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Effect of Age on Laparoscopic Surgery and Postoperative Chemotherapy in Elderly Patients With Colorectal Cancer

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Purpose: We aimed to evaluate the postoperative complications of laparoscopic colorectal cancer (CRC) surgery and the adverse events of postoperative chemotherapy in elderly patients compared to younger patients and to identify the factors influencing the termination of postoperative chemotherapy.

Methods: Between June 2015 and May 2018, 188 patients with CRC underwent laparoscopic surgery with curative intent. Patients aged ≥70 were defined as elderly. Postoperative complications and adverse events of chemotherapy were assessed by using the Clavien-Dindo classification and the Common Terminology Criteria for Adverse Events, respectively. The clinicopathological factors were analyzed retrospectively.

Results: Seventy-eight patients were considered elderly with a mean age of 77.5±5.5 years. Overall postoperative complications occurred in 68 patients (36.2%). Age and primary tumor location were independent predictors of overall postoperative complications. Smoking history was the only independent predictor of major postoperative complications. Of 113 patients who were recommended postoperative chemotherapy, 90 patients (79.6%) received postoperative chemotherapy. Overall adverse events occurred in 40 patients (44.4%). The American Society of Anesthesiologists physical status classification and chemotherapy regimen were significantly associated with overall adverse events. The chemotherapy regimen was the only factor significantly associated with severe adverse events. Of 90 patients, postoperative chemotherapy could not be completed in 11 (12.2%). Age was the only factor significantly associated with stopping postoperative chemotherapy (P=0.003).

Conclusion: This study shows that laparoscopic CRC surgery and postoperative chemotherapy were feasible in elderly patients. Further efforts are needed to ensure that elderly patients have the opportunity to make informed decisions regarding postoperative chemotherapy.

Keywords: *Elderly patients; Age; Colorectal cancer; Laparoscopic surgery; Adjuvant chemotherapy*

INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality in the elderly because more than 70% of the cases occur in people over 65 years of age [1]. Furthermore, its incidence is expected to increase by 60% by 2030 [2]. With increases in life expectancy, the number of elderly patients who need treatment for CRC will also increase.

Surgical intervention is the optimal treatment for patients with resectable CRC. Laparoscopic CRC surgery has advantages, such as less postoperative pain, quicker return of bowel function, shorter hospital stays, better cosmetic effects, and lower incidence of postoperative complications, compared to open CRC surgery [3, 4]. In addition, several randomized trials have demonstrated that laparoscopic CRC surgery provided equivalent oncologic results compared to open CRC surgery [4, 5]. Therefore, laparoscopic CRC surgery appears to be a suitable treatment for elderly patients. However, during laparoscopic surgery, pneumoperitoneum and changing position affect hemodynamics and the respiratory system, particularly in elderly patients [6]. Furthermore, elderly patients often exhibit more comorbidities than younger pa-

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tients, which could contribute to the increase in postoperative morbidity and mortality in elderly patients [1, 7]. Therefore, there is still conflicting evidence regarding the safety and benefits of laparoscopic CRC surgery for elderly patients.

In addition, postoperative chemotherapy for CRC has been used in the adjuvant setting for stage III and high-risk stage II patients and is administered to patients with metastatic disease [8]. The use of postoperative chemotherapy in elderly patients, however, remains controversial due to concerns over both toxicity and death from causes unrelated to cancer. Although several studies have suggested that advanced age alone should not be used to exclude patients from effective treatment [9, 10], elderly patients are significantly less likely to be referred for and receive guideline-recommended postoperative chemotherapy [11, 12].

Therefore, the aim of this study was to evaluate the postoperative complications of laparoscopic CRC surgery and the adverse events of postoperative chemotherapy in elderly patients compared to younger patients, and to identify the factors influencing the termination of postoperative chemotherapy.

METHODS

Consecutive patients who underwent laparoscopic surgery for CRC at our institution between June 2015 and May 2018, were retrospectively analyzed. The study included patients with tumor stages I, II, or III, as well as patients with metastatic disease who underwent surgery with curative intent (R0 resection). Patients were excluded if they underwent conventional open surgery or nonradical surgery, if there was evidence of concurrent malignancy, or if surgery was performed with palliative intent. This study was approved by the Institutional Review Board at the Soonchunghyang University Seoul Hospital (2019-08-019). Informed consent was waived according to the institutional rules for retrospective studies.

Clinicopathological factors, including patient age, sex, body mass index, previous operative history, medical history, the American Society of Anesthesiologists (ASA) physical status classification, the Charlson Comorbidity Index (CCI), primary tumor location, operative procedure, open conversion, operative time, estimated blood loss, the length of hospital stay, postoperative morbidity, mortality within 30 days following surgery, postoperative chemotherapy, chemotherapy regimen, chemotherapy dose, and mortality within 1 year following surgery were recorded after surgery.

Elderly age was defined as age 70 years or older, as in a previous study [13]. The primary tumor location was divided into the colon and the rectum. Tumor stage was classified by using the 8th edition of the American Joint Committee on Cancer staging system. Laparoscopic surgery was performed in all participants and the surgeon decided whether to perform a right or left hemicolectomy, anterior resection, low/ultra-low anterior resection, or colostomy procedure including abdominoperineal resection and Hartmann operation.

Operative mortality was defined as death within 30 days of surgery. Postoperative complications were accessed by using the Clavien-Dindo (CD) classification [14]. Overall postoperative complications were defined as those with CD grade II or higher, and complications with CD grades 0–I were defined as unremarkable recovery. Major postoperative complications were defined as those with CD grade III or higher, and minor postoperative complications were defined as those with CD grades 0–II, as in a previous study [15]. Anastomotic complications, including anastomotic leakage or an intraabdominal abscess, were detected by CT scanning. Postoperative ileus was defined as the absence of intestinal function for 72 hours or more after surgery and was confirmed by plain radiography. Urinary retention was defined as the inability to self-void after removing the urinary catheter, requiring catheterization or reinsertion of an indwelling catheter.

Standard postoperative chemotherapies were administered in accordance with the National Comprehensive Cancer Network (NCCN) guidelines [8]. Adverse events of postoperative chemotherapy were accessed by using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16]. Overall adverse events were defined as those with CTCAE grade II or higher, and adverse events with CTCAE grades 0–I were defined as an uneventful course. Severe adverse events were defined as those with CTCAE grade III or higher, and mild adverse events were defined as those with CTCAE grades 0–II, as in a previous study [17].

Categorical variables were analyzed using the chi-squared test or Fisher exact test. Continuous variables were compared using Student t-tests. Variables with P-values $\leq$ 0.1 in univariate analyzes were included in multivariate logistic regression to identify factors that were independently and significantly associated with postoperative complications, adverse events of postoperative chemotherapy, and withdrawal of postoperative chemotherapy. P-values $\leq$ 0.05 were considered statistically significant. Statistical analyzes were performed with the use of SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between June 2015 and May 2018, 230 patients underwent CRC surgery at our hospital. Of these, 188 patients were included in the study. A total of 42 patients were excluded because of conventional open surgery in 9 patients, transanal local excision in 14 patients, concurrent malignancy in 2 patients, and palliative surgery in 17 patients.

Baseline characteristics and postoperative outcomes are summarized in Table 1. There were no significant differences in baseline characteristics between the elderly patients and nonelderly patients, except for gender, smoking and alcohol history, hypertension, and ASA physical status classification. The mean age of the patients was 66.3 ± 11.8 years. The mean age of patients in the nonelderly and elderly groups were 58.4 ± 8.1 and 77.5 ± 5.5 years,

Table 1. Patient characteristics and postoperative outcomes (n=188)

Characteristic	Nonelderly (n=110)	Elderly (n=78)	P-value
Age (yr)	58.4±8.1	77.5±5.5	<0.001
Sex			0.007
Male	69 (62.7)	33 (42.3)	
Female	41 (37.3)	45 (57.7)	
Body mass index (kg/m^2)	23.4±2.9	24.1±3.8	0.172
Primary tumor location			0.100
Colon	60 (54.5)	52 (66.7)	
Rectum	50 (45.5)	26 (33.3)	
Operative procedure			0.223
Hemicolectomy	37 (33.6)	38 (48.7)	
Anterior resection	23 (20.9)	14 (17.9)	
LAR/ultra-LAR	44 (40.0)	23 (29.5)	
Colostomy	6 (5.5)	3 (3.8)	
Open conversion			0.280
No	107 (97.3)	73 (93.6)	
Yes	3 (2.7)	5 (6.4)	
Operative time (min)	280.2±115.1	259.0±88.3	0.174
Estimated blood loss (mL)	181.7±137.3	209.0±309.6	0.414
Previous operative history			0.144
No	83 (75.5)	51 (65.4)	
Yes	27 (24.5)	27 (34.6)	
Smoking history			0.016
No	69 (62.7)	62 (79.5)	
Yes	41 (37.3)	16 (20.5)	
Alcohol history			0.001
No	65 (59.1)	64 (82.1)	
Yes	45 (40.9)	14 (17.9)	
Hypertension			0.001
No	75 (68.2)	33 (42.3)	
Yes	35 (31.8)	45 (57.7)	
Diabetes			0.053
No	91 (82.7)	55 (70.5)	
Yes	19 (17.3)	23 (29.5)	
ASA PS classification			0.003
I	33 (30.0)	8 (10.3)	
II	66 (60.0)	62 (79.5)	
III–IV	11 (10.0)	8 (10.3)	

(*Continued to the next*)

Table 1. Continued

Characteristic	Nonelderly (n=110)	Elderly (n=78)	P-value
Charlson Comorbidity Index			0.091
0	75 (68.2)	40 (51.3)	
1	23 (20.9)	28 (35.9)	
2	9 (8.2)	8 (10.3)	
≥3	3 (2.7)	2 (2.6)	
T stage			0.052
0–2	51 (46.4)	25 (32.1)	
3–4	59 (53.6)	53 (67.9)	
N stage			1.000
0	63 (57.3)	44 (56.4)	
1–2	47 (42.7)	34 (43.6)	
Tumor stage			0.307
0–1	38 (34.5)	18 (23.1)	
2	25 (22.7)	25 (32.1)	
3	42 (38.2)	31 (39.7)	
4	5 (4.5)	4 (5.1)	
Histology of primary tumor			0.303
Well	23 (20.9)	14 (17.9)	
Moderately	81 (73.6)	55 (70.5)	
Mucinous or poorly	6 (5.5)	9 (11.5)	
Lymphatic invasion			0.096
No	72 (65.5)	41 (52.6)	
Yes	38 (34.5)	37 (47.4)	
Venous invasion			0.126
No	81 (73.6)	49 (62.8)	
Yes	28 (25.5)	29 (37.2)	
Perineural invasion			1.000
No	88 (80.0)	60 (76.9)	
Yes	22 (20.0)	18 (23.1)	
Length of hospital stay (day)	12.17±7.1	15.0±9.3	0.024
Clavien-Dindo classification grade			0.001
0	61 (55.5)	20 (25.6)	
I	18 (16.4)	21 (26.9)	
II	24 (21.8)	30 (38.5)	
III	7 (6.4)	7 (9.0)	
IV–V	0 (0)	0 (0)	
Reoperation	3 (2.7)	5 (6.4)	0.280
30-Day mortality	0 (0)	0 (0)	-

Values are presented as mean±standard deviation or number (%).
LAR, low anterior resection; ASA PS, American Society of Anesthesiologists physical status.

respectively. A total of 33 elderly patients (42.3%) were male. We performed rectal cancer surgery in 76 patients (40.4%), including low/ultra-low anterior resection in 67 patients (35.6%), and colostomy procedure in 9 patients (4.8%). A total of 8 patients (4.2%) were converted to conventional open surgery. In the postoperative outcomes, a significantly longer length of hospital stay characterized the elderly patients compared with the nonelderly patients. There was a significant difference in CD grade between the elderly patients and nonelderly patients (P = 0.001). Eight patients (4.3%) underwent reoperations. There was no patient mortality within 30 days after surgery.

Postoperative complications occurred in 164 cases, including 70 (37.2%) in grade I, 80 (44.8%) in grade II, 6 (3.2%) in grade IIIa, and 8 (4.2%) in grade IIIb, respectively. The most common com-

Table 2. Univariate and multivariate analysis of factors affecting overall postoperative complications after laparoscopic CRC surgery (n=188)

Characteristic	Unremarkable recovery (n = 120)	Overall complication (n = 68)	P-value	OR	95% CI	P-value
Age (yr)			0.009			0.003
Nonelderly	79 (65.8)	31 (45.6)		1		
Elderly	41 (34.2)	37 (54.4)		2.608	1.386–4.905	
Mean ± SD	64.7 ± 12.1	69.1 ± 10.8	0.014			
Sex			0.762			
Male	64 (53.3)	38 (55.9)				
Female	56 (46.7)	30 (44.1)				
Body mass index (kg/m^2)	23.8 ± 3.0	23.4 ± 3.7	0.371			
Primary tumor location			0.046			0.017
Colon	78 (65.0)	34 (50.0)		1		
Rectum	42 (35.0)	34 (50.0)		2.170	1.151–4.094	
Operative procedure			0.264			
Hemicolectomy	50 (41.7)	25 (36.8)				
Anterior resection	27 (22.5)	10 (14.7)				
LAR/ultra-LAR	39 (32.5)	28 (41.2)				
Colostomy	4 (3.3)	5 (7.4)				
Open conversion			0.140			
No	117 (97.5)	63 (92.6)				
Yes	3 (2.5)	5 (7.4)				
Operative time (min)	265.1 ± 104.7	282.5 ± 105.6	0.276			
Estimated blood loss (mL)	169.5 ± 135.0	234.6 ± 325.8	0.120			
Previous operative history			1.000			
No	85 (70.8)	49 (72.1)				
Yes	35 (29.2)	19 (27.9)				
Smoking history			0.509			
No	86 (71.7)	45 (66.2)				
Yes	34 (28.3)	23 (33.8)				
Alcohol history			0.871			
No	83 (69.2)	46 (67.6)				
Yes	37 (30.8)	22 (32.4)				
Hypertension			0.543			
No	71 (59.2)	37 (54.4)				
Yes	49 (40.8)	31 (45.6)				

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plication was mild electrolyte imbalance, but that spontaneously resolved in all patients without specific treatment. Among postoperative complications with CD grade III, intraabdominal abscess, anastomotic leakage, and bleeding occurred in 6 patients (3.2%), 6 patients (3.2%), and 2 patients (1.1%), respectively. Of these, revision surgery due to anastomotic leakage was performed in 6 patients (3.2%) and bleeder ligation due to postoperative bleeding was performed in 2 patients (1.1%). A percutaneous drainage catheter was inserted in 6 patients (3.2%) due to intraabdominal abscess (Supplementary Table 1).

Overall postoperative complications occurred in 68 patients (36.2%). We found significant differences in overall postoperative complications according to the age and primary tumor location in univariate analysis. In multivariate analysis, age (odds ratio [OR], 2.608; 95% confidence interval [CI], 1.386 to 4.905; P = 0.003) and primary tumor location (OR, 2.170; 95% CI, 1.151 to 4.094; P = 0.017) were independent predictors of overall postoperative complications after laparoscopic CRC surgery (Table 2).

Major postoperative complications occurred in 14 patients (7.4%). Compared to minor postoperative complications, operative time and smoking history were significantly different in univariate analysis. However, age was not significantly different between minor and major postoperative complications after laparoscopic CRC surgery (P = 0.578). In multivariate analysis, only smoking history was an independent predictor of major postoperative complications (OR, 1.785; 95% CI, 1.003 to 3.178; P = 0.049) (Table 3).

Of 188 consecutive patients, 113 patients (60.1%) were recom-

Table 2. Continued

Characteristic	Unremarkable recovery (n = 120)	Overall complication (n = 68)	P-value	OR	95% CI	P-value
Diabetes			0.363			
No	96 (80.0)	50 (73.5)				
Yes	24 (20.0)	18 (26.5)				
ASA PS classification			0.240			
I	28 (23.3)	13 (19.1)				
II	77 (64.2)	51 (75.0)				
III–IV	15 (12.5)	4 (5.9)				
Charlson Comorbidity Index			0.760			
0	74 (61.7)	41 (60.3)				
1	33 (27.5)	18 (26.5)				
2	11 (9.2)	6 (8.8)				
≥3	2 (1.7)	3 (4.4)				
T stage			0.122			
0–2	54 (45.0)	22 (32.4)				
3–4	66 (55.0)	46 (67.6)				
N stage			0.445			
0	71 (59.2)	36 (52.9)				
1–2	49 (40.8)	32 (52.9)				
Tumor stage			0.221			
0–1	41 (34.2)	15 (22.1)				
2	30 (25.0)	20 (29.4)				
3	42 (35.0)	31 (45.6)				
4	7 (5.8)	2 (2.9)				
Histology of primary tumor			0.238			
Well	26 (21.7)	11 (16.2)				
Moderately	82 (68.3)	54 (79.4)				
Mucinous or poorly	12 (10.0)	3 (4.4)				

Values are presented as mean ± standard deviation or number (%).
OR, odds ratio; CI, confidence interval; LAR, low anterior resection; ASA PS, American Society of Anesthesiologists physical status.

Table 3. Univariate and multivariate analysis of factors affecting major postoperative complications after laparoscopic CRC surgery (n=188)

Characteristic	Minor complication (n=174)	Major complication (n=14)	P-value	OR	95% CI	P-value
Age (yr)			0.578			
Nonelderly	103 (59.2)	7 (50.0)				
Elderly	71 (40.8)	7 (50.0)				
Mean±SD	66.4±11.9	64.9±10.7	0.636			
Sex			0.580			
Male	93 (53.4)	9 (64.3)				
Female	81 (46.6)	5 (35.7)				
Body mass index (kg/m^2)	23.8±3.2	22.3±3.3	0.118			
Primary tumor location			0.087			0.222
Colon	107 (61.5)	5 (35.7)		1		
Rectum	67 (38.5)	9 (64.3)		2.252	0.612–8.291	
Operative procedure			0.440			
Hemicolectomy	71 (40.8)	4 (28.6)				
Anterior resection	35 (20.1)	2 (14.3)				
LAR/ultra-LAR	59 (33.9)	8 (57.1)				
Colostomy	9 (5.2)	0 (0)				
Open conversion			0.111			
No	168 (96.6)	12 (85.7)				
Yes	6 (3.4)	2 (14.3)				
Operative time (min)	266.2±102.6	336.6±117.8	0.015	1.003	0.998–1.008	0.240
Estimated blood loss (mL)	177.4±148.1	338.1±626.2	0.231			
Previous operative history			0.549			
No	125 (71.8)	9 (64.3)				
Yes	49 (28.2)	5 (35.7)				
Smoking history			0.033			
No	125 (71.8)	6 (42.9)		1		
Yes	49 (28.2)	8 (57.1)		1.785	1.003–3.178	0.049
Alcohol history			1.000			
No	119 (68.4)	10 (71.4)				
Yes	55 (31.6)	4 (28.6)				
Hypertension			1.000			
No	100 (57.5)	8 (57.1)				
Yes	74 (42.5)	6 (42.9)				
Diabetes			0.739			
No	134 (77.0)	12 (85.7)				
Yes	40 (23.0)	2 (14.3)				
ASA PS classification			0.506			
I	37 (21.3)	4 (28.6)				
II	118 (67.8)	10 (71.4)				
III–IV	19 (10.9)	0 (0)				

(*Continued to the next page*)

Table 3. Continued

Characteristic	Minor complication (n=174)	Major complication (n=14)	P-value	OR	95% CI	P-value
Charlson Comorbidity Index			1.000			
0	106 (60.9)	9 (64.3)				
1	48 (27.6)	3 (21.4)				
2	15 (8.6)	2 (14.3)				
≥3	5 (2.9)	0 (0)				
T stage			0.408			
0–2	72 (94.7)	4 (28.6)				
3–4	102 (58.6)	10 (71.4)				
N stage			0.589			
0	100 (57.5)	7 (50.0)				
1–2	74 (42.5)	7 (50.0)				
Tumor stage			0.467			
0–1	54 (31.0)	2 (14.3)				
2	46 (26.4)	4 (28.6)				
3	66 (37.9)	7 (50.0)				
4	8 (4.6)	1 (7.1)				
Histology of primary tumor			0.897			
Well	35 (20.1)	2 (14.3)				
Moderately	125 (71.8)	11 (78.6)				
Mucinous or poorly	14 (8.0)	1 (7.1)				

Values are presented as mean±standard deviation or number (%).
OR, odds ratio; CI, confidence interval; LAR, low anterior resection; ASA PS, American Society of Anesthesiologists physical status.

mended to receive postoperative chemotherapy according to the NCCN guidelines and 90 of 113 patients (79.6%) received postoperative chemotherapy. Of these, there were 32 elderly patients (35.6%) and the mean age was 75.8±4.5 years. There were no significant differences in baseline characteristics between the elderly patients who received postoperative chemotherapy and nonelderly patients who received postoperative chemotherapy, except for hypertension, ASA PS classification, and postoperative complication. In the outcomes of postoperative chemotherapy, chemotherapy agents consisting of 5-fluorouracil, oxaliplatin, and irinotecan were administered in 17 patients (18.9%), 68 patients (75.6%), and 5 patients (5.5%), respectively. There were no significant differences in terms of CTCAE grade, chemotherapy setting, and chemotherapy dose between the elderly and nonelderly patients (Table 4).

Adverse events occurred in 109 cases, including 53 (58.9%) in grade I, 35 (38.9%) in grade II, 20 (20.2%) in grade III, and 1 (1.1%) in grade IV, respectively. The most common adverse event was mild peripheral sensory neuropathy. Treatment in the intensive care unit was required in 1 patient (1.1%) because of severe pulmonary embolism. There was no patient chemotherapy-related mortality within 1 year after surgery, whereas 3 patients who did not receive postoperative chemotherapy died because of their

Table 4. Characteristics and outcomes of patients who received postoperative chemotherapy according to the National Comprehensive Cancer Network guidelines (n=90)

Characteristic	Nonelderly (n=58)	Elderly (n=32)	P-value
Age (yr)	57.2±8.4	75.8±4.5	<0.001
Sex			0.828
Male	29 (50.0)	17 (53.1)	
Female	29 (50.0)	15 (46.9)	
Body mass index (kg/m^2)	23.1±2.4	23.6±3.7	0.458
Primary tumor location			0.127
Colon	30 (51.7)	22 (68.8)	
Rectum	28 (48.3)	10 (31.3)	
Smoking history			0.234
No	37 (63.8)	25 (78.1)	
Yes	21 (36.2)	7 (21.9)	
Alcohol history			0.490
No	37 (63.8)	23 (71.9)	
Yes	21 (36.2)	9 (28.1)	

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Table 4. Continued

Characteristic	Nonelderly (n=58)	Elderly (n=32)	P-value
Hypertension			0.004
No	47 (81.0)	16 (50.0)	
Yes	11 (19.0)	16 (50.0)	
Diabetes			0.058
No	50 (86.2)	22 (68.8)	
Yes	8 (13.8)	10 (31.3)	
ASA PS classification			0.001
I	20 (34.5)	1 (3.1)	
II	35 (60.3)	28 (87.5)	
≥III	3 (5.2)	3 (9.4)	
Charlson Comorbidity Index			0.116
0	43 (74.1)	17 (53.1)	
1	10 (17.2)	11 (34.4)	
≥2	5 (8.6)	4 (12.5)	
Tumor stage			0.943
2	16 (27.6)	10 (31.3)	
3	37 (63.8)	19 (59.4)	
4	5 (8.6)	3 (9.4)	
Postoperative complication			0.006
Clavien-Dindo grades 0–I	43 (74.1)	14 (43.8)	
Clavien-Dindo grades II–III	15 (25.9)	18 (56.3)	
Chemotherapy regimen			0.786
5-Fluorouracil	10 (17.2)	7 (21.9)	
Oxaliplatin	45 (77.6)	23 (71.9)	
Irinotecan	3 (5.2)	2 (6.3)	
Chemotherapy setting			1.000
Adjuvant	53 (91.4)	29 (90.6)	
Palliative	5 (8.6)	3 (9.4)	
CTCAE grade			0.288
0	19 (32.8)	6 (18.8)	
I	15 (25.9)	10 (31.3)	
II	14 (24.1)	6 (18.8)	
III	9 (15.5)	10 (31.3)	
IV	1 (1.7)	0 (0)	
Chemotherapy dose			0.149
Fully dosed	44 (75.9)	19 (59.4)	
Dose-reduced	14 (24.1)	13 (40.6)	
Dose reduction (%)			0.097
100	44 (75.9)	19 (59.4)	
≥75	12 (20.7)	13 (40.6)	
≥50	2 (3.4)	0 (0)	

Values are presented as mean±standard deviation or number (%).
ASA PS, American Society of Anesthesiologists physical status; CTCAE, the Common Terminology Criteria for Adverse Events.

comorbid disease (Supplementary Table 2).

Overall adverse events occurred in 40 patients (44.4%). We found significant differences in overall adverse events according to the ASA PS classification and chemotherapy regimen in univariate analysis. Age was not significantly different between the uneventful course group and overall adverse events group (P=0.508). In multivariate analysis, ASA PS classification grade II (reference: ASA grade I; OR, 4.625; 95% CI, 1.321 to16.187; P=0.017) and oxaliplatin (reference: 5-fluorouracil; OR, 4.767; 95% CI, 1.168 to 19.451; P=0.029) were independent predictors of overall adverse events of postoperative chemotherapy (Table 5).

Severe adverse events occurred in 20 patients (22.2%). Compared to mild adverse events, only the chemotherapy regimen was significantly different in univariate analysis. Age was not significantly different between mild and severe adverse events (P=0.185). In multivariate analysis, only irinotecan (reference: 5-fluorouracil; OR, 26.488; 95% CI, 1.414 to 496.322; P=0.028) was an independent predictor of severe adverse events of postoperative chemotherapy (Table 6).

Among the 90 patients who received postoperative chemotherapy, postoperative chemotherapy could not be completed in 11 patients (12.2%) because of severe adverse event in 4 patients, the patient's refusal to continue chemotherapy (in the absence of chemotherapy-related complications) in 6 patients, and follow-up loss in 1 patient (Supplementary Table 3). Only age was significantly different between patients who completed or stopped postoperative chemotherapy. There were no significant differences in terms of chemotherapy regimen, chemotherapy setting, dose reduction, and adverse events between the 2 groups. In multivariate analysis, only age was significantly associated with stopping postoperative chemotherapy (OR, 12.317; 95% CI, 2.390 to 63.491; P=0.003) (Table 7).

DISCUSSION

This study demonstrates the effect of age on laparoscopic surgery and postoperative chemotherapy in consecutive patients with CRC. We evaluated postoperative complications and the adverse events of postoperative chemotherapy by using the CD classification and the CTCAE version 5.0, respectively, in elderly patients compared to nonelderly patients. Our results indicated that major postoperative complications were not different between elderly and nonelderly patients with CRC, although the incidence of overall postoperative complications was higher in the elderly group. In addition, overall and severe adverse events of postoperative chemotherapy were not different between elderly and nonelderly patients, whereas chronologic age was highly associated with factors influencing the termination of postoperative chemotherapy.

There is still no general consensus on the definition of elderly. In a recent review article regarding older age life expectancy, the World Health Organization defined older adults as those aged 60

Table 5. Univariate and multivariate analysis of factors affecting overall adverse events of postoperative chemotherapy (n=90)

Characteristic	Uneventful course (n=50)	Overall adverse event (n=40)	P-value	OR	95% CI	P-value
Age (yr)			0.508			
Nonelderly	34 (68.0)	24 (60.0)				
Elderly	16 (32.0)	16 (40.0)				
Mean age (yr)	62.0±13.4	66.0±8.3	0.090			
Nonelderly	54.7±9.4	60.6 ±5.2	0.004			
Elderly	77.6±3.7	74.1±4.6	0.027			
Sex			0.144			
Male	22 (44.0)	24 (60.0)				
Female	28 (56.0)	16 (40.0)				
Body mass index (kg/m^2)	22.9±2.9	23.7±2.9	0.246			
Primary tumor location			0.203			
Colon	32 (64.0)	20 (50.0)				
Rectum	18 (36.0)	20 (50.0)				
Smoking history			0.115			
No	38 (76.0)	24 (60.0)				
Yes	12 (24.0)	16 (40.0)				
Alcohol history			0.265			
No	36 (72.0)	24 (60.0)				
Yes	14 (28.0)	16 (40.0)				
Hypertension			0.652			
No	36 (72.0)	27 (67.5)				
Yes	14 (28.0)	13 (32.5)				
Diabetes			0.061			0.396
No	44 (88.0)	28 (70.0)		1		
Yes	6 (12.0)	12 (30.0)		1.683	0.505–5.605	
ASA PS classification			0.018			0.057
I	17 (34.0)	4 (10.0)		1		
II	31 (62.0)	32 (80.0)		4.625	1.321–16.187	0.017
≥III	2 (4.0)	4 (10.0)		4.098	0.438–38.303	0.216
Charlson Comorbidity Index			0.260			
0	37 (74.0)	23 (57.5)				
1	9 (18.0)	12 (30.0)				
≥2	4 (8.0)	5 (12.5)				
Chemotherapy regimen			0.014			0.054
5-Fluorouracil	14 (28.0)	3 (7.5)		1		
Oxaliplatin	35 (70.0)	33 (82.5)		4.767	1.168–19.451	0.029
Irinotecan	1 (2.0)	4 (10.0)		13.531	0.977–187.293	0.052
Chemotherapy setting			0.132			
Adjuvant	48 (96.0)	34 (85.0)				
Palliative	2 (4.0)	6 (15.0)				

Values are presented as mean±standard deviation or number (%).
OR, odds ratio; CI, confidence interval; ASA PS, American Society of Anesthesiologists physical status.

Table 6. Univariate and multivariate analysis of factors affecting severe adverse events of postoperative chemotherapy (n=90)

Characteristic	Mild adverse event (n=70)	Severe adverse event (n=20)	P-value	OR	95% CI	P-value
Age (yr)			0.185			
Nonelderly	48 (68.6)	10 (50.0)				
Elderly	22 (31.4)	10 (50.0)				
Mean age (yr)	64.3±11.9	68.0±8.4	0.084	1.047	0.985–1.113	0.144
Nonelderly	56.1±8.6	62.3±4.8	0.032			
Elderly	75.9±4.3	75.8±5.1	0.971			
Sex			0.450			
Male	34 (48.6)	12 (60.0)				
Female	36 (51.4)	8 (40.0)				
Body mass index (kg/m^2)	23.0±2.8	24.1±3.1	0.122			
Primary tumor location			0.802			
Colon	41 (58.6)	11 (55.0)				
Rectum	29 (41.4)	9 (45.0)				
Smoking history			0.785			
No	49 (70.0)	13 (65.0)				
Yes	21 (30.0)	7 (35.0)				
Alcohol history			0.592			
No	48 (68.6)	12 (60.0)				
Yes	22 (31.4)	8 (40.0)				
Hypertension			0.783			
No	48 (68.6)	15 (75.0)				
Yes	22 (31.4)	5 (25.0)				
Diabetes			0.536			
No	57 (81.4)	15 (75.0)				
Yes	13 (18.6)	5 (25.0)				
ASA PS classification			0.056			0.418
I	20 (28.6)	1 (5.0)		1		
II	46 (65.7)	17 (85.0)		3.795	0.414–34.784	0.238
≥III	4 (5.7)	2 (10.0)		1.701	0.068–42.696	0.747
Charlson Comorbidity Index			0.579			
0	47 (67.1)	13 (65.0)				
1	15 (21.4)	6 (30.0)				
≥2	8 (11.4)	1 (5.0)				
Chemotherapy regimen			0.015			0.082
5-Fluorouracil	14 (20.0)	3 (15.0)		1		
Oxaliplatin	55 (78.6)	13 (65.0)		1.536	0.353–6.678	0.567
Irinotecan	1 (1.4)	4 (20)		26.488	1.414–496.322	0.028
Chemotherapy setting			0.369			
Adjuvant	65 (92.9)	17 (85.0)				
Palliative	5 (7.1)	3 (15.0)				

Values are presented as mean±standard deviation or number (%).
OR, odds ratio; CI, confidence interval; ASA PS, American Society of Anesthesiologists physical status.

Table 7. Univariate and multivariate analysis factors associated with stopping postoperative chemotherapy in patients who received postoperative chemotherapy (n=90)

Characteristic	Complete chemotherapy (n=79)	Stopped chemotherapy (n=11)	P-value	OR	95% CI	P-value
Age (yr)			0.001			
Nonelderly	56 (70.9)	2 (18.2)		1		
Elderly	23 (29.1)	9 (81.8)		12.317	2.390–63.491	0.003
Mean age (yr)	62.3±11.1	74.7±9.1	0.001			
Nonelderly	57.1±8.5	59.0±5.6	0.755			
Elderly	74.9±4.1	78.2±4.8	0.059			
Sex			0.523			
Male	39 (49.4)	7 (63.6)				
Female	40 (50.6)	4 (36.4)				
Body mass index (kg/m^2)	23.4±2.9	21.8±2.3	0.085	0.818	0.654–1.022	0.077
Primary tumor location			0.754			
Colon	45 (57.0)	7 (63.6)				
Rectum	34 (43.0)	4 (36.4)				
Smoking history			1.000			
No	54 (68.4)	8 (72.7)				
Yes	25 (31.6)	3 (27.3)				
Alcohol history			0.746			
No	52 (65.8)	8 (72.7)				
Yes	27 (34.2)	3 (27.3)				
Hypertension			0.728			
No	56 (70.9)	7 (63.6)				
Yes	23 (29.1)	4 (36.4)				
Diabetes			0.687			
No	64 (81.0)	8 (72.7)				
Yes	15 (19.0)	3 (27.3)				
ASA PS classification			0.454			
I	20 (25.3)	1 (9.1)				
II	54 (85.7)	9 (81.8)				
≥III	5 (6.3)	1 (9.1)				
Charlson Comorbidity Index			0.884			
0	53 (67.1)	7 (63.6)				
1	18 (22.8)	3 (27.3)				
≥2	8 (10.1)	1 (9.1)				
Chemotherapy regimen			0.742			
5-Fluorouracil	15 (19.0)	2 (18.2)				
Oxaliplatin	59 (74.7)	9 (81.8)				
Irinotecan	5 (6.3)	0 (0)				
Chemotherapy setting			0.589			
Adjuvant	71 (89.9)	11 (13.4)				
Palliative	8 (100)	0 (0)				

(*Continued to the next page*)

Table 7. Continued

Characteristic	Complete chemotherapy (n = 79)	Stopped chemotherapy (n = 11)	P-value	OR	95% CI	P-value
Adverse events			0.254			
CTCAE grades 0–II	63 (79.7)	7 (63.6)				
CTCAE grades III–IV	16 (20.3)	4 (34.6)				
Chemotherapy dose			0.295			
Fully dosed	57 (72.2)	6 (54.5)				
Dose-reduced	22 (27.8)	5 (45.5)				
Dose reduction (%)			0.447			
100	57 (72.2)	6 (54.5)				
≥75	20 (25.3)	5 (45.5)				
≥50	2 (2.5)	0 (0)				

Values are presented as mean ± standard deviation or number (%).
OR, odds ratio; CI, confidence interval; LAR, low anterior resection; ASA PS, American Society of Anesthesiologists physical status; CTCAE, the Common Terminology Criteria for Adverse Events.

years or older [18]. In contrast, several studies defined the elderly as 80 years-of-age and older, which may be more appropriate given the increase in the average life expectancy [19]. However, many clinical studies regarding the clinical features and prognosis of elderly patients with CRC defined elderly patients as those over 70 or 75 years old [20]. Therefore, we defined 70 years of age as the threshold between nonelderly and elderly, by considering the mean age of 66.3 ± 11.8 in the present study.

Previous studies have suggested that age is not an independent predictor of morbidity and mortality in laparoscopic CRC surgery [21, 22], although several studies showed that increased age increased the risk of postoperative complications [23, 24]. In fact, elderly patients naturally have more comorbidities and are more sensitive to surgical stress than nonelderly patients, which might affect the overall complication rates. A recent meta-analysis reported that the incidence of overall postoperative complications was slightly higher in elderly patients than in nonelderly patients, whereas there was no difference between elderly and nonelderly patients in anastomotic leakage and mortality [20]. In the present study, overall postoperative complication rates after laparoscopic CRC surgery did differ between the elderly and nonelderly patients (54.4% vs. 45.6%), because more postoperative complications with CD grade II requiring pharmacological treatment (38.5% vs. 21.8%) occurred in the elderly patients. However, there was no difference between the 2 groups in major postoperative complications requiring invasive treatment in this study, as in the meta-analysis. Therefore, we suggest that laparoscopic CRC surgery in elderly patients is feasible, although careful management is required after surgery in elderly patients depending on their intrinsic nature.

Several factors, including male gender, comorbidities, emergency procedures, long duration of operation, and distant metastasis, were reported to be predictive factors for major postoperative complications in CRC patients, although this finding is controversial [23, 24]. The current study showed that only smoking history was associated with major postoperative complications after laparoscopic CRC surgery. Smoking is known to cause microvascular disease, tissue ischemia, and hypoxia, which might be contributing factors to poor anastomotic healing [25]. In a study of over 47,000 patients, Sharma et al. [26] demonstrated that smoking increases the risk of major postoperative complications after all types of colorectal surgery. Our findings correlated with previous studies indicating an increased risk of major postoperative complications, although the effect of smoking on major postoperative complications was not fully understood. Therefore, a well-designed prospective study would be needed to validate the findings in this study.

Previous studies suggested that the incidence of toxic effects for postoperative chemotherapy was not increased among elderly patients with CRC [9, 10], although it remains a controversial issue [27]. In the real-world setting, patient age strongly influenced the recommendations for chemotherapy by both surgeons and oncologists [28]. This might be attributed to the degeneration of liver or kidney function seen more often in elderly patients, the risk of which could increase with treatment. However, for fit elderly patients, no significant interaction was observed between age and treatment efficacy and postoperative chemotherapy appeared to achieve similar survival benefits with no greater toxicity than that seen in nonelderly patients [11]. The present study indicated that age was not an independent predictor of overall and severe adverse events of postoperative chemotherapy in patients with CRC, probably because elderly patients had similar comorbidities and slightly higher ASA physical status classification. These findings suggest that postoperative chemotherapy is feasible in elderly patients who may be good candidates.

Although some studies reported that tumor types and chemo-

therapy regimen were associated with chemotherapy toxicity [29], the results remain controversial because of the heterogeneity of selection criteria and variations in multimodal treatment. In the current study, chemotherapy regimen was associated with overall and severe adverse events after postoperative chemotherapy in patients with CRC; the risk of overall and severe adverse events was higher in patients receiving chemotherapy consisting of oxaliplatin and irinotecan, respectively. However, the number of patients in the irinotecan group was too low in this study. Therefore, these findings should be confirmed in larger studies.

There were various studies identifying factors to discontinue postoperative chemotherapy [29]. We focused on age and the adverse events of postoperative chemotherapy as factors that stopped chemotherapy. Our results revealed that only age was significantly associated with the termination of postoperative chemotherapy, whereas the severity of adverse events related to chemotherapy did not differ between patients who completed or stopped postoperative chemotherapy. We thought that selection bias might have been present because patients who potentially could not tolerate postoperative chemotherapy were already excluded from receiving chemotherapy by the treatment recommendation process. Nevertheless, more than half of the patients who stopped postoperative chemotherapy could not complete postoperative chemotherapy because of reasons other than the side effects of chemotherapy which included old age, economic difficulties, lack of family support, and psychological problems. In particular, 4 of the 9 elderly patients (44.4%) who stopped postoperative chemotherapy discontinued treatment because of old age without any adverse events. Therefore, we suggest that patients and family members should receive education on the importance of establishing treatment based on patient disease stage and physiologic status, rather than chronologic age.

This study had some limitations. First, there was a potential for selection bias, compounded by the retrospective design and single-center study. In the present study, the number of males was lower than the number of females in the elderly patient group. One of the reasons for the lower number of males is because the mean lifespan of males is approximately 10 years shorter than that of females [18]. Therefore, patient baseline characteristics could be different and might have affected the outcomes of laparoscopic CRC surgery and postoperative chemotherapy. Secondly, the long-term outcomes for laparoscopic CRC surgery were not assessed. Previous studies have reported that the long-term outcomes did not differ between younger and elderly patients [30]. Thirdly, the number of patients that stopped postoperative chemotherapy was relatively small because patients who might have stopped chemotherapy were already excluded during the treatment recommendation process. Therefore, further large-scale prospective studies will be helpful to verify our results.

In conclusion, this study shows that laparoscopic CRC surgery and postoperative chemotherapy were feasible in elderly patients, whereas age was still considered a factor in the decision to stop postoperative chemotherapy. Therefore, we suggest that further efforts are needed to ensure that elderly patients have the opportunity to make informed decisions regarding postoperative chemotherapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1-3 can be found via https://doi.org/10.3393/ac.2019.10.03.

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