Original Article
Annals of COLOPROCTOLOGY
Ann Coloproctol 2024;40(6):594-601
pISSN: 2287-9714 • eISSN: 2287-9722
https://doi.org/10.3393/ac.2024.00171.0024

Robotic surgery may lead to reduced postoperative inflammatory stress in colon cancer: a propensity score–matched analysis

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Purpose: Robot-assisted surgery is readily applied to every type of colorectal surgeries. However, studies showing the safety and feasibility of robotic surgery (RS) have dealt with rectal cancer more than colon cancer. This study aimed to investigate how technical advantages of RS can translate into actual clinical outcomes that represent postoperative systemic response.
Methods: This study retrospectively reviewed consecutive cases in a single tertiary medical center in Korea. Patients with primary colon cancer who underwent curative resection between 2006 and 2012 were included. Propensity score matching was performed to adjust baseline patient characteristics (age, sex, body mass index, American Society of Anesthesiologists physical status, tumor profile, pathologic stage, operating surgeon, surgery extent) between open surgery (OS), laparoscopic surgery (LS), and RS groups.
Results: After propensity score matching, there were 66 patients in each group for analysis, and there was no significant differences in baseline patient characteristics. Maximal postoperative leukocyte count was lowest in the RS group and highest in the OS group ($P = 0.021$). Similar results were observed for postoperative neutrophil count ($P = 0.024$). Postoperative prognostic nutritional index was highest in the RS group and lowest in the OS group ($P < 0.001$). The time taken to first flatus and soft diet resumption was longest in the OS group and shortest in the RS group ($P = 0.001$ and $P < 0.001$, respectively). Among all groups, other short-term postoperative outcomes such as hospital stay and complications did not show significant difference, and oncological survival results were similar.
Conclusion: Better postoperative inflammatory indices in the RS group may correlate with their faster recovery of bowel motility and diet resumption compared to LS and OS groups.

Keywords: Colonic neoplasms; Postoperative period; Robotic surgical procedures

INTRODUCTION

Laparoscopic surgery (LS) and robotic surgery (RS) were introduced a few decades ago, and they have been used as alternative options for open abdominal surgery in many countries [1, 2]. In rectal cancer surgery, previous studies reported favorable postop-

Received: March 12, 2024; Revised: May 23, 2024; Accepted: June 24, 2024
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erative outcomes of RS over open surgery (OS) and LS, particularly in terms of functional outcomes [3, 4]. Regarding long-term oncological outcomes, RS is generally considered compatible with other methods; however, recent studies revealed better outcomes in special situations, such as advanced cases [5–8].

In contrast to rectal cancer, the benefit of RS in colon cancer remains largely controversial [9, 10]. However, challenging techniques, including central vessel ligation (CVL) with complete mesocolic excision (CME) and intracorporeal anastomosis, have recently prompted more surgeons to perform RS, resulting in a gradual increase in the number of robotic colectomies [11].

One of the benefits of minimally invasive surgery over open laparotomy for colorectal cancer is that it has reduced systemic inflammatory stress, which may lead to enhanced patient recovery [12]. It is also known that perioperative nutritional and inflammatory statuses were introduced as host-related prognostic factors for various cancers [13]. Additionally, the correlation of increased systemic inflammation with poorer long-term survival was reported by numerous studies [14].

This study aimed to compare the postoperative inflammatory stress outcomes of open, laparoscopic, and robotic colectomies using propensity score matching (PSM) to minimize possible confounding factors in the analysis. Minimally invasive surgery is known to cause less postoperative inflammatory stress, leading to faster recovery [13, 15–18]. In order to investigate and uncover the benefits of RS for colon resection by analyzing patients' perioperative inflammatory responses and nutritional statuses under the hypothesis that more meticulous RS reection was associated with less postoperative inflammatory stress [19, 20]. We compared biochemical markers of postoperative inflammatory stress among different surgical approaches, which was our primary end point and examined whether this difference could be translated into clinical outcomes, measured to be our secondary end point, along with long-term oncologic outcomes.

METHODS

Ethics statement

The study protocol was approved by the Institutional Review Board of Severance Hospital (No. 4-2022-0972). The requirement for informed consent was waived due to the retrospective nature of the study. This study is registered at the Research Registry (No. 9357) in accordance with the World Medical Association's 2013 Declaration of Helsinki. The retrospective study has been reported in line with the STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) criteria [21].

Study design

The records of consecutive patients who underwent curative colon cancer surgery between 2006 and 2012 at Severance Hospital (Seoul, Korea), a tertiary referral center, were retrieved from a prospectively maintained database and reviewed retrospectively. Eligibility criteria included patients over 18 years of age with primary colon cancer who underwent curative resection. Patients who did not have resection of primary lesion or who had emergency surgery were excluded; metastasis to solid organ requiring combined resection was also excluded. Enrolled patients were stratified into 3 groups according to their surgical approach: OS, LS, and RS. PSM was performed to eliminate confounding factors. After PSM, 66 patients were enrolled in each group (Fig. 1).

Data collection

Using electronic medical records of consecutive patients, we collected the following data: age, sex, tumor location, resection type, operative time, estimated blood loss, preoperative and postoperative laboratory results, pathologic reports (including histology, stage, number of harvested lymph nodes, and lymphovascular invasion status), postoperative complications, adjuvant therapy, and survival. For nutritional and inflammatory scores, we calculated the prognostic nutritional index (PNI) from serum albumin and neutrophil count using the previously described equation: "PNI = [10 × serum albumin (g/dL)] + 0.005 × lymphocytes/μL" [22].

Surgical procedure

All colon resections were conducted using either OS, LS, or RS techniques, and those that converted to OS intraoperatively were analyzed as initially intended methods. Details of the standard

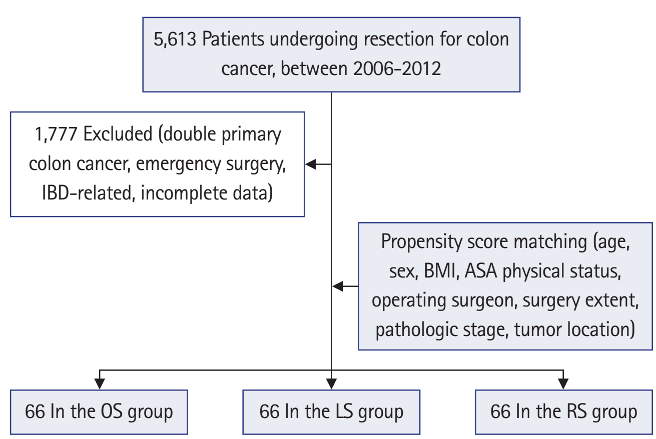


Fig. 1. Flowchart of the patient selection by propensity score matching. IBD, inflammatory bowel disease; BMI, body mass index; ASA, American Society of Anesthesiologists; OS, open surgery; LS, laparoscopic surgery; RS, robotic surgery.

surgical procedures performe at this study institution were described in a previously published study [23]. In brief, surgeries were performed under the principles of CME with CVL. For right- or left-sided colon cancer, the vessels were ligated at their roots from the superior and inferior mesenteric vessels, respectively. The da Vinci Surgical System Si (Intuitive Surgical) was used as the robotic instrument. A total of 7 colorectal surgeons, each of whom had independent experience in over 100 cases of OS and LS and 30 cases of RS, participated in this study.

Statistical analysis

Propensity scores were estimated using a logistic regression model based on baseline patient characteristics, including age, sex, American Society of Anesthesiologists (ASA) physical status, body mass index, tumor location, pathologic stage, extent of operation, and operating surgeon. Patients were matched 1:1:1 among the robotic, laparoscopic, and open methods using calipers of 0.1 with a standard deviation of the propensity score. Once all 3 groups were matched, data analysis was conducted for short-and long-term perioperative outcomes. The chi-square test or Mann-Whitney U-test was used to compare categorical baseline characteristics and perioperative outcomes. Student t-test or Wilcoxon signed rank test was used to compare continuous variables. The results were reported as mean, median, standard deviation, and interquartile range (IQR). For survival analysis, a log-rank test was used. Overall survival was defined as the interval between the surgery date and the date of death from any cause. All statistical analyses were conducted using IBM SPSS ver. 26.0 (IBM Corp), and statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

Between 2006 and 2012, there were 1,777 patients who underwent curative resection for colorectal cancer. After PSM, there were 66 patients in each of the OS, LS, and RS groups (Fig. 1). Table 1 shows the baseline patient characteristics in each group. The median age was 60 years (IQR, 49–67 years) for the OS group, 56 years (IQR, 47–63 years) for the LS group, and 59 years (IQR, 49–70 years) for the RS group. There were 31 male patients (47.0%) in the OS group, 28 (42.4%) in the LS group, and 31 (47.0%) in the RS group. The mean body mass index was 22.7 ± 3.0 kg/m^2 for the OS group, 23.5 ± 3.8 kg/m^2 for the LS group, and 23.5 ± 3.5 kg/m^2 for the RS group. Tumor location varied and was most commonly observed in the sigmoid colon, with other sites in the ascending, transverse, descending colon, and cecum. Preoperative carcinoembryonic antigen (CEA) was <5 ng/mL in most patients, among whom 50 (75.8%) underwent OS, 54 (81.8%) underwent

Table 1. Baseline characteristics of the patients

Characteristic	Before PSM (n = 1,777)				After PSM (n = 198)			
	OS (n = 637)	LS (n = 1,074)	RS (n = 66)	P-value	OS (n = 66)	LS (n = 66)	RS (n = 66)	P-value
Sex				0.185				0.832
Male	374 (58.7)	618 (57.5)	31 (47.0)		31 (47.0)	28 (42.4)	31 (47.0)	
Female	263 (41.3)	456 (42.5)	35 (53.0)		35 (53.0)	38 (57.6)	35 (53.0)	
Age (yr)	62 (54–70)	64 (55–71)	60 (49–70)	0.004*	60 (49–67)	56 (47–63)	59 (49–70)	0.163
Body mass index (kg/m^2)	23.1 ± 3.2	23.4 ± 3.1	23.5 ± 3.5	0.153	22.7 ± 3.0	23.5 ± 3.8	23.5 ± 3.5	0.337
ASA physical status				0.642				0.885
I–II	607 (95.3)	1,029 (95.9)	65 (98.5)		65 (98.4)	64 (97.0)	65 (98.5)	
III–IV	30 (4.7)	45 (4.1)	1 (1.5)		1 (1.6)	2 (3.0)	1 (1.6)	
Preoperative CEA (ng/mL)	2.5 (1.3–6.0)	2.2 (1.3–4.2)	2.1 (1.2–4.6)	0.049*	2.2 (1.2–5.1)	2.0 (1.1–3.1)	2.1 (1.2–4.6)	0.281
Location				0.048*				0.792
Ascending	295 (46.3)	461 (42.9)	17 (25.8)		15 (22.7)	13 (19.7)	17 (25.8)	
Transverse	6 (0.9)	14 (1.3)	3 (4.5)		2 (3.0)	7 (10.6)	3 (4.5)	
Descending	72 (11.3)	108 (10.1)	5 (7.6)		11 (16.7)	9 (13.6)	5 (7.6)	
Sigmoid	264 (41.4)	491 (45.7)	41 (62.1)		38 (57.6)	37 (56.1)	41 (62.1)	
Stage[a]				< 0.001*				0.824
I–II	226 (51.2)	787 (73.3)	45 (68.2)		42 (66.7)	47 (71.2)	45 (68.2)	
III–IV	311 (48.8)	287 (26.7)	21 (31.8)		22 (33.3)	19 (28.8)	21 (31.8)	

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.
PSM, propensity score matching; OS, open surgery; LS, laparoscopic surgery; RS, robotic surgery; ASA, American Society of Anestheologists; CEA, carcinoembryonic antigen.
[a]According to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition.
*$P < 0.05$.

https://doi.org/10.3393/ac.2024.00171.0024

LS, and 51 (77.3%) underwent RS. Regarding patients having CEA >5 ng/mL, 16 (24.2%) underwent OS, 12 (18.2%) underwent LS, and 15 (22.7%) underwent RS. There were no statistically significant differences in baseline patient characteristics among the 3 groups, especially after PSM was done.

Short-term postoperative outcomes

Table 2 shows perioperative and pathologic outcomes of patients after undergoing colectomies with different surgical modalities. Since the extent of operation was determined according to tumor location, anterior resection was most frequently performed in all 3 modality groups. The operation time was longest in the RS group (245.5±14.7 minutes), followed closely by the LS group (244.8±93.3 minutes), and shortest in the OS group (211.7±98.9 minutes). Pathologic stage was determined according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition [24], and the number of retrieved lymph nodes showed no significant difference among the 3 groups.

We assessed the patients' postoperative recovery in 3 categories: time to first flatus, time to resumption of soft diet, and length of hospital stay (Supplementary Table 1). Postoperative complications were also reviewed and categorized into overall and major complications, which were graded over III in the Clavien-Dindo classification of surgical complications. Regarding the time taken to first flatus postoperatively, OS patients took the longest to achieve their first flatus (4.1±2.0 days) compared to the LS (3.2±1.8 days) and RS groups (3.0±1.2 days). This difference was also statistically significant between OS and LS (P=0.020) and between OS and RS (P=0.001). However, the difference between LS and RS was not statistically significant (P=0.314). The time patients took to resume their soft diet was also the longest in the OS group (6.4±2.4 days) compared to the LS (4.6±2.2 days) and RS groups (4.3±1.8 days). While this difference showed statistical significance between the OS and the other 2 groups (both P<0.001), the difference between LS and RS groups did not (P=0.418).

The results of postoperative in-hospital recovery are shown in Fig. 2. The length of postoperative hospital stay was longest in the OS group (10.5±3.6 days) and shortest in the LS group (8.6±3.9 days) as compared to 9.9±7.3 days in the RS, with no significant difference among the 3 groups. In the OS group, 9 patients (13.6%) had postoperative complications, and 3 (4.5%) had major complications. In the LS group, 8 patients (12.1%) had complications, and 2 (3.0%) had major complications. In the RS group, 12 pa-

Table 2. Operative and pathologic outcomes

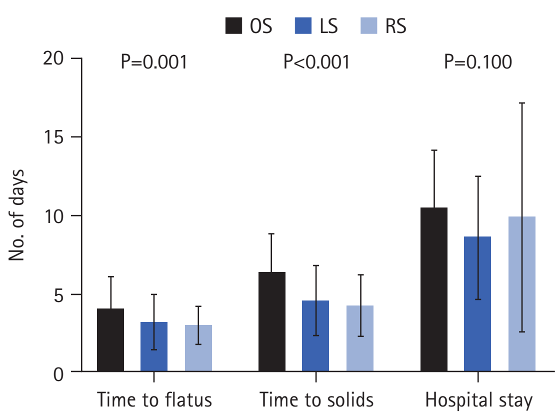
Outcome	Surgical method			P-value
	OS (n=66)	LS (n=66)	RS (n=66)	
Extent of operation				0.789
Right hemicolectomy	16 (24.2)	18 (27.3)	19 (28.8)	
Transverse colectomy	1 (1.5)	1 (1.5)	0 (0)	
Left hemicolectomy	9 (13.6)	9 (13.6)	6 (9.1)	
Anterior resection	40 (60.6)	38 (57.6)	41 (62.1)	
Operation time (min)	211.7±98.9	244.8±93.3	245.5±14.7	0.176
Estimated blood loss (mL)	50 (30–100)	40 (25–100)	50 (25–95)	0.744
Pathologic stage[a]				0.768
I	26 (39.4)	29 (43.9)	25 (37.9)	
II	18 (27.3)	18 (27.3)	20 (30.3)	
III	16 (24.2)	17 (25.8)	15 (22.7)	
IV	6 (9.1)	2 (3.0)	6 (9.1)	
No. of retrieved LNs	22 (12–31)	20 (13–30)	20 (12–29)	0.950
Histologic grade				0.400
1	11 (16.7)	17 (25.8)	15 (22.7)	
2	49 (74.2)	46 (69.7)	46 (69.7)	
3	6 (9.1)	3 (4.5)	5 (7.6)	
Lymphovascular invasion	11 (16.7)	12 (18.2)	11 (16.7)	0.965
Adjuvant therapy				0.885
Chemotherapy	34 (51.5)	31 (47.0)	29 (43.9)	
Chemotherapy+radiotherapy	2 (3.0)	0 (0)	0 (0)	

Values are presented as number (%), mean±standard deviation, or median (interquartile range). Percentages may not total 100 due to rounding.
OS, open surgery; LS, laparoscopic surgery; RS, robotic surgery; LN, lymph node.
[a]According to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition.

tients (18.2%) had postoperative complications, and 6 (9.1%) were graded above III in the Clavien-Dindo classification. Differences in postoperative complications among the 3 groups were not statistically significant.

Postoperative inflammatory biochemical markers

We examined the patients' postoperative inflammatory biochemical markers and the results were shown in Table 3 and Fig. 3. We investigated 3 items in the perioperative period: total leukocyte count, neutrophil count, and PNI. The maximal postoperative total leukocyte counts ($\times 10^3$) were 14.0 ± 3.8 for the OS group, 12.6 ± 3.1 for the LS group, and 12.5 ± 3.2 for the RS group. The differences in overall (P = 0.021) as well as in comparisons between OS with LS (P = 0.019) and OS with RS (P = 0.017) were statistically significant. However, the ratio of postoperative to preoperative total leukocyte counts did not show any statistically significant difference among the 3 groups. As expected from findings of leukocyte counts, results of neutrophil count were similar, with the highest in the OS group, followed by the RS and LS groups. PNI was calculated using the original formula [22], and a higher PNI value usually correlates with better nutritional status of the patient. The minimal postoperative PNI was 25.9 ± 6.7 in the OS group (lowest among the 3 groups), 26.7 ± 4.6 in the LS group, and 35.1 ± 4.9 in the RS group. Interestingly, there was a statistically significant difference between the OS and LS groups as compared to the RS group (both P < 0.001), but not between the OS and LS groups (P = 0.472). Differences in PNI were statistically significant (P < 0.001). Similar results regarding the ratio of postoperative to preoperative PNI were obtained, as summarized in Table 3 and Supplementary Table 2. A comparison of PNI among the 3 groups is shown in Fig. 3.



	Time to flatus	Time to solids	Hospital stay
OS (n=66)	4.1±2.0	6.4±2.4	10.5±3.6
LS (n=66)	3.2±1.8	4.6±2.2	8.6±3.9
RS (n=66)	3.0±1.2	4.3±1.8	9.9±7.3

Fig. 2. Differences in the numbers of days taken for first flatus and soft diet resumption, and hospital stay duration among the open surgery (OS), laparoscopic surgery (LS), and robotic surgery (RS) groups. Values are presented as mean ± standard deviation.

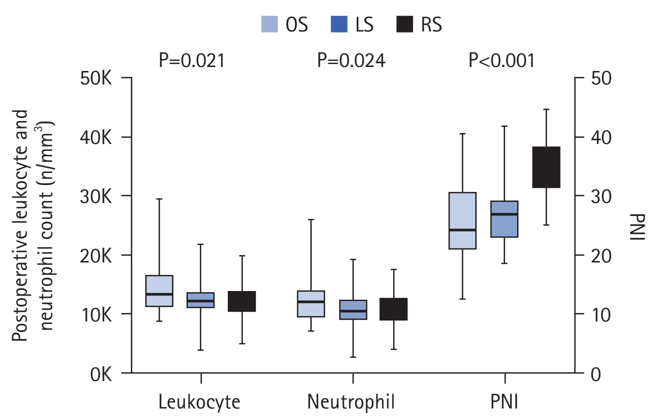


Fig. 3. Postoperative leukocyte and neutrophil counts and calculated PNI among the open surgery (OS), laparoscopic surgery (LS), and robotic surgery (RS) groups. PNI, prognostic nutritional index.

Table 3. Postoperative laboratory results

Laboratory result	Surgical method			P-value
	OS (n = 66)	LS (n = 66)	RS (n = 66)	
Maximal postoperative leukocyte ($\times 10^3$)	14.0 ± 3.8	12.6 ± 3.1	12.5 ± 3.2	0.021
Ratio against preoperative leukocyte	1.9 ± 0.5	2.0 ± 0.6	2.0 ± 0.6	0.673
Maximal postoperative neutrophil ($\times 10^3$)	12.2 ± 3.5	10.8 ± 2.9	10.9 ± 3.1	0.024
Ratio against preoperative neutrophil	2.9 ± 0.9	3.0 ± 1.2	2.9 ± 1.1	0.941
Minimal postoperative PNI	25.9 ± 6.7	26.7 ± 4.6	35.1 ± 4.9	< 0.001
Ratio against preoperative PNI	0.5 ± 0.1	0.5 ± 0.1	0.7 ± 0.1	< 0.001

Values are presented as mean ± standard deviation. PNI was calculated using the original formula: "PNI = [10 × serum albumin (g/dL)] + 0.005 × lymphocytes/μL" [22].
OS, open surgery; LS, laparoscopic surgery; RS, robotic surgery; PNI, prognostic nutrition index.

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Long-term oncological outcomes

Overall median follow-up duration was 59 months; 68.5 months for the OS group, 56.5 months for the LS group, and 56.0 months for the RS group. The 5-year overall survival, estimated using Kaplan-Meier analysis, was highest in the LS group, closely followed by the RS group, and lowest in the OS group (93.5% vs. 92.4% vs. 87.3%, log-rank P = 0.495) (Fig. 4). The 5-year disease-free survival was highest in the OS group, followed by the LS group, and lowest in the RS group (87.0% vs. 86.2% vs. 81.0%, log-rank P = 0.689) (Fig. 5). The survival rates did not differ significantly among the 3 groups.

DISCUSSION

Current practice in colorectal cancer treatment recognizes minimally invasive surgery as the standard approach, while open laparotomies are performed on selected cases. There have been comparisons of 2 different modalities, or of OS with minimally invasive surgery (RS and OS) but analyses of all 3 modalities at once have rarely been reported, with the vast majority of studies focusing on rectal cancer [25]. The strength of our study was that data analyzed were collected from a timeframe during when all 3 of OS, LS, and RS methods were readily applicable by well-experienced surgeons, avoiding surgeon-related confounding factors. We also used PSM to compensate for possible limitations of retrospective study design and to minimize other confounding factors. The absence of significant differences in basic characteristics of the 3 groups confirmed that the matching was well-performed.

While robotic colon resection for colon cancer patients had proven safety and efficacy in previous studies, its specific benefits for patients compared to other modalities remain to be determined [26]. Despite varying opinions about the role of RS in colon resection, the number of robotic operations performed worldwide has gradually increased [2]. This increase may be attributed to improved technical advancements through the evolution of the DaVinci system, which enabled multiquadrant intra-abdominal surgery [27]. Secondly, challenging procedures, including CME with CVL [11] and intracorporeal anastomosis [28], called for increased application of robotics. Lastly, as more surgeons are exposed to robotic systems, the general learning curve has been overcome collectively.

The hypothesis that we built our analysis upon was that RS would minimize the postoperative immunological burden due to increased efficiency in tissue handling and that PNI and leukocyte count would represent these differences. Measured postoperative leukocyte count, representing overall systemic inflammatory response extent, showed higher increase in OS compared to RS and LS (P = 0.021), and comparable values for RS and LS (12.6 ± 3.1 vs. 12.5 ± 3.2, P = 0.892). More interestingly, calculated PNI was more favorable in RS over other modalities (RS vs. OS, P < 0.001; RS vs. LS, P < 0.001), and comparable between OS and LS. In one study, Ahiko et al. [13] reported the prognostic value of nutritional status scores and inflammatory scores, including PNI for stage II and III colorectal cancer patients undergoing curative resection. According to our findings, RS resulted in significantly lowered inflammatory stress, althogh this difference might have been more distinct with a larger sample size.

The time interval from operation to first flatus and initiation of soft diet was shortest in the RS group (flatus time, P = 0.001; soft diet resumption, P < 0.001). Post hoc analysis failed to reach statistical significance for RS over LS. These short-term clinical outcomes were similar to other studies comparing OS with both RS

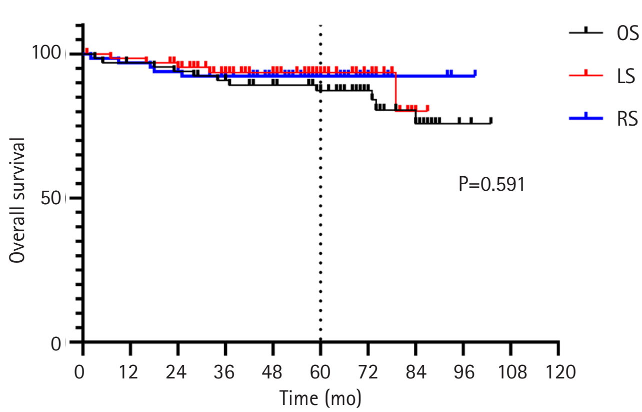

Fig. 4. Kaplan-Meier analysis of the overall survival among the open surgery (OS), laparoscopic surgery (LS), and robotic surgery (RS) groups.

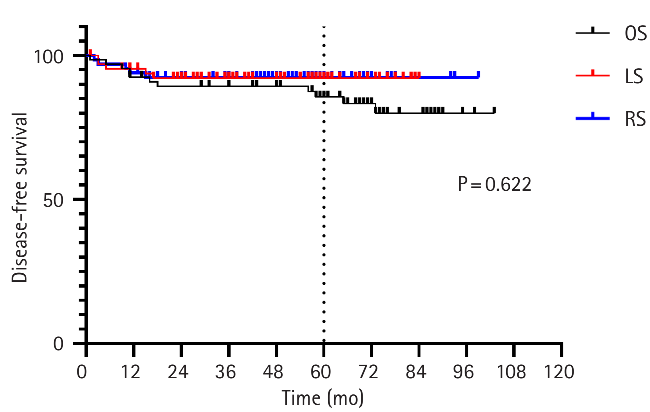

Fig. 5. Kaplan-Meier analysis of disease-free survival among the open surgery (OS), laparoscopic surgery (LS), and robotic surgery (RS) groups.

and LS together as minimally invasive surgery methods. Our findings regarding postoperative inflammatory and nutritional biomarkers did not translate into short-term clinical recovery as we anticipated, and even the length of hospital stay did not differ significantly. This observation, as mentioned in previous studies [25, 29], may result from the fact that length of hospital stay could be affected by patient-driven factors that are irrelevant to postoperative outcomes. The increasing acceptance of the widespread implementation of Enhanced Recovery After Surgery (ERAS) since its introduction along the timeframe of our study also affected aforementioned short-term clinical outcomes. The general paradigm of reducing hospital stay length according to the ERAS program might have offset the effect of different inflammatory stress statuses among the surgical modalities.

In accordance with previous findings in other studies, long-term oncologic outcomes were not significantly different among 3 surgical modalities [30, 31]. However, to further analyze the oncological effect of RS for colon cancer, future studies regarding specific circumstances, such as T4 category and CME with CVL, are warranted, as they were examined for rectal cancer.

Perioperative inflammatory and nutritional indices were more favorable for RS than for LS and OS. And expectedly, short-term outcomes of colon resection were better for minimally invasive surgery than for OS, and comparable between RS and LS. Long-term oncological outcomes did not differ among the 3 surgical methods. These findings indicate that RS resulted in minimal postoperative immunological stress via perioperative inflammatory and nutritional biochemical markers. We assumed that this difference could become clearer in more challenging situations in which the technical advantages of RS are fully utilized. The uncertain connection between favorable inflammatory stress indices and better short- and long-term outcomes should be confirmed in well-designed prospective studies with larger sample sizes in the future.

In conclusion, upon comparing 3 different surgical modalities for colon cancer resection, we were able to find possible association between improved postoperative inflammatory markers in robot-assisted surgery. These results may support future studies in search of benefits of RS in colon cnacer surgery.

ARTICLE INFORMATION

Conflict of interest

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

Funding

This study was supported by the Korea Institute For Robot Industry Advancement grant (No. 2023-04008), funded by the Korean Ministry of Trade, Industry and Energy.

Author contributions

Conceptualization: EJP, GTN, BSM; Data curation: GTN; Formal analysis: EJP, GTN; Funding acquisition: BSM; Investigation: EJP, GTN; Methodology: YJL, MYP, SYY, YDH, MSC, HH, KYL; Project administration: EJP, GTN, BSM; Visualization: EJP; Writing–original draft: EJP, GTN; Writing–review & editing all authors. All authors read and approved the final manuscript.

Supplementary materials

Supplementary Table 1. Postoperative in-hospital recovery
Supplementary Table 2. Postoperative laboratory results
Supplementary materials are available from https://doi.org/10.3393/ac.2024.00171.0024.

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