(chemo)radiotherapy and TME with LLND in similar patients, making it difficult to make a statement about which regimen is preferred in advanced rectal carcinoma. Western surgeons are hesitant to do lateral lymph node dissections for three reasons. First, in Western patients with a higher body mass index, nerve-sparing techniques are more difficult and the fear of excess morbidity is realistic. Further, it is well known that lateral lymph node status is reflective of overall mesenteric lymph node status and lateral lymph node positivity results in poor prognosis.[13,30] Lastly, although LLND has improved oncologic results in Japanese patients in historical studies and also the current study suggests that LLND is able to prevent residual tumor cells from developing into local recurrence, the clinical effectiveness of LLND has not been proved in a randomized fashion. Currently, the National Cancer Center Hospital is coordinating a multicenter randomized clinical trial comparing conventional TME with bilateral LLND in patients with rectal carcinoma. The results are awaited with anticipation, but it is questionable whether they will be applicable to Western patients.

Concluding, in this study patterns of local recurrence were evaluated in the treatment of rectal cancer, at or below the peritoneal reflection, with selective LLND. Overall local recurrence was 6.6% at 5 years. Local recurrence rate after standard TME was 0.8% in low-stage disease. In lymph-node-positive patients, 33% of the unilateral LLND patients had local relapse, significantly more than in the bilateral LLND group with 14% local recurrence. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

ACKNOWLEDGEMENTS The authors would like to express their gratitude to the Japan Prizewinners Program of the Dutch Government who financed the stay of M. Kusters in Tokyo and the Japan–Netherlands Institute (Executive Director Dr. W. G. J. Remmelink) for practical support.

The authors would also like to thank Drs. S. Ishiguro and Y. Kobayashi, from the Colorectal Surgery Department of the National Cancer Center Hospital, for help with obtaining data; as well as Drs. Y. Arai and M. Takahashi from the Department of Radiology, National Cancer Center Hospital, for assistance with imaging.

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Pelvic exenteration for clinical T4 rectal cancer: Oncologic outcome in 93 patients at a single institution over a 30-year period

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Background. *Patients with stage T4 rectal cancer are known to have poor survival and often require pelvic exenteration (PE). We describe the oncologic outcome of PE for patients with clinical T4 rectal cancer over a 30-year period.*
Methods. *Data for 93 patients with primary rectal cancer who underwent PE between 1975 and 2005 were reviewed retrospectively.*
Results. *Curative resection was performed in 91 patients (97.9%). Estimated 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) rates were 52% and 46%, respectively. Irradiation was administered in 18 patients (19.4%). Local recurrence was observed in 7 patients, of whom 6 had lymph node (LN) involvement. Estimated local recurrence rate at 2 years was 8.6% (2.0% in node-negative and 16.4% in node-positive patients). Multivariate analysis demonstrated that lateral pelvic LN involvement (P = .03), a carcinoembryonic antigen level of >10 ng/dL (P = .04), and lymphovascular invasion (P = .04) were significantly associated with decreased OS. Only lateral pelvic LN involvement was significantly associated with decreased RFS (P = .01).*
Conclusion. *For patients with clinical T4 rectal cancer, PE can provide an opportunity for long-term survival and good local control. Patients with lateral pelvic LN involvement should be offered adjuvant treatment pre- or postoperatively to improve prognosis after PE. (Surgery 2009;145:189-95.)*

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LOCALLY ADVANCED RECTAL CANCER IN THE PELVIS remains a challenge to surgeons. The key factor influencing local control and survival is margin-negative resection.[1] Patients with T4 rectal cancer, which directly invades adjacent organs or structures,[2] have poor survival.[1]

Pelvic exenteration (PE) is defined as operative resection of the rectum, distal colon, bladder, lower ureters, internal reproductive organs, draining lymph nodes (LN), and pelvic peritoneum.[1,3] PE allows rectal tumors invading adjacent organs to be resected en bloc and the provision of a margin-negative operation. It has been reported that PE is associated with high morbidity and mortality rates.[4] In our opinion, however, the key factor in reducing these rates and in guaranteeing optimal results is skill of the surgical teams.

Here, we evaluated the outcome of clinical T4 primary rectal cancer treated with PE and factors predicting long-term survival and recurrence based on our data set covering a period of >30 years.

Accepted for publication September 26, 2008.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2008.09.014

PATIENTS AND METHODS

Patients. PE with curative intent was performed in 93 patients with primary rectal cancer between January 1975 and September 2004 at our institution. All patients had biopsy-proven adenocarcinoma and were suspected of having cancer invasion to adjacent organs without distant metastases on the basis of either or both preoperative examination and intraoperative findings. Data for these patients came from a prospectively collected colorectal division database and were reviewed retrospectively with a focus on recurrence, survival, and clinicopathologic factors. The patients were followed until September 2007.

Preoperative evaluation and operative procedure. Preoperative examination included physical examination, digital rectal examination, bimanual examination (in women), and computed tomography. Tumors were grouped into lower rectum (0–7.0 cm from the anal verge), middle rectum (7.1–12.0 cm), and upper rectum and rectosigmoid (12.1–17.0 cm).[5] All tumors were confirmed to be located below the sacral promontory by contrast enema. Magnetic resonance imaging was introduced after 1988, and endoscopic ultrasonography was used after 1989. Either or both modality was performed for evaluation of the depth of tumor invasion and LN involvement.

PE with extended lateral pelvic LN dissection was performed, in principle, for tumors that were suspected to have extensive invasion to the trigone of the bladder, the prostate, or the urethra. LN dissection was performed around the inferior mesenteric artery in the upper lymphatic system, and laterally with combined resection of the bilateral internal iliac vessels. Periaortic LNs and inguinal LNs were not dissected unless the LNs were found to be swollen by preoperative imaging or intraoperatively. Details of extended LN dissection have been precisely described in previous reports.[3,6]

In some female patients, modified (anterior or posterior) PE was performed to preserve urinary or fecal continence and to reduce postoperative morbidity. In anterior PE, the lower rectum was retained in situ, with removal of the upper rectum, reproductive organs, and bladder. In posterior PE, the bladder was preserved and the uterus, vagina, and rectum were resected with preservation of the superior vesical artery and division of the distal internal iliac vessels.[7] Sacral invasion was treated by en bloc resection.[3,6] Most urinary reconstruction procedures were done using an ileal conduit.

Radiotherapy and chemotherapy. Radiotherapy was provided in cases of large or far-advanced tumors, in accordance with the surgeon's preference. Hypofractionation short-course radiation was performed before 1985. After that, our policy of preoperative radiotherapy was long-course radiation with or without chemotherapy because of adverse events. The doses varied from 30 to 50.4 Gy with hyperfractionation. In principle, intraoperative or postoperative radiation therapy was administered according to intraoperative findings, when extension of tumor into the operative margin was suspected or confirmed. In some patients, preoperative chemotherapy as well as radiotherapy was given, although no definite criteria for this treatment were available. Some patients with LN involvement received postoperative adjuvant chemotherapy. The standard regimen varied across the study period.

Determination of recurrence and survival. Local recurrence was defined as clinical or radiologic recurrence in the prior pelvic treatment field, and distant metastasis was defined as clinical or radiologic recurrence at any other site. Overall survival (OS) was the period from the date of surgery to the date of death or the date of the most recent follow-up. Recurrence-free survival (RFS) was the period from the date of surgery to the date of death, the first observation of local, or distant recurrence, or the date of the most recent follow-up, whichever occurred first.

Statistical analysis. Statistical analyses were performed using Stata Version 9.2 (Stata Corporation, College Station, Tex). OS and RFS curves were calculated using the Kaplan–Meier method. Cox regression analysis was used to identify factors significantly associated with OS and RFS. Results were considered significant when $P < .05$.

RESULTS

Patients and operation. Patient demographics are summarized in Table I. The study group was composed of 80 men (86%) and 13 women (14%), with a median age of 55 years (range, 26–80). Total PE was performed for 83 patients (80 men and 3 women), anterior PE for 9, and posterior PE for 1. Median operation time was 496 minutes (range, 220–1,073) and median blood loss during surgery was 1,850 mL (range, 370–8,000). In 6 patients, combined resection of the distal sacrum was done.[8]

Radiotherapy and chemotherapy. Radiotherapy of the pelvis was performed in 17 patients (18.8%), preoperatively in 13, postoperatively in 2, and both intraoperatively and postoperatively in 2. Doses varied between 20 and 50.4 Gy. Preoperative hypofractionation short-course radiation was done in 4 cases. Of 13 patients who received preoperative irradiation, 8 received preoperative chemoradiotherapy with a 5-fluorouracil–containing regimen, intravenously in 6 and orally in 2.

Postoperative adjuvant chemotherapy was performed in 25 patients. Among these, 3 received intravenous 5-fluorouracil plus leucovorin, 3 received intravenous mitomycin C, 1 received intravenous cisplatin and etoposide, and 18 received oral chemotherapy (carmofur in 14, uracil-tegafur in 4).

Pathologic analysis. Pathologic outcomes are listed in Table II. The mean number of LNs harvested was 51 (range, 2–110). All resected LNs were investigated histologically, and LN involvement

Table I. Characteristics of 93 patients undergoing PE for rectal cancer

	No. of patients
Age (yrs)	
<60	57
≥60	36
Gender	
Male	80
Female	13
Primary site	
Upper rectum and rectosigmoid	25
Middle rectum	13
Lower rectum	55
CEA level (ng/dL)	
<10	59
≥10	34
Type of operation	
Total PE	83
Modified PE	10
Radiotherapy	
Preoperative (chemoradiotherapy)	13 (8)
Intraoperative and/or postoperative	5
None	76
Postoperative adjuvant chemotherapy	
Done	25
None	68

CEA, Carcinoembryonic antigen.

Table II. Pathologic outcome of 93 patients undergoing PE for rectal cancer

	No. of patients
Tumor differentiation	
Well or moderately differentiated	80
Poorly differentiated or mucinous	13
T status	
pT4	46
Non-pT4	47
N status (direction)	
pn0	53
Upper LN involvement	18
Upper and lateral LN involvement	22
Lymphovascular invasion	
Absent	35
Present	58
Surgical margin	
Negative	91
Positive	2

LN, Lymph node.

was found in 40 patients. Of these 40, 18 patients had LN involvement in the mesorectum or along the inferior mesenteric artery (upper LN involvement) and 22 had involvement along the internal iliac artery (lateral LN involvement) as well as upper LN involvement. In patients with lower rectal cancer, 36.4% (20/55) had lateral LN involvement, and 7.7% (1/13) with middle and 4.0% (1/25) with upper rectal cancer had lateral LN involvement. Of 14 patients who received preoperative radiotherapy, 10 did not have LN involvement, 1 had only upper LN involvement, and 3 had both upper and lateral LN involvement.

Histologically, 46 (49.5%) of 93 patients who were suspected of having T4 cancer at preoperative or intraoperative evaluation had definite invasion into adjacent organs. Of 47 patients who did not have pathologic T4 disease, 16 had involved LNs that had invaded neighboring organs, mimicking the penetration of rectal cancer, and 7 had cancer deposits between the rectum and adjacent organs. The others had inflammatory changes resulting from abscess formation or radiotherapy, which caused fixation of the tumor. The surgical margin was positive in 2 patients (2.2%).

Mortality and morbidity profile. Surgery-related complications were observed in 34 of 83 (41.0%) patients who underwent total PE (Table III). The most frequent complication was perineal wound dehiscence (20.3%), followed by urinary tract infection (10.8%) and pelvic sepsis (8.4%). Eight patients required an additional operations, including stoma reconstruction in 4, reconstruction of the urinary tract in 2, and bypass operation because of anastomotic leakage in 2. Three patients who undergone anterior PE developed a complication, namely pelvic sepsis, leakage of the ureter, and acute colitis.

Two patients (2.2%) died within 30 days after surgery, 1 from cerebral hemorrhage and the second from sepsis after leakage of the intestine. One patient died of perineal infection followed by sepsis 7 months after surgery.

OS. Thirty-seven patients survived for 5 years and 28 patients for 10 years. With a median follow-up of 40 months (range, 1–305), the estimated 3-, 5- and 10-year survival rates were 61%, 52% and 50%, respectively (Fig 1).

RFS and pattern of local and distant recurrence. Recurrence occurred in 27 (29.0%) patients (Table IV). Of these, 4 had local recurrence, 20 had distant recurrence, and 3 had both local and distant recurrence. The estimated 3-, 5-, and 10-year RFS rates were 51%, 46% and 46%, respectively (Fig 1). The sites of distant metastases included the liver in 9, lung in 10, inguinal LN in 5, paraaortic LN in 2, and bone in 2. Among patients with lateral LN involvement, 59.1% developed recurrence by the last follow-up compared with 38.9% in those with upper LN involvement and 13.2% in those with no LN involvement.

Table III. Morbidity profile of 83 patients after total PE procedures

	No. of cases	%
Perineal wound dehiscence	17	20.5
Urinary tract infection	9	10.8
Pelvic sepsis	7	8.4
Leakage of intestine	3	3.6
Leakage of ureter	3	3.6
Acute renal failure	3	3.6
Bowel obstruction	2	2.4
Abdominal wound infection	2	2.4
Others	3	3.5

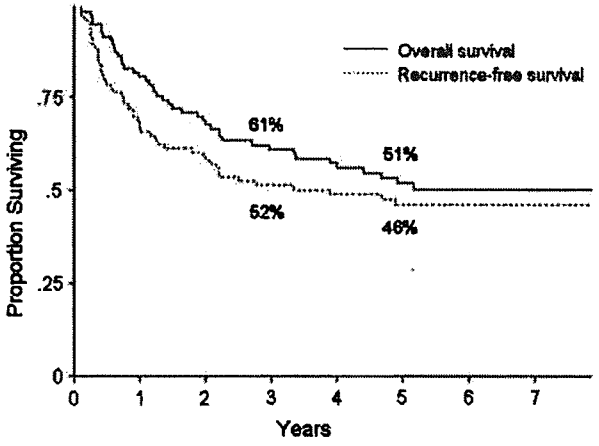

Fig 1. OS and RFS after PE in patients with clinical T4 rectal cancer. Estimated 3- and 5-year survival rates were 61% and 52%, respectively. Estimated 3- and 5-year RFS rates were 51% and 46%, respectively.

The estimated local recurrence rate at 2 years was 8.1%. Of the 18 patients receiving radiotherapy, 1 experienced local recurrence. Of the 7 patients with local recurrence, 6 had LN involvement (upper LN involvement in 3, upper and lateral LN involvement in 3). The patient who had no LN involvement followed by local recurrence was 1 of 2 who had a positive operative margin and who had received intraoperative and postoperative radiation therapy. The other patient with a positive operative margin did not develop local recurrence. The cumulative local recurrence rate was plotted by stratified LN involvement (Fig 2). The estimated 2-year local recurrence rate was 2.0% in patients with no LN involvement and 16.4% in those with involvement, with this difference being significant ($P = .01$). Even after the exclusion of patients who received preoperative radiotherapy, no patient without LN involvement experience local recurrence at 2 years.

Four of 6 patients who had inguinal LN recurrence underwent resection. With regard to liver metastasis, 1 patient had a hepatectomy, and 1 patient received radiofrequency ablation. None of the patients who developed pulmonary metastases underwent metastasectomy.

Factors associated with OS and RFS. The estimated OS at 5 years for patients without LN, with upper LN involvement, and with lateral LN involvement were 62%, 49%, and 31%, respectively. In the univariate model, lateral LN involvement was significantly associated with reduced survival (Fig 3). A carcinoembryonic antigen (CEA) level of ≥10 ng/dL, as well as lymphovascular invasion and poorly differentiated or mucinous carcinoma, were also significantly associated with poor survival (Table V). OS between patients with T4 and non-T4 rectal cancer did not significantly differ ($P = .92$).

On multivariate analysis, lateral LN involvement ($P = .03$), a CEA level of ≥10 ng/dL ($P = .04$), and lymphovascular invasion ($P = .04$) were significantly associated with decreased survival (Table VI). With regard to RFS, lateral LN involvement and lymphovascular invasion were significantly associated with a reduced RFS on univariate analysis ($P = .01$ and .05, respectively; Table V). On multivariate analysis, only lateral LN involvement was significantly associated with a reduced RFS ($P = .01$; Table VI).

DISCUSSION

To our knowledge, this study represents the largest single institution analysis to date of long-term outcome in patients with clinical T4 rectal cancer treated by PE. Estimated 5-year OS was 52% and estimated 5-year RFS was 46%, with an estimated local recurrence rate at 2 years of 8.1%. Lateral LN involvement was significantly associated with both decreased OS and RFS; a CEA level ≥10 ng/dL and lymphovascular invasion were also significantly associated with decreased survival. These factors are predictive of patients who are candidates for adjuvant therapy.

In previous articles on oncologic outcomes of primary rectal cancer in patients treated by PE, estimated 5-year survival rates were in the range of 43% to 64%.[9-15] However, none of these papers provided details of local recurrence rate in patients in the disease group. Comparison of our long-term results with those in similar reports is hampered by our less frequent use of preoperative or postoperative radiotherapy and differences in operative procedure, which in our case involved PE with lateral pelvic LN dissection. Nevertheless, it is interesting that the estimated 5-year survival rate in our series is quite similar to these previous rates.

Table IV. Recurrence profile after PE

	All (n = 93)	N0 (n = 53) No. (%)	Upper LN involvement (n = 18) No. (%)	Lateral LN involvement (n = 22) No. (%)
Recurrence	27	7 (13.2)	7 (38.9)	13 (59.1)
Local	7	1 (1.9)	3 (16.7)	3 (13.6)
Distant	23	6 (11.3)	5 (27.8)	12 (54.5)
Liver	9	2	2	5
Lung	10	3	2	5
Others	9	2	1	6

LN, Lymph node.

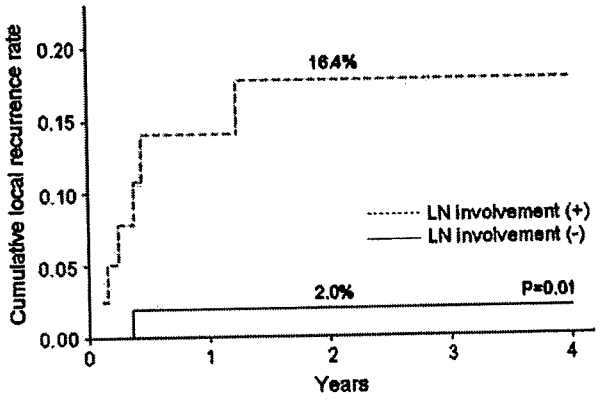

Fig 2. Cumulative local recurrence rate after PE in patients with clinical T4 rectal cancer stratified by LN involvement. Estimated 2-year local recurrence rate was 2.0% in patients without LN involvement (LN involvement [−]) and 16.4% in those with involvement (LN involvement [+]). The difference was significant ($P = .01$).

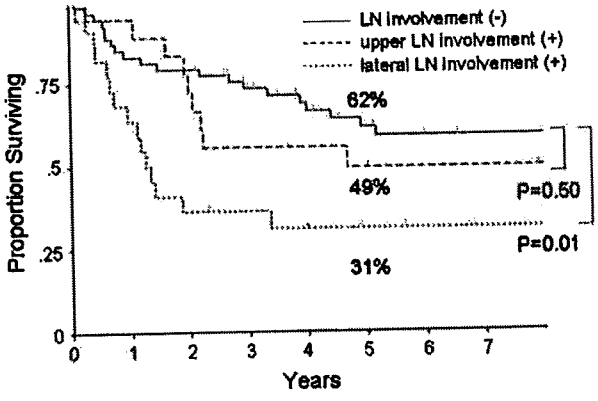

Fig 3. OS after PE in patients with clinical T4 rectal cancer stratified by the direction of LN involvement. Compared with patients without LN involvement (LN involvement [−]), those with lateral LN involvement (lateral LN involvement) had significantly decreased survival ($P = .01$), whereas those with only upper LN involvement (upper LN involvement) had no difference in survival ($P = .50$).

Inadequate excision seems to be the major determinant of a poor outcome in rectal cancer.[1,16] It has been reported that the status of circumferential resection margin strongly predicts local recurrence and poor survival.[17,18] The greatest benefit of PE is that it offers a much higher probability of resecting the tumor package without exposing malignant cells to the dissection plane.[19] We routinely combine PE with lateral pelvic LN dissection, and although the effectiveness of lateral pelvic LN dissection has not been confirmed,[20] en bloc resection of pelvic structures along with tissues lateral to the rectum likely minimizes the chance of a positive margin. Previous studies have reported that the number of resected LNs is closely correlated with increased survival for colorectal cancer,[21-23] indicating that the number of LNs suggests the adequacy of the operation and of pathologic examination.[21] The median number of harvested LNs in the study was 51. We believe this large number of LNs, as well as high frequency of curative resection, indicate that we performed optimal operations.

The efficacy of radiotherapy for local control in patients with rectal cancer has been consistently demonstrated.[24,25] In this study, however, only one fifth of patients received perioperative radiotherapy. It has been reported that LN involvement is associated with a higher risk of local recurrence.[26,27] Here, node-positive patients had a local recurrence rate of 16.4% at 2 years, indicating the limitation of surgery alone for clinical T4 rectal cancer with LN involvement. To improve local control, radiotherapy may be mandatory in positive-node patients with clinical T4 rectal cancer. On the other hand, the local recurrence rate at 2 years for node-negative patients was 2.0%. Furthermore, no local recurrence was seen in node-negative patients, even though they did not receive preoperative radiotherapy. We, therefore, assume that radiotherapy is not always indicated for node-negative patients, even those with T4 rectal cancer.

The fact that only 49.5% of patients diagnosed as having T4 rectal cancer had tumors invading

Table V. Univariate analysis of factors associated with OS and RFS

	OS			*RFS*		
Variable	*HR*	*95% CI*	P	*HR*	*95% CI*	P
Gender						
Male	1.00	—	—	1.00	—	—
Female	0.77	0.33–1.81	.55	0.94	0.43–2.09	.88
Age (yrs)						
<60	1.00	—	—	1.00	—	—
≥60	1.30	0.74–2.28	.36	1.32	0.77–2.25	.32
Primary site						
Upper rectum	1.00	—	—	1.00	—	—
Middle rectum	0.97	0.36–2.60	.96	1.07	0.42–2.72	.89
Lower rectum	1.67	0.86–3.24	.13	1.75	0.91–3.37	.09
CEA level (ng/dL)						
<10	1.00	—	—	1.00	—	—
≥10	**1.80**	**1.03–3.14**	**.04**	1.51	0.89–2.58	.13
Tumor differentiation						
Well or moderate	1.00	—	—	1.00	—	—
Poor or mucinous	2.08	1.00–4.33	.05	1.82	0.88–3.76	.10
T Status						
Non-pT4	1.00	—	—	1.00	—	—
pT4	1.03	0.59–1.78	.92	1.08	0.64–1.83	.78
LN involvement						
pN0	1.00	—	—	1.00	—	—
Upper LN involvement	1.29	0.58–2.52	.50	1.43	0.71–2.88	.32
Lateral LN involvement	**2.61**	**1.34–4.62**	**.01**	**3.07**	**1.68–5.63**	**.01**
Lymphovascular invasion						
Absent	1.00	—	—	1.00	—	—
Present	**2.08**	**1.13–3.83**	**.02**	**1.79**	**1.01–3.16**	**.04**
Radiation therapy						
None	1.00	—	—	1.00	—	—
Done	1.25	0.62–2.50	.53	1.08	0.56–2.09	.82
Adjuvant chemotherapy						
None	1.00	—	—	1.00	—	—
Done	1.14	0.63–2.04	.67	1.00	0.57–1.78	.99

Table VI. Multivariate model of factors associated with OS and RFS

Variable	*HR*	*95% CI*	P *value*
OS			
Lateral LN involvement	2.09	1.06–4.10	.03
CEA ≥10 ng/dL	1.84	1.04–3.25	.04
Lymphovascular invasion	2.00	1.05–3.82	.04
RFS			
Lateral LN involvement	2.61	1.38–4.92	.01

adjacent organs also deserves consideration. Balbay et al[28] reported that only 61% of 46 patients who underwent total PE for suspicion of bladder involvement had definite invasion, whereas in their series of 71 patients, Ike et al[13] reported that 50% of patients diagnosed with T4 rectal cancer who underwent total PE actually had T3 tumors. In this study, magnetic resonance imaging or endoscopic ultrasonography was introduced after 1988. The rate of actual T4 cancer was not different even after introduction of such modalities (51% before 1988 and 50% in/after 1989). These low rates of accuracy indicate the difficulty in reaching a precise preoperative diagnosis of tumor invasion even with current diagnostic modalities.

PE has functional, psychological, and psychosexual implications for patients postoperatively, and indications should therefore be determined with caution. The efficacy of preoperative chemoradiotherapy has been also improved and the frequency of complete sterilization of the tumor has increased, even for advanced rectal cancer.[29] Our policy for T4 rectal cancer has changed to more frequent adoption of preoperative chemoradiotherapy for better local control. Further improvement in sterilization or shrinkage of the tumor might allow the use of organ-preserving surgery in

patients with T4 rectal cancer. Until that time, we believe organ-preserving surgery in patients with T4 rectal cancer is risky. We now have a plan to conduct a new protocol using preoperative chemoradiotherapy for clinical T4 rectal cancer for better local control and organ preservation, but a policy of obtaining radical margins by PE is the safest way to prevent local recurrence.

In conclusion, this retrospective review of the oncologic outcome of PE with lateral pelvic LN dissection for patients with clinical T4 rectal cancer at a single institution over a period of >30 years showed a 5-year OS of 52% and a 5-year RFS of 46%. Lateral LN involvement was significantly associated with both decreased OS and RFS. A CEA level ≥10 ng/dL and lymphovascular invasion were also significantly associated with decreased survival. In addition to optimal surgery, patients with these factors should be offered pre- or postoperative adjuvant treatment. Confirmation of these findings in an additional data set is required.

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Journal of Plastic, Reconstructive & Aesthetic Surgery (2009) 62, 108–111

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

CASE REPORT

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

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Received 22 August 2006; accepted 11 September 2007

KEYWORDS
Enterocutaneous fistula;
Superior gluteal artery perforator flap;
Perforator flap;
Colorectal cancer

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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1748-6815/$ - see front matter doi:10.1016/j.bjps.2007.09.009

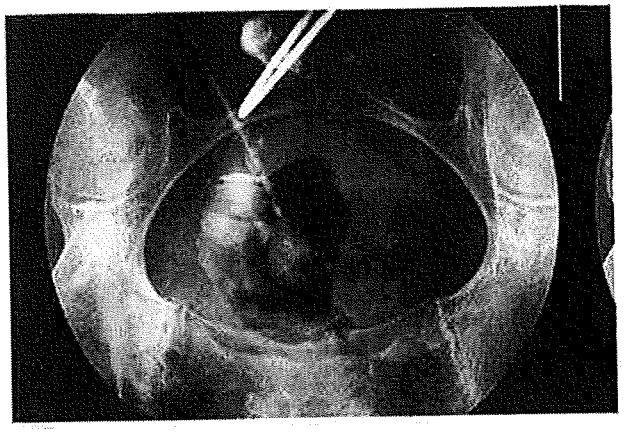

Figure 1 Fistulogram through a small hole at the sacral skin indicated a communication between the skin surface and the small intestine.

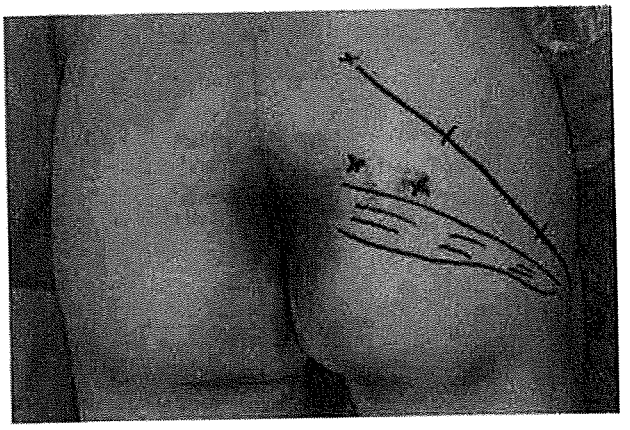

Figure 3 Damaged skin surrounding the fistula before surgery. A skin perforator (2 x's) from the superior gluteal artery was marked with a Doppler flowmetre.

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 × 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 × 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

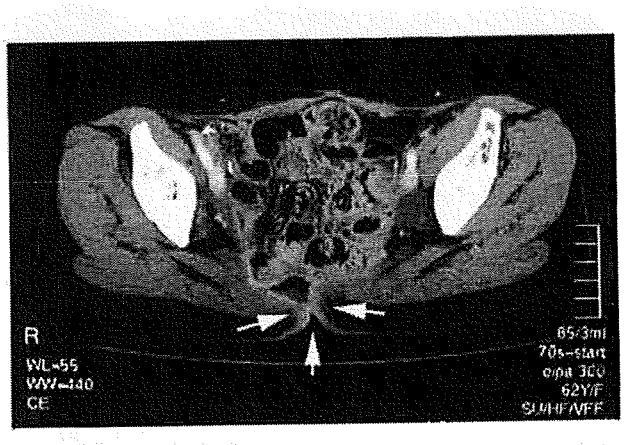

Figure 2 A preoperative computed tomogram indicated the presence of a fistula (arrows).

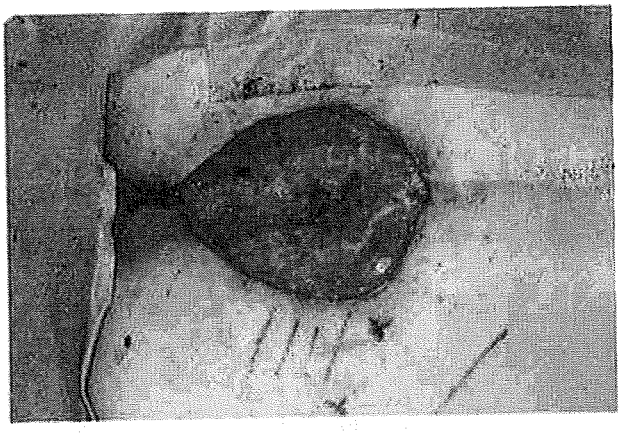

Figure 4 Debridement of the fistula and the surrounding skin during surgery. The diameter of the fistula was 1.0 cm.

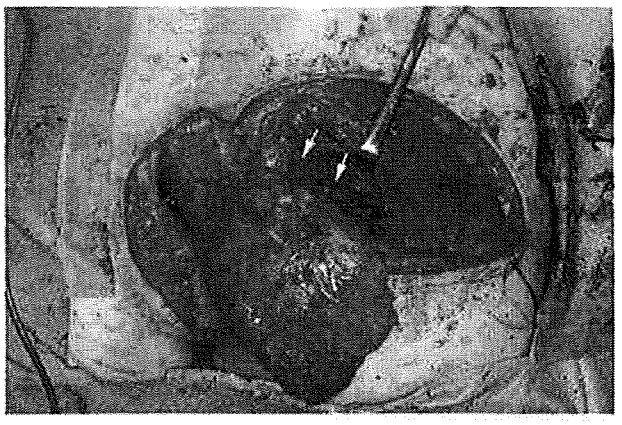

Figure 5 The superior gluteal artery perforator flap was elevated with two skin perforators (arrows).

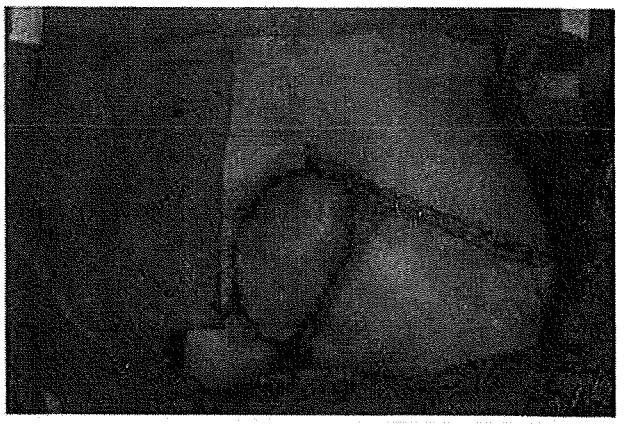

Figure 7 The soft-tissue defect was covered with the SGAP flap, and the flap donor site was closed directly.

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.

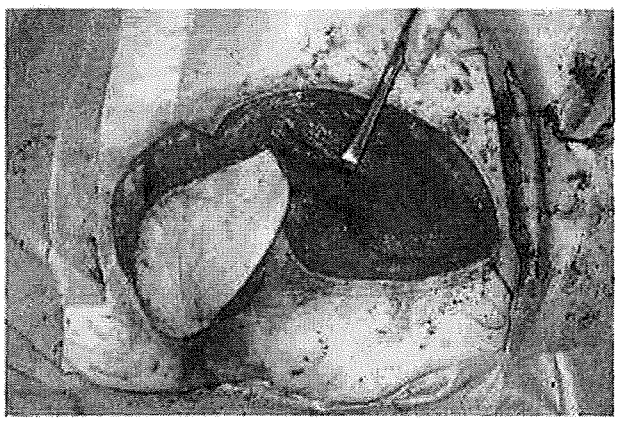

Figure 6 The flap was transposed medially.

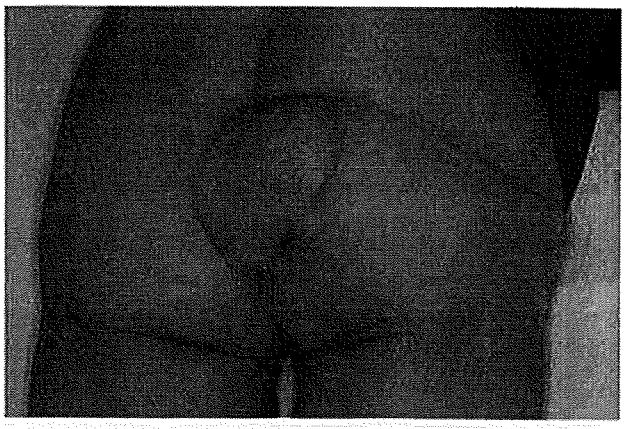

Figure 8 No sign of recurrence of the fistula 12 months after surgery.

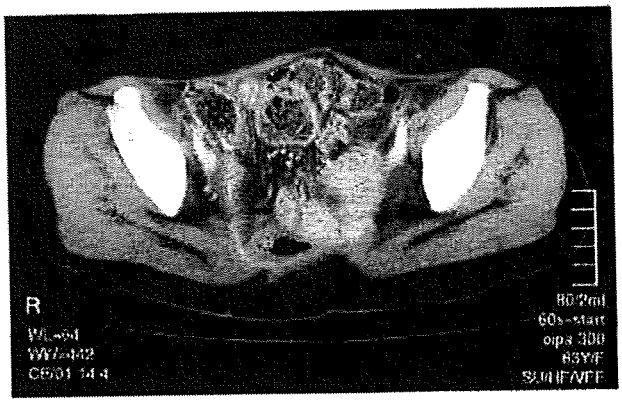

Figure 9 A computed tomogram shows successful coverage of the small intestine with sufficient flap volume.

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.

(*Ann Surg* 2009:249: 229–235)

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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The Japan Prizewinners Program (www.jpp-japan.nl) of the Dutch Government financed the stay of Miranda Kusters in Tokyo. There was no other financial support to any of the authors for this study.

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ISSN: 0003-4932/09/24902-0229
DOI: 10.1097/SLA.0b013e318190a664

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.

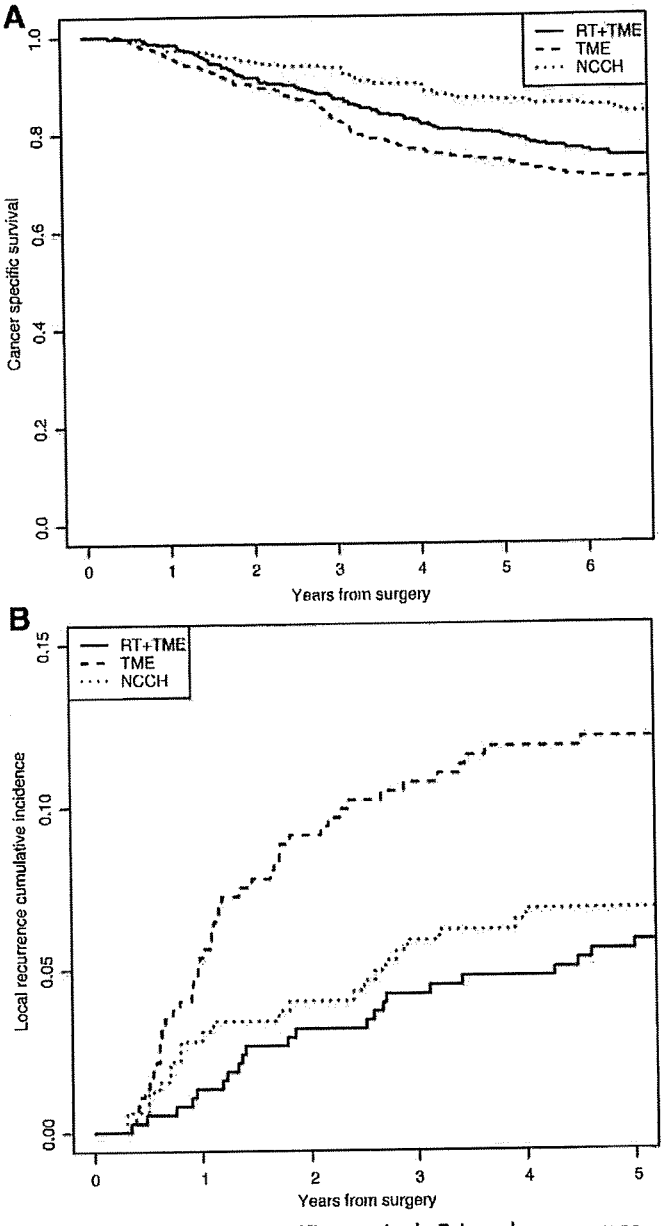

FIGURE 1. A, Cancer-specific survival, B,Local recurrence incidence.

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.

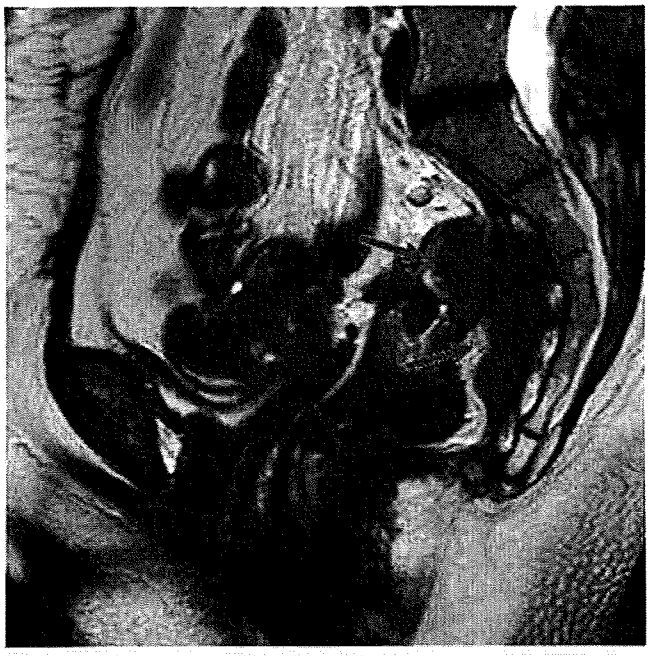

FIGURE 2. MR image of presacral local recurrence, sagittal MR image of locally recurrent mass in the presacral subsite.

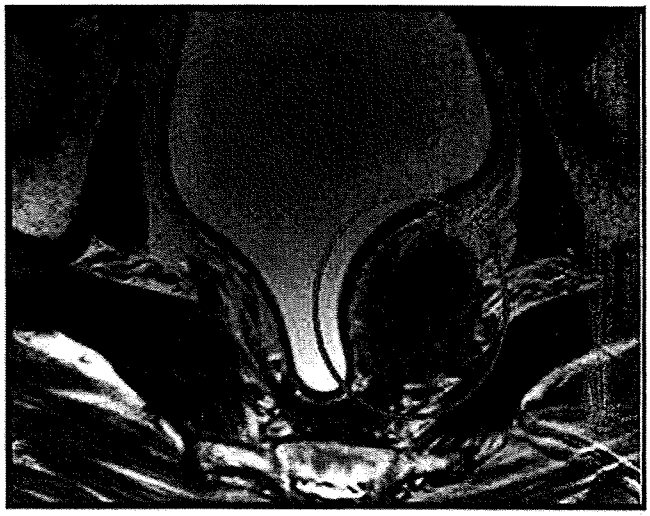

FIGURE 3. MR image of lateral recurrence, transverse MR image of local recurrence in the extramesorectal region (lateral subsite), highly suggestive of local relapse from nodal metastasis in the lateral lymph nodes.

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.

ACKNOWLEDGMENTS

The authors thank all participating clinical investigators of the Dutch TME trial, Dr. M. den Dulk, E. Klein Kranenbarg from the Data center of the Department of Surgery, Leiden University Medical Center, for providing the data; and Dr. S. Ishiguro and Y. Kobayashi, from the colorectal surgery department of the National Cancer Center Hospital, for the help with obtaining data; as well as Dr. Y. Arai and Dr. M. Takahashi from the department of Radiology, National Cancer Center Hospital, for assistance with respect to imaging. They express their gratitude to the Japan Prizewinners Program of the Dutch Government who financed the stay of M. Kusters in Tokyo and the Japan-Netherlands Institute (Executive Director Dr. W.G.J. Remmelink) for the practical support.

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