

Intersphincteric Resection in Patients with Very Low Rectal Cancer: A Review of the Japanese Experience

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PURPOSE: This study was designed to evaluate the feasibility and oncologic and functional outcomes of intersphincteric resection for very low rectal cancer.

METHODS: A feasibility study was performed using 213 specimens from abdominoperineal resections of rectal cancer. Oncologic and functional outcomes were investigated in 228 patients with rectal cancer located <5 cm from the anal verge who underwent intersphincteric resection at seven institutions in Japan between 1995 and 2004. **RESULTS:** Curative operations were accomplished by intersphincteric resection in 86 percent of patients who underwent abdominoperineal resection. Complete microscopic curative surgery was achieved by intersphincteric resection in 225 of 228 patients. Morbidity was 24 percent, and mortality was 0.4 percent. During the median observation time of 41 months, rate of local recurrence was 5.8

percent at three years, and five-year overall and disease-free survival rates were 91.9 percent and 83.2 percent, respectively. In 181 patients who received stoma closure, 68 percent displayed good continence, and only 7 percent showed worsened continence at 24 months after stoma closure. Patients with total intersphincteric resection displayed significantly worse continence than patients with partial or subtotal resection. **CONCLUSIONS:** Curability with intersphincteric resection was verified histologically, and acceptable oncologic and functional outcomes were obtained by using these procedures in patients with very low rectal cancer. However, information on potential functional adverse effects after intersphincteric resection should be provided to patients preoperatively. [Key words: Very low rectal cancer; Intersphincteric resection; Abdominoperineal resection; Coloanal anastomosis; Anal function]

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Local control and survival for patients with rectal cancer have been improving with the development of surgical techniques and combined adjuvant therapies.^{1,2} The advent of mechanical low-stapling and double-stapling techniques and sutured coloanal anastomosis has facilitated easier anastomosis at the distal rectum. These methods have increased the frequency of sphincter salvage. Nevertheless, permanent colostomy is still performed in approximately 20 percent of patients with low rectal cancer. Abdomi-

noperineal resection (APR) is a standard surgery for low rectal cancers located <5 cm from the anal verge or <2 cm from the dentate line (DL). These cancers may be associated with lymph node metastasis along the levator ani muscle or in the fatty tissue of the ischiorectal fossa,³ and also may have the potential for microscopic involvement of the rectal wall below the tumor.⁴ APR has been established as a standard procedure in patients with lower rectal cancer. Patients undergoing APR can experience some problems with quality of life, because permanent colostomy results in psychologic and social limitations.^{5,6}

In recent years, intersphincteric resection (ISR) with coloanal anastomosis has been proposed to avoid permanent colostomy for rectal cancers located <5 cm from the anal verge, although these tumors are not generally considered for sphincter-saving procedures.^{7–13} Several studies have reported that local control and functional results after ISR are satisfactory.^{7,10–14} Experiences with ISR, including partial external sphincteric resection (PESR), also have been reported in recent studies^{12,15}; however, data remain scarce. The rationale for ISR in patients with very low rectal cancer is described in this review article by using data from Japanese experiences and Western reports, and our theoretic background is provided based on the histologic evidence.

PATIENTS AND METHODS

Pathologic and Theoretic Background

The pathologic study was performed by a surgical pathologist (KS) at Kurume University. In this pathologic study of 213 surgical specimens from APR for lower rectal cancer or anal canal cancer excluding anal cancer, the external sphincter muscle, puborectalis muscle, and fatty tissue of ischiorectal fossa were investigated for direct invasion and skip metastasis. The entire tumor mass was sectioned at 5-mm intervals, including oral and anal parts up to 5 cm from the tumor. The same surgical pathologist (KS) made all final pathologic diagnoses.^{15,16}

Patient Population

A total of 228 consecutive patients (168 males) who underwent ISR between 1995 and 2004 were identified from the hospital databases, and medical charts were retrospectively reviewed. These 228 patients received ISR at seven institutions in Japan

that participated in the “Studies on preservation of anal function for very low rectal cancer patients,” sponsored by Grant-in-Aid 14-10 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. Median age was 58 (range, 27–77) years. All 228 patients displayed adenocarcinoma located <5 cm from the anal verge.

The anal verge was defined as the terminal part of the surgical and anatomic anal canal. The intersphincteric groove (ISG) exists between the terminal part of the internal sphincter (IS) and the subcutaneous part of the external sphincter (ES). Exact level of the lower edge of the tumor from the anal verge was assessed and measured by digital examination and endoscopy. All tumors found infiltrating the rectal wall on digital examination, computed tomography (CT), magnetic resonance imaging (MRI), or endorectal ultrasonography (US) were eliminated from consideration for local excision. Patients were classified according to International Union Against Cancer (UICC) standards¹⁷ after preoperative diagnosis using CT, MRI, US, colonoscopy, chest radiography, and biopsy.

An exception to selection of ISR was made if malignant infiltration of other organs or of the striated muscles of the pelvic floor (such as levator ani muscle or external sphincter) was suspected, if tumors displayed low differentiation on histopathology, or if preoperative anal function demonstrated marked insufficiency. Patients with synchronous metastases also were excluded from ISR. These patients were treated by using conventional APR. In the present study, ISR was performed mainly in very low rectal cancer patients with T3, T2, or T1 (massive invasion of the submucosa) disease lying <5 cm from the anal verge. All resected specimens were examined to determine macroscopic and microscopic surgical margins (distal and radial). Postoperative mortality and morbidity, local control, and survival also were investigated.

Surgical Technique and Classification

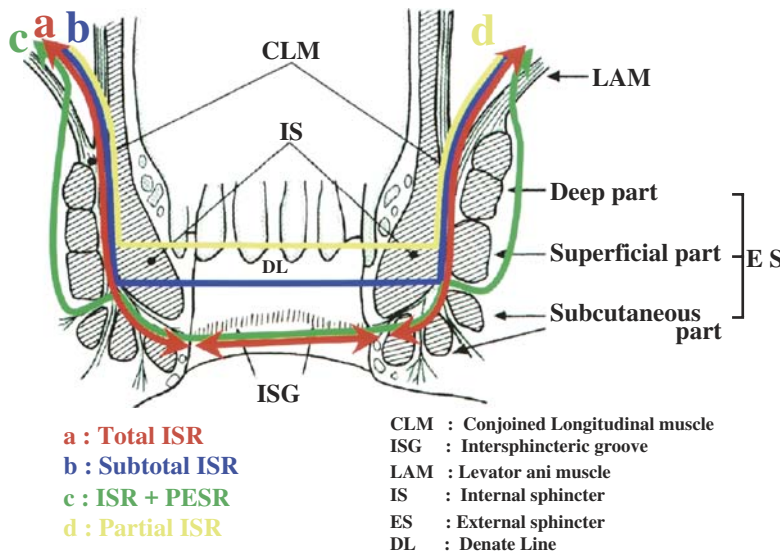
ISR was performed according to the methods previously reported by Schiessel *et al.*⁷ and others.^{10,12,15} The surgical technique included both abdominal and perianal approaches. Abdominal dissection was performed first. Total mesorectal excision (TME) with lateral node dissection was undertaken. During the abdominal approach, the autonomic nerve system was preserved to the fullest

extent possible, using Japanese methods previously described.¹⁸⁻²² The rectum was mobilized carefully as low as possible to the pelvic floor to facilitate the perianal approach. The IS was then exposed and circumferentially divided from the puborectalis muscle and ES. During these procedures, the tumor was evaluated through gentle palpation by the surgeon. If tumor had invaded beyond the rectum into the puborectalis muscle or ES at the anorectal junction or anal canal, the puborectalis muscle was resected and fatty tissue of the ischioanal fossa was visualized. ISR plus PESR was performed in those patients.

After the abdominal approach, perianal resection was performed. Circumferential incision of the mucosa and IS was initiated 1 to 2 cm distal to the tumor. The anal orifice was closed by pursestring suture to avoid spread of tumor cells during perianal operation.¹² Once the intersphincteric space was entered, careful dissection continued upward between the smooth and striated sphincters under constant guidance by the abdominal surgeon.

Total ISR involved complete excision of the IS for tumors spreading to or beyond the DL. The distal cut-end line was at the ISG. Total ISR was unnecessary in patients with tumor located ≥ 2 cm from the DL. Those patients underwent subtotal ISR. The distal cut-end line was between the DL and ISG, and the DL was included in the resected specimen. In patients with tumor located from >2 to 3 cm from the DL, the distal cut-end line was just on or above the DL. This procedure, partial ISR, sometimes includes conventional coloanal anastomosis procedures. When patients displayed tumor invading the ES, ISR plus PESR was performed. At least the subcutaneous part of the ES was preserved in these patients. ISR was classified into four types: total ISR; subtotal ISR; partial ISR; and ISR + PESR (Fig. 1).

After specimen removal and generous irrigation of the pelvic cavity, the sigmoid colon was pulled down and coloanal anastomosis with or without colonic pouch was made according to the method described by Parks.²³ Anastomoses were performed by using perianal manual suturing in all patients.



Type of ISR	Anastomotic line	Sacrificed sphincter
Partial	Just on DL or within 1cm oral side from DL	Partial IS
Subtotal	Between DL and ISG	Almost all of IS
Total	Just on ISG	Total IS without or with partial ES

Figure 1. Resecting lines in intersphincteric resection (ISR) are illustrated. PESR=partial external sphincteric resection.

Finally, a diverting stoma using terminal ileum or transverse colon was established. This stoma was closed at three to six months postoperatively.

Adjuvant Therapy

Preoperative radiochemotherapy was performed in 57 patients with T3 tumors who agreed to preoperative adjuvant therapy at the National Cancer Center Hospital East (NCCHE), National Defense Medical College, or Chiba University. Other patients underwent surgery alone, because preoperative radiochemotherapy for resectable rectal cancer is not standard in Japan. The 44 patients from the NCCHE received 45 Gy during a five-week period, followed by operation two weeks later. In addition, continuous infusion of 5-fluorouracil (250 mg/m²/day) was administered to these patients during radiotherapy to increase radiotherapeutic efficacy. Although reevaluation using CT, MRI, US, and colonoscopy was performed in these patients after completion of preoperative radiochemotherapy, all patients underwent ISR. Most patients with Stage III tumor (pTNM pathologic classification) received postoperative chemotherapy with 5-fluorouracil and folinic acid, or tegafur uracil, or others for six months or more.

Follow-Up and Functional Assessment

Follow-up examinations were performed every three months for two years postoperatively, and subsequently every six months. Examinations included clinical, laboratory (including tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9), and radiologic (abdominal and pelvic CT and chest radiography) investigations.

Functional outcomes also were assessed at the same time by using our functional questionnaire. This functional questionnaire asked about stool frequency (number of bowel movements per 24 hours), feces and flatus discrimination, urgency (ability to defer stool evacuation for >15 minutes), fragmentation (≥ 2 evacuations in 1 hour), soiling during the day and night, use of pads, use of medications, and alimentary restriction. Incontinence was assessed by using the continence scores of both the Jorge and Wexner,²⁴ and classification by Kirwan *et al.*²⁵

Median follow-up was 41 (range, 10–84) months. No patients were lost to follow-up, and 57 percent of patients were observed for ≥ 36 months.

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) were calculated by using Kaplan-Meier methods. Duration to final follow-up evaluation, treatment failure, or death was measured from the date of rectal resection. Assessment of local recurrence was evaluated by using a cumulative local disease-free survival curve. Assessment of recurrence and survival was performed in patients with microscopically curative surgery.

RESULTS

Pathologic Validity

Pathologic study of the 213 surgical specimens from APR for lower rectal cancer or anal canal cancer (excluding anal cancer) revealed neither direct invasion nor skip metastasis in subcutaneous external sphincter muscle or fatty tissue of the ischiorectal fossa; however, spread of cancer to the deep and superficial ES muscles or puborectalis muscle was observed in 14 percent. Curative operation was thus accomplished by using ISR in 86 percent of patients undergoing APR. When tumor invasion exceeds the IS at the surgical anal canal, safe surgical margins can be obtained using ISR with combined resection of the deep and superficial ESs. Complete radical surgery can theoretically be accomplished even if subcutaneous ES muscle is not resected.

Population

The study was comprised of 228 patients with very low rectal cancer (including surgical anal canal cancer) who underwent ISR between 1995 to October 2004. Tumor characteristics and surgical procedures are shown in Table 1. Median lower edge of the tumor was 3.4 (range, 2–5) cm from the anal verge. Tumor staging was T3 tumor (n = 103), T2 tumor (n = 78), or T1 (n = 46). Surgical procedure was subtotal ISR in 124 patients, total ISR with or without PESR in 69 patients with tumor located ≤ 2 cm from the anal verge, and partial ISR in 35 patients. These procedures were decided according to tumor localization. All patients underwent coloanal anastomosis by manual suturing. Anastomosis involved a colonic J-pouch (n = 51), coloplasty (n = 25), side-to-end anastomosis (n = 5), or straight anastomosis (n = 147).

Table 1.
Patients Undergoing ISR

	(n = 228)
Age (yr)	58 (27–77)
Male/female ratio	168/60
Tumor	
Distance from anal verge (cm)	3.4 (2–5)
Clinical stage	
T1	46
T2	78
T3	103
T4	1
Procedure	
Partial ISR	35
Subtotal ISR	124
Total ISR (with or without PESR)	69
Morbidity rate	24 percent (55/228)
Mortality rate	0.4 percent (1/228)

ISR = intersphincteric resection; PESR = partial external sphincteric resection.

Data are medians with ranges in parentheses or numbers of patients.

Fifty-seven patients received preoperative radiochemotherapy.

Morbidity and Mortality

Postoperative complications occurred in 55 patients (24 percent), including anastomotic leakage (n = 23), pelvic infection and abscess (n = 10), anastomotic stenosis (n = 7), colonic ischemia and necrosis (n = 4), anovaginal fistula (n = 3), postoperative bleeding (n = 3), mucosal prolapse (n = 3), and postoperative ileus (n = 2). In 9 of these 55

patients (4 percent), additional surgery, such as APR or Hartmann’s operation, was required because of postoperative massive hemorrhage, colon necrosis, or anastomotic insufficiency. Surgery-related death occurred in one patient (0.4 percent) who experienced a breakdown of colonic J-pouch and died of sepsis. No differences in morbidity were identified between the radiochemotherapy and surgery-alone groups.

Pathologic Findings

Radical resection of the tumor was achieved in all 228 patients. Surgery was judged as microscopically curative in 225 patients (98.7 percent) who displayed adequate cancer-free margins (distal and radial). Unclear surgical margins were noted in three patients with Type 3 tumor, because microscopic vessel involvements were observed very near to the surgical margins. These three patients were excluded from assessments for recurrence and survival, although none of these patients received additional surgery, such as APR, because obvious positive margins were not identified. Follow-up was performed as usual.

Recurrences

During the median observation time of 41 months, 30 of 225 patients developed recurrence. These recurrences comprised lung metastasis (n = 11), liver metastasis (n = 11), local recurrence including regional lymph node metastasis (n = 8), inguinal lymph node metastasis (n = 4), bone metastasis

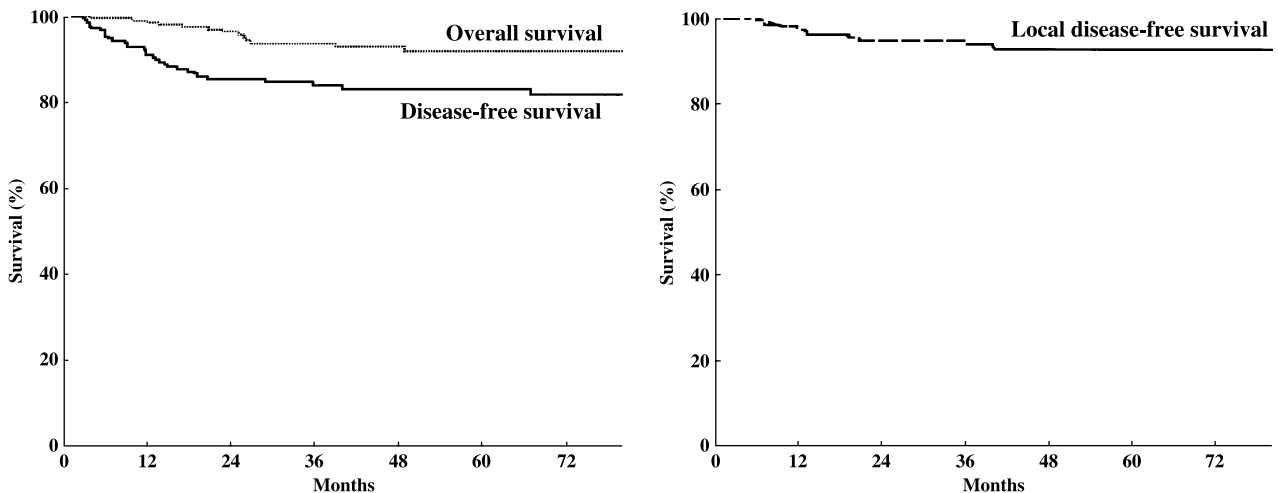


Figure 2. Overall survival was 91.9 percent and disease-free survival was 83.2 percent at five years. Acceptable local control also was obtained.

Table 2.
Functional Results After Stoma Closure

	(n = 181)			
	3 Months	6 Months	12 Months	24 Months
Continence				
Wexner score (n = 110)	17 ± 1.7	11.2 ± 4	8.4 ± 4.5	7.8 ± 4.2 ^a
Kirwan classification				
I Perfect	17	19	36	36
II Incontinence of flatus	11	12	16	32
III Occasional minor soiling	45	51	36	25
IV Frequent major soiling	19	16	12	7
V Incontinent (required colostomy)	8	2	0	0

ISR = intersphincteric resection.

Data are means ± standard deviations or percentages.

^a Partial ISR (mean, 6); subtotal ISR (mean, 7.8); total ISR with or without partial external sphincteric resection (mean, 11.1).

(n = 1), and abdominal wall metastasis (n = 1). In seven of eight patients with local recurrence, recurrence occurred in lateral nodes^{18–22} located between the pelvic plexus and lateral pelvic wall, or in the tissue surrounding the external iliac artery. Local recurrence in one patient occurred in the prostate with multiple lung metastases. Patients with liver or lung metastasis alone received curative partial hepatic or lung resection (n = 9). Patients with regional or inguinal lymph node metastasis also received lymphadenectomy (n = 4). Cumulative local recurrence rate was 5.8 percent at three years and 6.7 percent at five years (Fig. 2). No patients displayed anastomotic recurrence. No differences in recurrence rate or site were noted between preoperative radiochemotherapy and surgery-alone groups, although median observation time was shorter in the preoperative radiochemotherapy group (26 months) compared with the surgery-alone group.

Survival

A total of 18 patients died, with 16 deaths from distant metastasis. OS was 91.9 percent at five years, and DFS was 83.2 percent at five years (Fig. 2). No significant differences in OS or DFS were identified between preoperative radiochemotherapy and surgery-alone groups at three years (DFS: 75.1 vs. 85.8 percent).

Functional Outcome

Of 219 patients excluding patients with additional surgery, such as APR or Hartmann's operation, 181 received diverting stoma closure at a median of five

(range, 3–24) months postoperatively. Stoma closure is planned for 30 patients. Conversely, no plan for stoma closure was made in eight patients because of anal dysfunction (n = 3), early-phase recurrence (n = 3), or anovaginal fistula (n = 2). Continence status is shown in Table 2. Although only 30 percent of patients displayed good continence (Kirwan's Grade 1–11) at six months after stoma closure, 68 percent of patients showed good continence at 24 months after stoma closure. Worsened continence was observed in only 7 percent of patients.

Wexner score was investigated sufficiently in 110 patients, with scores of 11.2 ± 4 at six months after stoma closure, 8.4 ± 4.5 at 12 months, and 7.8 ± 4.2 at 24 months. Anal function improved monthly until 24 months after stoma closure. However, day or night soilings were sometimes observed at 24 months after stoma closure in patients with total ISR. Mean Wexner score at 24 months after stoma closure was 6 in the partial ISR group, 7.8 in the subtotal ISR group, and 11.1 in the group that underwent total ISR with or without PESR. Although no significant differences in Wexner score were apparent between partial and subtotal ISR groups, patients who underwent total ISR with or without PESR exhibited significantly worse continence than those with partial or subtotal ISR (Wexner score, 11.1 vs. 6 and 7.8, respectively; *P* < 0.05).

DISCUSSION

The general consensus is that most rectal cancers <5 cm from the anal verge or <2 cm from the dentate line are treated by using APR. In recent years,

however, the need for a margin of ≥ 2 cm margin has been challenged, and a distal margin of 1 to 2 cm is now considered sufficient in most instances. Sphincter-saving operations, such as ultralow and conventional coloanal anastomosis for cancer of the lower third of the rectum, have been reported by specialized teams, with local recurrence rates of 4 to 13 percent.²⁶⁻³¹ Although ultralow and coloanal anastomosis have been associated with some controversial functional results, patients without permanent stoma have been widely accepted as displaying better quality of life. However, most tumors in these studies have been located ≥ 5 cm from the anal verge. In more recent years, ISR with coloanal anastomosis has been reported for rectal cancer located < 5 cm from the anal verge by a few specialized teams.⁷⁻¹³ However, some fears of oncologic results and poor anal functions have been noted, as patients display reduced surgical margins compared with APR and the internal sphincter is removed.

This study was designed to investigate the pathologic evidence and oncologic and functional results of ISR. In the present series, tumors were located ≤ 5 cm from the anal verge. All these patients would have required APR if treated using standard procedures. According to pathologic examination using resected specimens from APR in this study, curative operation can be accomplished by ISR in almost all patients undergoing APR. In fact, 225 of 228 patients (98 percent) who underwent ISR were considered to display histologically curative results. These results demonstrate the pathologic appropriateness of ISR and the possibility of preserving anal function during the surgical treatment of very low rectal cancers.

Rullier *et al.*¹³ reported 92 rectal carcinomas at 3 cm from the anal verge, finding that the distal resection margin was 2 cm and negative in 98 percent of cases. They also reported that median circumferential margin was 5 (range, 0-15) mm and positive (≤ 1 mm) in ten cases (11 percent). These results show that radical tumor resection can be achieved by ISR procedures in almost all patients with very low rectal cancer.

Morbidity in our study was relatively high, with 55 of 228 patients (24 percent) experiencing complications, although the rate of serious complications was low. Our findings do not differ from those of other reports. Rullier *et al.*¹³ reported similar results, with a morbidity rate of 27 percent, whereas Schiessel *et al.*⁷ described a rate of 18.4 percent (7/38 patients). Unfortunately, one procedure-related

death occurred in the present study. Morbidity rate was particularly high in the first half of our study, although no changes in surgical technique were enacted during this period. Careful treatment and skillfulness in this procedure are needed for these patients if surgery-related complications are to be kept at a minimum.

Although an increase in local recurrence was feared in ISR because of reduced surgical margins compared with APR, cumulative five-year local recurrence rate was 6.7 percent in this series. All local recurrences in this study were outside the normal TME planes. These recurrences would not have been prevented using standard APR and seemed to result from inadequate lateral node dissection. Rullier *et al.*¹³ reported that 1 of 58 patients (2 percent) developed local recurrence during a median observation of 40 months. Schiessel *et al.*⁷ reported that 4 of 38 patients (10.5 percent) exhibited local recurrence during a median follow-up of three years. Local control in this study does not differ substantially from rates in these other reports. These results demonstrate that acceptable local control can be obtained by using ISR procedures. However, two of three patients with unclear surgical margins in this study developed local recurrence with distant metastases during a median observation of 28 months. Achievement of complete microscopic resection seems important for local control. The five-year overall survival rate in our series was 91.9 percent, whereas the five-year disease-free survival rate was 83.2 percent. Rullier *et al.*¹³ reported similar results, with an 81 percent five-year survival rate. Conversely, data for APR patients who underwent surgery in our seven institutions during the same time period showed that APR patients displayed tumors with the same background compared with patients who received ISR, with a median five-year DFS of 65.1 (range, 63.6-70) percent, and median five-year local recurrence rate was 10 (range, 3-19) percent. These data led us to consider the oncologic results of ISR obtained in this study as acceptable. The limit for ISR procedures seems to be circumferential clearance, rather than distal.

Some fears were held for functional outcomes after ISR procedures, because loss of the rectum and IS may induce anal dysfunctions, such as stool frequency, urgency, fragmentation, soiling, and fecal incontinence.^{14,32} Approximately 30 to 60 percent of low colorectal or coloanal anastomoses induce functional disturbances collectively termed anterior resection

syndrome.³³⁻³⁷ Most authors believe preservation of the whole anal sphincter and mucosa is crucial for maintenance of good continence. APR thus represents a standard surgery when distance between the lower edge of the tumor and the anal ring is <2 cm.³⁸ However, in this study, 93 percent of patients showed good or relatively good continence (Kirwan's Grade 1-111) at 24 months after stoma closure. Mean Wexner score was 7.8 at 24 months after stoma closure. Bretagnol *et al.*¹⁴ and others have reported similar results.^{7,10-12} However, seven patients displayed worsened continence. In addition, three patients could not undergo closure of the diverting stoma because of anal dysfunction. Furthermore, patients who underwent total ISR with or without PESR displayed significantly worsened continence compared with partial and subtotal ISR groups in our experience. Information on the potential functional adverse effects after total ISR should be provided to patients preoperatively.

Fecal incontinence after ISR is primarily caused by anal-sphincter insufficiency. Physiologic studies have shown that removal of the internal anal sphincter is associated with a significant decrease in resting pressure.^{7,10,12} Anal sphincter insufficiency also may be caused by injury of the external anal sphincter during ISR. Furthermore, neorectal insufficiency may facilitate fecal incontinence, as demonstrated by randomized studies comparing straight and J-pouch coloanal anastomoses.^{14,39,40} Anal functions in ISR procedures need to be investigated to compare straight, J-pouch, and transverse coloplasty coloanal anastomoses. More careful intraoperative management, additional surgery, such as colonic pouch, biofeedback treatment, and careful patient selection may facilitate improved outcomes in terms of anal function.

CONCLUSIONS

Curability with ISR procedures was verified histologically in patients with very low rectal cancer. Acceptable oncologic and functional results were obtained by using ISR procedures in patients with very low rectal cancer <5 cm from the anal verge. These procedures can be recommended for APR candidate patients; however, information on potential functional adverse effects after ISR should be provided to patients preoperatively.

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