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Original Article

Comparing the initiation of adjuvant chemotherapy after robotic and laparoscopic colon cancer surgeries: A case-controlled study with propensity score matching

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Purpose: Early initiation of adjuvant chemotherapy after colon cancer surgery has shown better oncologic outcomes in previous studies. However, the clinical impact of robotic and laparoscopic surgeries on the initiation of adjuvant chemotherapy has not been widely evaluated. Hence, the study's aim was to compare the influence of both surgical approaches on the initiation of adjuvant chemotherapy after colon cancer surgery.

Methods: From June 2011 to September 2017, 289 patients underwent curative robotic or laparoscopic surgery followed by adjuvant chemotherapy for stage II and III colon cancer. To control for different demographic factors in the two groups, propensity score case matching was used at a 1:4 ratio. Finally, 190 patients were matched with 38 patients of the robotic surgery group and 152 patients of the laparoscopic surgery group.

Results: The operation time was longer in the robotic surgery group (297 minutes vs. 170 minutes, respectively; $P<0.001$). However, conversion rate, number of retrieved lymph nodes, first flatus, first soft diet, length of stay, postoperative complication rate, and Clavien-Dindo grade were not significantly different between the two groups. Additionally, there was no difference in the time to initiation of adjuvant chemotherapy between the two groups (31.5 days vs. 29.0 days, respectively; $P=0.226$). Disease-free and overall survival rates were also not significantly different.

Conclusion: Robotic and laparoscopic surgeries showed no different impact on the initiation of adjuvant chemotherapy. This finding suggests that the two surgical approaches offer similar postoperative outcomes.

Keywords: Colonic neoplasm, Adjuvant chemotherapy, Minimally invasive surgery, Robotic surgical procedure, Laparoscopy

INTRODUCTION

Adjuvant chemotherapy after resection of the primary colon cancer reduces the risk of disease recurrence by 40% and mortality by 33% [1]. Early initiation of adjuvant chemotherapy after colon cancer surgery has shown better oncologic outcomes in previous studies [2-6]. The European Society for Medical Oncology (ESMO) guideline recommends that adjuvant chemotherapy should be given as soon as possible, from the third to the 12th week pos-toperatively [7]. In contrast, the National Comprehensive Cancer Network guideline does not recommend a precise timing of adjuvant chemotherapy, but it introduces some studies that revealed how starting early adjuvant chemotherapy showed better oncologic outcomes [8]. One of the benefits of minimally invasive surgery such as laparoscopic and robotic surgeries is earlier postoperative recovery than open surgery [9,10]. However, the clinical impact of laparoscopic and robotic surgeries on the initiation of adjuvant chemotherapy has not been widely evaluated. Therefore, this study's aim was to compare those surgical approaches' influence on the initiation of adjuvant chemotherapy after colon cancer surgery.

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METHODS

Study population and study design

From June 2011 to September 2017, 830 consecutive patients underwent colon cancer surgery at Keimyung University Dongsan Medical Center. Patient data were collected from the prospectively managed electric database. Thirty patients who were less than 20 years old, underwent emergency surgery, or had simultaneous surgery for other organ diseases were excluded. Four hundred and ninety-one out of 800 patients had pathologic stage II and III colon cancer (245 and 246, respectively). Of the 491 patients, 327 received adjuvant chemotherapy (120 and 207, respectively). To compare minimally invasive surgery, 38 patients who underwent open laparotomy were excluded.

Ultimately, 289 patients were enrolled. Thirty-eight patients underwent robotic surgery (RS) and 251 patients underwent laparoscopic surgery (LS). To control for different demographic factors in the two groups, propensity score case matching was used at a 1:4 ratio. Propensity scores were generated with the baseline characteristics, including age, sex, body mass index, American Society of Anesthesiologists (ASA) score, previous abdominal surgery, tumor location and pathologic stage. Finally, 190 patients were matched with 38 patients of RS group and 152 patients of LS group (Fig. 1).

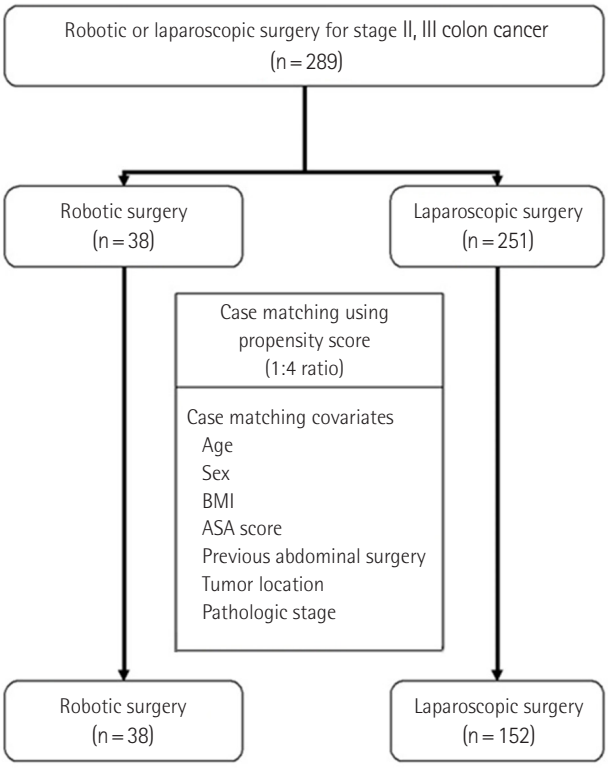

Fig. 1. Study design. BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 1. Preoperative and pathologic factors (before and after case matching)

Variable	Before matching			After matching		
	Robotic (n = 38)	Laparoscopic (n = 251)	P-value	Robotic (n = 38)	Laparoscopic (n = 152)	P-value
Age (yr)	60.9 ± 9.1	66.3 ± 10.5	0.003	60.9 ± 9.0	62.3 ± 10.0	0.428
Sex			0.367			0.536
Male	24 (63.2)	139 (55.4)		24 (63.2)	104 (68.4)	
Female	14 (36.8)	112 (44.6)		14 (36.8)	48 (31.6)	
BMI (kg/m^2)	33.4 ± 62.6	23.7 ± 3.2	0.346	33.4 ± 62.6	23.9 ± 3.0	0.354
ASA score			0.001			0.220[a]
I	20 (52.6)	64 (25.5)		20 (52.6)	57 (37.5)	
II	17 (44.7)	145 (57.8)		17 (44.7)	87 (57.2)	
III	1 (2.6)	42 (16.7)		1 (2.6)	8 (5.3)	
Previous abdominal surgery	10 (26.3)	46 (18.3)	0.246	10 (26.3)	34 (22.4)	0.606
Tumor location			0.013			0.543[a]
Proximal colon	6 (15.8)	100 (39.8)		6 (15.8)	33 (21.7)	
Distal colon	32 (84.2)	149 (59.4)		32 (84.2)	117 (77.0)	
Multiple	0	2 (0.8)		0	2 (1.3)	
AJCC stage			0.843			0.763
II	13 (34.2)	90 (35.9)		13 (34.2)	56 (36.8)	
III	25 (65.8)	161 (64.1)		25 (65.8)	96 (63.2)	

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer.
[a]Fisher exact test.

Statistical analysis

Statistical analyses were performed with PASW Statistics 18 software (SPSS Inc., Chicago, IL, USA) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). The data are displayed as frequencies and percentages for categorical variables and were analyzed with the Pearson's chi-square test or Fisher exact test. The Kolmogorov-Smirnov test was used to test the distribution of continuous variables. Normally distributed variables were examined with Student t-test and the results are presented as mean (standard deviation). Conversely, non-normally distributed continuous variables were subjected to examination with the Mann-Whitney U test, and the results are expressed as median (interquartile range). The Kaplan-Meier method was used to analyze survival. Additionally, prognostic factors were analyzed using the Cox-regression model. Two-tailed values of $P < 0.05$ were considered statistically significant.

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center (IRB No. 2019-12-022). Informed consent was waived due to the retrospective design of the study.

RESULTS

Demographic and preoperative data before and after propensity score matching

Before propensity score case matching, a higher mean age, higher percentage of ASA scores, and less percentage of distal colon cancers were noted in the LS group.

The mean age was 60.9 years in the RS group and 66.3 years in the LS group (P = 0.003). ASA scores I, II, and III were 52.6%, 44.7%, and 2.6% in the RS group and 25.5%, 57.8%, and 16.7% in the LS group, respectively (P = 0.001). Tumors located in the proximal colon, distal colon, and multiple sites were 15.8%, 84.2%, and 0% in the RS group and 39.8%, 59.4, and 0.8% in the LS group (P = 0.013).

After propensity score case matching, these factors were well balanced. The mean ages were 60.9 years and 62.3 years, respectively (P = 0.428). The ASA score became similar (52.6%, 44.7%, and 2.6% vs. 37.5%, 57.2%, and 5.3%, respectively; P = 0.220). Moreover, tumor location was not significantly different (15.8%, 84.2%, and 0% vs. 21.7%, 77.0, and 1.3%, respectively; P = 0.543) (Table 1).

Pathologic results and chemotherapy regimen after propensity score matching

Percentages of AJCC stages II and III in both groups were similar (34.2% and 65.8% vs. 36.8% and 63.2%, respectively; P = 0.763) (Table 1). Other pathologic data including T stage, N stage, differentiation, lymphovascular invasion, and perineural invasion were not significantly different between the two groups. FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) was the most used adjuvant chemotherapy regimen (78.9% vs. 88.2%, respectively; P = 0.186). The mean number of retrieved lymph nodes was not different between the two groups (Table 2).

Perioperative results after propensity score matching

The median operation time was longer in the RS group than in the LS group (297 minutes vs. 170 minutes; respectively; P < 0.001) (Table 3). Despite that conversion was required only in the LS group, statistical difference was not shown between both groups (0 case vs. 6 cases, respectively; P = 0.257). The reasons for conversion were dense adhesions of the small intestine caused by previous surgery (n = 3), invasion of the abdominal wall (n = 2), and a huge

Table 2. Pathologic results and chemotherapy regimen (after case matching)

Variable	Robotic (n = 38)	Laparoscopic (n = 152)	P-value
pT stage			0.232[a]
1	4 (10.5)	6 (3.9)	
2	3 (7.9)	6 (3.9)	
3	25 (65.8)	105 (69.1)	
4	6 (15.8)	35 (23.0)	
pN stage			0.693
0	13 (34.2)	56 (36.8)	
1	18 (47.4)	61 (40.1)	
2	7 (18.4)	35 (23.0)	
Retrieved lymph node	26 ± 14	25 ± 9	0.364
Differentiation			0.395
Well	1 (2.6)	1 (0.7)	
Moderately	34 (89.5)	131 (86.2)	
Poorly	3 (7.9)	20 (13.2)	
Lymphovascular invasion			0.259
Negative	17 (44.7)	53 (34.9)	
Positive	21 (55.3)	99 (65.1)	
Perineural invasion			0.325
Negative	27 (71.1)	95 (62.5)	
Positive	11 (28.9)	57 (37.5)	
Chemotherapy regimen			0.186
FOLFOX	30 (78.9)	134 (88.2)	
5-FU/LV	2 (5.3)	8 (5.3)	
Capecitabine	6 (15.8)	10 (6.6)	

Values are presented as number (%) or mean ± standard deviation.
pT, pathologic tumor; pN, pathologic node; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin.
[a]Fisher exact test.

Table 3. Perioperative results (after case matching)

Variable	Robotic (n = 38)	Laparoscopic (n = 152)	P-value
Conversion	0	6 (3.9)	0.257[a]
Operation time (min)	297 (219–374)	170 (142–230)	< 0.001
Postoperative complication	11 (28.9)	30 (19.7)	0.217
SSI, superficial	2	9	
SSI, organ/space	0	3	
Anastomosis leakage	2	2	
PMC	2	5	
Thrombophlebitis	0	1	
FUO	0	1	
Ischemic colitis	0	2	
Paralytic ileus	2	3	
Small bowel obstruction	2	2	
Urinary retention	0	1	
Chyle leakage	1	1	
Clavien-Dindo grade			0.835[a]
I	3 (27.3)	9 (30.0)	
II	8 (72.7)	19 (63.3)	
IIIa	0	1 (3.3)	
IIIb	0	1 (3.3)	
First flatus (day)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.961
First soft diet (day)	7.0 (6.8–8.0)	7.0 (6.0–8.0)	0.062
Length of stay (day)	10.0 (9.0–13.0)	10 (9.0–12.0)	0.564
Time to initiation of adjuvant chemotherapy (day)	31.5 (27.0–34.3)	29.0 (25.0–35.0)	0.226

Values are presented as number (%) or median (interquartile range).
SSI, surgical site infection; PMC, pseudomembranous colitis; FUO, fever of unknown origin.
[a]Fisher exact test.

cancer mass (n = 1).

Postoperative complication rate seemed higher in the RS group; however, there was no statistical difference (11/38, 28.9% vs. 30/152, 19.7%, respectively; P = 0.217). Clavien-Dindo grade also was not significantly different between the two groups. Most complications were classified as Clavien-Dindo grade I or II in both groups. Grade III complications occurred in two patients in the LS group. One patient had organ/space surgical site infection, which was treated with percutaneous drainage (grade IIIa). Another patient experienced anastomotic leakage requiring laparotomy and diverting ileostomy (grade IIIb). None of the patients in the RS group had grade III complications.

There were no differences in the length of stay, first flatus, and first soft diet. Regarding the time to initiation of adjuvant chemotherapy, there was no difference between the two groups as well (31.5 vs. 29.0 days, respectively; P = 0.226).

Disease-free and overall survival rates

Survival analysis between RS and LS groups is shown in Fig. 2. The 5-year overall survival and disease-free survival rates were not significantly different between the two groups. The 5-year overall survival rate was 86.1% in the RS group and 78.0% in the LS group (P = 0.356). Meanwhile, the 5-year disease-free survival rate was the same in both groups (82.9% vs. 82.9%, respectively; P = 0.987).

In stage II colon cancer patients, the 5-year overall survival rate was lower in the RS group (66.7%) than in the LS group (82.5%), but statistical difference was not shown (P = 0.810). The 5-year disease-free survival rate was similar between the two groups (91.7 vs. 90.9%, respectively; P = 0.997) (Fig. 3). In stage III colon cancer patients, the 5-year overall survival rate was higher in the RS group (95.0%) than in the LS group (74.8%) without statistical difference (P = 0.173). Moreover, the 5-year disease-free survival rate was similar (77.3 vs. 77.8%, respectively; P = 0.967) (Fig. 4).

Risk factors of disease-free survival and overall survival

Univariate and multivariate analyses were carried out to assess the surgical approach (robotic and laparoscopic surgeries) as an independent prognostic factor with respect to overall survival and dis-

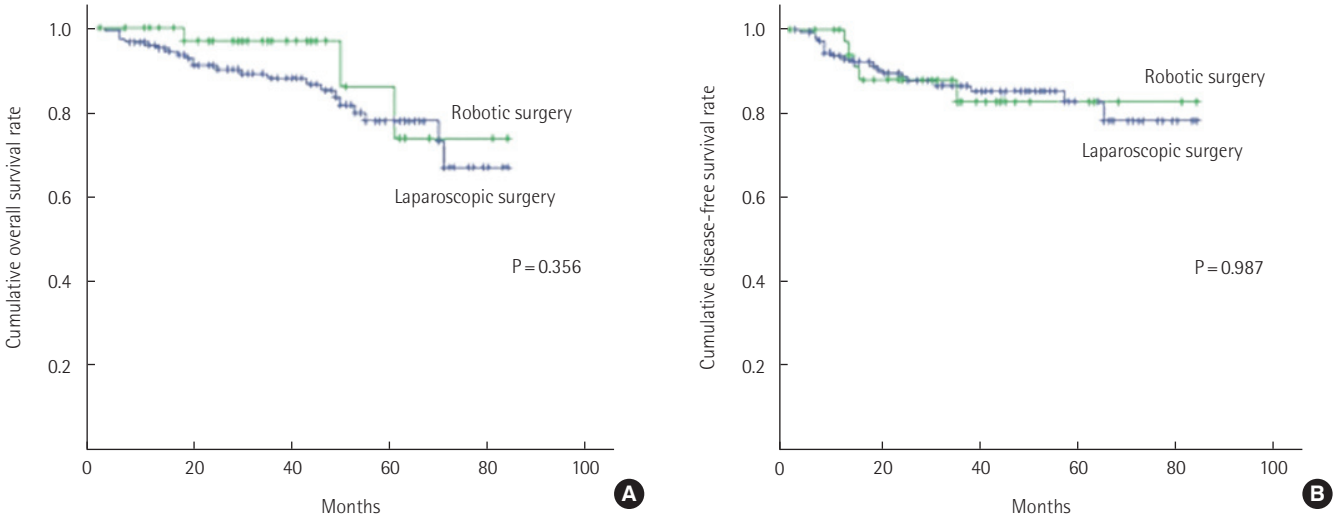

Fig. 2. Five-year overall survival curves (A) and disease-free survival curves (B) between robotic and laparoscopic surgery groups.

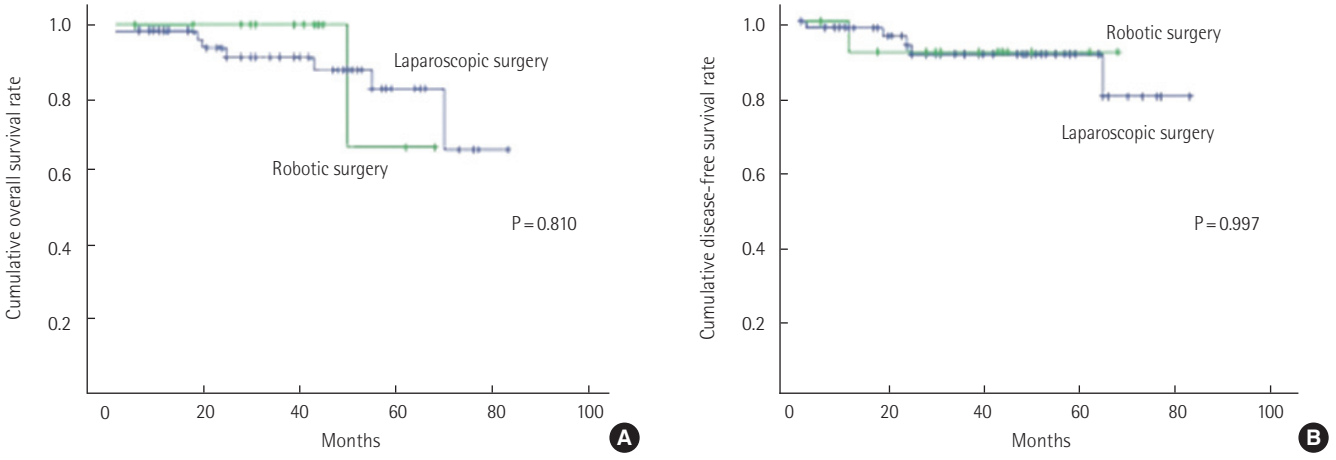

Fig. 3. Five-year overall survival curves (A) and disease-free survival curves (B) in patients with stage II.

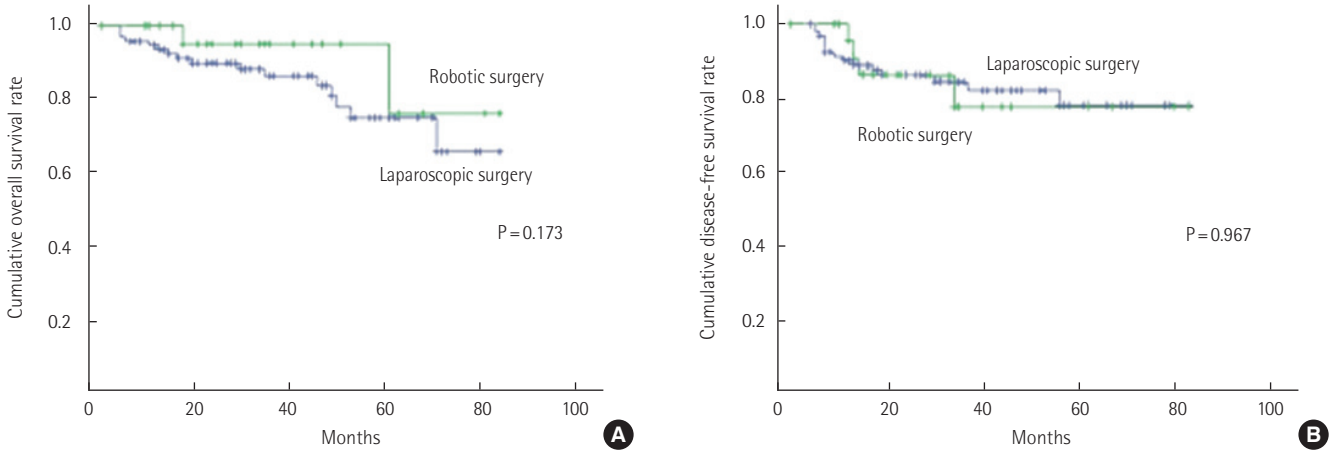

Fig. 4. Five-year overall survival curves (A) and disease-free survival curves (B) in patients with stage III.

Table 4. Univariate and multivariate analyses of risk factors for overall survival after surgery

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr) < 60 vs. ≥ 60	1.285 (0.583–2.835)	0.534		
Sex Male vs. female	0.345 (0.119–1.000)	0.050		
BMI (kg/m^2) < 25 vs. ≥ 25	1.054 (0.478–2.324)	0.896		
ASA score I vs. II, III	2.010 (0.845–4.781)	0.115		
Surgical approach Laparoscopic vs. robotic	0.571 (0.171–1.908)	0.363		
Tumor location Proximal vs. distal colon	1.080 (0.407–2.868)	0.877		
pT stage T1, 2 vs. T3, 4	1.379 (0.324–5.869)	0.663		
pN stage N0 vs. N1, 2	1.371 (0.595–3.158)	0.459		
AJCC stage II vs. III	1.371 (0.595–3.158)	0.459		
Differentiation WD+MD vs. PD	3.385 (1.409–8.132)	0.006	2.808 (1.160–6.798)	0.022
Lymphovascular invasion Absent vs. present	3.190 (0.952–10.684)	0.060		
Perineural invasion Absent vs. present	2.227 (1.023–4.851)	0.044	2.681 (1.182–6.085)	0.018
Chemotherapy regimen FOLFOX vs. 5-FU/LV, capecitabine	3.699 (1.471–9.304)	0.005	4.087 (1.538–10.860)	0.005
Complication Absent vs. present	0.880 (0.331–2.337)	0.798		
Length of stay (day) ≤ 10 vs. > 10	0.591 (0.256–1.363)	0.217		
Time to initiation of adjuvant chemotherapy (day) ≤ 30 vs. > 30	0.559 (0.243–1.286)	0.171		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; pT, pathologic tumor; pN, pathologic node; AJCC, American Joint Committee on Cancer; WD, well differentiation; MD, moderate differentiation; PD, poor differentiation; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin.

ease-free survival.

Factors associated with poorer overall survival in univariate analysis included poor differentiation, perineural invasion, and 5-fluorouracil/leucovorin (5-FU/LV) or capecitabine chemotherapy regimen. Similarly, in multivariate analysis, the abovementioned factors were also associated with poorer overall survival (Table 4).

During a median follow-up period of 35 months, 25 patients experienced colon cancer recurrence (5/38, 13.2% vs. 20/152, 13.2%, respectively). In univariate analysis, the factors associated with poorer disease-free survival were poor differentiation, lymphovascular invasion, and perineural invasion. Meanwhile, in multivariate analysis, only poor differentiation and lymphovascular invasion were associated with poorer disease-free survival (Table 5).

DISCUSSION

Minimally invasive LS for colon cancer has been accepted widely for short-term outcomes, such as reduced postoperative pain, rapid resumption of bowel transit, better cosmesis, and a reduced postoperative systemic immune response compared to open sur-

Table 5. Univariate and multivariate analyses of risk factors for disease-free survival after surgery

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr) < 60 vs. ≥ 60	1.265 (0.568–2.817)	0.565		
Sex Male vs. female	0.593 (0.236–1.485)	0.264		
BMI (kg/m2) < 25 vs. ≥ 25	1.124 (0.505–2.502)	0.775		
ASA score I vs. II, III	1.135 (0.510–2.528)	0.756		
Surgical approach Laparoscopic vs. robotic	1.008 (0.378–2.688)	0.987		
Tumor location Proximal vs. distal colon	1.143 (0.491–4.172)	0.512		
pT stage T1, 2 vs. T3, 4	2.996 (0.405–22.171)	0.283		
pN stage N0 vs. N1, 2	2.013 (0.803–5.043)	0.136		
AJCC stage II vs. III	2.013 (0.803–5.043)	0.136		
Differentiation WD+MD vs. PD	3.403 (1.413–8.193)	0.006	3.182 (1.318–7.685)	0.010
Lymphovascular invasion Absent vs. present	5.948 (1.401–25.260)	0.016	4.788 (1.116–20.536)	0.035
Perineural invasion Absent vs. present	2.578 (1.165–5.705)	0.019	2.109 (0.945–4.705)	0.068
Chemotherapy regimen FOLFOX vs. 5-FU/LV, capecitabine	2.280 (0.681–7.635)	0.181		
Complication Absent vs. present	1.438 (0.601–3.445)	0.415		
Length of stay (day) ≤ 10 vs. > 10	0.824 (0.364–1.869)	0.644		
Time to initiation of adjuvant chemotherapy (day) ≤ 30 vs. > 30	1.130 (0.515–2.479)	0.760		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; pT, pathologic tumor; pN, pathologic node; AJCC, American Joint Committee on Cancer; WD, well differentiation; MD, moderate differentiation; PD, poor differentiation; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin.

gery [11]. Long-term oncologic outcomes are at least equivalent in both minimally invasive laparoscopic and open surgeries [12,13].

When compared to the LS, the advanced techniques of the robotic surgical system provide better visualization and movements, enabling more precise and safer surgery. This led to the rapid adoption of the robotic surgical system by the enthusiastic surgeons. In the field of colon cancer surgery, the expectation that RS offers much better benefits than LS has not been realized. In the literature, the comparative studies comparing clinical outcomes between the two surgeries have not shown consistent results. A population analysis comparing robotic and laparoscopic colectomies for colon cancer reported that robotic and laparoscopic groups were similar in short-term outcomes. However, the robotic group was associated with decreased conversion to an open surgery and length of stay [14]. In a randomized, controlled study comparing robotic and laparoscopic surgeries for right colon cancer, conversion to an open surgery, length of stay, and morbidity were similar, but the RS group had longer operation time and higher cost [15].

We supposed that a different method other than generally used

ones is necessary to compare robotic and laparoscopic surgeries for colon cancer. The interval between surgical resection and adjuvant chemotherapy would be a proliferation period of micrometastases [16,17]. Hence, early initiation of adjuvant chemotherapy could result in better oncologic outcomes. Occasionally though, patients' health factors or surgical complications prevent the early initiation. Therefore, surgical techniques that make recovery faster and have less surgical complications are required for early initiation of adjuvant chemotherapy. Based on these facts, the interval between surgical resection and adjuvant chemotherapy might indirectly represent the extent of tissue damage by surgical technique, recovery from the surgery, and oncologic outcome. Thus, we decided to use the interval between surgical resection and adjuvant chemotherapy as a parameter comparing robotic and laparoscopic surgeries for colon cancer.

In the literature, there is one study comparing open, laparoscopic and robotic surgeries in the initiation timing of adjuvant chemotherapy. It revealed that laparoscopic and robotic surgeries resulted in shorter time for initiation of chemotherapy than open surgery. When comparing laparoscopic and robotic surgeries, RS showed shorter time for initiation than LS. That was, however, a retrospective study limited by selection bias [18]. To reduce the selection bias, we used propensity score matching.

In our study, there was no difference in the time to initiation of adjuvant chemotherapy between the two groups (31.5 days vs. 29.0 days, respectively; P = 0.226). Other factors, associated with the initiation of adjuvant chemotherapy, also showed similar results, which include conversion rate to open surgery, return of bowel function, postoperative complication rates, and length of stay.

The robotic system allows the surgeon to perform more delicate and complex movement with stability than laparoscopy. These advantages enhance the precision and accuracy of anatomical dissection, especially in the deep and narrow pelvis [19]. The surgical field for colon cancer surgery, however, is much wider than the pelvic cavity, which does not require much the advantages of RS. The surgical procedure for colon cancer is closely identical in the two surgeries, and intraperitoneal tissue trauma is also similar. These factors may in part explain that postoperative data are not significantly different between the two groups.

Five-year overall survival and disease-free survival rates were not significantly different between robotic and LS groups in this study. In univariate and multivariate analyses, surgical approach was not an independent prognostic factor with respect to overall survival and disease-free survival. In the present study, robotic and laparoscopic surgeries for colon cancer showed equivalent influence on oncologic outcomes. A limited number of studies comparing long-term oncologic outcomes of the two surgeries have been conducted, where a discrepancy among the oncologic outcomes was found. Moreover, a retrospective study of right colectomy for colon cancer demonstrated that RS is related to higher lymph node retrieval compared to both open and laparoscopic surgeries. The influence of this result on the oncologic outcomes was not evaluated [20]. A cohort study analyzing long-term oncologic outcomes found no difference in disease-free survival, all-cause mortality and recurrence-free survival between two surgeries [21]. The comparison study of robotic and laparoscopic surgeries for right colon cancer showed similar 5-year disease-free and overall survival rates [15]. In contrast, one study demonstrated higher 5-year overall survival rate in the RS group, even though lymph node retrieval was similar [14]. These differences have raised the need for more studies providing highly convincing evidence and reliability.

There are some limitations in this study. Firstly, this is not a randomized, controlled study. Primarily, selection bias could be a weakness of this study. Propensity score matching, however, was used to overcome the selection bias and improve reliability. Secondly, data in this study were collected in a single center, and the number of enrolled cases is relatively small. A multicenter trial would therefore be necessary to gather larger data. Thirdly, assessment regarding the quality of life was not included as well as pain score, cosmesis, patients' satisfaction, etc. Therefore, a prospective study assessing the quality of life is anticipated.

In conclusion, robotic and laparoscopic surgeries showed no different impact on the initiation of adjuvant chemotherapy. This finding suggests that the two surgical approaches offer similar postoperative outcomes. It is however important to reveal the other benefits of RS over LS for colon cancer, compensating the high cost of RS.

CONFLICT OF INTEREST

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

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