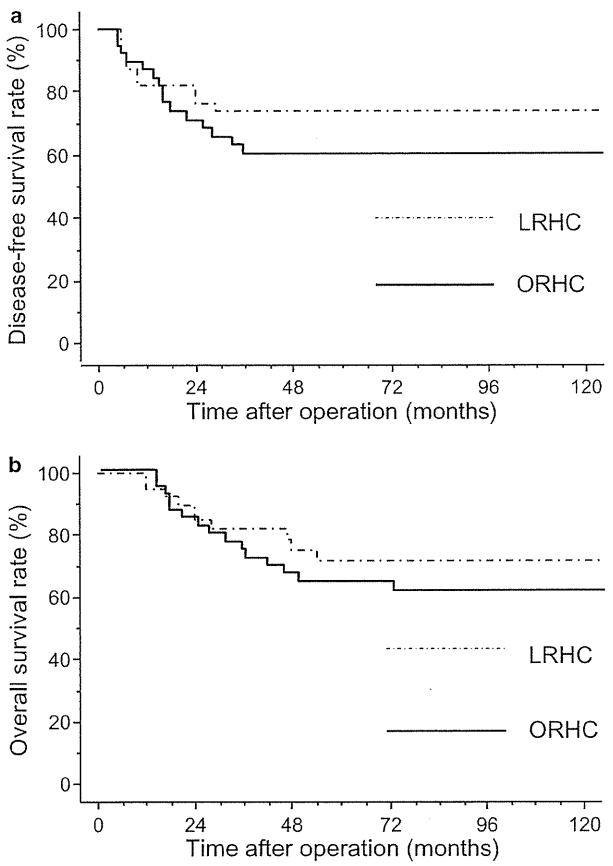

Fig. 2. **a** Comparison of the disease-free survival rates in patients with stage III colon cancer between the laparoscopic right hemicolectomy (*LRHC*) group and the open right hemicolectomy (*ORHC*) group. **b** Comparison of the overall survival rates in patients with stage III colon cancer between the LRHC group and the ORHC group

the origin of the vascular supply of an intent tumor with this procedure. Left-sided colon cancer can be easily treated by a laparoscopic high ligation of the inferior mesenteric artery with an extended lymphadenectomy. In right-sided colon cancer there are two feeders, i.e., the ileocolic and the right colic arteries, with wide-range variations of vascular architecture. A laparoscopic lymphadenectomy intracorporeally performed is therefore more difficult for right-sided colon cancer than for a left-sided tumor. The same degree of a lymphadenectomy as achieved by an ORHC was reported to be feasible in an LRHC.[8,11] In the present study, the number of lymph nodes removed was not significantly different in the LRHC group and the ORHC group. Three-dimensional CT may allow for the identification of the vascular supply, thereby simplifying the procedure for a complete lymphadenectomy along the feeding arteries in an LRHC.

Some reports have now suggested that laparoscopic surgery for colon cancer is generally an acceptable procedure with less invasiveness in comparison to open surgery,[1–4] although these studies have been conducted for heterogeneous group of patients in terms of tumor location. From the limited information of right-sided colon cancer carried out in a single center, the currently available data suggest that LRHCs have the same morbidity[10,13] and oncologic clearance,[11,13] faster postoperative recovery,[13] and similar survival rate[12] as in ORHCs. These results are consistent with the present study. The operation time was significantly longer for an LRHC.[10,12,13] In contrast, the current study found no significant differences in the operation time between the two groups. One study showed that LRHC was significantly more expensive than ORHC.[10,12]

In the current limited retrospective study, LRHC was confirmed to be a useful procedure for the treatment of right-sided colon cancer. Further prospective studies in multiple institutions are needed to establish LRHC as a standard procedure.

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Activation of nuclear factor kappa B and induction of migration inhibitory factor in tumors by surgical stress of laparotomy versus carbon dioxide pneumoperitoneum: an animal experiment

Anwar Tawfik Amin · Norio Shiraishi · Shigeo Ninomiya · Masaaki Tajima · Masafumi Inomata · Seigo Kitano

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Abstract
Background Surgical trauma may be associated with enhanced tumor growth and establishment. The authors studied the effect of carbon dioxide (CO_2) pneumoperitoneum versus laparotomy on tumor necrosis factor-α (TNFα), migration inhibitory factor (MIF) expression, and nuclear factor kappa B (NFκB) activity in human gastric cancer.
Methods Nude mice were inoculated intraperitoneally with human gastric cancer cells (MKN45). Then laparotomy, CO_2 pneumoperitoneum, and anesthesia alone were performed randomly. Tumor growth and associated TNFα and MIF expression and NFκB activity were determined.
Results Total tumor weight, especially at the anterior abdominal wall, was higher after laparotomy than after CO_2 pneumoperitoneum ($p < 0.05$). The mRNA expression of TNFα was higher 24 and 48 h after laparotomy than after CO_2 pneumoperitoneum ($p < 0.05$ and $p < 0.01$, respectively). At all the examined time points, MIF mRNA expression also was higher after laparotomy than after CO_2 pneumoperitoneum ($p < 0.05$ until 1 week or $p < 0.01$ at 2 weeks). The NFκB protein was more activated after laparotomy than after CO_2 pneumoperitoneum 6 h subsequent to surgical procedures.
Conclusion After CO_2 pneumoperitoneum, tumors have less TNFα and MIF expression and less NFκB activity than after laparotomy. This may be associated with less tumor growth, supporting minimal invasive techniques in gastrointestinal oncologic surgery.

Keywords Laparotomy · MIF · NFκB · Pneumoperitoneum · TNFα · Tumor growth

A. Tawfik Amin (✉) · N. Shiraishi · S. Ninomiya · M. Tajima · M. Inomata · S. Kitano
Department of Gastroenterological Surgery, Oita University Faculty of Medicine, 1-1 Idaigaoka, Yufu, Oita 879-5593, Japan
e-mail: anwar71@med.oita-u.ac.jp; anwartawfik2010@yahoo.com

A. Tawfik Amin
South Egypt Cancer Institute, Surgery Department, Assiut University, Assiut, Egypt

Surgery is the most effective method for the treatment of malignant tumors. However, surgical trauma seems to be associated with enhanced incidence of tumor growth and establishment [1–4]. At the same time, the mechanisms by which surgical trauma may have an impact on tumor growth and progression still are unclear.

Laparoscopic surgery, accepted as a minimally invasive procedure, recently has been adapted for gastrointestinal cancers [5–7]. Although few clinical studies have shown the oncologic feasibility of laparoscopic surgery, several animal studies mostly have shown that laparoscopic procedures are associated with significantly less increase in tumor growth and metastasis than open surgery [1–4]. However, a more precise conception regarding the ability of laparoscopic techniques to treat malignant tumors still is needed [1–3, 5].

A few animal and clinical studies have evaluated the induction of adhesion molecules, inflammatory response, cytokines, and growth factors such as TNFα and vascular endothelial growth factor (VEGF) after laparoscopic and open surgery [3, 4, 7, 8] . These factors may act as indicators for the extent of surgical stress and may modify the biologic activity of dormant cancer cells after surgery. However, these factors have not been evaluated in the tumors after surgery. It is known that these factors are regulated by DNA-binding proteins such as nuclear factor kappa B (NFκB) [1, 2, 9].

As a major regulator of gene transcription, NFκB is involved in immune, inflammatory, and stress responses. In response to cell stimulatory factors such as TNFα and other cytokines, NFκB undergoes rapid phosphorylation and translocation into the nucleus to activate target genes [9, 10]. Findings show that NFκB promotes the expression of diverse target genes involved in cell proliferation, cell adhesion, and inflammatory responses [11]. However, it is unclear whether surgical stress activates NFκB in malignant cells or not.

Macrophage migration inhibitory factor (MIF) is one of the molecules upregulated by activated NFκB. MIF is well known as an important factor in the control of cell proliferation, differentiation, angiogenesis, and tumor progression [12–15]. Recently, overexpression of MIF has been shown to induce angiogenesis and a deteriorating prognosis after radical hepatic resection for hepatoma [16]. There is a possibility that surgical stress induces TNFα, which leads to increased MIF expression via NFκB. This may result in enhanced growth and invasiveness of cancer cells [17].

This study therefore aimed to evaluate the expression of TNFα and MIF mRNA as well as the activation of NFκB in tumors after CO_2 pneumoperitoneum and laparotomy in nude mice with peritoneally disseminated human gastric carcinoma.

Materials and methods

Cell preparation

All cell culture reagents were purchased from Gibco BRL (Life Technologies, Rockville, MD, USA). The human gastric cancer (MKN45) cells' poorly differentiated human gastric carcinoma cell line was grown in RPMI 1640 medium supplemented with 10% fetal bovine serum and an antibiotic/antimycotic agent containing 100 IU/ml of penicillin, 0.1 mg/ml of streptomycin, and 2.5×10^{-4} mg/ml of amphotericin B. The cells were cultured in dishes in a 5% CO_2 atmosphere at 37°C.

To prepare tumor cells for inoculation, cells in the exponential growth phase were harvested by 0.25% trypsin-ethylenediaminetetraacetic acid (EDTA), then washed and resuspended in phosphate-buffered saline (PBS). Cell viability was determined by trypan blue exclusion, and only single-cell suspensions of 90% viability were used.

Animal models

Male 6-week-old BALB/c nude mice were obtained from Seac Yoshitomi (Tokyo, Japan) and maintained under specific pathogenic free laboratory conditions. All procedures were performed according to the Animal Experimentation and Ethical Guidelines of Oita University. The animals were kept 1 week before tumor inoculation, and animal weight was 25 to 30 g at that time.

To create the murine peritoneal dissemination model, the mice were intraperitoneally injected with MKN45 cells (3×10^6 cells) as previously described [18]. They then were exposed to laparotomy, CO_2 pneumoperitoneum, anesthesia alone as a control condition, or no procedure. All the mice were anesthetized by diethyl ether inhalation and fixed to the operating table in the supine position using adhesive tape.

In the laparotomy group, a 3-cm laparotomy was performed in the midline. The abdominal content was exposed for 20 min. Then the incision was closed using polyglycolic acid sutures 3-0, and the animal was allowed to recover. In the CO_2 pneumoperitoneum group, CO_2 pneumoperitoneum was created and maintained for 20 min under pressure of approximately 6 cm H_2O, as previously reported [19]. Each mouse in the anesthesia group underwent only diethyl ether anesthesia for 20 min. In the no procedure group, the mice were killed immediately with overinhalation of diethyl ether.

The effect of the surgical procedure on TNFα and MIF mRNA expression and NFκB protein activity in peritoneal tumors was evaluated in experiment 1. On day 21, after peritoneal dissemination model preparation, the mice were exposed to laparotomy, CO_2 pneumoperitoneum, anesthesia alone, or immediate killing without any surgical procedure. After 1, 6, 24, and 48 h, and after 1 and 2 weeks, animals (7 mice per time point) were killed and tumor nodules collected. All nodules were frozen immediately in liquid nitrogen, then stored at –80°C.

The effect of surgical procedures on the growth of peritoneal tumor nodules was evaluated in experiment 2. On day 3 after peritoneal dissemination model induction, a laparotomy CO_2 pneumoperitoneum or anesthesia only procedure was performed. The animals were killed at 3 weeks. All macroscopic tumor nodules were collected and weighed. Tumor growth was assessed at the abdominal wall, omentum, mesentery, peritoneum, liver, and retroperitoneum.

Analysis of TNFα and MIF mRNA expression by reverse transcription-polymerase chain reaction (RT-PCR)

Briefly, total RNA from tumor tissue was isolated by an automated procedure using the tissue Mini Kit (BioRobot; Qiagen, Tokyo, Japan) according to the manufacturer's instructions, and purified total RNA was stored at –80°C. Total RNA (1 μg) was reverse transcribed at 22°C for 10 min, then at 37°C for 60 min and 80°C for 5 min. Amplification with specific primers for human TNFα, MIF, and glyceraldehyde-3 phosphate dehydrogenase (GAPDH) was

Table 1 Primer sequences used for reverse transcription-polymerase chain reaction (RT-PCR)

Primer	Sequence	Length (bp)
TNFα	F 5′-CAGAGGGAAGAGTTCCCCAG-3′	324
	R 5′-CCTTGGTCTGGTAGGAGACG-3′	
MIF	F 5′-CTCTCCGAGCTCACCCAGCAG-3′	255
	R 5′-CGCGTTCATGTCGTAATAGTT-3′	
GAPDH	F 5′- GCCAAAAGGGTCATCATCTCTG-3′	348
	R 5′-CATGCCAGTGAGCTTCCCGT-3′	

bp basepair, *TNFa* tumor necrosis factor-α, *MIF* migration inhibitory factor, *GAPDH* glyceraldehyde-3 phosphate dehydrogenase

performed (1 min at 94°C for denaturing; 1 min at 54°C [GAPDH], 55°C [TNFα], or 60°C [MIF] for annealing; and 1 min at 72°C for extension, for 33 cycles). The primer sequences used are in Table 1 [20–22].

Amplified products were electrophoresed using 6x loading buffer triple dye (Wako, Nippon Gene, Tokyo, Japan) on 1.8% agarose gel, with GAPDH used as an internal control and to estimate mRNA relative expression. Bands were analyzed using scanning densitometry by image J analysis software (U.S. National Institutes of Health, Bethesda, MD, USA).

Analysis of NFκB activity

Lysates from frozen tumor tissue at the sixth hour after the procedure were homogenized. Cytoplasmic and nuclear extracts were prepared using NE-PER nuclear and cytoplasmic extraction reagents (Pierce Biotechnology, Rockford, USA) according to the manufacturer's instructions. The amount of NFκB protein in each extract was measured by the Western blot method. Cytoplasmic and nuclear extracts were electrophoresed on 10% sodium dodecyle sulfate (SDS)–polyacrylamide gels. Protein then was electroblotted onto Sequi-Blot polyvinylidene difluoride membranes (Bio-Rad Laboratories, Hercules, CA, USA) as previously described [23].

Next, the membranes were incubated in 5% nonfat milk in TBST-20 (Tris-buffered saline with 1% Tween 20) overnight. The membranes were first incubated with a specific mouse monoclonal antibody that can detect NFκB P65 at 1:200 dilution, then incubated with horseradish peroxidase-conjugated immunoglobulin-G (IgG) antibody (Santa Cruz Biotechnology, Santa Cruz, CA).

Antibody-labeled proteins were detected using protocols and reagents contained in the enhanced chemiluminescence (ECL) detection reagent and analysis system (Amersham Biosciences UK Ltd., Buckinghamshire, UK) on hyperfilm ECL (Amersham Biosciences Corp., Piscataway, NJ, USA). Bands were analyzed using scanning densitometry by image J analysis software.

Statistical analysis

Both TNFα and MIF mRNA, expressed as a ratio in relation to GAPDH mRNA and tumor weight, were shown as mean ± standard deviation. Associations between variables were tested using a nonrepeated analysis of variance (ANOVA) test. Then groups were compared post hoc by Student's *t*-test. All *p* values less than 0.05 were considered statistically significant.

Results

Effect of surgical procedures on tumor growth

Total tumor weight was significantly higher after laparotomy than after CO_2 pneumoperitoneum ($p < 0.05$) or anesthesia ($p < 0.0001$) (Fig. 1). Interestingly, only tumors located in the anterior abdominal wall showed a significant difference in tumor weight ($p < 0.01$ for laparotomy vs CO_2 pneumoperitoneum, Table 2).

Expression of TNFα mRNA after the surgical procedure

Using RT-PCR, we examined TNFα mRNA expression in peritoneal tumors after laparotomy versus CO_2

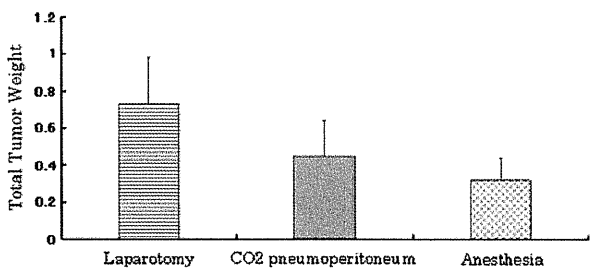

Fig. 1 Total tumor weight for peritoneal dissemination in a murine model. Tumor growth was greater in the laparotomy group than in the anesthesia ($p < 0.01$) and carbon dioxide pneumoperitoneal ($p < 0.05$) groups

Table 2 Mean tumor weight in mice 3 weeks after carbon dioxide (CO_2) pneumoperitoneum and laparotomy

Variable	Laparotomy	CO_2 Pneumo	*p* Value
Subcutis	0.39 ± 0.12	0.21 ± 0.09	0.01
Omentum	0.13 ± 0.05	0.13 ± 0.06	NS
Mesentery	0.10 ± 0.06	0.05 ± 0.06	NS
Liver	0.10 ± 0.07	0.02 ± 0.02	NS
Retroperitoneum	0.02 ± 0.04	0.02 ± 0.04	NS
Total	0.74 ± 0.02	0.41 ± 0.19	<0.05

CO_2 Pneumo carbon dioxide pneumoperitoneum, *NS* not significant

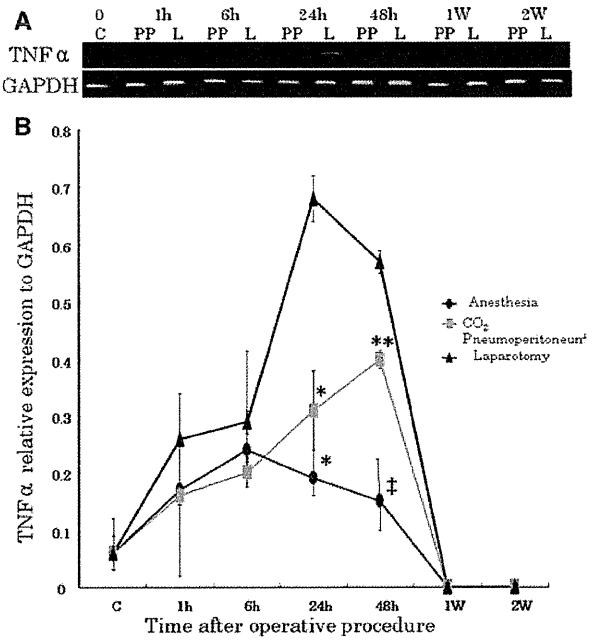

Fig. 2 Tumor necrosis factor-α (TNFα) mRNA relative expression in gastric tumors after carbon dioxide pneumoperitoneum and laparotomy in a tumor-bearing mouse model. **A** Reverse transcription-polymerase chain reaction (RT-PCR) representation. **B** Time course after experiment. A significant difference in TNFα expression was continued for up to 48 h of the experiment's time course. * $p < 0.05$; ** $p < 0.01$; ‡ $p < 0.001$. *L* laparotomy, *PP* carbon dioxide pneumoperitoneum

pneumoperitoneum. The TNFα mRNA expression started to increase in all groups 1 h after the experiment, then continued to increase progressively until 24 h in the laparotomy group and 48 h in the CO_2 pneumoperitoneal group. After that, the TNFα mRNA expression in both groups started to decrease from its peak, soon reaching the control level. Expression of TNFα mRNA was significantly higher 24 h and 48 h after laparotomy than after CO_2 pneumoperitoneum ($p < 0.05$ and $p < 0.01$ respectively). In the anesthesia-only group, TNFα mRNA expression started to decrease toward the control level soon after 6 h (Fig. 2A, B).

Expression of MIF mRNA after the surgical procedure

Because TNFα upregulates MIF expression, we examined MIF mRNA expression by RT-PCR. Expression of MIF mRNA started to increase significantly in all groups 6 h after the experiment, then continued to increase significantly and progressively until 48 h in the laparotomy and CO_2 pneumoperitoneal groups. Thereafter, MIF mRNA expression in both groups started to decrease. However, in

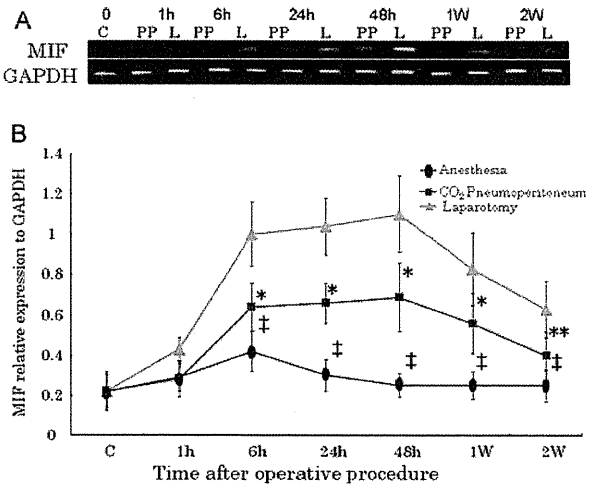

Fig. 3 Migration inhibitory factor (MIF) mRNA relative expression in gastric tumors after carbon dioxide pnemoperitoneum and laparotomy in a tumor-bearing mouse model. **A** Reverse transcription-polymerase chain reaction (RT-PCR) representation. **B** Time course after the experiment. A significant difference in MIF expression continued until the end of the experiment time course. * $p < 0.05$; ** $p < 0.01$; ‡ $p < 0.001$. *L* laparotomy, *PP* carbon dioxide pneumoperitoneum

contrast to TNFα, they did not reach the control level until the end of the observation period (i.e., 2 weeks).

Expression of MIF mRNA was significantly higher after laparotomy than after CO_2 pneumoperitoneum at all the examined time points ($p < 0.05$ until 1 week or $p < 0.01$ at 2 weeks). Additionally, the level in the anesthesia group started to fall toward the control level soon after 6 h (Fig. 3A, B).

Nuclear shift of NFκB protein after the surgical procedure

Using Western blotting, the NFκB protein shift into the nucleus was examined. The shift in NFκB protein from the cytoplasm into the nucleus was higher and more progressive with laparotomy than with CO_2 pneumoperitoneum 6 h after the experiment, as shown in Fig. 4.

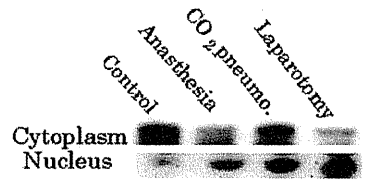

Fig. 4 Western blot for nuclear factor kappa B (NFκB) protein that shows shifting of the NFκB protein from the cytoplasm into the nucleus 6 h after the experiment, which was higher after laparotomy than after carbon dioxide pneumoperitoneum or anesthesia

Discussion

Surgical resection is the most important method for treating malignant solid tumors [24]. However, several reports show that surgical stress possibly enhances the growth of the dormant malignant cells [3, 25, 26] . Also, the mechanisms by which surgical trauma might enhance tumor growth and metastasis still are not totally understood [3, 4, 27].

Recently, minimally invasive surgeries such as laparoscopic procedures have become popular worldwide [6, 7]. The feasibility of laparoscopic surgery with minimal invasiveness for malignant tumors has been examined in the experimental and clinical settings, but it still is controversial [1–3, 5]. Furthermore, few studies have investigated the effect of surgical stress on the expression of cytokines and growth factors, which affect tumor growth and progression [1–4, 7, 25].

In this study, we showed that CO_2 pneumoperitoneum with minimal invasiveness induces less tumor growth and lower TNFα and MIF mRNA expression in peritoneal tumors than laparotomy. Moreover, we showed less activation of the DNA-binding protein; NFκB, after CO_2 pneumoperitoneum than after laparotomy.

In our study, we used nude mice with malignant peritoneal inoculation. Using this model, we showed that tumor weight was higher after laparotomy than after CO_2 pneumoperitoneum. Interestingly, the weight was higher after laparotomy than after CO_2 pneumoperitoneum only for tumors located in the anterior abdominal wall (Table 2). This finding may be associated with some growth factors induced at injury sites after laparotomy that induce not only wound healing but also tumor attachment and growth at wound sites [3, 11, 28]. These data suggest that minimally invasive surgery may be more feasible for the treatment of cancer in clinical settings.

This model also is convenient and useful for clarifying the association of surgical stress modes such as CO_2 pneumoperitoneum and laparotomy with oncologic microbiology. We could analyze the gene expression of TNFα and MIF and activation of NFκB protein after surgical procedures by using peritoneal tumor nodules in this model. The cytokine TNFα is known to promote several inflammatory events associated with tumor growth and progression [29]. It is recognized as an essential mediator of the stress response that influences immune cell function, proliferation, differentiation, and apoptosis [30]. Recently, TNFα has been reported to activate NFκB, a DNA-binding protein in epithelial cells that is essential for malignant progression [31].

In our study, TNFα mRNA was less expressed sooner after CO_2 pneumoperitoneum than after laparotomy. These data suggest that TNFα mRNA is expressed early after surgery and that less invasive surgery may cause a lower level of TNFα expression.

To our knowledge, this is the first study to investigate the association of NFκB activation in tumors with surgical stress. In our study, NFκB protein was activated less after CO_2 pneumoperitoneum than after laparotomy.

Ravi et al. [11] found that activation of NFκB causes the expression of many important genes involved in cell cycle progression, cell survival, cell adhesion/angiogenesis, and immune/inflammatory responses. The activation of NFκB not only enables malignant transformation and tumor progression but also provides a mechanism by which tumor cells escape immune surveillance and resist therapy. Hagemann showed that the activation of NFκB, caused by TNFα, induces MIF expression [17]. In the current study, lower expression of MIF in the CO_2 pneumoperitoneum group seemed to be associated with lower activation of NFκB after CO_2 pneumoperitoneum than after laparotomy.

Findings have shown MIF to be an important factor in the control of cell proliferation, differentiation, angiogenesis, and tumor progression [13–15]. Recent studies have shown that MIF may play a critical role in the development of cancers as a link between inflammation and tumorigenesis [14]. It has been shown that overexpression of MIF induces angiogenesis and deteriorates prognosis after surgery [16]. Lower expression of MIF after CO_2 pneumoperitoneum may be related to the lower tumor weight in the CO_2 pneumoperitoneum group.

In clinical settings, tumor recurrence may be explained by the residual microscopic cancer cells after surgical resection [25, 26]. Even after complete resection of primary and secondary hepatic malignancies, recurrent disease develops in nearly two-thirds of patients, and it is believed to arise from residual microscopic cancer undetected at surgery [32]. Also, microscopic viable gastric cancer cells repeatedly have been identified within the peritoneal cavity after gastrectomy [33]. Our results show that overexpression of TNFα and MIF induced by surgical stress may have a relation to the growth and progression of microscopic cancer after surgery and that less invasiveness of surgical procedures may be important from the oncologic point of view.

In conclusion, CO_2 pneumoperitoneum with minimal invasiveness induced lower levels of TNFα and MIF mRNA expression and less NFκB activation than laparotomy. This correlation needs further study. Less invasive surgical procedures may be important from the oncologic point of view. More animal experiments and clinical research to clarify the relation of surgical stress to tumor growth and progression on a microbiologic basis are necessary. Consideration of the perioperative period as oncologically risky may lead to a search for new strategies or drugs such as anti-NFκB and anti-TNFα to minimize the effect of surgical stress on tumor growth and progression.

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ORIGINAL ARTICLE

Risk Factors for Anastomotic Leakage Following Intersphincteric Resection for Very Low Rectal Adenocarcinoma

Takayuki Akasu · Masashi Takawa · Seiichiro Yamamoto · Tomohiro Yamaguchi · Shin Fujita · Yoshihiro Moriya

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Abstract
Background The aim of this study was to perform a retrospective analysis of the risk factors for anastomotic leakage following intersphincteric resection (ISR) for very low rectal cancer.
Methods Between 1993 and 2007, 120 patients with T1–T3 rectal adenocarcinomas located 1 to 5 cm (median 3 cm) from the anal verge underwent ISR without radiotherapy. Univariate and multivariate analyses of 47 prospectively recorded parameters were conducted.
Results All patients had total mesorectal excision after complete bowel preparation. Of them, 103 underwent partial resection, and 17 underwent complete resection of the internal sphincter. Some 108 patients had a defunctioning stoma. Morbidity and mortality rates were 33% and 0.8%, respectively. Fifteen patients (13%) developed clinical leakage, and six (5%) had severe leakage causing relaparotomy, permanent stoma, or death. Univariate analysis of risk factors for clinical leakage revealed tumor annularity, intraoperative blood transfusion, and pulmonary disease to be significant. Multivariate analysis showed transfusion (hazard ratio, 6.5 [95% confidence interval, 1.4 to 30]; p=0.018) and pulmonary disease (6.3 [1.6 to 26]; p=0.009) to be independently significant. Moreover, transfusion (71 [3.0 to 1000]; p=0.008), colonic J-pouch (32 [1.8 to 500]; p=0.018), and pulmonary disease (32 [1.1 to 1000]; p=0.044) were independently associated with severe leakage.
Conclusions This study suggests intraoperative blood transfusion and pulmonary disease as independent risk factors for clinical and severe leakage following ISR and colonic J-pouch as that for severe leakage. By considering these factors, we may be able to stratify high-risk patients and prepare countermeasures.

Keywords Rectal cancer · Surgery · Intersphincteric resection · Anastomotic leakage · Risk factor

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T. Akasu (✉) · M. Takawa · S. Yamamoto · T. Yamaguchi · S. Fujita · Y. Moriya
Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: takasu@ncc.go.jp

Introduction

Although abdominoperineal resection is standard surgery for patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge,[1] intersphincteric resection (ISR) has recently been considered as an alternative option to avoid permanent colostomy for selected patients.[2–4] ISR is defined as a procedure obtaining sufficient margins by removing part or whole of the internal sphincter and restoring bowel continuity for patients with rectal cancers involving or neighboring the anal canal.

Careful performance of ISR has been reported to allow satisfactory results both in the short and long term.[4–11] Furthermore, reported rates of anastomotic leakage follow-

ing ISR have been as comparatively low as 5% to 16% in experienced hands.[7–11] However, anastomotic leakage after rectal cancer surgery can result in reoperation, morbidity, mortality, permanent stoma, prolonged hospitalization, anal stenosis, and anal dysfunction and may be associated with a higher local recurrence rate.[12,13] To reduce such complications, clarification of the risk factors for anastomotic leakage should help in identifying high-risk patients and planning countermeasures. The aim of this study was, therefore, to perform a retrospective exploratory analysis of risk factors for anastomotic leakage following ISR for very low rectal adenocarcinomas.

Patients and Methods

Between October 1993 and February 2007, 122 patients with T1 to T3 rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. All of the T1 tumors were accompanied by massive submucosal invasion. Selection criteria for ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) less than 2 cm; (4) no involvement of the external sphincter; and (5) no signs of disseminated disease. Preoperatively, the patients were assessed with chest and abdominal computed tomography (CT), digital anorectal examination, and radiological studies, including endorectal ultrasonography, thin-section helical CT, or high-resolution magnetic resonance imaging.

Univariate and multivariate analyses of 47 prospectively recorded clinicopathologic variables were conducted for the 120 consecutive patients who did not receive neoadjuvant radiotherapy. Data from the remaining two given radiotherapy were excluded from the present analysis. Approval by the institutional review board was not required for the observational study. All patients gave informed consent for usage of their data for analysis.

Surgical Procedures

The day before surgery, bowel lavage with 2 L of polyethylene glycol was carried out, and all patients received parenteral antibiotic prophylaxis no more than 30 min before skin incision. The surgical procedures were as described previously[11] and basically similar to those originally documented by Schiessel et al.[4,7] The intersphincteric plane between the puborectalis and the internal sphincter was dissected cautiously as caudad as possible under direct vision, using long right-angle retractors and electrocautery. When the lower edge of the tumor was reached, the anal canal was closed just below the tumor and then irrigated with povidone iodine followed by saline. After retractors were applied to the anal canal, the anal canal mucosa and internal sphincter were circumferentially incised, and the intersphincteric plane was dissected cephalad. A resection margin of at least 1 cm was always attempted. If the rectum was not closed in the abdominal phase, it was closed using sutures during per-anal dissection. After removal of the rectum, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made using 3-0 absorbable vertical mattress sutures. A pelvic drain was placed, and a defunctioning stoma was made.

Definition of Anastomotic Leakage

Clinical anastomotic leakage was defined as clinically apparent leakage including gas, pus, or fecal discharge from the pelvic drain or peritonitis. All anastomotic leakages were confirmed as extravasation of endoluminally administered water-soluble contrast material on radiography or computed tomography. An abscess around the anastomosis or a rectovaginal fistula was also considered as leakage. Radiological examination was performed by the surgeon and only when there was clinical suspicion of anastomotic leakage. Pouch fistula, pouch necrosis, and necrosis of neorectum were also regarded as evidence of a leakage. Severe leakage was defined as causing emergency relaparotomy, permanent stoma, or death.

Statistical Analysis

The chi-square test was used to compare proportions. The influence of each variable on the risk of clinical anastomotic leakage or severe leakage was calculated using the chi-square test. All variables associated with clinical leakage or severe leakage at $p<0.05$ were entered in a multivariate analysis using the multiple logistic regression model with the forward stepwise method (likelihood ratio). All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Japan). A two-sided p value of less than 0.05 was considered significant.

Results

Of 39 patients (33%) who suffered complications, 30 were treated conservatively and nine received reoperations. Fifteen patients (13%) had clinical anastomotic leakage, and six underwent an emergency relaparotomy (Table 1). Five of those six had permanent stoma and one dying of

Table 1 Details of the Patients with Anastomotic Leakage

Severity	Reconstruction	Site of leakage	Treatment
Severe[a]	Colonic J-pouch (5)[a]	Pouch necrosis (2)[a] Anterior wall of pouch (1)	Pouch resection, colostomy and drainage (3)[a]
		Pouch anal anastomosis (1)	Ileostomy and drainage (1)
		Pouch-vaginal fistula (1)	Drainage and fistulectomy (1)
	Straight end to end (1)	Anovesical fistula (1)	Drain irrigation and fistulectomy (1)
Minor	Straight end to end (6)	Anastomosis (6)	Transanal drainage (3), Observation (2), Drain irrigation (1),
	Transverse coloplasty (3)	Anastomosis (3)	Drain irrigation (1), Transanal drainage (1), Observation (1)

Numbers in parentheses are numbers of patients

[a] One patient died

anastomotic leakage and sepsis (30-day mortality rate= 0.8%). Seven patients had permanent stoma due to complications (six patients) or local recurrence (one). Other complications included wound infection (nine patients), bowel obstruction (six), urinary tract infection (four), anal pain (two), cholecystitis (two), anastomotic stenosis (one), anal prolapse (one), peristomal hernia (one), and thrombocytopenia (one).

Of the 47 variables analyzed, 28 are summarized in Table 2. The remaining 19 variables were tumor size, pT, pN, pM, lateral pelvic lymph node metastasis, preoperative vital capacity, serum carcinoembryonic antigen, CA19-9, C-reactive protein, hemoglobin A1c levels, white blood cell count, hamatocrit, lymphocyte count, arterial blood oxygen tension, carbon dioxide tension, bicarbonate, base excess, liver disease, and drinking habit.

There were 92 male and 28 female patients with a median age of 57 years (range 26 to 75 years). Thirteen had pulmonary disease including chronic obstructive pulmonary disease in eight patients and restrictive respiratory disease in five. The median distance from the anal verge to the tumor was 3 cm (range 1 to 5 cm).

All patients underwent total mesorectal excision. In addition, 46 patients received extended lateral pelvic lymph node dissection. Sixty-seven patients underwent high ligation of the inferior mesenteric artery. A total of 103 patients underwent partial resection of the internal sphincter, and 17 underwent complete resection. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. Combined resection of adjacent organs was performed for 12 patients. Two patients with solitary liver metastases and one with a solitary lung metastasis underwent complete resection of their metastases. Mobilization of the splenic flexure was performed for 35 patients. A colonic J-pouch was constructed for 24 patients, a transverse-coloplasty pouch for 38, and a straight anastomosis for 58. Some 108 patients had a defunctioning stoma which was closed 3 months after ISR. Median operating time was 339 min (range 200 to 590 min). Median blood loss was 462 mL (range 45 to 3,644 mL), and nine patients received intraoperative blood transfusions (Table 2).

The median tumor diameter was 3.7 cm (range 1 to 12 cm). Pathologic findings are shown in Table 2. Resection margins were macroscopically negative in all patients but microscopically positive in four. The median number of lymph nodes removed at surgery was 29 (range 4 to 88), and 108 patients (90%) underwent dissection of 12 or more.

Univariate Analysis

Clinical anastomotic leakage was statistically significantly associated with tumor annularity, intraoperative blood transfusion, and pulmonary disease (Table 2). Severe leakage was significantly associated with tumor annularity, extended lateral pelvic lymph node dissection, a colonic J-pouch, intraoperative transfusion, preoperative serum total protein and albumin levels, the preoperative platelet count, and pulmonary disease (Table 2). Neither overall clinical leakage nor severe leakage showed significant association with the 19 variables not shown in Table 2.

Multivariate Analysis

In a multivariate analysis for clinical leakage, the significant variables in the univariate analysis were entered. Pulmonary disease (hazard ratio, 6.3 [95% confidence interval, 1.6 to 26]; p=0.009) and intraoperative transfusion (6.5 [1.4 to 30]; p=0.018) were found to be independently significant. The incidences of clinical leakage for patients with 0, 1, and 2 positive risk factors were estimated to be 8%, 28%, and 100%, respectively.

In a multivariate analysis for severe leakage, the eight significant variables in the univariate analysis were used.

Table 2 Univariate Analyses of 28 Clinicopathologic Variables Related to Clinical Anastomotic Leakage and Severe Leakage

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Gender					
Male	92	12 (13)	1	5 (5)	1
Female	28	3 (11)		1 (4)	
Age					
<60 years	71	6 (8)	0.16	2 (3)	0.22
≥60 years	49	9 (18)		4 (8)	
Distance of the tumor from the anal verge					
<2.5 cm	21	1 (5)	0.47	0 (0)	0.59
≥2.5 cm	99	14 (14)		6 (6)	
Tumor annularity					
<3/4	101	10 (10)	0.033	3 (3)	0.033
≥3/4	16	5 (31)		3 (19)	
Unknown	3				
Histopathologic grade					
Well-differentiated	59	9 (15)	0.62	3 (5)	1
Moderately differentiated	53	6 (11)		3 (6)	
Poorly differentiated	8	0 (0)		0 (0)	
Pathological UICC TNM stage					
Stage I	50	7 (14)	0.91	1 (2)	0.23
Stage II	21	3 (14)		3 (14)	
Stage III	46	5 (11)		2 (4)	
Stage VI	3	0 (0)		0 (0)	
Microscopic resection margins					
Negative	116	15 (13)	1	6 (5)	1
Positive	4	0 (0)		0 (0)	
Internal sphincter resection					
Partial	103	15 (15)	0.13	6 (6)	0.59
Complete	17	0 (0)		0 (0)	
Combined resection					
No	108	15 (14)	0.36	6 (6)	1
Yes	12	0 (0)		0 (0)	
Extended lateral pelvic lymph node dissection					
No	74	8 (11)	0.57	1 (1)	0.03
Yes	46	7 (15)		5 (11)	
High ligation of the inferior mesenteric artery					
No	50	6 (12)	1	3 (3)	1
Yes	67	9 (13)		3 (4)	
Mobilization of the splenic flexure					
No	63	8 (13)	1	1 (2)	0.129
Yes	35	5 (14)		3 (9)	
Reconstruction					
Straight anastomosis	58	7 (12)	0.18	1 (2)	0.001
Transverse coloplasty	38	3 (8)		0 (0)	
Colonic J-pouch	24	5 (21)		5 (21)	
Defunctioning stoma					
No	14	1 (7)	1	0 (0)	1
Yes	106	14 (13)		6 (6)	
Anastomosis height from the anal verge					
<2.0 cm	57	5 (9)	0.28	1 (2)	0.21
≥2.0 cm	63	10 (16)		5 (8)	

Table 2 (continued)

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Operating time					
<6 h	68	8 (12)	0.79	1 (1)	0.084
≥6 h	52	7 (13)		5 (10)	
Blood loss					
<500 mL	64	6 (9)	0.29	2 (3)	0.42
≥500 mL	56	9 (16)		4 (7)	
Intraoperative blood transfusion					
No	111	11 (10)	0.014	2 (2)	<0.001
Yes	9	4 (44)		4 (44)	
Preoperative body mass index					
<25	89	10 (11)	0.53	4 (4)	0.65
≥25	31	5 (16)		2 (6)	
Preoperative FEV_1 (%)					
<70%	8	3 (38)	0.061	2 (25)	0.051
≥70%	112	12 (11)		4 (4)	
Preoperative serum total protein level					
Normal (6.3–8.3 g/dL)	113	13 (12)	0.21	4 (4)	0.039
Abnormal	7	2 (29)		2 (29)	
Preoperative serum albumin level					
Normal (3.7–5.2 g/dL)	110	12 (11)	0.11	3 (3)	0.007
Abnormal	10	3 (30)		3 (30)	
Preoperative blood hemoglobin level					
Normal (11.3–14.9 g/dL)	85	8 (9)	0.13	2 (2)	0.059
Abnormal	35	7 (29)		4 (11)	
Preoperative platelet count					
Normal (125,000–375,000/μL)	115	13 (11)	0.12	4 (3)	0.02
Abnormal	5	2 (40)		2 (40)	
Diabetes mellitus					
No	106	12 (11)	0.38	6 (7)	1
Yes	14	3 (21)		0 (0)	
Cardiovascular disease					
No	98	10 (10)	0.15	4 (4)	0.30
Yes	22	5 (23)		2 (9)	
Pulmonary disease					
No	107	10 (9)	0.011	3 (3)	0.017
Yes	13	5 (38)		3 (23)	
Smoking habit					
No	79	11 (14)	0.58	6 (8)	0.094
Yes	41	4 (10)		0 (0)	

The remaining 19 variables not shown here did not demonstrate any significant association

FEV_1 forced expiratory volume in the first second of expiration

Intraoperative transfusion (hazard ratio, 71 [95% confidence interval, 3.0 to 1,000]; $p=0.008$), a colonic J-pouch (32 [1.8 to 500]; $p=0.018$), and pulmonary disease (32 [1.1 to 1,000]; $p=0.044$) were independently associated with adverse outcomes. The incidences of severe leakage for patients with 0, 1, 2, and 3 positive risk factors were estimated to be 0%, 6%, 67%, and 100%, respectively.

Discussion

In this study, the incidences of clinical anastomotic leakage and mortality after ISR were 13% and 0.8%, respectively. These are comparable to the respective incidences of 5% to 16% and 0 to 0.8% in recent ISR series.[7–11] Since these figures are even comparable to the 2.8% to 19.2% and 0%

to 2.5% observed with anterior resection,[14–26] appropriately administered ISR can be regarded as safe in terms of leakage and mortality. However, such figures should be interpreted cautiously because incidences of anastomotic leakage depend on the definition, patient selection, and treatment details. Patient factors like gender,[15,16,18,22,25] age,[25] American Society of Anesthesiology score,[25] heart disease,[26] malnutrition,[17] weight loss,[17] obesity,[15] smoking habit,[26] and alcohol abuse[17] have been reported to independently influence the incidences of leakage after anterior resection, and so have treatment factors such as neoadjuvant chemoradiotherapy,[18,22] bowel preparation,[19] timing of surgery,[25] surgeon caseload,[25] anastomotic level,[14,15,18,19,22] intraoperative contamination,[17,18] pelvic drainage,[21] defunctioning stoma,[16,20,21,24] operation time,[17] and blood transfusion.[17,19]

To our knowledge, there have only been few studies addressing risk factors for anastomotic leakage following ISR. Rullier et al.[15] investigated 272 anterior resections for rectal cancer, in which 131 anastomoses were situated 5 cm or less from the anal verge. Multivariate analysis of their overall population showed that male sex and the level of anastomosis were independent factors for leakage. In a second analysis of 131 very low anastomoses, obesity was an independent factor. The authors concluded that a protective stoma is suitable after anastomoses situated at or less than 5 cm from the anal verge, particularly for men and obese patients.

In the present study, all of the patients had undergone complete bowel preparation, elective surgery by high-volume colorectal specialists, and pelvic drainage, all of which have been reported to be independently beneficial for reducing leakage.[19,21,25] Most had a defunctioning stoma as well.[16,20,21,24] None had received neoadjuvant chemoradiotherapy considered to be an independent risk factor for leakage.[18,22] Therefore, these already known significant factors could not be evaluated in this study. Our multivariate analysis revealed intraoperative blood transfusion and pulmonary disease to be independently associated with overall clinical leakage and severe leakage, and a colonic J-pouch was associated with severe leakage. These results suggest that under the circumstances prevailing in our institution, we can stratify high-risk patients by using these factors and prepare countermeasures against them.

Although the exact mechanism whereby anastomotic leakage may be related to blood transfusion is unclear, it is known that allogeneic blood transfusion induces immunosuppression and predisposes to postoperative infection.[27] Allogeneic leukocytes have a critical role in the induction of transfusion-induced immunosuppression.[27] Tang et al.[27] reported that intra- or postoperative blood transfusion was an independent risk factor for overall surgical site infection, incisional infection, and organ/space infection with and without clinical anastomotic leakage in a prospective study of 2,809 consecutive patients undergoing elective colorectal resection. Therefore, susceptibility to infection induced by transfusion may promote development of anastomotic leakage.

To avoid intraoperative transfusion, it is preferable to treat anemia before surgery using oral and parenteral iron therapy. Transfusion should be reserved for patients with cardiovascular instability and continued and excessive blood loss. Furthermore, it should be given before the operation because deleterious effects appear to be more likely with intra- or postoperative transfusion.[27] Operative blood loss should be minimized by cautious procedures. If excessive blood loss is expected, autologous blood transfusion should be considered, especially in the presence of other risk factors.

In line with previous reports on intestinal anastomotic leakage, we found an independent association with pulmonary disease. Jonsson et al.[28] measured oxygen tension and collagen deposition in subcutaneous wounds in 33 postoperative patients and found that this and the resultant tensile strength are limited by perfusion and tissue oxygen tension. Hopf et al.[29] measured subcutaneous wound oxygen tension in 130 surgical patients and observed that this factor is a strong predictor of infection. Millan et al.[23] determined intramucosal pH at colorectal anastomoses, which reflects blood supply and oxygenation of the mucosa, and found that it can accurately predict the risk of anastomotic leakage. Smoking is a major cause of chronic obstructive pulmonary disease and is known as an independent risk factor for anastomotic leakage after anterior resection.[26] Therefore, although the exact pathophysiology remains to be clarified, it is reasonable to speculate that pulmonary disease predisposes to anastomotic hypoxia which in turn hinders wound healing, aggravates infection, and promotes anastomotic dehiscence.

Because of their chronic and irreversible nature, the chronic obstructive pulmonary disease and restrictive respiratory diseases seen in our series are difficult to treat. However, intensive respiratory management including continuous pulse oximetry monitoring, supplemental oxygen, appropriate analgesia, bronchoscopy when needed, and early mobilization, similar to the management applied after esophageal cancer surgery,[30] may prevent the respiratory complications and hypoxemia which can lead to anastomotic leakage.

Although the incidence of leakage with a colonic J-pouch was reported to be significantly lower than with straight coloanal anastomosis[31] and transverse coloplasty[32] in anterior resection, we paradoxically found a J-pouch to be an independent risk factor for severe leakage in our ISR series. Of the five patients who underwent J-pouch construction and suffered severe leakage, four were male, four received an intraoperative transfusion, and two had

pulmonary disease. Therefore, it appears that a colonic J-pouch reconstruction after ISR may confer extra risk on males with intraoperative transfusion and/or pulmonary disease. Since males have a longer anal canal than females, the presence of a bulky J-pouch and anastomosis may increase the sphincteric squeeze pressure and worsen anastomotic blood and oxygen supply, thereby predisposing to leakage. Thus, in the presence of other risk factors, countermeasures including a switch to other reconstruction methods may need to be considered.

There are limitations to the present study. First, the study design is retrospective, and this may cause biases. Especially, because all or nearly all patients had complete bowel preparation, elective surgery by high-volume colorectal specialists, pelvic drainage, and defunctioning stoma and did not have neoadjuvant chemoradiotherapy, the significance of these factors could not be evaluated in this study. Second, because the numbers of events were limited particularly for severe leakage, many other risk factors which were significant in the previous studies on leakage after anterior resection were not significant in this study. Thus, further confirmation with a larger number of patients would be preferable.

In conclusion, the present retrospective exploratory study suggests that intraoperative blood transfusion and pulmonary disease are independently significant risk factors for overall and severe anastomotic leakage after ISR, and a colonic J-pouch was associated with severe leakage. By taking account of these factors, we may be able to stratify high-risk patients and prepare countermeasures. However, because numbers of patients and events in this study were limited, further investigation and validation are warranted with larger datasets or in future prospective trials.

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Accelerated learning curve for colorectal resection, open versus laparoscopic approach, can be attained with expert supervision

T. Maeda · K. Y. Tan · Fumio Konishi · S. Tsujinaka · K. Mizokami · J. Sasaki · Y. J. Kawamura

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Abstract
Background Laparoscopic colorectal resection (LCR) is gaining popularity. Nonetheless, open surgery remains an important technique. Thus, surgeons should be technically proficient in both open and laparoscopic surgery. One question however remains unanswered: Can training for open and LCR occur simultaneously? The objective of this paper is to review the learning curve for open and laparoscopic colon resection of one surgeon who underwent a rigorous training program.
Methods A review of consecutive patients who underwent surgery for colon and rectosigmoid junction cancers by one trainee surgeon was performed. This surgeon had completed his basic surgical residency but had limited experience in colorectal cancer surgery. In total, 75 patients were included in this study. All operations were supervised by at least one staff surgeon with experience of more than 300 LCR cases. The trainee surgeon was allowed to train in both laparoscopic and open colorectal resection simultaneously.
Results Forty-three patients underwent laparoscopic resection, while 32 patients underwent open surgery. Age, gender, mean body mass index (BMI), preoperative risk, and history of past abdominal surgery showed no significant difference between laparoscopic and open groups. There were no differences in tumor stage [International Union against Cancer (UICC)] or tumor size ($p = 0.068$ and 0.228, respectively). The morbidity rate for open and laparoscopic surgery was 3.1% (1/32) and 4.7% (2/43), respectively ($p = 0.484$). Operation time decreased with increasing experience, and plateaued after 25 cases in the laparoscopic group and 22 cases in the open group. The learning curve for open cases was 11 cases, and 7 for laparoscopic surgery.
Conclusions Surgeons who have completed a basic surgical residency but have limited colorectal surgery experience can learn both open and laparoscopic colorectal surgery simultaneously in an effective manner under supervision by well-experienced surgeons.

Keywords Laparoscopic colorectal resection · Learning curve · Trainee surgeon

Laparoscopic colorectal resection (LCR) is gaining popularity. Prospective randomized control studies have revealed some benefits of LCR for colorectal cancer compared with open surgery [1–5]. Nonetheless, open surgery remains an important technique. Thus, surgeons should be technically proficient in both open and laparoscopic surgery.

LCR is believed to be technically more difficult than open surgery and thought to require more intensive training to ensure safe and oncologic operation [6, 7]. There are many reports regarding the learning curve for performing LCR [7–15]. The learning curve is generally accepted to be approximately 30 procedures based on decline in operative time, intraoperative complications, and conversion rate. One question however remains unanswered: Can training for open and LCR occur simultaneously?

T. Maeda · K. Y. Tan · F. Konishi (✉) · S. Tsujinaka · K. Mizokami · J. Sasaki · Y. J. Kawamura
Department of Surgery, Jichi Medical School Saitama Medical Centre, 1-847 Amanumacho, Omiyaku, Saitamashi, Saitamaken 330-8503, Japan
e-mail: DZD00740@nifty.ne.jp

T. Maeda
e-mail: takafumim@hotmail.com

K. Y. Tan
Department of Surgery, Alexandra Hospital, Singapore, Singapore

We hypothesized that surgeons who have finished a basic 4-year surgical residency program according to the Japanese system can learn both open and laparoscopic colorectal cancer resection efficiently simultaneously as long as they are well supervised. The objective of this study is to review the learning curve for open and laparoscopic colon resection of one surgeon who underwent a rigorous training program.

Patients and methods

A review of consecutive patients who underwent surgery for colon and rectosigmoid junction cancers from May 2005 to December 2007 by one trainee surgeon at Jichi Medical University Saitama Medical Center was performed. This surgeon had completed his basic surgical residency but had limited experience in colorectal cancer surgery and D3 dissection. Prior to commencement of the colorectal training, this surgeon had performed 350 cases of general surgery operations as first surgeon, including 80 cases of appendectomy, 62 cases of hernia repair, 46 cases of laparoscopic cholecystectomy, 10 cases of gastrectomy, and 21 cases of colectomy. Colectomies included five cases of ileocecal resection, nine cases of sigmoid colectomy, and seven cases of right hemicolectomy. He had also been an assistant in more than 1,000 other cases during a 4-year surgical residency program in Japan.

Because this study was designed to investigate the learning curve for laparoscopic and open colorectal surgery under supervision by experts, difficult cases were excluded from this study. Exclusion criteria were as follows: (1) patients who underwent combined procedures such as cholecystectomy, hepatectomy, and hysterectomy, (2) tumor located near the splenic flexure or in the rectum, and (3) T4 tumors that directly invaded adjacent organs or structures. In total, 75 patients were included in this study. All operations were supervised by at least one staff surgeon with experience of more than 300 LCR cases. The trainee surgeon was allowed to train in both laparoscopic and open colorectal resection simultaneously. When the surgeon performed more than 80% of the procedure, it was credited to this surgeon. Patient characteristics and oncological outcomes were analyzed.

Standardized procedures were performed for all cases. For left-sided lesions, medial-to-lateral approach was performed in laparoscopic surgery, while lateral-to-medial approach was done in open surgery. Laparoscopic left-sided colon resection began with ligation of proximal vascular pedicles, followed by mobilization and resection of bowel with anastomosis. For right-sided lesions, both procedures were performed using lateral-to-medial approach, which began with mobilization of the bowel, followed by exploration of the retroperitoneum, ligation of vascular pedicles, and resection of bowel with anastomosis. D3 dissection (exposure of the root of the feeding vessels) was performed when indicated.

Quality assessment and analysis of learning curve was performed by plotting cumulative summation (CUSUM) curves, and the moving average method was used to assess changes in operation time for both laparoscopic surgery and open surgery. CUSUM curve has emerged as a popular tool to monitor quality of surgery [16]. CUSUM allows one to judge whether a given variation in performance is acceptable, or whether the variation is greater than could be expected from random variation and thus may be a concern. As previous report utilized CUSUM to assess the learning curve for surgical treatment, CUSUM (S_n) was defined as $S_n = \Sigma(X_i - X_0)$, where X_i is an individual attempt and X_0 is the predetermined acceptable failure rate for the procedure, with X_i assigned a score of 0 for success and 1 for failure [13, 14]. The acceptable failure rate was defined such that, when the target success rate was set at 90%, the acceptable failure rate was 10% (X_0 was set at 0.1). For the CUSUM curve we defined "failure" has occurring when any of the following occurred: (1) perioperative major morbidity and mortality, (2) intraoperative blood loss >1,000 ml, or (3) long operative time more than two standard deviations above the department average (>240 min for open surgery, >270 min for LCR).

The moving average method was also used to assess changes in operation time for qualification of the learning curve. Creating an average of values that moves with the addition of new data results in smoothing of the value of the variable being analyzed.

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL) for Windows. The chi-square test or Fisher's exact test was used for comparison of categorical variables as appropriate, and Student's t-test was used for comparison of continuous variables. Values of $p < 0.05$ were regarded as statistically significant.

Results

A total of 75 patients were included in this study. The choice of surgical procedure was basically determined by patient preference, with LCR performed as default. Consequently, 43 patients underwent laparoscopic resection, while 32 patients underwent open surgery. Patient characteristics are presented in Table 1. Age, mean BMI, American Society of Anesthesiologists (ASA) score, and history of past abdominal surgery showed no significant difference between laparoscopic and open groups.

Tumor characteristics are listed in Table 2. There were no differences in tumor stage (UICC) or tumor size

Table 1 Patient demographics: comparison between laparoscopic and open cases

Factor	Laparoscopic, $N = 43$	Open, $N = 32$	p
Mean age (years)	66.1 ± 8.8	69.9 ± 10.5	0.095
Male sex	21	22	0.085
Mean BMI (kg/m^2)	22.7 ± 2.69	23.8 ± 4.48	0.187
ASA ≥ 3	3	4	0.451
Past abdominal surgery	9	7	0.921

($p = 0.068$ and 0.194, respectively). Extent of lymph node involvement or distant metastasis did not show significant difference. There were a significantly larger number of harvested lymph nodes in the laparoscopic group ($p = 0.012$). Operative outcomes are listed in Table 3. In laparoscopic surgery, operative time was significantly longer, while estimated blood loss was significantly less. The morbidity rate for open and laparoscopic surgery was 3.1% (1/32) and 4.7% (2/43), respectively ($p = 0.484$). Morbidities were small bowel obstruction for open surgery, and major leakage and bleeding that required blood transfusion for laparoscopic surgery. Mortality rate was 0% in both groups during this study. There were three cases of conversion to open surgery from initially performed laparoscopic surgery during this study; reasons for conversion were severe small bowel adhesion to abdominal wall due to previous laparotomy for duodenal ulcer in one case, and two cases of bleeding which were difficult to control by laparoscopic operation.

Table 2 Tumor characteristics: comparison between laparoscopic and open cases

Factor	Laparoscopic, $N = 43$	Open, $N = 32$	p
Location			
Cecum	3	7	
Ascending colon	14	2	
Transverse colon	3	7	
Descending colon	0	3	
Sigmoid colon	17	7	
Recto sigmoid	6	6	
Tumor stage			
T0 and 1	13	6	
T2	9	4	
T3	21	22	0.068
N stage ≥ 1	17	14	0.714
M stage 1	1	3	0.179
Mean maximum diameter (mm)	33.1 ± 18.8	38.8 ± 21.4	0.228
Mean lymph nodes harvested	20.9 (7–42)	15.9 (2–31)	0.015

Table 3 Operative outcomes

Factor	Laparoscopic, $N = 43$	Open, $N = 32$	p
Type of colon resection			
Ileocecal resection	4	2	
Right colectomy	15	12	
Left colectomy	0	3	
Sigmoid colectomy	18	8	
Anterior resection	6	6	
Operative time (median)	224 (120–350)	150 (85–335)	<0.01
Estimated blood loss (ml)	64.7 ± 96.5	210.6 ± 203.2	<0.005
Conversion rate	7.0% (3/43)	–	

The moving average of the operation time for open and laparoscopic surgery is shown in Fig. 1. For both groups, operation time decreased with increasing experience, and plateaued after 25 cases in the laparoscopic group and 22 cases in the open group.

CUSUM curves are shown in Fig. 2. In the laparoscopic group, surgical morbidity was observed in two cases, and operative time was longer than 270 min in five cases. In the open group, surgical morbidity occurred in one case, and operative time exceeded 240 min in three cases. There were no cases exceeding 1,000 ml blood loss in either approach. The learning curve for open cases was 11 cases and 7 for laparoscopic surgery.

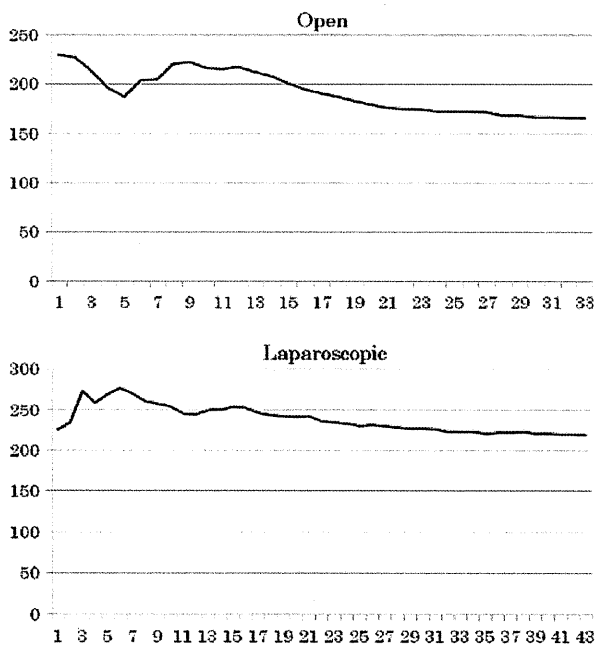

Fig. 1 Moving average of the operating time

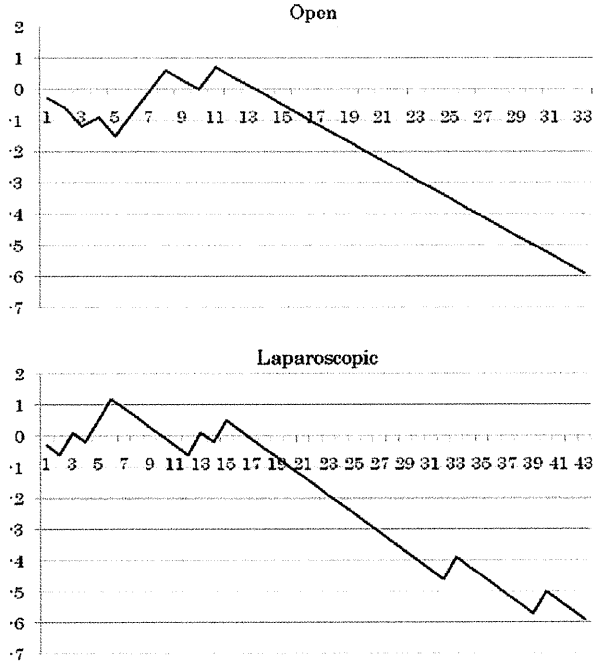

Fig. 2 Cumulative summation (CUSUM) score; upward slopes indicate that at least one failure was recorded in the case index number. Case was scored as +0.9 for failure or −0.3 otherwise, then the score was sequentially added

Discussion

The 4-year basic surgical residency program in Japan involves attainment of basic surgical skills. Basic surgical residents start with basic procedures such as appendectomy, cholecystectomy, and hernia repair [17–21]. They then progress to open colorectal cancer surgery. LCR is learned later, after proficiency in open colorectal resections. With efforts to standardize LCR technique and supervision from expert surgeon in LCR, it has become easier for a trainee surgeon to learn the technical skills of LCR. We thus hypothesized that LCR could be learned simultaneously with open colorectal surgery.

In this study, we excluded tumors that were located near the splenic flexure, at the descending colon, and the rectum, as these locations are technically more difficult and may not be suitable for operation by trainee. Cases of tumors that were invading adjacent organs were also excluded for similar reasons.

Previous reports evaluating the learning curve of laparoscopic colorectal surgery included some different factors from those utilized herein [7, 9, 13, 22, 23]. To evaluate quality of LCR, we did not include number of lymph nodes harvested, as standard D2 or D3 operations for early and advanced tumors, respectively, were performed in all cases. Extent of dissection was ensured by the supervisor in every case. Conversion to open surgery was also not included in this study. In our previous study, trainee surgeon did not cause more conversion in LCR if they were well supervised [24]. So, we do not believe that conversion to open surgery is a good indicator to assess quality of LCR under good supervision. Besides, conversion rate should be evaluated as proficiency of laparoscopic surgery only. We considered blood loss more than 1,000 ml and long operative time as failure, as our previous study showed that these were independent predictors of poorer outcome (data to be published in the *American Journal of Surgery*).

Monitoring quality in surgical treatment has been a topic of interest for many. Direct observation by a supervisor and graphical representation of the learning curve are two common ways of assessing individual competence, but both are likely to be subjective [25, 26]. Assessment of surgeon competency should be dynamic and enable quantitative and continuous evaluation of surgeon performance. CUSUM allows continuous monitoring of surgical performance using clearly defined situations of failure and provides objective evaluation. CUSUM has emerged as a popular tool for performance monitoring in surgery since its first application to evaluate surgical outcomes by de Leval et al. [27]. CUSUM methodology has been applied to describe quality in colorectal surgery in several studies [8, 13, 14]. In this study, the CUSUM curve demonstrated downward slope after 11 cases in open group and 7 cases in laparoscopic group, which implies that the surgeon had acquired sufficient skills for index procedures.

The moving time average stabilized after 25 cases for laparoscopic colorectal surgery and 22 cases for open surgery, which implies that a further 18 and 11 cases were required to stabilize operation time in laparoscopic and open surgery, respectively. These patterns suggest that the trainee surgeon was able to perform the procedure safely at an early stage, and this was then followed by reduction in operative time when technical skills were further improved.

The learning curve for LCR in our study was similar to one previous report [13], while other reports demonstrated larger number of cases for the learning curve [7, 10, 12, 15]. The accelerated learning curve demonstrated herein is likely to be a result of the following: Firstly, the trainers in this series were extremely experienced in both laparoscopic and open colorectal surgery. Each of the trainers had carried out more than 300 cases of LCR. With this experience, it was possible for them to impart a technique for both open and laparoscopic surgery that has already been well established and standardized. This enabled easier learning, as the trainee did not have to contend with different techniques of different supervising surgeons. Secondly, the ever-present supervision of the experienced staff surgeons enabled the trainee to commit fewer mistakes intraoperatively, especially in identification of anatomical structures