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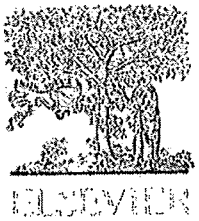

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CASE REPORT

Reconstruction of an enterocutaneous fistula using a superior gluteal artery perforator flap

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KEYWORDS
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Summary Enterocutaneous fistula is an uncommon complication of surgery for colorectal cancer. However, once a fistula has developed, treatment is complicated by previous treatments. Here, we describe an enterocutaneous fistula that developed after multiple treatments for rectal cancer in a 62-year-old woman. The woman had previously undergone several colorectal surgeries, radiation therapy and five courses of chemotherapy. Four years after the final surgery, an enterocutaneous fistula developed between the small intestine and the sacral skin. The fistula was resected, and the resulting defect was successfully reconstructed with a superior gluteal artery perforator flap.

Case report

A 62-year-old woman presented with an enterocutaneous fistula that developed 4 years after ablative surgery for recurrent rectal cancer. Her past medical history was as follows: initial treatment for rectal cancer was carried out with low anterior resection of the rectum in 1998. Eight months later, a Miles' operation was carried out for recurrent rectal cancer. However, the tumour recurred, and additional treatments, including two additional surgeries, radiation therapy up to 40 Gy and five courses of chemotherapy, were carried out at another hospital. Finally, magnetic resonance imaging showed a recurrent tumour at the anterior aspect of the sacrum, and the patient was transferred to the division of colorectal surgery of our hospital in July 2001. The final surgery for tumour ablation in August 2001 included total pelvic exenteration and partial resection of the sacrum. The patient was free of tumour recurrence for the next 4 years.

Discharge from an abscess of the skin over the sacrum was observed in April 2005. A fistulogram and a computed tomogram indicated the presence of an enterocutaneous fistula between the small intestine and the sacral skin (Figures 1,2). The distal opening of the fistula was pinhole-sized, and

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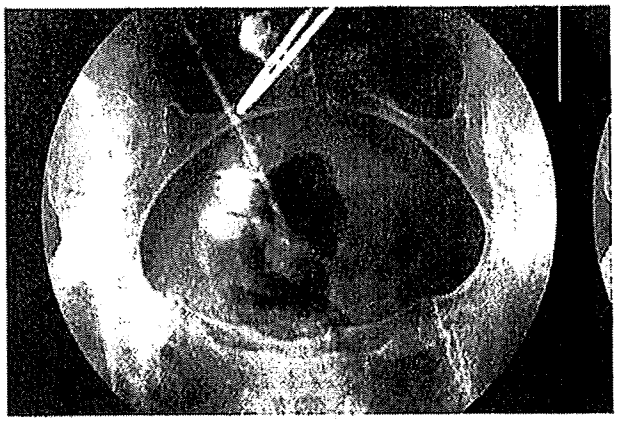

Figure 1 Fistulogram through a small hole at the sacral skin indicated a communication between the skin surface and the small intestine.

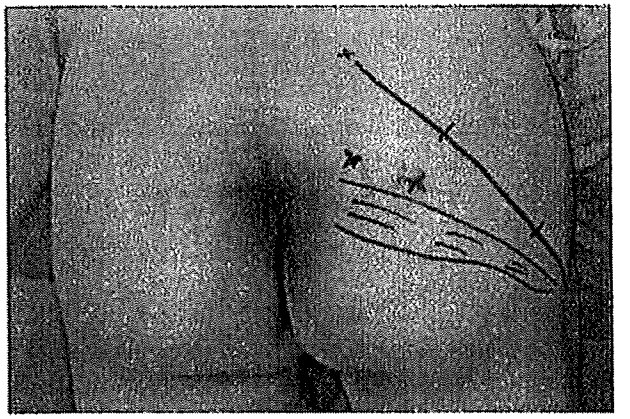

Figure 3 Damaged skin surrounding the fistula before surgery. A skin perforator (2 x's) from the superior gluteal artery was marked with a Doppler flowmetre.

the surrounding skin had been damaged by irradiation and local inflammation (Figure 3). The woman was referred to the division of plastic and reconstructive surgery for treatment of the fistula. Preoperative physical status of the woman was rated as PS2 according to the classification of the American society of Anesthesiologists, and the woman had no limitation in daily activities.

Debridement of the fistula and reconstructive surgery were carried out in May 2005. The woman was placed in the prone position and given general anaesthesia. The fistula was excised with all surrounding irradiated skin. The resulting skin defect measured 7.0 x 12.0 cm, and the diameter of the fistula after debridement was 1.0 cm (Figure 4). The proximal opening of the fistula at the small intestine was closed primarily with absorbable monofilament sutures, and the skin defect was reconstructed with a superior gluteal artery perforator (SGAP) flap from the right buttock. The flap was harvested with a 7 x 14 cm skin paddle that included two skin perforators from the superior gluteal artery and vein (Figure 5). The flap was transposed medially and sutured to the surrounding skin; the donor site was closed primarily (Figures 6,7). Slight congestion of the transferred flap was observed immediately after surgery, but colour of the flap was improved gradually within a few hours without any treatment. The patient was placed in prone or lateral position after surgery for 2weeks to avoid excessive pressure to the flap. On the seventh day after surgery a small area of wound dehiscence developed, but the wound healed with conservative treatment. The woman started oral feeding 28 days after surgery. Twelve months after repair, the enterocutaneous fistula has not recurred (Figsures 8,9).

Discussion

Enterocutaneous fistula sometimes develops in patients with inflammatory gastrointestinal diseases, such as Crohn's disease and tuberculosis, and in patients with cancer.[1–3] However, enterocutaneous fistula is an uncommon complication of surgery for colorectal cancer. Such fistulae are related to anastomotic leakage or unnoticed injury of the intestine during surgery.[4,5] On the other

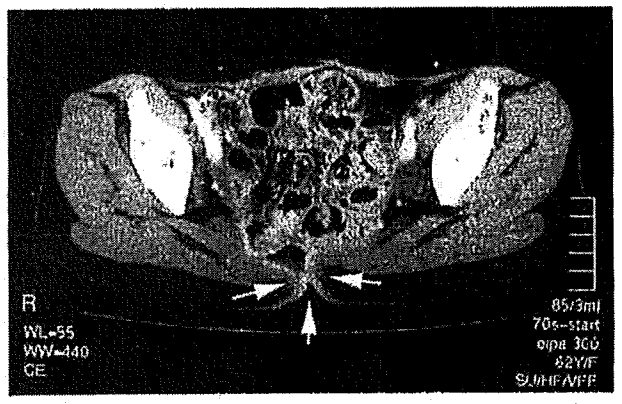

Figure 2 A preoperative computed tomogram indicated the presence of a fistula (arrows).

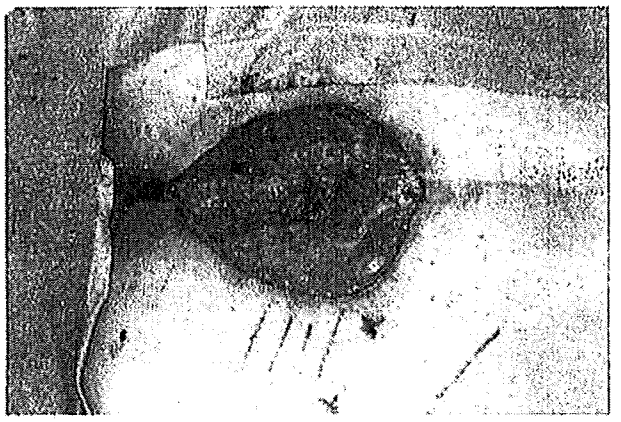

Figure 4 Debridement of the fistula and the surrounding skin during surgery. The diameter of the fistula was 1.0 cm.

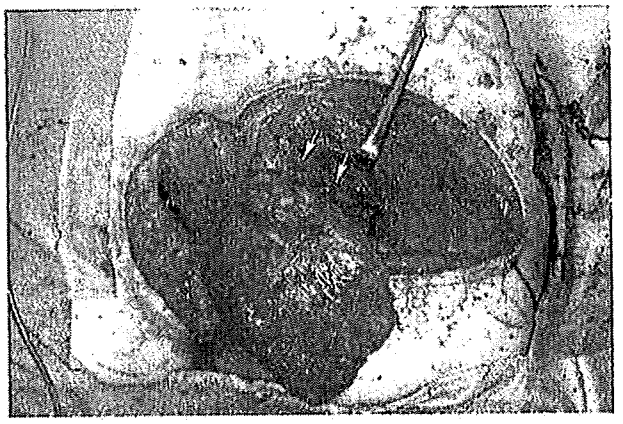

Figure 5 The superior gluteal artery perforator flap was elevated with two skin perforators (arrows).

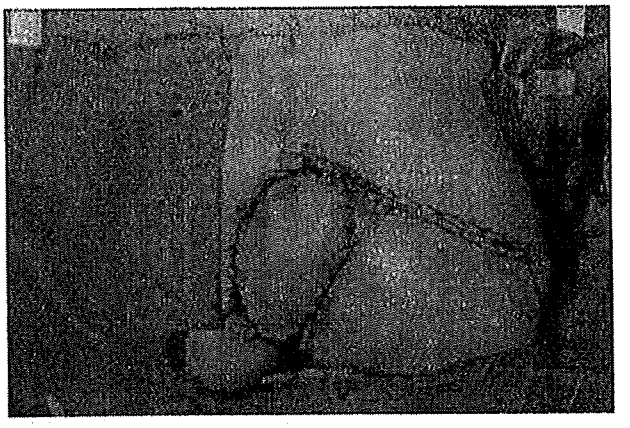

Figure 7 The soft-tissue defect was covered with the SGAP flap, and the flap donor site was closed directly.

hand, it is well known that various bowel diseases, such as enterocolitis, haemorrhage, intestinal stricture or fistula can develop if the irradiation field includes the pelvic organs. These complications arise in 12.7% of patients who have received radiation therapy. Among these, severe complications that require surgical repair can develop in 3%.[6] These bowel diseases can develop from as early as 1 month to more than 20 years after radiotherapy.[7] In our patient, we observed no perioperative signs, suggesting the development of anastomotic leakage. Furthermore, the enterocutaneous fistula developed 4 years after surgery within the area of damaged sacral skin. Therefore, the enterocutaneous fistula is most likely a late complication of radiotherapy.

Enterocutaneous fistula can be treated conservatively. Total parenteral nutrition and bowel rest allow 30–75% of fistulae to heal.[4,5,8] However, if the intestine has also been damaged, the cure rate with conservative treatment is probably lower.[1] We did not expect spontaneous closure in our patient because of the numerous previous treatments, including four surgeries, irradiation and chemotherapy. Therefore, we treated the fistula surgically. In carrying out surgery to repair the fistula, we avoided laparotomy or lararoscopy because we expected severe fibrous adhesions in the abdominal cavity owing to the previous surgeries.

During surgery, the small fistula of the intestine was easily closed primarily with monofilament absorbable suture. However, if the fistula had been too large to allow primary closure, a two-island skin flap would have been considered. The final stage of surgery was coverage of the soft-tissue defect of the sacral region.

Possible choices for coverage of soft tissue defect over the closed fistula include gluteus maximus, biceps and gracilis musculocutaneous flaps and a SGAP flap. The SGAP flap has several advantages over the other flaps, with perhaps the greatest being preservation of the integrity of the functioning muscle. Since Koshima et al.[9] published their early results with gluteal perforator-based flaps for repair of sacral pressure sores, the SGAP flap has been used for various types of reconstruction.[10] However, we believe that the SGAP flap is the best choice for reconstruction of the sacral region in cases without wound infection. If a wound was severely infected, transfer of the flap containing well-vascularised muscle should be selected.

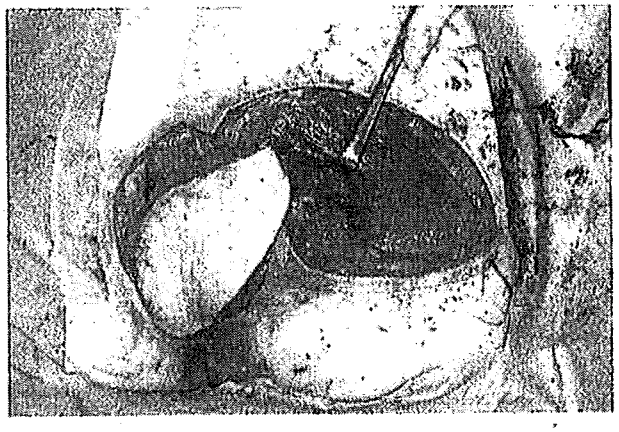

Figure 6 The flap was transposed medially.

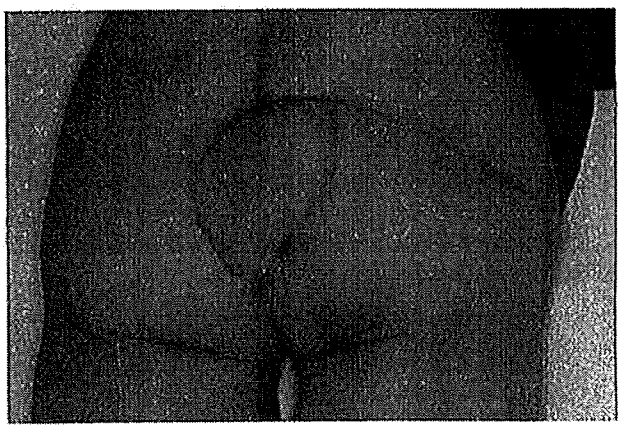

Figure 8 No sign of recurrence of the fistula 12 months after surgery.

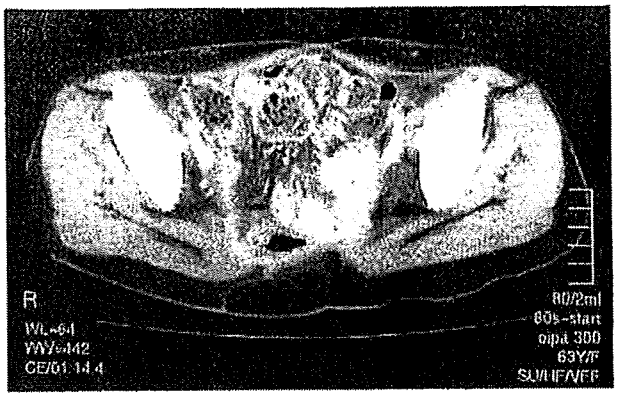

Figure 9 A computed tomogram shows successful coverage of the small intestine with sufficient flap volume.

In conclusion, we report a rare case of enterocutaneous fistula developing after treatment of recurrent colorectal cancer. The enterocutaneous fistula was successfully treated with an SGAP flap. The SGAP flap is a useful choice for treatment of enterocutaneous fistulae of the sacral region.

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A Comparison Between the Treatment of Low Rectal Cancer in Japan and the Netherlands, Focusing on the Patterns of Local Recurrence

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Purpose: Differences exist between Japan and The Netherlands in the treatment of low rectal cancer. The purpose of this study is to analyze these, with focus on the patterns of local recurrence.

Methods: In The Netherlands, 755 patients were operated by total mesorectal excision (TME) for low rectal cancer, 379 received preoperative radiotherapy (RT+TME). Applying the same selection criteria resulted in 324 patients in the Japanese (NCCH) group, who received extended surgery consisting of lateral lymph node dissection and a wider abdominoperineal excision. The majority received no (neo) adjuvant therapy. Local recurrence images were examined by a radiologist and a surgeon.

Results: Five-year local recurrence rates were 6.9% for the Japanese NCCH group, 5.8% in the Dutch RT+TME group, and 12.1% in the Dutch TME group. Recurrence rate in the lateral pelvis is 2.2%, 0.8%, and 2.7% in the Japanese, RT+TME group, and TME group, respectively. The incidence of presacral recurrences was low in the NCCH group (0.6%), compared with 3.7% and 3.2% in the RT+TME and TME groups, respectively.

Conclusions: Both extended surgery and RT+TME result in good local control, as compared with TME alone. Preoperative radiotherapy can sterilize lateral extramesorectal tumor particles. A wider abdominoperineal resection probably results in less presacral local recurrence. Comparison of the results is difficult because of differences in patient groups.

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The main purpose of curative surgical treatment for rectal cancer is en bloc excision of the primary tumor with its locoregional lymph nodes. It has been demonstrated that nonradical removal of the tumor leads to persistence of tumor cells that contributes to the development of recurrent rectal cancer growth.[1,2] Local recurrence is known to cause severe morbidity.

With the total mesorectal excision (TME) procedure the rectum with its primary lymphovascular field of drainage is removed as an intact package, by dissection under direct vision along preexisting embryologically determined planes. Since its introduction, the TME approach has led to striking results, reflected by lower local recurrence rates and improved survival, and has been advocated as being superior to conventional surgery.[3,4]

However, the results of the TME technique for low tumors are not as good as for midrectal or higher tumors, with still a considerable local recurrence rate.[5,6] This is ascribed to the difficulty to obtain a wide circumferential margin (CRM) and the higher rate of perforations of the mesorectum and bowel wall, especially in the case of abdominoperineal resection (APR).[5,7,8]

In Western countries, the addition of (neo)adjuvant therapy to improve the local recurrence rate has been well studied. Both short and long course of preoperative (chemo)radiation have been shown to be effective.[9–12] However, it has also been shown that short-term radiotherapy cannot prevent local recurrence development when advanced tumor growth or surgical failure results in a positive CRM.[13]

In Japan, extended surgery is the gold standard and the APR technique involves a wide perineal skin incision, together with resection of ischiorectal adipose tissue and the levator ani muscle,[14] aiming for a wider circumferential tumor-free margin than in a standard Western APR. However, in Japan, the main focus is on the immediate harvesting of lymph nodes from the fresh specimen, which precludes assessment of the CRM at a later stage. Lateral lymph node dissection (LLND), in which dissection of the iliac and obturator lymph nodes with the primary tumor is performed, is the standard treatment for advanced rectal cancer located at or below the peritoneal reflection.[15,16] It has been reported that local recurrence and survival rates have improved since the introduction of LLND and are known to be significantly better than Western series with surgery only.[15,17]

The question remains whether local recurrence can be prevented best by more frequent use of adjuvant (chemo)radiation or by more extended surgery. The aim of this study was to compare the patterns of local recurrence after TME surgery, TME surgery with short-term preoperative radiotherapy, and Japanese extended surgery. The prospective databases of the Dutch TME trial and the National Cancer Center Hospital in Tokyo, with accurate follow-up, were used. The hypothesis is that recurrences in the lateral pelvic subsite would occur less often in the Japanese group than in the Dutch TME group, because the lateral lymph nodes are excised, with the mesorectum and perirectal fat tissue. In addition, the Japanese APR technique is more wide than the one used during the Dutch TME trial, also possibly leading to different patterns of recurrence in other pelvic subsites.

PATIENTS AND METHODS

Study Population

Patients were selected from the databases of the Dutch TME-trial and of the National Cancer Center Hospital (NCCH) in Tokyo.

A selection was made from a large prospective randomized multicenter study, the radiotherapy plus TME trial, in which 1530 Dutch patients were included between January 1996 and December

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1999. This trial analyzed the effect of short-term preoperative radiotherapy (5 × 5 Gy) in patients operated with a total mesorectal excision (RT+TME), compared with patients with TME alone (TME).[10] Inclusion criteria were the presence of a primary adenocarcinoma of the rectum, without evidence of metastatic disease at time of surgery, and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy, and pathology were used.[18] Follow-up of all patients was conducted according to the trial protocol.[7] For the current study, the following patients were excluded from the analysis: no resection (n = 37), distant metastasis at operation (n = 91), and no tumor at operation (n = 15).

In the prospective database of the NCCH, Tokyo, a selection was made from January 1993 to April 2002, resulting in 923 consecutive patients operated for confirmed primary adenocarcinoma of the rectum. The patients underwent a low anterior resection (LAR), Hartmann, APR, or when a stage T4 tumor was suspected, pelvic exenteration. Surgery at the NCCH is performed according to the guidelines of the Japanese Research Society for cancer of the colon and rectum.[19] Lateral lymph node dissection was performed in low rectal cancer, when based on preoperative evaluation or intraoperative findings, TNM stage II or III disease was suspected. A decision was made for each patient individually, based on the side and the extension of the tumor, whether a uni- or bilateral LLND was performed. Accurate documentation of lymph node status and localization was obtained because all lymph nodes were dissected from the fresh specimen and their location and numbers were mapped in relation to the major arteries. After that, the specimen and all lymph nodes were examined histopathologically. Follow-up of all patients consisted of thoracic CT, abdominal CT, and pelvic CT-imaging every 6 months. For this study, similar selection criteria were applied to the patients from the NCCH as for the TME-trial patients, excluding the following patients: metastasis at the time of surgery (n = 134), other malignant diseases or double colorectal carcinoma (n = 62), fixed tumor during rectal examination (n = 15), and in situ carcinoma (n = 22).

The median follow-up of the Dutch RT+TME and TME patients alive was 7.0 years and of the Japanese NCCH patients 7.9 years.

Patient Selection

For both the Dutch and the Japanese groups, patients with low rectal tumors were selected. To match the groups as closely as possible, 2 different definitions of low rectal tumors had to be interpreted. In the Dutch TME trial, low rectal cancer was defined as tumors of which the lower edge was within 5 cm of the anal verge as measured by endoscopy. In Japan, the peritoneal reflection is the most important landmark in defining the location of the tumor and "low" rectal carcinoma is defined as a tumor of which the major part is located at or below the reflection.[20] The distance from the anal verge is often unreported. The anterior peritoneal reflection has been measured to be at 9 cm from the anal verge by intraoperative endoscopy.[21] With a mean tumor diameter of 4 cm in the Dutch TME trial, the distance between the lower border and the anal margin of the Japanese low cancers can thus be estimated as maximal 9−(4/2) = 7 cm. To match the tumors of the Japanese group, we therefore selected tumors from 0 cm up to 7.0 cm from the anal verge in the Dutch groups. Using these criteria, 324 Japanese patients were selected with rectal tumors at or below the peritoneal reflection and 755 patients from the Dutch database with tumors with the lower border from 0 cm up to 7.0 cm.

Definitions

In the Japanese group, the total amount of harvested lymph nodes consisted of mesorectal lymph nodes, and when LLND was done, also the lateral lymph nodes. In the Dutch group, the lymph node harvest consisted only of the mesorectal lymph nodes. The UICC 5th edition, 1997, classification system was used for both groups to define TNM-staging. All patients who developed local recurrence, defined as any recurrence of rectal cancer in the small pelvis, were identified from the databases. Local recurrence was either diagnosed clinically, radiologically, or histologically.

Methods

Analysis were made comparing 3 groups; the RT+TME group, the TME group, and the NCCH group. For all locally recurrent patients the available preoperative images and the images at the time of discovery of the local recurrence were retrieved. A specialized oncologic radiologist (R.B.) and a surgeon (G.B.) reviewed the images together for both the groups.

Examining the images, the site of the local recurrence was determined. The sites were classified into the following regions: lateral, presacral, perineal, anterior, or anastomotic. The same borders for the respective sites were used as defined by Roels et al.[22] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In 1 patient in the RT+TME group and in 2 patients in the NCCH group, insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). χ^2 tests and one-way ANOVA tests, Bonferroni corrected, were used to compare individual variables. The cancer-specific survival was defined as the time between rectal cancer surgery and death caused by cancer. Survival was estimated using the Kaplan-Meier method. Cox regression was used to assess differences in survival outcomes between groups; results are reported as hazard ratios with associated 95% confidence intervals. All P values were 2-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[23] Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. To account for possible confounding factors, multivariate analyses of local recurrence and cancer-specific survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects ($P < 0.10$) and group (RT+TME, TME, NCCH) were then selected for multivariate Cox regression.

RESULTS

Patient Characteristics

Patient characteristics and treatment details are listed in Table 1. The age at operation of the Japanese patients was significantly lower than that of the Dutch patients. In the Japanese group significantly more sphincter saving procedures had been performed, compared with the Dutch group. Lateral lymph node dissection was not performed in the Dutch patients, whereas 59% of the Japanese patients underwent unilateral or bilateral LLND.

Table 2 shows an overview of the pathology results of the Japanese and the Dutch groups. Early T-stage cancer was found significantly more in the Japanese group, whereas stages T3 and T4 cancer were found more in the Dutch. The average amount of

TABLE 1. Patient Characteristics and Treatment Details

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Sex				0.52
Male	244 (64)	234 (62)	215 (66)	
Female	135 (36)	142 (38)	109 (34)	
Age (yrs)				<0.001
Mean (SD)	64 (11)	64 (11)	58 (11)	
Type of resection				<0.001
Low anterior resection	160 (42)	159 (42)	195 (60)	
Abdominoperineal resection	193 (51)	199 (53)	113 (35)	
Hartmann	24 (6)	15 (4)	3 (1)	
Pelvic exenteration	2 (1)	3 (1)	13 (4)	
Lymph node dissection				<0.001
Standard TME	379 (100)	376 (100)	134 (41)	
Unilateral LLND	0	0	69 (21)	
Bilateral LLND	0	0	121 (38)	
Neoadjuvant therapy				<0.001
Preoperative radiotherapy	379 (100)	0	0	
None	0	376 (100)	324 (100)	
Adjuvant therapy				<0.001
Postoperative radiotherapy	3 (1)	52 (14)	5 (2)	
Postoperative chemotherapy	16 (4)	13 (3)	23 (7)	
None	360 (95)	315 (84)	297 (92)	

Values in parentheses are percentages.

TABLE 2. Pathologic Results

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Amount of lymph nodes resected				<0.001
Mean (SD)	7.3 (6.0)	9.3 (6.4)	33.7 (18.5)	
T-stage				<0.001
T1	19 (5)	21 (6)	52 (16)	
T2	143 (38)	131 (35)	107 (33)	
T3	209 (55)	210 (56)	160 (49)	
T4	8 (2)	14 (4)	5 (2)	
N stage			*/†	0.82/0.62
N0	244 (64)	229 (61)	198/192 (61/59)	
N1	80 (21)	82 (22)	75/80 (23/25)	
N2	55 (15)	64 (17)	51/52 (16/16)	
TNM-stage*				0.27
Stage I	129 (34)	123 (33)	125 (39)	
Stage IIa	111 (29)	100 (27)	72 (22)	
Stage IIb	4 (1)	6 (2)	1 (0)	
Stage IIIa	27 (7)	19 (5)	26 (8)	
Stage IIIb	53 (14)	63 (17)	49 (15)	
Stage IIIc	55 (15)	64 (17)	51 (16)	
Tumor size (cm)				0.09
Mean (SD)	4.0 (1.6)	4.6 (1.7)	4.3 (2.1)	
Distal margin (cm)				0.46
LAR (SD)	2.1 (1.5)	1.9 (1.7)	1.9 (0.9)	
APR (SD)	4.3 (1.7)	4.1 (1.9)	4.2 (2.7)	

Values in parentheses are percentages.
*On basis of mesorectal lymph nodes.
†With extra positive lateral lymph nodes.

harvested lymph nodes was 34 in Japanese group and 8 in the Dutch groups. The N stages, whether lateral nodes were included or not, did not differ significantly. TNM stage did not differ significantly between the groups.

The cancer-specific survival was higher in the Japanese extended surgery group than both in the Dutch TME group as in the Dutch RT+TME group (Fig. 1A). The hazard ratios for death (95% CI) of the Dutch TME and RT+TME groups with respect to the Japanese group were 2.0 (1.2–3.3) and 1.7 (1.1–2.8), respectively.

Local Recurrence Patients

Twenty-three patients (6.9% 5-years percentage) in the Japanese extended surgery group, 24 patients (5.8%) in the Dutch RT+TME group, and 46 patients (12.1%) in the Dutch TME group were diagnosed with local recurrence (Table 3, Fig. 1B). The hazard ratio for local recurrence (95% CI) of the Dutch TME group compared with the Japanese group was 1.6 (1.0–2.8). The hazard ratio (95% CI) of the Dutch RT+TME compared with the Japanese group was 1.0 (0.6–1.8). The mean time to local recurrence in the Japanese group is 2.1 years, 1.5 years in the TME-group, and 2.6 years in RT+TME-group.

In the Japanese patients with local recurrence, 11 patients (48%) had distant metastases before or at the time of local recurrence diagnosis. In the Dutch TME patients with local recurrence this was the case in 9 patients (20%), in the RT+TME local recurrence this was the case in 13 patients (54%). When distant metastases diagnosed within 1 month of local recurrence diagnosis were considered as being simultaneous, these distant metastases rates were 62%, 30%, and 88% for the Japanese, Dutch TME, and Dutch RT+TME local recurrence patients, respectively. At the time of last follow-up or death 95%, 77%, and 88% had metastases in the respective groups.

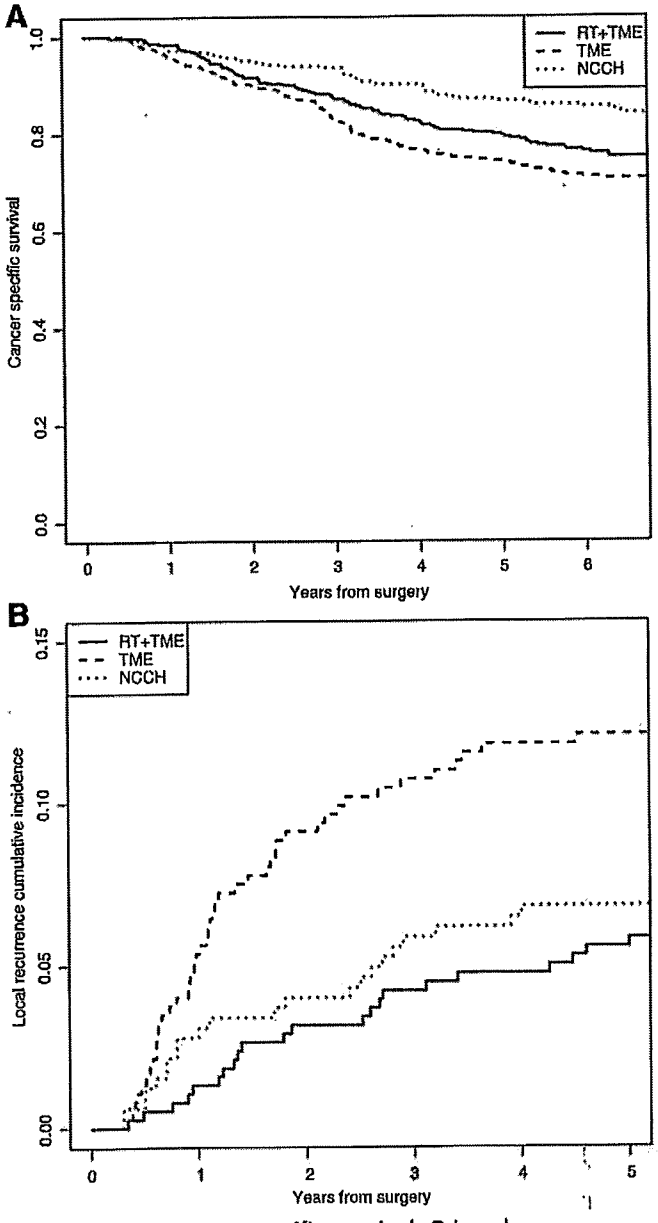

FIGURE 1. A, Cancer-specific survival, B,Local recurrence incidence.

Patterns of Local Recurrence

In Table 3 the patterns of local recurrence for the 3 groups are shown. Presacral recurrences (Fig. 2) occurred in 3.7% of the RT+TME patients and in 3.2% of the TME patients. In the Japanese group only 0.6% of the patients developed presacral recurrence. When only looking at the patients operated by APR, 5-year local recurrence rates in the presacral subsite were 6.5% in the RT+TME group, 4.4% in the TME group, and 1.8% in the Japanese group.

In this study, the lateral recurrence (Fig. 3) rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The hazard ratio of lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) is significantly different from zero (HR = 5.3, 95% CI: 0.6–43.9). In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. When only T3 and T4 tumors are selected, similar trends are observed.

Circumferential Resection Margin and Lateral Lymph Nodes

In the Dutch TME-group, 23% (88/376) of the patients showed CRM involvement on pathologic examination. Of these CRM-positive patients, the 5-year local recurrence percentage was 33%. In the CRM-negative cases, this was 9%. In the RT+TME-group, 20% (77/379) of the patients showed CRM involvement. Of these CRM-positive patients, the 5-year local recurrence rate was 25%. In the CRM-negative cases, 3% developed local recurrence in 5 years, versus 9% in the TME-group (HR = 0.4, 95% CI: 0.2–0.8).

Of the Japanese group it is not possible to report on CRM involvement; the immediate harvesting of lymph nodes from the fresh specimen precludes assessment of the CRM at a later stage. For the 190 patients operated by uni- or bilateral LLND, the 5-year local recurrence rate was 36% in the lateral node positive patients and 7% in the lateral negative patients (HR = 6.4, 95% CI: 2.6–15.7).

DISCUSSION

We compared Western and Japanese treatment results, looking at the patterns of local recurrence. The Japanese group differs from the Dutch groups in that the patients received extended surgery consisting of lateral lymph node dissection and a wider APR.

The main limitation of the present study is the difficult comparison of the group of Japanese patients with the group of Dutch patients. There are many sources of potential bias, such as nonrandomization and upstaging, as described previously.[24] Japanese patients are younger and have tumors with lower T-stage,

TABLE 3. Patterns of Local Recurrence

	Absolute No. LR 5-yrs (%)			Relative Distribution of LR*		
	RT+TME 379 pts	TME 376 pts	NCCH 324 pts	RT+TME 24 pts	TME 46 pts	NCCH 23 pts
presacral	14 (3.7%)	12 (3.2%)	2 (0.6%)	58%	26%	9%
lateral	3 (0.8%)	11 (2.7%)	8 (2.2%)	13%	24%	35%
anterior	4 (0.8%)	11 (3.0%)	1 (0.3%)	17%	24%	4%
anastomosis	2 (0.5%)	8 (2.1%)	5 (1.6%)	8%	17%	22%
perineum	0 (0%)	4 (1.1%)	5 (1.6%)	0%	9%	22%
unknown	1 (0%)	0 (0%)	2 (0.6%)	4%	0%	4%
	24 (5.8%)	46 (12.1%)	23 (6.9%)			
Hazard Ratio,	1.0	1.6	1.0			
95% CI†	0.6–1.8	1.0–2.8				

*Local recurrence per pelvic subsite, as a percentage of all local recurrences.
†Hazard Ratio for local recurrence after multivariate analysis, with 95% CI as compared to the NCCH group.

FIGURE 2. MR image of presacral local recurrence, sagittal MR image of locally recurrent mass in the presacral subsite.

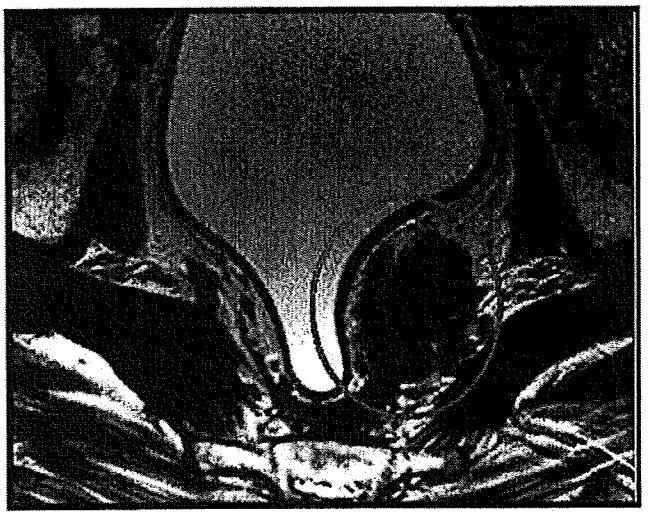

FIGURE 3. MR image of lateral recurrence, transverse MR image of local recurrence in the extramesorectal region (lateral subsite), highly suggestive of local relapse from nodal metastasis in the lateral lymph nodes.

although differences in local recurrence are still significant after multivariate analysis. Lymph node yield is much higher in the Japanese patients, which is probably because of differences in pathologic examination methods.[17] The differences in survival are undoubtedly more related to these differences than to any treatment effect. The definition and measurement of distal rectal cancer is different in the 2 countries, and although we tried to match the 2 groups as closely as possible, 1 or the other group may contain more distal tumors. The findings of the present study and the interpretation of the results therefore require some caution. Notwithstanding these limitations, the present study can give insight in the merits of the approaches and the mechanism of preventing local recurrences.

In this study extended surgery, as performed in the NCCH in Japan, results in good local control (5-year local recurrence rate, 6.9%). This is significantly less than after TME-surgery alone, which showed 12.1% local recurrence. Preoperative radiotherapy and TME-surgery also results in good local control (5.8%). The better local control is also reflected in the fact that the recurrences develop later when radiotherapy is given (2.6 years postoperatively) or more extended surgery is performed (2.1 years), compared with the 1.5 years after TME surgery. The high percentage of distant metastases at time of local recurrence diagnosis after RT+TME or extended Japanese surgery can also be seen as a marker of good local control, because now mainly patients with the worst disease get local recurrence, as if local recurrence is a sign of systemic disease.

The Japanese wider perineal resection is likely to result in less positive margins than in standard perineal resections, where the "coning in" is probably responsible for the high percentage of 23% involved margins in standard TME. Almost in 1 of 4 of these margin positive patients developed a local recurrence in this study. Unfortunately, pathology techniques differ between Japan and The Netherlands, making it impossible to draw firm conclusions on CRM involvement in the Japanese group. It has been described that recurrence rates after APR are far worse than after LAR. Even the pioneer of TME surgery, professor Heald, reported local recurrence in only 5% of cases 10 years after LAR, but in his patients who

underwent an APR, the local recurrence rate was as high as 36%.[25] Heald et al recently published an anatomic and radiologic study, in which they observed that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor.[26] Also Nagtegaal et al[5] concluded that following the mesorectum downward along the sphincter muscles is associated with increased occurrence of positive CRM. In the TME-trial, perforations in the anal canal were described, stressing the need for a more extended approach.[8,27] Holm et al recently reported on extended abdominoperineal resection, showing a low risk of CRM involvement.[28] It could be suggested that a wider perineal approach has a major contribution to good local control.

In the Dutch TME trial presacral recurrences were the most common type of recurrences. This was also reported in a large overview reported by Roels et al.[22] It is intriguing that this type of recurrence was uncommon in the Japanese group. The exact pathogenesis of presacral recurrences has been puzzling, as it is the easiest plane of dissection of a rectal cancer operation with often a wide margin of mesorectal fat. One could hypothesize that presacral recurrences result from implants of tumor cells originating from positive margins or tears or perforations at the tumor site. Through the force of gravity these implants would occur most often in the midline in the low/mid presacral area. Seventy-five percent of the presacral recurrences develop after APR surgery in the Dutch group, and radiotherapy apparently cannot sterilize these tumor particles. If this hypothesis were to be correct, presacral recurrences would occur less often with surgical techniques that avoid tumor spill, such as the wider perineal resections in the Japanese group. Of course this theory remains speculative.

The effect of the application of uni- or bilateral LLND on prevention of lateral recurrence is questionable. In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. In this study, the lateral recurrence rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The difference in lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) shows that radiotherapy plays a significant role in the reduction of local recurrence in the lateral pelvic subsite. Further, the significant lower local recurrence rate of CRM-negative RT+TME patients compared with CRM-negative TME-patients suggests the sterilization of tumor deposits outside the mesorectum. Only few reports are published about local recurrence in the lateral pelvis. In the overview report of Roels et al,[22] 6% of all patients and 21% of the patients with local recurrence had a relapse in the lateral pelvic subsite. Also Kim et al[29] reported recently that even after preoperative chemoradiotherapy combined with TME 24 of 366 (6.6%) patients with stage T3 or T4 tumors up till 8 cm from the anal verge developed lateral recurrence. Syk et al[30] reported only 2 of the 33 recurrent tumors originating from lateral pelvic lymph nodes in a population-based cohort. However, the study did not focus on low rectal tumors only and might be biased because patients who had a R1-resection or short distal resection margin were excluded. In the current report only low rectal tumors were studied and incomplete resection was not an exclusion criterion.

In the choice between more extensive surgery or preoperative radiotherapy as a means to improve the local recurrence rate, the morbidity associated with the treatment plays a major role. Patients who undergo radiotherapy have been shown to have an increased risk of sexual dysfunction and incontinence. In the Dutch TME-trial, 76% of the TME and 67% of the RT+TME male patients who were previously active were still active.[31] For female patients, these figures were 90% and 72%, respectively. Preoperative radiotherapy resulted in more erection and ejaculation problems in men, and vaginal dryness and pain during intercourse in women. Fecal incontinence was observed in 51.3% of the RT+TME patients, as compared with 36.5% in the TME patients. Regarding the lateral lymph node dissection, before nerve-sparing surgery, sexual dysfunction was present in as many as 96% of the patients.[32] LLND with nerve-sparing techniques 50% to 75% of the men are reported to be sexually active, although ejaculation is often compromised.[33,34] Urinary function is maintained well, but there are no reports on fecal continence. Although in Japan nerve-sparing techniques in LLND surgery are used to minimize damage the autonomic nervous system in the pelvis,[15,35] most Western surgeons feel that in Western patients, with a higher body mass index, nerve preserving techniques are more difficult and will lead to an excess morbidity. There is 1 report on results in 9 Western patients with locally advanced rectal cancer operated by LLND and ANP, with 1 patient with erection dysfunction and 1 patient suffering from retrograde ejaculation.[36] Currently, the National Cancer Center Hospital in Tokyo coordinates a multicenter randomized clinical trial comparing conventional TME versus LLND in patients with low rectal carcinoma, addressing the questions of survival benefit and morbidity. The inclusion of about 600 patients will be completed by the end of 2009.

Magnetic resonance imaging (MRI) is currently considered as the most reliable in staging rectal cancer. Preoperative MRI modalities are further improving and techniques are developed to distinguish better between nonmetastatic and metastatic lymph nodes by, for example, lymph node specific contrast enhancement.[37] With present day MRI, sometimes patients are identified with clearly involved or suspected lateral lymph nodes. As often preoperative chemoradiation is the choice of treatment in these cases, it is doubtful whether the lateral lymph nodes can be fully sterilized. Also, the risk for disseminated disease is high and prognosis is unfavorable for lateral lymph node positive patients. For these patients, it may be wise to consider a combination of treatments: neoadjuvant chemoradiation, a lateral lymph node dissection, and possibly even systemic therapy.

In conclusion, both extended surgery and preoperative radiotherapy with standard TME surgery result in good local control in the treatment of distal rectal cancer, as compared with TME alone.

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ORIGINAL ARTICLE – COLORECTAL CANCER

Male Urinary and Sexual Functions After Mesorectal Excision Alone or in Combination with Extended Lateral Pelvic Lymph Node Dissection for Rectal Cancer

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ABSTRACT

Background. Mesorectal excision reduced the incidence of genitourinary dysfunction compared with conventional surgery. In Japan, extended lateral pelvic lymph node dissection (ELD) is added to mesorectal excision when lateral pelvic node metastasis is suspected. The aim of this study was to evaluate male genitourinary function after mesorectal excision or mesorectal excision plus ELD for rectal cancer.

Methods. According to the degree of pelvic-plexus preservation (PPP) and ELD, patients were grouped into PG1, mesorectal excision alone (bilateral PPP without ELD) ($n = 27$); PG2, bilateral PPP with ELD ($n = 12$); PG3, unilateral PPP with ELD ($n = 26$); and PG4, no PPP with ELD ($n = 4$). The assessment included measurements of the time interval to residual urine becoming <50 mL, interviews assessing sexual function, and nocturnal penile tumescence measurements.

Results. Proportions of patients with residual urine becoming <50 mL within 14 days after surgery were 96% in PG1, 73% in PG2, 23% in PG3, and 0% in PG4 ($P < .001$). Proportions of patients answering the ability to maintain sexual intercourse at 1 year were 95% in PG1, 56% in PG2, 45% in PG3, and 0% in PG4 ($P < .001$). Proportions of patients having nocturnal penile rigidity of >65% at 1 year were 95% in PG1, 33% in PG2, 50% in PG3, and 0% in PG4 ($P < .001$).

Conclusions. Patients undergoing mesorectal excision alone can expect excellent genitourinary function, but functional results after mesorectal excision plus ELD are far worse. Degrees of dysfunction depend on the extents of both autonomic nerve resection and ELD.

Urinary and sexual dysfunctions are well-recognized complications after rectal cancer surgery.[1–3] Damage to the lumbar splanchnic nerves, superior hypogastric plexus, or hypogastric nerves results in ejaculatory dysfunction, whereas injury to the pelvic splanchnic nerves or pelvic plexuses causes urinary and erectile complications. These nerves are located just outside the mesorectal fascia, which envelops the rectum and mesorectum.

Blunt and blind dissection in conventional rectal cancer surgery frequently results in damage to these nerves with resulting reported rates for urinary and sexual dysfunction of 10% to 30% and 40% to 60%, respectively.[4–7] In contrast, mesorectal excision, a new world standard, removes the mesorectal fascia, including the mesorectum, completely and preserves the pelvic autonomic nerves by precise and sharp dissection under direct vision.[8,9] Introduction of mesorectal excision has been reported to reduce the incidences of urinary and sexual problems to 0% to 12% and 10% to 35%, respectively.[10–15]

In Japan, mesorectal excision is also standard for stage I to III rectal cancer above, and stage I rectal cancer below, the peritoneal reflexion. For stage II to III rectal cancer below the peritoneal reflexion, however, extended lateral pelvic lymph node dissection (ELD) with pelvic autonomic nerve preservation (PANP) is usually added.[2,16] Because the incidence of lateral pelvic lymph node metastasis is estimated to be 6.5% to 9.4% for T1–4 tumors and

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approximately 16% in T3 tumors, ELD is performed for patients having clinically positive lateral pelvic lymph nodes or those at high risk of such metastases.[2,16,17] In addition, if the autonomic nerves are directly invaded or threatened by the tumor, they are resected partially or completely. Clearly, precise understanding of functional results under such circumstances would be of major benefit for appropriate preoperative explanation and treatment choice for patients.

There have been several cross-sectional studies of Japanese-style surgery, but few longitudinal studies with objective evaluation of urinary and sexual functions. The purpose of this study was a longitudinal and objective evaluation of male urinary and sexual functions after mesorectal excision or mesorectal excision plus ELD for rectal cancer.

PATIENTS AND METHODS

Between March 1992 and January 2000, a total of 69 men with rectal cancer underwent radical surgery at the National Cancer Center Hospital, Tokyo. All patients were <70 years old, reported normal urination and erection within 3 months before operation, agreed to be examined with the RigiScan instrument (Timm Medical Technologies, Eden Prairie, MN), and gave informed consent for examination, treatment, and use of their data for analysis.[18,19] Approval by the institutional review board was not required for this observational study. Data on patient characteristics, treatment, pathology, and urinary and male sexual function were collected prospectively, and they were analyzed retrospectively. The median age of the 69 patients was 54 (range, 33–67) years. The median distance between the tumor and the anal verge was 5 (range 0–12) cm.

Treatment

All of the patients underwent mesorectal excision or mesorectal excision plus ELD with or without complete or partial PANP in each procedure, which was performed by each author. Type of surgery, extent of lymph node dissection, extent of PANP, and combined resection of neighboring organs were determined by each surgeon according to preoperative and intraoperative findings on tumor location, transmural invasion depth, and lymph node involvement, as outlined above and described previously.[2,16,17] Lymph node dissection and PANP were classified as detailed below.

Classification of Extent of Lymph Node Dissection

Abdominopelvic lymph node dissection consists of upward dissection and lateral pelvic lymph node dissection (LD).[16] Extent of LD is classified as follows: LD1, mesorectal excision alone; LD2, LD1 plus dissection of the internal iliac lymph node; LD3, LD1 plus complete resection of the internal iliac and obturator lymph nodes; and LD4, LD3 plus combined resection of the internal iliac artery and vein. ELD is LD3 or LD4.[16] Upward dissection, right LD, and left LD were classified and recorded separately.

Classification of PANP

Preservation or resection of the pelvic plexuses and hypogastric nerves were recorded separately for each patient on each side. Partial preservation of the pelvic plexus was defined as preservation of only the lower half. If a nerve (or plexus) is preserved but the pathway from the nerve (or plexus) to a target organ is completely disrupted, the nerve (or plexus) is regarded as being resected. Resection or complete disruption of the superior hypogastric plexus are regarded as being equal to no preservation of the bilateral hypogastric nerves.

Combinations of pelvic plexus preservation and LD were classified as follows: PG1, mesorectal excision alone (bilateral pelvic plexus preservation with bilateral LD1); PG2, bilateral pelvic plexus preservation with ipsilateral or bilateral ELD; PG3, contralateral pelvic plexus preservation with ipsilateral or bilateral ELD; and PG4, no preservation of the pelvic plexuses.

Combinations of hypogastric nerve preservation and LD were classified as follows: HG1, mesorectal excision alone (bilateral hypogastric nerve preservation with bilateral LD1); HG2, bilateral hypogastric nerve preservation with ipsilateral or bilateral ELD; HG3, contralateral hypogastric nerve preservation with ipsilateral or bilateral ELD; HG4, no preservation of the hypogastric nerves.

Evaluation of Urinary Function

To assess urinary function objectively, the interval between the date of surgery and the date of residual urine becoming <50 mL was measured without any medication. A Foley catheter was put in place immediately before surgery. Intermittent clamping of the catheter was started on the fifth postoperative day, and the catheter was removed when the patient felt urinary sensation. Residual urine measurement was then started and performed at least twice. When two successive measurements showed <50 mL, further measurements were canceled and the date of residual urine becoming <50 mL was recorded. If residual urine did not become <50 mL during the hospital stay, patients were instructed to do self-catheterization and record data for residual urine. Data sheets were then collected on an outpatient basis.

Evaluation of Male Sexual Function

To evaluate male sexual function objectively, nocturnal penile tumescence was measured before and 12 months after surgery with a RigiScan instrument.[18,19] Patients measured nocturnal penile tumescence during two successive nights by themselves.[18,19] Tumescence and rigidity were measured at the tip of the penis (5 mm proximal from the glans penis) and at the base of the penis (5 mm distal from the root of the penis). The highest rigidity value that was maintained for >5 minutes at the tip was considered as representative.[18] When rigidity recovered to the preoperative value at optional 6-month measurement, further measurements were canceled and the last rigidity represented the value at 1 year.

To assess male sexual function subjectively, patients were interviewed with a standardized questionnaire about male sexual function without any medication before and 12 months after surgery. Table 1 summarizes classification of grades of subjective erectile function. Grades of subjective ejaculatory function are classified as follows: grade 4, normal ejaculation; grade 3, ejaculation of decreased semen; grade 2, no ejaculation, with orgasm; grade 1, no ejaculation, without orgasm. The most favorable functional status within 3 months was regarded as representative. When the functional status recovered to the preoperative level at optional 6-month interview, further interviews were canceled and the last status was taken to represent the function at 1 year.

Statistical Analysis

Mann-Whitney *U*-tests were used to compare quantitative variables, and χ^2 tests were used to compare proportions. Kruskal-Wallis tests were used to analyze variance. The significance of pairwise correlation was evaluated with the Spearman's correlation coefficient. All statistical analyses were performed by SPSS for Windows, version 11.0 J (SPSS-Japan Inc., Tokyo, Japan). All *P* values were two sided, and a *P* value of <.05 was considered to be statistically significant.

RESULTS

Treatment Results and Pathology

Forty-four patients underwent a low anterior resection, and 25 underwent an abdominoperineal resection. Rates of sphincter preservation did not differ among surgeons (23 of 33 vs. 10 of 20 vs. 11 of 16, $P = .37$). Twenty-nine patients had a mesorectal excision alone, 15 one with unilateral ELD, and 25 one with bilateral ELD. Combined resection of the liver was performed for three patients, the bladder and prostate for one, the liver and seminal vesicles for one, the prostate and neurovascular bundle for one, and the internal iliac vessels for one. Combinations of pelvic plexus preservation and LD were PG1 in 27 patients, PG2 in 12, PG3 in 26, and PG4 in 4 (Table 2). Combinations of hypogastric nerve preservation and LD included HG1 in 21 patients, HG2 in 6, HG3 in 17, and HG4 in 25. Adjuvant radiotherapy was provided to one patient with a low anterior resection in the PG2 and HG3 group because of lateral pelvic lymph node metastasis.

Sixty-seven patients had adenocarcinomas, and two carcinoid tumors. Histopathologic International Union Against Cancer tumor, node, metastasis system stages were stage 0 in 1 patient, stage I in 22, stage II in 14, stage III in 26, and stage IV in 6. Eight patients had lateral pelvic lymph node metastasis, and six had distant metastases (liver, four patients; para-aortic lymph node metastasis, two patients). Sixty-eight patients had R0 and one R1 resections. At 1 year after surgery, 61 patients were free of disease, 7 were alive with disease, and 1 was dead of disease.

Pelvic Nerve Function

Patient characteristics in each grade of combinations of pelvic-plexus preservation and LD (PG group) are summarized in Table 2. Age ($P = .40$), pathological stage ($P = .077$), incidence of postoperative pelvic sepsis ($P = .52$), disease status at 1 year ($P = .14$), and distribution of operator (data not shown, $P = .75$) did not differ among the PG groups.

TABLE 1 Classification of subjective erectile function

Grade	Maintaining intercourse ≥ 5 min	Maintaining intercourse < 5 min	Intercourse possible	Erection possible
5	Yes	Yes	Yes, easy	Yes
4	No	Yes	Yes, easy	Yes
3	No	No	Yes, difficult	Yes
2	No	No	No	Yes
1	No	No	No	No

TABLE 2 Patient characteristics in each group

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	27	12	26	4
Age (y)				
Median	57	53	53	57
Range	33–67	43–66	38–65	52–62
Distance of the tumor from the anal verge (cm)				
Median	8	5	5	4
Range	1.5–12	2.5–10	0–10	3–8
Sphincter preservation				
Yes	26	5	12	1
No	1	7	14	3
Pathological UICC TNM stage				
0	1	0	0	0
I	13	4	5	0
II	4	3	5	2
III	8	3	13	2
IV	1	2	3	0
Postoperative pelvic sepsis				
No	24	11	20	3
Yes	3	1	6	1
Disease status at 1 y				
No evidence of disease	26	11	20	4
Alive with disease	1	1	5	0
Dead of disease	0	0	1	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses, *UICC* International Union Against Cancer, *TNM* tumor, node, metastasis system

Although distance of the tumor from the anal verge and rate of sphincter preservation did not differ among PG2, PG3, and PG4 groups, patients in the PG1 group had significantly longer distance ($P = .005$) and more frequent sphincter preservation ($P < .001$) than their counterparts in the other PG groups.

Urinary Function At the initial interview, none of the 69 patients had urinary dysfunction. Postoperative days for residual urine becoming <50 mL could be evaluated in 67 patients, and results are summarized in Table 3. With the other two patients, those days could not be evaluated because of severe postoperative complications. Proportions of patients with residual urine becoming <50 mL within 14 days after surgery were 96% in PG1, 73% in PG2, 23% in PG3, and 0% in PG4, with the variation being significant ($P < .001$). Median postoperative days for residual urine becoming <50 mL were 6.5 (range, 5–18) in PG1, 12 (range, 5–83) in PG2, 27.5 (range, 7–324) in PG3, and 217 (range, 81–256) in PG4. There were significant differences between PG1 and PG2 ($P = .004$), between PG2 and PG3 ($P = .004$), and between PG3 and PG4 ($P = .004$).

Subjective Erectile Function At the initial interview, three patients reported an inability for erection, and they rejected further evaluation of sexual function but agreed to be assessed for urinary function. Of the other 66 patients who reported an ability for intercourse, 55 patients had grade 5 subjective erectile function, 8 patients had grade 4, and 3 patients had grade 3 (Table 4). The last three patients were excluded from further analyses of erectile functions. Preoperative erectile function did not differ among each PG group ($P = .86$).

Subjective erectile function at 1 year was evaluated in 55 patients; the results are shown in Table 4. Proportions of patients reporting an ability to maintain intercourse at 1 year were 95% in PG1, 56% in PG2, 45% in PG3, and

TABLE 3 Postoperative days for residual urine becoming <50 mL according to pelvic plexus preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	27	12	26	4
Postoperative days				
≤7	16	2	1	0
8–14	9	6	5	0
15–21	1	1	5	0
22–30	0	1	3	0
31–60	0	0	6	0
>60	0	1	6	4
Not available	1	1	0	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses

TABLE 4 Subjective erectile function at 1 year according to pelvic-plexus preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	23	12	24	4
Erection grade before surgery				
Grade 5	20	10	22	3
Grade 4	3	2	2	1
Erection grade at 1 year				
Grade 5	16	2	4	0
Grade 4	5	3	6	0
Grade 3	0	0	2	0
Grade 2	1	2	3	0
Grade 1	0	2	5	4
Not available	1	3	4	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses

0% in PG4, with the variation being significant ($P < .001$). There were significant differences between PG1 and PG2 ($P = .002$) and between PG3 and PG4 ($P = .023$), but not between PG2 and PG3 ($P = .91$).

Nocturnal Penile Rigidity Nocturnal penile rigidity before surgery was evaluated in 63 patients. Median tip penile rigidities before surgery were 77% (range, 56%–99%) in PG1 ($n = 23$), 75% (range, 43%–87%) in PG2 ($n = 12$), 75% (range, 40%–95%) in PG3 ($n = 24$), and 76% (range, 58%–77%) in PG4 ($n = 4$). Preoperative nocturnal penile rigidity did not differ among the PG groups ($P = .64$).

Nocturnal penile rigidity at 1 year was evaluated in 44 patients, and the data are shown in Fig. 1. Proportions of patients having nocturnal tip penile rigidity of >65% at 1 year were 95% in PG1 ($n = 19$), 33% in PG2 ($n = 9$), 50% in PG3 ($n = 14$), and 0% in PG4 ($n = 2$), with the variation being significant ($P < .001$). Median tip penile rigidities were 83% (range 57%–100%) in PG1, 54% (0%–84%) in PG2, 60% (0%–87%) in PG3, and 11% (1%–20%)

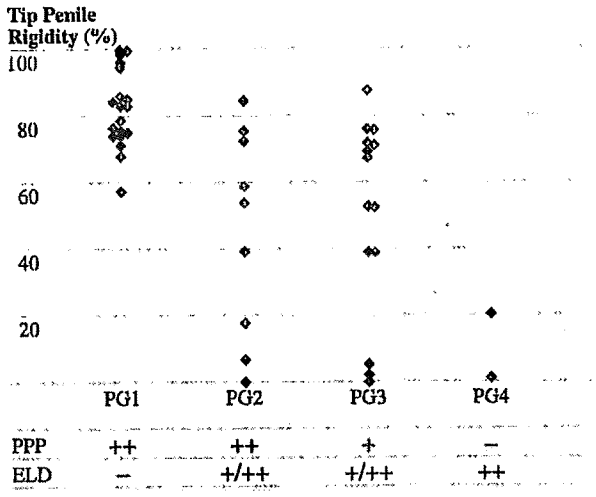

FIG. 1 Nocturnal tip penile rigidity 1 year after surgery according to the degrees of pelvic-plexus preservation (PPP) and extended lateral pelvic lymph node dissection (ELD). ++, bilateral; +, unilateral; −, none. PG1, mesorectal excision alone (bilateral PPP without ELD); PG2, bilateral PPP with ipsilateral or bilateral ELD; PG3, contralateral PPP with ipsilateral or bilateral ELD; PG4, no PPP

in PG4. There was a significant difference between PG1 and PG2 ($P = .001$), but not between PG2 and PG3 ($P = .89$) and between PG3 and PG4 ($P = .15$). There was a significant correlation between subjective erectile function grades and the nocturnal tip penile rigidity 1 year after surgery (Spearman's correlation coefficient = .73, $P < .001$)

Hypogastric Nerve Function

Although patient characteristics in each hypogastric nerve function group (HG group) are not shown, age ($P = .44$), incidence of postoperative pelvic sepsis ($P = .84$), disease status at 1 year ($P = .34$), and distribution of operator ($P = .53$) did not differ among the HG groups. Neither distance of the tumor from the anal verge nor rate of sphincter preservation differed among HG2, HG3, and HG4 groups; however, patients in the HG1 group had significantly longer distance ($P = .003$) and more frequent sphincter preservation ($P = .004$) than their counterparts in the other HG groups. In addition, patients in the HG2 group had a significantly higher stage than those in the HG3 group ($P = .022$).

Subjective Ejaculatory Function Of the 65 patients who reported an ability for ejaculation at the initial interview, 48 had grade 4 ejaculatory function, and 17 had grade 3 (Table 5). Preoperative ejaculatory function did not differ among the HG groups ($P = .34$).

Subjective ejaculatory function at 1 year could be evaluated in 56 patients, and the results are shown in Table 5. Proportions of patients reporting an ability to have normal ejaculation at 1 year were 56% in HG1, 20% in HG2, 14% in HG3, and 0% in HG4, with the variation being significant ($P = .001$). There was a significant difference between HG3 and HG4 ($P < .001$), but not between HG1 and HG2 ($P = .32$) and between HG2 and HG3 ($P = .10$).

TABLE 5 Subjective ejaculatory function at 1 year according to hypogastric-nerve preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	HG1	HG2	HG3	HG4
Hypogastric nerve preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	18	6	16	25
Ejaculation grade before surgery				
Grade 4	11	5	12	20
Grade 3	7	1	4	5
Ejaculation grade at 1 year				
Grade 4	10	1	2	0
Grade 3	8	4	5	0
Grade 2	0	0	7	14
Grade 1	0	0	0	5
Not available	0	1	2	6

HG1 mesorectal excision alone (bilateral hypogastric nerve preservation without extended lateral pelvic lymph node dissection [ELD]), *HG2* bilateral hypogastric nerve preservation with ipsilateral or bilateral ELD, *HG3* contralateral hypogastric nerve preservation with ipsilateral or bilateral ELD, *HG4* no preservation of the hypogastric nerves

DISCUSSION

This study clearly demonstrated that >90% of male patients who had normal urinary and sexual functions preoperatively and who underwent mesorectal excision with complete PANP and without ELD had a normal urination within 14 days and an ability to maintain intercourse and to ejaculate at 1 year. The results were obtained both subjectively and objectively in a prospective longitudinal fashion. In accordance with previous cross-sectional or longitudinal studies that used interview or self-administered questionnaire, functional benefit of mesorectal excision over any other radical operation was confirmed.[2,10–15,20–23]

Moreover, we found that degrees of urinary and sexual dysfunction greatly depended not only on the extent of autonomic nerve resection, but also on the extent of LD. When the unilateral pelvic plexus or hypogastric nerve was removed, the rates for patients with normal functions almost halved. Furthermore, complete resection of the pelvic plexuses or hypogastric nerves resulted in complete destruction of these functions. Similar observations were reported in previous cross-sectional or longitudinal studies that used interviews or self-administered questionnaires.[2,12,20,21]

In this investigation, the addition of ELD influenced urinary and sexual functions adversely, independently of the extent of PANP. Several cross-sectional studies that used self-administered questionnaire reported similar observations, but one revealed no influence of ELD on functions.[12,22–24] Although exact mechanisms of dysfunction caused by ELD despite PANP are not clear, mechanical injury to nerve fibers during lymph node dissection and/or ischemic injury due to devascularization by dissection may play a role. The influence of ELD seems smaller and more unpredictable than that of autonomic nerve resection. This is probably because the extent of LD varies case by case. The more extensive lymph node metastasis looks, the more aggressively an operator should resect.

On the other hand, the influence of ELD seems more limited on ejaculatory function than on erectile function. This may be because the distance between the pelvic splanchnic nerves and the internal iliac vessels, along which the lymph nodes are located, is smaller than that between the hypogastric nerve and these vessels. The shorter the distance, the higher the probability of injury to the nerve during dissection along the vessels.

This study had a number of limitations. First, patients in the PG1 group had higher-lying tumors and more frequent sphincter preservation than patients in other PG groups, although age, stage, pelvic sepsis, disease status at 1 year, and preoperative urinary and erectile functions were comparable. This bias is inevitable because autonomic nerve resection and ELD are indicated only in low-lying tumors. The previously reported high incidence of male sexual dysfunction with abdominoperineal resection was caused by damage to the neurovascular bundle during dissection of the lower rectum rather than sphincter resection itself.[10] Indeed, our PG1 patients with tumors located within 5 cm who underwent cautious dissection of the neurovascular bundle retained excellent functions. A similar argument is applicable to the bias with hypogastric nerve function. Second, the use of a validated self-administered questionnaire is preferable to a nonvalidated questionnaire or interview to avoid unreliability or influence of attending physisian.[25] Because there were no validated questionnaires at the beginning of this study, we used both interview and nocturnal penile tumescence measurement, the latter being an objective index to assess erectile function, which is essential for differentiating psychogenic and organic erectile dysfunctions.[18,19] Third, because this study included only one patient who received adjuvant radiotherapy, who belonged to the PG2 and HG3 group and who had mild urinary dysfunction and severe erectile and ejaculatory dysfunction, effects of radiotherapy on genitourinary function could not be evaluated. Finally, the present findings on functional influence of ELD may not be applicable outside of Japan. However, in the context of clinically suspected lateral pelvic node metastasis, an attempt to perform ELD can be generally recommended.[9] Where this is the case, the present findings should facilitate appropriate preoperative explanation and treatment choice for patients.

To prevent unnecessary injury to the pelvic autonomic nerves, we should avoid both inadvertent and intentional damage. The former is caused by inability to identify the nerves during surgery, either as a result of a lack of knowledge of anatomy or simple failure in identification. If an appropriate anatomical plane—the "holy plane"—is entered with correct knowledge, the nerves can be easily identified as whitish and firm fibers.

Intentional damage results from either excessive nerve resection or ELD caused by overestimation of direct invasion and metastasis. Accuracy of evaluation of pelvic anatomy and tumor extent has now been improved by high-resolution magnetic resonance imaging.[26] This proved to be sufficiently accurate for predicting the involvement of the mesorectal fascia adjacent to the pelvic autonomic nerves with an accuracy of 88% in a large prospective study.[27] Thus, it can be recommended to reduce overestimation of nerve invasion. Excessive ELD is caused by either overestimation of lateral pelvic lymph node metastasis or prophylactic ELD for patients who are at risk but who do not have clinical metastasis. Although ELD for clinical metastasis is allowed in Western countries, prophylactic ELD is widely practiced only in Japan.[2,9,12,16,17,20–23] Because the incidence of such metastasis is approximately 16% even in T3 tumors, accurate diagnosis should reduce unnecessary ELD.[17] Koh et al. reported that there were four

distinct uptake patterns of ultrasmall particles of iron oxide on T2*-weighted magnetic resonance imaging in mesorectal lymph nodes.[28] Furthermore, these patterns were associated with metastasis. Such application of new technology advances may also be beneficial for diagnosis of lateral pelvic lymph node metastasis.

In conclusion, patients undergoing mesorectal excision alone reported preservation of excellent sexual and urinary function. The functional results after mesorectal excision plus ELD, however, were worse than those after mesorectal excision alone. Degrees of sexual and urinary dysfunction depend on the degrees of both autonomic nerve resection and LD. Therefore, unnecessary resection of the pelvic autonomic nerves and ELD should be avoided if oncologic safety is not compromised.

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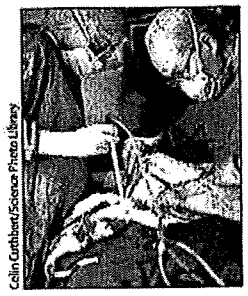
Differences in rectal cancer surgery: east versus west



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In this issue of *The Lancet Oncology*, Georgiou and colleagues[1] report the results of their meta-analysis of observational studies comparing extended lymphadenectomy (EL) for rectal cancer with non-EL. After analysing 20 studies published over the past 25 years, the authors concluded that the efficacy of EL was insufficient to recommend it instead of conventional surgery.

Although this paper is important, its role in clinical decision making for rectal cancer is unclear for a number of reasons. During the past 25 years, imaging modalities and surgical techniques have made remarkable progress. In EL, nerve-sparing surgery with lateral nodal dissection (LND) was developed, while in non-EL, total mesorectal excision has become the standard. In surgery, techniques of LND can vary from "node picking" to "en-bloc dissection". Even without accounting for time effect or bias, interpreting the results of Georgiou and colleagues is problematic.

Also problematic are the author's failure to take lateral nodal metastases (LNM) into account. The definition of low rectum is slightly different between Japan and the west. LNM are found only in cancers of the low rectum, below the peritoneal reflection. It is well-known that the deeper the invasion and the lower the tumour, the higher the risk of LNM.[2] Heald once described LNM as "a Japanese mystery": LNM are not considered of surgical importance in the west. However, progress in MRI has been made, and the preoperative evaluation of LNM has become more reliable. Whether or not the sterilisation of LNM by pre-operative radiotherapy or chemoradiotherapy (pre-[C]RT) is possible is also an important point. There are no reports on the efficacy of pre-(C)RT for the treatment of LNM, but some researchers claim that the sterilisation of LNM can be achieved.[3]

Overtreatment, which is seen in both Japanese and western populations, also needs to be addressed. LND in patients without extra-mesenteric metastasis is overtreatment. However, in Japanese hospitals, LND was done in almost all cancers of the low rectum of T2 stage or higher until 1985. Although this wide application of LND clarified the frequency and sites of LNM, LND caused dysfunction. Because of this, Japanese surgeons investigated pelvic autonomic nerve anatomy, and developed nerve-sparing surgery with LND.[4,5] A randomised trial of nerve-sparing surgery with LND versus total mesorectal excision has been started in Japan to measure the effectiveness of LND for occult LNM. For high-risk patients, such as those with obvious LNM or c-stage IIIb disease, a randomised trial of pre-CRT with extended surgery versus pre-CRT with total mesorectal excision should be done in Japan.

Overtreatment is also a problem in the west. In particular, many cases of rectal cancer that can be locally controlled by surgery alone are actually treated with pre-(C)RT. As a result, the incidence of dysfunction rises, with accompanying costs. For the treatment of rectal cancer, the role of surgery is central. In reports about neoadjuvant radiotherapy in the west, patients with T1 and T2 tumours were also included in the Swedish and Dutch trials, whereas in a German trial, the patient population was restricted to only those with T3 or T4 and N-positive disease, indicating an improvement in patient selection over time. Since the incidence of local recurrence in tumours above the peritoneal reflection is low, the clinical significance of pre-(C)RT for this population is disputed. However, in the west, tumours up to 15 cm from the anal verge are treated with pre-(C)RT. If pre-(C)RT is expected to result in downsizing of the tumour, overtreatment could be avoided by setting size criteria, in addition to T stage, in treatment protocols. Radiation increases occlusion, induces changes in hyaline in the blood and lymph vessels, and affects fibrosis over time, and brings about organ dysfunction. Owing to fibrosis, surgery for local recurrence after pre-(C)RT becomes very difficult, and radiation carcinogenesis can also develop.[6] For patients whose life expectancy is long, the adverse effects of pre-(C)RT should be taken into account. Therefore, since we now know more about the risk factors for local recurrence, and imaging modalities have been improved, high-risk tumours can be selected accurately. The east and the west should join hands and define research criteria for surgery and neoadjuvant treatment to prevent over-treatment and dysfunction, and to improve future oncological results.

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