the prior report, 12 of the 75 patients who underwent second hepatectomy had received their first hepatectomy at other hospitals. In the present series, all the patients had undergone both first and second hepatectomies at our hospital. This means that we had full access to pathologic data from both procedures, ruling out any possibility that the first resection had been an incomplete one, and had not been performed at a specialized center such as ours. Okano et al.[27] reported that portal vein invasion, hepatic vein invasion, neural invasion, and absence of macroscopic bile duct invasion were prognostic factors for poor outcome in patients undergoing initial hepatectomy. Similarly, we found that histopathologic evidence of invasions of the portal vein or hepatic vein at the first hepatectomy were associated with poor prognosis in patients undergoing a second hepatectomy. To date, to our knowledge, no previous report has indicated that pathological findings other than surgical margin can be predictive of survival after second hepatectomy. It is therefore suggested that not only adequate hepatic resection but also detailed examination by a specialized pathologist is important for more precise selection of patients for second hepatectomy.

All three independent risk factors we found to be important can be recognized before the second hepatectomy, thus permitting a prognosis to be estimated before patients undergo a second hepatectomy. We grouped the patients according to their risk factors. Survival expectancies at 5 years for patients with no risk factors, with one or two, and with three risk factors were 62%, 31%, and 0%, respectively. Considering these results, second hepatectomy will most benefit patients with no risk factors. In addition, no further treatments are needed for those patients. Patients with one or two of these risk factors may require adjuvant therapy after a second hepatectomy to improve survival. There is not much evidence of the efficacy of chemotherapy after hepatectomy, even now. So far, no evidence of improved overall survival has been shown, but the tested regimens included only fluorouracil, floxuridine, and leucovorin, and did not include irinotecan or oxaliplatin.[28–30] A clinical trial comparing progression-free interval in patients undergoing surgical resection and/or ablation for hepatic metastases from colorectal cancer treated with adjuvant therapy comprising oxaliplatin and capecitabine versus without hepatic arterial infusion of floxuridine was conducted by National Surgical Adjuvant Breast and Bowel Project (NSABP-C09). This year, we are going to start a comparative trial to evaluate the efficacy of adjuvant chemotherapy with oxaliplatin added to the simplified bimonthly 5-FU and leucovorin regimen[31] as compared with surgery alone in patients undergoing curative hepatectomy. These results will permit us to determine the strategy to take with patient treatment after hepatectomy.

Generally, neoadjuvant chemotherapy for the patients with hepatic metastases is the strategy for initially unresectable tumors. Adam et al.[32] showed the results of neoadjuvant chemotherapy in 701 patients with initially unresectable colorectal liver metastases. Ninety-five cases (13.5%) were found to be resectable, and patients underwent a potentially curative resection with a 5-year survival rate of 35%. Tanaka et al.[33] studied neoadjuvant chemotherapy for 48 patients with five or more bilobar hepatic metastases. They found that 25 patients with neoadjuvant chemotherapy had a better 5-year survival rate than 23 patients who did not receive neoadjuvant chemotherapy (39 vs. 21%, $P = .039$). Multivariate analysis showed that neoadjuvant chemotherapy was an independent predictor of survival. Adam et al.[6] have adopted neoadjuvant chemotherapy for recurrent liver metastases before second hepatectomy, except in patients with small and solitary disease without concomitant extrahepatic disease.

Neoadjuvant chemotherapy before hepatectomy carries a risk of missing the opportunity for resection in patients whose tumors are initially resectable if tumor progression subsequently occurs during the course of chemotherapy. On the other hand, immediate resection carries a risk of missing occult metastases in the liver or at other sites. It was pointed out that the risk of missing the opportunity for resection could be avoided by frequent evaluation and the use of effective currently available chemotherapy regimens. Allen et al.,[34] in a study of neoadjuvant chemotherapy for patients with synchronous liver metastases, reported that none of those tumors became unresectable during the course of chemotherapy. Leonard et al.[35] commented that the role of neoadjuvant chemotherapy in patients with resectable liver metastases was not confirmed, and well-designed prospective trials were needed. One clinical trial was conducted to evaluate the feasibility and risks of the preoperative chemotherapy with oxaliplatin, 5-FU, and leucovorin and surgery for resectable colorectal liver metastases by the European Organization for Research and Treatment of Cancer.[36] The trial had been closed, and the interim results were that 93% of the patients receiving preoperative chemotherapy underwent surgery, and their surgery-related mortality and morbidity were low. The results on survival will be available in 2006. In our institution, the policy for liver metastases is immediate resection when the metastases are found to be resectable, even if they have recurred for the second or third time. For patients with no risk factors, or with one or two of these risk factors, immediate surgery without neoadjuvant chemotherapy is appropriate considering our results. Although we cannot deny that hepatectomy is the best and most potentially curative treatment for recurrent hepatic metastases, neoadjuvant chemotherapy followed by surgery is likely to be preferable for patients who have all three risk factors, to achieve better outcome.

Yamamoto et al.[15] showed that the presence of extrahepatic disease was independently associated with poor survival, but because our series included only three patients with concomitant extrahepatic metastases, we were unable to confirm this. All three patients had solitary lung metastasis; one underwent pulmonary resection concomitant with second hepatectomy, and the other two underwent the two procedures synchronously. The first two patients died after 7 and 19 months, respectively, and the third is alive, without recurrence, at 37 months. Thus, we think that the presence of pulmonary metastases does not contraindicate repeat hepatic resection if it is anticipated that surgical resection of lung disease will result in cure.

In conclusion, we have been able to identify three risk factors that predict poor survival in patients with recurrent liver metastases from colorectal cancer: (1) synchronous first hepatectomy, (2) four or more lesions present at the time of second hepatectomy, and (3) invasions of the portal vein or hepatic vein evident at the first hepatectomy. Second hepatectomy is beneficial for patients without any risk factors. Before second hepatectomy, we should consider the use of chemotherapy for patients with any of these risk factors—especially in patients with two or three factors—in the adjuvant or neoadjuvant setting to prolong survival. These results need to be confirmed and validated with another data set or by future prospective trials according to the scoring scheme we showed.

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Original Paper

Surgical Outcomes of Laparoscopic *vs.* Open Surgery for Rectal Carcinoma - A Matched Case-control Study

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ABSTRACT
Background/Aims: The present study evaluated the short- and middle-term surgical outcomes of laparoscopic surgery (LS) for rectal carcinoma in comparison with a case-control series of open surgery (OS).
Methodology: Between February 1998 and December 2004, 47 patients with rectal carcinoma underwent LS. These patients were compared with a conventional OS group matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.
Results: The median follow-up period for the LS group and the OS group was 25 and 49 months, respectively. In the LS group, median operative time was significantly longer but median blood loss was lower than those in the OS group. There was one requiring conversion to OS. Postoperative intervals until liquid and solid intakes, and hospital stay were significantly shorter in the LS group. Postoperative complications rates are similar and anastomotic leakage occurred in one patient in each group. In the LS group, the levels of white blood cell count on postoperative day 1 and C-reactive protein on postoperative days 1 and 2 were significantly lower than those in the OS group.
Conclusions: LS for rectal carcinoma provides benefits during the early postoperative period without increase in morbidity or mortality.

KEY WORDS:
Laparoscopic surgery; Laparoscopic anterior resection; Rectal carcinoma; Case-control study; Surgical outcome

ABBREVIATIONS:
Laparoscopic Surgery (LS); Open Surgery (OS); Intersphinctic Rectal Resection and Handsewn Coloanal Anastomosis (ISR-CAA); Abdominoperineal Resection (APR); Randomized Clinical Trial (RCT); White Blood Cell (WBC); C-Reactive Protein (CRP)

INTRODUCTION

Since the first report of laparoscopic colectomy in 1991 by Jacobs *et al.* (1), laparoscopic surgery has been tried and applied to a wide range of colorectal disease, including colorectal carcinoma. Recently many studies have demonstrated several advantages of laparoscopic surgery (LS) over conventional open surgery (OS), including reduced surgical blood loss, decreased postoperative pain and ileus, shorter hospital stay and favorable effects on immunologic status (2-5). With regard to long-term oncological safety, which is the most important concern for LS for malignancies, there have been no reports indicating that LS is inferior to conventional OS by randomized clinical trial (RCT) (6-8).

However, laparoscopic approach to rectal carcinoma is very difficult from a technical standpoint compared for that of colon carcinoma. Following laparoscopic anterior resection for rectal carcinoma, anastomotic leakage has been reported to occur in 7.2-20% (9-15), and as a result, some reports recommended routine covering ileostomy with this procedure even for patients who would not require ileostomy if they selected open anterior resection (9). In fact, many RCTs regarding laparoscopic resection for colorectal carcinoma have excluded patients with middle and lower rectal carcinoma (6-8). Due to the lack of comparative studies, it remains controversial as to whether LS for rectal carcinoma can be regarded minimally invasive surgery.

Since our first laparoscopic surgery for colonic carcinoma in 1993, about 400 patients have undergone laparoscopic resection for colorectal disease at our institution. Because the safety of LS in cancer patients remains to be established, candidates for radical surgery were patients preoperatively diagnosed with T1 or T2 disease. Additionally, LS cases also included patients who were preoperatively diagnosed with T3 but who preferred to undergo LS, as well as those with colon or upper rectal carcinoma for which palliative resection was considered necessary. In June 2001, we unified our surgical and postoperative management procedures, as a consequence, the complication rate and mean length of hospitalization have been reduced at our institution (16,17).

The aim of this study was to analyze the short-term and the middle-term surgical outcomes of LS for patients with rectal carcinoma and compare them with a matched group of patients who underwent similar conventional OS.

METHODOLOGY

Patients

Between February 1998 and December 2004, we

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TABLE 1 Patient Characteristics

		LS group	OS group	*P* value
No. of patients		47	47	
Sex ratio (male: female)		28: 19	28: 19	>0.999
Age (yr; mean and range)		60 (35-76)	60 (39-84)	0.551
Body mass index (kg/m^2, mean and range)		23.0 (17.3-32.4)	23.2 (18.1-33.8)	0.934
Prior abdominal surgery (%)		13 (27.7)	15 (31.9)	0.823
Location	Upper rectum	25	25	
	Middle rectum	10	10	
	Lower rectum	12	12	
Surgical procedure	Anterior resection	43	43	
	Abdominoperineal resection	1	1	
	Anterior resection with ISR-CAA	3	3	
	Covering ileostomy	11	9	
	Transverse-coloplasty pouch	4	4	
Year of surgery	1997-1999	1	16	
	2000-2002	20	21	
	2003-	26	10	
Pathological stage	UICC Stage 0	2	2	
	UICC Stage I	34	34	
	UICC Stage II	1	1	
	UICC Stage III	10	10	
Follow-up period (month)		24.6 (3.0-65.8)	49.2 (3.7-99.3)	<0.001

ISR-CAA: intersphincteric rectal resection and handsewn coloanal anastomosis.

TABLE 2 Intraoperative and Postoperative Results

	LS group	OS group	*P* valve
Operative time (min.)	255 (117-472)	150 (94-475)	<0.001
Blood loss (mL)	60 (5-477)	72 (10-945)	0.021
Conversion	1	-	-
Liquid intake (days)	1 (1-4)	4 (1-7)	<0.001
Solid intake (days)	3 (2-8)	5 (3-80)	<0.001
Hospital stay (days)	8 (7-23)	15 (10-101)	<0.001

Values are medians (range).

TABLE 3 Morbidities and Mortality

		LS group	OS group	*P* valve
Mortality		0	0	>0.999
Morbidity	Wound sepsis	3	3	>0.999
	Bowel obstruction	1	7	0.059
	Anastomotic leakage	1	1	>0.999
	Anastomotic bleeding	1	0	0.500
	Neurogenic bladder	0	1	0.500
	Pneumonia	1	0	0.500
	Pulmonary embolism	0	1	0.500
Total (No. of patients)		7 (14.9%)	12 (25.5%)	0.304

performed 47 curative laparoscopic resections for patients with rectal carcinoma. All patients were evaluated before surgery by clinical investigation including total colonoscopy, barium enema and computed tomography. To evaluate co-morbid conditions, cardiopulmonary function and renal function test were performed. We excluded the following groups of patients from LS: patients with tumors larger than 7cm, patients with a history of extensive adhesions, patients with intestinal obstruction, and patients with severe obesity (body mass index >32kg/m^2) and patients who did not consent to LS.

The analyzed parameters included age, gender, body mass index, prior abdominal surgery, operative time, blood loss, days until resumption of diet and length of postoperative hospital stay. Pathological staging was performed according to TNM classification. White blood cell (WBC) count and C-reactive protein (CRP) in serum were measured preoperatively and on postoperative day 1 routinely, and on postoperative day 2, if necessary.

Each laparoscopic case was compared with the control OS group of patients matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.

Laparoscopic Technique

Techniques for laparoscopic resection have previously been described (16,17). Initial port placement was performed using the open technique and pneumoperitoneum was induced using carbon dioxide. Two 5-mm ports were then inserted into the left lower mid-abdominal and the left lower quadrant regions, and two other 12-mm ports were inserted into the mid-lower and right mid-abdominal regions under laparoscopic guidance.

The left colon was initially mobilized laterally to medially until the left ureter and superior hypogastric nerve plexus were identified. The mobilization of splenic flexure was performed if necessary. Then, a window was made between the mesocolon containing the arch of the inferior mesenteric vessels and the superior hypogastric nerve plexus, starting at the bifurcation, with support from an assistant holding the sigmoid mesocolon ventrally under traction and to the left using a 5-mm bowel grasper through the left lower quadrant port. After the dissection proceeding to the origin of the inferior mesenteric artery, taking care not to injure the superior hypogastric nerve plexus and the roots of the sympathetic nerves, intracorporeal high ligation of the inferior mesenteric artery was performed. After cutting the inferior mesenteric vein and left colic artery, mobilization of the rectum and mesorectum was performed. The avascular plane between the intact mesorectum anteriorly, and the superior hypogastric nerve plexus, right and left hypogastric nerves, and Waldeyer's fascia posteriorly was entered by sharp dissection, and extended down to the level of the levator muscle for middle and lower rectal carcinomas, taking care to protect the pelvic nerves. For upper rectal lesions, mesorectal tissue extending down to 5cm below the tumor was excised routinely using ultrasonic shears (Laparoscopic Coagulating Shears, Ethicon Endo-Surgery Inc, Cincinnati, OH). Middle and lower rectal tumors were treated by total mesorectal excision. Immediately before rectal transection, laparoscopic rectal clamping was performed just above the anticipated point of rectal transection, using a bowel clamping device introduced through the 12-mm mid-lower port. Rectal washout was performed routinely using 1,000mL of a 5 percent povidone-iodine solution. Rectal transection was then performed by multiple firing technique, using Endo GIA Universal staples, introduced through the 12-mm right mid-abdominal port. A 4- to 5-cm incision was then made over the mid-lower 12-mm port site, and the bowel was exteriorized under wound protection and divided with appropriate proximal clearance. After inserting the anvil head of the circular stapler into the end of the proximal colon, the proximal colon was internalized and the incision was closed. Intracorporeal anastomosis under laparoscopic view was performed by the double-stapling technique (DST) using a circular stapler (ECS 29mm or 33mm, Ethicon Endo-Surgery Inc, Cincinnati, OH). Patients with low anastomosis within 1cm from the dentate line and incomplete "doughnuts" underwent covering ileostomy.

For patients with lesions located within 5cm of the dentate line with more than 2cm of the distal free margin to the dentate line (with no evidence of carcinoma invasion into the sphincters or pelvic floor), laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis (ISR-CAA) was performed. This surgical technique was described previously (18). For patients undergoing abdominoperineal resection (APR), laparoscopic procedures were followed by perineal dissection in the standard fashion, and end colostomy creation using the left lower abdominal port site.

Statistical Analysis

Statistical analysis was performed using Student's t test, the Mann-Whitney U test, and the Fisher's exact test as appropriate. A P valve of less than 0.05 was considered significant.

RESULTS

Patient demographic characteristics are summarized in **Table 1**. Cases and controls were well matched for gender, age, tumor site, surgical procedure, extent of resection and TNM stage; however, the follow-up period in the OS group was significantly longer than that in the LS group. There were no significant differences in the patient's characteristics, including BMI and rate of prior abdominal surgery, between the two groups. In both groups, three patients underwent ISR-CAA and a transverse-coloplasty pouch was created in 4 patients. Overall, covering ileostomy was required for 11 patients in the LS group, and 9 patients in the OS group. All the patients with covering ileostomy underwent subsequent ileostomy closure.

Surgical and postoperative results are demonstrated in **Table 2**. In the LS group, operative time was significantly longer but blood loss was significantly lower. There was one case requiring conversion to OS because of severe adhesion after repeated cesarean section. Liquid and solid intakes were started on median postoperative days 1 and 3 in the LS group, which was significantly shorter than that in the OS group. Similarly, the median postoperative hospital stay was 8 days in the LS group, which was significantly shorter than 15 days in the OS group. All patients were discharged to home.

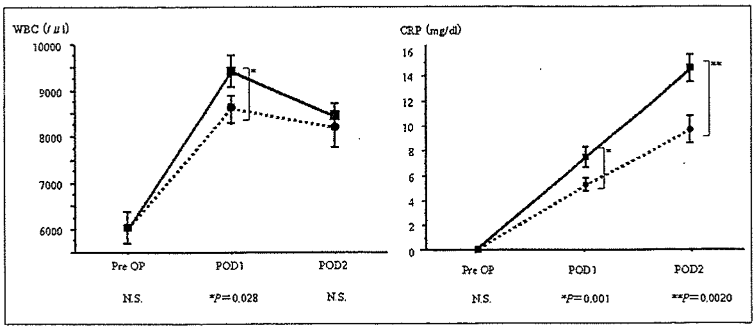

FIGURE 1 The level of white blood cell (WBC) count **(a)** on postoperative day (POD) 1 and the level of serum C-reactive protein (CRP) **(b)** on POD 1and 2 were significantly lower in LS group (●) than OS group (■). Each bar represents the mean standard error.

The postoperative complications are listed in **Table 3**. There were no perioperative mortalities in either group. The rate of postoperative bowel obstruction was 2.1% (1/47) in the LS group and 14.9 % (7/47) in the OS group (P=0.059). An anastomotic leakage occurred in one patient in each group. In the LS group, one patient, who had covering ileostomy during the initial operation, experienced anastomotic leakage that was conservatively managed. In the OS group, a patient with an anastomotic leakage required emergency operation for abdominal drainage and diverting ileostomy. Another patient in the LS group experienced anastomotic bleeding, that was conservatively managed. There was no significant difference in total complication rates between the two groups.

Preoperative and postoperative levels of WBC and CRP in serum are presented in **Figure 1**. In the LS group, the level of WBC on postoperative day 1 and the level of CRP on postoperative day 1 and 2 were significantly lower than those in the OS group.

At the end of the study period, there were no patients who had developed a recurrence or died in this series.

DISCUSSION

To date, there are few studies comparing surgical outcomes between LS *versus* OS for rectal carcinoma (11,19). In this study, we were able to demonstrate that the minimal invasiveness of LS, which has been demonstrated for colon carcinoma, can be preserved in LS for rectal carcinoma as well. Needless to say, the quality of surgery during LS for rectal carcinoma is important. If the rate of conversion to OS increases, outcomes of LS will be shifted to outcomes of OS, thus making it difficult to detect differences between the two groups. In addition, if the complication rate increases, hospitalization after surgery can be prolonged, resulting in a loss of the advantages of LS. In this study, there was only one case requiring conversion to OS, and the anastomotic leakage rate was lower (2.1%, 1/47) than the rates previously reported. We consider that these facts contributed greatly to demonstrating the minimal invasiveness of LS for rectal carcinoma. And the fact that WBC on postoperative day 1 and CRP values on postoperative day 1 and 2 were significantly lower in the LS group can be regarded as objective data suggesting the minimal invasiveness of LS.

At our institution, there has been much consideration given to the technical safety of LS, and surgeons with a thorough expertise in OS had accumulated enough experience in LS for colon carcinoma, which is technically relatively easy to perform. Thereafter, the indications were expanded to include rectal carcinoma. As a result, LS for rectal carcinoma has been successfully performed with significantly reduced blood loss, earlier start of oral intake and shortened postoperative hospital stay, as compared to OS. At present, the long-term oncological outcome of LS for rectal carcinoma remains unclear and hence the indications for LS for rectal carcinoma remain limited, but it may be technically possible to gradually reduce those limits and expand our indications.

One of the advantages of LS for rectal carcinoma is that by inserting a flexible scope into the narrow pelvis to magnify the operative field, the surgeon can safely mobilize the rectum because of easy identification of the loose connective tissue between the mesorectum and the surrounding tissues such as the hypogastric nerves and the pelvic nerve plexuses, which is not always easy to recognize under direct vision during OS. Another advantage of LS is that everyone participating in the operation can have the same field of view. However, there are several technical limitations in LS. It is often very difficult to occlude and transect the bowel in LS, especially when the tumor is located in the lower rectum. Furthermore, lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with T3 and T4 lower rectal carcinoma in Japan, and lateral lymph node dissection by laparoscopy remain an unexplored frontier (16,20). In particular, previous studies have reported an anastomotic leakage rate of 7.2 to 20% in patients who underwent laparoscopic low anterior resection (9-15), and some authors have recommended covering ileostomy as a routine in this procedure (9). However, this can deteriorate the short-term quality of life of the patient and can also promote local recurrence in the long term (21). Therefore, the utmost effort should be made to avoid this complication.

At our institution, patients with low anastomosis within 1cm from the dentate line, incomplete doughnuts with DST, and laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis underwent covering ileostomy. However, the decision to perform protective ileostomy in this series was based on much looser criteria than those used in OS in order to avoid major anastomosis complications that could lead to permanent stoma or fatal outcome, especially in the early LS cases involving lower rectal carcinoma. In the future, it may be appropriate to set the same indications for ileostomy as in OS.

In sphincter-preserving surgery for rectal carcinoma, whether performed by LS or by OS, the procedure for dissection and anastomosis is the phase with the highest technical difficulty. For patients with lesions located more than 2cm of the distal free margin to the dentate line with no evidence of carcinoma invasion into the sphincters or pelvic floor, we usually perform laparoscopic DST anastomosis. However, as we previously indicated, during LS for lower rectal carcinoma, the closer the site of dissection of the rectum is to the anus, the more difficult the rectal dissection technique is, thus increasing the use of endolinear staplers needed to perform the dissection. In such cases, it is important to securely penetrate the first and second crossing points using a circular stapler to prevent anastomotic leakage (17).

One of the distinctive points of the present study is that only one patient underwent laparoscopic APR. Recently, laparoscopic ISR-CAA has been reported for patients with lesions located in the lower rectum with greater than 2cm of distal free margin to the dentate line (18). This technique allows a sufficient distal margin to be obtained under direct vision in order to preserve the sphincter and avoid APR. As a consequence, only one patient underwent laparoscopic APR. Although we considered that laparoscopic ISR-CAA was possible in that case, the patient's choice was laparoscopic APR.

With regard to the oncological outcome which is the most important factor in terms of a carcinoma surgery, recently reported results of three RCTs in patients with colon carcinoma or upper rectal carcinoma indicating that the treatment outcome of LS is equal to or better than that of OS (6-8). However, many RCTs have excluded patients with middle and lower rectal carcinoma because of great technical difficulties, and there has been only case series reporting experiences of a single or multiple institutions (2,9-14). Further investigations based on multicenter RCT are necessary for middle and lower rectal carcinoma cases as well.

In conclusion, the findings of the present study demonstrated that LS for rectal carcinoma could be performed safely compared to OS without increased morbidity or mortality. The radical resection of middle and lower rectal carcinoma is a procedure that requires advanced technical skills in OS, to say nothing of LS. With improvements in technology and surgical experience, the indications for this procedure are expected to expand. However, at present, as the oncological outcome remains unclear, expansion of the indications to include advanced lower rectal carcinoma should proceed cautiously.

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Abdominal Sacral Resection for Posterior Pelvic Recurrence of Rectal Carcinoma: Analyses of Prognostic Factors and Recurrence Patterns

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Background: Local recurrence of rectal cancer presents challenging problems. Although abdominal sacral resection (ASR) provides pain control, survival prolongation, and possibly cure, reported morbidity and mortality are still high, and survival is still low. Thus, appropriate patient selection and adjuvant therapy based on prognostic factors and recurrence patterns are necessary. The purpose of this study was to evaluate the results of ASR for posterior pelvic recurrence of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

Methods: Forty-four patients underwent ASR for curative intent in 40 and palliative intent in 4 cases. All but one could be followed up completely. Multivariate analyses of factors influencing survival and positive surgical margins were conducted.

Results: Morbidity and mortality were 61% and 2%, respectively. Overall 5-year survival was 34%. The Cox regression model revealed a positive resection margin (hazard ratio, 10 [95% confidence interval, 3.8–28]), a local disease-free interval of < 12 months (4.2 [1.8–9.8]), and pain radiating to the buttock or further (4.2 [1.6–11]) to be independently associated with poor survival. The logistic regression model showed that macroscopic multiple expanding or diffuse infiltrating growths were independently associated with a positive margin (7.5 [1.4–40]). Of the patients with recurrence, 56% had failures confined locally or to the lung.

Conclusions: ASR is beneficial to selected patients in terms of survival. To select patients, evaluation of the resection margin, the local disease-free interval, pain extent, and macroscopic growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

Key Words: Therapy—Surgery—Rectal cancer—Local recurrence—Recurrence—Prognostic factor.

Posterior pelvic recurrence[1–3] (PPR) of rectal carcinoma, which involves the sacrum and/or sacral nerves, presents challenging clinical problems. It may cause sacral nerve pain, perineal ulcers, fistula formation, bleeding, bowel and/or urinary tract obstruction, sepsis, and, finally, death.[4] These conditions are difficult to treat, and chemotherapy provides only minimal benefits at present.[4–6] Radiotherapy may give pain relief, but its effectiveness is limited and temporary.[4,7–9] Conventional abdominoperineal resection or local excision is only palliative.[10,11]

In 1981, Wanebo and Marcove[11] reported the advantage of the abdominal sacral resection (ASR), which was first described by Brunschwig and Barber[12] in 1969, for PPR of rectal carcinoma. Although published data on this operation are still limited and

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there have been few long-term follow-up studies, this aggressive operation provides pain control, prolongation of survival, and possibly cure.[13–22] However, reported morbidity and mortality are significantly high,[13–22] and survival is still low.[13–22] Therefore, appropriate selection of patients, especially with reference to the probable prognosis, is necessary. In addition, adjuvant therapy based on recurrence patterns may be required. The purpose of this study was to evaluate the results of ASR for PPR of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

PATIENTS AND METHODS

Between March 1983 and May 2000, 44 patients with PPR of rectal carcinoma that involved the sacrum on computed tomography (CT) were considered candidates for ASR and admitted to the National Cancer Center Hospital, Tokyo. There were 35 men and 9 women, with a median age of 55 years (range, 32–73 years). Of these, 40 patients underwent initial operation at other hospitals. Selection criteria for curative-intent ASR were as follows: (1) medical fitness for ASR; (2) no signs of disseminated disease on preoperative imaging; (3) tumors involving the sacrum but not the first sacral bone and the bony lateral walls; and (4) tumors anatomically confined within the pelvis, with or without resectable solitary liver metastasis. The imaging studies routinely performed before resection were abdominal and pelvic CT, abdominal ultrasonography, and chest roentgenogram until 1989; pelvic magnetic resonance imaging and chest CT were added thereafter.

Of the 44 patients for whom ASR was attempted, 40 received curative-intent ASR, and 4 received palliative-intent ASR because of 1 or 2 lung metastases in 3 and 3 liver metastases in 1. Of the 40 who received curative-intent ASR, 33 patients underwent macroscopic curative ASR, 2 with solitary liver metastasis underwent macroscopic curative ASR with complete resection of liver metastasis, 1 with 4 peritoneal metastases adjacent to the main tumor underwent macroscopic curative ASR with complete resection of peritoneal metastases, and the remaining 4 underwent palliative ASR because of macroscopic residual local tumor in 3 and residual lymph node metastases in 1. Of the four who received palliative-intent ASR, three with lung metastases underwent palliative ASR leaving only residual lung metastases in two and both residual lung and local tumors in one, and one with three liver metastases underwent macroscopic curative ASR with complete resection of liver metastases. Conseuently, 37 underwent macroscopic curative resection, and 7 underwent macroscopic palliative resection. Of them, 27 patients received no radiation, 13 received preoperative adjuvant radiation of 30 to 73 Gy (median, 44 Gy), and 4 received 44 to 50 Gy (median, 50 Gy) as previous treatment.

Data for these patients were collected and entered prospectively into the database of the Colorectal Surgery Division. They included the following: (1) patient demographics; (2) treatment and pathology of the primary rectal cancer; (3) presentation of PPR; (4) treatment and pathology of recurrent tumor; (5) operative details; (6) hospital course, including complications; and (7) outcome. Of these, 15 variables were selected for prognostic factor analysis (Table 1) by consideration of their potential relationship to survival after ASR, as indicated by previous studies.[13–15,17–19,22] The local disease–free interval (LDFI) was defined as the interval between the initial curative operation and the occurrence of symptoms or detection of asymptomatic PPR by CT.

Surgical Procedure

Our surgical procedure was basically similar to that originally described by Wanebo and Marcove[11] and Wanebo et al.;[13] however, it was slightly modified.[23] Our sacral resection was performed immediately after the abdominal phase as a one-stage procedure instead of a two-stage procedure.[13] The presence of liver metastasis did not preclude continuation of the procedure if it was solitary and if the disease-free interval was sufficiently long. Solitary liver metastasis was resected simultaneously. We did not make full-thickness fascial myocutaneous flaps for sacroperineal wound closure but sutured the wound simply because there were no patients with large exposed tumors at the perineum.

After the patient was placed in a supine position with flexed and abducted thighs, dissection was started at the aortic bifurcation, and the common and external iliac vessels were dissected. The internal iliac vessels were divided at their root or beyond the superior gluteal artery. Adipose tissue, lymphatics, and the nodes surrounding these vessels, including obturator nodes, were removed completely, and the muscular pelvic side walls and the sacral nerve roots were exposed. The upper limit of the tumor was identified, and the anterior surface of the sacrum was dissected down to the planned level of sacral transection. When the tumor adhered or invaded into

TABLE 1. *Univariate Predictors of Adverse Outcome*

Variable	No. of Patients	Overall survival (%)			P
		1-yr	3-yr	5-yr	
Overall	44	90	47	34	
Gender					
Female	9	87	45	45	.41
Male	35	91	48	32	
Age					
< 60 years	30	96	55	40	.10
≥ 60 years	14	92	31	23	
Primary cancer stage					
I, II	2, 13	93	64	48	.046
III	22	90	39	31	(I, II, III vs. IV)
IV	7	85	28	14	
Initial surgery					
Local excision, anterior resection	1, 20	90	51	36	.83
Abdominoperineal resection	23	90	44	34	
Initial lymphadenectomy					
Conventional	33	93	55	41	.25
Extended	11	81	27	18	
Local-disease-free interval (months)					
≤ 12	17	75	20	20	.0042
> 12	27	96	62	43	
Preoperative CEA level (ng/ml)					
≤ 10	23	91	70	49	.025
> 10	21	90	25	20	
Extent of preoperative pain					
None, perineum	15, 17	93	55	43	.0006
Buttock	7	85	35	0	(none, perineum vs. buttock, more)
Thigh, leg	3, 2	50	0	0	
Tumor extent					
Solitary pelvic tumor	24	95	55	40	.17
Pelvic metastasis	12	75	43	29	(solitary tumor vs. others)
Distant metastasis	8	85	28	28	
Largest tumor diameter (cm)					
≤ 5	26	92	50	40	.086
> 5	18	88	40	24	
Sacral involvement					
Adhesion	27	84	56	37	.85
Periosteum, marrow	11, 6	94	32	32	
Resection margin					
Microscopic negative	24	95	81	62	< .0001
Microscopic positive	13	91	16	8	(microscopic negative vs. others)
Gross positive, residual	7	71	0	0	
Pathological grade					
Well, moderate	4, 29	90	40	35	.49
Mucinous, adenosquamous	6, 1	85	57	42	(poor, signet vs. others)
Poor, signet-ring cell	3, 1	75	75	0	
Macroscopic growth pattern					
Solitary expanding	15	92	70	70	.0027
Multiple expanding	5	80	40	20	(solitary vs. others)
Diffuse infiltrating	24	87	34	13	
Preoperative radiation					
Yes	13	91	55	46	.55
No	31	90	44	29	

CEA, carcinoembryonic antigen.

urogenital organs, the remaining rectum, pelvic nerves or muscles, and involved organs were all resected en bloc to avoid incomplete resection and cancer cell spillage. To facilitate resection and hemostasis and to shorten operating time, a combined abdominal and perineal approach was used.

After dissection of the lateral, cephalad, anterior, and caudal aspects of the tumor with surrounding organs to be resected was accomplished, the patient was placed in a prone position with flexed and abducted thighs. A posterior sacral incision including the perineal lesion was made, and the sacrum and gluteal muscles were exposed. The gluteal muscles, sacrotuberous ligament, sacrospinous ligaments, and pyriformis muscles were divided as far from the tumor as possible. After the level of abdominal dissection and the extent of the tumor were confirmed by hand in the pelvic cavity, a laminectomy proximal to the planned level of sacral transection was performed to preserve the noninvolved sacral nerve roots and ligate the dura. The sacrum was transected by an osteotome, and en-bloc resection of the tumor with the sacrum and the surrounding organs was accomplished. The gluteal muscles and skin were closed primarily. Again, the patient was placed in a supine position with flexed and abducted thighs. A colostomy and an ileal conduit were made.

Extent of Resection

Levels of sacral transection included S2 in 6 patients, S2–3 in 19, S3 in 5, S3–4 in 11, S4 in 1, and S4–5 in 2. Thirty-nine patients underwent total pelvic exenteration, one underwent posterior pelvic exenteration, and four underwent abdominoperineal resection. En-bloc resection of entire pelvic lymph nodes with the bilateral internal iliac arteries and veins was performed for all patients. Resected organs included the rectum in 20 cases, the urinary bladder in 39, the uterus and vagina in 8, the external genitalia in 2, the obturator internis muscle in 12, the gluteus maximus muscle in 5, and the small intestine in 7. Urinary diversions were an ileal conduit in 37 patients and a ureterocutaneostomy in 2. Three patients underwent complete resection of one, one, and three synchronous liver metastases. In addition, one patient underwent complete resection of four peritoneal metastases.

Follow-Up

One patient returned to Indonesia and was lost to follow-up. The other 43 were followed up completely, with a median follow-up time for live patients of 4.7 years (range, 1.2–15.8 years). They were examined with abdominal and pelvic CT, chest roentgenogram or CT, and carcinoembryonic antigen (CEA) measurement every 4 months for 0 to 1 years, every 6 months for 2 to 4 years, and annually for 5 to 10 years.

Statistical Analysis

Survival, disease-free survival, and local disease–free survival distributions were estimated by using the Kaplan-Meier product-limit method. Univariate comparisons of survival were made by using the log-rank test, and multivariate analysis was performed by using the Cox regression model with the forward stepwise method (likelihood ratio). All variables were dichotomized for analysis. Differences in proportions were analyzed by Fisher's exact test and by multivariate analysis with the logistic regression model and the forward stepwise method (likelihood ratio). All statistical analyses were performed with SPSS for Windows, version 10.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two sided, and a P value of $<.05$ was considered to be statistically significant.

RESULTS

Pathologic Findings

Histological diagnoses of the PPR cases are listed in Table 1. The bone marrow or periosteum of the sacrum was histologically involved in 17 patients. The remaining 27 had no sacral invasion, but dense fibrotic tissues adhered extensively to the sacrum, and cancer cells were found within them. Of 13 patients with pelvic lymph node involvement, 12 had intrapelvic metastases alone, and 1 had both intrapelvic and extrapelvic metastases. Eight patients had distant metastasis, including liver metastasis in three, lung metastasis in three, peritoneal metastasis in one, and distant lymph node metastasis in one.

Resection margins were microscopically negative in 24 patients, microscopically positive in 13, macroscopically positive in 3, and grossly residual in 4 (lung, n = 2; lung and local, n = 1; lymph node, n = 1; Table 1). The sites of macroscopic positive margins included cut ends of the sacrum and/or presacral connective tissue in two, cut ends of the sacral nerves and the external iliac artery in one, and the lateral pelvic sidewall in one. The major artery was involved only in one patient with prior extended lateral pelvic lymph node dissection. The sites of microscopic positive margins included the cut end of the sacrum in two, the cut end of the presacral connective tissue in three, the cut ends of the sacrospinous ligament and sacrotuberous ligament in one, the cut ends of the sacrospinous ligament and obturator internis muscle in one, the cut end of the obturator lymph node in one, and the cut ends of the sacral nerves in one.

Macroscopic growth patterns were based on macroscopic views of sections of resected specimens and were classified as solitary expanding growth, multiple expanding growth, and diffuse infiltrating growth (Fig. 1; Table 1). Expanding growth featured smooth gluteal muscles were exposed. The gluteal muscles, sacrotuberous ligament, sacrospinous ligaments, and pyriformis muscles were divided as far from the tumor as possible. After the level of abdominal dissection and the extent of the tumor were confirmed by hand in the pelvic cavity, a laminectomy proximal to the planned level of sacral transection was performed to preserve the noninvolved sacral nerve roots and ligate the dura. The sacrum was transected by an osteotome, and en-bloc resection of the tumor with the sacrum and the surrounding organs was accomplished. The gluteal muscles and skin were closed primarily. Again, the patient was placed in a supine position with flexed and abducted thighs. A colostomy and an ileal conduit were made.

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Macroscopic growth patterns were based on macroscopic views of sections of resected specimens and were classified as solitary expanding growth, multiple expanding growth, and diffuse infiltrating growth (Fig. 1; Table 1). Expanding growth featured smooth

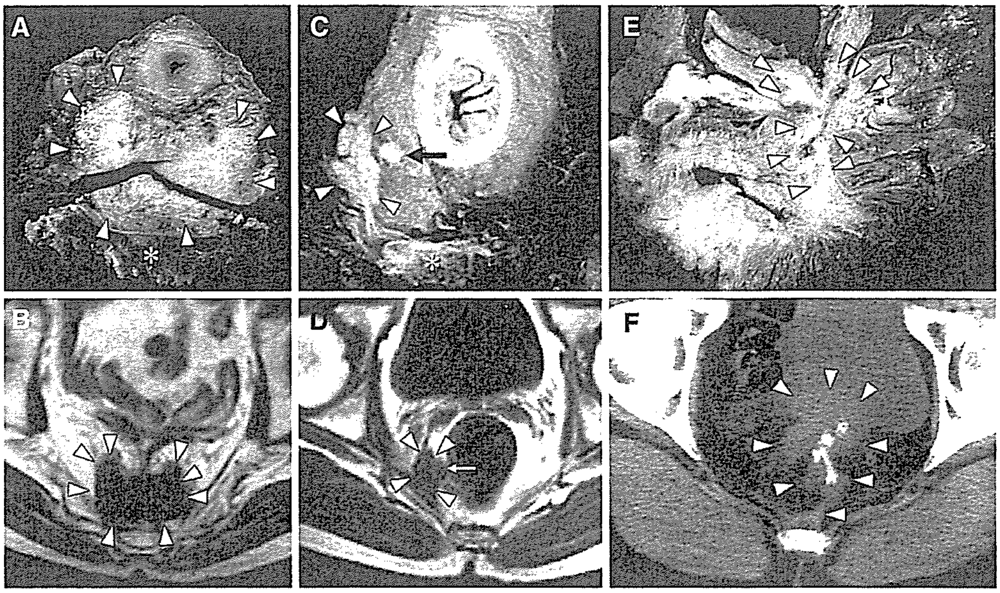

FIG. 1. (A) A section after abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. This tumor was macroscopically classified as solitary expanding growth. (B) Corresponding magnetic resonance image of (A). (C) A section of tumor macroscopically classified as multiple expanding growth. (D) Corresponding magnetic resonance image of (C). (E) A section of tumor macroscopically classified as diffuse infiltrating growth. (F) Corresponding computed tomography of (E). Arrowheads, main tumor; arrow, satellite tumor. *Sacrum.

and clear margins. Any tumors showing irregular or obscure margins were therefore classified into the diffuse infiltrating category.

Morbidity and Mortality

The median operating time was 751 minutes (range, 263–1377 minutes). The median blood loss was 3208 mL (range, 856–26160 mL), and all of the patients underwent transfusion. Of the 27 patients with postoperative complications (morbidity, 61%), 10 (23%) had major complications that necessitated surgical interventions or resulted in hospital death, and 17 (38%) had minor complications that could be managed conservatively (Table 2). The number of complications per patient was as follows: 4 in 1 patient, 3 in 5 patients, 2 in 10 patients, and 1 in 11 patients. One patient who had pelvic sepsis, residual tumor regrowth, bowel obstruction, and renal failure died on the 66th postoperative day (mortality, 2%).

Eleven (65%) of 17 patients who had received adjuvant or previous radiation had postoperative complications, compared with 16 (59%) of 27 who had not received radiation (P = .76). In contrast, 7 (41%) of 17 with adjuvant or previous radiation experienced major complications, compared with 3 (11%) of 27 without irradiation (P = .03). The median hospital stay was 38 days (range, 22–316 days).

TABLE 2. *Complications*

Complication	No. Patients
Major complications	
Pelvic sepsis	8
Bowel obstruction	3
Intestinal fistula	2
Ureteroileostomy leakage	2
Ureterocutaneostomy stenosis	1
Ileal conduit necrosis	1
Renal failure	1
Uncontrollable bleeding	1
Postoperative bleeding	1
Tracheal stenosis	1
Minor complications	
Wound dehiscence/infection	6
Bowel obstruction	12
Urinary tract infection	10
Ureteroileostomy stenosis	1
Neurogenic bladder	2

Survival

The median survival for all the patients undergoing ASR was 2.3 years (range, .1–15.8 years). The estimated overall 1-, 3-, and 5-year survival rates were 90%, 47%, and 34%, respectively, including one hospital death (Fig. 2). Of the 15 patients who survived >4 years, 9 were disease free, and 5 survived >8 years. The disease-free 1-, 3-, and 5-year survival rates were 44%, 26%, and 24%, respectively. The local disease–free 1-, 3-, and 5-year survival rates were 63%, 47%, and 47%, respectively (Fig. 2).

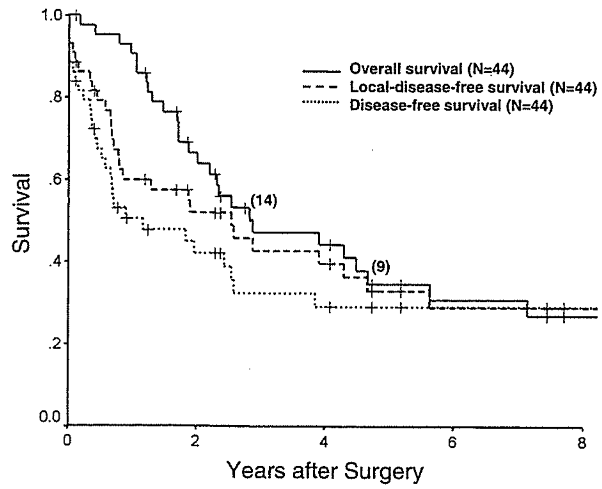

FIG. 2. Overall, disease-free, and local disease-free survival distributions for the 44 patients undergoing abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. The numbers in parentheses for the overall survival curve indicate the patients alive at 3 and 5 years.

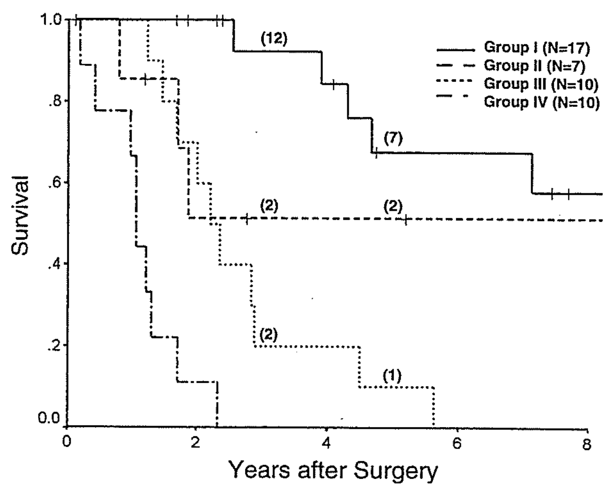

FIG. 3. Overall survival curves for group I (microscopic negative margin and local disease-free interval [LDFI] of > 12 months), group II (microscopic negative margin and LDFI < 12 months), group III (positive margin and LDFI > 12 months), and group IV (positive margin and LDFI < 12 months). The numbers in parentheses for each curve indicate the patients alive at 3 and 5 years.

Prognostic Factors

Results of univariate analysis of prognostic factors are summarized in Table 1. The overall survival of the patients with microscopic positive resection margins was significantly worse than that of those with microscopic negative margins (P < .0001) but was not significantly better than that of those with macroscopic positive margins or macroscopic residual tumor (P = .11). Patients with macroscopic positive margins or macroscopic residual tumor did not survive > 2.3 years.

The survival of patients with buttock pain was significantly worse than that of those without pain or with perineal pain (P = .043) and was significantly better than that of those with thigh or leg pain (P = .0046). The latter died within 1.2 years.

Of the eight patients with distant metastasis, two undergoing resection of solitary liver metastasis were alive and disease free for 7.6 and 2.7 years, one undergoing resection of three liver metastases died of disease at 1.3 years, one undergoing resection of four peritoneal metastases was alive with disease at 1.1 years, three with one or two lung metastases died of disease at 2.3, 2.0, and 1.6 years, and one with para-aortic lymph node metastasis died at 1.7 years.

The univariate analysis of the 15 variables (Table 1), when dichotomized, showed a positive resection margin, pain extending to the buttock or further, multiple growths or diffuse infiltrating growth, LDFI of < 12 months, a preoperative CEA level > 10 ng/mL, and primary cancer stage IV to be associated with significantly worse survival. The other nine factors did not show any significant association with outcome.

The multivariate analysis of the 15 dichotomized variables revealed that only a positive resection margin (hazard ratio, 10 [95% confidence interval, 3.8–28]; P < .001), an LDFI of < 12 months (4.2 [1.8–9.8]; P = .001), and pain radiating to the buttock or further (4.2 [1.6–11]; P = .004) were independently associated with worse survival.

When the most significant independent factors were considered together, the 5-year overall survival rates of the 17 patients with microscopic negative margins and an LDFI > 12 months (group I), the 7 with microscopic negative margins and an LDFI < 12 months (group II), the 10 with positive margins and an LDFI > 12 months (group III), and the 10 with positive margins and an LDFI < 12 months (group IV) were 67%, 51%, 10%, and 0%, respectively (Fig. 3). There were significant survival differences between group I and group III (P < .0001), group III and group IV (P = .0014), and group II and group IV (P = .01). Group IV patients did not survive > 2.3 years.

Risk Factors for a Positive Resection Margin

To clarify the risk factors for a positive resection margin, the most significant prognostic factor on multivariate analysis, univariate and multivariate analyses were conducted. Three patients who under-

TABLE 3. *Univariate predictors of positive resection margin*

Variable	Microscopic resection margin Negative	Positive	*P*
Gender			
Female	5	3	1.0
Male	19	14	
Age, years			
< 60	19	10	.18
≥60	5	7	
Primary cancer stage			
I/II/III	23	12	.066
IV	1	5	
Initial surgery			
Local excision, anterior resection	13	8	.76
Abdominoperineal resection	11	9	
Lymphadenectomy at initial surgery			
Conventional	20	13	.70
Extended	4	4	
Local-disease-free interval (month)			
≤12	7	9	.20
> 12	17	8	
Preoperative CEA level (ng/ml)			
≤10	16	6	.062
> 10	8	11	
Extent of preoperative pain			
None, perineum	21	9	.029
Buttock, thigh, leg	3	8	
Tumor extent			
Solitary pelvic tumor	17	7	.11
Pelvic metastasis, distant metastasis	7	10	
Largest tumor diameter (cm)			
≤5	15	9	.75
> 5	9	8	
Sacral involvement			
Adhesion	14	11	.75
Periosteum, marrow	10	6	
Pathological grade			
Well, moderate, mucinous, adenosquamous	21	16	.63
Poor, signet-ring cell	3	1	
Macroscopic growth pattern			
Solitary expanding	12	2	.018
Multiple expanding, infiltrating	12	15	
Preoperative radiation			
Yes	8	3	.31
No	16	14	

CEA, carcinoembryonic antigen.

went palliative-intent resection as a result of gross residual lung metastases were excluded from this study. Univariate analysis revealed that the incidences of microscopic positive margins were significantly higher in patients with multiple expanding or diffuse infiltrating growth (56% vs. 14%; P = .018) and in patients with pain extending to the buttock or further (72% vs. 30%; P = .029; Table 3). On multivariate analysis of the 14 dichotomized variables, excluding resection margin, multiple expanding or diffuse infiltrating growth was independently associated with positive margin (hazard ratio, 7.5 [95% confidence interval, 1.4–40]; P = .019).

TABLE 4. *Sites of first recurrence after abdominal sacra resection in 37 patients undergoing macroscopic curative resection*

Site	No. Patients (9
Local	
Local alone	6 (24)
Local, lung	3 (12)
Local, adrenal gland	1 (4)
Local, lung, liver	1 (4)
Local, lung, pancreas	1 (4)
Local, liver, para-aortic lymph node	1 (4)
Lung	
Lung alone	5 (20)
Lung, para-aortic lymph node	2 (8)
Liver, lymph node	1 (4)
Para-aortic lymph node	1 (4)
Peritoneum	1 (4)
Brain	1 (4)
Unknown	1 (4)

Recurrence Patterns

Of the 37 patients who underwent macroscopi curative resection, 25 (68%) experienced furthe recurrence. Sites of their first recurrence after ASI are listed in Table 4. Of them, 13 patients (52%) ha local failure, 7 (28%) had lung metastasis, and 1 (56%) had failures confined locally or to the lung Sites of local failure were the cut end of the sacrum i five, the sacral cut end and buttock in one, and th pelvic side wall or ischium in 3. None of the 25 pa tients with recurrence was treatable by surgery, s these patients were given chemotherapy, radiother apy, and/or best supportive care.

Of the 13 patients who developed local failure, had positive margins, and 4 had negative margins o histological analysis. Of the 24 patients without loca failure, 20 had microscopic negative margins, and had microscopic positive margins. The rate for loca failure was significantly higher in patients witl microscopic positive margins than in those witl microscopic negative margins (69% [9 of 13] vs. 179 [4 of 20]; P = .003). When the accuracy of th microscopic status of surgical margins in predictioi of local failure was evaluated, the sensitivity was 699 (9 of 13), the specificity was 83% (20 of 24), the po sitive predictive value was 69% (9 of 13), the negativ predictive value was 83% (20 of 24), and the overal accuracy rate was 78% (29 of 37). Of the 13 patient with microscopic positive margins, 9 developed loca recurrence that corresponded well to histologica findings, 1 experienced local failure at a different sit with a positive margin, and 3 had no obvious loca failure at the last follow-up.

DISCUSSION

The most effective treatment for PPR of rectal carcinoma is a curative resection, that is, complete resection with microscopic negative margins.[13,15,17–19,22] Because the tumor involves contiguous organs, including the sacrum, retained rectum, internal iliac vessels, and genitourinary organs, by either invasion or dense adhesion, combined resection of these organs—that is, ASR—is mandatory for clear surgical margins and possible cure. The overall 5-year survival rate after ASR is reported to be 25% to 31% in the largest series[13,14] and was 34% in this study. Such results have never been achieved with other therapeutic modalities, including chemotherapy and radiotherapy.[4–9]

However, morbidity and mortality after ASR are reported to be 26% to 82%[13,15–18,21,22] and 0% to 9%,[13–22] respectively. In our series, they were 61% and 2%, and 23% of our patients experienced major complications resulting in reoperation or death, and their mean hospital stay was 135 days. In addition, most patients lose genitourinary functions and must endure permanent stomas. These costs are very high and sometimes even catastrophic for those who nevertheless do not obtain long-term survival. Therefore, appropriate patient selection based on survival benefit determined on the basis of prognostic factors is necessary. Also, efforts toward seeking effective adjuvant therapy aiming at the most common sites of recurrence are mandatory. Thus, we analyzed prognostic factors and recurrence patterns after ASR in this study.

Several factors that can be estimated before surgery have been reported to be significantly associated with prognosis on either univariate or multivariate analysis. These include residual tumor extent,[13,15,17–19,22] distant metastasis,[14] initial operation,[13] disease-free interval,[14] preoperative CEA level,[13,14] preoperative CEA doubling time,[14] and proliferating cell nuclear antigen labeling index.[24] In addition, whether significant or not, there are factors definitely indicative of a poor prognosis. Wanebo et al.[13,25] reported that patients with positive margins, bone marrow involvement, or pelvic lymph node involvement had a median survival of only 10 months. Strong suspicion of such factors thus contraindicates ASR. However, the number of patients so far studied is still not sufficiently large to allow definitive patient selection criteria to be established.

We tested 15 factors in multivariate analysis because previous studies indicated their potential relationship to survival after ASR.[13–15,17–19,22,24,25] Of these, microscopic positive margins, LDFI < 1 year, and preoperative pain exceeding the buttock showed a significant independent association with a poor prognosis. Microscopic margin status is the most significant, as reported so far.[13,15,17–19,22] Of our patients with microscopic positive margins, 69% developed local recurrence, and this caused persistent pain and a poor prognosis. Although some previous studies claimed a benefit of palliative resection for both survival and pain,[26] it usually leads to a very poor prognosis and fails to relieve pain, as previously reported.[25,27] Therefore, palliative resection leaving a gross residual tumor should not be attempted. In addition to conventional imaging,[28,29] recent advances in radiological imaging, including thin-section magnetic resonance imaging[30] and multidetector row CT,[31] allow us to accurately evaluate tumor extent so that cautious interpretation can preclude such unnecessary surgery.

The extent of preoperative pain corresponds well with tumor extent and invasiveness and therefore predicts survival.[17] In this study, the survival of the patients with buttock pain was significantly worse than that of patients without pain or with perineal pain and was significantly better than that of patients with thigh or leg pain. Thigh or leg pain, caused by involvement of the first or second sacral nerves, indicates lateral and/or cephalad extension of the tumor, which usually renders curative resection impossible. Indeed, in our series, the affected patients died within 1.2 years. In contrast, if the pain remains within the buttock, there is the possibility of curative resection.

The factors relating to tumor growth rate can predict prognosis only if patients have residual tumors after ASR. Maetani et al.[14] and Onodera et al.[24] reported a significant association of disease-free interval[14] and preoperative CEA doubling time[14] with survival. These parameters reflect not only the growth rate of locally recurrent tumors, but also that of distant metastases. The proliferating cell nuclear antigen labeling index[24] can reflect a growth rate specific to local recurrence, so it may predict prognosis more accurately. Although LDFI has not been studied so far, it is easier to measure than the labeling index, and it is also specific to local recurrence. As this study showed, patients with an LDFI of > 12 months and clear surgical margins are the best candidates for ASR, and a 5-year survival of 67% can be expected. Conversely, if the LDFI is < 12 months, thus indicating rapid tumor growth, and resection is palliative, a 2-year survival of only 11% is expected. In such cases, ASR should not be attempted. Palliative resection is indicated only for patients with an LDFI of > 12 months and preferably > 18 months.[11]

Primary cancer stage, preoperative CEA level, and macroscopic growth pattern were prognostically significant only in univariate analysis in this study. Thus, they are related to any of the previously described independent factors, but they are worth considering to a certain degree when decisions are made. Macroscopic growth pattern, which has not been investigated so far, especially influences the surgical margin status and is important when deciding the extent of resection.

As our logistic regression model showed, multiple expanding or diffuse infiltrating growth is independently associated with positive resection margins. The curative resection of the tumors with multiple expanding or infiltrating growth (44%) is clearly more difficult than with solitary expanding growth (86%). Therefore, cautious evaluation of both growth pattern and tumor extent by magnetic resonance imaging or CT is needed to determine a correct line of resection.

Although tumor extent (distant and pelvic metastases)[14,25] and initial operation type[13,25] have been reported to be significant prognostic factors, this was not confirmed here, presumably at least partly because of differences in patient backgrounds and selection criteria. As described previously,[11] the presence of pulmonary, multiple liver, peritoneal, and extrapelvic lymph node metastases leads to a very poor prognosis, with a median survival of only 1.6 years in our cases, so these patients should not undergo ASR. However, solitary liver metastasis may be an exception. Indeed, in our series, two patients with solitary liver metastases survived disease free for 7.6 and 2.7 years after ASR and liver resection. In such cases, aggressive surgery seems justified.

Because adjuvant external beam radiotherapy has been reported to be beneficial for local control and prolongation of survival in primary rectal carcinoma,[32,33] many surgeons have recommended its application for ASR.[13,15–18,20] In this multivariate study, however, a prognostic benefit of preoperative radiotherapy could not be detected. This may be at least partly caused by the small number of patients, so further investigation is necessary. Marijnen et al.[34] reported that preoperative radiotherapy for primary rectal cancer has a beneficial effect in patients with more than 1-mm resection margins but that it cannot compensate for microscopically nonradical resection resulting in positive margins. Therefore, preoperative radiation should be given only to patients for whom surgical margins are expected to be attained but insufficient.

The situation with intraoperative radiotherapy may be different.[13,15–17] Hahnloser et al.[17] reported that the overall 5-year survival rate of patients undergoing palliative resection and intraoperative radiotherapy with or without external beam radiotherapy was 21%. Survival rates for their patients with no fixation, one fixation, two fixations, and three or more fixations were 43%, 24%, 20%, and 0%, respectively. Although candidates for ASR usually have two or more fixations and the expected survival of those with positive margins is not good, intraoperative radiotherapy may benefit those undergoing ASR despite a positive margin.

As to recurrence patterns after ASR, this study showed that, in 56% of our patients, recurrence was confined locally or to the lung. Wanebo et al.[13] reported this to be the case for 68% of their series, in line with other previous studies.[35,36] Thus, in addition to precise resection based on precise evaluation of tumor extent with thin-section magnetic resonance imaging or multidetector row CT, adjuvant therapies aiming at local and lung recurrences may be necessary. For local control, preoperative and intraoperative radiotherapy may be helpful. For lung metastases, systemic adjuvant chemotherapy using 5-fluorouracil–based chemotherapy or newly developed drugs (or their combination) may be effective.[5,6]

Although this retrospective exploratory study featured only a relatively small number of patients, we conclude that ASR is beneficial for a selected subset of patients in terms of survival prolongation and even cure. To select appropriate patients, evaluation of resection margin, LDFI, pain extent, and growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

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Adjuvant Chemotherapy with Uracil–Tegafur for Pathological Stage III Rectal Cancer after Mesorectal Excision with Selective Lateral Pelvic Lymphadenectomy: A Multicenter Randomized Controlled Trial*

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Background: Although adjuvant radiotherapy was proved to be effective for local control of rectal cancer even after standardized mesorectal excision, the role of adjuvant chemotherapy after such standardized surgery remains to be clarified. We aimed to assess the efficacy of a combination of uracil and tegafur for pathological stage III rectal cancer treated by standardized mesorectal excision with selective lateral pelvic lymphadenectomy.
Methods: We randomly assigned patients with completely resected stage III rectal cancer, who underwent standardized mesorectal excision with selective lateral pelvic lymphadenectomy, to receive either oral uracil–tegafur (400 mg/m^2 tegafur per day) for one year or no treatment. Standardization and quality control of the surgery and pathological techniques were ensured by use of the guidelines of the Japanese Society for Cancer of the Colon and Rectum. The primary endpoint was relapse-free survival. The secondary endpoint was overall survival.
Results: We enrolled and randomized 276 patients. Excluding two ineligible patients, 274 were included in the analysis. Planned interim analysis 2 years after accrual termination revealed significant prolongation of relapse-free survival ($P = 0.001$) and overall survival ($P = 0.005$) in the uracil–tegafur group. The 3-year relapse-free survival and overall survival rates were 78 and 91% in the chemotherapy group and 60 and 81% in the surgery-alone group, respectively. Local recurrence rates were low in both groups. Grade 3 events occurred in 17% of the chemotherapy patients, but no grade 4 or more events occurred.
Conclusion: Adjuvant chemotherapy with uracil–tegafur improves survival of patients with stage III rectal cancer after standardized mesorectal excision with selective lateral pelvic lymphadenectomy.

Key words: adjuvant chemotherapy – uracil–tegafur – rectal cancer – surgery

INTRODUCTION

The quality of surgical procedures has prognostic significance for local control and survival in rectal cancer (1,2). However, the lack of standardization for surgery and limitations of surgical information in previous adjuvant trials is well documented (3). The Dutch Colorectal Cancer Group was the first to adopt standardized mesorectal excision (4,5) in a rectal cancer adjuvant study (6). Mesorectal excision involves complete resection of the mesorectum by precise, sharp dissection under direct visualization (4,5) and is recommended in the Guidelines 2000 for Colon and Rectal Cancer Surgery (5).

The Dutch group clearly showed that preoperative radiotherapy is effective for local control even when standardized mesorectal excision is performed (6). Previous studies evaluating adjuvant radiotherapy, but not using standardized surgery, also showed its advantages in local control and

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