Original Paper

Solo Surgery in Laparoscopic Colectomy: A Case-matched Study Comparing Robotic and Human Scopist

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KEY WORDS:
Laparoscopic-assisted colectomy, Solo-surgery, Voice-controlled robotic arm, Colon-lifting method

ABSTRACT

Background/Aims: Recent technical developments have enabled solo surgery in laparoscopic surgery. Our experience of solo surgery using the voice-guided robotic arm in laparoscopic colectomy for colorectal cancer was analyzed.

Methodology: The colon-lifting method was used in this study. The laparoscope was handled by AESOP3000™. The colon was retracted anteriorly by the thread that passed through the mesocolon. This method enables lymphadenectomy by stretching of feeding vessels and obviates the need for an assistant. The short-term outcomes and survival between robotic arm and human scopist in a series of laparoscopic colectomies were compared with a case-matched control study.

Results: The numbers of both group patients were 11 respectively. There was no conversion to open surgery in both groups. The operation time (Robotic *vs.* Human=269 min. *vs.* 265) and laparoscopic time (209 *vs.* 212) were not significant differences. There were also no significant differences in the bleeding, the morbidity rate and the numbers of dissected lymph nodes between the two groups. The five-year overall (81.8% *vs.* 72.7%) and disease-free (72.7% *vs.* 62.3%) survivals showed no significant differences.

Conclusions: Laparoscopic solo-surgery in colectomy is safe and feasible, without any deterioration of the curative potential of the procedure.

INTRODUCTION

We have developed a new technique of colon lifting method using a thread in laparoscopic-assisted colectomy (LAC) for colorectal cancer (1). In this method, the colon is fixed to the abdominal wall; eliminating the need for a first surgical assistant and hence enabling the performance of solo surgery LAC by using a robot arm instead of a scopist. The aim of this study was to report on our experience of laparoscopic colorectal surgery by the colon lifting-method using a voice-controlled robotic arm (AESOP 3000 TM; Computer Motion, Inc., Santa Barbara, CA, U.S.A.), as "solo surgery". The use of a robotic arm during laparoscopic surgery is becoming more and more popular with laparoscopic surgeons. However, there are few published reports documenting the advantages and disadvantages of the use of a robotic arm, except for some that have documented its efficacy and beneficial influence on the operative outcomes, maintenance of a good operative view, and good cost effectiveness (2-6).

We used the robotic arm system as the scopist for laparoscopic colectomy using the colon-lifting method for colorectal cancer. A case-matched control study was performed in order to compare with the same conditions. Safety, quality of lymph node dissection, and the medical costs saving in solo surgery were analyzed.

METHODOLOGY

From June 2002 to January 2004, a series of 11 patients with adenocarcinoma of the colon and upper rectal cancer underwent LAC with the aid of a robotic arm. Patients with inability to withstand pneumoperitoneum with 10cm H_2O pressure due to cardio respiratory insufficiency were excluded. LAC is currently indicated for colorectal cancer cases with a tumor less than 5cm in diameter and classified into a stage lower than T3N1M0. The operative procedure with the aid of the robotic arm was only performed in patients who gave their informed consent and when the robotic arm system was available for use. Since our hospital owns only one robotic arm, we were not able to use it for all of our cases undergoing LAC. During the same period indicated above, 67 patients underwent LAC by the same surgeon with the assistance of a human scopist; that is, all of the operations were performed by the same surgeon. In order to compare outcomes with same

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conditions, the robotic arm and human scopist groups were matched in terms of the following variables: gender; age (within 10 years); American Society of Anesthesiologists (ASA) score (within one point); operative year; tumor location (right-side and transverse colon, left-side of the colon, rectosigmoid and rectum) and International Union Against Cancer Tumor-Node-Metastasis (TNM) stage (0, I, II or III). We compared the operative outcomes between the surgery conducted with the aid of robotic arm and that conducted with the assistance of a human scopist. The outcome data measured included the type and incidence complications, the operative time, the severity of intraoperative bleeding, the number of dissected lymph nodes, the length of postoperative hospital stay, and the survival.

Operative technique

The operative steps were guided by an identified operator's voice over the microphone. The orders being given, namely, the menu and the moving direction, were displayed on the monitor. All patients underwent LAC by the colon-lifting method. The mesocolon was pierced near the line of transection with the dissecting forceps, and a 2-0 Nylon thread was passed through it. The pulling site of the mesocolon was set at a distance of 10 cm or more from the tumor in order to prevent dissemination of the cancer cells. The colon was retracted anteriorly by slowly pulling the thread, and fixed to the abdominal wall with a pair of forceps. The main nutrient artery was stretched in the mesocolon, so as to enable the lymph node dissection to be performed easily. In the laparoscopic procedure using this method, therefore, the first surgical assistant was not required, because the colon was fixed to the abdominal wall without having to be held by an assistant; in addition, there was little risk of careless handling of the tumor. Retroperitoneal dissection was performed from the medial side; resulting in a non-touch technique. When conducted with the assistance of a human scopist, the procedure is a two-person method (**Figure 1**), while when performed with the aid of the robotic arm, only the primary surgeon is needed to perform the surgery (**Figure 2**). In both methods, however, an assistant is required at the time of the small laparotomy and the extracorporeally anastomotic procedure.

Statistical Analysis

The statistical analysis was performed with the SPSS software package (version 11.0J for Windows; SPSS Inc., Chicago, IL). The continuous variables were compared between groups using the Student's t-test. The Pearson's Chi-squared test or the Fisher's exact test was used to compare discrete variables. Survival curves were produced using the Kaplan-Meier method. Statistically significant differences between the groups were determined by the log-rank test. A p value <0.05 was considered statistically significant (two-tailed test).

RESULTS

Patient characteristics and short-term outcomes

There was no conversion to open surgery in both groups. There were no significant differences in the patient characteristics between the two groups due to a case-matched control study (**Table 1**). There was no significant difference in the follow-up period between the two groups (63.4±21.4 *vs.* 61.7±21.8, p=0.8615). There was no significant difference in the total operation time, laparoscopic time and the severity of intraoperative bleeding. Further, there was no significant difference in the number of dissected lymph nodes, proximal and distal margin. None of the patients in either group required a blood transfusion. The morbidity rates between the two groups were equal. There was 1 rectal cancer case of anastmotic leakage in the robotic arm group. The postoperative duration of hospital stay was longer in the robotic arm group than in the human scopist group due to the anastmotic leakage case, but the difference was not significant (**Table 2**).

The long-term outcomes

The five-year overall (81.8% *vs.* 72.7%, p=0.6562) and disease-free (72.7% *vs.* 62.3%, p=7918) survivals were no significant differences (**Figure 3**). Three patients in the robotic arm group had recurrence, one each in the bone, liver and peritoneum, and

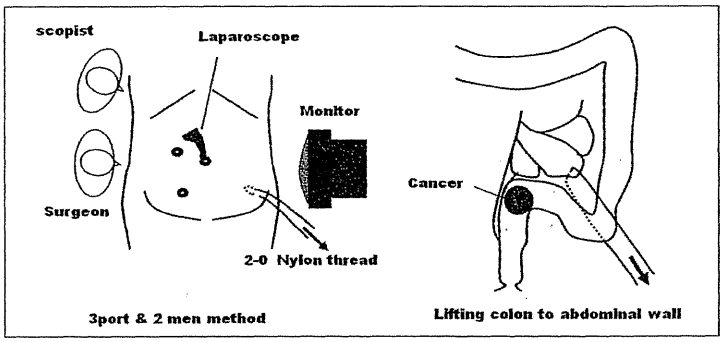

FIGURE 1 Human scopist with the colon lifting method. This figure shows the sigmoid colectomy. A Nylon thread was passed through the site of oral transected mesocolon and the colon was fixed at the left lower abdominal wall. The operative field was stable and this method enabled 3–port & 2– man method.

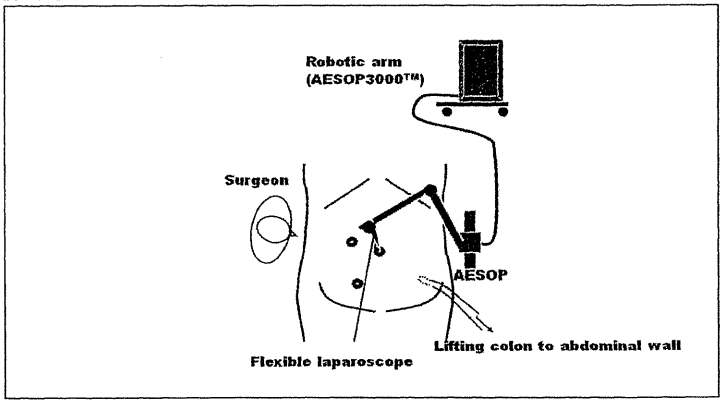

FIGURE 3 The overall and disease–free survival curves in both groups. There were no significant differences in the overall and disease–free survivals.

TABLE 1 Patient Characteristics in Both Groups

	Robotic group	Human group	*p*-Value
Gender			
Male/Female	7/4	7/4	1.0000
Age (years)	64.4 + 9.2	62.5 + 12.9	0.6928
ASA score*	1.4 + 0.5	1.6 + 0.5	0.2195
Operative year			1.0000
2002	5	5	
2003	5	5	
2004	1	1	
Site of tumor			
Right & Transverse colon	2	2	
Left colon	4	4	1.000
Rectosigmid & Rectum	5	5	
pTNM stage			
0	1	1	
I	4	4	1.0000
II	4	4	
III	2	2	
Follow-up period (months)	63.4 + 21.4	61.7 + 21.8	0.8615

*: American Society of Anesthesiologists score

one patient had peritoneal and lung metastases in the human scopist group. The patients with peritoneal and bone recurrence died 22 and 21 months, respectively, after the operation in the robotic arm group. The patients with hepatic recurrence underwent hepatectomy 13 months after the resection of primary lesion, and were alive up to 53 months after hepatectomy. The patients with peritoneal and lung metastases died 47 months after the operation in the human scopist group. One patient suffered with esophageal cancer and 2 patients died of other diseases in the human scopist group. The local recurrence was absent among the two groups.

Medical cost saving

In Japan, the personal charges of the surgeon are very low; being about 6,000 yen (about 61 US dollars) per hour at our hospital. The cost of using disposable instruments per operation were 4,000 yen for the surgery conducted with the assistance of the human scopist and 1,000 yen for that conducted with the aid of the robotic arm. Therefore, the saving of medical cost of one operation using the robotic arm, considering that the duration of assistance by the human laparoscopist necessary was 3 hours, was about 21,000 yen (6,000yen×3hours +1,000 yen; about 214 US dollars).

DISCUSSION

We have previously reported on the benefits of the colon-lifting method for laparoscopic colectomy, namely that it requires fewer operating staff and trocars, and can be performed without any decrease of the curative potential of the procedure. In this method, the colon is retracted anteriorly by pulling a thread fixed to the abdominal wall during the dissecting maneuvers (1). Since the colon is thus fixed to the abdominal wall, a first surgical assistant, besides the laparoscopist, is not required. With the aid of the robotic arm, therefore, we were able to perform solo surgery using this method.

We have reported on the advantages of the robotic arm in thoracoscopic surgery for esophageal cancer (7). The surgeons using the robotic arm system could obtain a more stable, close-up, and longer-lasting operative view during HALS and VATS for esophageal cancer than the open surgery group. In the current study, we compared the advantages of the robotic arm over the assistance of a human laparoscopist in LAC for colorectal cancer. With respect to the steadiness of holding the scope, the robotic arm provided excellent steadiness of handling. One of the most important advantages of the robotic arm, which unfortunately does not lend itself easily to quantitative analysis, is that it is a tremor-free technique. This has been reported to be especially significant during internal mammary artery harvesting (8). Baca *et al.* reported that the benefits

TABLE 2 Comparison of the Operative Procedure and Short-term Outcomes

	Robotic group	Human group	*p*-Value
Total Operation time (min)	268.7 + 60.8	264.7 + 53.8	0.8720
Laparoscopic time (min)	208.7 + 54.2	212.0 + 45.3	0.8794
Intraoperative bleeding (mL)	129.7 + 97.7	108.1 + 94.2	0.6028
Number of dissected lymph nodes	25.9 + 17.5	23.3 + 13.6	0.6969
Proximal margin (mm)	157.7 + 103.5	151.9 + 81.0	0.8847
Distal margin (mm)	93.8 + 70.1	73.1 + 41.4	0.6928
Morbidity (%)	2 (18.2)	2 (18.2%)	1.0000
Anastomotic leakage	1	0	
Surgical wound infection	1	2	
Postoperative hospital stay (days)	11.7 + 5.9	9.3 + 2.8	0.2258

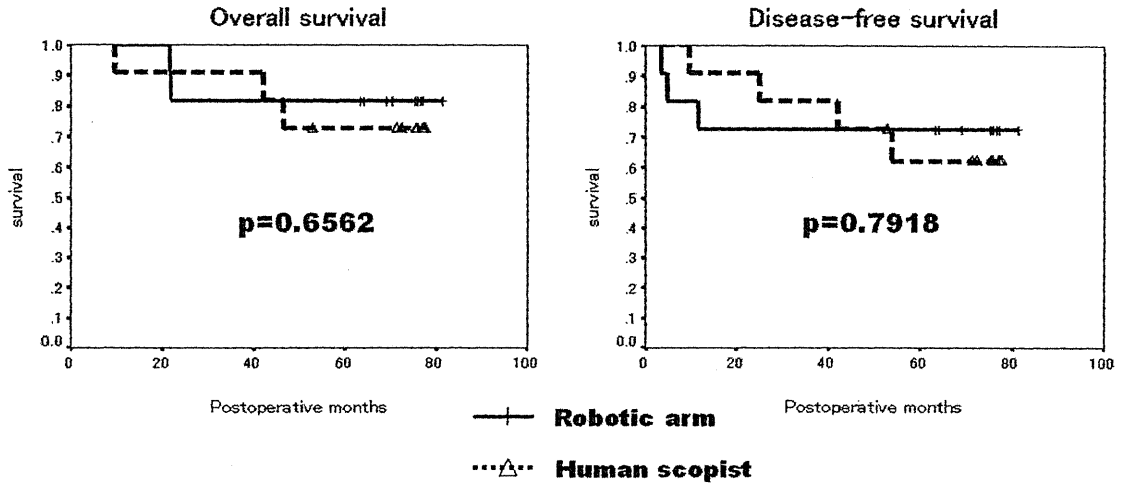

FIGURE 2 Schema of the access ports and the voice–controlled robotic arm site. This figure shows the set–up of the robotic arm. It was set at the opposite side of a surgeon.

that accrue from the use of robotic assistance are a greater stability of view, less inadvertent smearing of the lens, and the absence of fatigue, based on his experience of 200 laparoscopic procedures for various indications (9). It would also appear that the operative environment is highly satisfactory for the surgeon, because a wide operative field can be maintained.

The differences of the total and laparoscopic operation times in the robotic arm group were longer than those in the human scopist group, but were not significant. However, the operative time for laparoscopic surgery could be shortened by about 60 minutes through learning and experience. According to the literature, the time taken for solo surgery with the aid of a robotic scope holder was shorter than that for surgery with human assistance in a large control group of over 400 cholecystectomies on phantoms containing animal organs (10). Besides, the operative cost of surgery with robotic assistance was also lower than that incurred for surgery conducted with the assistance of a human scopist (11).

The robotic arm movements of the robotic arm system were fine-tuned and rigid under proper pronunciation of the orders in most of the cases. However, sometimes, the movements were slow and limited in range. In cases with unexpected bleeding or injury, slow movements of the robotic arm could prove to be an obstacle to the surgeon. In this context, some experiences with other types of robots have been reported (12-15). Nebot reported that the EndoAssist robot was significantly quicker for most of the tasks examined than the AESOP (13). However, numerous reports have shown that the movements of the AESOP system are quicker and more accurate than those of other robots (12, 15).

Some benefits of the robotic arm for laparoscopic procedures involving various organs have been reported, however, there are no clinical reports that can be considered as providing a high level of evidence, except for the randomized study of laparoscopic Nissen fundoplication with either human- or AESOP- assisted camera control in pigs (16). We reported that there were no significant differences between the two groups in terms of the operative time or surgeon's movements, except for the setup and breakdown times, which take about 10 minutes for set-up. In our view, the advantages of the robotic arm system for laparoscopic surgery are the improved stability of view and the absence of surgeon fatigue.

However, the current study was limited because it was not a randomized trial. A high-quality large-scale RCT is necessary to obtain stronger evidence. Well- randomized clinical studies with quantitative analysis to compare parameters between robotic and human camera control in a series of laparoscopic procedures are essential to endorse this contention.

CONCLUSION

Laparoscopic colectomy for colorectal cancer by the colon-lifting method conducted with the aid of the robotic arm permits solo laparoscopic surgery for colorectal cancer, without any decrease of the curative potential of the procedure. Some of the benefits that can accrue from the use of robotics are that it saves human resources and provides greater stability of view, and allows curative maneuvers by the non-touch technique. Thus, the use of the robotic arm is advantageous in terms of saving on the medical costs and maintaining a high quality of the laparoscopic procedure.

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ORIGINAL ARTICLE

Novel procedure, SILSOID colectomy, is a bridge between conventional and single-incisional laparoscopic colectomy

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Keywords
Colectomy; single-incisional laparoscopic surgery; transumbilical incision

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Abstract

Introduction: Laparoscopic colectomy (LC) is a widely accepted treatment for various diseases of the colon. Transumbilical single-incisional laparoscopic surgery (SILS) offers excellent cosmetic results compared with standard multiport laparoscopic surgery. We describe a new hybrid laparoscopic procedure, SILSOID colectomy, which combines conventional LC with SILS.
Methods: We performed SILSOID colectomy to treat four patients with colorectal disease. Three ports were inserted through the single transumbilical incision, and an additional port was inserted in the flank at a site that depended on the location of the lesion. Division and anastomosis of the colon were performed extracorporeally.
Results: SILSOID colectomy was carried out uneventfully in all four cases. The median operation time was 220 minutes (range, 179–320 min), and the median blood loss was negligible (range, negligible–285 mL), respectively. Although one patient experienced a postoperative wound infection, no other postoperative complications occurred.
Conclusion: SILSOID colectomy is safe and feasible and it can be used as an alternative to conventional LC. We consider this procedure to be a bridge between conventional LC and more advanced laparoscopic procedures, such as SILS.

Introduction

Laparoscopic colectomy (LC) is less invasive and more cosmetic than open colectomy (OC), and recently it has been used to treat patients with cancerous lesions as well as patients with benign lesions. In fact, several randomized controlled trials demonstrated that even in patients with advanced colon cancer, LC resulted in an oncological outcome that was similar to the outcome after OC (1–5).

Transumbilical single-incisional laparoscopic surgery (SILS) (6) and natural orifice transluminal endoscopic surgery (NOTES) (7) have recently been developed as new, more cosmetic approaches, and they have been applied to appendectomy and cholecystectomy (6,7). However, very specialized techniques are required to perform both procedures, and it takes a long time to acquire those specialized techniques. We developed a hybrid procedure, SILSOID colectomy, which is a more cosmetic approach that combines conventional LC and SILS. "SILSOID" means a procedure that is similar to SILS because it requires one additional port other than the umbilicus incision. In this article we report our initial experience with SILSOID colectomy in four cases and provide a detailed description of the procedure.

Materials and Methods

Indications and Patients

SILSOID colectomy is indicated for the treatment of patients with lesions located in the cecum, ascending colon, and sigmoid colon. In cancer patients, the indications for SILSOID colectomy are limited to preoperative diagnosis of T1 carcinoma. We limited the location of lesions because it was thought to be difficult to perform anastomosis using the double stapling technique in SILSOID colectomy. The details regarding all four patients are shown in Tables 1 and 2. We used this procedure to

Table 1 Clinical and operative data on four patients

Case	Age/sex	BMI (kg/m^2)	Reason for previous laparotomy	Disease	Procedure	Operative time (min)	Blood loss (mL)	Hospital stay (days)
1	72/M	21.5	Gastric cancer (distal gastrectomy)	Sigmoid colon cancer	Sigmoidectomy	225	Negligible	8
2	76/F	23.2	None	Ascending colon cancer	RHC	179	Negligible	7
3	58/M	24.7	HCC (partial resection of liver)	Sigmoid colon cancer	Sigmoidectomy	320	285	14
4	32/F	17.4	None	Crohn's disease	ICR stricture plasty	215	Negligible	11

BMI, body mass index; ICR, ileocecal resection; HCC, hepatocellular carcinoma; RHC, right hemi-colectomy.

Table 2 Histological data on four patients

Case	Histology	Size (mm)	Depth of invasion	Involvement of lymph nodes (metastatic/harvested)	Length of resected bowel (mm)
1	Well-differentiated tubular adenocarcinoma	35	pMP	6/18	115
2	Well-differentiated tubular adenocarcinoma	20	pSM	0/22	260
3	Moderately differentiated tubular adenocarcinoma	40	pSS	0/10	225
4	Crohn's disease	–	–	–	600

treat four patients with colorectal disease. Three of them had colon cancer: cancer of the ascending colon in one, and cancer of the sigmoid colon in two. The remaining patient had Crohn's disease with ileocecal stricture. Both patients with sigmoid colon cancer had a history of laparotomy for other cancerous lesions.

Surgical technique

The patient was placed in the modified lithotomy position. A 4-cm incision was made in the umbilicus, and the rectus abdominis fascia was fully exposed. It was easy to access the abdominal cavity by the open laparotomy approach because there was not the rectus abdominis fascia and the peritoneum was easily recognized around the umbilicus region. First, a 5-mm port was inserted under direct vision. When a left-sided colectomy was planned, a second 5-mm port was inserted in the left flank, whereas when a right-sided colectomy was planned, the second 5-mm port was inserted in the right flank. Two additional 5-mm ports were then inserted beside the first port through the single incision under laparoscopic guidance (Figure 1a and b). Thus, SILSOID colectomy was performed by using a total of four ports.

The pedicle of the mesenteric artery was retracted with forceps inserted through the flank, and the colon was fully mobilized by the medial approach (Figure 1c and d). These procedures were performed by parallel technique using conventional rigid forceps. The incision in the rectus abdominis fascia was extended and a lap protector mini (Hakko Medical, Tokyo, Japan) was applied to avoid wound infection and seeding of cancer cells. The affected colon was pulled out and divided extracorporeally. The anastomosis was performed extracorporeally by a functional end-to-end technique using a linear stapler. Finally, a 19-Fr Blake drain was inserted through the port in the flank.

Results

SILSOID colectomy was successfully completed in all four patients without any unanticipated extension of the umbilical skin incision or conversion to open or conventional laparoscopic surgery. The details regarding each patient are shown in Table 1. Median operation time was 220 min (range, 179–320 min), and median blood loss was negligible (range, neglibible–285 mL). In three patients with cancer, the median number of harvested lymph nodes was 18 (10–22), and median length of resected bowel was 242.5 (115–600) mm. One patient developed a postoperative wound infection, but there were no other postoperative complications. Clear liquids were allowed on postoperative day (POD) 2, and a diet was resumed on POD 3. All patients were discharged after an uneventful postoperative course and median hospital stay was 9.5 (7–14) days. The patients' wounds were more cosmetic than those of the conventional LC (Figure 2).

Discussion

More than 18 years have passed since Jacobs *et al.* first reported LC in 1991 (8). Today, LC has become the mainstay of operative procedures in colorectal surgery. In

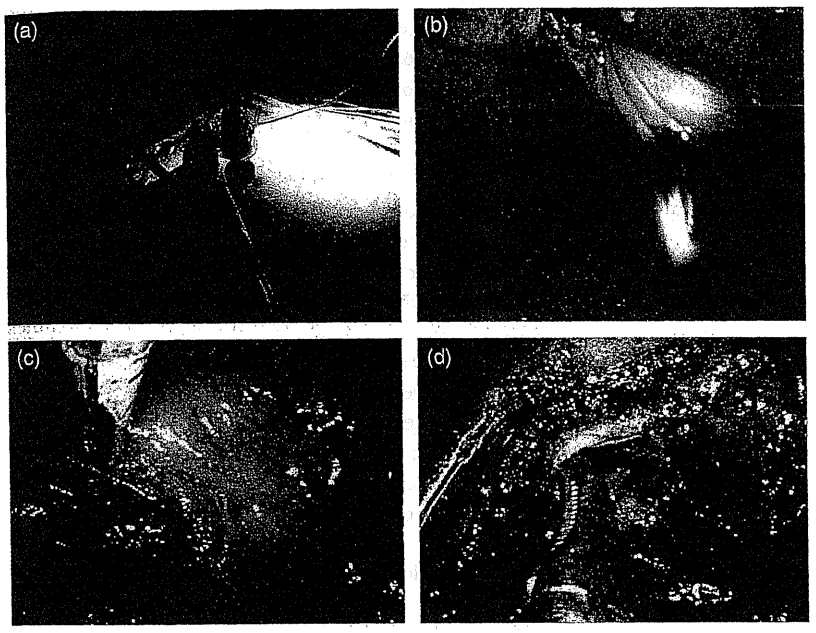

Figure 1 (a) Placement of the three ports on the umbilical incision. (b) Insertion of second umbilical port under laparoscopic guidance. (c) Ileocolic vein. (d) The exteriorized branch of the inferior mesenteric artery.

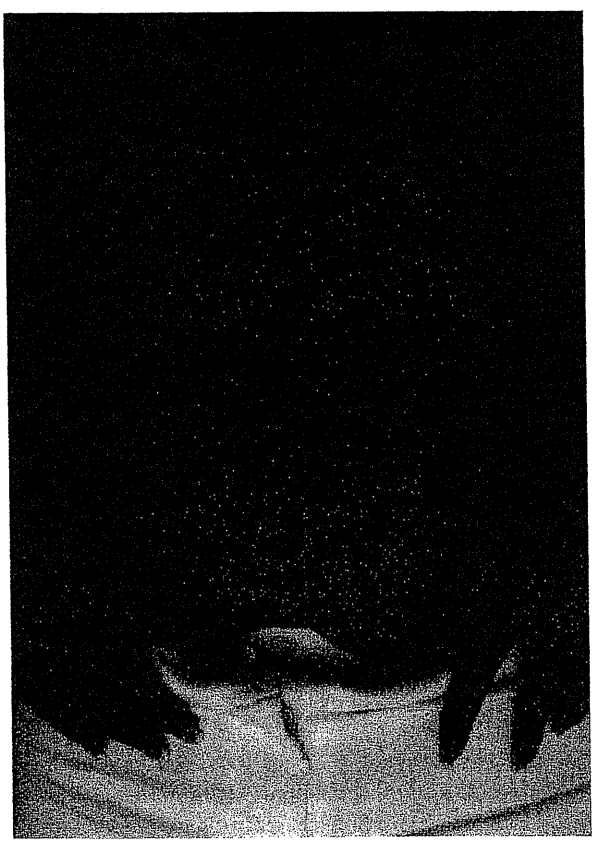

Figure 2 View of the postoperative scar 6 weeks after surgery (Patient 4).

an attempt to reduce the number and size of the ports used for laparoscopic surgery, SILS and NOTES have recently been devised as new laparoscopic procedures for cholecystectomy and appendicectomy (6,7). However, there have been few reports of application of these advanced approaches to gastric or colorectal surgery (9–11). In this article we have reported finding that SILSOID colectomy was safe and feasible. Moreover, the additional techniques or training required for SILS, NOTES and robotic surgery might not be needed. Also, SILSOID colectomy can be performed using standard operating room equipment with a few modifications. Thus, SILSOID colectomy is a more reasonable and economical alternative to conventional LC than SILS or NOTES is.

SILSOID colectomy may have some advantages in terms of rapid postoperative recovery and less postoperative morbidity because it involves less parietal trauma and a lower risk of morbidity associated with insertion of ports (i.e., port-orifice infection, hemorrhage, incisional hernia) (12). An assessment of the impact of SILSOID colectomy on quality of life is warranted, because the benefits of this procedure were not evaluated in our patients.

Pure SILS is likely to be restricted in the movement of a forceps because of the conflict against the laparoscope. However, since the length of the incision for SILSOID colectomy is about 4 cm, and the distance between the three ports is greater than in pure SILS, there was little restriction of forceps movement. In our cases, SILSOID colectomy could be completed without special training of cross-technique, which was an un-physiological technique often required in pure SILS. Intraoperative bowel injury was not experienced and surgical outcomes, including number of harvested lymph nodes and length

of resected bowel, were also acceptable, suggesting that SILSOID is feasible. Thus, SILSOID colectomy seemed to be very useful and an important step toward expanding the potential indications for SILS.

Despite some modifications of the SILSOID colectomy technique, it required a longer operative time because of some limitations in surgical techniques and instruments. This procedure does not avoid the confliction of forceps and laparoscope, and requires specialized skill in laparoscopic surgery and patience to overcome some difficulties. Because SILS has been adapted to abdominal surgery recently, a useful training system has not been established, and the development of new surgical instruments has been progressing. Although our study demonstrated that SILSOID colectomy was feasible, this procedure should be performed by experts due to these problems.

In conclusion, in our experience, SILSOID colectomy is a safe and feasible procedure that can be performed with conventional and clinically available instrumentation. Although further assessment is needed, this procedure shows promise of becoming an alternative to conventional LC and pure SILS colectomy.

Acknowledgment

There was no conflict of interest in this study.

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Evaluation of factors affecting the difficulty of laparoscopic anterior resection for rectal cancer: "narrow pelvis" is not a contraindication

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Abstract
Background This study aims to evaluate the clinical and anatomical factors, particularly pelvic dimensions that influence the difficulty of performing laparoscopic anterior resection for rectal cancer.
Methods We studied 50 consecutive patients who underwent laparoscopic anterior resection with double-stapling technique (DST) anastomosis for rectal cancer between January 2006 and February 2010. Staging was performed by computed tomography. Five pelvic dimensions (anteroposterior and transverse diameters of pelvic inlet and outlet, and pelvic depth) were measured using three-dimensional volume-rendering images. We also examined a number of other clinical characteristics, including gender, history of laparotomy, body mass index (BMI), operator, tumor location, tumor depth, nodal involvement, and tumor diameter. Univariate and multivariate analyses were performed to determine the predictive significance of these variables on surgical difficulty based on operative time and intraoperative blood loss.
Results Males had significantly shorter pelvic inlets and outlets and significantly greater pelvic depth than females. However, gender did not significantly affect surgical outcomes, although males did tend to experience greater blood loss. Maximum tumor diameter ($p = 0.014$), BMI ($p = 0.001$), operator ($p < 0.001$), and tumor location ($p = 0.009$) were independent predictors of operative time, which, in turn, was related to intraoperative blood loss ($p < 0.001$).
Conclusions Maximum tumor diameter, BMI, operator experience, and tumor location can be used to predict the operative time required to complete laparoscopic anterior resection with DST anastomosis for rectal cancer, with no correlations between pelvic dimensions and operative time. The difficulty of the procedure was not related to patients' pelvic dimensions, which led us to conclude that "narrow pelvis" is not a contraindication for this surgery. Based on these results, we suggest that laparoscopic anterior resection should be performed by experienced surgeons in patients with large tumors, high BMI, and/or extraperitoneal rectal cancer.

Keywords Laparoscopic anterior resection · Rectal cancer · Body mass index · Pelvic dimension · Narrow pelvis · Volume-rendering image

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Laparoscopic procedures for rectal cancer have been reported to be safe and effective for a number of reasons, including relatively low levels of pain and blood loss, early resumption of bowel movement, and short postoperative hospital stay [1–6]. Additionally, randomized studies have shown that laparoscopic total mesorectal excision (TME) and lymph node dissection are productive surgical techniques with survival and recurrence rates comparable to those of open procedures [4, 6–8]. However, while laparoscopic surgery is the standard treatment for colon cancer, it is not commonly performed in cases of rectal cancer because it is technically challenging and may be associated with disadvantages such as long

operative time [1, 2, 4] and increased rate of positive surgical margins [9].

Rectal surgery is performed through a narrow and funneling bony inlet, which makes access and visualization difficult in the deep pelvis. Even in the relatively simpler open approach, it is difficult to maintain a clear surgical field, to recognize precise anatomy, and to accurately perform rectal mobilization and excision while preserving urogenital functions. Recent studies have suggested that the quality of open rectal surgery is influenced not only by the surgeon's skill but also by the patient's clinical and anatomical factors, such as gender, tumor height, and pelvic size [10–12]. Similar relationships possibly influence the outcomes when using the laparoscopic approach, but evaluation of the influence of such clinical and anatomical factors on laparoscopic rectal surgery has been limited [13, 14]. The purpose of this study is to evaluate the influence of various clinical and anatomical factors, particularly pelvic dimensions, on operative time and intraoperative blood loss, which were selected as dependent variables to represent the level of difficulty in performing laparoscopic anterior resection with double-stapling technique (DST) anastomosis for rectal cancer.

Patients and methods

Patients

We studied 50 consecutive patients who underwent laparoscopic anterior resection with DST anastomosis for rectal cancer located below the inferior edge of the S2 vertebra between January 2006 and February 2010.

The indications for laparoscopic surgery were rectal cancer without involvement of the lateral lymph nodes or invasion of the adjacent organs, as determined by computed tomography (CT) and pelvic magnetic resonance imaging (MRI) during preoperative examinations. An additional indication was evidence of metastatic disease that could not be curatively resected using open surgery.

In Japan, preoperative radiotherapy or chemotherapy is not routinely administered in the treatment of rectal cancer; it is currently being used in clinical trials or mainly in patients with locally advanced, very low tumors to increase the chance of sphincter-preserving surgery. In this study, no patients underwent preoperative radiotherapy or chemotherapy.

Data for age, gender, history of laparotomy, body mass index (BMI), tumor location, tumor size, tumor staging, operative time, amount of blood loss, conversion to open surgery, pathology, 30-day morbidity, and mortality were collected prospectively. Tumors were staged according to the sixth tumor–node–metastasis (TNM) classification of the International Union against Cancer (UICC) on the basis of the histological findings of the surgical specimens.

Surgical procedures

The surgeries were performed by an experienced expert surgeon (T.Y.) or by trainees with 3–6 years of experience, operating under the expert's supervision.

Anterior resection is used for the treatment of early cancer located just above the dentate line and advanced cancer located >1 cm above the dentate line; these criteria enable the acquisition of adequate distal margin after rectal transection. Here, patients were placed in Lloyd–Davis position with the head and right side of the bed lowered. First, a 12-mm camera port was inserted below the umbilicus using the open method. After creation of a pneumoperitoneum, four working ports were inserted: a 5-mm port in the right and left upper abdominal quadrants each, and a 12-mm port in the right and left lower abdominal quadrants each. The mesocolon was mobilized using the mediolateral approach, and the inferior mesenteric artery was divided near its origin in order to achieve wide lymphadenectomy. This permitted TME, except in cases of intraperitoneal rectal cancer, where tumor-specific mesorectal excision (TSME) was performed instead. The rectum was transected intracorporeally using an Endo-Cutter (Ethicon Endo-Surgery, Cincinnati, OH, USA) and anastomosed with DST. No diverting stoma was created.

Pelvimetry

All patients underwent abdominopelvic CT (Aquilion 16; Toshiba Medical Systems Corporation, Tochigi, Japan). In most cases, the slice interval was adjusted to 5 mm. Sequences were volume-rendered using a DICOM 3D viewer, INTAGE Realia (KGT Inc., Tokyo, Japan). Volume-rendering (VR) images were obtained from the extracted volume data using INTAGE Volume Player (KGT Inc., Tokyo, Japan). A single observer (S.O.) blinded to all clinical information regarding the patients made all measurements in the VR images. Five pelvic dimensions were measured: anteroposterior and transverse diameters in the pelvic inlet (the axis from the superior aspect of the pubis symphysis to the sacral promontory and the longest lateral axis in the iliopectineal line), anteroposterior and transverse diameters in the pelvic outlet (the axis from the inferior aspect of the pubis symphysis to the tip of the coccyx and the distance between the tips of the ischial spines, i.e., interspinous distance), and the pelvic depth (the distance between the sacral promontory to the tip of the coccyx) (Fig. 1).

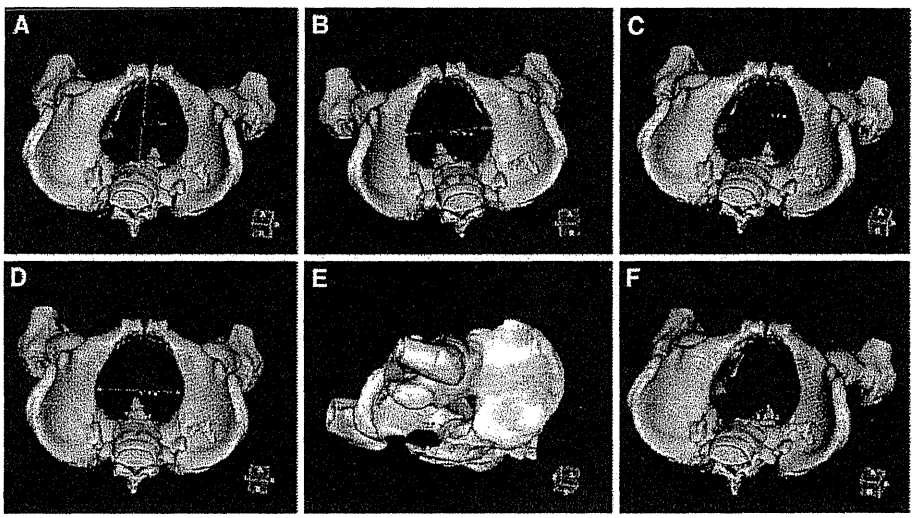

Fig. 1 Anteroposterior (**A**) and transverse (**B**) diameters in the pelvic inlet, anteroposterior (**C**) and transverse (**D**, **E**) diameters in the pelvic outlet, and length of pelvic depth (**F**) were measured using three-dimensional VR images

Statistical analysis

The sample size was calculated to detect moderate correlation (correlation coefficient: $|r| = 0.4$) with α of 0.05 (two-sided) and β of 0.2 (power of 80%), suggesting a total study population of 47 patients. All statistical analyses were performed using SPSS version 15.0 (Statistical Package for Social Sciences™; SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$. Where appropriate, we used Fisher's exact test, chi-square test, Student's t test, Welch's test, or Pearson's product-moment correlation coefficient to investigate relationships between patients' clinical and anatomical characteristics and surgical difficulties. Multivariate analysis was performed using a multiple linear regression model with a stepwise method (significance level to enter = 0.05; significance level to stay = 0.1).

To assess intraobserver variation, measurements of the pelvic dimensions of 10 patients were repeated after an interval of 4 weeks, with the observer blinded to the initial results [10, 14]. According to the Pearson's product-moment correlation coefficient, the intraobserver variation was 0.946. The two sets of measurements were highly correlated ($p < 0.001$), indicating that they accurately described pelvic anatomy.

Results

Patient and tumor characteristics are summarized in Table 1. Anastomosis height was significantly greater in males than in females ($p = 0.014$). All five pelvic dimensions differed significantly between male and female patients. Females had significantly longer measurements for the pelvic inlet and outlet (all $p < 0.003$), while males had significantly greater pelvic depth ($p < 0.001$). Overall, this indicated that male pelvises were significantly narrower and deeper than female pelvises.

Although males tended to experience more blood loss during surgery ($p = 0.11$), there were no significant differences between the genders in surgical outcomes (Table 2). In no case was there conversion to open surgery, death or positive circumferential resection margins (CRM). Complications were identified in two male patients: one wound infection and one anastomotic leakage. The overall morbidity rate was 4%, and the anastomotic leakage rate was 2%.

Univariate analysis showed that age ($p = 0.012$), BMI ($p = 0.009$), operator ($p = 0.006$), and maximum tumor diameter ($p = 0.003$) were significantly associated with operative time (Table 3). Although operative time tended to increase as anteroposterior pelvic inlet diameter decreased ($p = 0.151$) and pelvic depth increased ($p = 0.103$), these relationships were not significant.

Stepwise linear regression analysis showed that the optimal model for predicting operative time included maximum tumor diameter, BMI, operator, and tumor location ($p < 0.001$, Table 4). Operative time increased as maximum tumor diameter and BMI increased, but decreased with an expert performing the operation and for intraperitoneal tumor location. Operative time, in turn, was the only factor significantly associated with blood loss ($p < 0.001$); no other variables had any relationship with blood loss.

Discussion

In this study, multivariate analysis showed that larger maximum tumor diameter, higher BMI, trainee performing

Table 1 Patients' clinical and anatomical characteristics

	Male ($n = 30$)	Female ($n = 20$)	p Value
Age (years)	66 (60, 79)	70 (58, 75)	0.93
Previous laparotomy (no.)	9	9	0.43
BMI (kg/m^2)	21.5 (18.7, 22.6)	21.4 (18.0, 23.4)	0.87
Operator			0.82
Expert (no.)	17	12	
Trainee (no.)	13	8	
Tumor location of lower edge			0.20
Intraperitoneal (no.)	19	9	
Extraperitoneal (no.)	11	11	
Tumor depth			0.81
Tis/T1/T2 (no.)	19	12	
T3/T4 (no.)	11	8	
Nodal involvement			0.75
N0 (no.)	22	13	
N1/N2 (no.)	8	7	
Maximum tumor diameter (cm)	4.0 (1.8, 5.2)	3.3 (2.0, 4.1)	0.38
Procedure			0.72
High anterior resection (no.)	2	1	
Low anterior resection (no.)	28	19	
Anastomosis height from anal verge (cm)	6.0 (4.0, 6.8)	4.0 (4.0, 5.0)	**0.014**
Pelvic dimensions			
Inlet			
Anteroposterior (cm)	11.0 (10.3, 11.8)	11.9 (11.5, 12.7)	**<0.001**
Transverse (cm)	12.3 (11.9, 12.7)	12.9 (12.4, 13.3)	**0.002**
Outlet			
Anteroposterior (cm)	10.0 (9.4, 10.3)	10.6 (10.1, 11.4)	**0.003**
Transverse (cm)	9.7 (9.1, 10.0)	11.1 (10.7, 11.9)	**<0.001**
Depth (cm)	12.4 (11.4, 12.7)	11.2 (10.0, 11.8)	**<0.001**

All continuous variables are described as median (first quartile, third quartile)

Bold font in table means that the p-values were statistically significant

Table 2 Surgical outcomes in relation to gender

	Male ($n = 30$)	Female ($n = 20$)	p Value
Operative time (min)	305 (271, 325)	277 (254, 333)	0.26
Blood loss (ml)	25 (8, 58)	5 (0, 23)	0.11
Complication (no.)	2	0	0.66
Anastomotic leakage (no.)	1	0	0.84
Conversion (no.)	0	0	na
Mortality (no.)	0	0	na
Positive CRM (no.)	0	0	na

CRM circumferential resection margin

the operation, and extraperitoneal tumor location were significantly associated with longer operative time in laparoscopic anterior resection with DST anastomosis for rectal cancer, while pelvic dimensions had no correlations with operative time. Furthermore, operative time was the only factor significantly associated with intraoperative blood loss. The present findings are valuable in suggesting that pelvic dimensions were not definitive factors as compared with maximum tumor diameter, BMI, operator experience, and tumor location in predicting the difficulty of performing this procedure.

Interest in pelvimetry began with attempts to predict cephalopelvic disproportion in pregnant women prior to labor. Pelvimetry has been utilized for patients with rectal cancer, using MRI [10–12] and CT [13, 14] images; in these cases, measurements were made on two-dimensional reconstructed (axial and sagittal) images. However, these cross-sectional images only permit measurement of distances between points that exist in the same orthogonal coordinate axis. We preferred the use of three-dimensional VR images, because they allow precise measurements along any axis and can be especially beneficial in cases with anatomically strained pelvis or mismatched alignments between patients and imaging devices. The precision and sensitivity of this technique were demonstrated by its ability to correctly indicate that male pelvises are narrower and deeper than female pelvises, as well as by the strong correlation between the two sets of

Table 3 Correlations between operative time and operative parameters

Variable	*p* Value
Gender (male versus female)	0.131
Age	**0.012**
Previous laparotomy	0.430
BMI	**0.009**
Operator (expert vs. trainee)	**0.006**
Tumor location (intraperitoneal versus extraperitoneal)	0.338
Tumor depth (Tis/T1/T2 vs. T3/T4)	0.247
Nodal involvement (N0 vs. N1/N2)	0.471
Maximum tumor diameter	**0.003**
Anastomosis height from anal verge	0.338
Pelvic dimensions	
Inlet	
Anteroposterior	0.151
Transverse	0.250
Outlet	
Anteroposterior	0.481
Transverse	0.324
Depth	0.103

Bold font in table means that the *p*-values were statistically significant

4 Variables included in the final stepwise linear regression model explaining variations in operative time

	B	*β*	*p* Value
Intercept	190.871		<0.001
Maximum tumor diameter (cm)	8.075	0.289	0.014
BMI (kg/m^2)	6.828	0.382	0.001
Operator (expert)	–66.755	–0.576	<0.001
Tumor location (intraperitoneal)	–42.945	–0.373	0.009
$R^2 = 0.463$			
Model utility test: $p < 0.001$			

measurements in the intraobserver variation test ($r = 0.946$, $p < 0.001$).

In this study, we chose to evaluate cases of rectal cancer that underwent laparoscopic anterior resection with DST anastomosis, because intracorporeal rectal transection and anastomosis is one of the most difficult procedures in laparoscopic rectal surgery and therefore should be considered separately from cases that undergo abdominoperineal resection or intersphincteric resection with transanal hand-sewn anastomosis. We selected operative time and intraoperative blood loss as dependent variables representing technical difficulties during this procedure. Other variables, including complications, anastomotic leakage, conversion, mortality, and positive CRM, occurred at such low rates that they could not be analyzed. This indicates that the procedure can be performed safely and without morbidity or conferring any oncologic disadvantage.

It is not immediately clear why anastomosis height was significantly greater in males than in females. Unlike previous authors [13, 15], we did not find that operative outcome differed significantly between the two genders. These results may partly be explained by the fact that pelvic procedures can be completed more easily in wider and shallower female pelvises, but may also be disrupted by the presence of the uterus.

Patients in this study had BMI ranging from 12.0 to 27.8 kg/m^2; these values are lower than those in Western populations. Nevertheless, our results agreed with previous reports that found a positive association between operative time and BMI [14]. This is likely associated with greater mesorectal volume, which restricts the pelvic working space for the procedures. Therefore, visceral fat may be an even better predictor of surgical difficulty than BMI [16, 17]. Further, larger maximum tumor diameter reflects larger tumor volume, which again restricts the pelvic working space. Space can also be restricted by the location of tumors; i.e., when tumors are positioned extraperitoneally, surgeons have a narrower space in which to perform rectal dissection, transection, and anastomosis, since the pelvic width becomes narrower as one approaches deeper into the pelvis. Thus, cumulatively, higher BMI, larger maximum tumor diameter, and extraperitoneal tumor location impact operative time by limiting pelvic free space for the procedures and reducing visibility, maximum retraction, and access to the depths of the pelvis via the pelvic inlet.

In keeping with our previous finding, operative time was longer when procedures were performed by trainees [18]. Pelvic space cannot be expanded by pneumoperitoneum, as can be done in the upper abdomen, and limited working space directly affects the difficulty of safe and quick access, required to optimize visibility and retraction. We presume that these issues do not present as great a problem to expert surgeons because they have more experience in creating an appropriate surgical field and obtaining a good view for identifying and dissecting anatomical structures even in a limited pelvic working space.

Although pelvic depth tended to correlate with operative time, we did not find any significant patterns linking pelvic dimensions with operative outcomes. These results are contrary to those previously reported elsewhere [13, 14]. We hypothesize that this is because BMI, maximum tumor diameter, and tumor location have greater effect on pelvic working space than do pelvic dimensions. Additionally, this study included cases of both intraperitoneal and extraperitoneal rectal cancer, while a similar previous study focused only on extraperitoneal rectal cancer [14]. Furthermore, the procedures in our study were performed by both experts and trainees, rather than experts only [14].

Thus, these differences in inclusion criteria may explain why we did not detect any significant correlations between pelvic dimensions and operative time.

Our study has certain limitations. The sample size of this study was small, although the study was not statistically underpowered. However, future examinations with larger sample size would elucidate our results further. Additionally, other variables, including complications, anastomotic leakage, conversion, mortality, and positive CRM, should be examined to generalize the present findings.

In summary, our results indicate that "narrow pelvis" is not a contraindication for laparoscopic resection of rectal cancer. We also recommend that this procedure be performed by experienced surgeons in patients with large tumors, high BMI, and/or extraperitoneal rectal cancer.

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ORIGINAL ARTICLE – COLORECTAL CANCER

Effects of Intraperitoneal Chemotherapy with Mitomycin C on the Prevention of Peritoneal Recurrence in Colorectal Cancer Patients with Positive Peritoneal Lavage Cytology Findings

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ABSTRACT

Background. The detection of intraperitoneal free cancer cells in colorectal cancer (CRC) patients is associated with a poorer prognosis. The aim of this study was to investigate the effects of intraperitoneal chemotherapy (IPC) with mitomycin C (MMC) on preventing peritoneal recurrence in CRC patients with positive peritoneal lavage cytology findings.

Methods. A total of 52 CRC patients who had no clinically confirmed peritoneal dissemination and whose status of peritoneal lavage cytology was positive were investigated. Conventional peritoneal lavage cytology was performed. Overall, 31 of the 52 patients (59.6%) were administered IPC with MMC. Before closure of the abdomen, 4 silicon catheters were inserted into peritoneal cavity. After closure, the perfusate (diluting 20 mg MMC with 500 ml saline) was instilled from the catheter, and all catheters were clumped. All catheters were opened 1 h later.

Results. The mean follow-up period was 83.1 months. According to univariate analyses of all 52 patients and the subgroup of 36 patients with stage II or III tumors, patients with IPC had a significantly better peritoneal recurrence-free survival and cancer-specific survival than patients who did not receive IPC ($P < 0.005$). In multivariate analysis, IPC remained an independent prognostic factor for peritoneal recurrence-free survival in all patients.

Conclusions. It appears that IPC with MMC is an effective treatment to prevent peritoneal recurrence and prolong the cancer-specific survival in CRC patients without peritoneal dissemination, but who have positive peritoneal lavage cytology. It is necessary to verify the effectiveness of IPC with MMC in a prospective trial.

The prognosis of colorectal cancer (CRC) depends on local tumor growth, lymph node involvement, and the presence of peritoneal or distant metastasis.[1] Complete removal of the tumor is the most effective treatment for CRC. However, metastases after curative resections are often unavoidable, and it is well known that the most common sites of recurrence are the liver, lung, and local.[2] For liver or lung metastases, hepatectomy or pulmonary resection have been aggressively used.[3,4] For local recurrence, aggressive surgical resection may be beneficial.[5,6] Peritoneal recurrence is less common than recurrence to other sites and therefore is prognostically less important than other sites of recurrence.[7] The detection of intraperitoneal-free cancer cells is associated with a higher recurrence rate and poorer prognosis.[8–12] Free malignant cells, which are present within the peritoneal cavity in CRC patients before surgery, may indicate early peritoneal seeding. The detection of these cells intraoperatively, through peritoneal lavage cytology, leads to identification of patients who are more likely to develop peritoneal carcinomatosis. Positive peritoneal lavage cytology in CRC patients also contributes to the identification of those who need more frequent postoperative follow-up and possibly adjuvant chemotherapy.[8,9,12]

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Peritoneal dissemination of CRC results in considerable morbidity and eventual mortality as it leads to intractable ascites, intestinal obstruction, and further tumor proliferation. Peritoneal dissemination, therefore, is a sign of the terminal stage of the disease, and most of the patients with peritoneal metastases have a very poor prognosis.[13] Surgery is usually impractical for peritoneal recurrence because of the multiplicity and microscopic size of the lesions. Thus, it is important to establish an effective prophylactic treatment for peritoneal recurrence in CRC patients. Systemic chemotherapy is inefficient because cytotoxic agents do not penetrate into the peritoneal cavity at a high enough concentration to effectively eliminate microscopic residual disease.[14] Intraperitoneal chemotherapy (IPC), has the benefit of delivering higher concentrations of cytotoxic drug locally to the site of the tumor, while minimizing systemic toxicity compared with intravenous chemotherapy. The primary use of mitomycin C (MMC) has been for the treatment of gastrointestinal carcinomas including CRC, either as a single agent or in combination with other chemotherapeutic agents. In gastric cancer, IPC with MMC prevents the peritoneal recurrence and improves the overall survival of patients.[15–17] IPC has also been used for CRC patients as an adjuvant treatment or as treatment for advanced disease.[18–20] However, the efficacy of the significance of using IPC with MMC on patient response and survival is still unclear.

The aim of this study was to investigate the significance of IPC with MMC for CRC patients with positive peritoneal lavage cytology findings. This study is a retrospective study, not a randomized-controlled trial.

PATIENTS AND METHODS

Patients

From January 1985 through December 2006, intraoperative peritoneal lavage cytology was performed in 1677 patients who underwent a resection for CRC. A total of 52 patients (3.1%) who had no clinically evident peritoneal dissemination and whose status of peritoneal lavage cytology was positive were investigated in the present study. There were 16 patients with stage IV cancer enrolled in this study. The sites of distant metastases were the liver in 13 patients, para-aortic lymph nodes in 2 patients, and lung in 1 patient. Adjuvant chemotherapy was administered to 42 patients (28 with stage II and III disease and 14 with stage IV). Also, 36 patients took oral chemotherapy with 5-fluorouracil (5-FU) derivatives, and 6 patients received intravenous chemotherapy with 5-FU and leucovorin. They did not receive combination chemotherapy such as FOLFOX or FOLFIRI. To confirm the presence or absence of distant metastases, the cancer was preoperatively staged in all patients with abdominal plus pelvic computed tomography (CT) and chest CT. The tumors were classified according to the UICC TNM system.[21]

Peritoneal Lavage Cytology

Peritoneal lavage cytology was performed using the conventional method, as described previously.[12] Briefly, peritoneal lavage cytology was performed immediately after the laparotomy before the manipulation of the tumor. Intraoperatively, 100 ml of physiological saline solution (37°C) was instilled into the Douglas cavity. The collected lavage fluid was immediately heparinized and centrifuged at 2000 rpm for 3 minutes, and the sediment was smeared on 4 glass slides. The slides were stained by the Giemsa and Papanicolaou methods and evaluated by 2 experienced cytologists who were blinded to the clinical information. A slide was classified as positive if at least 1 cancer cell was detected. A suspicion of malignancy was classified as negative.

Intraperitoneal Chemotherapy with MMC

Before closure of the abdomen, silicon catheters (typically 4) were inserted through the abdominal wall into the peritoneal cavity. The tips of the catheters were positioned bilaterally at the upper and lower abdomen. After closure of the abdomen, the perfusate (diluting 20 mg MMC with 500 ml saline (37°C)) was instilled into the abdomen from the catheter positioned in the lower abdomen, and all catheters were clamped. We did not take action particularly to promote the distribution of this drug. All catheters were opened 1 h later. In addition, there was no active attempt to remove the chemotherapy perfusate. IPC with MMC was not randomized. The surgeon performed the IPC based on the general status of patients or the degree of surgical invasiveness.

Patient Follow-up

Follow-up for recurrence included the following procedures and tests: a physical examination, serum tumor markers, hepatic imaging (ultrasound, CT, or both), abdominal plus pelvic CT, and chest x-ray or CT every 4–6 months for the first 3 years and every 6 months for the next 2 years; colonoscopy every 1–2 years. Peritoneal recurrence was defined as radiologic or histocytologic evidence of cancer recurrence in the abdominal cavity. Liver metastasis, intra-abdominal lymph node metastasis, and local recurrence, defined as radiologic or histocytologic evidence of cancer recurrence, were excluded.

Statistical Analysis

A statistical analysis was performed using the StatView version 5.0 software package (Abacus Concepts, Berkeley, CA). Associations between the clinicopathologic parameters were assessed using the chi-square test or the Fisher exact test for discrete variables. The *t* test was performed for continuous variables. Peritoneal recurrence-free survival curves and cancer-specific survival curves were estimated using the Kaplan-Meier technique and were compared using the log-rank test. For cancer-specific survival, only cancer-related deaths were considered; data on patients who had died from other causes or who were still alive at the end of the study were censored. A Cox proportional hazards model was used to assess risk (expressed as hazard ratio [HR]) under simultaneous contributions from several covariates. *P* values of <0.05 were considered statistically significant.

RESULTS

Postoperative Mortality and Morbidity

None of the patients died postoperatively, nor were any deaths related to the use of IPC with MMC. Grade 3–4 complications for surgery did not occur in any of the patients. Only 1 patient (1.9%) had an IPC-related event, which was grade 3 skin ulceration at the drain insertion site. Other grade 3–4 complications for IPC related did not occur.

Relationship Between Intraperitoneal Chemotherapy and Clinicopathologic Factors

The mean follow-up period was 83.1 months (range, 16–189 months). Overall, 31 of the 52 patients (59.6%) were administered IPC with MMC. In Table 1, comparison of the CRC patients shows no significant differences between the 2 groups regarding age, gender, tumor size, tumor site, depth of invasion, regional lymph nodes, TNM stage, lymphatic invasion, or adjuvant chemotherapy. Positive peritoneal lavage cytology was found only in patients with T3 and T4 tumors. A significant correlation was found between IPC with MMC and the histologic grade or venous invasion ($P = 0.0138$ and 0.0361, respectively).

Univariate Analyses of Factors Affecting Peritoneal Recurrence-Free and Cancer-Specific Survival

IPC with MMC and various clinicopathologic factors were evaluated for their impact on prognosis in univariate analyses of the data from all 52 patients (Table 2). In univariate analysis, the histological grade and IPC were significantly associated with peritoneal recurrence-free survival ($P = 0.0257$ and 0.0003, respectively). The histological grade, depth of invasion, lymphatic invasion, venous invasion, distant metastasis, and IPC were significantly associated with cancer-specific survival ($P = 0.0152$, 0.0181, 0.0066, 0.0135, 0.0006, and 0.0001, respectively). However, adjuvant chemotherapy and regional lymph node status were not associated with peritoneal recurrence-free and cancer-specific survival.

Kaplan-Meier curves for peritoneal recurrence-free survival and cancer-specific survival in the 52 patients with

TABLE 1 Characteristics of the patients with colorectal cancer according to intraperitoneal chemotherapy with mitomycin C ($N = 52$)

	Intraperitoneal chemotherapy (+) ($N = 31$)	Intraperitoneal chemotherapy (−) ($N = 21$)	*P* value
Age (mean ± SD, years)	60.7 ± 9.6	60.7 ± 11.6	0.9926
Gender			
Male	13	12	0.2815
Female	18	9	
Tumor size (mean ± SD, cm)	5.2 ± 2.1	4.9 ± 1.7	0.6415
Tumor site			
Colon	18	14	0.5316
Rectum	13	7	
Histologic grade			
Well	13	2	0.0138
Others	18	19	
Depth of invasion			
T3	17	6	0.0613
T4	14	15	
Regional lymph nodes			
N (−)	7	1	0.1225
N (+)	24	20	
TNM stage			
II	5	1	0.1972
III	19	11	
IV	7	9	
Lymphatic invasion			
No	7	1	0.1225
Yes	24	20	
Venous invasion			
No	9	1	0.0361
Yes	22	20	
Adjuvant chemotherapy			
No	8	2	0.1739
Yes	23	19	

Well well-differentiated adenocarcinoma, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, mucinous adenocarcinoma, *SD* standard deviation

TABLE 2 Univariate analysis of the clinicopathologic factors for peritoneal recurrence-free and cancer-specific survival in all patients ($N = 52$).

	No. of patients ($N = 52$)	Peritoneal recurrence-free 5-year survival	*P* value	Cancer-specific 5-year survival	*P* value
Age (years)					
<60	22	70.9	0.5206	31.8	0.3292
≥60	30	73.6		38.6	
Gender					
Male	25	75.4	0.4920	37.3	0.5460
Female	27	69.5		34.1	
Tumor size (cm)					
<5	22	73.7	0.6214	35.0	0.6308
≥5	30	70.6		35.6	
Tumor site					
Colon	32	72.8	0.6258	30.9	0.3632
Rectum	20	70.6		43.6	
Histologic grade					
Well	15	92.9	0.0257	60.0	0.0152
Others	37	59.6		25.1	
Depth of invasion					
T3	23	80.1	0.4984	53.3	0.0181
T4	29	61.7		21.7	
Regional lymph nodes					
N (−)	8	83.3	0.6823	54.7	0.0969
N (+)	44	69.8		31.6	
Lymphatic invasion					
No	8	83.3	0.6823	85.7	0.0066
Yes	44	69.8		26.7	
Venous invasion					
No	10	90.0	0.1884	71.4	0.0135
Yes	42	66.3		28.4	
Distant metastasis					
No	36	71.7	0.8667	45.4	0.0006
Yes	16	80.8		7.7	
Adjuvant chemotherapy					
No	10	71.1	0.7399	45.1	0.2482
Yes	42	72.4		31.6	
Intraperitoneal chemotherapy					
No	21	40.1	0.0003	9.5	0.0001
Yes	31	88.0		54.3	

Well well-differentiated adenocarcinoma, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, mucinous adenocarcinoma

and without IPC are shown in Fig. 1a and b. The 5-year peritoneal recurrence-free survival rate was 88.0% in patients with IPC versus 40.1% in those without IPC (Fig. 1a). The 5-year cancer-specific survival rate was 54.3% versus 9.5% (Fig. 1b). A significant difference was found in both survival curves ($P = 0.0003$ and 0.0001, respectively).

In addition, separate univariate analyses of the clinical and pathologic factors were performed in patients with stage II or III tumors (Table 3). In this univariate analysis, histological grade and IPC were significantly associated with peritoneal recurrence-free survival ($P = 0.0258$ and 0.0047, respectively). The histological grade, depth of invasion, and IPC were significantly associated with cancer-specific survival ($P = 0.0045$, 0.0341, and 0.0037, respectively). Adjuvant chemotherapy and regional lymph nodes status were not associated with peritoneal recurrence-free or cancer-specific survival.

Figure 1c and d show the Kaplan-Meier curves in patients with stage II or III tumors ($N = 36$). In these patients, the 5-year peritoneal recurrence-free survival rate was 85.6% for patients with IPC versus 45.5% for those without IPC (Fig. 1c), and the cancer specific-survival rate was 67.5% versus 16.7% (Fig. 1d). A significant difference was found in both survival curves ($P = 0.0047$ and 0.0037, respectively).

Multivariate Analysis of Prognostic Factors

Multivariate Cox regression analyses of data from all patients demonstrated that only IPC was an independent risk factor for peritoneal recurrence-free survival [HR, 5.32-fold ($P = 0.0274$)] (Table 4). For cancer-specific survival, distant metastasis was an independent risk factor [HR, 5.24-fold ($P < 0.0001$)]. IPC was not a significant risk factor; however, it showed a tendency for patients to have a poorer survival [HR, 2.16-fold ($P = 0.0938$)]. Regional lymph nodes status was not significant risk factor for recurrence.

Patterns of Recurrence

The patterns of recurrence between the 2 groups in patients with stage II or III tumors were compared (with some overlap, Table 5). The overall peritoneal recurrence rate was 25.0% (9 of 36 patients). The overall peritoneal recurrence rate was 12.5% (3 of 24) in the IPC (+) group and 50.0% (6 of 12) in IPC (−) group. The incidence of peritoneal recurrence in the IPC (+) group was significantly lower than that of the IPC (−) group ($P = 0.0362$). As for the other recurrent sites, no significant difference was observed between the 2 groups.

DISCUSSION

Peritoneal carcinomatosis from CRC is generally considered a terminal stage. However, recently, aggressive

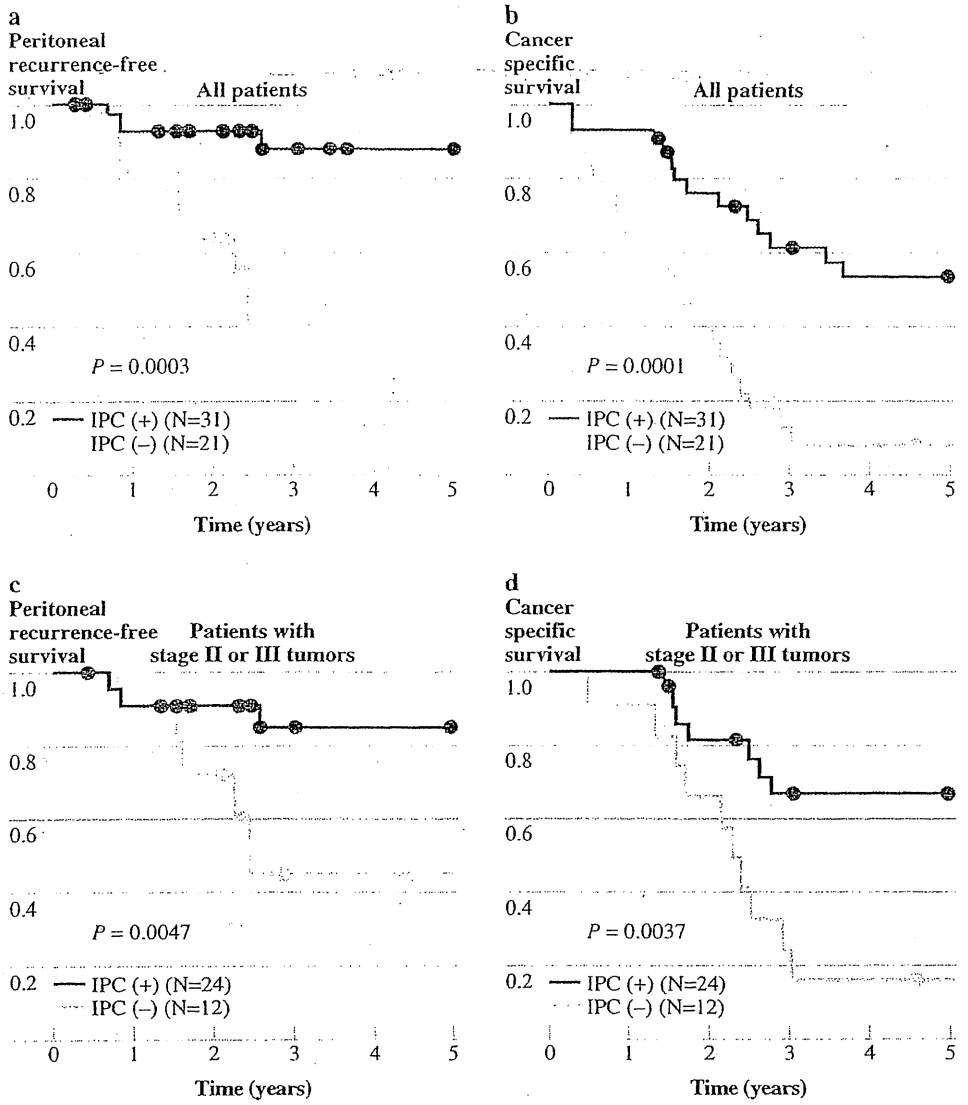

FIG. 1 Peritoneal recurrence-free survival curves (a) and (c) and cancer-specific survival curves (b) and (d) after intraperitoneal chemotherapy (IPC) with mitomycin C in all patients and patients with stage II or III tumors. A significant difference was found in both survival curves

approaches that combine cytoreductive surgery and perioperative IPC have provided good long-term survival in selected patients.[22–27] In a randomized trial of either the standard systemic chemotherapy (5-FU and leucovorin) or cytoreduction and hyperthermic IPC in patients with peritoneal carcinomatosis of CRC, the median disease-specific survival time was 12.6 months in the systemic chemotherapy group and 22.2 months in the group treated with cytoreduction followed by hyperthermic IPC and combined with adjuvant chemotherapy ($P = 0.028$).[24] A study by Elias et al. reported that the median survival time of patients with peritoneal carcinomatosis of CRC was 23.9 months in those who received systemic chemotherapy and 62.7 months in those who were treated by cytoreduction followed by hyperthermic IPC and systemic chemotherapy ($P < 0.05$).[26] The complete cytoreductive surgery was the most important prognostic factor. However, the toxicity of these aggressive therapies was relatively high. Postoperative mortality was 3.3–3.8%.[24,27] Grade 3–4 complications occurred in 31% of the patients, and the expertise of the center had a strong impact on prognosis.[27] Clearly, there is a significant learning curve, and this is not a procedure that can be undertaken occasionally.[28,29]

The major concerns regarding IPC are catheter malfunction or infection, peritonitis, and impaired anastomotic or abdominal wound healing. In a rat model, Hillan et al. demonstrated no difference between intraperitoneal (IP) saline and IP 5-FU administration with respect to anastomotic healing strength.[30] In our study, only 1 patient (1.9%) developed a grade 3 skin ulceration of the drain insertion site for IPC. This patient was treated by conservative therapy. Our IPC was therefore easy and safe.

Studies using conventional cytology to evaluate abdominal washing fluid specimens have found malignant