(%)	
Hypertension	105	(29)	68	(41)	0.007
Diabetes	60	(17)	24	(15)	0.544
Cardiovascular disease	32	(8.9)	30	(18)	0.003
Respiratory disease	12	(3.3)	20	(12)	< 0.001
Liver disorder	21	(5.8)	7	(4.2)	0.447
Renal disorder	14	(3.9)	12	(7.3)	0.106
Cerebral/psychiatric disease	23	(6.3)	24	(15)	0.003
Cancer history	27	(7.5)	19	(12)	0.137
Others	46	(13)	28	(17)	0.202
Total	204	(57)	123	(75)	< 0.0001

Table 3 Postoperative complications

	Young group (≤ 75 y/o) (*N* = 361)		Elderly group (≥ 75 y/o) (*N* = 165)		*P* value
	N	(%)	*N*	(%)	
Anastomotic leakage	20	(5.5)	9	(5.5)	0.968
Ileus	22	(6.1)	5	(3.0)	0.140
Bleeding	7	(1.9)	6	(3.6)	0.245
Respiratory complication	9	(2.5)	7	(4.2)	0.278
Wound infection	34	(9.4)	17	(10)	0.750
Others	25	(6.9)	14	(8.5)	0.526
CDc grade					
≥ II	85	(24)	42	(25)	0.635
≥ III	45	(12)	19	(12)	0.582

Univariate and multivariate analyses of possible prognostic factors in the elderly group

We performed univariate and multivariate analyses of prognostic factors for OS in the elderly group (Table 5). In the Cox hazard analysis, univariate analysis showed that the N factor ($P < 0.01$) and severe postoperative complications ($P < 0.05$) were significantly associated with worse OS. Multivariate analyses were performed for the T factor, N factor, and severe postoperative complications where $P < 0.1$ in univariate analysis. Multivariate analysis showed that the N factor (0 or 1 vs 2, HR: 5.858, 95% CI 2.113–13.997, $P < 0.01$) and severe postoperative complications (not occurred vs. occurred, HR: 2.854, 95% CI 1.271–5.802, $P < 0.05$) were independent prognostic factors for OS.

Table 4 Propensity score matching of the young and elderly groups

Variables	Young group (≤ 75 y/o) (*N* = 148)		Elderly group (≥ 75 y/o) (*N* = 148)		*P* value
	N	(%)	*N*	(%)	
Propensity score	0.34	(±0.081)	0.34	(±0.081)	0.982
Gender					
Male	87	(59)	97	(66)	0.231
Female	61	(41)	51	(34)	
Primary tumor location					
Right	56	(38)	60	(41)	0.964
Left	59	(40)	55	(37)	
Rs	12	(8.1)	12	(8.1)	
Ra and Rb	21	(14)	21	(14)	
Histological type					
Tub1 or Tub2	144	(97)	140	(95)	0.239
Others	4	(2.7)	8	(5.4)	
T factor					
T1	25	(17)	29	(20)	0.730
T2	40	(27)	32	(22)	
T3	69	(47)	73	(49)	
T4	14	(9.5)	14	(9.5)	
N factor					
N0	120	(81)	114	(77)	0.687
N1	21	(14)	25	(17)	
N2	7	(4.7)	9	(6.1)	
CEA					
≤ 3.4 U/dL	94	(64)	88	(59)	0.474
≥ 3.4 U/dL	54	(36)	60	(41)	

CEA carcinoembryonic antigen

Discussion

In comparing the prognoses of patients younger and older than 75 years (respectively) with Stage I–III CRC after PSM analysis, we identified a significant difference between the age groups for OS, but not for CSS or RR. This implies that similar surgical outcomes can be expected for both the young and elderly patients by selecting appropriate patients for surgery. CRC remains a major public health problem worldwide and an increasing percentage of patients affected are aged 75 years or older [9]. In 2017, an estimated 1,800,000 new cases of CRC were diagnosed in the world [10]. As the worldwide birthrate declines and the population ages, evidence-based measures to treat older patients are becoming increasingly necessary.

Although several studies have addressed the prognosis of older cancer patients, whether age is an independent prognostic factor in CRC is still controversial [6, 11–14]. Oh BY et al. reported that in a matched cohort, the disease-free survival and CSS of elderly patients who underwent

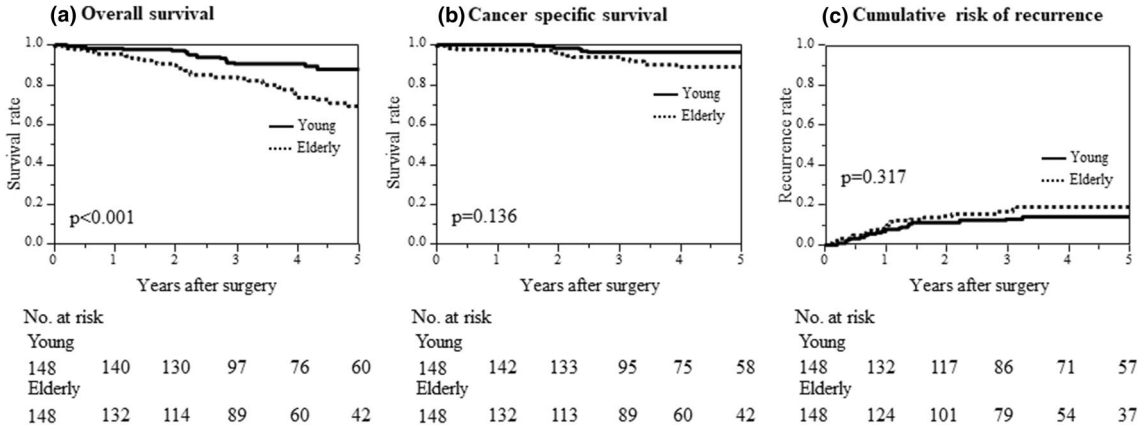

Fig. 1 Survival outcomes of patients aged ≥ 75 years vs. those of propensity-matched younger patients. **a** Overall survival, **b** cancer-specific survival, and **c** cumulative risk of recurrence after curative surgery

Table 5 Univariate and multivariate analyses of the prognostic factors for overall survival in the elderly group

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender						
Female	1					
Male	1.380	0.738–2.704	0.319			
Primary tumor location						
Left	1					
Right	1.091	0.528–2.332	0.817			
Rs	1.558	0.495–4.205	0.421			
Ra and Rb	1.611	0.599–4.009	0.329			
Comorbidity						
Without	1					
With	1.098	0.557–2.365	0.796			
T factor						
T1/T2	1			1		
T3	1.761	0.889–3.671	0.106	1.383	0.678–2.942	N.S
T4	2.505	0.927–6.263	0.069	2.690	0.993–6.744	N.S
N factor						
N0/1	1			1		< 0.01
N2	5.425	2.035–12.145	0.002	5.858	2.113–13.997	
Histological type						
Others	1					
Tub1 or Tub2	2.040	0.619–12.600	0.276			
Postoperative complication (CDc ≥ III)						
Not occurred	1					0.013
Occurred	2.642	1.187–5.303	0.019	2.854	1.271–5.802	
CEA						
≤ 3.4 U/dL	1					
≥ 3.4 U/dL	1.656	0.880–3.091	0.117			

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic, *CDc* Clavien–Dindo classification

radical surgery were comparable to those of younger patients, even though their postoperative morbidity and mortality were higher. They also reported that the standard anti-cancer treatments by stage were insufficient for elderly patients, who seldom received treatments with curative intent for recurrence, considering their general condition

[15]. With improved surgery and anesthesia techniques, elderly people can expect tumor prognoses similar to those for younger patients [16]. However, the survival gain is less for elderly patients than for younger patients [17, 18]. In our study, elderly patients had higher median ASA scores and more comorbidities. Elderly patients have more right-colon tumors, so they undergo right hemicolectomy more frequently than younger patients. Right-colon cancers are reportedly more common in elderly patients, consistent with our findings [19, 20]. However, the incidences of postoperative complications in our study were comparable, which is also consistent with past reports [5, 16]. After matching tumor factors and evaluating long-term prognosis, CSS and RR were equivalent in the two age groups. The elderly patients' morbidity and mortality were relatively low, possibly because the study cohort was limited to those with resectable Stage I–III CRC.

The International Society of Geriatric Oncology (SIOG) recommend that CRC patients > 65 years of age who require surgery should undergo preoperative whole-patient evaluations for the most common physiological effects of aging, physical and mental ability, and social support [21]. Furthermore, the 2013 SIOG consensus recommendations for the treatment of CRC in elderly patients stress the importance of assessing general condition and surgical risks before surgery in these patients [22]. When treating elderly patients, we need to look not only at their diseases, but also at factors such as their social environments, including familial environment, degree of care required, and economic background [23, 24]. The surgeon must evaluate several factors comprehensively and adapt clinical decisions accordingly. Therefore, better prognostic tools to stratify elderly patients are urgently needed.

The multivariate analysis for OS in the elderly patients revealed that the N factor and severe postoperative complications were independent prognostic factors. As others have reported, severe complications greatly affect the long-term outcomes after surgery for CRC [25–27]. Our results show the importance of taking care to prevent postoperative complications and to fully evaluate their risk before surgery. Devoto L et al. [28] suggested that the preoperative investigations and perioperative planning with the use of high dependency and intensive care facilities are the keys to success. Careful preoperative assessment, with comorbidities and multiple cancers in mind, and deciding whether the patient's general condition can withstand general anesthesia and surgery are critical.

This study had some limitations. First, it was a retrospectively designed, single-center study. Second, as it included only patients who underwent radical resections, our results are not generalizable to older patients who cannot undergo surgery, including those with more advanced cancers or unresectable diseases. Nevertheless, we believe that the prognostic expectations for appropriately selected elderly patients may be equal to those for younger patients.

Conclusion

By selecting appropriate patients, the outcomes of CRC surgery can be equivalent in young and elderly patients.

Compliance with ethical standards

Conflict of interest We have no financial conflicts of interest to disclose.

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