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ORIGINAL ARTICLE

Phase II Study of Single Intraperitoneal Chemotherapy Followed by Systemic Chemotherapy for Gastric Cancer with Peritoneal Metastasis

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Abstract

Background We conducted a phase II study involving a single administration of intraperitoneal chemotherapy with paclitaxel followed by sequential systemic chemotherapy with S-1+ paclitaxel for advanced gastric cancer patients with peritoneal metastasis.

Methods Gastric cancer patients with peritoneal metastasis were enrolled. Paclitaxel (80 mg/m^2) was administered intraperitoneally at staging laparoscopy. Within 7 days, patients received systemic chemotherapy with S-1 (80 mg/m^2/day on days 1–14) plus paclitaxel (50 mg/m^2 on days 1 and 8), followed by 7-days rest. The responders to this chemotherapy underwent second-look laparoscopy, and gastrectomy with D2 lymph node dissection was performed in patients when the disappearance of peritoneal metastasis had been confirmed. The primary endpoint of the study was overall survival rate.

Results Thirty-five patients were enrolled. All patients were confirmed as having localized peritoneal metastasis by staging laparoscopy. Eventually, gastrectomy was performed in 22 patients. The median survival time of the total patient population and those patients in which gastrectomy was performed was 21.3 and 29.8 months, respectively. The overall response rate was 65.7 % for all patients. The frequent grade 3/4 toxic effects included neutropenia and leukopenia.

Conclusions Sequential intraperitoneal and intravenous paclitaxel plus S-1 was well tolerated in gastric cancer patients with peritoneal metastasis.

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Keywords Gastric cancer · Peritoneal metastasis · Intraperitoneal chemotherapy · Gastrectomy

Introduction

Gastric cancer (GC) is a life-threatening disease worldwide. Recent advances in the treatment of GC have improved clinical outcomes.[1] However, GC patients with peritoneal metastasis (PM) still have a poor overall prognosis.[2] Recently, numerous modalities have been tried in the treatment of PM, such as aggressive surgery, intraperitoneal chemotherapy (IPC), and hyperthermia. However, none of these modalities have shown a satisfactory clinical outcome.[3–5] Consequently, there is no standard treatment for patients with PM.

S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) and paclitaxel (PTX) have a high rate of transition into the peritoneal cavity and a high efficacy against the diffuse type of adenocarcinoma which can easily disseminate.[6,7] Therefore, S-1 and PTX are suitable for PM systemic chemotherapy. In addition, in advanced and/or recurrent gastric cancer patients, several previous trials involving combination chemotherapy with S-1 and intravenous paclitaxel have reported on the safety and efficacy for measurable lesions.[8,9]

PTX has another advantage in the treatment of PM; when administered intraperitoneally it exhibits delayed clearance from the peritoneal cavity because of its high molecular weight and bulky structure. In our recent study we demonstrated the possible effectiveness of PTX for IPC.[10] The advantage of IPC exposure is best expressed as the achievement of a maximal concentration and area under the curve (AUC) ratios of the drug, between the peritoneal cavity and the peripheral blood.[10] Our study showed that the average maximal concentration and AUC ratios for paclitaxel were 1,065:1.[10] However, the clinical effects of intraperitoneal chemotherapy using PTX are unclear.

Therefore, we have developed a new regimen that involves the addition of a single intraperitoneal (IP) administration of PTX to the established systemic chemotherapy regimen of S-1 and PTX for the treatment of PM from GC. In our preliminary study, we confirmed the safety of the regimen.[10] In the present study, we carried out a phase II clinical trial to evaluate the efficacy, response, and safety of this novel multimodal treatment for GC.

Patients and Methods

This study was a prospective phase II study carried out between January 2005 and October 2008. During this period, we performed staging laparoscopy for patients in whom the presence of PM was suspected, for example, a nodular and irregular outer border of the thickened gastric wall, nodules on the peritoneal surface, or a small amount of ascites detected by multi-detector row CT (MDCT). Additionally, with the exception of possible PM, there was a lack of non-curative factors such as distant metastasis to the liver, lung, or lymph nodes. In these patients, the following eligibility criteria that were required for enrolment in this study included: (1) the presence of GC confirmed by histopathology; (2) the presence of PM confirmed by staging laparoscopy; (3) a performance status (Eastern Cooperative Oncology Group [ECOG]) <2; (4) age younger than 75 years; (5) no prior chemotherapy or surgery for gastric or other cancers; (6) adequate bone marrow function (leukocyte count >3,000 ml^{-1} and platelet count >100,000 ml^{-1}), (7) adequate liver function (serum bilirubin level <1.5 $mg dl^{-1}$ and serum transaminase levels less than twice the upper limit of the normal level); (8) adequate renal function, serum creatinine level <1.5 $mg dl^{-1}$; (9) no other severe medical conditions, such as symptomatic infectious disease, intestinal pneumonia, active hemorrhage/bleeding, or obstructive bowel disease; and (10) no current pregnancy or lactation. In accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1964, as revised in 1975 and 1983, written informed consent was obtained from the patients before the initiation of treatment and especially before surgery. Patients predicted to be eligible were informed about the therapeutic strategy, emphasizing its potential benefits as well as the possible risk of mortality and morbidity, prior to treatment and especially surgery. Informed consent was given by all patients.

Intraperitoneal Chemotherapy After Staging Laparoscopy

After PM was confirmed at staging laparoscopy, PTX was administered at a dose of 80 mg/m^2.[10] In each patient, PTX dissolved in isotonic saline to a final volume of 1 L was instilled into the peritoneal cavity at the end of the staging laparoscopy. Drainage of the drug solution was not carried out.[10]

Post IPC Systemic Chemotherapy

One week after IPC, S-1 was administered orally twice daily at a dose of 80 mg/m^2/day for 14 consecutive days, followed by 7-days rest. PTX was administered i.v. at a dose of 80 mg/m^2 on days 1 and 8 as previously reported.[8] The treatment course was repeated every 3 weeks until the observation of unacceptable toxicity, disease progression, or responses which might enable a macroscopically curative operation.

Evaluation of Toxicity, Tumor Response, and Indication of Gastrectomy with En Bloc D2 Lymph Node Dissection

Toxicity was measured using the common toxicity criteria of the National Cancer Institute, Version 2.0. In the patients

who had a target lesion, we evaluated the antitumor effects after two and five courses of the treatment and classified them based on the RECIST guidelines. Regarding the patients who had no target lesions, we evaluated the antitumor effects based on the wall thickness of the primary tumor by means of MDCT using the air filling technique. The area in the stomach where the wall thickness was measured corresponded to the area with a biopsy proven tumor mass. A patient was considered a responder in the case of tumor response or a 30 % improvement in wall thickness in one transverse, coronal, and sagittal image and was evaluated using second-look laparoscopy. In cases where there were negative PM findings at second-look laparoscopy, we performed gastrectomy with en bloc D2 lymph node dissection.

Gastrectomy with En Bloc D2 Lymph Node Dissection

The surgical procedure was either total gastrectomy for proximal tumors or subtotal gastrectomy when the primary tumor was located distally in the stomach, with a 5 cm "safe" margin. In all cases, an en bloc D2 lymph node dissection was performed according to the Japanese Gastric Cancer Association guidelines.[11]

Postoperative Chemotherapy

At more than 1 week after the operation, we performed postoperative chemotherapy. Initially one or two courses of weekly PTX,[12] followed by S-1 (80 mg/m^2/day, on days 1–14, every 3 weeks) was administered for more than 1 year or until recurrence was confirmed. Treatment after recurrence was at the physician's discretion.

Statistical Analysis

The JCOG 9205 study reported that the median survival time was 7.1 months (95 % confidence interval (CI), 5.8–8.2 months) in the 5-FU alone arm in patients with advanced and/or recurrent GC.[13] In our study, the median survival time is expected to be shorter than that in the JCOG9205 study owing to the fact that we evaluated patients who had PM. However, the median survival time of the patients whose treatment included an operation is expected to be longer than was the case in the JCOG9205 study. Based on these findings, on the premise that the threshold median survival time is 5 months and the expected median survival time is 9 months, the necessary number of subjects was calculated to be 32 with alpha=0.1 (one-tailed) and beta=0.2. The planned sample size was set at 35, with the consideration of approximately 10 % of patients being ineligible. The accrual time was 3 years and the follow-up time was 2 years after closure of recruitment. The primary endpoint of this study was overall survival. Secondary endpoints were response rate (RR) and safety.

Survival analyses were performed using the Kaplan–Meier method. The survival period was calculated from the first staging laparoscopy date to death or the day of most recent follow-up. Statistical analysis was conducted using the statistical software GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA, USA).

The clinicopathologic classifications were determined according to the criteria of the TNM Classification of Malignant Tumours, seventh edition. Toxicity and operative complications were measured using the common toxicity criteria of the National Cancer Institute, version 2.0.

Results

During the accrual time, we performed staging laparoscopy in 43 patients. Of these patients, only 35 with PM were enrolled in the current study and fully evaluated. The PM lesions were located mainly on the diaphragm, falciform ligament, and peritoneum. The remaining eight patients could not be enrolled in this study, because they did not have PM. Patient characteristics are listed in Table 1. All patients showed PM at first staging laparoscopy and underwent at least five cycles of systemic chemotherapy. Second-look laparoscopy was performed in 23 patients who were judged as responders according to our criteria. Gastrectomy with lymph node dissection was performed in 22 out of the 23 patients (96.6 %). In the remaining patient who still had PM at the second-look laparoscopy, gastrectomy was not performed. The flow diagram of the treatment protocol is shown in Fig. 1.

Table 1 Patient characteristics and tumor response (n=35)

	Number of patients	
Median age, years (range)	64 (32–75)	
Male/female	23/12	
ECOG performance status 0/1	35/0	
Histological type		
Intestinal	10	
Diffuse	25	
Tumor response		
RECIST guidelines (n=13)		
Complete response	1	8 %
Partial response	7	54 %
Stable disease	3	23 %
Progressive disease	2	15 %
Wall thickness (n=22)		
Over 30 % decrease	15	68 %
Increase	7	32 %

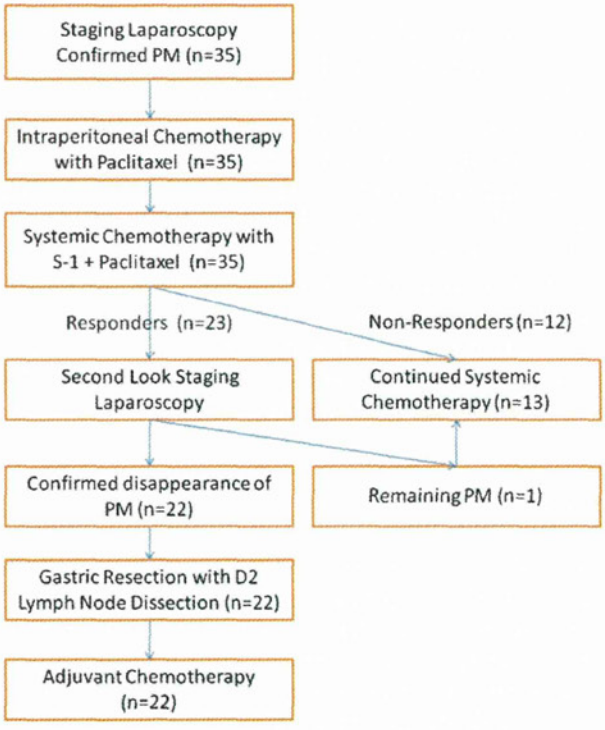

Fig. 1 Flow diagram of the treatment protocol. *PM* patients with peritoneal metastasis

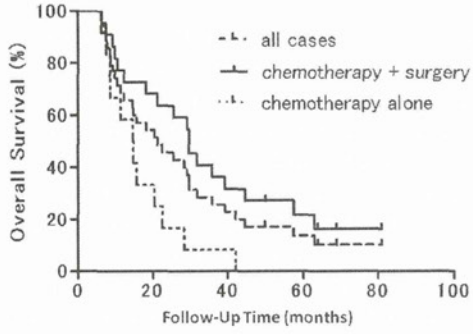

Fig. 2 Kaplan–Meier survival curve for the 35 eligible patients and the patients grouped according to whether or not surgery was carried out. (1) The 35 eligible patients: median survival was 21.3 months with a 1- and 2-year survival rate of 68.6 and 45.7 %, respectively. (2) Chemotherapy+surgery group: median survival was 29.7 months with 1- and 2-year survival rates of 77.3 and 63.6 %, respectively. (3) Chemotherapy alone group: median survival was 14.7 months with a 2-year survival rate of 15.4 %

Survival

At the time of analysis, 31 patients had died and the median follow-up time for the remaining four patients was 69.1 months. The median survival time (MST) of all patients was 21.3 months (95 % CI, 11.4 to 29.8 months), and the 1-year, 2-year, and 5-year overall survival (OS) rates were 68.6 % (95 % CI, 53.2 to 84.0 %), 45.7 % (95 % CI, 29.2 to 62.2 %) and 13.7 % (95 % CI, 2.1 to 25.4 %), respectively. In the patient that underwent gastrectomy, the 1-, 2-, and 5-year OS rates were 77.3 % (95 % CI, 59.8 to 94.8 %), 63.6 % (95 % CI, 43.5 to 83.7 %), and 21.8 % (95 % CI, 4.1 to 39.5 %), respectively, and MST was 29.7 months (95 % CI, 12.3 to 44.6 months). In the patient that received chemotherapy only, the 1- and 2-year OS rates were 53.8 % (95 % CI, 26.7 to 80.9 %) and 15.4 % (95 % CI, 0.0 to 35.0 %), respectively, and the MST was 14.7 months (95 % CI, 7.8 to 20.4 months). There was no patient survival beyond 5 years. The Kaplan–Meier survival curve is shown in Fig. 2.

Response

Thirteen patients had measurable target lesions and the remainder did not. Classification of the patients who had target lesions and were assessed for RR was based on the RECIST guidelines. The RR was 61.5 % (8/13), with one patient showing a complete response, and seven patients showing a partial response. While, out of the 22 patients without a measurable target lesion, a 30 % decrease in wall thickness was seen in 15/22 (68.2 %) (Table 1). Therefore, according of our evaluation of antitumor effects, 23/35 (65.7 %) patients were diagnosed as "responders".

Toxic Reactions

Hematological and non-hematological toxic reactions are listed in Table 2. No patient experienced abdominal pain or any other toxicity related to IPC. During IPC, a grade 3 toxicity reaction was noted in three patients (8.6 %). There were no grade 4 toxicity reactions. However, during systemic chemotherapy the grade 4 toxic reaction of neutropenia was observed in two patients. Frequent grade 3/4 toxic effects included leukopenia (5.7 %), neutropenia (20 %), alanine aminotransferase (ALT) elevation (2.9 %), and bilirubin (2.9 %). There were no treatment-related deaths.

Outcome of Second-Look Laparoscopy

The 23 patients that we diagnosed as responders underwent second-look laparoscopy. Unfortunately, only one patient who was judged as a responder due to a change in wall thickness remained with PM. Therefore, radical resection of all gross and microscopic disease (R0) after induction chemotherapy was accomplished in 22 patients.

Surgical Outcome

Gastrectomy was performed in 22 patients, including total gastrectomy in 19 and distal gastrectomy in three. In almost

Table 2 Adverse events associated with intraperitoneal and systemic chemotherapy

Number of patients (%)										
	Intraperitoneal chemotherapy					Systemic chemotherapy				
Grade (CTCAE v2.0)	1	2	3	4	3/4	1	2	3	4	3/4
Hematological toxicities										
Anemia	7 (20)	5 (14.2)	2 (5.7)	0 (0)	2 (5.7)	20 (57.1)	9 (25.7)	0 (0)	0 (0)	0 (0)
Leucopenia	4 (11.4)	3 (8.6)	1 (2.9)	0 (0)	1 (2.9)	7 (20)	10 (29)	2 (5.7)	0 (0)	2 (5.7)
Neutropenia	4 (11.4)	2 (5.7)	1 (2.9)	0 (0)	1 (2.9)	2 (5.7)	7 (20)	5 (14.2)	2 (5.7)	7 (20)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST elevation	2 (5.7)	1 (2.9)	0 (0)	0 (0)	0 (0)	6 (17.1)	0 (0)	0 (0)	0 (0)	0 (0)
ALT elevation	4 (11.4)	0 (0)	1 (2.9)	0 (0)	1 (2.9)	6 (17.1)	1 (2.9)	1 (2.9)	0 (0)	1 (2.9)
Bilirubin	1 (2.9)	3 (8.6)	0 (0)	0 (0)	0 (0)	6 (17.1)	3 (8.6)	1 (2.9)	0 (0)	1 (2.9)
Creatinine	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)
Non-hematological toxicities										
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17)	2 (6)	0 (0)	0 (0)	0 (0)
Anorexia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (37)	2 (6)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17)	2 (6)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (11)	1 (2.9)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neuropathy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (20)	0 (0)	0 (0)	0 (0)	0 (0)

all patients, we found a decrease in the size of the main tumor at the time of gastrectomy. The operative complication rate was 9 %, including one case of anastomotic leakage and pancreatic fistula. The details of the 22 patients and the postoperative final tumor stage are listed in Table 3.

Postoperative Chemotherapy

Postoperative chemotherapy was initiated in all 22 patients that underwent gastrectomy, and was completed in all patients. The adverse events of the postoperative chemotherapy were relatively mild, and throughout the treatment period, there were no grade 4 toxic effects.

Discussion

In the current study, our new combination regimen showed a 1-year OS rate of 68.6 % with a MST of 21.3 months. Recent studies targeting unresectable or recurrent GC patients have shown a 1-year OS rate of about 50 %. Our survival results are encouraging in that patents with PM are generally considered to show a particularly poor prognosis.

PM is currently treated with systemic chemotherapy as a palliative, not curative therapy.[14] In brief, there are no GC patients with PM that who survived for over 5 years that had only received chemotherapy.[15] Otherwise, R0 resection is indispensable for curing the gastric cancer. Therefore, we must carefully consider the advantages and disadvantages associated with surgery for GC patients with PM. We might perform gastrectomy on patients who exhibit a response to chemotherapy. In our study, the patients with gastrectomy showed a 1-year OS rate of 77.2 % with a MST of 29.7 months. Additionally, three patients who survived beyond 5 years had undergone gastrectomy. To care for the GC patients, R0 resection was required. Therefore, the GC patients in which PM disappeared after chemotherapy might undergo gastrectomy. Consequently, the survival rates of patients who underwent gastrectomy after chemotherapy were better than those of patients who received chemotherapy alone. This finding indicated that our treatment strategy was appropriate for these patients.

Generally, the effects of chemotherapy are determined by tumor response. However, the evaluation of tumor response in GC patients with PM is difficult because they frequently do not have a target lesion. Therefore, we have developed a new evaluation technique for the chemotherapeutic effect using MDCT with the air filling technique. Using this technique, PM was found to have disappeared in 14 out of 15 (93.3 %) patients who were judged as being responders. Thus, our new evaluation technique was useful in these patients.

With regard to intraperitoneal chemotherapy, toxicity reactions were mild, with only grade 3 toxicity reactions being noted in three patients. Therefore, intraperitoneal chemotherapy with PTX was safe in these patients. During

Table 3 Surgery, pathological results, and postoperative complications in 22 patients

	n	%
Type of resection		
Total gastrectomy	19	86.3
Distal gastrectomy	2	9.0
Pancreaticoduodenectomy	1	4.5
R0 resection rate	22	100
D2 lymph node dissection	22	100
Tumor stage		
CR	1	4.5
M	1	4.5
SM	2	9.0
MP	1	4.5
SS	16	72.7
SE	1	4.5
Nodal stage		
N0	10	45.5
N1	2	9.0
N2	5	22.7
N3a	1	4.5
N3b	4	18.2
Postoperative complications		
Anastomotic leakage	1 (Gr. 2)	4.5
Bleeding	0	0
Intestinal occlusion	0	0
Intra-abdominal abscess	0	0
Pancreatic fistula	1 (Gr. 2)	4.5
Pneumonia	0	0
Surgical site infection	0	0
Death resulting from complication	0	0
Any postoperative complication	2	9.0

Gr. toxicity grade according to the Clavien–Dindo classification

systemic chemotherapy, neutropenia was the main toxic effect; it was more frequent and severe with S-1 plus PTX chemotherapy.[8,9] Non-hematological toxicity effects were relatively mild and were similar to those reported in previous studies.[8,9]

In the present study, the postoperative morbidity rate was 9 %. In previous studies, postoperative morbidity of the patients after chemotherapy for advanced gastric cancer has been reported to occur with a frequency of 31–44.9 %.[16–18] These results indicated that our novel multimodal treatment for GC with PM is feasible and effective.

In conclusion, novel multimodal treatment for GC with PM was well tolerated and active in GC patients with PM. This regimen should be evaluated further in a randomized phase III trial.

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RESEARCH Open Access

Analysis of the clinical factors associated with anal function after intersphincteric resection for very low rectal cancer

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Abstract

Background: Intersphincteric resection (ISR) has been used to avoid permanent colostomy in very low rectal cancer patients. This study aimed to assess the surgical safety and oncologic and functional outcomes of ISR.

Methods: The records of 30 consecutive very low rectal cancer patients who underwent ISR without neoadjuvant therapy were retrospectively analyzed; survival and locoregional recurrence rates were calculated by the Kaplan-Meier method. Incontinence was assessed by a functionality questionnaire and the Wexner score.

Results: The median distance between the distal margin of the dentate line was 10 mm. A total of 12, 4, and 14 patients underwent partial ISR, subtotal ISR, and total ISR, respectively. The mean distal resection margin was negative in all cases, and circumferential resection margin was positive in two cases. Morbidity was 33.3%: anastomotic stricture in seven patients, colonic J-pouch prolapse in two patients, and an anovaginal fistula in one patient. During the median, 56.2-month follow-up period, local, distant, and combined recurrences occurred in four, three, and two patients, respectively. The 5-year overall and disease-free survival rates were 76.5% and 68.4%, respectively. Local recurrence rates were 5.2% for the patients with Tis-T2 tumors as compared with 45.5% for those with T3 tumors ($P = 0.008$). The mean Wexner scores and stool frequencies, 12 months after stoma closure in 19 patients, were 11.5 and 6.6 per 24 h, respectively. Significant differences were not seen in the Wexner scores between partial ISR and subtotal/total ISR (11.8 ± 2.6 and 9.1 ± 5.6). Stool frequency ($P = 0.02$), urgency ($P = 0.04$), and fragmentation ($P = 0.015$) were worse in patients with anastomotic stricture than in those without; there was no symptom improvement in patients with anastomotic stricture.

Conclusions: The anastomotic strictures in patients undergoing ISR may have negatively affected anal function. For total ISR patients, at least, informed consent stating the possibility of a permanent colostomy is necessary.

Keywords: Intersphincteric resection, Very low rectal cancer, Wexner score

Background

Over the last two decades, surgical treatment for patients with very low rectal cancer has radically evolved, allowing permanent colostomy to be avoided in these patients. Reappraisal of the distal margin has allowed increased potency of sphincter-preserving resections. Moreover, total mesorectal excision (TME) [1], coupled with techniques such as end-anal stapling and coloanal anastomosis using the double-stapling technique (DST) [2], can be used to preserve the sphincter without compromising on the oncological results [3-5].

However, when the tumor is located close to the dentate line, conventional anterior resection using the interperitoneal approach with DST may not allow a secure distal resection margin. To resolve this problem, partial or total internal sphincteric resection (ISR) and coloanal anastomosis per anus can be used for safe surgical resection of the tumor [6-11]. ISR has been proposed to achieve distal clearance in selected patients with very low rectal tumors extending to the upper part of the internal sphincter muscle. Furthermore, it has been

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proposed to restore the anal structure, preserve fecal continence, and reduce the numbers of patients requiring a permanent stoma.

ISR has been widely recognized to achieve a safe distal resection margin, which can be as small as 1 to 2 cm [12,13]. However, with this procedure, which involves dividing the rectum between the internal sphincter and the external sphincter or the levator ani, it remains unclear whether a secure circumferential resection margin (CRM) of the tumor can be obtained. Further, partial or total ISR procedures have been shown to possibly interfere with fecal continence [7,8,14-16].

Anal incontinence is considered to influence various factors in patients receiving ISR, including preoperative radiation therapy [17,18], reconstruction methods [9], extent of sphincter preservation [19], tumor level, and height of the anastomosis [20]. Moreover, fecal incontinence-related quality of life (QOL) scores were poorer in ISR patients than the patients with low anterior resection [16]. Although ISR was proposed as an alternative procedure to avoid abdominoperineal resection (APR), a colostomy is a viable option for patients who suffer from fecal incontinence, which offers a definitive cure along with an improved quality of life [21].

To evaluate the feasibility of ISR in very low rectal cancer patients, it is necessary to clarify the oncologic results and functional outcomes related to this procedure. The aims of this study were to evaluate the surgical safety of the procedure, to assess its oncologic and functional outcomes, and to identify factors predictive of anal dysfunction in the absence of radiotherapy.

Methods

Patients

We reviewed the medical charts of all 30 consecutive patients who had undergone ISR for very low rectal adenocarcinoma between April 2001 and August 2010 at the Department of Surgery, Faculty of Medicine, Kinki University. Written informed consent forms concerning this procedure were obtained for all patients in our hospital. In all cases, tumor stage was evaluated before surgery by digital examination; colonoscopy; chest, abdominal and pelvic computed tomography (CT); and pelvic magnetic resonance imaging (MRI). Anorectal manometry was not routinely performed. Preoperative criteria for the exclusion of patients for ISR were clinical T4 tumors, poorly differentiated adenocarcinoma (revealed by biopsy specimens), infiltrating gross appearance of the tumors, and some degree of preoperative incontinence. Among patients with T1 tumors considered for transanal local excision, ISR was proposed for those patients with a risk of lymph node metastases in the case of tumors with adverse pathologic features. Resectable distant metastases were not a preoperative exclusion criterion for ISR, and therefore, ISR was performed in one patient with synchronous liver metastasis.

The histopathological findings and tumor stage classification were based on the Union for International Cancer Control (UICC) TNM classification (seventh edition) [22]. In Japan, preoperative chemoradiotherapy (CRT) for resectable T3 rectal tumors, irrespective of lymph node involvement, was not routinely performed, and none of the patients included in this study had received preoperative CRT or pre or postoperative radiotherapy.

Surgical technique

The principle of the ISR procedure is based on an anatomic dissection plane between the internal sphincter muscle, which is an extension of the muscular layer of the rectum, and the external sphincter muscle. Surgical intervention was commenced with a high ligation of the inferior mesenteric artery using the abdominal approach. The rectum was dissected to the levator ani with TME. Further, the intersphincteric plane was entered from the nearest anorectal junction if possible. If this dissection was technically difficult to perform until a sufficient distal margin was obtained via the abdominal approach, then the transanal approach of the operation was commenced after perineal exposure using a retractor (Lone Star retractor, Lone Star Medical Products Inc, Houston, TX, USA). The distal margin was 1 cm for Tis-T2 tumors, and 2 cm below the inferior extent of the tumor for T3 tumors. Total ISR involved complete excision of the internal sphincter muscle, that is, the distal line of resection was along the intersphincteric groove. For partial ISR, the distal resection line was along the dentate line, and for subtotal ISR, the distal resection line ran from the dentate line to intersphincteric groove [11,19]. If the tumor was close to the external sphincter or the levator ani muscle, additional partial external sphincter resection (ESR) [11] was performed.

The proximal rectal side of the cut edge was immediately closed and irrigated with 1,500 ml of a 5% povidone-iodine solution to reduce the risk of tumor-cell dissemination [7,23]. Then, the dissection was carried out longitudinally along the plane between the internal and external sphincters to reach the abdominal excision. After the rectum was removed through the abdomen, colonic J-pouch and anal anastomosis procedures with interrupted suture were performed. The anastomosis was protected with a diverting loop ileostomy or transverse colostomy in all the patients.

Follow-up and local recurrences

All 30 patients were followed for a median of 56.2 months (range; 13.3 to 168.4 months), and 20 patients were available for follow-up for more than 2 years. All

patients were followed using a standardized protocol, including a clinical examination with digital palpation, and laboratory tests, including tumors markers (carcinoembryonic antigen (CEA), CA-19-9), every 3 months for the first 3 years, and then every 6 months for 2 years, and then once a year. Abdominal and pelvic computed tomography and chest radiography were performed every 6 months for the first 3 years. A colonoscopy was performed 3 or 6 months after surgery for planning stoma closure, and then once every year for 3 years. Most patients with stage III rectal cancer received postoperative chemotherapy with oral tegafur, uracil, and/or folic acid for 6 to 12 months. Local recurrence was defined as the presence of any anastomotic, pelvic, or lateral node recurrences documented either by clinical or pathologic exanimation, irrespective of the presence of distant metastases.

Anal functional assessments

Functional outcomes were assessed using our functional questionnaire. We prospectively collected questionnaires regarding anal function from our patients every 3 months after closure of the diverting stoma. In this questionnaire, patients were asked about stool frequency (number of bowel movements per 24 h), fecal urgency (ability to defer stool evacuation for >15 minutes), stool fragmentation (>2 evacuations in 1 h), dyschesia (taking more than 15 minutes to defecate), nocturnal defecation, use of intestinal transit regulators, and need to wear a pad. Incontinence was assessed by the Wexner continence score [24], and we considered anal function to be poor if the Wexner score was 15 or more at 12 months [17,18]. Anastomotic stricture or occlusion was determined when the surgeon's forefinger could not pass through the anastomotic site 3 months after surgery.

Statistical analysis

Statistical analyses were performed using JMP10 software (SAS Institute Inc., Cary, NC, USA). Overall and disease-free survival were analyzed using Kaplan-Meier curves and the log rank test. For disease-free survival, patients who failed locally, systemically, or both were censored at the time of the first failure.

Univariate and multivariate regression analyses were used to evaluate the impact of age, gender, type of surgery, type of reconstruction, and anastomotic stricture. The changes in anal function between the different groups of patients over time were compared using Wilcoxon signed-rank test, and comparisons between the anastomotic stricture group and the non-stricture groups were performed using the Mann–Whitney U test. Statistical significance was indicated at the P <0.05 level.

Results

Patients and tumor characteristics are shown in Table 1.

During the study period, ISR covered 144 patients (26.3%) who underwent surgery for lower-third rectal cancer, located below the peritoneal reflex, 49 patients of conventional anterior resection with DST, 35 patients of abdominoperineal resection, and 20 patients of local excision. The study population was made up of 30 patients (16 men and 14 women) with a median age of 58.9 years (range, 31 to 75 years); 1 patient (3.3%) had a pTis of a large villous tumor, 8 patients had a pT1 tumor (26.7%), 10 patients had a pT2 tumor (33.3%) and 11 patients had a pT3 tumor (36.7%). According to the UICC TNM classification system, the tumors were classified as stage 0 in 1 patient, stage I in 16 patients, stage IIA in 5 patients, stage IIIB in 5 patients, and stage IVA in 1 patient.

Table 1 Clinicopathological characteristics of patients who received intersphincteric resection (n = 30)

Characteristic	Value
Age, years[a]	60.5 ± 9.9
Histopathological grade[b]	
G1	12
G2	16
Muc	2
Tumor location	
Anterior wall	14
Posterior wall	12
Left wall	1
Right wall	2
Circ	1
Tumor size, cm[a]	3.8 ± 1.5
<4 cm	18
≥4 cm	12
pT stage	
Tis	1 (3.3%)
T1	8 (26.7%)
T2	10 (33.3%)
T3	11 (36.7%)
TNM stage	
0	1
I	16
IIA	5
IIIA	2
IIIB	5
IVA	1

[a]Values denote mean ± SD.
[b]Differentiation of adenocarcinoma: G1 = well differentiated; G2 = moderately differentiated; Muc = mucinous carcinoma. Circ = circumferential tumor.

Surgical and histopathological findings are shown in Table 2.

In this study, partial ISR, subtotal ISR, and total ISR were performed in 12, 4, and 14 patients, respectively. Furthermore, 4 of 11 patients (36.4%) with T3 tumors intraoperatively decided to undergo additional partial ESR. The mean distance between the distal edge of the tumor and the dentate line was 8.9 ± 8.0 mm (range, -3 to 25 mm) in all the patients. Tumor location was significantly different for each ISR procedure (partial ISR, 16.0 ± 4.6 mm; subtotal ISR, 5.0 ± 4.1 mm; total ISR, 3.5 ± 5.1 mm).

Assessment of the fixed surgical specimens revealed that the median distal edge of the tumor was 7 mm (range, 3 to 22 mm), and it was negative in all cases. The median circumferential margin of the tumor was 3 mm (range, 0.5 to 9 mm). The circumferential resection margin was positive (<1 mm) in two patients with T3 tumor without partial ESR. Reconstruction of the colonic J-pouch was performed in 26 patients, and straight coloanal anastomosis was performed in 4 patients due to narrow pelvis or bulky mesocolic fat tissue.

Mortality and morbidity

There was no mortality. Complications were encountered in ten patients (33.3%). Anastomotic leakage occurred in seven patients, who were treated with perianal drainage. The colonic J-pouch prolapsed in two patients who underwent total ISR. One patient had an anovaginal fistula, requiring repair of fistula using perineal muscular rotation flap, and subsequent stoma closure. Anastomotic stricture or complete occlusion of an anastomosis occurred in seven patients. Of these seven patients, five patients required dilation of the anastomosis using finger bougie, endoscopic balloon dilation, or surgical stricture plasty before stoma closure. Two patients suffered complete occlusion of the anastomosis.

Table 2 Differences in clinicopathological characteristics between intersphincteric resection (ISR) procedures

	Partial ISR, (n = 11)	Subtotal ISR, (n = 4)	Total ISR, (n = 14)
Sex			
Male	6	2	6
Female	6	2	8
Type of reconstruction			
Colonic J-pouch	9	4	13
Straight	3	0	1
Combined with partial ESR	0	2	2
Distance between the distal edge of the tumor andthe dentate line, mm[a]	16.0 ± 4.6	5.0 ± 4.1	3.5 ± 5.1
Distal resection margin, mm[a]	8.7 ± 6.0	9.5 ± 10.5	7.2 ± 5.4
CRM, mm[a]	3.2 ± 2.7	4.8 ± 3.1	3.6 ± 2.1
No. of stoma closures[b]	9 (81.8)	2 (50)	8 (57.1)

[a]Values indicate mean ± SD.
[b]Data in parentheses represent percentage values in each group.
CRM = circumferential resection margin; ESR = external sphincteric resection; ISR = intersphincteric resection.

Oncologic results

Local, distant, and combined recurrence occurred in four, three, and two patients, respectively. Six patients died of cancer recurrence. For all patients who received ISR, the 5-year overall and disease-free survival rates were 76.5% and 68.4%, respectively.

The median disease-free interval for six patients with local recurrence was 13 months (range, 8 to 14 months) (Table 3). All of the four isolated local recurrence episodes developed within the first 2 years. All the patients who experienced local recurrence had pT3 tumors, except one patient who had a pT2 tumor. The local recurrence rates were significantly lower in patients with Tis to T2 tumors (5.2%) than in those with T3 tumors (45.5%; $P = 0.008$; Figure 1).

Aspects of stoma closure

Of the 29 ISR patients, excluding 1 with stage IVA disease, 19 (65.5%) underwent stoma closure by February 2010, including 3 patients who had undergone straight anastomosis. The median interval between ISR and stoma closure was 7 months (range, 3 to 14 months). The median follow-up interval after stoma closure was 35 months (range, 4 to 68 months). Nine, two, and eight patients received stoma closure in the partial ISR, subtotal ISR, and total ISR groups, respectively (Table 2).

Definitive stoma closure could not be performed in 11 patients. Of the 11 patients, 5 had insufficient anal condition (complete anastomotic occlusions in 2, prolapse of colonic J-pouch in 2, obvious loose anastomosis in 1). The patients who developed colonic J-pouch prolapse or obvious loose anastomosis had received total ISR. Four patients were diagnosed with distant metastases or local relapse of the disease before stoma closure. Two patients did not undergo stoma closure for social reasons. Three out of four patients with additional partial ESR did not achieve stoma closure because of a colonic J-pouch prolapse or local recurrence.

Evaluation of anal function

Anal function was evaluated in 19 patients who underwent stoma closure. At 12 months after stoma closure, the mean Wexner score for all patients was 11.5 (range, 1 to 19). In the patients with partial ISR, the Wexner scores were improved from 13.0 ± 3.1 at 3 months to 12.1 ± 3.0 at 6 months ($P = 0.04$). In contrast, in the patients with subtotal or total ISR, no significant differences were found between the Wexner scores at 3 months and 6 months (13.0 ± 3.8 and 11.5 ± 4.9,

Table 3 Characteristics of six patients with local recurrence after intersphincteric resection (ISR)

Patient	TNM	T stage	Histological type	Surgical procedure	Distal resection margin, mm	Circumferential resection margin, mm	Localization	Distant metastases	Treatment	Outcome
1	IIA	T3	G2	tISR + pESR	7	2	Pelvic wall	NS	CRT	45 months, O
2	IIIB	T3	G2	sISR + pESR	25	2	Pelvic wall	NS	CRT	70 months, S
3	IIIB	T3	G2	pISR	12	5	Pelvic wall	Bone, lung	Cx	31 months, P
4	IIA	T3	G2	pISR	10	0.5	Lateral node	Adrenal gland	Cx	36 months, P
5	I	T2	G1	pISR	3	6	Anastomosis	NS	APR	22 months, S
6	IIB	T3	G1	pISR	3	0.5	Lateral node	NS	CRT	17 months, S

Distal resection margins and circumferential resection margins were measured on the histological slides.
APR = abdominoperineal resection; CRT = chemoradiotherapy; Cx = chemotherapy; ESR = external intersphincteric resection; ISR = intersphincteric resection; NS = not stated; O = other origin of death; P = primary death; S = survived.

respectively; $P = 0.14$), but an upward trend was observed in the Wexner scores at 6 months and 12 months (11.5 ± 4.9 vs 9.1 ± 5.6, respectively, $P = 0.06$). At 3, 6, and 12 months, the Wexner scores were not significantly different between patients who underwent partial and subtotal or total ISR (Table 4). In the patients without anastomotic stricture, the Wexner scores were significantly improved at 6 months and 12 months compared with those at 3 months. However, five patients, including the one with subtotal ISR and an additional partial ESR, required finger bougie, endoscopic balloon dilation, or stricture plasty for anastomotic stricture, no improvement in the Wexner score was observed.

Table 5 shows the anal function based on the questionnaires answered at 3, 6, and 12 months after stoma closure, with or without anastomotic stricture. At 12 months after stoma closure, patients without anastomotic stricture were showed improved urgency (from 12/14 to 3/12; $P = 0.008$) and nocturnal defecation (from 9/14 to 5/12; $P = 0.014$). However, patients with anastomotic stricture did not report improvement in any symptom. Compared to patients with anastomotic stricture, the non-stricture group showed significantly better results with regard to stool frequency (5.1 ± 2.9 vs 9.0 ± 5.3; $P = 0.02$), urgency (3/12 vs 4/5; $P = 0.04$), and fragmentation (4/12 vs 5/5; $P = 0.015$) at 12 months.

The results of the univariate analysis revealed that poor anal function, as assessed by the Wexner score, was significantly associated with gender (male; $P = 0.047$) and the presence of anastomotic stricture ($P = 0.018$) at 12 months. The surgical procedure (partial or subtotal/total ISR), type of reconstruction (straight or colonic J-pouch), and age (<70 or ≥70) were not significantly associated with anal function. The results of the multivariate analysis also showed that gender ($P = 0.283$) was not significantly associated with anal function and that the presence of anastomotic stricture ($P = 0.093$) only demonstrated a trend towards being significantly associated with anal function (data not shown).

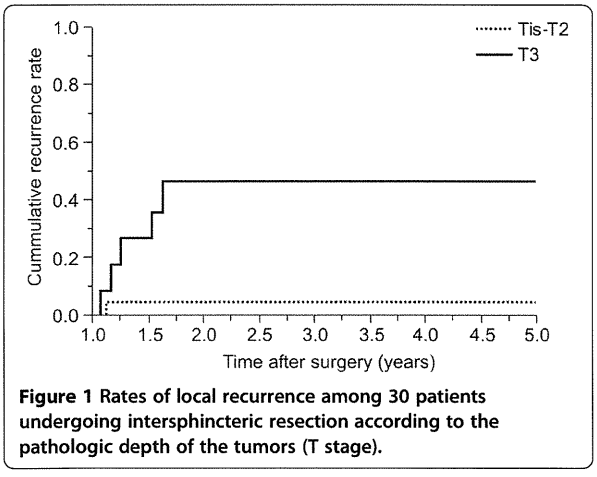

Figure 1 Rates of local recurrence among 30 patients undergoing intersphincteric resection according to the pathologic depth of the tumors (T stage).

Discussion

Although ISR is the sphincter-preserving procedure for very low rectal cancer, there are concerns regarding local control and defecatory function. In this study, we report the outcomes of ISR of very low rectal cancer, less than 2.5 cm from the dentate line, with a median follow-up period of 56 months. Our data show that this operation is feasible, with no postoperative mortality found in the study group. Moreover, it is associated with favorable

Table 4 Wexner scores at 3, 6, and 12 months in patients who underwent intersphincteric resection (ISR) followed by stoma closure

Procedure/findings	3 months	6 months	12 months
Surgical procedure			
Partial ISR (n = 9)	13.3 ± 3.1	12.1 ± 3.0*	11.8 ± 2.6
Subtotal or total ISR (n = 10)	13.0 ± 3.8	11.5 ± 4.9	9.1 ± 5.6
Anastomotic stricture			
Yes (n = 5)	15.4 ± 2.9	13.4 ± 4.5	13.6 ± 3.9
No (n =14)	12.4 ± 3.3	11.2 ± 3.9*	9.0 ± 4.5*

Data are shown as mean ± SD. Data at 6 and 12 months were statistically compared with those at 3 months using the Wilcoxon signed-rank test.
*P <0.05.

Table 5 Anal dysfunction after stoma closure in patients with anastomotic stricture and those with no anastomotic stricture

Symptoms related to anal function	3 months		6 months		12 months	
	Non-stricture	Stricture	Non-stricture	Stricture	Non-stricture	Stricture
Stool frequency, times/day	6.4 ± 3.6	11.4 ± 3.0**	6.8 ± 2.8	7.0 ± 2.1	5.1 ± 2.9	9.0 ± 5.3**
Urgency	12/14	4/5	8/13	2/5	3/12*	4/5**
Fragmentation	10/14	5/5	7/13	4/5	4/12	5/5**
Dyschesia	2/14	3/5	2/13	0/5	2/12	0/5
Medication use	4/14	4/5	3/13	4/5**	2/12	3/5
Nocturnal defecation	9/14	5/5	5/13*	5/5	5/12*	4/5

Data associated with each anal dysfunction at 6 and 12 months were statistically compared with those at 3 months for each condition of anastomotic sites using Wilcoxon signed-rank test. *P <0.05.
Data associated with each anal dysfunction of the stricture group were statistically compared with those of the non-stricture group at 3, 6, and 12 months using the Mann–Whitney U test. **P <0.05.

oncological outcomes for Tis-T2 tumors. With regard to the Wexner score, total ISR did not produce worse outcomes than partial ISR did, with the exception that permanent stoma were necessitated by unfavorable anastomosis. However, anastomotic stricture, which occurred as a postoperative complication, was found to negatively affect anal function.

From an oncological point of view, local control of the disease remains the most important objective in rectal cancer surgery. The local recurrence rate of very low rectal cancer for ISR varied widely, ranging between 0% [23] to 31% [25]. With ISR, the rate of secure distal resection margin was in the range of 95% [23] to 100% [18], and our results showed a median distance of 7 mm, and a definite negative distal margin in all patients. Therefore, ISR was found to provide an optimal distal resection margin, which is difficult to attain by using only the abdominal approach for very low rectal cancer. Rate of positive CRM of the rectal cancer also influenced factor of local recurrence. In our study group, 6.7% of all patients had a CRM ≤1 mm, and similar results were reported in the range of 0% to 13.3% [18,26]. Preoperative CRT was considered useful for preventing local recurrence in low rectal cancer patients requiring ISR [14,23]. Kuo *et al.* [26] reported a positive CRM rate of 13.3%, but a local recurrence rate of 7.7% in their ISR series of 26 patients; 88.5% of these patients had undergone preoperative CRT. Paradoxically, Hohenberger and colleagues [27] reported that in ISR patients with lower-third rectal cancer without radiotherapy, the local recurrence rate was high, at 46.5%. In our study, local recurrence was significantly higher in patients with T3 tumors than in those with Tis-T2 tumors. Akasu *et al.* [28] reported that both T3 tumors and a positive microscopic resection margin in patients who underwent ISR were significantly associated with local recurrence. Because ISR involves dissection of the rectum between the internal sphincter muscle and the external sphincter muscle, in patients with T3 tumors with expanding microscopic tumor cells near the levator ani or the external sphincter muscles, during surgical resection, there is a considerable risk of cutting into the tumor or achieving a very short distance of a few millimeters to the CRM. Thus, for a group of patients with T3 tumors, ISR was applied to attain good responses to neoadjuvant CRT, leading to secure CRM.

Partial or total resection of the internal sphincter muscle resulted in defecatory dysfunction with frequent defecation, urgency, and fecal incontinence [16,18,29]. Moreover, preoperative radiotherapy against T3 tumors or lymph node involvement was found to have a negative impact on anal function after ISR [17,18,26]. In the study by Ito *et al.* [17], of all the patients who underwent ISR, 40% received radiotherapy and were found to have a mean Wexner score of 10 at 12 months. Moreover, Denost *et al.* [20] reported a median Wexner score of 11 in most of the patients who received radiotherapy.

It has been shown that colonic J-pouch reconstruction in conjunction with ISR can minimize the anal dysfunction-related side effects of a sphincteric resection [9]. Hida *et al.* [30] reported the long-term benefits of colonic J-pouch reconstruction suggesting that it improves reservoir function to a greater extent than straight anastomosis does, especially in patients in whom the anastomosis is less than 4 cm from the anal verge. In addition, Dennett *et al.* [31] reported that colonic J-pouch is effective in very low rectal cancer surgery, causing apparent reduction in the incidence of anastomotic leaks and in bowel frequency. In our study, the mean Wexner score was 11.5 in most patients with colonic J-pouch reconstruction, and none of the patients had received radiation therapy. In previous studies, total ISR was performed in 8.9% [29] to 33.7% [20] of all the ISR patients. A possible reason for the poorer outcomes about Wexner score in our study was that the number of patients who required total ISR accounted for approximately half the ISR patients (42.1%), because coloanal anastomosis using conventional DST was technically possible in a few patients who required partial ISR during our study period.

The outcome for continence is reported to be worse after total ISR than after subtotal or partial ISR [19,20]. In our results for Wexner scores, anal function between total or subtotal ISR and partial ISR were not different, but patients of partial ISR had earlier recovery than those of subtotal or total ISR. Our functional results are limited because of the differences in stoma closure rates between partial ISR and subtotal/total ISR patients. The rates of stoma closure in patients with subtotal or total ISR were lower than those in patients undergoing partial ISR. This result in itself indicates poor anal function outcomes for subtotal/total ISR. Especially with respect to the three patients with total ISR, stoma closure was not possible because of the high risk of major incontinence.

Postoperative complication rates varied between reported series from 18% to 64% [15]. Common complications included leakage, anastomotic stricture, fistula, pelvic sepsis, and prolapse. In a previous literature review, anastomotic leakage rates of 5% to 48% [32] were reportedly associated with ISR, and they varied depending on whether asymptomatic leaks were radiologically detected. Also, Tilney and Tekkis [9] reviewed 21 studies and reported an overall anastomotic leak rate of 10.5% and anastomotic stricture rate of 5.8%. Similar rates were reported in the current series: anastomotic leakage occurred in 7 of 30 patients (23.3%) and anastomotic stricture in 12% of the patients. Anastomotic leakage is an important feature since it has been found to lead to postoperative anastomotic stricture [33] and poor postoperative anorectal function [34]. However, in our study, there were no independent factors associated with anal dysfunction in the multivariate analysis, but patients with anastomotic stricture showed worse outcomes (frequency, urgency, and fragmentation) than patients without anastomotic stricture. In addition, symptoms related to anal function were not reduced in these patients. In our study, anastomotic stricture or occlusion occurred in five of seven patients with anastomotic leakage; thus, stricture formation could be attributed to leakage caused by ischemia or infection of the anastomotic site. Therefore, it is necessary to fully explain the possibility of fecal incontinence or of a permanent stoma to the patients before obtaining informed consent. Fecal QOL in our patients who had an anastomotic stricture was worse, and they might have little benefit from preserving the anal continuity with ISR.

Our study has some limitations: it was a retrospective study and the sample size was relatively small. There could be potential bias due to possible difference between those who were ambitious of receiving the anal sphincter preserving surgery and those who did not, which could affect the self-evaluation for gastrointestinal questionnaire. With regard to the additional partial ESR performed only in one patient with stoma closure, this was not taken into consideration while estimating anal function.

Conclusions

In summary, ISR is an oncologically safe procedure for pTis or pT2 tumors among very low rectal cancer patients. Also, total ISR, that is, complete removal of the internal sphincter muscles, carried risks of worse anal function or possibility of a permanent stoma. The complications associated with anastomosis, especially stenosis, resulted in poorer anal function. Larger studies are needed to evaluate functional results in ISR patients who suffer from anastomotic stricture.

Abbreviations

CRM: circumferential resection margin; DST: double-stapling technique; ESR: external sphincter resection; ISR: intersphincteric resection; TME: total mesorectal excision.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

TT, KO, JH, KU, TY, KD, MT, FS: made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. TT, KO, JH: drafted the article and revised it critically for important intellectual content. TT, KO, JH, KU, TY, KD, MK, FS: responsible for final approval of the manuscript. All authors read and approved the final manuscript.

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REVIEW ARTICLE

High ligation of the inferior mesenteric artery in rectal cancer surgery

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Abstract In rectal cancer surgery, it is unclear whether the inferior mesenteric artery (IMA) should be ligated as high as possible, at its origin, or low, below the origin of the left colic artery. We reviewed all relevant articles identified from MEDLINE databases and found that despite a trend of improved survival among patients who underwent high ligation, there is no conclusive evidence to support this. High ligation of the IMA is beneficial in that it allows for en bloc dissection of the node metastases at and around the origin of the IMA, while enabling anastomosis to be performed in the pelvis, without tension, at the time of low anterior resection. High ligation of the IMA does not represent a source of increased anastomotic leak in rectal cancer surgery and postoperative quality of life is improved by preserving the hypogastric nerve without compromising the radicality of the operation. More importantly, high ligation of the IMA improves node harvest, enabling accurate tumor staging. Although the prognosis of patients with node metastases at and around the origin of the IMA is poor, the survival rate of patients with rectal cancer may be improved by performing high ligation of the IMA combined with neoadjuvant and adjuvant therapy.

Keywords Rectal cancer · Inferior mesenteric artery · High ligation · Low ligation

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Introduction

In rectal cancer surgery, it is unclear whether the inferior mesenteric artery (IMA) should be ligated at a high position, flush with the aorta, or at a low position, below the origin of the left colic artery. The advantage of the high-ligation technique is that it allows for en bloc dissection of the lymph node metastases at and around the origin of the IMA, and enables anastomosis to be performed in the pelvis, without tension, at the time of low anterior resection. It also contributes to the accuracy of tumor staging. In contrast, the low-ligation technique allows for adequate blood supply to the colon proximal to the anastomoses at the time of low anterior resection [1]. There is also little or no risk of injury of the hypogastric nerve plexus and its possible consequence of ejaculation disorder [2, 3].

It has been reported that there is no significant difference in survival rates between the two techniques [4–8]. Based on these considerations, we set to identify, interpret, and discuss the available evidence related to performing IMA high ligation in rectal cancer surgery and identify future directions.

Dispute about the best position for ligation of the IMA

Since Miles [9] and Moynihan [10] proposed low- and high-ligation techniques, respectively, for rectal carcinoma surgery in the same year, 1908, the ideal position for arterial ligation has been debated. Miles introduced the concept of the upward spread of carcinoma and recommended division of the IMA just distal to the left colic branch with subsequent en bloc excision of the nodes and bowel below. Conversely, Moynihan argued that ligation and division of the IMA should be flush with the aorta to remove even more proximal nodes. When Dukes [11], Ault

et al. [12], State [13], and McElwain et al. [14] all demonstrated that the upward lymphatic extension of cancer was confined with remarkable consistency to the glands intimately related to the IMA right up to the aorta, Moynihan's high ligation became a logical extension of radical excision for rectal cancer. Furthermore, Gabriel et al. [15] and Morgan and Griffiths [16] reported that the survival of patients with Dukes C1 (the highest nodes encompassed by surgical resection, uninvolved) was better than that of patients with Dukes C2 (the highest nodes, involved). Thus, Moynihan's philosophy is still now supported by most colorectal surgeons. On the other hand, Dunphy and Pikula [17] proposed a modified procedure instead of high ligation, in which fatty tissues and nodes are dissected free and excised in the angle between the IMA and aorta, and the artery is ligated below the left colic branch.

Doubt was first cast on this approach by reports of poor survival after high ligation [4, 5]. Those patients with involved nodes above the left colic artery, for whom the high ligation was supposed to have been most advantageous, did not appear to have a better prognosis than others treated more conservatively. In other words, there was no significant difference in survival rates between the two techniques [4–8, 18, 19]. Because surgical cure is unlikely if cancer has spread to the nodes at the origin of the IMA, low ligation has been performed more frequently since 1970s [20].

Heald and Ryall [21] showed the world how total mesorectal excision (TME) following high ligation of the IMA can be readily affected with preservation of the inferior hypogastric plexuses and the hypogastric nerves. Local recurrence accounts for 34–45 % of recurrences after surgery for rectal cancer [22–24]. In fact, the local recurrence rates after TME reported by MacFarlane et al. [25], Arbman et al. [26], Enker et al. [27], Leo et al. [28], Law and Chu [29], Kapiteijn et al. [30], Tocchi et al. [31], Vironen et al. [32], Bülow et al. [33] and Wibe et al. [34] were 5.0, 3.3, 5.7, 9.2, 11.4, 8.2, 9.0, 9.0, 11.0, and 10.0 %, respectively. Considering that conventional operations are associated with an average local recurrence rate of 30 % worldwide [35–37], the local recurrence rate after TME is relatively low. Havenga et al. [38] reported that autonomic nerve preservation, in association with TME following high ligation of the IMA, reduced the local recurrence rate and minimized urinary and sexual dysfunction in patients undergoing rectal cancer surgery. Since 1990s, the goal of most specialist units has become TME with nerve preservation as standard practice [25–27, 39–42]. Our impression is that the vast majority of surgeons use high ligation to emulate the technique espoused by Heald. Furthermore, high ligation is advocated by many surgeons because in laparoscopic surgery it allows the easy creation of mesenteric windows [43–48].

The guidelines for the prevention, early detection, and management of colorectal cancer in Australia recommend high ligation, although this is based on weak evidence (Grade IV in the I-to-V scale) [49]. In contrast, the Guidelines for Colon and Rectal Cancer Surgery from the National Cancer Institute of the United States recommend low ligation [50]. However, the evidence to support low ligation is weak (level II–III in the I-to-V scale of evidence and grade C in the A-to-D scale of recommendation grades). These guidelines also recommend that all nodes suspicious for metastasis proximal to the origin of the left colic artery be biopsied or removed, or that the level of resection should be extended to include the nodes of concern [50].

One recent review article on the ligation level of IMA recommended high ligation because of improved node retrieval rates and accuracy of tumor staging [51]. Conversely, another recent review article recommended low ligation because it was anatomically less invasive with respect to circulation of the proximal colon limb of anastomosis [52]. This article also stated that the anatomic disadvantage of high ligation in relation to impaired perfusion of the proximal limb and anastomotic leakage has not been proven sufficiently [52].

The Japanese Classification of Colorectal Carcinoma [53] divides central regional node spread in colorectal cancer into two levels: central spread N3 (main node), with nodes at the origin of the primary feeding artery; and central spread N2 (intermediate node), with nodes other than the main nodes, which lie along the primary feeding artery. For invasive colorectal cancer, the Japanese Classification of Colorectal Carcinoma [53] recommends ligating the primary feeding artery at its origin. Therefore, in Japan, high ligation of the IMA is performed routinely for invasive rectal cancer; and widely in combination with lateral pelvic node dissection.

Ligation level and survival (Table 1)

In relation to 5-year survival rates, Grinnell [5] reported that high ligation resulted in a 7.3 % higher survival rate when only Dukes C tumors were considered. Similarly, Uehara et al. [54] reported no significant difference in survival rates between the two groups for lower rectal cancer and could not demonstrate any effect of prophylactic lymph node dissection at the root of the IMA on patients with any stage of disease. Moreover, they reported that lymph node dissection without the root of the IMA did not result in increased para-aortic or mediastinal lymph node metastases [high tie 1.9 % (4/207) vs. low tie 3.8 % (3/78)], which they had attributed to failing to perform lymph node dissection. Kawamura et al. [55] reported that

Table 1 Survival after high versus low ligation of the inferior mesenteric artery in rectal cancer surgery

References	Site of tumor	5-year survival (%)	
		High tie* (*n*)	Low tie (*n*)
Rosi et al. [4]	Rectum	65.1 (66)	56.0 (82)
	Rectosigmoid	58.3 (24)	47.0 (17)
Grinnell [5]	Rectum, sigmoid and descending colon	5.7 % higher than low tie (151)	(150)
Bacon et al. [6]	Upper rectum	58.3 (139)	52.3 (NA)
	Lower rectum	53.4 (118)	49.5 (NA)
Pezim and Nicholls [7]	Rectum, rectosigmoid	64.5 (543)	65.2 (690)
Surtees et al. [8]	Rectum, rectosigmoid (Dukes C ctage)	55.7 (150)	54.3 (100)
Slanetz and Grimson [59]	Rectum, colon	70.8 (1027)	68.1 (1053)
Adachi et al. [62]	Rectum, sigmoid colon	83.2 (134)	91.5 (38)
Uehara et al. [54]	Lower rectum	74.6 (133)	77.8 (78)

NA Not available

* *P* value not significant versus low tie

the incidence of local lymph node recurrence did not differ significantly between their high and low tie groups (2.3 % (3/132) vs. 1.8 % (7/379), respectively).

Pezim and Nicholls [7] reported that patients with Dukes stage C2 in a high-ligation group fared significantly worse (22.2 vs. 52.2 % 5-year survival rate). They hypothesized that many of the Dukes stage C2 patients in the low-ligation group would have in fact had Dukes stage C1 cancer, had a high ligation been performed. A subsequent paper from the same institution [8] analyzed the survival of patients with Dukes stage C rectal cancers. The number of harvested nodes was higher in the high-ligation group (mean 14.2 vs. 11.9). The 5-year survival rate of patients with Dukes C1 cancers did not differ significantly between the high- and low-ligation groups (64 vs. 54 %, respectively). However, for those with Dukes C2 tumors, although there was an apparently improved survival rate after treatment by low IMA ligation, this was not significant. One explanation would be that many of the Dukes C2 cases in the low-ligation group would have in fact been staged C1, had a high IMA ligation been performed, thus creating a stage-migration phenomenon [56]. To minimize this effect, a subgroup of patients in the high-ligation group with involvement of the 12th node from the tumor was compared with a Dukes C2 tumor subgroup of patients in the low-ligation group, with no significant survival differences observed. They concluded that high ligation of the IMA did not improve survival. Rouffet et al. [57] favor low ligation because it yielded a 5-year survival rate of 64 %, comparable to high ligation (62 %), in a French multicenter, randomized trial of left colectomy and high ligation of the IMA versus segmental colectomy and low ligation of the IMA. The 12-year survival rates in this study were 54 versus 47 % for low versus high ligations, respectively. Because the survival rate after high ligation was only slightly higher, some colorectal surgeons now perform low ligation [52].

On the other hand, Leggeri et al. [58] reported a good prognosis after rectal cancer surgery with high ligation of the IMA, with 5-year survival rates of 68.1 % after sphincter-saving surgery and 57.5 % after abdominoperineal resection of the rectum. Slanetz and Grimson [59] reported a stage-specific survival benefit of high ligation. The level of IMA ligation had no influence on the 5-year survival rates of patients with Dukes stage A colon or rectal tumors. Patients with Dukes stage B colon cancers had significantly higher survival rates following high IMA ligation (83.9 vs. 73.9 %), but this trend was not seen in the rectal cancer subgroup. In patients with Dukes C colorectal cancers, high-IMA ligation significantly increased the 5-year survival to 52.9 versus 45.2 % of those who underwent low ligation. No significant advantage of high IMA ligation was evident in the survival rates of patients with Dukes C1 or C2 rectal cancers and Dukes C2 colon cancers, although those with Dukes C1 colon cancers fared better (58.6 vs. 49 %). However, when five or more nodes were involved, the level of ligation did not influence survival rates. This confirms previous findings that the positive effect of high IMA ligations is lost when the apical node is involved (Dukes stage C2) and with an increasing number of nodes being involved [5, 7]. Nevertheless, in patients with intermediate node involvement only, removing the uninvolved central nodes by performing high ligation of the IMA almost doubled the 5-year survival rate (41.7 vs. 25.9 %) and reduced the rate of death from recurrent cancer from 66.7 to 38.9 % [59]. Read et al. [60]

favored high ligation for left-sided colonic cancers based on multivariate analysis data, with high ligation of the IMA trending toward a good prognosis for both locoregional control at 5 years (96 %) and 5-year disease-free survival (84 %). More radical excision of lymphatic drainage may be more effective for carcinoma of the rectum; however, this has not been consistent for proximal lymphatic spread if data from retrospective studies are to be believed.

IMA root nodal metastasis and survival

Lymph node involvement is a major prognostic factor for survival after rectal cancer surgery. High ligation includes the apical group of nodes at and around the origin of the IMA within the resection; however, the incidence of metastasis to the IMA root nodes is reported to be relatively low, ranging from 0.3 to 11.1 % (Table 2) [6, 7, 54, 57–59, 61–66]. Bacon et al. [67] reported that positive nodes would have been left behind in 9 % (8/90) of patients operated on if a high ligation had not been carried out. Pezim and Nicholls [7] studied 5-year survival rates after the high-ligation technique and found it to be as low as 18.7 % of patients with IMA root nodal metastasis as opposed to 63.6 % of patients without IMA root nodal metastasis. Furthermore, Grinnell [5] and Uehara et al. [54] reported no survivors among their patients with IMA root nodal metastases; however, as many patients with IMA root nodal metastases had metastases in more proximal nodes, an operation with high ligation would result in a noncurative resection. Because the 5-year survival rate of patients with IMA root nodal metastases is low after high ligation, the low-ligation technique is used in rectal cancer surgery in some specialist units [20].

Interestingly, four studies on high ligation reported significantly positive 5-year survival data for patients with IMA root nodal metastases [58, 64, 66, 68]. Leggeri et al. [58] reported that the 5-year survival rate of Dukes stage C patients was clearly influenced by the level of proximal node involvement, being 68.2 % of patients with marginal node involvement, 25 % of those with intermediate node metastases, and 30 % of those with central node metastases. The survival rate of patients with IMA root node metastases was approximately half of that for those without IMA root node metastases. Because of the retrospective design of their study, it was impossible to find out what the survival rates of patient with IMA root positive node metastases would have been if those nodes were left in place. Furthermore, the impact afforded by the knowledge of nodal status may have altered the outcome. Conceivably, patients with IMA root nodal-positive metastases may have been treated in a more nihilistic manner, whereas those without IMA root nodal metastases may have been treated aggressively with adjuvant therapy, accounting for the twofold difference in survival. Cosimelli et al. [68] reported an overall 5-year survival rate of 58.5 % after rectal

Table 2 Inferior mesenteric artery root nodal metastasis and survival

References	Site of tumor	Metastatic Incidence[a] % (*n*)	5-year survival of pts with metastasis %
Morgan and Griffiths [16]	Rectum, sigmoid and descending colon	8.4 (18/214)	NA
Rosi et al. [4]	Rectum, rectosigmoid	8.3 (3/36)	NA
Grinnell [5]	Rectum, sigmoid and descending colon	10.6 (19/179)	No survivors who were free of cancer
Bacon et al. [6]	Rectum, sigmoid and descending colon	11.1 (11/99)	27.3
Pezim and Nicholls [7]	Rectum, rectosigmoid	5.5 (32/586)	18.7
Surtees et al. [8]	Rectum, rectosigmoid (Dukes C ctage)	NA	32.0
Leggeri et al. [58]	Rectum	4.2 (10/239)	30.0
Cosimelli et al. [68]	Rectum, sigmoid colon	5.6 (17/302)	42.7
Slanetz and Grimson [59]	Rectum	7.5 (22/294)	18.2
Hida et al. [66]	Rectum, rectosigmoid	8.6 (17/198)	38.5
Adachi et al. [62]	Rectum, sigmoid colon	0.7 (1/135)	NA
Steup et al. [61]	Lower rectum	0.3 (1/373)	NA
Kim et al. [71]	Rectum, sigmoid colon	3.6 (73/2040)	38.0
Kanemitsu et al. [64]	Rectum, sigmoid colon	1.7 (20/1188)	40.0
Uehara et al. [54]	Lower rectum	1.9 (4/207)	0
Chin et al. [65]	Rectum	2.9 (29/1002)	13.8
	Sigmoid colon	3.6 (14/387)	50.0

NA Not available

[a] No. of patients with metastasis/total no. of patients

cancer surgery with high ligation of the IMA. In this study, TME was performed, and systemic chemotherapy, with or without high-dose pelvic radiotherapy, was administered to selected Dukes B and C patients, suggesting that modern multimodality oncologic therapy combined with nerve-sparing TME, as advocated by Heald [69], can achieve high survival rates even for patients with Dukes stage C2 tumors, contrary to previous reports [5, 7]. Kanemitsu et al. [64] calculated that high-IMA ligation increased the curative resection rate by 9 %, but only 0.7 % of those patients were likely to be cured by this. Lymph node metastases at the root of the IMA were found in 1.7 % of the 40 % of patients who survived for 5 years, which compares well with data for patients with intermediate node metastases, who had a survival rate of 50 % at 5 years. This metastatic incidence (1.7 %) represented the frequency of residual metastatic nodes that would normally have been left behind in a low ligation. Furthermore, they reported that the high tie might save the occasional patient and prove helpful when nodal metastases are limited to below the level of the left colic artery by providing a greater margin of safety when the artery, including all the surrounding glands and lymphatics, is excised by a single block dissection. Liang et al. [70] postulated that the high tie would provide good and similar locoregional control of tumors with or without lymph node metastasis because 92.9 % of the recurrences in 28 patients developed within 3 years after surgery and all of those in patients with Dukes A/B, C1, or C2 cancers were distant metastases (recurrence rates: 20.0 % of 10 patients, 27.0 % of 74 patients, and 42.9 % of 14 patients, respectively; $P > 0.05$). Kim et al. [71] reported that high tie resulted in similar loco-regional recurrences among patients with and those without IMA root node metastasis (recurrence rates: 20.4 % of 54 patients and 16.0 % of 94 patients, respectively).

Based on these considerations, we set to clarify the indications for high ligation of the IMA in rectal cancer surgery [66]. First, we examined regional node metastases of rectal cancer, using the clearing method (xylene clearance), which makes it possible to identify nodes smaller than 4 mm in maximum diameter and to detect small metastatic nodes that would be undetected by the conventional manual method [72]. The mean number of nodes examined per patient was 73.5, being 14553 nodes in 198 patients. The incidence of metastasis was 56.6 % and the incidence of metastasis to the IMA root nodes was 8.6 %, which was higher than reported previously. These differences may be attributed to the detection of metastatic nodes smaller than 4 mm in maximum diameter by the clearing method. It is believed that the greater the number of nodes examined and the higher the incidence of metastasis, the more accurate the evaluation of the extent of node dissection for cancer control. IMA root nodal metastases developed more frequently in patients with pT3 and pT4 rectal cancer, at incidences of 9.4 and 20.8 %, respectively. For both pT1 and pT2 tumors, the incidence of metastasis to the IMA root nodes was 0 %. Among the 198 patients, 144 underwent curative resection. The 5-year survival rate of the 13 patients with IMA root nodal metastasis was 38.5 %, being significantly lower than the 73.4 % of those without IMA root node metastasis. The 5-year survival rate of patients with IMA root nodal metastasis was still higher than that reported in the literature, which could be because we examined metastatic nodes smaller than 4 mm in maximum diameter by the clearing method and performed extended node dissection following high ligation of the IMA. We concluded that although the survival rate of patients with IMA root nodal metastases was lower than that of those without metastases, IMA root nodal dissection should be performed after high ligation of the IMA for patients with pT3 and pT4 cancers. Upper lymphatic spread along the IMA was strongly related to the depth of tumor invasion. Kanemitsu et al. [64] reported that the incidence of IMA nodal metastasis for pT1, pT2, pT3, and pT4 tumors was 0, 0.4, 2.6, and 2.9 %, respectively. Chin et al. [65] reported that the IMA metastasis incidence for pT1, pT2, pT3, and pT4 tumors was 0, 1.0, 2.6, and 4.3 %, respectively. Nodal metastases at the origin of IMA occurred more frequently in patients with pT3 and pT4 tumors. In contrast, nodal metastases rarely developed at the origin of IMA in patients with pT1 and pT2 cancers. These studies [64–66] suggested that the low tie might be sufficient for pT1 and pT2 rectal cancers. However, according to an accompanying Invited Editorial by Wexner [43], high ligation should be performed for all patients with rectal carcinomas because it is impossible to know at the time of surgery, which patients have pT3 and pT4 lesions. Wexner also states that no method of preoperative or intraoperative assessment allows for 100 % sensitivity and specificity toward this issue. The problem with using preoperative staging to guide the extent of node dissection is that no imaging technique offers absolute staging accuracy [73, 74]. It has been our policy to perform high-tie procedure to cure patients with cancer of the rectum. However, its contraindications are an age of 85 years or more, advanced arteriosclerosis, and extreme obesity. Obviously, the high tie technique should not be used as a palliative procedure. The low-tie technique has been adopted as a standard procedure, when adequate exposure to allow ligation of the IMA on the aorta is considered too hazardous, such as after abdominal aorta replacement surgery for an aneurysm.

Although it is widely accepted that IMA high ligation does not improve survival, most data originated from studies on operations performed 4–5 decades ago, when TME and adjuvant chemo- and radiotherapy were not common practice. More recent reports challenge this belief [59, 62, 64, 66]. However, most of these studies originate in Japan, where IMA