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ORIGINAL ARTICLE

Oncologic outcome of colorectal cancer patients over age 80: a propensity score-matched analysis

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Abstract

Purpose It remains unclear whether old age is a poor prognostic factor in colorectal cancer (CRC). We compared oncologic outcomes in CRC patients according to age, using 80 as the dividing point.

Methods CRC patients who underwent radical surgery from 2000 to 2011 were evaluated. We performed matched and adjusted analyses comparing oncologic outcomes between patients with ≥ 80 and < 80 years old.

Results Among 9562 patients, 222 were elderly. The median age was 82.0 years in elderly patients and 59.0 years in young patients. Elderly patients received less neoadjuvant or adjuvant therapy compared to young patients ($p < 0.001$). After recurrence, significantly fewer elderly patients received additional treatments ($p < 0.001$). Before matching, disease-free survival (DFS) and cancer-specific survival (CSS) were significantly lower for elderly patients compared to those for young patients ($p < 0.001$ and $p < 0.001$, respectively). After matching, DFS and CCS were not significantly different between the two groups ($p = 0.400$ and $p = 0.267$, respectively). In a multivariate analysis for prognostic factors, old age was not an independent poor prognostic factor of DFS and CCS ($p = 0.619$ and $p = 0.137$, respectively).

Conclusions Elderly patients aged ≥ 80 years with CRC had similar oncologic outcome to young patients, and age was not an independent prognostic factor.

Keywords Chemotherapy · Colorectal cancer · Old age · Surgery · Survival

Introduction

Colorectal cancer (CRC) is the third most common malignancy and a leading cause of cancer-related deaths worldwide [1]. Median age at diagnosis of CRC is 68 years, and about 35% of CRC patients are diagnosed when they are over 75 years old [2]. As the size of the elderly population grows, most surgeons and oncologists will confront an increasing number of elderly patients with CRC in the near future [2]. However, elderly patients may have multiple comorbidities and decreased physical or physiological functions, so postoperative morbidity and mortality may occur more often in these patients. Therefore, elderly patients have been less likely to receive curative surgery and adjuvant therapy compared to younger patients [2, 3]. As life expectancy increases, however, appropriate cancer treatments for elderly patients with CRC should be carefully considered.

Most studies have used a cutoff age of 65 to denote elderly patients with CRC, while others have used cutoff ages of 60, 70, or something else. However, there are still few studies that define elderly patients as over 80. In addition, potential bias is a concern for many studies due to a lack of equal distribution between age groups [2, 4, 5]. Therefore, it is necessary to adjust patient characteristics and compare oncologic outcomes

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between elderly and young patients. An analysis focusing on elderly patients over 80 years old will particularly help to establish therapeutic strategies for this particular age group.

In this study, we aimed to investigate oncologic outcomes of elderly patients aged ≥ 80 years with CRC.

Materials and methods

Patients

A total of 9562 records of patients with CRC who underwent surgical resection from January 2000 to December 2011 at a tertiary university-based hospital were retrospectively reviewed. All had histologically confirmed primary adenocarcinoma of the colorectum and underwent radical surgery for the primary tumor and synchronous metastatic lesions. Patients were excluded if they had hereditary CRC, recurrent disease, local excision, and palliative surgery (Fig. 1). This study was approved by the Samsung Medical Center Institutional Review Board.

Treatments and postoperative surveillance

All patients underwent radical surgery with or without neoadjuvant or adjuvant treatments. In colon cancer, adjuvant chemotherapy was recommended to patients with high risk stage II, stage III, or stage IV diseases. High risk stage II was defined as the number of harvested lymph nodes less than 12, poorly differentiated histology, lymphatic or vascular invasion, perineural invasion, bowel obstruction or perforation, or positive resection margins. In rectal cancer, neoadjuvant chemoradiotherapy was recommended to patients with a clinical T3-T4 and/or node-positive rectal cancer located less than 10 cm from the anal verge. These patients also received adjuvant chemotherapy. Adjuvant chemotherapy was also recommended to rectal cancer patients with stage II-IV diseases who did not received neoadjuvant chemoradiotherapy. In addition to these criteria, general conditions and comorbidities of patients were considered to determine neoadjuvant or adjuvant treatments.

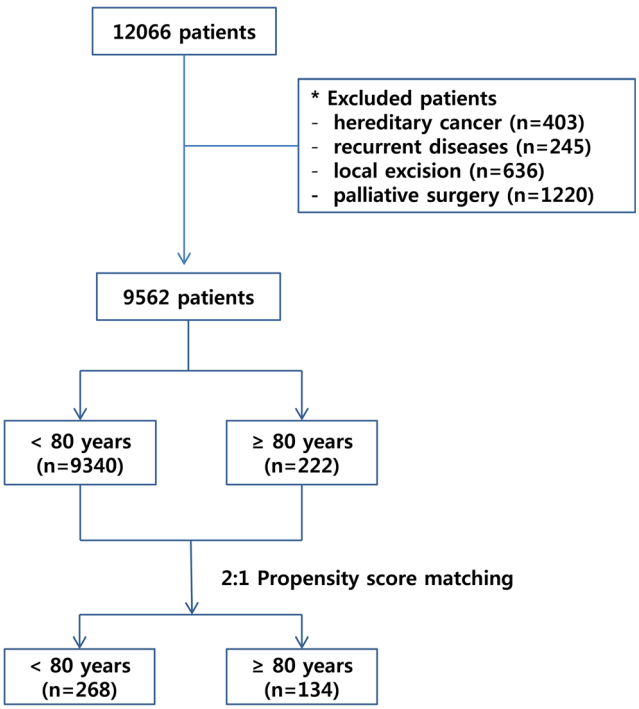

Fig. 1 Flow chart of this study

Postoperative surveillance was performed at visits every 3 months for the first 2 years and then every 6 months for up to 5 years. Most patients were evaluated with physical examination, serum carcinoembryonic antigen (CEA) level, and chest X-ray at each visit. Abdominopelvic CT and chest CT were performed every 6 months for 5 years after surgery [6]. Colonoscopy was performed at the first year and then biennially.

Assessment of clinical outcomes

Patients were categorized into elderly patients aged ≥ 80 and young patients aged < 80 years. Performance status of patients was evaluated by the American Society of Anesthesiologists (ASA) class. We compared clinicopathologic features and cancer treatments between the two groups. To analyze survival according to age group, we adjusted patient characteristics between the two groups and compared survival outcomes. In addition, we identified prognostic factors in a matched cohort. The primary endpoint of this study was survival outcomes in elderly patients, and the secondary endpoint was differences in cancer treatment according to age. DFS was defined as the period from the surgery for a cancer to the time that the patient survives without any signs or symptoms of cancer recurrence. CSS was defined as the period from surgery to the cancer-related death in the absence of other causes of death. OS was defined as the period from the surgery to the death from any cause.

Statistical analysis

Statistical analyses were performed using the R software version 3.0.2 and SPSS for Windows version 20.0. Categorical variables were compared using the chi-squared test. A propensity score-matched analysis was performed to minimize confounding bias between the two groups. We adjusted variables such as gender, ASA class, CEA level, location of tumor, method of operation, stage, cell type, lymphatic invasion, vascular invasion, perineural invasion, neoadjuvant treatment, and adjuvant treatment. Before and after matching, survival rates were analyzed using the Kaplan–Meier method and log-

Table 1 Patient characteristics before and after matching

Variables	Before matching			After matching		
	< 80 years ($n = 9340$)	≥ 80 years ($n = 222$)	*p*-value	< 80 years ($n = 268$)	≥ 80 years ($n = 134$)	*p*-value
Median age, years (range)	59 (16–79)	82 (80–95)		66 (29–79)	82 (80–95)	
Gender, n (%)			0.012			0.672
Male	5697 (61.0%)	117 (52.7%)		141 (52.6%)	67 (50.0%)	
Female	3643 (39.0%)	105 (47.3%)		127 (17.4%)	67 (50.0%)	
ASA class, n (%)			< 0.001			0.671
1	4437 (47.5%)	37 (16.7%)		43 (16.0%)	17 (12.7%)	
2	4417 (47.3%)	142 (63.9%)		184 (68.7%)	96 (71.6%)	
3	480 (5.1%)	41 (18.5%)		41 (15.3%)	21 (15.7%)	
4	6 (0.1%)	2 (0.9%)		0 (0.0%)	0 (0.0%)	
CEA level, n (%)			< 0.001			0.904
< 5 ng/ml	6935 (74.2%)	136 (61.3%)		198 (73.9%)	100 (74.6%)	
≥ 5 ng/ml	1716 (18.4%)	48 (21.6%)		70 (26.1%)	34 (25.4%)	
Unknown	689 (7.4%)	38 (17.1%)		0 (0.0%)	0 (0.0%)	
Location of tumor, n(%)			0.002			0.809
Colon	5798 (62.1%)	160 (72.1%)		200 (74.6%)	98 (73.1%)	
Rectum	3542 (37.9%)	62 (27.9%)		68 (25.4%)	36 (26.9%)	
Method of operation, n(%)			< 0.001			0.828
Open	5617 (60.1%)	161 (72.5%)		167 (62.3%)	82 (61.2%)	
Laparoscopic	3723 (39.9%)	61 (27.5%)		101 (37.7%)	52 (38.8%)	
Stage, n (%)			< 0.001			0.450
0	496 (5.3%)	6 (2.7%)		0 (0.0%)	0 (0.0%)	
I	1955 (20.9%)	28 (12.6%)		39 (14.6%)	17 (12.7%)	
II	2886 (30.9%)	102 (45.9%)		129 (48.1%)	60 (44.8%)	
III	3491 (37.4%)	79 (35.6%)		80 (29.8%)	50 (37.3%)	
IV	512 (5.5%)	7 (3.2%)		20 (7.5%)	7 (5.2%)	
Cell type, n (%)			0.013			0.773
WD/MD	8343 (89.3%)	185 (83.3%)		224 (83.6%)	114 (85.1%)	
PD/MUC/SRC	854 (9.2%)	33 (14.9%)		44 (16.4%)	20 (14.9%)	
Unknown	143 (1.5%)	4 (1.8%)				
LI, n (%)			0.093			0.909
Yes	2285 (24.5%)	60 (27.0%)		84 (31.3%)	41 (30.6%)	
No	5158 (55.2%)	130 (58.6%)		184 (68.7%)	93 (69.4%)	
Unknown	1897 (20.3%)	32 (14.4%)		0 (0.0%)	0 (0.0%)	
VI, n (%)			0.262			0.887
Yes	1241 (13.3%)	33 (14.9%)		44 (16.4%)	21 (15.7%)	
No	5676 (60.8%)	142 (64.0%)		224 (83.6%)	113 (84.3%)	
Unknown	2423 (25.9%)	47 (21.1%)		0 (0.0%)	0 (0.0%)	
PNI, n (%)			0.511			0.387
Yes	899 (9.6%)	22 (9.9%)		46 (17.2%)	18 (13.4%)	
No	5623 (60.2%)	141 (63.5%)		222 (82.8%)	116 (86.6%)	
Unknown	2818 (30.2%)	59 (26.6%)		0 (0.0%)	0 (0.0%)	
Neoadjuvant Tx, n(%)			< 0.001			0.333
Yes	881 (9.4%)	2 (0.9%)		0 (0.0%)	1 (0.7%)	
No	8459 (90.6%)	220 (99.1%)		268(100.0%)	133 (99.3%)	
Adjuvant Tx, n(%)			< 0.001			0.748
Yes	5335 (57.1%)	23 (10.4%)		34 (12.7%)	15 (11.2%)	
No	4005 (42.9%)	199 (89.6%)		234 (87.3%)	119 (88.8%)	

ASA American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *MUC* mucinous carcinoma, *SRC* signet ring cell carcinoma, *LI* lymphatic invasion, *VI* vascular invasion, *PNI* perineural invasion, *Tx* treatment

rank test. Multivariate analyses were performed using a Cox proportional hazard model to identify prognostic factors. *P* values were derived from two-tailed tests and $p < 0.05$ was considered statistically significant.

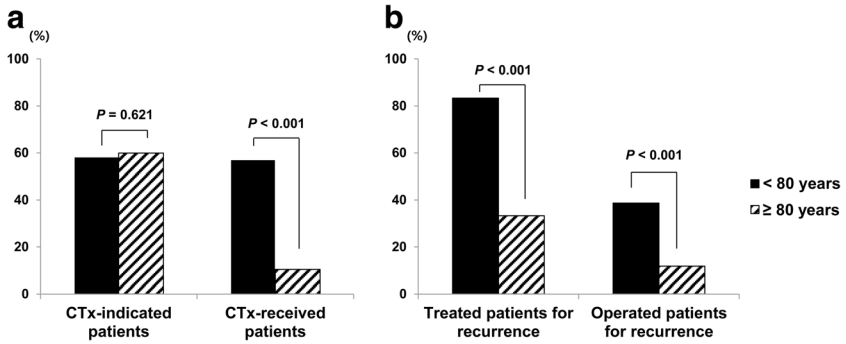

Fig. 2 The tendency for under-treatment of colorectal cancer in elderly patients. **a** Rates of patients who received adjuvant chemotherapy (CTx) according to age overall ($n = 9562$). CTx was indicated at a similar rate between young (58.3%, $n = 5441$) and elderly patients (59.9%, $n = 133$). However, CTx was received at significantly lower rates in elderly patients (10.4%, $n = 23$) than in young patients (57.1%, $n = 5335$). **b** Rates of patients treated for recurrence according to age among patients with recurrence ($n = 1763$). Significantly fewer elderly patients (33.3%, $n = 17$) than young patients (83.4%, $n = 1428$) were treated for recurrence. In addition, significantly fewer elderly patients (11.8%, $n = 6$) than young patients (38.7%, $n = 662$) received surgery

Results

Patient characteristics

Among a total of 9562 patients, 222 (2.3%) were elderly patients aged ≥ 80 years. The median age was 82.0 (range, 80–95) years in elderly patients and 59.0 (range, 16–79) years in young patients. As shown in Table 1, many variables were differently distributed between elderly and young patients. Female sex, high ASA class, elevated level of preoperative CEA, colon cancer, open surgery, stage II, and poor histology were more common in elderly patients than those in young patients. In addition, very few elderly patients received neoadjuvant or adjuvant therapy compared to young patients.

Elderly patients had higher comorbidities than young patients (68.0 vs. 51.8%; $p < 0.001$). In addition, elderly patients showed a tendency to have multiple comorbidities compared to young patients (36.9 vs. 18.5%; $p < 0.001$). The most common comorbidities were hypertension, diabetes, pulmonary diseases, and cardiovascular diseases. Postoperative 30-day morbidity and mortality were significantly higher in elderly patients than those in young patients (26.6 vs. 16.8%; $p < 0.001$ and 1.4 vs. 0.1%; $p = 0.002$, respectively). Postoperative 90-day mortality was also higher in elderly patients than that in young patients (2.3 vs. 0.3%, $p = 0.001$).

Features of cancer treatment according to age

All patients underwent radical surgery for the primary tumor and synchronous metastatic lesions. Of the 222 elderly patients, 133 met the eligibility criteria for adjuvant chemotherapy as mentioned above, but only 23 (17.3%) actually received adjuvant chemotherapy. Furthermore, only three such patients received intravenous chemotherapy, while the others received oral chemotherapy. In contrast, 5335 (98.1%) young patients received adjuvant chemotherapy among 5441 young patients who met the criteria for adjuvant chemotherapy (Fig. 2a).

During follow-up, recurrences occurred in 1712 (18.3%) young and 51 (23.0%) elderly patients ($p = 0.078$). There was no significant difference in recurrence patterns between the two groups ($p = 0.343$; Table 2), but significantly fewer elderly patients received additional treatment for recurrence than young patients ($p < 0.001$). Recurrence occurred in 51 elderly patients, of which 17 (33.3%) received additional treatment for their recurrences. Of the 17, only 6 patients received aggressive surgical treatment, while the others received palliative treatments. In addition, among seven elderly patients who had only local recurrence, only one received surgical treatment; the others did not receive any treatment. In contrast, among 1712 young patients with recurrence, 1428 (83.4%) received treatment for their

Table 2 Recurrence pattern according to age

Recurrence pattern	< 80 years ($n = 1712$)	≥ 80 years ($n = 51$)	*P*-value
Local only	139 (8.1%)	7 (13.7%)	
Systemic only	1315 (76.8%)	36 (70.6%)	0.343
Both	258 (15.1%)	8 (15.7%)	

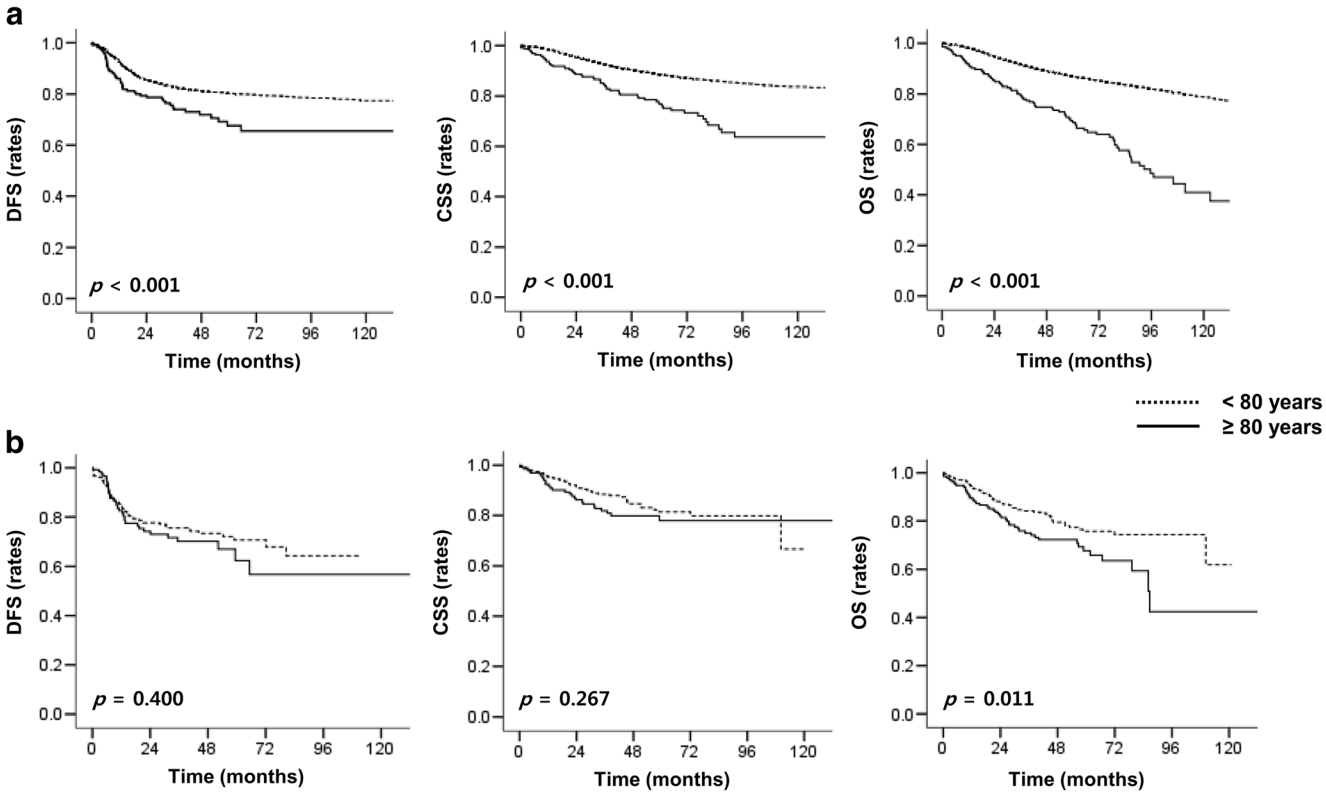

Fig. 3 Kaplan–Meir plots according to age before and after matching. **a** Before matching, elderly patients showed significantly lower disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) rates compared to young patients. **b** After matching, DFS and CSS were not significantly different between the two groups

recurrences, including 662 patients who received aggressive surgical treatment (Fig. 2b).

Survival outcomes according to age

To identify the impact of age on oncologic outcomes of CRC, we analyzed disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) according to age. The median follow-up was 58.4 (range, 0.1–184.1) months. Overall, elderly patients showed significantly smaller DFS, CSS, and OS rates compared to young patients ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively; Fig. 3a).

However, there was a confounding bias for comparing survival according to age, because patient characteristics were not equally distributed between these two groups. Therefore, we adjusted the patients at a one-to-two ratio using a propensity score-matched analysis, and there were 134 elderly patients and 268 young patients in the matched cohort. After matching, we determined that the groups were well balanced for all variables (Table 1). In matched patients, there were no differences in DFS and CSS according to age ($p = 0.400$ and $p = 0.267$, respectively) (Fig. 3b). Although there was still a difference in OS, the degree of difference was reduced compared to that before matching (Fig. 3b).

To identify whether age was an independent prognostic factor of survival in CRC, Cox proportional hazard modeling was performed in matched patients. Age and factors that were significant in the univariate analysis were included in the multivariate analysis. In the multivariate analysis, old age was not an independent poor prognostic factor of DFS and CSS ($p = 0.619$ and $p = 0.137$, respectively) (Table 3).

Discussion

In this study, we investigated oncologic outcomes of elderly patients aged ≥ 80 years with CRC. Because patient characteristics were not equally distributed, we performed a propensity score matching to compare elderly and young patients, resulting in well balanced for all variables. Overall, unmatched elderly patients showed significantly lower DFS and CSS rates compared to young patients. After matching, DFS and CSS were not different between the two groups. In matched patients, old age was not an independent poor prognostic factor for DFS and CSS.

Many studies have investigated survival outcomes of patients with CRC according to age [4, 5, 7–9]. Most studies suggest poorer oncologic outcomes in elderly patients, although the idea

Table 3 Prognostic factors of survival in matched patients

Variables	Disease-free survival			Cancer-specific survival		
	Univariate	Multivariate		Univariate	Multivariate	
	p-value	HR (95% CI)	*p*-value	*p*-value	HR (95% CI)	*p*-value
Age						
80 vs. <80 years	0.400	1.114 (0.728–1.706)	0.619	0.268	1.462 (0.886–2.414)	0.137
Gender						
female vs. male	0.215			0.745		
ASA class	0.689			0.100		
2 vs. 1						
3 vs. 1						
CEA level						
≥5 vs. <5 ng/ml	< 0.001	1.756 (1.111–2.775)	0.016	< 0.001	1.693 (0.983–2.913)	0.058
Location of tumor						
rectum vs. colon	0.699			0.240		
Method of operation						
laparoscopic vs. open	0.014	0.665 (0.408–1.083)	0.101	0.020	0.551 (0.298–1.016)	0.056
Stage	< 0.001		< 0.001	< 0.001		< 0.001
II vs. I		1.460 (0.498–4.285)	0.491		6.116 (0.803–46.574)	0.080
III vs. I		4.495 (1.523–13,264)	0.006		15.558 (1.976–122.492)	0.009
IV vs. I		6.794 (1.969–23.447)	0.002		33.001 (3.828–284.504)	0.001
Cell type						
PD/MUC/SRC vs. WD/MD	0.014	1.046 (0.625–1.751)	0.865	0.001	1.634 (0.924–2.890)	0.092
Lymphatic invasion						
yes vs. no	< 0.001	1.555(0.964–2.508)	0.071	0.001	0.855 (0.487–1.500)	0.584
Vascular invasion						
yes vs. no	< 0.001	1.127 (0.668–1.846)	0.635	< 0.001	1.533 (0.839–2.800)	0.165
Perineural invasion						
yes vs. no	< 0.001	1.906 (1.171–3.101)	0.009	0.002	1.057 (0.577–1.936)	0.858
Neoadjuvant treatment						
yes vs. no	1.000			0.978		
Adjuvant treatment						
yes vs. no	< 0.001	1.009 (0.622–1.638)	0.971	0.002	0.874(0.480–1.589)	0.658

ASA American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *MUC* mucinous carcinoma, *SRC* signet ring cell carcinoma, *HR* hazard ratio, *CI* confidence interval

that age is an independent prognostic factor in CRC has been controversial [4, 10–15]. A previous meta-analysis of oncologic outcomes according to age showed worse oncologic outcomes in elderly patients with CRC [11]. In metastatic CRC, elderly patients were associated with poorer survival compared to patients of middle age [4]. In contrast, a different study found no significant difference in both DFS and OS according to age [2]. In our study, elderly patients had comparable oncologic outcomes to young patients in a matched cohort.

The aging process results in physiologic declines in vital organ function, which can directly affect tolerance to surgery or chemotherapy [7]. Accordingly, it is necessary to consider both the risks and benefits of treatment for elderly cancer patients and a study showed the effect of geriatric evaluation in this regard [16]. Many studies have investigated the feasibility of cancer treatment for elderly patients with CRC. Recent studies have suggested that older patients can benefit from radical surgery [2, 17–19], although the risk of postoperative morbidity and mortality is higher in elderly patients [20, 21]. In our study, DFS and CSS of elderly patients who underwent radical surgery were comparable to young patients, even though they suffered from more postoperative morbidity and mortality than young patients. This finding provides evidence that radical surgery is essential for optimal survival outcomes in elderly patients. It is better to decide radical surgery based on their comorbidities and general condition

rather than age itself. If the general condition of elderly patients is good, it is better to treat them as well as young patients. It may also be helpful to determine the appropriate treatment such as minimally invasive surgery for elderly patients [22].

Despite the growing elderly population, there are no old age-specific guidelines for optimal cancer treatment. The current indications for chemotherapy in elderly patients with CRC remain controversial. Some studies have shown improved survival in elderly patients who received adjuvant chemotherapy [23–25], whereas others did not [2, 26]. Elderly patients might experience morbidity and mortality from comorbidities rather than their cancer. With this concern, many studies have reported that elderly patients are less likely to be offered cancer treatment compared to young patients [11, 17, 27, 28]. In our study, we found that standard anti-cancer treatments by stage were insufficient in elderly patients and elderly patients seldom received treatments with curative intent for their recurrences. This tendency for under-treatment along with low functional reservoirs might result in worse survival of elderly patients before matching.

There were some limitations in our study. This study was retrospectively performed at a single institution. We did not evaluate the effect of under-treatment on survival due to an insufficient number of elderly patients with standardized treatment. In addition, we did not analyze the efficacy of neoadjuvant treatment, because only two elderly patients received neoadjuvant treatment in our cohort. Despite these limitations, our study had the strength of a propensity score matching for the survival analysis to overcome confounding bias of patient characteristic differences between age groups. In addition, we included a large number of patients aged ≥ 80 years. Furthermore, we analyzed the features of treatment after recurrence in an attempt to approach disease progression.

Conclusions

In conclusion, elderly patients aged ≥ 80 years had equivalent outcomes compared to patients aged < 80 years after radical surgery, suggesting that age should not be a determining factor alone in terms of treatment of CRC. Radical surgery is feasible for patients aged ≥ 80 years with CRC, but there was a tendency to under-treat elderly patients after operation. Further analysis will be needed to evaluate the efficacy of adjuvant treatments in this particular age group. Clinical trials to suggest appropriate cancer treatment for elderly patients with CRC are warranted.

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Compliance with ethical standards

This study was approved by the Samsung Medical Center Institutional Review Board.

Conflict of interest The authors declare that they have no conflict of interest.

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