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ORIGINAL ARTICLE

Surgical stress response after colorectal resection: a comparison of robotic, laparoscopic, and open surgery

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Abstract
Background The perioperative immune status of colorectal robotic surgery (RS), laparoscopic surgery (LS), and open surgery (OS) patients has not been compared. Our aim was to evaluate perioperative stress and immune response after RS, LS and OS.
Methods This prospective study included 46 colorectal surgery patients from the Department of Surgical Oncology of the University of Tokyo Hospital. Peripheral venous blood samples were obtained preoperatively and on postoperative days 1, 3, and 6. We evaluated expression of HLA-DR (marker of immune competence), C-reactive protein (CRP) levels, and lymphocyte subset counts (natural killers, cytotoxic T cells and helper T cells).
Results Fifteen, 23, and 8 patients underwent RS, LS and OS, respectively. HLA-DR expression was the lowest on day 1 and gradually increased on days 3 and 6 in all the groups. There was no significant difference in postoperative HLA-DR expression between the RS and LS group. However, on day 3, HLA-DR expression in the RS group was significantly higher than in the OS group ($p = 0.04$). On day 1, CRP levels in the LS group were significantly lower than in the RS group ($p = 0.038$). There were no significant perioperative changes in the lymphocyte subset cell count between the three groups.
Conclusions Perioperative surgical stress, as evaluated by immunological parameters, was comparable between robotic and laparoscopic surgery and higher with open surgery. Robotic surgery may be an alternative to laparoscopic surgery, as a minimally invasive surgery option for colorectal cancer.

Keywords Robotic surgery · Laparoscopic surgery · Colorectal resection · HLA-DR · Lymphocyte subsets

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Introduction

Laparoscopy is now widely used in colorectal cancer patients. Previous studies have reported [1–3] significant short-term benefits after using a laparoscopic approach in colon surgery: reduction in intraoperative blood loss, postoperative pain, ileus, and hospital stay without increasing adverse events. It was recently reported [4–7] that there were no differences in the oncologic outcomes between colorectal cancer patients who underwent open surgery and those who underwent laparoscopic surgery. Moreover, many studies [8–10] have reported differences in immune response after laparoscopic and open surgery for colorectal cancer, and laparoscopic surgery has been related to decreased up-regulation of innate immunity and better-preserved cellular immunity when compared to open surgery [11].

Since the beginning of the 2000s, robotic surgery has become widely used in many centers. Robotic technology is especially useful when the operative field is small and delicate work is required [12]. Because precise dissection is required in the pelvis, robotic-assisted resection is especially used in rectal cancer patients [13].

Some studies have compared the feasibility and efficacy of robotic surgery with that of laparoscopic surgery for the

treatment of colorectal cancer [14–16]. However, no studies have compared patients' perioperative immune status after robotic, laparoscopic, and open colorectal surgery. Therefore, the aim of our study was to evaluate the effect of robotic, laparoscopic, and open colorectal surgery on the stress response of patients in the perioperative period.

Materials and methods

From June 2012 to November 2013, we conducted a prospective study on 46 consecutive patients who had given written informed consent to this study before surgery. The study protocol was approved by the hospital ethics committee. Patients with immunological dysfunction (advanced liver disease, human immunodeficiency virus infection, hepatitis B or C virus infection), use of steroids or high preoperative C-reactive protein (CRP) levels (>3.0 mg/dL) were excluded from this study. Patients who had undergone preoperative chemoradiotherapy and chemotherapy were also excluded, because many studies [17–19] have reported that chemoradiotherapy or radiotherapy suppresses the perioperative inflammatory response. All participating patients underwent colorectal surgery at the Department of Surgical Oncology of the University of Tokyo Hospital. Before surgery, all cases were diagnosed as primary cancers. All operations consisted of bowel resection with mesenteric excision, and the type of surgical procedure used depended on surgeon preference. However, in our department, robotic surgery was only performed in rectal cancer patients.

Data sampling

Peripheral venous blood samples were obtained preoperatively and on postoperative days 1, 3, and 6. Leukocyte phenotype analysis was started <6 h after collecting the blood samples.

Analysis of leukocyte phenotype and cell surface markers

Samples were collected in ethylenediaminetetraacetic acid collection tubes, and blood cell counts were analyzed using an automated hematology analyzer (XE-5,000, Sysmex, Kobe, Japan). Lymphocyte subsets and HLA-DR expression were also analyzed using flow cytometry, as described previously, with small modifications [20]. Briefly, whole blood was treated with FACS Lysing Solution (Becton–Dickinson, CA, USA) to lyse red cells and fix leukocytes with 1 % formaldehyde. Then, leukocytes were incubated with 10 μL of each antibody for 20 min at room temperature and analyzed in the flow cytometer. The lymphocyte region was gated, and two-color flow cytometric analysis for each cell phenotype on 10,000 events was performed on the FACS Calibur flow cytometer (Becton–Dickinson) using the Multiest software package (Becton–Dickinson); the data were analyzed using the CellQuest software (Becton–Dickinson). A combination of fluorescein isothiocyanate and phycoerythrin-conjugated monoclonal antibody (Becton–Dickinson) was used to identify lymphocyte subsets and HLA-DR expression, as follows: CD3(−)/CD19(+) for the B lymphocytes, CD3(+)/CD4(+) for the helper T lymphocytes, CD3(+)/CD8(+) for the cytotoxic T lymphocytes, CD3(−)/CD56(+) for the natural killer (NK) cells, and CD14(+)/HLA-DR(+) for the HLA-DR expression on monocytes. Expression levels of HLA-DR were quantified by assessing major histocompatibility complex class II expression.

Statistical analysis

The analysis of the differences between groups of blood cell counts or number of lymphocyte subsets, and clinicopathological variables was performed using Chi-square tests, Kruskal–Wallis tests, and analysis of variance tests. The statistical analyses were performed using JMP 10 software (SAS International Inc., NC, USA), and p values <0.05 were considered to be statistically significant.

Results

Patients

Patient characteristics are summarized in Table 1. A total of 46 patients underwent surgery. Fifteen, 23, and 8 patients underwent robotic surgery (RS), laparoscopic surgery (LS), and open surgery (OS), respectively. No case was converted to open surgery, in this study. The patients who had advanced rectal cancer underwent lateral lymph node dissection (seven RS patients and one LS patient). In this study, one patient received an allogeneic red blood cell transfusion during open surgery. Seven patients had postoperative complications: one was an RS patient who developed ileus; three were LS patients, two with wound infection and one with urinary tract infection; and three were OS patients, one with wound infection, one with intra-abdominal abscess, and one with ileus. There were two cases in which the tumor invaded a surrounding organ and was removed by en bloc resection (one LS patient: the sigmoid colon cancer invaded the left ovary, seven OS patient: the rectal cancer invaded the prostate). In the OS group, two patients who had liver metastases underwent only primary tumor resection.

Table 1 Clinical characteristics of patients and type of operation performed

	Robotic surgery ($n = 15$)	Laparoscopic surgery ($n = 23$)	Open surgery ($n = 8$)	p value
Sex				0.73
Men	9	14	6	
Women	6	9	2	
Age (range)	61.1 (37–77)	62.9 (42–80)	62.3 (50–84)	0.9
BMI ± SD	22.5 ± 1.9	22.3 ± 2.8	21.6 ± 3.7	0.75
Location of primary tumor				<0.01
Colon	0	12	5	
Rectum	15	11	2	
Ileum	0	0	1	
ASA grade				0.72
I	4	5	1	
II	11	17	7	
III	0	1	0	
Size of primary tumor ± SD (mm)	38.2 ± 23.8	33.9 ± 18.3	68.6 ± 28.5	<0.01
Depth of tumor invasion				
T0	0	1	0	
T1	3	3	0	
T2	2	2	1	
T3	9	11	3	
T4	1	6	4	
T1 × 2 versus T3 × 4				0.53
Lymph node metastasis				0.77
Absent	8	11	5	
Present	7	12	3	
Type of procedure				
Ileocecal resection	0	6	1	
Left hemicolectomy	0	0	1	
Sigmoidectomy	0	6	2	
High anterior resection	0	4	2	
Abdominoperineal resection	0	1	0	
Low anterior resection	14	6	1	
Intersphincteric resection	1	0	0	

BMI body mass index, *SD* standard deviation, *ASA* American Society of Anesthesiologists

There were no significant differences in age, gender, body mass index, depth of tumor invasion, and lymph node metastases among the three groups. However, the location and size of the primary tumor were significantly different among the groups ($p < 0.01$, respectively). All tumors in the RS group were located in the rectum, whereas the OS group included one patient with an ileal tumor. Tumor size was larger in the OS group than the RS and LS groups.

Laboratory data

Perioperative changes in HLA-DR expression on monocytes are shown in Fig. 1.

HLA-DR expression was the lowest on day 1 and gradually increased on days 3 and six in all the groups. There was no significant difference in postoperative HLA-DR expression between the RS group and LS group. However, on day 3, HLA-DR expression in the RS group was significantly higher than in the OS group ($p = 0.04$).

CRP levels are shown in Fig. 2. On day 1, CRP levels in the LS group were significantly lower than in the OS group ($p = 0.038$). CRP level was the highest on day 3 in each group, and the CRP level of the OS group was the highest on each postoperative day ($p = 0.019$ on day 1, $p = 0.026$ on day 3; one-way analysis of variance). On day 6, CRP levels in the RS group were lower than in the LS group, but the difference was not statistically significant ($p = 0.34$).

The numbers of lymphocyte subsets are shown in Fig. 3. In each group, the number of NK cells decreased from

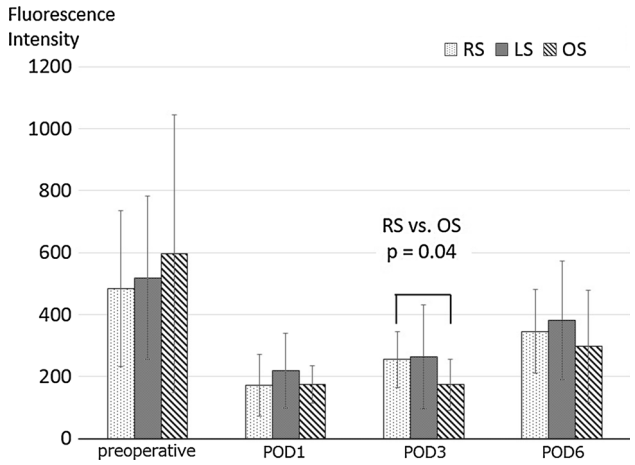

Fig. 1 Postoperative changes in HLA-DR expression on monocytes. Results are expressed as mean ± standard deviations. *POD* postoperative day

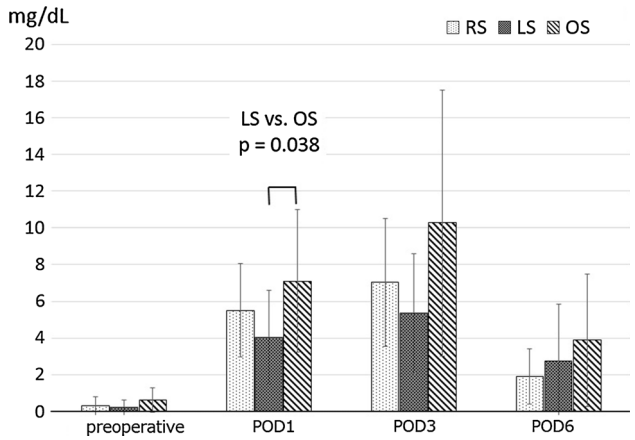

Fig. 2 Postoperative changes in C-reactive protein (CRP) levels. Results are expressed as mean ± standard deviations. *POD* postoperative day

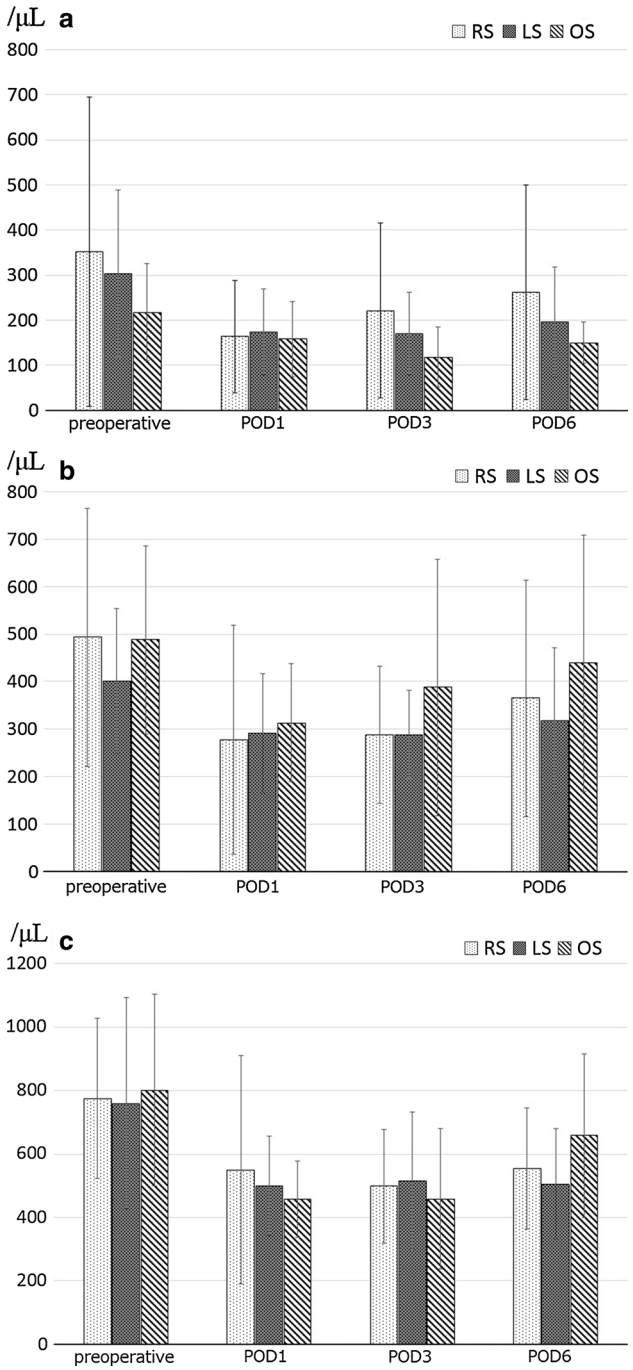

Fig. 3 Postoperative changes in the natural killer (NK) cell count (**a**), cytotoxic T lymphocyte (CTL) cell count (**b**), and helper T cell count (**c**). Results are expressed as mean ± standard deviations. *POD* postoperative day

before surgery to postoperative day 1 and an increase was observed on days 3 and 6. There were no significant differences among the three groups at each time point. The changes through time in cytotoxic T lymphocyte cell count and helper T cell count were similar to those observed in HLA-DR expression, but there were no significant differences among the three groups. There were no significant changes in the B cell count during the perioperative period.

Discussion

Recently, robotic technology has been spreading into the field of colorectal surgery. Compared to conventional laparoscopy, robotic technology offers the benefits of a stable camera platform, enhanced dexterity, three-dimensional visualization, more intuitive instrument manipulation, tremor elimination, and excellent ergonomics [12, 21]. Several reports [13, 16, 22] have shown that robotic surgery has a lower conversion rate than laparoscopic surgery and a similar operating time, overall complication rate, and cost. Robotic colorectal surgery is as safe as laparoscopic

colorectal surgery. However, the surgical stress response after robotic colorectal resection has not been studied thus far.

Some studies have assessed the perioperative stress response in robotic and laparoscopic gastrectomy. Hyun et al. [23] retrospectively compared the postoperative granulocyte-to-lymphocyte ratio as a marker of surgical stress, both preoperatively and on postoperative days 1, 4, and 7. There were no significant differences between the granulocyte-to-lymphocyte ratios of patients who underwent robotic-assisted gastrectomy and laparoscopic-assisted gastrectomy on any of these days. They concluded that the level of surgical stress is similar in both surgical approaches. Park et al. [24] assessed serum levels of CRP, fibrinogen, interleukin 6, interleukin 10, and tumor necrosis factor α and reported that the stress response was not reduced with the robotic approach as compared with the laparoscopic approach.

The RS group had higher values of HLA-DR expression on monocytes than the OS group. However, the difference was only statistically significant on day 3. HLA-DR expression on monocytes is a measure of immune competence and is associated with adequate presentation of antigens and specific immune responses [25]. Major surgery induces immune reactions with reduced HLA-DR expression on monocytes [26, 27]. Kono et al. [28] reported that the decrease in the expression of HLA-DR on monocytes was prolonged after an esophagectomy in comparison with that after cholecystectomy and gastrectomy. Patients undergoing esophagectomy exhibit higher surgical stress than those undergoing cholecystectomy and gastrectomy. It is thought that continuous low HLA-DR expression indicates higher surgical stress. Moreover, some studies [9, 10] have reported that laparoscopic colon surgery patients had a better-preserved HLA-DR expression than open colon surgery patients. Our study findings reveal that the surgical stress of the RS group was lower than that of the OS group.

The CRP level was used as a nonspecific marker for the extent of the acute-phase reaction caused by trauma or inflammation. The postoperative increase in the serum CRP level can be used to monitor the magnitude of surgical trauma [29, 30]. In our study, the OS group showed the highest magnitude of surgical trauma after surgery. Meanwhile, the CRP level of the RS group was slightly lower than that of the LS group on day 6. The RS group included only rectal tumor patients, which may have influenced the changes in CRP levels.

In relation to the lymphocyte subsets, the NK cell and helper T cell counts decreased after surgery. However, we did not observe any significant differences in the preoperative and postoperative values among the three groups of lymphocyte subsets.

The present study has several limitations. It is limited by the absence of a randomized controlled study design, and there were some important differences in patient clinicopathological characteristics between the study groups, such as primary tumor location and size. Moreover, one patient received an allogeneic red blood cell transfusion during the operation. Allogeneic blood transfusion mediates immunosuppression in transfused patients [31], and this might have affected our results. In our department, robotic surgery was performed only in rectal tumor patients. This is the reason for the difference in primary tumor location observed between the groups. Furthermore, the size of the tumor may have influenced the operator when deciding to use a particular surgical approach. Since the Japanese public health insurance system does not cover the cost of robotic surgery, this may have influenced patient selection for robotic surgery and could have resulted in selection bias. Furthermore, in our study, robotic surgery was only performed for rectal resection, not colon resection. Generally, it is assumed that rectal resection causes more surgical stress than colon resection; therefore, a possible conclusion of our study is that RS may cause less surgical stress than LS. However, many studies [32–34] have reported that robotic surgery is more expensive than laparoscopic surgery. Reducing the cost of robotic surgery is an issue to be addressed in the future.

Conclusions

Postoperative surgical stress in RS and LS patients, as evaluated by the immunological parameters in our study, was comparable. Surgical stress was lower in both RS and LS patients than in OS patients. However, because this was a non-matched study, further study is required to clarify the immunological benefits of robotic surgery on colorectal resection.

Conflict of interest None.

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