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Sex Differences Between cT4b and pT4b Rectal Cancers

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We retrospectively evaluated rectal cancer surgery cases in which resection had been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences. We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs. We investigated invasion of adjacent organs in terms of pathologic findings according to sex differences. Among males, 4 cases (13.8%) had received combined radical resections of more than 2 organs, while the number of such female cases was 15 (46.9%). The difference between males and females was statistically significant ($P = 0.006$). Among male cases, histopathologic invasion was present in 4 (13.8%), while 9 female cases (28.1%) showed this feature. Nevertheless, there was not a statistically significant difference between males and females ($P = 0.08$); the rate in females was roughly twice that in males. No significant difference was recognized in the overall survival rates between males and females, but more females than males experienced local recurrence. In cases with rectal cancer invading neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

Key words: Rectal cancer – Invasion of other organs – Sex differences

It is important to prevent local recurrences of rectal cancer. Obtaining a sufficient circumferential resection margin (CRM) is thus a critical surgical procedure.[1,2] This is especially true for local advanced rectal cancer with distant invasion of adjacent organs (pT4b). Total pelvic exenteration remains the first-line surgical treatment for pT4b cases,[3] but recently organ-sparing therapy has also frequently been chosen.[4] However, the mode of invasion in highly aggressive rectal cancer has been less well studied. We retrospectively evaluated rectal cancer surgery cases in which resection had

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Table 1 Clinicopathological findings

	Male cases (%), N = 29	Female cases (%), N = 32
Age	60 ± 9	63 ± 12
Size (cm)	3.5 ± 2.0	5.9 ± 1.9
Figure		
Polypoid type	1 (3.4)	1 (3.1)
Ulcerated with clear margin type	24 (82.8)	22 (68.8)
Ulcerated with infiltration type	4 (13.8)	8 (25.0)
Diffuse infiltrating type	0 (0.0)	1 (3.1)
Unclassified type	0 (0.0)	0 (0.0)
Histology		
Well-differentiated and moderately differentiated	27 (93.1)	30 (93.8)
Others (poorly differentiated, mucinous, and Signet-ring cells)	2 (6.9)	2 (6.3)
Surgical procedure		
Low anterior resection	14 (48.4)	14 (43.8)
Hartmann's procedure	1 (3.4)	5 (15.6)
Abdominoperineal resection	11 (37.9)	10 (31.3)
Total pelvic exenteration	3 (10.3)	3 (9.3)
TNM		
IIA	0 (0.0)	0 (0.0)
IIB	11 (37.9)	8 (25.0)
IIC	0 (0.0)	2 (6.2)
IIIA	0 (0.0)	0 (0.0)
IIIB	7 (24.2)	6 (18.8)
IIIC	11 (37.9)	16 (50.0)

been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences.

Materials and Methods

We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, between January 1990 and December 2001. Intraoperatively, if we recognized the primary rectal cancer as having invaded adjacent organs, combined radical resection was performed. None of our patients had received either chemotherapy or radiation therapy prior to surgery. Complete dissection of all regional lymph nodes with mesorectal excision was carried out in all cases. In Japan, lateral lymph node dissection is generally indicated if the lower margin of the primary cancer is located below the peritoneal reflection or anal canal with invasion into the muscularis propria or beyond. There were no cancer cells in the CRM in any of our cases. The resected specimens were fixed in 10% formalin for several days, and sections were prepared across the maximum diameter of the tumor and stained with hematoxylin and eosin (HE), without specific immunostaining. The slides were then evaluated by simple light microscopy.

We conducted a review of the relevant hospital records to obtain clinicopathologic information about the patients, including sex and age, macroscopic configuration of the tumor, maximum tumor size, and histologic type of the tumor. Adenocarcinomas of the rectum are graded predominantly on the basis of their glandular appearance and are classified as well/moderately differentiated (W/M) or others (poorly differentiated, mucinous, and Signet-ring cells), according to the World Health Organization (WHO) histopathologic classification of tumors of the colon and rectum,[5] and the Japanese Classification of Colorectal Carcinoma.[6]

This study included cases with rectal cancer defined as a tumor whose lowest border is located between the anal verge and the sacral promontory and the rectosigmoid colon. Tumors are classified into 5 types on the basis of their macroscopic appearance: (1) polypoid, (2) ulcerated with clear margin, (3) ulcerated with infiltration, (4) diffuse infiltrating, and (5) unclassified. Surgical procedures are classified into 4 approaches: (1) low anterior resection, (2) Hartmann's procedure, (3) abdominoperineal resection, and (4) total pelvic exenteration. In terms of the TNM staging system, all cases were classified as having stage II or stage III tumors. Most notably, we investigated invasion of adjacent organs

Table 2 The resected organs in males and females

Male: Resection 29 cases	Resection cases			Histopathological invasion (+)
Seminal vesicles	14 (48.3%)	25 (86.2%)	a	0 (0.0%)
Prostate	2 (6.9%)			0 (0.0%)
Urinary Bladder	9 (31.0%)			1 (3.4%): Urinary Bladder
Seminal vesicles + Prostate	1 (3.4%)	4 (13.8%)		1 (3.4%): Seminal vesicles
Seminal vesicles + Urinary bladder + Ureter	1 (3.4%)			1 (3.4%): Ureter
Seminal vesicles + Prostate + Ureter	1 (6.9%)			0 (0.0%)
Prostate+ Urinary bladder + Ileum	1 (6.9%)			1 (3.4%): Ileum
Total				4 (13.8%)[c]

Female: Resection 32 cases	Resection cases			Histopathological invasion (+)
Uterus	5 (15.6%)	17 (53.19%)	b	0 (0.0%)
Ovary	5 (15.6%)			0 (0.0%)
Vagina	6 (18.8%)			2 (6.3%): Vagina
Ureter	1 (3.1%)	15 (46.9%)		0 (0.0%)
Uterus + Ovary	4 (12.5%)			1 (3.4%): Uterus
Uterus + Vagina	7 (21.9%)			2 (6.3%): Vagina
Uterus + Urinary bladder + Sigmoid colon	1 (3.1%)			1 (3.1%): Sigmoid colon
Vagina + Urinary bladder	2 (6.3%)			2 (6.3%): Vagina + Urinary bladder
Uterus + Ovary+ Urinary bladder	1 (3.1%)			1 (3.1%): Uterus + Urinary bladder
Total				9 (28.1%)[d]

[a]Significantly different, $P = 0.006$.
[b]Significantly different, $P = 0.006$.
[c]Significantly different, $P = 0.08$.
[d]Significantly different, $P = 0.08$.

in terms of pathologic findings, according to sex differences (Table 1). After the operation, TNM stage III cases were administered oral chemotherapy, with oral 5-fluorouracil, 5′-doxifluridine, carmofur, or uracil-tegafur with leucovorin being the most commonly used drugs, for approximately 6 to 12 months.[7–9] None of the patients received radiation therapy.

All data are expressed as mean ± SD. The χ^2 test was subsequently performed to identify factors possibly influencing pathologic invasion and recurrence. The log-rank test was used to evaluate the difference in local disease-free survival rates between groups. Statistical significance was set at $P < 0.05$.

Results

Table 2 shows the resected organs and whether histopathologic invasion was present (pT4b). In male cases, combined radical resections involved the seminal vesicles, prostate, urinary bladder, and/or ileum. The seminal vesicles were the most commonly resected adjacent organs (14 of 29 cases; 48.3%). Four cases (13.8% of males) underwent combined radical resection of more than 2 organs. In female cases, combined radical resection involved the uterus, ovaries, vagina, urinary bladder, ureters, and sigmoid colon. The vagina was the most commonly resected adjacent organ (6 of 32 cases; 18.8%). Fifteen cases (46.9% of females) underwent combined radical resection of more than 2 organs. There was a statistically significant difference between males and females in the number of patients undergoing combined radical resection ($P = 0.006$). The results (Table 2) for histopathologic invasion are shown. Histopathologic invasion was present in only 4 males (13.8%). Yet, among females, histopathologic invasion was observed in 9 cases (28.1%). The difference between males and females was not statistically significant ($P = 0.08$), but the rate in females was roughly twice that in males. Figure 1 shows the partially resected posterior wall of the vagina. The cancer had spread showing discontinuity, and the shortest distance between the deepest part of the cancer and the incised surface was only 500 μm.

Figure 2 shows the overall survival rates of the patients enrolled in this study. No significant differences in the overall survival rate were observed between T4a cases in males with and in females ($P = 0.561$), or T4b cases in males with and in females ($P = 0.728$). But there was a statistically significant difference between T4a cases and T4b cases in males ($P = 0.005$), and in T4a cases and T4b cases in females ($P < 0.001$) in the overall survival rate.

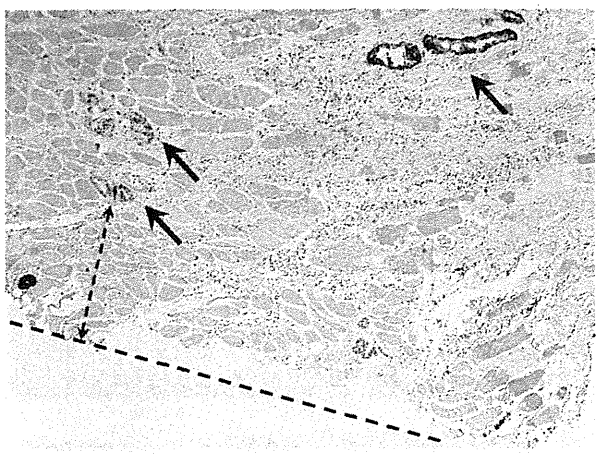

Fig. 1 This figure shows the partially resected posterior wall of the vagina. The cancer shows discontinuous spread (black arrow), and the shortest distance between the deepest part of the cancer and the incised surface (dotted line) was only 500 μm (dotted black arrow). H&E (×100).

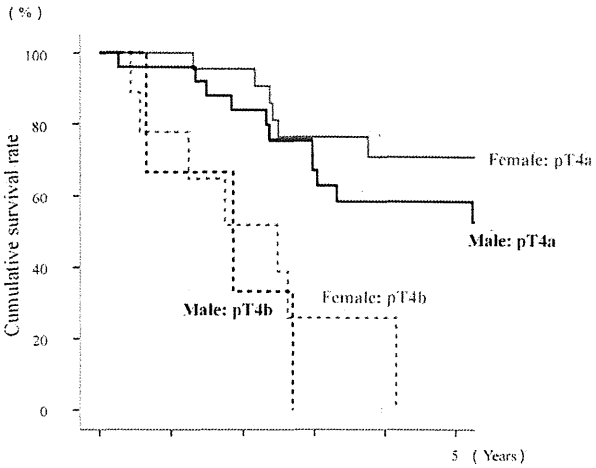

Fig. 2 This figure shows the overall survival rates of the study patients. Male: pT4a vs. Female pT4a : p=0.561; Male: pT4b vs. Female pT4b : p=0.728; Male: pT4a vs. Male pT4b : p=0.005; Female: pT4a vs. Female pT4b : p<0.561.

Table 3 shows the organs affected by recurrence in males and females. While no significant difference was recognized in local recurrence rates between males and females undergoing resection ($P = 0.220$), the number of local recurrences in females receiving resection exceeded that in males.

Discussion

Previously, we reported pathologic studies of combined radical resection of seminal vesicles in the treatment of rectal cancer, and we emphasized that it is possible to ensure a sufficiently large CRM and to thereby attenuate local recurrence.[10] However, most previously published reports do not make reference to sex differences. This study is the first, to our knowledge, to demonstrate sex differences in response to combined radical resection for the treatment of rectal cancer. Our data therefore have prognostic significance. Bonfanti *et al* report extensively on the organs resected for invasive colorectal cancer, providing considerable detail, but do not mention sex differences.[11]

Recently, many studies have examined neoadjuvant treatment with chemotherapy and pelvic radiotherapy for locally advanced rectal cancer. Neoadjuvant treatment, employing chemotherapy and pelvic radiotherapy, contributes to better outcomes, with the former inhibiting distant metastases and the latter inhibiting local recurrences.[12] However, because of the lack of pathologic findings without neoadjuvant treatment (*i.e.*, the spread of rectal cancer in the absence of other factors), this study provides data critical for determining the optimal treatment of pT4b cases.

It is of major interest that the rate of histopathologic invasion in females exceeded that in males. The reason is unclear, but in 15 female cases (46.9%) multiple organs were resected based on an intraoperative diagnosis of cT4b, making it reasonable to speculate that female anatomic structures are more susceptible to tumor invasion. This study showed tumors to be in proximity to the incised surface.

The local recurrence rate in females was approximately twofold that in males, such that the surgical margins in females were apparently insufficient. The many recurrences in our female patients prompted us to speculate that the operative method employed might be less than optimal in women. When rectal cancer invaded the posterior wall of the vagina, partial resection of the vagina was often deemed necessary, but this procedure was found to be insufficient to prevent recurrence. If intraoperative cT4b is recognized, it is essential that adequate combined resection be performed. Harris *et al* report that an aggressive surgical strategy with complete resection is predictive of long-term survival.[13] And, the high-potency adjuvant treatment with chemo-

Table 3 The organs affected by recurrence in males and females

	Male cases (%), N = 29	Female cases (%), N = 32
All recurrence cases	9 (31.0)	10 (31.3)
Local	1 (3.4)	4 (12.5)
Anastomosis line	1 (3.4)	1 (3.4)
Distant (lung, liver, bone)	5 (17.2)	4 (12.5)
Distant peritoneum	1 (3.4)	1 (3.4)
Lymph nodes	1 (3.4)	0 (0.0)

[a]Significantly different, $P = 0.220$.

[b]Significantly different, $P = 0.220$.

therapy is essential for pT4b cases in males and females.[13]

Our data showed that no pathologic invasion cases account for about 80% of resected adjacent organs in males and females. So, it is essential to rule out the cases except pT4b, but it is very difficult intraoperatively. The reasonably accurate diagnostic imaging is essential before operation.

In rectal cancer cases with invasion of neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

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BRIEF ARTICLE

Can mosapride citrate reduce the volume of lavage solution for colonoscopy preparation?

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Abstract

AIM: To evaluate the possibility of reducing the volume of polyethylene glycol (PEG)-electrolyte solution using adjunctive mosapride citrate for colonoscopy preparation.

METHODS: This was a single-center, prospective, randomized, investigator-blinded, non-inferiority study involving 252 patients of both sexes, aged from 20 to 80 years, scheduled for screening or diagnostic colonoscopy in our department. A total of 126 patients was randomized to receive 1.5 L PEG-electrolyte solution plus 15 mg of mosapride (1.5 L group), and 126 received 2 L PEG-electrolyte solution plus 15 mg of mosapride (2 L group). Patients completed a questionnaire on the acceptability and tolerability of the bowel preparation process. The efficacy of bowel preparation was assessed using a 5-point scale based on the Aronchick scale. The primary end point was adequate bowel preparation rates (score of excellent/good/fair) *vs* (poor/inadequate). Acceptability and tolerability, as well as disease detection, were secondary end points.

RESULTS: A total of 244 patients was included in the analysis. There were no significant differences between the 2 L and 1.5 L groups in age, sex, body mass index, number of previous colonoscopies, and the preparation method used previously. The adequate bowel preparation rates were 88.5% in the 2 L group and 82.8% in the 1.5 L group [95% lower confidence limit (LCL) for the difference = -14.5%, non-inferiority P = 0.019] in the right colon. In the left colon, the adequate bowel preparation rates were 89.3% in the 2 L group and 81.1% in the 1.5 L group (95% LCL = -17.0%, non-inferiority P = 0.066). Compliance, defined as complete (100%) intake of the PEG solution, was significantly higher in the 1.5 L group than in the 2 L group (96.8% *vs* 85.7%, P = 0.002). The proportion of abdominal distension (none/mild/moderate/severe) was significantly lower in the 1.5 L group than in the 2 L group (36/65/22/3 *vs* 58/48/18/2, P = 0.040). Within the subgroup who had undergone colonoscopy previously, a significantly higher number of patients in the 1.5 L group than in the 2 L group felt that the current preparation was easier than the previous one (54.1% *vs* 28.0%, P = 0.001). The disease detection rate was not significantly different between the two groups.

CONCLUSION: Although the 1.5 L group had better acceptability and tolerability, 15 mg of mosapride may be insufficient to compensate for a 0.5-L reduction of PEG solution.

Key words: Mosapride citrate; Bowel preparation; Polyethylene glycol-electrolyte solution; Prokinetics; Colonoscopy

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INTRODUCTION

Polyethylene glycol (PEG)-electrolyte solution is widely used worldwide for bowel cleansing. By consensus of the American Society for Gastrointestinal Endoscopy, the American Society of Colon and Rectal Surgeons, and the Society of American Gastrointestinal and Endoscopic Surgeons, PEG-electrolyte solution is the gold standard for colonoscopic bowel preparation (Grade I A), and aqueous sodium phosphate (NaP) is an alternative regimen to PEG-electrolyte solutions (Grade I A)[1]. Several meta-analyses on the available bowel preparations have favored NaP, concluding that it was effective and better tolerated by patients than PEG-electrolyte solution[2-4]. However, the disadvantages of NaP are its associated side effects. Significant changes in serum electrolyte levels[5], even in patients without renal failure, have prompted recommendations for serum electrolyte evaluation prior to the administration of NaP[6,7].

On the other hand, osmotically balanced electrolyte lavage solutions offer safe and effective cleansing, but volume-related discomfort and adverse experiences have decreased the percentage of patients completing the pre-examination preparation[1,8,9]. This is mainly due to the large volumes of fluid required for bowel preparation, the unpleasant taste, and an increase in the incidence of side effects[10]. Although 3-4 L of this solution is used in Western countries, approximately 2 L of this solution, along with a laxative, is usually considered adequate for bowel preparation in Japan. Despite the lower volume in Japan, the need to drink such large volumes of liquid with an unpalatable taste has a negative impact on patient compliance[11]. Therefore, more effective bowel preparation regimens for colonoscopy are required to improve the acceptability and tolerability of the procedure.

Mosapride citrate (mosapride) is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist. Mosapride enhances gastric emptying and motility by facilitating acetylcholine release from the enteric cholinergic neurons, without blocking the dopaminergic D2 receptors[12]. It is known to be effective in gastroesophageal reflux disease[13], functional gastrointestinal disorders, such as functional dyspepsia[14], chronic gastritis with delayed gastric emptying, and diabetic gastroparesis[15]. Since 5-HT4 receptors are also located in the human colon and rectum[16,17], mosapride is also expected to have a prokinetic effect on the colo-rectum. A few clinical studies have reported that mosapride in combination with PEG-electrolyte solution may enhance bowel cleansing and improve patient acceptability and tolerability[18,19]. Furthermore, we previously conducted a randomized, double-blind, placebo-controlled study with mosapride in addition to PEG-electrolyte solution and demonstrated that co-administration of mosapride with PEG-electrolyte solution improved the quality of bowel preparation for colonoscopy, especially in patients without severe constipation[20]. Among the subgroup that had undergone previous colonoscopy, a significantly higher number of mosapride-group patients than placebo-group patients felt that the current preparation was easier. However, mosapride could not improve symptoms such as nausea, abdominal distension, abdominal pain, and willingness to repeat the same regimen compared with placebo. In short, mosapride did not sufficiently improve patient acceptability and tolerability. Therefore, it appears that it is necessary to reduce the volume of PEG-electrolyte solution to improve patient acceptability and tolerability.

The aim of this study was to evaluate the reduction of PEG-electrolyte solution volume when combined with mosapride citrate for colonoscopy preparation.

MATERIALS AND METHODS

This was a prospective, randomized, investigator-blinded study, comparing 1.5 L PEG plus mosapride (1.5 L group), with 2 L PEG-electrolyte solution plus mosapride (2 L group) dosing for patients who underwent colonoscopy. All patients provided written, informed consent prior to entering the study. The study was conducted at Aichi Cancer Center Hospital (ACCH), Nagoya, from January 2010 to June 2010, and was reviewed and approved by the ethics committee of ACCH. This trial was registered in an international clinical trial registry (UMIN000001556).

Study population

All consecutive outpatients of both sexes, aged 20 to 80 years, who were scheduled for screening or diagnostic colonoscopy at ACCH were evaluated for inclusion in the study. Patients with the following clinical features were excluded: significant cardiac, renal, hepatic, or metabolic co-morbidities, ascites, severe constipation (< 2 bowel movements a week), known allergy to PEG-electrolyte solution, history of gastric stapling or bypass procedure, or a history of prior colonic or rectal surgery. Patients were excluded if there was a suspected diagnosis of intestinal obstruction because of advanced colorectal cancer.

Randomization and blinding

Patients were randomly allocated to receive one of two different bowel preparation regimens using a computer-generated random-number list. Patients were randomized in block sizes of two, with serially numbered, sealed, opaque envelopes. Concealed allocation was accom-

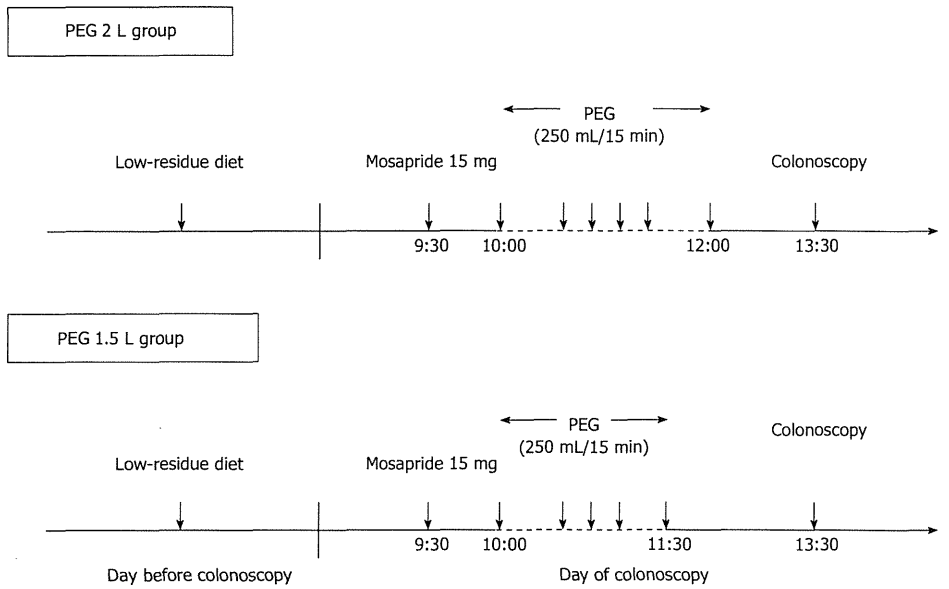

Figure 1 Steps in preparation for colonoscopy. PEG: Polyethylene glycol.

plished through non-research personnel who were not involved in this study. Patients were instructed not to discuss their bowel preparation with anyone other than the unblinded research assistant. With the exceptions of the patient and the unblinded research assistant, all other individuals participating in this study, including the endoscopists and endoscopy nurses, were blinded to the allocated treatment group. Comparisons between the 1.5 L group and the 2 L group were made in an investigator-blind fashion.

Bowel preparation methods

The day before colonoscopy, all patients were instructed to eat a pre-packaged, low residue diet (Enimaclin CS; Horii Pharmaceutical Ind., Ltd., Osaka, Japan) that consisted of a lunch, snack, and dinner, and asked to drink more than 2 liters of clear liquid. On the day of the colonoscopy, all participants reported to the endoscopy room at 9:00 am and received in-hospital bowel preparation. In-hospital preparation was important to ensure uniformity and remove any confounding caused by poor patient adherence. More than 10 toilet facilities were made available in the endoscopy unit for patient comfort. Six mosapride tablets (15 mg) (Gasmotin; Dainippon Sumitomo Pharma Co., Ltd. Osaka, Japan) were administered orally with water at half past nine. After 30 min, both groups were instructed to drink 0.25 L of PEG-electrolyte solution (Niflec; Ajinomoto Pharmaceuticals Co., Ltd. Tokyo, Japan) every 15 min (Figure 1). Colonoscopies were performed from half past thirteen, and the start times were recorded for each patient.

Evaluation of bowel preparation

The efficacy of bowel preparation was assessed using the Aronchick scale[21]. Participating endoscopists were trained to use the Aronchick scale to achieve a good level of agreement. Investigators performed calibration exercises involving more than 20 colonoscopies prior to study commencement, based on their interpretation of scale anchors, to ensure that their findings agreed. The final assessment of bowel preparation was divided into two categories, adequate and failure. Bowel preparation rated as fair, good, or excellent, based on the Aronchick scale, was considered adequate; poor or inadequate ratings were considered failure. After colonoscopy, two observers, one who was the operator and the other who was a fellow in the procedure room, decided the score by mutual agreement. They scored the quality of the preparation on the right side (proximal to splenic flexure) colon and on the left side (distal to splenic flexure) colon and rectum separately. If the decision was discordant, a third expert reviewer graded and scored the recorded images later, and this evaluation was used in the final analysis. Twelve experienced colonoscopists carried out all colonoscopy procedures, each of whom had performed more than 1000 colonoscopies.

During or immediately following the colonoscopy, the investigator completed a physician questionnaire regarding assessment of bowel preparation, amount of irrigation fluid used, time needed to reach the cecum, and ease of insertion to the cecum and difficulty in observing the lumen of the colo-rectum because of peristalsis.

Patient tolerance and other measurements

The nursing staff recorded the time required to drink the indicated volume of lavage solution. They also recorded the time and number of bowel movements from the start of ingestion to the appearance of clear excretion. Until one hour after finishing the PEG-electrolyte solution plus mosapride, the nursing staff checked patients' excretions.

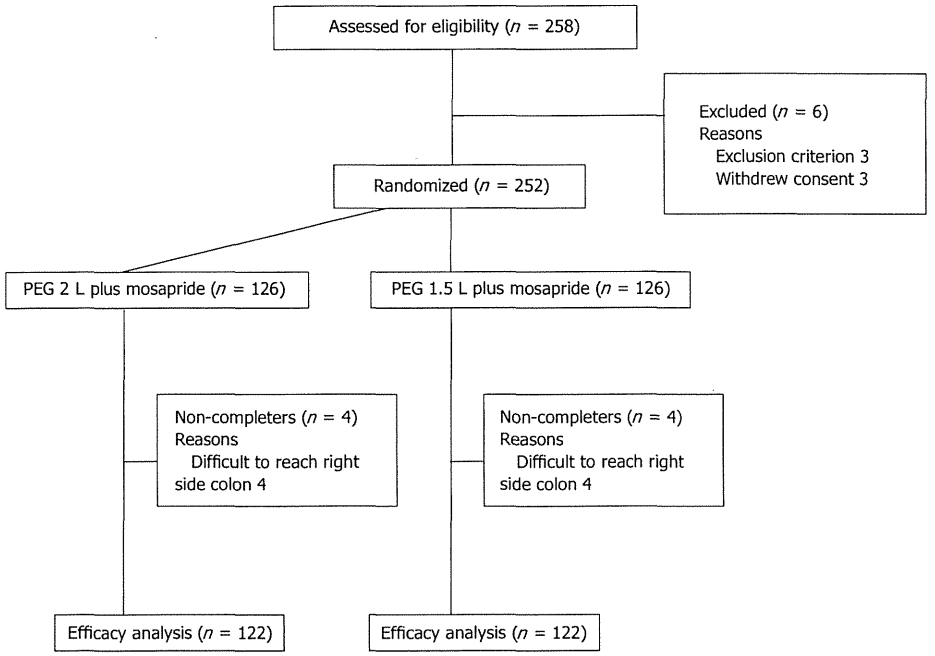

Figure 2 Patient disposition flow chart. PEG: Polyethylene glycol.

If there was a solid stool with muddy excretions or no excretion at that time, the patient was given an additional preparation, such as additional PEG-electrolyte solution or enemas. The patients who received an additional preparation were defined by the Aronchick scale as inadequate. The patient questionnaire consisted of 20 questions[20]. The adverse events were scored using a 4-point scale, where 1 = none, 2 = mild, 3 = moderate, and 4 = severe. The patients completed the questionnaire form before undergoing colonoscopy and submitted it to the nursing staff.

End points

The primary end point was the difference in the rate of adequate colon cleansing between the 1.5 L PEG-electrolyte solution plus 15 mg of mosapride (1.5 L group) and the 2 L PEG-electrolyte solution plus 15 mg of mosapride (2 L group). Secondary end points included differences in patients' acceptability and tolerance of solutions, time to first defecation, frequency of defecation, complete time for colonic preparation, time needed to reach the cecum, amount of irrigation fluid used, subjective difficulty in colonoscopy insertion to the cecum and in observing the lumen of the colo-rectum because of peristalsis, and disease detection rates.

Statistical analysis

Based on a previous study[20], the adequate bowel preparation rate for the PEG-electrolyte solution plus mosapride was expected to be less than 80%. It was expected that about 80% of the 1.5 L group would be judged adequate, and the non-inferiority margin was set at -15%. This study was designed to have 80% power to establish non-inferiority (using a one-sided significance level of 0.025 and a target sample size of 250).

The primary efficacy analysis was based on an intent-to-treat analysis and included patients who were randomized and received any treatment. In patients in this group, the preparation was classified as adequate or inadequate based on the colonoscopists' score of cleansing. Patients who did not undergo colonoscopy because of preparation-related adverse events, or preparation failure, or in whom the right colon could not be reached because of bowel obstruction or technical reasons were excluded. The rates of adequate preparation were compared between the groups by χ^2 test or Fisher's exact test for categorical variables.

For the secondary end points, the Mann-Whitney *U* test was used to compare continuous variables. Categorical variables were tested using the corrected χ^2 test or 2-sided Fisher's exact tests as appropriate. The criterion for significance was $P < 0.05$.

All statistical analyses were performed using Statistical Analysis Software (SAS Ver. 9.2 for the PC, SAS Institute Inc., Cary, NC, United States).

RESULTS

Patients' characteristics

A total of 252 patients was randomized into two groups (Figure 2). Although 252 patients were analyzed, colonoscope insertion to the right colon failed in 4 patients in each group (advanced stenosing cancer in two, and patient refusal in six because of pain). These eight patients were excluded from the efficacy analysis. The baseline characteristics of the patients are shown in Table

Table 1 Baseline characteristics

Variable	2.0 L	1.5 L	*P* value
Patients (*n*)	126	126	
Age (yr, mean ± SD)	65.3 ± 9.9	66.3 ± 9.6	NS
< 60	30	25	
60 - < 70	51	44	NS
≥ 70	45	53	
Male	77	67	NS
Female	49	59	
Indication (*n*)			
Screening	40	41	
Surveillance	67	63	NS
Diagnostic	19	22	
Body mass index (kg/m^2)	22.5 + 3.2	22.3 + 2.7	NS
Previous colonoscopy			
None (first time)	44	41	NS
≥ 2	82	85	
Previous preparation for colonoscopy (*n*)			
2L PEG	82	85	NS

PEG: Polyethylene glycol; NS: Not significant.

1. There was no significant difference in age, sex, body mass index, number of previous colonoscopies, and the preparation method used previously between the 2.0 L and 1.5 L groups.

Bowel cleansing efficacy

The efficacy of bowel preparation is shown in Table 2. The adequate bowel preparation rates were 88.5% in the 2 L group and 82.8% in the 1.5 L group (95% lower confidence limit, lower confidence limit (LCL), for the difference = -14.5%, non-inferiority $P = 0.019$) in the right side colon. In the left colon, the adequate bowel preparation rates were 89.3% in the 2 L group and 81.1% in the 1.5 L group (95% LCL = -17.0%, non-inferiority $P = 0.066$). In the right side colon, there were significant differences in the proportion of the overall colon-cleansing score between the two groups ($P = 0.006$). Eleven patients (8.7%) required additional preparation in the 2 L group. On the other hand, 18 patients (14.3%) required additional preparation in the 1.5 L group. However, there was no significant difference in required additional preparation between the two groups.

As shown in Table 3, there were no differences in frequency of defecation, time needed to reach the cecum, elapsed time from last fluid intake to colonoscopy, amount of irrigation fluid used, and subjective difficulties in insertion to the cecum and in observing the lumen of the colo-rectum between the two groups.

Patient acceptability, tolerability, and safety

There was no significant difference in compliance as defined by > 80% intake of the prescribed PEG-electrolyte solution volume. However, complete (100%) intake of the PEG solution was significantly higher in the 1.5 L group than in the 2 L group ($P = 0.002$) (Table 3). The proportion of abdominal distension was significantly less in the 1.5 L group than in the 2 L group ($P = 0.040$), but symptoms such as nausea, vomiting, abdominal pain, and circulatory reactions were similar in both groups. The proportion of patients willing to repeat the same preparation regimen was significantly higher in the 1.5 L group ($P = 0.034$). Furthermore, among the subgroup of patients who had undergone colonoscopy more than twice previously, a significantly higher number of patients in the 1.5 L group than in the 2 L group felt that the current preparation was easier than in the past ($P = 0.001$).

Table 2 Overall colon-cleansing efficacy *n* (%)

Variable	Right side colon		Left side colon and rectum		*P* value[1]	
	2.0 L	1.5 L	2.0 L	1.5 L	Right	Left
Patients (*n*)	122	122	122	122		
Overall score (*n*)						
Excellent	36	22	48	37		
Good	52	38	49	45		
Fair	20	41	12	17	0.006	NS
Poor	3	3	2	5		
Inadequate	11	18	11	18		
No. adequate	108 (88.5)	101 (82.8)	109 (89.3)	99 (81.1)	NS	NS

[1]*P* value by χ^2 test. PEG: Polyethylene glycol; NS: Not significant.

Disease detection rate

In this study, 11 colorectal cancers were detected in 11 patients (4.4%), 4 (3.2%) in the 2 L group and 7 (5.6%) in the 1.5 L group (Table 4). A total of 177 polyps was detected in 74 patients (58.7%) in the 2 L group, and 187 polyps were detected in 73 patients (57.9%) in the 1.5 L group. The proportions of polyps by size and location were similar in the two groups.

DISCUSSION

In this study, 1.5 L PEG-electrolyte solution plus mosapride was found to be non-inferior to 2 L PEG-electrolyte solution plus mosapride with respect to adequate bowel preparation rates only in the right colon, not in the entire colo-rectum. On the other hand, patient tolerability, especially abdominal distension, and acceptability were superior in the 1.5 L group compared to the 2 L group.

This is the first study, to the best of our knowledge, that has evaluated the effect of mosapride when used in conjunction with reduced dose, 1.5 L PEG-electrolyte solution for colonoscopy preparation. We previously conducted a randomized, double-blind, placebo-controlled study with mosapride in addition to PEG-electrolyte solution and demonstrated that co-administration of mosapride with PEG-electrolyte solution improved the quality of bowel preparation for colonoscopy, especially in patients without severe constipation[20]. On the other hand, the beneficial effect of mosapride on gastric emptying[22] was expected to ameliorate nausea, vomiting, and fullness of the abdomen during bowel preparation. Mishima *et al*[19] showed that administration of mosapride prior to PEG-electrolyte solution significantly decreased the incidence of uncomfortable abdominal symptoms. However, there were no significant differences in the

Table 3 Results of preparation, endoscopic findings and patient questionnaire *n* (%)

Variable	2.0 L	1.5 L	*P* value
Patients	126	126	
Time to first defecation (min, mean ± SD)	55.7 ± 27.4	56.4 ± 27.8	NS
Frequency of defecation (times, median, quartile)	7 (4-15)	7 (4-15)	NS
Time to preparation (min, mean ± SD)	157.3 ± 51.9	159.6 ± 57.1	NS
Elapsed time from last fluid intake to colonoscopy (min, mean ± SD)	169.4 ± 56.5	179.7 ± 61.1	NS
Cecal intubation rate	122 (96.8)	122 (96.8)	NS
Insertion time (min, median, quartile)[1]	11.4 (3-76)	10.1 (3-47)	NS
Feel of peristalsis	20 (16.4)	25 (20.5)	NS
Amount of irrigation fluid			
None	38	41	
< 50 mL	74	74	NS
50-100 mL	9	9	
> 100 mL	5	2	
Compliance > 80%	121 (96.0)	125 (99.2)	NS
100% intake	108 (85.7)	122 (96.8)	0.002
Any symptom			
Nausea (none/mild/moderate/severe)	109/13/3/1	117/5/3/1	NS
Vomiting (none/mild/moderate/severe)	0/0/1/0	0/0/0/0	NS
Distension (none/mild/moderate/severe)	36/65/22/3	58/48/18/2	0.04
Abdominal pain (none/mild/moderate/severe)	98/26/2/0	107/18/1/0	NS
Circulatory reactions (none/mild/moderate/severe)	0	0	NS
Willingness to repeat			
The same preparation regimen (much/fair/never)	78/19/29	97/12/17	0.034
How easy/difficult to take preparation compared to previous (easy/no difference/difficult)	23/54/5	46/36/3	0.001

[1]Insertion time was calculated without including the patients whose cecal portion was not examined. NS: Not significant.

Table 4 Characteristics of the endoscopic diagnosis *n* (%)

Variable	2.0 L		1.5 L		*P* value (2.0 L *vs* 1.5 L)	
	Right side colon	Left side colon	Right side colon	Left side colon	Right	Left
Patients	126		126			
Cancer patients	3	1	5	2[1]	NS	NS
Polyp patients	74 (58.7)		73 (57.9)			
Proportion of polyps						
< 5 mm	60	62	65	70		
5-10 mm	15	29	20	19	NS	NS
> 10 mm	6	5	8	5		
Total polyps per study arm	81	96	93	94	NS	NS
Polyps per patient, mean ± SD	0.71 ± 1.19	0.79 ± 1.20	0.78 ± 1.19	0.78 ± 1.11	NS	NS
Diverticulosis	30		37			

[1]Advanced stenosing cancer. NS: Not significant.

frequencies of these symptoms between the mosapride group and the placebo group in the previous study[20]. Therefore, we think that there is a need to reduce the volume of PEG-electrolyte solution to improve patients' acceptability and tolerability. In the present study, it was assumed that 2 L PEG-electrolyte solution plus mosapride was the standard regimen for bowel preparation based on the results of the previous study. Thus, the study was designed to compare a 1.5 L PEG group with a 2 L PEG group.

In the present study, the patients' acceptability and tolerability were superior in the 1.5 L group. The 0.5 L reduction of PEG-electrolyte solution significantly improved patients' acceptability and tolerability; 100% intake of PEG-electrolyte solution was significantly higher in the 1.5 L group than in the 2 L group. For Japanese patients with relatively smaller physiques than Western patients, 2 L PEG-electrolyte solution may be too much to drink. With respect to adverse events, abdominal distension was more common than nausea, vomiting, and abdominal pain. The proportion of abdominal distension was significantly improved in the 1.5 L group compared with the 2 L group. This may be the reason why willingness to repeat the same preparation regimen was significantly higher in the 1.5 L group, and a significantly higher number of patients in the 1.5 L group than in the 2 L group felt that the current preparation was easier.

Although 0.5-L volume reduction improved patient acceptability and tolerability, it would not make sense to decrease the volume of solution if the adequate bowel

preparation rates were worse, and it prolonged the time to preparation. In the present study, 1.5 L PEG was non-inferior to 2 L PEG with respect to adequate bowel preparation rates in the right colon, but the proportion for the overall colon-cleansing score was significantly higher in the 2 L PEG group than in the 1.5 L PEG group. Furthermore, although there was no significant difference between the two groups, 18 patients required additional preparation in the 1.5 L group compared with 11 patients in the 2 L group. One of the reasons why the times to preparation were similar in the two groups is that it took longer for the patients who required additional preparation in the 1.5 L group compared with the 2 L group. From these results, we cannot help but recognize that the dose of 15 mg may be insufficient to compensate for the 0.5-L reduction in PEG solution with respect to cleansing efficacy. In the present study, 15 mg of mosapride was given for colonoscopy preparation. The dose of 15 mg per day is the recommended usual dosage of mosapride citrate for adult patients with chronic gastritis. Since the effects of mosapride are reported to be dose-dependent[23], additional studies that address the optimal dosage are required to clarify the best bowel preparation method for colonoscopy.

Over the years, many researchers have investigated several different combinations and dosages of prokinetic agent or laxatives in search of acceptable, tolerable, and efficacious low-volume bowel preparation that may lead to a better experience for the patient and a more thorough colonoscopic examination[24-26]. Cisapride has been used as a prokinetic agent along with lavage solution for bowel preparation and has been demonstrated to shorten the required time period for precolonoscopic bowel preparation and to decrease the lavage solution volume[27,28], although these results have been difficult to reproduce[29]. However, cisapride was withdrawn from the market because of severe cardiac effects[30]. Other prokinetic agents, including metoclopramide and tegaserod, have been co-administered with oral lavage solution in an attempt to improve the quality of bowel preparation and patient tolerance to lavage solution through increasing the amplitude of gastric contraction and peristalsis of small intestine, and shortening transit time[31,32]. However, the effect of these agents had not yet been clearly established, and the results of studies that have evaluated these agents have thus far been contradictory[33]. The effects of prokinetic agents with the reported timings and doses may not be enough to compensate for the large volume of PEG solution.

Stimulant laxatives such as bisacodyl and magnesium citrate have been used as adjuncts to low-volume PEG-electrolyte solution, achieving results similar to those with full-volume PEG-electrolyte solution[8,34]. Recently, Cohen *et al*[35] compared a reduced-dose 2 L PEG formulation plus ascorbic acid with 2 L PEG formulation plus bisacodyl. The authors found that the use of PEG plus ascorbic acid resulted in better colon cleansing and higher adenoma detection rates than PEG plus bisacodyl. Moreover, Repici *et al*[36] compared a new iso-osmotic sulphate-free formulation (2 L formulation of PEG-citrate-simethicone) in combination with bisacodyl with 2 L formulation PEG plus ascorbic acid. The authors reported that low-volume PEG-citrate-simethicone with bisacodyl provided better bowel cleansing and similar tolerability and acceptance compared with PEG plus ascorbic acid. Unfortunately, these low-volume formulations are currently not available in Japan. In the previous study[20], we selected mosapride from among several prokinetic agents because it is a highly selective agonist for 5-HT4 receptors and does not affect other receptors, including dopamine D2 receptors. However, the results of this study did not demonstrate the efficacy of mosapride in reducing lavage solution volume. A combination with some laxatives may improve the cleansing efficacy of our low-volume 1.5 L PEG formulation plus mosapride.

Few studies designed to assess the quality of bowel preparation for colonoscopy have also examined the disease detection rates, including adenoma detection rates[37-39]. Previous studies demonstrated that a better bowel preparation led to a higher rate of colon lesion detection, enhancing the ability to discern smaller lesions and thus improving the thoroughness of colonoscopy[37,38]. In the present study, there were no differences between the two groups in the polyp detection rate, the proportion of the size of polyps, total polyps per study arm, and polyps per patient. These findings may lead to the conclusion that the efficacy of bowel preparation with 1.5 L PEG is non-inferior to 2 L PEG with respect to bowel cleansing. However, polyp detection rates are indeed affected by several variables, such as patients' background, colonoscopy indication, and endoscopist technique, as well as endoscopy technology, that would introduce uncertainly into the results of this study. Additional studies are necessary to demonstrate the relationship between bowel preparation and the adenoma detection rate.

There are several limitations to consider in interpreting the present results. First, the study was conducted in a single hospital with a small number of patients. Although we hypothesized that the non-inferiority margin was -15%, that margin might be inappropriate. The sample size may have been too small to elucidate the non-inferiority of 1.5 L PEG, which may explain why non-inferiority in only a limited part of colon could be demonstrated. Second, for the evaluation of bowel preparation, the Aronchick scale was used. The merit of the Aronchick scale is that in cases in which additional bowel preparation was needed, such cases could be defined as "inadequate" using the Aronchick scale. However, the Aronchick scale was designed to assess bowel preparation of the entire colon. In the present study, it was scored separately on the right side colon and left side colon; a different scoring system, such as the Ottawa scale[40] and the Boston scale[41], that evaluates different colon segments individually and generates a summary score may have been more appropriate. Finally, biochemical parameters were not evaluated in the two groups. However, co-administration of mosapride at a dose of 40 mg and

PEG-electrolyte solution is already approved in Japan for barium enema examination preparation[42], based on its excellent safety profile.

In conclusion, co-administration of mosapride with 1.5 L PEG-electrolyte solution was non-inferior to mosapride with 2.0 L PEG-electrolyte solution for adequate bowel preparation rates only in the right colon, although better acceptability and tolerability compared to the larger PEG-electrolyte solution volumes were found. A mosapride dose of 15 mg may provide insufficient cleansing efficacy to compensate for a 0.5-L reduction in PEG-electrolyte solution.

COMMENTS

Background

Although polyethylene glycol (PEG) electrolyte solution has been used for colonoscopy preparation since 1980, the need to drink large volumes is a limiting factor that affects patient tolerance. Low-volume bowel preparation regimens for colonoscopy are reported to improve patients' acceptance and compliance.

Research frontiers

Mosapride citrate (mosapride) is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist. Mosapride enhances gastric emptying and motility by facilitating acetylcholine release from enteric cholinergic neurons, without blocking the dopaminergic D2 receptors. Since 5-HT4 receptors are also located in the human colon and rectum, mosapride is also expected to have a prokinetic effect on the colo-rectum.

Innovations and breakthroughs

The present randomized trial compared 1.5 L PEG plus mosapride with 2 L PEG plus mosapride dosing for patients who underwent colonoscopy in terms of cleansing effectiveness, patient compliance, tolerability, and disease detection rates.

Applications

The low-volume preparation (1.5 L PEG) represents a valid alternative to high-volume preparations (2 L PEG) with regard to patient compliance and tolerability. However, optimal visualization of colonic wall seems to be one of the primary advantages of high-volume preparations. A mosapride dose of 15 mg may provide insufficient cleansing efficacy to compensate for a 0.5-L reduction in PEG solution.

Terminology

PEG-electrolyte solution: PEG-electrolyte solution is used worldwide for bowel cleansing. Approximately 2 L of this oral solution with some laxatives are usually required for adequate bowel preparation in Japan.

Peer review

This randomized trial compared 1.5 L PEG plus mosapride with 2 L PEG plus mosapride in terms of cleansing effectiveness, patient acceptability, physical tolerability, and endoscopic findings. This is an interesting and well written study. The conclusion sounds good and useful for the general practice.

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Benefit of the measurement of mesorectal extension in patients with pT3N1-2 rectal cancer without pre-operative chemoradiotherapy: Post-operative treatment strategy

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Abstract. A treatment strategy based on the distance of mesorectal extension (DME) for pT3N1-2 rectal cancer patients without pre-operative chemoradiotherapy has not yet been defined. The present study aimed to describe the benefit of the measurement of mesorectal extension in stratifying treatment for pT3N1-2 rectal cancer patients. Data from 512 patients with pT3N1-2 rectal cancer undergoing curative surgery at 28 institutes were analyzed in this study. DME was measured histologically, and the optimal prognostic cut-off point of the DME was determined using Cox regression analyses. Survival was calculated using the Kaplan-Meier method. The patients were subdivided into two groups based on the optimal prognostic cut-off point: DME ≤4 mm and DME >4 mm. The DME was found to be a powerful independent risk factor for predicting distant and local recurrences. The recurrence-free 5-year survival rates of patients with DME >4 mm were significantly poorer for Stages IIIB (53.3%; p=0.0015; HR, 1.76; 95% CI, 1.233-2.501) and IIIC (32.9%; p=0.0095; HR, 1.64; 95% CI, 1.119-2.407) than for patients with DME ≤4 mm (69.7 and 50.4%, respectively). The cancer-specific survival rates of patients with DME >4 mm were also significantly worse than those with DME ≤4 mm. A value of 4 mm provides the best cut-off point for subdividing the mesorectal extension to predict oncologic outcomes. Measurement of mesorectal extension appears to be of benefit in stratifying patients for post-operative adjuvant treatments.

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Key words: rectal cancer, mesorectal extension, TNM staging system, prognosis, adjuvant treatment

Introduction

It is currently unknown whether the distance of mesorectal extension (DME) is applicable as a parameter for adjuvant treatment and is associated with the prognosis of rectal cancer. In 1990, the clinical importance of subdividing the mesorectal extension at a cut-off point of 4 mm was advocated (1). In 1993, the International Union Against Cancer (UICC) proposed optional subdivisions for pT3 and pT4 tumors (2). Thereafter, several studies have shown the prognostic heterogeneity of pT3 rectal cancers (3-12). However, appropriate treatment strategy for T3/pT3 rectal cancer based on the DME remains unclear. In European countries, the standard strategy for T3 rectal cancer is preoperative chemoradiotherapy (CRT) (13,14). However, not all T3 rectal cancers are necessarily suitable for CRT. Moreover, it is considerably difficult to evaluate not only DME but also conventional prognostic factors such as lymphatic, venous and perineural invasion in pathological specimens following preoperative CRT. When preoperative CRT is not administered to certain patients with T3 rectal cancers, it appears to be vital to accurately assess the DME and to evaluate the prognosis following surgery. In the current study, we analyzed a large collection of data obtained from a multi-institutional study promoted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). This study confirms the benefit of the measurement of mesorectal extension and selection of patients for postoperative adjuvant treatment strategy in pT3N1-2 rectal cancers based on the TNM classification (6th edition) (15,16).

Patients and methods

Patients. Approval from the ethics committees of both the JSCCR and the local Institutional Review Board were obtained in order to review medical records and to permit follow-up patient contact. However, informed consent could not be obtained from all patients, since this study was retrospective and some patients may be deceased. Data were obtained from 1009 patients with pT3 rectal cancer from 28 institutes that are members of the Study Group of the JSCCR on Extramural Mesorectal Extension of Rectal Cancer. All patients had a primary rectal adenocarcinoma located in the middle or lower rectum. Patients with rectosigmoid colon cancer were not included in this study. Histologically defined curative surgery was performed between 1995 and 1999. Patients undergoing non-curative surgery (R2 operation) were excluded from this study. Patients were staged according to the pathological TNM classification (6th edition) (15,16). The present study focused on postoperative treatment strategy in patients with Stage III (pT3N1-2) disease. After staging, 512 patients with Stage III disease remained enrolled in this study, including 321 with Stage IIIB and 191 with Stage IIIC diseases. Clinicopathological information was available and eligible for analysis. Neither radiotherapy nor neoadjuvant chemotherapy was performed prior to surgery in these enrolled patients. All 512 patients underwent total mesorectal excision. According to the postoperative adjuvant treatment protocol of each institute, peroral 5-fluouracil (5-Fu)-based chemotherapy, such as 5'-DFUR (doxifluridine), HCFU (1-hexylcarbamoyl-5-fluorouracil), or UFT (tegafur-uracil) were most frequently administrated. Clinicopathological data and follow-up system were based on the Japanese rules defined by the JSCCR (17). The follow-up system consisted of the measurement of serum tumor markers, chest X-ray and abdominal ultrasound examination every three months for the first three years, and then every six months for the next two years. When the development of recurrence was suspected by serum tumor markers, digital examination and/or ultrasonography, the final diagnosis was carried out using rectoscopy, computed tomography (CT) and/or magnetic resonance imaging (MRI) and other diagnostic tools. Local recurrence was defined as the presence of a radiologically confirmed or histologically proven tumor non-hematogenously occurring in the pelvis within the field of the initial surgery. Distant metastasis included hematogenous metastases to the liver, lung, bone, brain, kidney or other organs. The other-organ recurrences were defined as recurrence other than local recurrence or distant metastasis, i.e., peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal and inguinal lymph node metastases. The outcomes of all patients were investigated in detail. From January 1995, eligible surviving patients were followed for a median of 86 months (range, 1-166).

Measurement of mesorectal extension. All surgically resected specimens were opened along the anti-tumor or anti-mesenteric side. Specimens were fixed in 20% formalin for at least 48 h after being pinned to a wood or cork board. One or more longitudinal sections of the tumor were sliced at the point of maximum extramural invasion and were embedded in paraffin after being divided into blocks of suitable size. These tissue blocks were then routinely processed for hematoxylin and eosin and Elastica Von Gieson staining. Tumor category pT3 sections were subdivided based on the histological measurement of the maximum depth of invasion beyond the outer border of the muscular layer (in mm). Without any knowledge of clinical information, histological measurement was performed according to our previous methods (18). When the outer border of the muscular layer was completely identifiable (sometimes identifiable as fragments of muscle), the distance from the outer border of the muscular layer to the deepest part of the invasion was measured. When the outer border of the muscular layer was not entirely identifiable, due to destruction by the invasion or excessive inflammatory reaction, an estimate of the outer border was obtained by drawing a straight solid line between both break points in the muscular layer.

Statistical analysis. Statistical analysis was performed using StatView 5.0 and JMP 8.0 (SAS Institute, Inc., Cary, NC, USA) software for Windows. All clinicopathological independent variables (13 items) were coded for analysis. Overall recurrence, distant metastasis, local recurrence and survival were coded as dependent variables. Cox regression analyses were used to determine the optimal cut-off point of the mesorectal extension for postoperative recurrence. The Cox regression analysis was also used to estimate the independent risk factors for either distant metastasis or local recurrence. The Kaplan-Meier method and the log-rank test were used for calculating survival rates. Statistical significance was determined at $p<0.05$ and the confidence interval (CI) was determined at 95%.

Results

Distance of ME. The DME in these 512 cases (pT3N1-2 tumor) was measured histologically. The mean DME was 5.4±4.4 mm, and the median DME was 4.3 mm (range, 0.1-28.4).

Postoperative recurrence pattern. Postoperative overall recurrence occurred in 247 (48.2%) of the 521 patients. A total of 55 patients (10.7%) had local recurrence only, and 124 (24.2%) had distant metastasis only. Furthermore, 30 patients (5.9%) had both local and distant recurrences. The remaining 38 patients exhibited other recurrences, that is, peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal and inguinal lymph node metastases.

Cut-off point for subdividing mesorectal extension. The multivariate Cox regression analyses for recurrence-free survival are shown in Table I. A cut-off value of 4 mm showed the highest Chi-square (17.463), lowest p-value (p=0.00003), and high hazard ratio (HR, 1.72). The L/U ratio (lower/upper limits of CI) showed higher reliability (0.5950) among other cut-off points. A cut-off value of 4 mm was found to be the best predictor of recurrence-free survival. Overall, the best cut-off point was determined to be 4 mm, therefore, the patients were divided into two groups according to mesorectal extension: ≤4 mm and >4 mm.

Independent risk factors for distant metastasis and local recurrence. Distant and/or local recurrence-related independent variables used for analyses are listed in Table II.

Table I. Cut-off points of distance of mesorectal extension for recurrence-free survival using multivariate Cox regression analysis.

DME (mm)	No. of patients	RF survival at 5 years (%)	Chi-square	HR (95% CI, L-U)	L/U ratio	p-value
>1 vs. ≤1	445 vs. 67	52 vs. 64	4.174	1.53 (1.012-2.317)	0.4368	0.0411
>2 vs. ≤2	391 vs. 121	51 vs. 65	10.366	1.70 (1.224-2.370)	0.5165	0.0013
>3 vs. ≤3	330 vs. 182	48 vs. 65	14.423	1.71 (1.290-2.270)	0.5683	0.0001
>4 vs. ≤4	267 vs. 245	46 vs. 63	17.463	1.72 (1.328-2.232)	0.5950	0.00003
>5 vs. ≤5	204 vs. 308	44 vs. 60	16.331	1.67 (1.297-2.155)	0.6019	0.00005
>6 vs. ≤6	167 vs. 345	46 vs. 58	11.059	155 (1.191-2.006)	0.5937	0.0009
>7 vs. ≤7	135 vs. 377	43 vs. 58	13.061	1.63 (1.246-2.140)	0.5822	0.0003
>8 vs. ≤8	98 vs. 414	39 vs. 58	16.071	1.80 (1.341-2.407)	0.5572	0.00006
>9 vs. ≤9	79 vs. 433	39 vs. 57	12.495	1.74 (1.273-2.386)	0.5335	0.0004
>10 vs. ≤10	59 vs. 453	39 vs. 56	11.980	1.82 (1.287-2.575)	0.4998	0.0005

DME, distance of mesorectal extension; RF, recurrence-free; HR, hazard ratio; CI, confidence interval; L, lower limit; U, upper limit.

Table II. Independent risk factors for distant metastasis and local recurrence using multivariate Cox regression analysis.

Variable	Distant metastasis			Local recurrence		
	Rate of DM (%)	HR (95% CI)	p-value	Rate of LR	HR (95% CI)	p-value
Gender Male vs. female	28 vs. 31	n.a.		15 vs. 16	n.a.	
Size of tumor >5 vs. ≤5 cm	26 vs. 31	n.a.		15 vs. 16	n.a.	
Location of tumor Lower vs. middle	31 vs. 24	1.28 (0.845-1.947)	0.2425	11 vs. 18	1.44 (0.784-2.629)	0.2411
Gross type Infiltrative vs. expansive	27 vs. 29	n.a.		20 vs. 15	n.a.	
Histology Others vs. well	30 vs. 27	n.a.		15 vs. 16	n.a.	
Lymphatic invasion ly2-3 vs. ly0-1	30 vs. 28	n.a.		17 vs. 14	n.a.	
Venous invasion v2-3 vs. v0-1	29 vs. 29	n.a.		14 vs. 17	n.a.	
DME >4 vs. ≤4 mm	34 vs. 24	1.82 (1.300-2.538)	0.0005	18 vs. 13	1.74 (1.107-2.744)	0.0164
CRM ≤1 vs. >1 mm	28 vs. 29	n.a.		14 vs. 16	n.a.	
Number of retrieved LN <12 vs. ≥12	25 vs. 29	n.a.		14 vs. 15	n.a.	
Operative methods APR vs. SSO	34 vs. 25	1.50 (1.025-2.197)	0.0370	11 vs. 20	1.97 (1.160-3.339)	0.0121
Autonomic nerve-saving Yes vs. no	29 vs. 26	n.a.		16 vs. 13	n.a.	
Chemotherapy Yes vs. no	27 vs. 31	n.a.		17 vs. 14	n.a.	

DM, distant metastasis; LR, local recurrence; HR, hazard ratio; CI, confidence interval; n.a., variables not selected for multivariate analyses as they were not significant in univariate analysis. Well, well-differentiated adenocarcinoma; others, moderately differentiated, poorly differentiated, and mucinous adenocarcinoma; ly0-1, v0-1, negative-to-minimal invasion; ly2-3, v2-3, moderate-to-severe invasion; DME, distance of mesorectal extension; CRM, circumferential resection margin; LN, lymph node; APR, abdominoperineal resection; SSO, sphincter-saving operation.

Table III. Distant metastasis and local recurrence at the cut-off value of 4 mm using Cox regression analysis.

	Distant metastasis			Local recurrence		
TNM Stage (6th edition)	No. of DM patients (%)	HR (95% CI)	p-value	No. of LR patients (%)	HR (95% CI)	p-value
Stage IIIB (n=321)	86 (26.8)			40 (12.5)		
≤4 mm (n=159)	34 (21.4)	1		16 (10.1)	1	
>4 mm (n=162)	52 (32.1)	1.79 (1.154-2.773)	0.0094	24 (14.8)	1.66 (0.878-3.151)	0.1186
Stage IIIC (n=191)	68 (35.6)			45 (23.6)		
≤4 mm (n=86)	24 (27.9)	1		16 (18.6)	1	
>4 mm (n=105)	44 (41.9)	1.82 (1.106-3.008)	0.0186	29 (27.6)	1.79 (0.964-3.331)	0.0652
Overall (n=512)	154 (30.0)			85 (16.6)		
≤4 mm (n=245)	58 (23.7)	1		32 (13.1)	1	
>4 mm (n=267)	96 (36.0)	1.83 (1.314-2.541)	0.0003	53 (19.9)	1.75 (1.125-2.736)	0.0132

DM, distant metastasis; LR, local recurrence; HR, hazard ratio; CI, confidence interval.

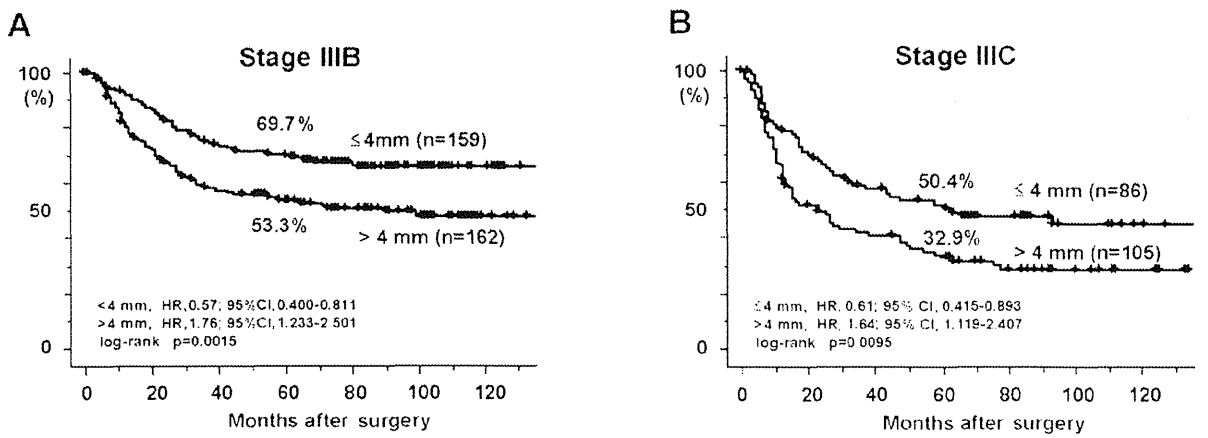

Figure 1. Recurrence-free 5-year survival. The recurrence-free 5-year survival rates of patients with DME >4 mm were significantly poorer at Stages (A) IIIB (53.3%; p=0.0015) and (B) IIIC (32.9%; p=0.0095) than those of patients with DME ≤4 mm. DME, distance of mesorectal extension.

Multivariate Cox regression analysis showed that the DME was a powerful independent risk factor for distant metastasis (HR, 1.82; 95% CI, 1.300-2.538; p=0.0005) and for local recurrence (HR, 1.74; 95% CI, 1.107-2.744; p=0.0164).

Distant metastasis and local recurrence based on the cut-off value. Stage-specific distant metastasis and local recurrence occurred in 86 (26.8%) and 40 patients (12.5%), respectively, at Stage IIIB, and 68 (35.6%) and 45 patients (23.6%), respectively, at Stage IIIC (Table III). Taking into account the cut-off value of 4 mm, the rates of distant metastasis at IIIB and IIIC were significantly higher (32.1 and 41.9%, respectively) in patients with DME >4 mm compared to patients with DME ≤4 mm (21.4 and 27.9%, respectively). Local recurrence showed a trend toward a higher rate at the cut-off value at any Stage.

Recurrence-free and cancer-specific survival rates. The recurrence-free 5-year survival rates of the DME >4 mm group were significantly worse [53.3% at Stage IIIB (HR, 1.76; 95% CI, 1.233-2.501; p=0.0015) and 32.9% at Stage IIIC (HR, 1.64; 95% CI, 1.119-2.407; p=0.0095)] than those of the patients with a DME ≤4 mm (69.7 and 50.4%, respectively; Fig. 1A and B). The cancer-specific 5-year survival rates of the DME >4 mm group were also significantly worse at Stage IIIB (64.3%; HR, 1.61; 95% CI, 1.099-2.371; p=0.0134) and at Stage IIIC (42.6%; HR, 1.93; 95% CI, 1.288-2.901; p=0.0011) than those of patients with a DME ≤4 mm (78.2 and 65.9%, respectively; Fig. 2A and B).

Discussion

In the early 1990s, the clinical importance of subdividing the mesorectal extension for pT3 and pT4 tumors was advocated (1,2). Thereafter, the importance was reported by several authors, who showed the prognostic heterogeneity of pT3 rectal cancers (1,3,5-11). At a cut-off point of 4 mm, the DME >4 mm was confirmed as an independent adverse prognostic factor for survival using multivariate analysis (1,7,8). Other authors found prognostic heterogeneity of N1-2 tumors between pT3a (≤5 mm) and pT3b (>5 mm) groups (4) and reported prognostic

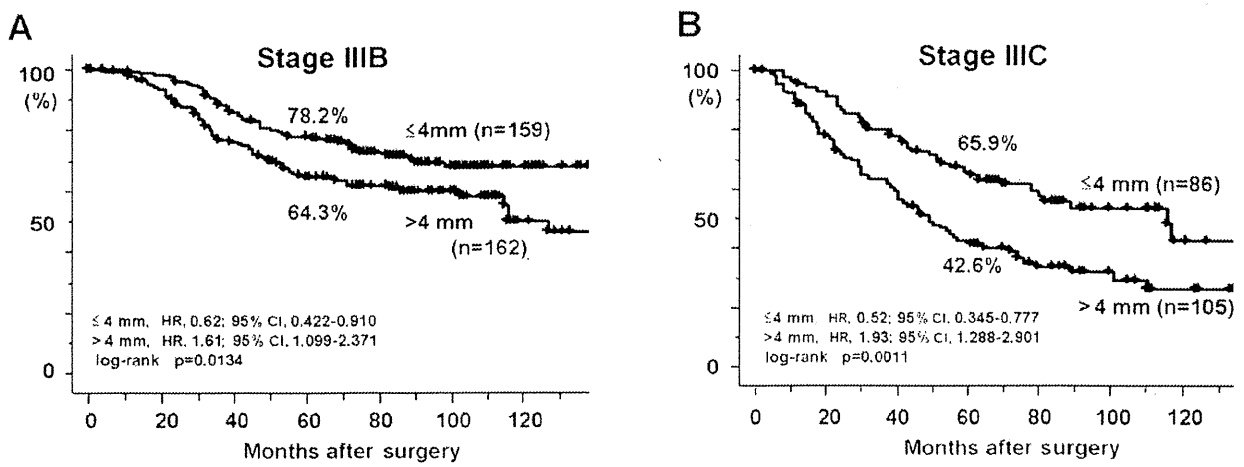

Figure 2. Cancer-specific 5-year survival. The cancer-specific 5-year survival rates of patients with DME >4 mm was significantly worse at Stages (A) IIIB (64.3%; p=0.0134) and (B) IIIC (42.6%; p=0.0011) than those of patients with DME ≤4 mm. DME, distance of mesorectal extension.

heterogeneity of pT3N1-2 tumors at the cut-off point of 6 mm from two different patient databases (6). Thus, the majority of studies found prognostic heterogeneity of mesorectal extension in pT3 rectal cancers at various cut-off points. However, the clinical significance and statistical appropriateness of these cut-off points remain controversial, partly because these studies had small sample sizes with underpowered statistical analyses and included cohorts from only a single institution. Based on the statistical analyses in the present study, the appropriate prognostic cut-off point was theoretically set at a value of 4 mm, and the patients were divided into two groups based on mesorectal extension: DME ≤4 mm and DME >4 mm. A recent multi-institutional study by our group demonstrated that a cut-off point of 4 mm independently delineated adverse prognosis among pT3N0 rectal cancers based on TNM classification (6th edition) (18). However, the appropriate postoperative treatment strategy for pT3N1-2 rectal cancers based on the DME remains unclear.

Dutch and Swedish trials have reported that preoperative CRT has decreased local recurrence rate to 15% in Stage III rectal cancers (13,14), which is similar to our data without using preoperative CRT. However, there have been only a few reports on the correlation of DME and local recurrence. Merkel *et al* (4) reported that the local recurrence rate was significantly higher in pT3b tumors with DME >5 mm (N1-2; 34.0%) compared with pT3a tumors ≤5 mm (N1-2; 17.1%). Another study did not find any correlation between local recurrence and DME (6). Our data showed no significant difference with regard to stage-specific local recurrence at the cut-off point in any stage due to the small number of patients. Overall, our study indicates that local recurrence occurs at a high rate in Stage III patients with a DME of >4 mm (p=0.0132, Table III).

Multivariate Cox regression analysis showed that the DME was an important parameter to predict distant and local recurrences, and was more effective than conventional prognostic parameters such as lymphatic invasion, venous invasion, circumferential resection margin, and total number of retrieved lymph nodes (Table II). As the DME becomes deeper, it is considered that undetectable lymphovascular invasions or micro-tumor deposits increase in the mesorectal adipose tissues. These isolated tumor cells may cause local recurrence and/or distant metastases. In European countries, preoperative CRT is the standard strategy for selected patients with T3 rectal cancer to eradicate those isolated tumor cells and to control local recurrence. However, it is considerably difficult to evaluate not only DME but also those pathological parameters following preoperative CRT. The current study also determined that the DME was a useful predictor to estimate survival rates (Figs. 1 and 2), which was similar to results reported by other authors (4,6). When preoperative CRT is not applied for some patients with pT3 rectal cancer, it appears to be vital to accurately assess the DME and evaluate the prognosis following surgery (3). In addition, the present study supported the reproducibility of a cut-off point of 4 mm even in pT3N1-2 disease as in pT3N0 disease (TNM 6th edition) (18).

Diagnostic techniques using MRI enable accurate measurement of the mesorectal extension that strongly correlates with the pathological measurement (19,20). If the cut-off value can be applied to the preoperative MRI-based diagnosis, then this would be more efficient for stratifying the appropriate patients for preoperative CRT. In the present series between 1995 and 1999, postoperative adjuvant chemotherapy was administered orally under the criteria for each institute. More intensive adjuvant treatments are required for patients with a DME of >4 mm to eradicate isolated tumor cells, prevent postoperative recurrence and improve survival.

In conclusion, a value of 4 mm provides the best cut-off point for subdividing the mesorectal extension to predict oncologic outcomes. The current study suggests that DME is a highly beneficial parameter with which to stratify patients for postoperative adjuvant treatments. However, further prospective studies are required to assure the reproducibility and validity of this cut-off point.

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