rence is a potential problem after laparoscopic surgery (7). However, several studies have reported that wound-site recurrence also occurs at a given rate (0.6% to 7.6%) after open surgery (21,22). To date, there have been few reports of port-site recurrence after laparoscopic surgery, initially considered an important risk factor. The incidence of port-site recurrence is estimated to be less than 1% (23).

In conclusion, short- and long-term outcomes after laparoscopic surgery for advanced colorectal cancer in our study are comparable to those in many previous randomized controlled trials. We believe that technical progress in laparoscopic surgery and increased experience among surgeons will allow the indication range of this procedure to be extended to advanced colorectal cancer. In February 2009, the enrollment of 1010 patients was completed in a randomized controlled trial (Japan Clinical Oncology Group: JCOG0404) in Japanese patients with Stage II and III colorectal cancer. The endpoints of this trial include survival rates, complications, and conversion rates to open surgery (24). This study is expected to confirm the safety and therapeutic usefulness of laparoscopic surgery in Japan.

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ORIGINAL CONTRIBUTION

The Association Between Anal Function and Neural Degeneration After Preoperative Chemoradiotherapy Followed by Intersphincteric Resection

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BACKGROUND: Preoperative chemoradiotherapy for rectal cancer is administered to improve local control, but it can also induce severe anal dysfunction after surgery.

OBJECTIVE: The goals of the study were to assess the influence of preoperative chemoradiotherapy on pathological findings and to examine the correlation of these findings with the cause of severe anal dysfunction after intersphincteric resection.

DESIGN: Peripheral nerve degeneration was evaluated histopathologically with the use of hematoxylin and eosin-stained sections of surgical specimens after intersphincteric resection, based on karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. Each item was scored to quantify the level of neural degeneration, and the relationship between degeneration and anal function was examined at 12 months after closure of the stoma. Anal function was assessed by questionnaire, and incontinence was evaluated based on the Wexner score.

SETTING: This study was conducted at the National Cancer Center Hospital East from 2001 to 2006.

PATIENTS: The subjects were 68 patients with lower rectal cancer who underwent intersphincteric resection with (n = 47) or without (n = 21) preoperative chemoradiotherapy.

MAIN OUTCOME MEASURES: The findings in the 2 groups were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

RESULTS: Neural degeneration was significantly higher in the chemoradiotherapy group, and the neural degeneration and Wexner scores had a significant correlation ($P = .003$, $r = 0.477$).

CONCLUSION: Preoperative chemoradiotherapy induced marked neural degeneration around the rectal tumor. The significant correlation between the degeneration score and postoperative anal function suggests that this score may be a useful marker to predict the influence of preoperative chemoradiotherapy on anal function after surgery.

KEY WORDS: Chemoradiotherapy; Internal sphincteric resection; Neural degeneration; Rectal cancer; Anal function.

Innovative treatment for lower rectal cancer has recently tended toward preservation of the anus. Low anterior resection with coloanal anastomosis[1] and intersphincteric resection (ISR)[2] are advanced anus-preserving operations for the treatment of low rectal cancer with avoidance of a colostomy. Anastomoses are made near to or under the dentate line in the anal canal, and the procedures have a tolerable and clinically acceptable local recurrence rate.[3,4] Preoperative chemoradiotherapy (CRT) or

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radiotherapy is also thought to be necessary to decrease local recurrence following ISR.[5–7]

Investigations of functional outcome after ISR[6,8–11] have shown that satisfactory anal function is preserved in most patients, but some have severe dysfunction[11,12] and conversion to colostomy may be necessary as an additional treatment.[8,12] Preoperative CRT has been found to be most strongly associated with poor anal function after ISR, suggesting that patients with rectal cancer who undergo ISR after preoperative CRT are likely to experience incontinence.[13,14] Lim et al[15] reported that a conventionally fractionated 45-Gy dose of preoperative CRT caused poor anorectal function because of damage to the pudendal nerve. Rectal function may also be worsened by radiation-induced proctitis and induction of rectal compliance due to fibrosis of the rectal wall,[16,17] and direct radiation injury to the internal anal sphincter muscles can also cause anal sphincter dysfunction.[18]

Given this background, it is likely that pathological analysis of the anal sphincter muscle area may show an association with anal sphincter dysfunction. However, the relationship between histopathological findings and CRT in the anal sphincter muscle area has not been studied. Therefore, we examined the degree of tissue degeneration, with a particular focus on neural degeneration and tissue fibrosis, in surgical specimens resected from patients who underwent surgery with or without preoperative CRT. In previous reports[19,20] on esophageal carcinoma, toxicities such as neuropathy have been observed during CRT, suggesting that neuropathy may be based on neural degeneration. The aim of this study was to investigate neural degeneration pathologically, because this may cause anal dysfunction. Findings in patients with or without preoperative CRT were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

PATIENTS AND METHODS

Patients

Between 2001 and 2006, 68 patients underwent ISR for very low rectal cancer at the National Cancer Center Hospital East, Chiba, Japan. Of these patients, 47 received CRT before surgery and 21 underwent surgery alone (control group). For ISR cases from 2002 to 2004, CRT was performed for all patients who gave consent. The subjects examined before and after this period and ISR cases in which patients did not consent to CRT were examined as the surgery-only group. Cases in which infiltration in the external sphincter muscle was shown by MRI in the preoperative diagnosis of tumor depth were excluded from our indication for ISR. A diverting stoma was constructed in each patient, and the stoma was finally closed in all the patients. Questionnaires on postoperative anal function[8] were collected from 59 of the 68 patients at 12 months after closure of the stoma. Our operative indications for ISR were a tumor edge 5 cm above the anal verge or 3 cm above the dentate line; adenocarcinoma confirmed histologically by preoperative biopsy; and age less than 76 years.[8] Preoperative stage was determined according to the International Union Against Cancer classification.[21]

Surgical Procedure

ISR was performed as described previously.[8] First, dissection was performed by the abdominal approach until total mesorectal excision was complete. The outside layer of the internal sphincter muscle was then exposed and circumferentially divided from the puborectal muscle and the external sphincter. After the abdominal approach was completed, perianal resection was performed. The mucosa and the internal sphincter muscle were incised 1 to 2 cm distal to the tumor. If the tumor had invaded the external sphincter, ISR plus partial resection of the external sphincter was performed with preservation of at least the subcutaneous part of the external sphincter. The decision of whether to create a pouch (either a J-pouch or a transverse coloplasty pouch) was left to the discretion of the surgeon.

Preoperative Therapy

Forty-seven patients with clinical T3 tumors agreed to undergo CRT. Over a 5-week period, a dose of 45 Gy was administered along with intravenous infusion of 5-fluorouracil (250 $mg \cdot m^{-2} \cdot d^{-1}$) to increase the efficacy of radiotherapy. Nerve-sparing resection surgery was performed 2 weeks after completion of preoperative CRT.[22]

Pathological Evaluation

Hematoxylin and eosin-stained sections of the surgical specimens were used for pathological evaluation. The sections were evaluated by 2 authors (S.F. and Y.N.) who were blinded to the clinical information for the patients.

Pathological Examination of Nerves Near the Internal Sphincter Muscle

Before pathological evaluation, the numbers of nerves in the hematoxylin and eosin-stained sections were counted in low-power magnification fields (10 × 10). Ten nerves around the primary lesion were selected and photographed, and the consistency of features of the nerves in each photograph was evaluated. In this manner, pathological neural degeneration was evaluated for 10 nerves near to the tumor in each patient, based on the following features: karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. To obtain a total degeneration score, the presence of the first 4 features was scored as 1 point each. Adventitial neuronal changes were evaluated based on a 3-point scale, with 1, 2, and 3 defined as perineurial hypertrophy, perineurial fibrosis, and intraneural fibrosis.

Therefore, the degeneration score ranged from 0 to 7. The association between this score and anal function was examined at 12 months after surgery.

Fibrosis

The degree of fibrosis of the primary tumor was evaluated on a 4-point scale, with grades 0, 1, 2, and 3 reflecting <10%, 10% to 30%, 30% to 50% and ≥50% replacement of tumor tissue by fibrosis in the section with the maximum tumor diameter.[18]

Abscess Formation

The presence of an abscess in the tumor was examined based on aggregates of neutrophil infiltration (0, absence of abscess; 1, presence of abscess). An abscess was defined as an area of neutrophilic aggregation with a diameter larger than 500 μm observed microscopically.

Assessment of Anal Function

The functional outcome was assessed by the use of the continence score of Jorge and Wexner (Wexner score).[23] Questionnaires were collected from patients during consultation in the physician's office after the patient had filled out the questionnaire by themselves at home. Questionnaires to evaluate the Wexner score were given at 12 months after stoma closure. Thus, the relationship between the degree of degeneration and postoperative anal function was examined based on the Wexner score at 12 months after stoma closure. This score reflects the postoperative anal function, because gradual improvements in Wexner scores are seen from 3 to 6 months and further slight improvements occur between 6 and 24 months.[13]

Statistical Analysis

A Student *t* test and Fisher exact test were used to examine histological differences between the CRT and control groups. A Mann-Whitney *U* test was used to examine the relationship between CRT and Wexner scores. The Mann-Whitney *U* test was also used to examine the relationship between histological findings (karyopyknosis, vacuolar degeneration, acidophilic change, and denucleation) and Wexner scores. A Kruskal-Wallis test was used to examine the relationship between histological findings (adventitial neuronal changes, fibrosis, and abscess) and Wexner scores. Spearman analysis was used to examine the correlation between degeneration scores and Wexner scores. All statistical analyses were performed using SPSS for Windows, v.13.0 J (SPSS-Japan Inc., Tokyo, Japan). A *P* value of <.05 was considered to be significant.

RESULTS

The clinical characteristics of the 68 patients are shown in Table 1, including preoperative CRT, mean tumor distance from the anal verge, extent of excision of the internal sphincter muscle, resection of the external sphincter, and pathological stage. There were no significant differences between the CRT and control groups in age, sex ratio, and anal verge distance. Total ISR was used less frequently in the control group. Regarding the pathological stage, 66% of cases in the CRT group were stages I and II, whereas 58% of cases in the control group were stage III. There were no significant differences in clinical stage ($P = .70$) and pathology stage ($P = .12$) between the CRT and control groups. Many cases in the CRT group were stage I or II and total ISR was performed in some of these cases (Table 1).

TABLE 1. Clinical characteristics of the patients

	CRT group	*Control group*	*P*
Patients	47	21	
Median age (range)	56 (27–77)	60 (39–72)	.22
Sex, M:F	35:12:00	15:06	.79
Median AV (cm)	3.5 (0–5.0)	4.0 (2.5–5.5)	.66
Operative procedure (%)			
Total ISR	20 (43)	1 (5)	.03
Subtotal ISR	22 (47)	13 (62)	
Partial ISR	5 (11)	7 (33)	
PESR	13 (28)	7 (33)	.63
Clinical/pathology stage (%)			
I	9 (19)/25 (53)	4 (19)/4 (19)	.70/.12
II	16 (34)/6 (13)	8 (38)/5 (24)	
IIIa	9 (19)/5 (11)	5 (24)/6 (29)	
IIIb	11 (23)/8 (17)	3 (14)/6 (29)	
IV	2 (4)/2 (4)	1 (5)/0 (0)	
Postoperative complications (%)	14 (29)	9 (43)	.29
Anastomotic leakage	5 (11)	3 (14)	.67
Pelvic abscess	6 (12)	5 (24)	.25

AV = anal verge; ISR = intersphincteric resection; CRT = chemoradiotherapy; PESR = partial external sphincter resection.

Postoperative complications occurred in 14 subjects (29%) in the CRT group (anastomotic leakage in 5 (11%) and pelvic abscess in 6 (12)), and in 9 subjects (43%) in the control group (anastomotic leakage in 3 (14%) and pelvic abscess in 5 (24%)). There was no significant difference in the rate of postoperative complications between the 2 groups. The average time between the primary operation and closure of the stoma was 227 days (range, 80–665 days) in the CRT group and 247 days (range, 85–558 days) in the control group.

Tissue fibrosis of grade 2 or 3 was observed in 73% of cases in the CRT group, whereas fibrosis of grade 0 or 1 accounted for 86% of cases in the control group. The incidence of more severe fibrosis was significantly higher in the CRT group ($P < .001$). No intratumor abscess was present in 79% of cases in the CRT group, but abscesses were observed in 52% of cases in the control group, giving a significantly higher incidence of abscess formation in the control group ($P = .010$).

TABLE 2. Pathologic findings

	CRT group (n = 47)	*Control group (n = 21)*	*P*
Fibrosis grade: 0/1/2/3, n (%)	2/11/13/21 (4/23/28/45)	16/2/2/1 (76/10/10/5)	<.001
Abscess grade: 0/1, n (%)	37/10 (79/21)	10/11 (48/52)	.010
Karyopyknosis, n (%)	19 (40)	0 (0)	.001
Vacuolar degeneration, n (%)	32 (68)	4 (19)	<.001
Acidophilic degeneration of cytoplasm, n (%)	15 (32)	0 (0)	.002
Adventitial neuron change: 0/1/2/3, n (%)	2/25/7/13 (4/53/15/28)	17/4/0/0 (81/19/0/0)	<.001
Denucleation, n (%)	26 (55)	0 (0)	<.001

Karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, adventitial neuron change, and denucleation were evaluation items of neurodegeneration. CRT = chemoradiotherapy.

The incidence of neural degeneration was significantly higher in the CRT group and the incidence of vacuolar degeneration (68%) was particularly high in the CRT group compared with the control group. In the adventitia and perineurium of neurons, only perineurial hypertrophy (grade 1) occurred in the control group, whereas perineurial and intraneural fibrosis (grades 2 and 3) was found in 43% of cases in the CRT group, indicating a significantly higher frequency of severe effects in the CRT group ($P \leq .001$ to $P = .01$) (Table 2). Representative histopathological findings for neurons are shown in Figure 1.

Association with Anal Function 12 Months After Surgery

No patient had a Wexner score of ≥2 preoperatively, and none had problems with preoperative anal function. The median values of the Wexner scores at 12 months after stoma closure in the CRT and control groups were 8.0 and 5.0, indicating that function was significantly poorer in the CRT group ($P = .018$ by Mann-Whitney U test) (Fig. 2).

In a comparison of Wexner scores based on background factors in the CRT group, sex, age, type of resection (partial, subtotal, total ISR), and partial resection of the external sphincter were not associated with poor anal function after ISR. Postoperative anal dysfunction did not show a significant association with each feature of neural degeneration or with Wexner score in the CRT group (karyopyknosis, $P = .05$; vacuolar degeneration, $P = .298$; acidophilic change, $P = .090$; denucleation, $P = .067$; and adventitial neuronal changes, $P = .081$). However, there was a significant correlation between the total degeneration score and the Wexner score ($P = .003$, $r = 0.477$ by Spearman analysis) (Fig. 3).

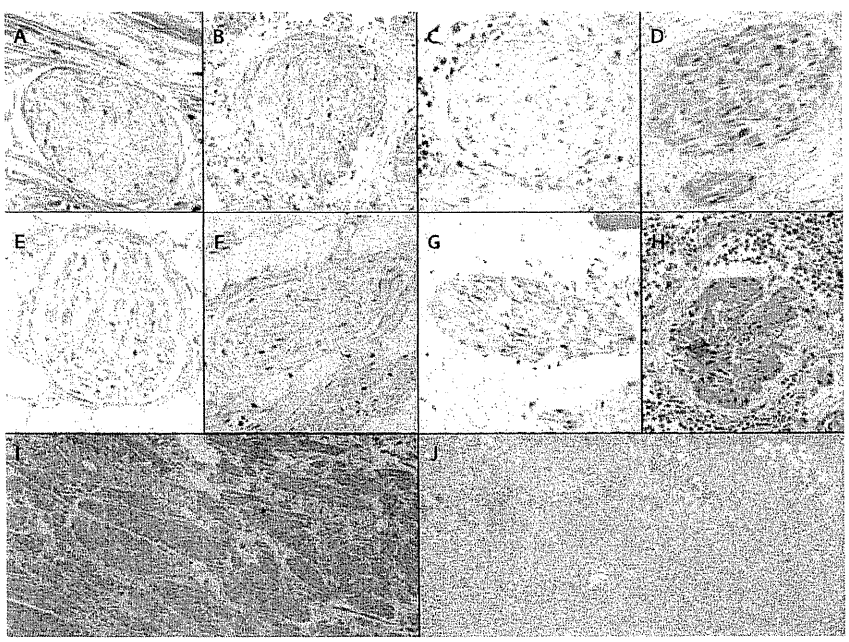

FIGURE 1. Pathological evaluation. The hematoxylin and eosin sections were assessed under a standard light microscope at low-power magnification (×100). The nerve evaluation items are (A–H): A, Normal. B, Karyopyknosis. C, Vacuolar degeneration. D, Acidophilic degeneration of cytoplasm. E, Denucleation. F, Adventitial neuron change grade 1. G, Adventitial neuron change grade 2. H, Adventitial neuron change grade 3. The degree of fibrosis was evaluated by grades: I, grade 1; J, grade 3.

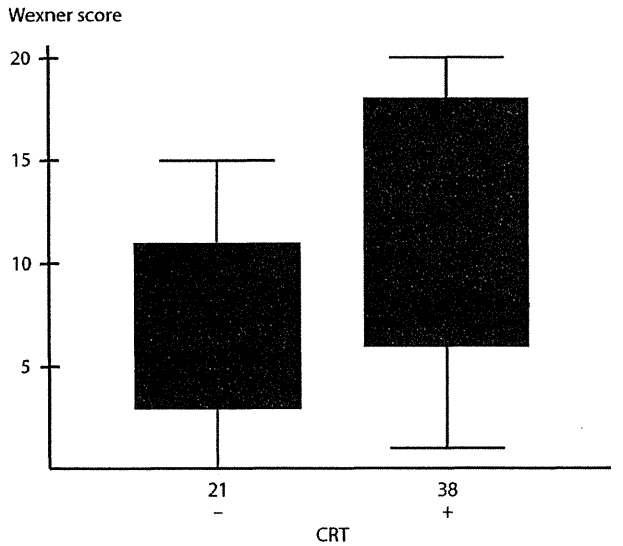

FIGURE 2. Relationship between CRT and Wexner score. Wexner score comparison at 12 months after stoma closure between the CRT and control groups resulted in median values of 8.0 and 5.0 (P = .018 by Mann-Whitney U test). CRT = chemoradiotherapy.

DISCUSSION

The results of the study showed that preoperative CRT had a negative effect on anal function regardless of the surgical method. This suggests that it is important to examine neural degeneration around the internal sphincter muscle for prediction of anal dysfunction. Many cases were of pathological stages I and II because of downstaging by CRT, but total ISR was performed in some of these cases. This approach was used because we were unable to judge the position of the tumor edge on the anal side before preoperative CRT, which prevented maintenance of a clear distal margin. However, this had no influence on the analysis of the Wexner score because the comparison of this score with anal dysfunction was performed only within the CRT group. Moreover, of the factors investigated, preoperative CRT had the greatest effect on anal dysfunction after ISR, and total ISR was more strongly associated with anal dysfunction than either subtotal or partial ISR. Therefore, a negative effect of preoperative CRT on anal function was found regardless of the extent of internal sphincter muscle preservation.[13]

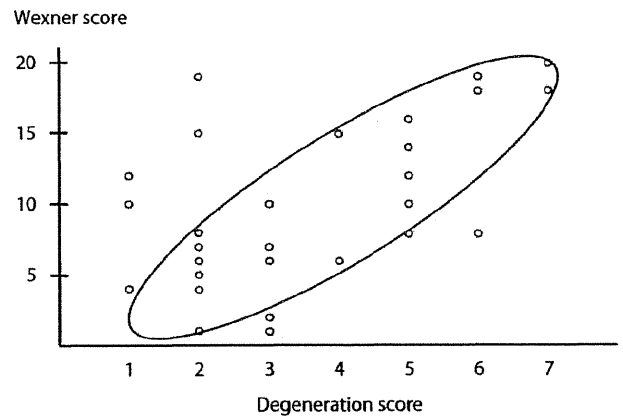

FIGURE 3. Association between the degeneration score and Wexner score. The correlation between the original score (range, 0–7) and the Wexner score was investigated. Correlation was significant with P = .003 and a correlation coefficient of r = 0.477 by Spearman analysis.

The cause of the negative effect of conventionally fractionated CRT on anorectal function is still unclear. Lim et al[15] suggested that poor anorectal function after preoperative CRT was due to damage to the pudendal nerve, and rectal function may also be worsened by radiation-induced proctitis and reduced rectal compliance.[16,17] Moreover, anal sphincter dysfunction may be caused by direct radiation injury to the internal anal sphincter muscles.[18] Our results showed a significantly higher incidence of neural degeneration and fibrosis in the CRT group. In this study, we did not include cases treated with radiation therapy only. However, in another series, we found that treatment with radiation alone caused tissue degeneration, including neural degeneration similar to that caused by CRT. We also evaluated another 8 patients with colorectal cancer who received preoperative folinic acid/fluorouracil/oxiliplatin (FOLFOX) treatment. The incidence of neural degeneration was significantly higher in the CRT group than in the FOLFOX cases. There were no differences in any items of neural degeneration between the FOLFOX cases and control groups, suggesting that radiation may exert a critical damage on tissue damage. In the pathological evaluation, patients treated with preoperative chemotherapy alone had no neural degeneration, with results similar to those in the control group. These results suggest that radiation plays a critical role in tissue damage.

The tissue and nerves were evaluated in surgical tissue specimens, but these specimens and the left internal and external sphincter muscles were similarly affected by CRT, which suggests that the histological changes in the analyzed specimens were also present in the body. The nerve examined in the study is an autonomic nerve that is distributed longitudinally in the intestine and innervates the internal sphincter muscle. After surgery, the somatic and pudendal nerves are involved in anal function and mainly innervate the external sphincter muscle of the anus. Although their origins are different, examination of these 2 nerves may be appropriate for assessment of neural degeneration, because neuronal failure of these nerves may cause anal dysfunction. In this study we evaluated tissue degeneration in the neural range affected by CRT, including the sphincter muscle, and these results are important for prediction of anal function after surgery.

In the CRT group, surgery was performed within 2 to 3 weeks after completion of preoperative CRT, and the investigated histological changes occurred during this period. Anal function improved with the postoperative course in some cases, suggesting that nerves and tissue including muscle can regenerate and result in improved anal function. However, an investigation of anal function after ISR in patients who underwent surgery at our hospital suggested that functional recovery cannot be expected in cases with unfavorable function at 6 to 12 months after surgery.[13] Because CRT-induced early-phase tissue degeneration is associated with anal function at 12 months after surgery (as found in this study), tissue degeneration early after CRT may have a long-term effect on anal function.

Various factors may exert an influence on anal function, and this makes it difficult to predict postoperative anal function before surgery. However, the results of this study showed a significant correlation between the degeneration score defined in the study and the Wexner score in the Spearman analysis. Furthermore, there was no significant relationship between each histological finding and Wexner score, and no significant association between each item for evaluation of neural degeneration and Wexner score in multivariate regression. These results suggest that tissue degeneration should be evaluated by examining various items, rather than based on only a single item, because neural degeneration associated with anal dysfunction may be reflected by several critical items. A further study is needed to identify these important items.

Postoperative maintenance of anal function is important after ISR and further research is necessary to develop a compensatory treatment for maintenance of function (for example, reconstruction of functional muscles) for CRT cases with functional failure. Simultaneous management of therapeutic benefit and anal function is required following ISR, and we intend to examine approaches to maintenance of the therapeutic benefit of preoperative CRT in a future study. For example, preoperative chemotherapy alone may be appropriate based on the improvement of colorectal cancer observed with this approach.

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Outcome of 141 cases of self-expandable metallic stent placements for malignant and benign colorectal strictures in a single center

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Abstract
Background The use of a self-expandable metallic stent (SEMS) has emerged as an alternative treatment option for malignant colorectal obstruction. Although the technical success rate of SEMS has been widely reported, outcome data are limited.
Methods This retrospective study evaluated the short- and long-term outcomes of colorectal SEMS for malignant and benign disease in patients who underwent SEMS at a single center.
Results One surgeon inserted all stents under endoscopic and fluoroscopic guidance; 141 SEMS procedures were performed in 133 patients (82 males, mean age 69 years). The SEMS procedure was undertaken for: palliation of malignant obstruction in 30 patients (36 cases), and the technical success rate was 94%; a bridge to surgery for colorectal cancers in 98 patients/cases, and the technical success rate was 91%; benign stricture in 5 patients (7 cases), and the technical success rate was 100%. Due to anatomical differences, the success rate was lower at the cecum, descending colon, and sigmoid than in the recto-sigmoid and rectum. In 11 cases of technical failures, the failures were due to technical problems in 9 cases (82%) and due to the state of the stricture in 2 cases (18%). Procedure-related complications occurred in 6 patients (4%): perforation in 3 and migration in 3. All perforation cases and one migration case underwent emergency surgery. There was no mortality. In the bridge to surgery group, postoperative complications were much lower in the clinical success cases (6%) than in the failure group (36%). In the palliation treatment group, long-term SEMS migration occurred in 4 patients (14%), and re-obstruction occurred in 5 patients (18%); the mean insertion period was 201 (range: 10–576) days.
Conclusions Colorectal SEMS had feasible short and long-term results and low morbidity, making it a viable option for various types of colorectal obstruction with careful attention to the indications.

Keywords Colorectal obstruction · Stent · Self-expandable metallic stent (SEMS) · Bridge to surgery

The use of a self-expandable metallic stent (SEMS) has emerged as an alternative treatment option for patients with malignant colorectal obstruction [1–7]. Colorectal SEMS decompression has several benefits in the setting of metastatic or unresectable disease, including the potential avoidance of a diverting stoma, lower morbidity, lower mortality, shorter hospitalization, earlier administration of chemotherapy, and decreased medical costs [8–10]. Recently, the placement of colonic SEMS as a bridge to surgery has been advocated in patients with potentially resectable colorectal cancer [10–13]. Furthermore, the role of endoscopic SEMS in benign conditions, such as radiation- or inflammation-induced stricture, colovaginal fistula, and postoperative anastomotic stenosis, has been investigated with varying degrees of success [14–20]. The purpose of this study was to review the results of our use of endoscopic SEMS in patients with malignant and benign conditions of the colon and rectum.

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Patients and methods

Institutional Review Board approval was obtained before the study was carried out. A retrospective review was conducted of all patients who underwent a SEMS placement for colorectal stricture between 1993 and 2010 at Toho University Ohashi Medical Center, Tokyo, Japan. All SEMS procedures were performed by the same board-certified colorectal surgeon proficient in therapeutic endoscopy. Data analyzed included patient demographics, past medical history, type and location of pathology, reason for intervention, intent of intervention (definitive versus bridge to surgery), type of stent, and outcome measures such as technical success rate, procedure-related complications, stent migration rate, rate of endoscopic reintervention, and subsequent operative intervention.

Technique and postprocedure care

A preprocedural water-soluble contrast-agent (gastrografin) enema was routinely given to assess the location, anatomy, and characteristics of the pathology, such as length and degree of stricture and presence or absence of fistula. Bowel preparation and intravenous antibiotics were individualized based on the clinical presentation and degree of obstruction. Informed consent for endoscopic SEMS was obtained from all patients with possible emergency operative intervention. All procedures were performed in the radiology room under fluoroscopic and endoscopic guidance, with or without intravenous sedation. A flexible colonoscope (Olympus, Tokyo, Japan) was used for all cases. Access across the lesion was established using a guidewire (Radifocus™ plastic-coated guidewire, Terumo, Tokyo, Japan, or Jagwire™ or Amplatz Super stiff wire, Boston Scientific, Natick, MA, USA). Balloon dilation was not routinely performed. The choice of which SEMS to use (with respect to length, diameter, wire-guided versus through the scope) was tailored according to the characteristics of the stricture. Four different types of SEMS were deployed during the study period: Z-stent™ (Wilson-Cook Medical, Winston-Salem, NC, USA), esophageal Ultraflex™ (Boston Scientific), colonic Wallstent™ (Boston Scientific), and Niti-S enteral colonic stent (Tae Woong Medical, Gyeonggi-do, Korea). All SEMSs were bare (noncovered), with a diameter of 18–22 mm. Esophageal stents were used in the study because of the lack of availability of colonic stents in Japan, and all colonic stents were imported personally. All patients were observed in the recovery unit for 1–3 h and then transferred to the ward. A full liquid diet was resumed within 2–4 days after the procedure in patients who underwent the procedure successfully, and the diet was advanced as tolerated. Patients were instructed to avoid constipation and to take laxatives such as Milk of Magnesia on an as-needed basis. Postprocedural plain abdominal radiographs were obtained selectively. When stent migration was suspected, a plain abdominal X-ray was performed to confirm the diagnosis. Endoscopic or fluoroscopic surveillance of the SEMS was performed in the majority of patients at intervals of 3–6 months.

Results

A total of 141 SEMS procedures were performed in 133 patients during the study period. There were 82 males (62%) and 51 females (38%), with a mean age of 69 years (median = 70 years, range = 37–94 years). All patients were inpatients. The intent of the procedure was definitive treatment in 35 patients (26%) [43 cases (30%)] and bridge to surgery in 98 patients (74%) [98 cases (70%)]. The stricture was malignant in 134 cases (95%) and benign in 7 (5%). Table 1 summarizes the etiology of the strictures and the technical success rate for each. The SEMS procedure was undertaken for palliation of malignant obstruction in 30 patients (36 cases), with a technical success rate of 94%; bridge to surgery for colorectal cancers in 98 patients/cases, with a technical success rate of 91%; and benign stricture in 5 patients (7 cases), with a technical success rate of 100% (2 cases of ischemic colitis in 1 patient and 7 cases of postoperative anastomotic stenosis in 6 patients).

Table 2 summarizes the location of pathology and the corresponding technical success rate. The most common location of pathology was the sigmoid (44%), followed by rectosigmoid (23%), upper rectum (15%), descending colon (10%), transverse colon (6%), cecum (1%), and lower rectum (1%). The technical success rate was lower at the cecum (50%), descending colon (86%), and sigmoid (90%) than at the rectosigmoid (97%) and rectum (95–100%). The lower technical success rates in the cecum and around the SD junction were due to the poor field of

Table 1 Etiology and technical success rate for malignant and benign strictures

	Success/try cases	Technical success rate (%)
Malignant		
Palliative	34/36	94
Bridge to surgery	89/98	91
Benign		
Ischemic colitis	2/2	100
Postoperative anastomotic stenosis	5/5	100
Total	130/141	92

Table 2 Location of pathology and technical success rate

	Success/try cases	Technical success rate (%)
Cecum	1/2	50
Ascending	0/0	
Transverse	9/9	100
Descending	12/14	86
Sigmoid	56/62	90
Rectosigmoid	31/32	97
Upper rectum	20/21	95
Lower rectum	1/1	100
Total	130/141	92

vision with an endoscope. Endoscopic balloon dilation of the stricture was performed in only one patient.

Nine of the 11 technical failures (82%) were due to technical problems: inability of the guidewire to traverse the stricture in four, perforation of the distal side of the stricture by the guidewire in one, inability to advance the stent delivery device in 1, perforation with the delivery device in one, tumor perforation by the SEMS the day following the procedure in one, and SEMS migration in one. In the other two cases (18%), the failures were due to the state of the stricture: multiple strictures and fistula formation to the small intestine.

Successful stent deployment but persistent pseudo-obstructions were found in two cases in the bridge-to-surgery group. One patient had a mass of packed hard feces and one had decreased bowel peristalsis due to Parkinson's disease. Clinical success was achieved in 128 (91%) of 141 cases.

Procedure-related complications were observed in six patients (4%): perforation in three and stent migration in three. All perforation cases and one migration case underwent emergency surgery. Two migrations were saved with additional SEMS delivery. There was no mortality.

All patients in the bridge-to-surgery subgroup underwent subsequent surgical intervention (Table 3). All clinical success cases, 87 patients, underwent elective surgery with mechanical preparation. The mean preoperative period after SEMS delivery was 7.7 days (range = 3–27 days). The stoma creation rate was 10% in this group, and the operative complication rate was 5.7%. All clinical failure cases, 11 cases, underwent emergency surgery; in 8 cases (73%), a stoma was created.

The most common reason for palliative treatment was unresectable distant metastases with primary colorectal cancer in 14 cases (47%), followed by advanced age in 7 (23%), unresectable recurrent colorectal cancer in 6 (20%), and other organ cancers invading the colorectum in 3 (10%). Figure 1 depicts the long-term outcome of patients who were treated with SEMS for palliation.

Table 3 Clinical outcome of "bridge to surgery" cases ($N = 98$)

Technical success rate	89/98 cases (91%)
Clinical success (release of obstruction)	87/98 (89%)
Preoperative period after SEMS delivery	7.7 ± 4.4 days (mean ± SD, range = 3–27 days)
Stoma creation	
Clinical success	9/87 (10%)
Clinical failure	8/11 (73%)
Postoperative complication (success cases)	5/87 (6%)
Wound infection	1
Intra-abdominal abscess	1
SBO	1
Anastomotic Leakage	2
Mortality	0
Postoperative complication (failure cases)	4/11 (36%)
Wound infection	2
Intra-abdominal abscess	1
SBO	1
Pneumonia	1
Mortality (pneumonia)	1/11 (9%)

During a mean follow-up of 8 months, stent migration occurred in four patients (14%) and reobstruction occurred in five patients (18%) (Fig. 1). Endoscopic reintervention, stent in stent, was undertaken in six patients (21%): two for stent migration and four for tumor overgrowth/ingrowth. The long-term operative intervention rate was 7% (2 patients for stent migration). The mean insertion period was 201 days (median = 152 days, range = 10–576 days).

The benign group comprised one patient with ischemic colitis and four patients with postoperative anastomotic stenosis. Reobstruction occurred in two patients (40%)

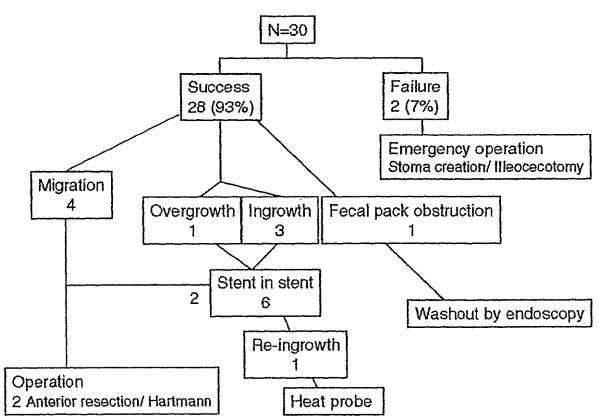

Fig. 1 Short-term and long-term outcomes of patients with SEMS for palliation

after SEMS removal with endoscopy; endoscopic reintervention, stent in stent, was undertaken.

Discussion

Endoscopic SEMS endoprostheses have been clinically applied later for colorectal diseases than for other lesions. Recently, SEMS has been used as palliative treatment for strictures caused by malignant diseases in patients with incurable stages or advanced age, or as a "bridge to surgery" for obstructive colorectal cancers, and good clinical results have been increasingly reported [1–15]. As minimally invasive interventions continue to evolve and gain wider acceptance, colonic SEMS will play an increasing role in the treatment of colonic obstruction. Since the 1990 s there have been numerous studies that have explored the role and documented the utility of endoscopic SEMS to relieve metastatic and incurable large-bowel obstruction [1–9]. More recently, the advantages of preoperative SEMS placement, as a bridge to surgery, have been demonstrated in patients presenting with obstructing but resectable malignancy, converting an emergency operation to an elective one [10–13]. Potential benefits of SEMS under such circumstances include lower morbidity and mortality and avoidance of fecal diversion in a higher proportion of patients. In the present study, SEMS was technically successful in the majority of patients who needed it as a bridge to surgery, palliative treatment, and benign stricture treatment. There were 11 technical failures in which a major problem was the guidewire passing through the stricture. Advanced endoscopes, better guidewire kits, and advanced techniques are needed. Difficult regions for SEMS delivery were the cecum and SD junction. Around that area of the colon it was difficult to get a good front view due to the particular anatomical characteristics. Improvement of EMS devices could increase the success rate of insertion around the SD junction, but the placement of stents in the cecum will remain relatively difficult because of the very special anatomy.

In the bridge-to-surgery group, clinically successful cases had fewer postoperative complications (6%) compared to the failure group (36%). This is the same as had been previously observed by us and other groups [13, 21, 22].

Over the long term, all patients who underwent palliative treatment for malignant stricture avoided surgical intervention with diversion, except two patients who had stent migration laparotomy. The remaining four patients who had tumor overgrowth/ingrowth and two patients with stent migration were successfully treated with reintervention, stent in stent, endoscopically. Although the role of SEMS has been more limited in the setting of benign disease, there is an increasing interest in exploring the effectiveness and durability of endoluminal SEMS for conditions such as radiation- or inflammation-induced stricture, colovaginal fistula, and postoperative anastomotic stenosis; their use in these circumstances have been investigated with varying degrees of success [14–20]. In the present study, five patients underwent SEMS procedures for benign conditions. Technical success in the benign subgroup was similar to that in the malignant cases. However, because of reports of high perforation and migration rates and a lack of long-term outcome results, careful attention is needed before adoption of this technique [20, 23].

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原　著

腹膜播種を伴う原発性大腸癌に対する外科的治療の成績

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はじめに：腹膜播種を伴う原発性大腸癌手術症例における予後規定因子を明らかにすることを目的とした．**方法**：2002年から2010年まで当院で手術施行した原発性大腸癌2,024例のうち，手術時に腹膜播種を認めた71例（3.5%）を対象とした．**結果**：腹膜播種の内訳はP1：19例，P2：20例，P3：32例であった．それらの3年生存率（生存期間中央値）はそれぞれ，P1：50.0%（34.6か月），P2：48.2%（22.3か月），P3：9.6%（13.3か月）でP1 vs. P3（$P<0.01$），P2 vs. P3（$P<0.05$）で有意な差を認めた（観察期間中央値14.4か月）．予後規定因子に関する多変量解析では，手術根治度（HR，3.91：$P<0.05$）が有意な予後規定因子として抽出された．手術根治度B（N＝16）と手術根治度C（N＝55）の3年生存率は，それぞれ78.4%，15.9%であった（$P<0.01$）．手術根治度B 15例（P3 1例除く）における腹膜播種程度別の無再発生存率，全生存率は有意な差を認めなかった（$P=0.37$，$P=0.82$）．**考察**：腹膜播種を伴う原発性大腸癌における予後規定因子は，手術根治度であった．P1，P2では，腹膜播種の程度によらず，手術根治度Bを目指すことによって生存期間の延長が期待できる可能性が示唆された．

はじめに

大腸癌治療ガイドライン[1]では，限局性播種で，他に切除不能な遠隔転移がなく，過大侵襲とならない切除であれば，原発巣切除と同時に腹膜播種巣を切除することが望ましいと記載されている．しかし，腹膜播種を伴った症例の予後は不良で[2)~5)]，腹膜播種巣切除の有効性を証明する大規模臨床試験もない．

そこで，腹膜播種を伴う原発性大腸癌手術症例における予後規定因子について後ろ向きに解析を行い，外科的治療の有用性を検討することを目的とした．

対象と方法

2002年9月から2010年2月まで，当院で手術施行した原発性大腸癌2,024例（単発または多発を含む）のうち，手術時に腹膜播種を認めた71例（3.5%）を対象とした．予後規定因子を抽出するにあたり，臨床病理学的因子および治療関連因子についてそれぞれ2群に分けてCoxの比例ハザードモデルにて単変量解析を行い，$P<0.1$であった因子を共変量としてCoxの比例ハザードモデル（Step-Wise regressionによる変数減少法）にて多変量解析を行った．累積生存率はKaplan-Meier法で算出し，有意差はlog-rank検定で判定した．いずれの場合もP値0.05未満を有意差ありとした．本稿における用語はすべて「大腸癌取扱い規約（第7版）」[1]に従った．

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Table 1 Clinicopathological features of 71 patients with peritoneal dissemination

	Peritoneal Dissemination			
	P1 (N = 19)	P2 (N = 20)	P3 (N = 32)	Total (N = 71)
Median age (range) years	64 (35–76)	68 (43–85)	64 (37–90)	64 (35–90)
Sex				
Male	13	3	16	32
Female	6	17	16	39
Median carcinoembryonic antigen (range) ng/ml	15.9 (0.7–1,797)	22.5 (2.7–1,153)	21.4 (0.7–1,489)	20.5 (0.7–1,797)
Tumor location				
Proximal colon	6	11	20	37
Distal colon and rectum	13	9	12	34
Macroscopic type				
Type 1, 2	15	18	24	57
Type 3, 4	4	2	8	14
Median tumor size (range) mm	55 (40–190)	54 (55–100)	57 (54–90)	55 (30–190)
Tumor annularity				
<90 percent	8	5	7	20
≥90 percent	11	15	25	51
Histopathological grading				
Well/Mod	15	18	27	60
Poor/Sig	4	2	5	11
Distant metastasis excluding peritoneal dissemination				
Positive	12	12	23	47
Non-regional lymph node metastasis	4	5	12	21
Liver metastasis	10	9	18	37
Lung metastasis	4	2	2	8
Other organ	0	3	1	4
Negative	7	8	9	24
Resection of primary lesion	17	15	19	51
Resection of peritoneal dissemination	17	11	1	29
Curativity				
Cur B	8	7	1	16
Cur C	11	13	31	55
Additional chemotherapy				
Positive	14	15	20	49
Negative	5	5	12	22

結　果

1. 患者背景

腹膜播種を伴った71例全例と，腹膜播種程度別の患者背景をTable 1に示す．年齢の中央値は64歳，男性32例，女性39例であった．大動脈周囲リンパ節転移を含めた遠隔リンパ節転移は21例，肝転移は37例，肺転移は8例に認められた．腹膜播種程度別の遠隔転移の比率はそれぞれ差を認めなかった．腹膜播種程度別の手術根治度Bの割合は，P1 8/19例(42%)，P2 7/20例(35%)，P3 1/32例(3%)であった．化学療法は49例に施行し，その内訳はFOLFOXまたはFOLFIRI 26例（うち1例は＋bevacizumab)，5-FU/LVまたはUFT/LV 15例，IFL 5例，TS-1＋L-OHP＋bevacizumab 1例，capecitabine 1

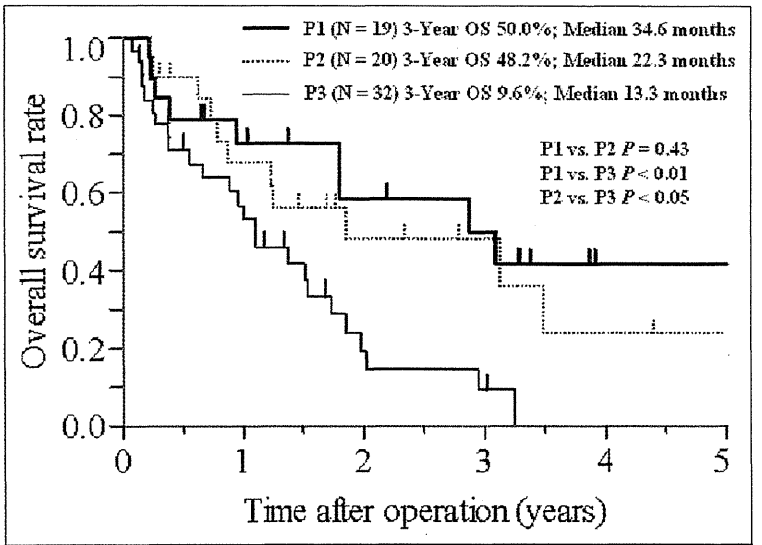

Fig. 1 Overall survival rate for all patients according to the degree of peritoneal dissemination. OS, Overall survival.

Table 2 Univariate analysis of clinicopathological factors affecting overall survival

Variable	Hazard ratio	95% C.I.	*P* value
Age (<65 years vs. ≥65 years)	1.12	0.62–2.02	0.706
Sex (Female vs. Male)	1.28	0.71–2.28	0.413
Tumor location (Distal colon and rectum vs. Proximal colon)	1.24	0.69–2.42	0.474
Macroscopic type (Type 1, 2 vs. Type 3, 4)	1.07	0.48–2.14	0.850
Tumor size (<50 mm vs. ≥50 mm)	1.95	0.99–4.19	0.054
Tumor annularity (<90 percent vs. ≥90 percent)	1.31	0.70–2.65	0.410
CEA (<100 vs. ≥100) (ng/ml)	1.86	0.91–3.57	0.087
Depth of tumor invasion (SS, SE, A vs. Si, Ai)	1.20	0.64–2.20	0.558
Lymphnode metastasis (pN0, pN1, pN2 vs. pN3)	2.16	1.07–4.09	0.034
Peritoneal dissemination (P1, P2 vs. P3)	2.56	1.39–4.79	0.003
Distant metastasis excluding peritoneal dissemination (Negative vs. Positive)	2.73	1.36–6.07	0.004
Histopathological grading (Poor/Sig vs. Well/Mod)	2.17	0.87–7.24	0.102
Curativity (cur B vs. cur C)	4.97	2.10–14.64	<0.001
Additional chemotherapy (Positive vs. Negative)	1.36	0.71–2.49	0.339

CEA, carcinoembryonic antigen; C.I., confidence interval.

例，肝動注1例であった．術前術後に化学療法施行例が1例，そのほかは術後に化学療法施行症例であった．

2. 臨床病理学的因子・治療関連因子と予後

腹膜播種を伴った71例全例の観察期間中央値は14.4か月（0.9～69.5か月），3年と5年の全生存率はそれぞれ30.7%，18.6%であった．腹膜播種程度別の3年生存率（生存期間中央値）はそれぞれ，P1：50.0%（34.6か月），P2：48.2%（22.3か月），P3：9.6%（13.3か月）で，P1 vs. P2では生存期間に有意な差を認めなかったが，P1 vs. P3（$P<0.01$），P2 vs. P3（$P<0.05$）では有意な差を認めた（Fig. 1）．

Coxの比例ハザードモデルにて単変量解析を行ったところ，腫瘍最大径・術前CEA値・リンパ節転移・腹膜播種の程度・腹膜播種以外の遠隔転移有無（肝転移を含む）・手術根治度が$P<0.1$として抽出

Table 3 Multivariate analysis of clinicopathological factors affecting overall survival

Variable	Hazard ratio	95% C.I.	*P* value
Tumor size (<50 mm vs. ≥50 mm)	1.97	0.93–4.17	0.077
Lymphnode metastasis (pN0, pN1, pN2 vs. pN3)	1.92	0.98–3.87	0.059
Peritoneal dissemination (P1, P2 vs. P3)	1.84	0.96–3.51	0.066
Curativity (cur B vs. cur C)	3.91	1.38–11.03	0.010

C.I., confidence interval.

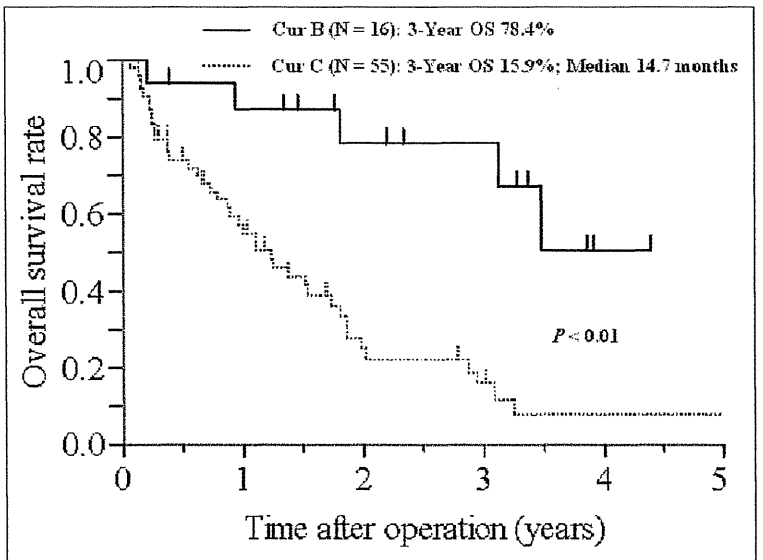

Fig. 2 Overall survival rate for patients with peritoneal dissemination according to curativity. OS, Overall survival.

された（Table 2）．これらの因子を共変量とし，Cox の比例ハザードモデル（Step-Wise regression による変数減少法）にて多変量解析を行ったところ，手術根治度が独立した予後規定因子として抽出された（Table 3）．手術根治度 B（16 例），手術根治度 C（55 例）の 3 年生存率はそれぞれ，78.4%，15.9% と有意に手術根治度 B で良好であった（$P<0.01$）（Fig. 2）．手術根治度 B 16 例のなかで，P3 は 1 例であったため，それを除き P1，P2 における無再発生存率（Fig. 3），全生存率を検討すると腹膜播種程度別では有意な差を認めなかった（$P=0.37$，$P=0.82$）．

手術根治度 B が得られた症例で腹膜播種以外の遠隔転移を認めた症例は 2 例のみであった．1 例は P1，大動脈周囲リンパ節転移を認め，それらを切除後，16 か月で側方リンパ節再発を認めたが，47 か月生存中である．もう 1 例は P2，脾転移を認め，それらを切除後，7 か月で肝再発を認め 38 か月で原病死した．

3. 非治癒因子数別の予後

手術根治度 C 55 例のうち，非治癒因子数別の 3 年生存率は，1 つ（9 例），2 つ以上（46 例）でそれぞれ 52.5%，9.3% と 1 つのみ有する症例において有意に予後が良好であった（$P<0.01$）（Fig. 4）．非治癒因子数が 1 つであった症例における非治癒因子の内訳は，肝転移 6 例，腹膜播種 2 例，大動脈周囲リンパ節転移 1 例であった（いずれも原発巣切除）．肝転移 6 例のうち，2 例で異時性肝切除を行い，生存期間はそれぞれ 22 か月，70 か月であった（いずれも死亡）．

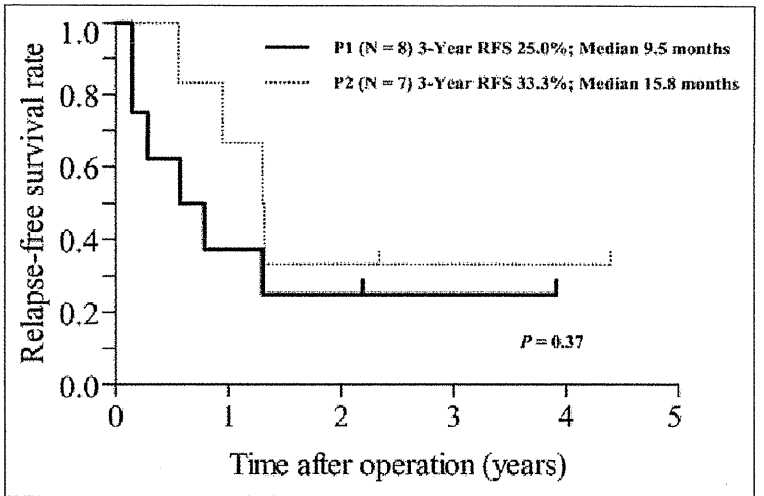

Fig. 3 Relapse-free survival rate for patients with curativity B according to the degree of peritoneal dissemination. RFS, Relapse-free survival.

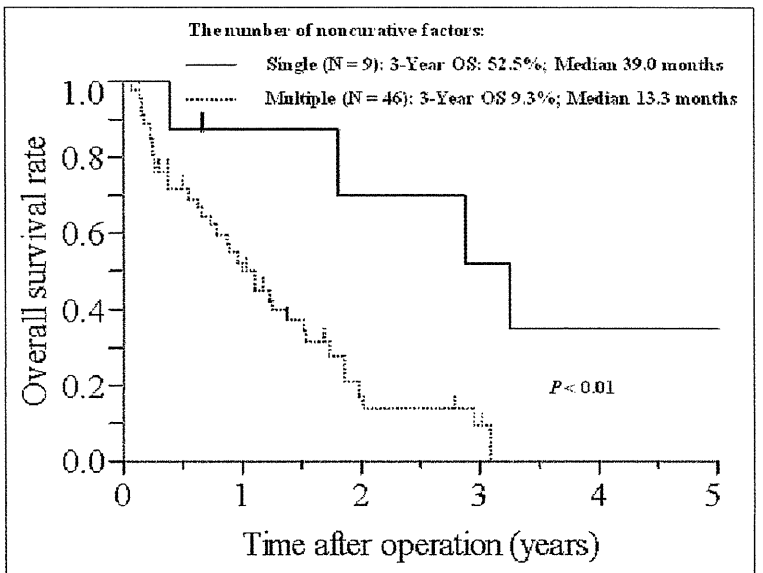

Fig. 4 Overall survival rate for non-curative patients according to the number of non-curative factors. OS, Overall survival.

考　察

大腸癌腹膜播種の頻度は4.3～7.3%と必ずしも多くないが，その予後は不良である[2)～5)]．その要因の一つとして，腹膜播種を来した症例は，同時に他臓器への転移を来していることがあげられる．我々の検討では，手術時に腹膜播種以外の遠隔転移（肝転移を含む）を47例（66.2%）に認め，そのうち手術根治度Bが得られたのは2例のみであった．このように腹膜播種は同時に他の遠隔転移を伴うことが多く，予後が不良な因子の一つであるが，原発および転移巣の完全切除が得られれば比較的良好な予後が期待できる症例も報告されている[3)4)]．

当院における腹膜播種症例の3年生存率，生存期間中央値はそれぞれ30.7%，20.7か月，腹膜播種程度

別の3年生存率（生存期間中央値）はそれぞれ，P1：50.0%（34.6か月），P2：48.2%（22.3か月），P3：9.6%（13.3か月）であった．平井ら[4]は生存期間中央値が，P1：17.7か月，P2：13.8か月，P3：6.6か月と報告し，横溝ら[3]は3年生存率，生存期間中央値はそれぞれ12.4%，5.4か月と報告している．さらに，高橋ら[6]は3年生存率がP1：15.0%，P2：13.2%，P3：4.8%と報告している．手術根治度Bが得られた症例の割合は，横溝ら[3]は21%，高橋ら[6]は31%で，当院の23%（16/71例）と同等またはそれ以上にもかかわらず，当院の成績が良好であった要因としては，対象症例が開院以来の2002年から2010年の比較的新しい症例であったため，奏効率の高い新規化学療法レジメンや分子標的治療薬が使用され，生存期間が改善した可能性がある．また，観察期間中央値が14.4か月と比較的短かったことも要因と考えられる．

予後規定因子についてはこれまで，占居部位[4]，組織型[2]，リンパ節転移の有無[2]，肝転移の有無[2]，原発巣切除の有無[3]，化学療法の有無[3]，手術根治度[3][4]，非治癒因子の数[4]などが報告されている．我々の検討では，多変量解析の結果，予後規定因子として手術根治度が抽出された．手術根治度に関しては，手術根治度Bが得られた症例において，P1とP2の転帰は有意な差を認めなかった．さらに，手術根治度Bは，手術根治度Cよりも有意に転帰が良好であった．つまり，P1とP2では，手術所見で完全切除が得られると判断すれば，それらの病巣を積極的に切除し，手術根治度Bを目指した手術を行うことで予後の改善が得られる可能性があると考えられる．腹膜播種の程度は転帰を反映していなかったことより，今後は諸家の報告にある予後不良因子[2]~[4]を組み合わせた分類を作成する必要があると思われる．ただし，P3で手術根治度Bが得られたのは1例のみなので，今回の検討からはP3における手術根治度Bを目指した手術療法の有効性を示すことはできない．少なくともP3で手術根治度Bを目指すことは，大腸癌治療ガイドライン[1]における「過大侵襲」となることがほとんどであると思われる．

このように手術根治度Bが得られれば転帰の改善が期待できるが，実際には多くの場合手術根治度Cとなり，その転帰は非常に悪い．自験例では，77.5%の症例が手術根治度Cとなった．そこで，主に海外では，以前からより強力な治療戦略として，腹膜播種巣の完全切除＋腹腔内化学療法の有効性が報告されている[7][8]．特に2003年にオランダで行われた大腸癌腹膜播種のランダム化比較試験では，減量手術＋術中温熱化学療法群が有意に減量手術＋標準的化学療法群より生存率が高いことが報告された[9]．我々の検討において，手術根治度Bが予後規定因子として抽出されたということは，減量手術の有効性を示唆している可能性がある．しかし，本治療法のエビデンスは十分ではなく，また腹腔内温熱化学療法に関連した合併症や治療の煩雑さを考慮すると，本邦で導入するには適正に計画された臨床試験として本治療法の有効性と安全性を確認していく必要があると思われる[1]．

肝転移に関して，肝転移の多くは他の遠隔転移を同時に伴うため切除不能となることが多く，我々の検討でも肝切除を行えた症例は2例のみであった．それらの症例は，同時性肝転移に対して原発巣および腹膜播種切除後に，異時性に肝切除を行い22か月，70か月生存した症例であった．症例数は少ないが，このように原発巣，腹膜播種，肝転移を切除可能であれば，それらを切除することによって転帰が改善する可能性があると考えられた．また，非治癒因子数が1つでそれが肝転移であれば，本症例のように異時性に切除が行え，長期生存例の可能性もあると考えられた．

診断に関しては，術前に腹膜播種を診断することは容易ではない．de Breeら[10]は，CTの場合，5cm以上の感度は59–67%であるが，1cm以下の病変であれば9–24%であると報告している．また，Tanakaら[11]はCTよりFDG-PETの方が正診率が高く，特に15mm以上であれば診断が可能であると報告している．しかし，粟粒大の播種性病変を手術時に認めることも多く，それらを手術前に診断することは困難である．よって，画像で腹膜結節を認めなくとも，腹水や腹膜脂肪織濃度の上昇および腸管壁の造影効果の上昇，腸間膜の肥厚，大網の血管の拡張など[5]を認める場合は，腹膜播種を疑い，手術時に注意深く観察することが重要である．

今回の検討では，手術根治度が予後規定因子として抽出されたが，当院での過去のデータから解析し

た後ろ向きの検討であるため，腹膜播種症例の選択自体にある程度の bias があることは否めない．しかし，後ろ向き検討ではあるが Stage IV 大腸癌において外科的治療の有効性が示唆されたことの意義は大きいと考える．

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