

Acute inflammatory response to colorectal cancer resection according to different laparotomy incision lengths

Tohru NAKAGOE,¹ Toshikazu MATSUO,² Shirou NAKAMURA,² Masa-aki JIBIKI,¹ Hiroshi HISANO,¹ Tatsuhiko NOGAWA¹

¹Department of Surgery, Nagasaki Saiseikai Hospital, 2-5-1 Katafuchi, Nagasaki 850-0003, Japan

²Department of Surgery, Ohmura Municipal Hospital, 133-2 Kogashima-cho, Ohmura, Nagasaki 856-8561, Japan

The aim of this study was to clarify a correlation between acute inflammatory response to surgery and different laparotomy lengths in patients who underwent colorectal cancer resection via a single minimal laparotomy.

Between April 2005 and May 2008, 131 consecutive patients (59 women, 72 men), who were scheduled to undergo elective surgery for resection of primary colorectal cancer using a single minimal skin incision, were enrolled in this study to investigate the correlation between postoperative acute inflammatory responses (as measured by serum C-reactive protein (CRP) levels and white blood cell count (WBC)) and different laparotomy lengths. According to the length of laparotomy, the patients were grouped into 3 categories, "small-incision" (≤ 7 cm), "medium-incision" (>7 and ≤ 14 cm), and "large-incision" (>14 cm) for comparison. Statistical analyses were conducted using the Kruskal-Wallis test with multiple comparison post-hoc and chi-square tests.

The small-, medium-, and large-incision groups included 68 (51.9%), 42, (32.1%) and 21 (16.0%) patients, respectively. On the 1st postoperative day, median serum levels of CRP and WBC of the small-incision group were significantly lower than those of the medium-incision and large-incision groups (CRP, $P=0.0051$ and $P=0.0015$, respectively; WBC, $P=0.049$ and $P=0.0007$, respectively). In addition, the median serum levels of CRP and WBC on the 1st postoperative day were proportional to the length of laparotomy.

These data suggested that the extent of acute inflammatory response may be proportional to length of laparotomy. In addition, only the use of small-incisions (≤ 7 cm) among the three investigated categories of laparotomy lengths may be a factor which is associated with statistical significance with minimal invasiveness of colorectal cancer resection.

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Keywords: Small skin incision; Colorectal cancer; Acute inflammatory response; CRP

Introduction

Currently, conventional surgery via laparotomy remains the procedure of choice for colorectal cancer resection. The evolution of minimally invasive surgery allowed the use of minilaparotomy (open surgery with the intent to minimize the length of skin incision) and advanced laparoscopic techniques.^{1,2,3} Reduced hospital stay, less wound pain, earlier resumption of diet, earlier return of bowel function, and re-

duced incidence of postoperative infections are recognized benefits of the minimally invasive techniques.^{1,2,3} Possible explanations include the smaller incision and better preservation of immune system function with a limited inflammatory response to tissue injury.^{4,5} The purpose of this study was to clarify a correlation between acute inflammatory response to surgery and different laparotomy lengths in patients who underwent colorectal cancer resection via a single minimal laparotomy.

Address correspondence: Tohru Nakagoe, M.D., Department of Surgery, Nagasaki Saiseikai Hospital, 2-5-1 Katafuchi, Nagasaki 850-0003, Japan

TEL: +81-95-826-9236, FAX: +81-95-827-5657, E-mail: nakagoe-t@nsaisei.or.jp

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Patients and Methods

Patients

Between April 2005 and May 2008, 131 consecutive patients (59 women, 72 men; median age 71 (range 36-94) years), who were scheduled to undergo elective surgery for resection of primary colorectal cancer using a single minimal skin incision, were enrolled in this study to investigate the correlation between postoperative acute inflammatory responses (as determined by serum C-reactive protein (CRP) levels and white blood cell count (WBC)) and different laparotomy lengths. Informed consent for this study was obtained from each patient. Excluded from the study were patients with only the creation of a stoma.

Sixteen tumors were located in the appendix or cecum, 18 in the ascending colon, 19 in the transverse colon, 1 in the descending colon, 25 in the sigmoid colon, and 53 in the rectum.

American Joint Committee on Cancer (AJCC) Classification and Stage groupings were used for tumor assessment.⁶ Levels of lymph node dissection were classified according to the Japanese Classification of Colorectal Carcinoma.⁷

Operation

All of the operations were performed by a single surgeon (T.N.). At the beginning of the operation, a small skin incision (≤ 7 cm in length) was made in all patients. When such a small skin incision approach was unsuccessful because of intraoperative issues (e.g., anatomical, technical, and/or other problems with the primary tumor⁸), minimal elongations of the skin incisions were made. During the operation, specific efforts were made to minimize the incision lengths to accomplish the resection of colorectal cancer. The operative procedures were reported previously.^{8,9,10,11} No hand-port or laparoscope was used in this series.

There were 23 ileocecal resections, 16 right hemicolectomies, 11 transverse colectomies, 3 left partial colectomies, 27 sigmoidectomies, 38 anterior resections, 11 abdominoperineal resections, and 2 Hartmann's procedures. Curative and non-curative resections were performed in 117 and 14 patients, respectively.

Twenty-two patients underwent combined resections concurrent with surgery via a single laparotomy wound. Of the 22 patients, 12 underwent combined resections of involved adjacent organs (five abdominal walls, two urinary bladders, two stomachs, two seminal vesicles, two adnexae, one vagina, one colon, one uterus, one diaphragm, and one

ileum) because of adhesion or invasion of the primary tumor, and the remaining 10 underwent combined resections of other site organs or another site of the colon because of diseases such as gallstones, gastric cancer, colonic tumors, and tuberculosis of the ileum (five cholecystectomies, one gastrectomy, three colectomies/surgical polypectomies, and resection of the ileum, respectively).

Definition

In this study, we defined "small-incision" as completion of the operation employing the original small skin incision (≤ 7 cm in length).^{8,9} "Medium-incision" was defined as laparotomy incision length between > 7 cm and ≤ 14 cm, while "large-incision" was >14 cm in length. The cut-off value (14cm) was used because a maximum value of laparotomy incision length in the 131 patients included in the study was 21cm. The patients were grouped into "small-incision", "medium-incision", and "large-incision" categories for comparison.

Measurement of serum CRP level and WBC

Circulating CRP levels and WBC were determined before the operation and 1 day, 7 days, and 14 days after operation (1st postoperative day (1POD), 7th postoperative day (7POD), and 14th postoperative day (14POD), respectively). Serum CRP levels and WBC were measured using latex turbidimetric immunoassay (Mitsubishi Chemical Corp., Tokyo, Japan) and Sysmex XT-2000i automated hematology analyzer (Sysmex Corp., Kobe, Japan), respectively. The cutoff value of CRP recommended by the manufacturer for diagnostic use was 0.3 mg/dL.

Statistics

Statistical analyses were performed using STATISTIC A™ (StatSoft, Tulsa, OK, USA). Numerical values are given as medians (interquartile range (IQR)). Continuous and categorical data were analyzed by the Kruskal-Wallis test with multiple comparison post-hoc and chi-square tests, respectively. All tests were two tailed and $P < 0.05$ was considered significant.

Results

Of the 131 patients who were scheduled to undergo resection for colorectal cancer using a minimal skin incision,

success of the small-incision was achieved in 68 patients (51.9%). Medium- and large-incisions were performed in 42 (32.1%) and 21 (16.0%) patients, respectively. There were no intraoperative complications such as massive bleeding, bowel perforation, or problems with the anastomosis. The median length of the laparotomy incision in the 131 patients included in the study was 7.0 (IQR 7.0-12.0) cm.

As shown in Table 1, the groups with longer skin incisions had longer operation time and greater operative blood loss: differences were statistically significant. In addition, the multiple comparison post-hoc test demonstrated significant differences in these variables between the small-incision and medium-incision groups ($P<0.0001$ and $P<0.0001$ respectively), and between the small-incision and large-incision groups ($P<0.0001$ and $P=0.0001$, respectively). However, there were no differences in such variables between the medium-incision and large-incision groups.

The proportion of type of operation between the three groups differed significantly ($P<0.0001$): success rate of

the rectal resection in the small-incision group was lower than that of the right colon and the left colon resections. However, there were no differences in level of lymph node dissection,⁷ concurrent resection of other site organ, and Dukes stage during surgery between the three groups (Table 1).

Postoperative changes of serum CRP levels and WBC

In all three groups, median serum levels of CRP and WBC on the 1st postoperative day (POD) increased compared with preoperative median serum levels. However, the median serum levels of CRP and WBC measured on 7POD or 14 POD decreased in all groups when compared with those of 1POD (Figure 1 and Figure 2).

Median pre-operative serum levels of CRP and WBC did not differ between the three groups. However, median serum levels of CRP on 1POD between the three groups differed significantly ($P=0.0002$). Median serum levels of CRP in the small-incision group on 1POD were significantly lower

Table 1. Comparison of operative procedures and Dukes stage between the three groups.

Variable	No. of patients (%)			<i>P</i>
	Large-incision (n=21)	Medium-incision (n=42)	Small-incision (n=68)	
Operating time (min)*	282 (240,332)	222 (191,265)	160 (128,186)	<0.0001
Operative blood loss (ml)*	260 (160,410)	132 (80,250)	50 (30,83)	<0.0001
Type of operation				<0.0001 [‡]
Resection of the right colon (n=53)	6 (11.3)	10 (18.9)	37 (69.8)	
Resection of the left colon (n=29)	3 (10.3)	7 (24.1)	19 (65.5)	
Resection of the rectum (n=49)	12 (24.5)	25 (51.0)	12 (24.5)	
Level of lymph node dissection [†]				0.30 [‡]
D1 (n=17)	2 (11.8)	3 (17.7)	12 (70.6)	
D2 (n=55)	12 (21.8)	18 (32.7)	25 (45.5)	
D3 (n=59)	7 (11.9)	21 (35.6)	31 (52.5)	
Concurrent resection of other organ				0.23 [‡]
No (n=111)	16 (14.4)	34 (30.6)	61 (55.0)	
Yes (n=20)	5 (25.0)	8 (40.0)	7 (35.0)	
Stage during surgery [§]				0.090 [‡]
I (n=40)	5 (12.5)	9 (22.5)	26 (65.0)	
II (n=28)	4 (14.3)	6 (21.4)	18 (64.3)	
III (n=49)	8 (16.3)	21 (42.9)	20 (40.8)	
IV (n=14)	4 (28.6)	6 (42.9)	4 (28.6)	

* Values are medians (interquartile ranges). Statistical analyses were conducted by the Kruskal-Wallis test.

[‡] Chi-square test.

[†] Level of lymph node dissection.[‡]

[§] Stage defined by findings during surgery, including findings based on histopathological explorations. Preoperative clinical findings were also referred to.

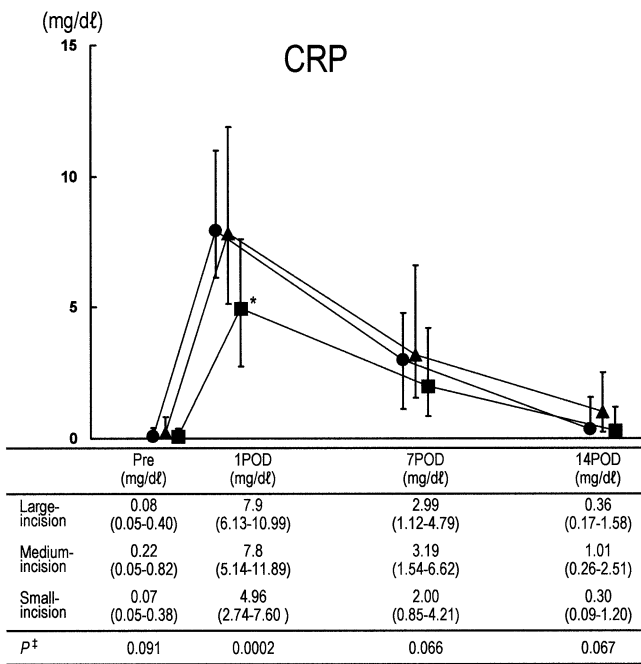


Figure 1. Postoperative changes of serum C-reactive protein (CRP) levels in 131 patients who underwent colorectal cancer resection using large incisions () (n=21), medium incisions () (n=42), or small incisions () (n=68). Values are medians and interquartile ranges. Pre, preoperative. POD, postoperative day. *, $P=0.0051$ and $P=0.0015$ (Medium-incision vs Small-incision and Large-incision vs Small-incision, respectively). P^\ddagger , Kruskal-Wallis test.

than those of the medium- and large-incision groups ($P=0.0051$ and $P=0.0015$, respectively) (Figure 1).

The median WBC on 1POD and 7POD were significantly differed between the three groups ($P=0.0005$ and $P=0.0033$, respectively). Median WBC of the small-incision group on 1POD was significantly lower than that of the medium- and large-incision groups ($P=0.049$ and $P=0.0007$, respectively). Similarly, median WBC of the small-incision group on 7POD was significantly lower than that of the medium- and large-incision groups ($P=0.022$ and $P=0.015$, respectively) (Figure 2).

Postoperative early outcomes

There was no operative mortality. The frequency of postoperative complications between the three groups differed significantly ($P=0.031$): groups with larger length of skin incision had higher rates. The rate of surgical site infection was proportional to the length of laparotomy, although the difference was not significant (Table 2).

There were significant differences in median postoperative intervals until first standing and first walking between the three groups ($P=0.011$ and $P=0.012$, respectively).

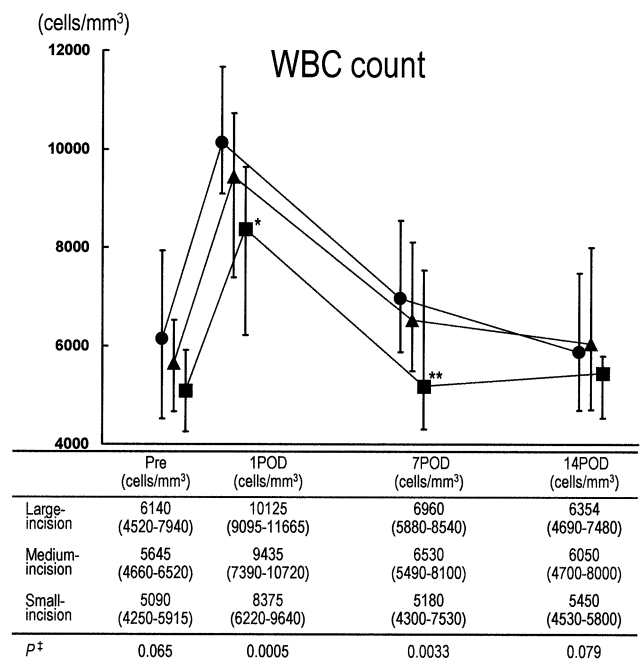


Figure 2. Postoperative changes of white blood cell (WBC) count in 131 patients who underwent colorectal cancer resection using large incisions () (n=21), medium incisions () (n=42), or small incisions () (n=68). Values are medians and interquartile ranges. Pre, preoperative. POD, postoperative day. *, $P=0.049$ and $P=0.0007$ (Medium-incision vs Small-incision and Large-incision vs Small-incision, respectively). **, $P=0.022$ and $P=0.015$ (Medium-incision vs Small-incision and Large-incision vs Small-incision, respectively). P^\ddagger , Kruskal-Wallis test.

Median postoperative intervals until first standing and first walking in the small-incision group were significantly shorter than that in the large-incision group ($P=0.044$ and $P=0.022$, respectively) (Figure 3).

There were also significant differences in median analgesic usage and postoperative hospital stay ($P=0.015$ and $P=0.0001$, respectively). Median analgesic usage in the small-incision group was significantly less than that in the large-incision group ($P=0.020$). Median postoperative hospital stay in the small-incision group was shorter than that in the medium- and the large-incision groups ($P=0.049$ and $P=0.0001$, respectively) (Figure 4).

Discussion

In the current study, the patients who underwent colorectal cancer resection were grouped into "small-incision" (≤ 7 cm in length), "medium-incision" (>7 and ≤ 14 cm), and "large-incision" (>14 cm) categories. Postoperative acute inflammatory response (CRP and WBC) to surgeries with small incisions was reduced compared with medium- and

Table 2. Comparison of postoperative complications between the three groups.

Variable	No. of patients (%)			P
	Large-incision (n=21)	Medium-incision (n=42)	Small-incision (n=68)	
No (n=119)	17 (80.9)	36 (85.7)	66 (97.1)	0.031*
Yes (n=12)	4 (19.1)	6 (14.3)	2 (2.9)	
SSI [‡]	3 (14.3)	3 (7.1)	1 (1.5)	
Anastomotic leakage	0	2	0	
Intestinal obstruction	1 [†]	0	1	
Myocardial infarction	0	1	0	
Pneumonia	1 [†]	0	0	

*Chi-square test.

[‡]SSI, Surgical site infection.

[†]One patient developed both intestinal obstruction and pneumonia.

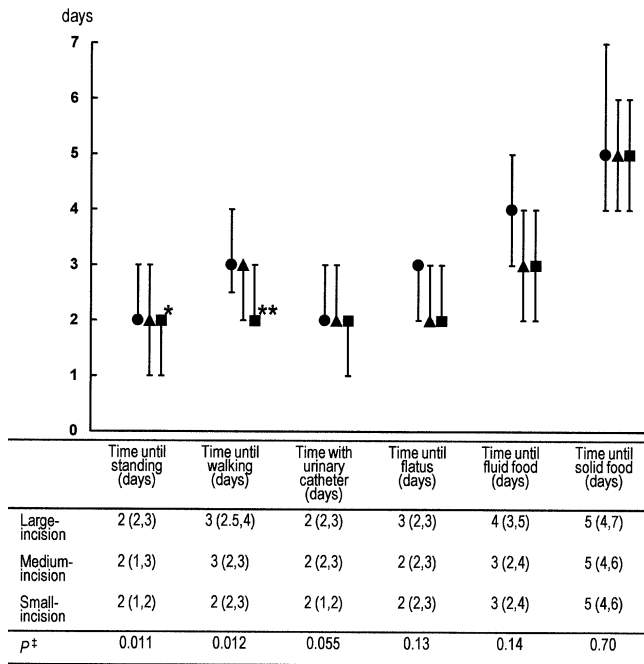


Figure 3. Postoperative course in 131 patients who underwent colorectal cancer resection using large incisions () (n=21), medium incisions () (n=42), or small incisions () (n=68). Values are medians and interquartile ranges. *, *P*=0.020 (Large-incision vs Small-incision). **, *P*=0.049 and *P*=0.0001 (Medium-incision vs Small-incision and Large-incision vs Small-incision, respectively). *P*[‡], Kruskal-Wallis test.

large incisions. In addition, the postoperative serum median levels of CRP and WBC were proportional to the length of laparotomy.

Surgical trauma from colorectal cancer resection includes an acute phase response.¹² A temporary environment is created in which there is mechanical release of tumor cells, enhanced angiogenesis, secretion of growth factors,

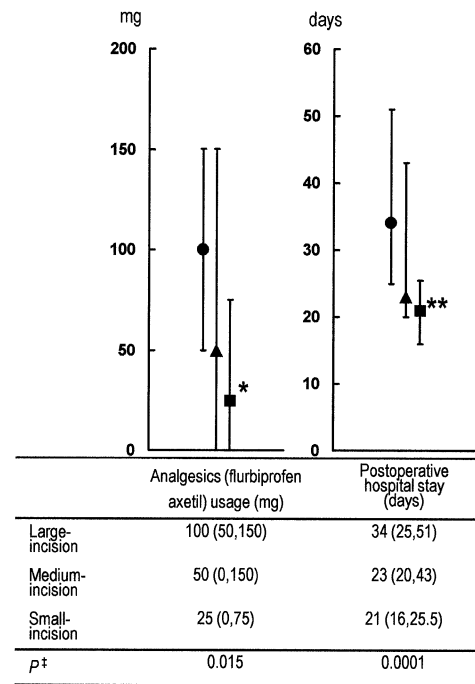


Figure 4. Postoperative course in 131 patients who underwent colorectal cancer resection using large incisions () (n=21), medium incisions () (n=42), or small incisions () (n=68). Values are medians and interquartile ranges. *, *P*=0.020 (Large-incision vs Small-incision). **, *P*=0.049 and *P*=0.0001 (Medium-incision vs Small-incision and Large-incision vs Small-incision, respectively). *P*[‡], Kruskal-Wallis test.

and immunosuppression, leaving the host potentially vulnerable to the spread and development of tumor cells.¹³ The extent of the acute phase response is directly proportional to the magnitude of trauma involved.¹⁴ New minimally invasive techniques including the use of minilaparotomy, when compared with similar open surgery, have been shown to reduce inflammatory responses with smaller increases

in serum levels of systemic cytokines and C-reactive protein.^{2,4,15} However, there have been few studies on postoperative acute inflammatory response and/or immunologic function according to different laparotomy lengths. Evans et al.² compared immune function after laparoscopy (≤ 7 cm in length), minilaparotomy (< 15 cm), and conventional (≥ 15 cm) colorectal tumor resection. The authors concluded that TH1 lymphocyte function (interferon- γ , tumor necrosis factor- α , and interleukin-2) was improved transiently and immune homeostasis restored earlier in patients undergoing laparoscopic (≤ 7 cm in length) colorectal cancer resection, which may influence disease recurrence.

There is accumulating evidence that surgical stress causes impairment of systemic immune responses, which may promote susceptibility to infection as well as growth of remnant cancer cells in cancer patients.¹⁴ Poon et al. reported that laparoscopic surgery was associated with reduction of rate of surgical site infection by more than 50% when compared with open surgery, and thus, it would have a strong impact on the prevention of surgical infection.¹⁶ Most literature reports are in agreement that laparoscopic surgery is associated with better preservation of immune function, reduction of the inflammatory response, and lower rate of postoperative infections as compared to open surgery.¹⁷ In the current study, the group with larger skin incisions had higher rate of surgical infection, although the difference was near significant ($P=0.061$).

Unfortunately, the current report was not based on a randomized control study. Further studies are needed to clarify the extent of surgery-related alteration in the immune system and the clinical importance. A better understanding of the impact of surgery on the immune system may provide opportunities for pharmacologic manipulation of postoperative immune function to improve clinical results.¹²

In the current study, postoperative acute inflammatory response to colorectal cancer resections with small incisions was reduced compared with medium- and large incisions. In addition, the small-incision group demonstrated less invasiveness compared with the medium-incision group or the large-incision group, when invasiveness was evaluated by postoperative early outcomes. These data suggested that only the use of small incisions among the three investigated categories of laparotomy lengths may be a factor which is associated with statistical significance with less

invasiveness of colorectal cancer resection. Therefore, our results strongly indicate that during the operation, it is necessary for surgeons to make specific efforts to minimize the incision lengths, if possible "small incisions" (≤ 7 cm in length), during colorectal cancer resections.

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