RESULTS

Clinicopathology

Patient characteristics and treatment details are listed in Table 1. Of the 351 studied patients, 145 had standard TME surgery without LLND, 73 underwent unilateral LLND, and 133 patients received bilateral LLND. LLND was performed in significantly younger patients and more often in combination with a non-sphincter-saving procedure, compared with patients who had not undergone an LLND. The tumors in the LLND patients had higher T- and N-stages and were significantly larger. Comparing the clinicopathological characteristics between the unilateral and the bilateral LLND, no significant differences were found, except that unilateral LLND was more often combined with autonomic nerve preservation (ANP).

Mean lymph node harvest was 21 LNs in standard TME (Table 1). After unilateral LLND the mean number of recovered LNs was 38, and after bilateral LLND this was 45 ($p = 0.004$).

Table 2 shows the outcomes of lymph node involvement for all 351 patients, stratified by T-stage. Overall lymph node involvement was 42%, and lateral lymph node

TABLE 1 Clinicopathological characteristics

	No LLND ($n = 145$)	Unilateral LLND ($n = 73$)	Bilateral LLND ($n = 133$)	p^*	p^{**}
Sex ratio (M:F)	96:49 (66:34)	47:26 (64:36)	86:47 (65:35)	0.95	0.97
Mean age (years)	61	57	57	0.03	0.98
Operation					
Sphincter-saving	112 (77)	36 (49)	63 (47)		
Not sphincter-saving	33 (23)	37 (51)	70 (53)	<0.001	0.79
Adjuvant chemotherapy					
No	139 (96)	67 (92)	121 (91)		
Yes	6 (4)	6 (8)	12 (9)	0.24	0.85
T-stage					
T1	52 (36)	3 (4)	3 (2)		
T2	47 (32)	27 (37)	37 (28)		
T3	46 (32)	40 (55)	83 (62)		
T4	0 (0)	3 (4)	10 (8)	<0.001	0.37
Meso LN positive					
0	102 (70)	44 (60)	64 (48)		
1–3	30 (21)	19 (26)	39 (29)		
>4	13 (9)	10 (14)	30 (23)	0.003	0.28
Lat LN positive					
No	–	62 (85)	109 (82)		
Yes	–	11 (15)	24 (18)	–	0.59
ANP					
No	3 (2)	2 (3)	17 (13)		
Yes	142 (98)	71 (97)	116 (87)	<0.001	0.02
Differentiation					
Well	75 (52)	27 (37)	50 (38)		
Moderate	67 (46)	44 (60)	75 (56)		
Poor	2 (2)	2 (3)	8 (6)	0.18	0.29
Tumor size					
0–4 cm	106 (73)	31 (42)	42 (32)		
>4 cm	39 (27)	42 (58)	91 (68)	<0.001	0.12
Diss. LN (mean)	21	38	45	<0.001	0.004

Values in parentheses are percentages

* p value between no LLND, unilateral LLND, and bilateral LLND

** p value between unilateral LLND and bilateral LLND

Meso mesorectal; *Lat* lateral; *LN* lymph node; *ANP* autonomic nerve preservation

TABLE 2 Lateral lymph node dissection and lymph node status, stratified by T-stage

Stage	LLND		LNI		LNI	LLNI
T1: 58	No LLND	52 (90%)	N0	47	8/58 = 14%	1/58 = 2%
			Upper pos	5		
	LLND	6 (10%)	N0	3		
			Upper pos, lat neg	2		
			Upper neg, lat pos	0		
			Upper pos, lat pos	1		
T2: 111	No LLND	47 (42%)	N0	33	32/111 = 29%	7/111 = 6%
			Upper pos	14		
	LLND	64 (58%)	N0	46		
			Upper pos, lat neg	11		
			Upper neg, lat pos	2		
			Upper pos, lat pos	5		
T3: 169	No LLND	46 (27%)	N0	22	97/169 = 57%	19/169 = 11%
			Upper pos	24		
	LLND	123 (73%)	N0	50		
			Upper pos, lat neg	54		
			Upper neg, lat pos	5		
			Upper pos, lat pos	14		
T4: 14	No LLND	0 (0%)	N0	–	12/14 = 86%	8/14 = 57%
			Upper pos	–		
	LLND	14 (100%)	N0	1		
			Upper pos, lat neg	4		
			Upper neg, lat pos	0		
			Upper pos, lat pos	8		
Total: 351		207/351 = 59%*			149/351 = 42%	35/351 = 10%

LLND lateral lymph node dissection; *LNI* lymph node involvement (upper and lateral lymph nodes); *LLNI* lateral lymph node involvement; Upper, upper lymph nodes; *Lat* lateral lymph nodes; *pos* positive; *neg* negative

* Percentage of patients submitted to LLND

involvement was 10%. Jump metastases (mesorectal lymph nodes negative and lateral lymph nodes positive) occurred in 3% (7/207) of the patients with LLND.

Local Recurrence

At time of last follow-up 23 of the total of 351 patients had developed local recurrence (6.6% 5-year local recurrence rate). In the patients who had not undergone LLND, only one patient (0.8%) had local recurrence at the site of the anastomosis. In the unilateral LLND group, 12 of the 73 patients (5-year 15.4%) had local relapse. This was more than in the bilateral LLND group, with 10 of 133 local recurrences (5-year 8.3%). In N+ patients (Fig. 1), the difference between the uni- and bilateral LLND (32.8% versus 14.2%, respectively) was significant ($p = 0.04$).

In multivariate analysis (Table 3) including uni- and bilateral LLND patients, lateral lymphadenectomy, mesorectal lymph node N-stage, and lateral lymph node positivity were independent risk factors for local recurrence. Compared with patients with bilateral LLND the relative risk for local recurrence was 4.0 for unilateral LLND patients.

Table 4 reports the sites of the local recurrences for the uni- and bilateral LLND groups. The rate of lateral recurrence in the unilateral LLND patients was 5.6%, and in the bilateral LLND patients was 3.3%. It was noticed that the three patients who developed lateral local recurrence on the ipsilateral side after unilateral LLND had lower lymph node harvest (mean 28 LNs) than the patients who developed no lateral recurrence after unilateral LLND (mean 38 LNs). However, the number of patients is too low to draw any firm conclusion from this finding.

Distant Recurrence and Survival

At local recurrence diagnosis 40% of the unilateral LLND patients and 60% of the bilateral LLND patients had distant metastases. One year after local recurrence diagnoses these figures were 70% and 80% in the uni- and bilateral LLND patients, respectively.

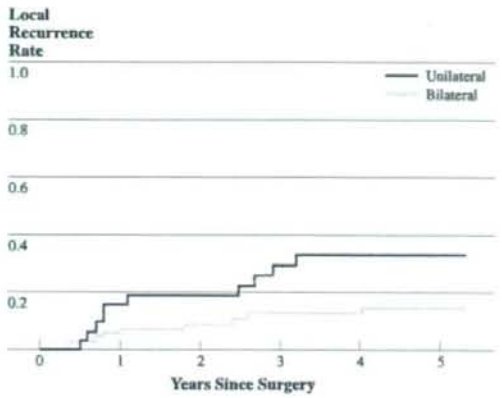

FIG. 1 Local recurrence in N+ patients

Figure 2 shows the survival curves of the TME-only, and uni- and bilateral LLND patients. Overall 5-year survival was 89% for patients who had standard TME. Five-year overall survival in the unilateral LLND group was 78%, which did not differ significantly from the bilateral LLND group (77%) ($p = 0.37$).

The multivariate Cox regression analysis, when including the uni- and bilateral LLND groups, identified T-stage, mesorectal lymph node N-stage and lateral lymph node positivity as independent factors for death risk.

Two years after local recurrence diagnosis 37% of the unilateral LLND patients was still alive, as compared with 60% of the bilateral LLND patients. The number of patients is however too low to conclude significant better survival for bilateral LLND patients.

TABLE 3 Multivariate analysis for local recurrence

Variable	HR	95% CI	*p*
Lateral dissection			0.003
Unilateral	1.00		
Bilateral	0.25	0.10–0.64	
T-stage			0.09
T1 + T2	1.00		
T3 + T4	2.99	0.84–10.73	
N-stage mesorectal LN			0.008
0 pos	1.00		
1–3 pos	2.71	0.75–9.85	
> 4 pos	7.22	2.01–25.94	
Lateral LN status			0.007
Negative	1.00		
Positive	3.53	1.41–8.85	

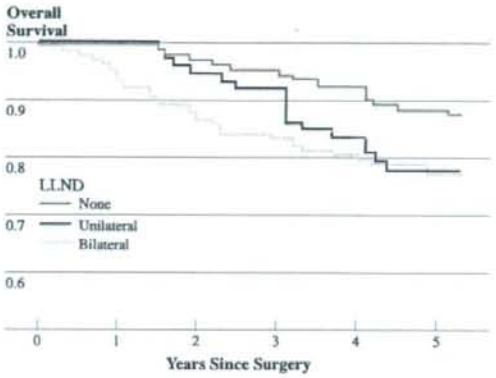

FIG. 2 Overall survival in all patients

TABLE 4 Sites of local recurrence

Site of local recurrence	All patients			Only N+ patients		
	Unilateral LLND ($n = 73$)	Bilateral LLND ($n = 133$)	*p*	Unilateral LLND ($n = 32$)	Bilateral LLND ($n = 74$)	*p*
Lateral	5 (5.6)	4 (3.3)		4 (13.2)	3 (4.6)	
Ipsilateral	*3 (3.4)*			*3 (9.9)*		
Contralateral	*2 (2.2)*			*1 (3.3)*		
Presacral	2 (2.8)	0 (0)		2 (6.7)	0 (0)	
Perineal	2 (2.8)	2 (1.7)		1 (3.1)	2 (3.4)	
Anterior	0 (0)	1 (0.9)		0 (0)	1 (1.8)	
Anastomotic	3 (4.2)	2 (1.6)		3 (9.8)	2 (3.0)	
Unknown	0 (0)	1 (0.8)		0 (0)	1 (1.4)	
Total	12	10		10	9	
5-Year LR rate	15.4%	8.3%	0.06	32.8%	14.2%	0.04

Values in parentheses are the 5-year local recurrence rates per subsite

DISCUSSION

Lateral lymph node dissection (LLND) was introduced in Japan in the 1970s and results in good survival and low local recurrence rates.[7–9] Since approximately 1984 several forms of nerve-sparing techniques, combined with LLND, have been developed. Bilateral and even unilateral complete autonomic nerve preservation (ANP) combined with LLND often maintains urinary function, but reports vary about the results in sexual function.[16–20] In the many decades of LLND surgery in Japan constant evaluation has taken place with the purpose of preventing overtreatment and minimizing morbidity.[21] Nowadays the policy in many Japanese hospitals is highly case-oriented, adapting the degree of surgical resection and ANP to the extent of cancer spread.[22] Whereas in the 1970s and 1980s in the National Cancer Center Hospital (NCCH) in Tokyo the standard procedure was to perform bilateral LLND in case of advanced rectal cancer, lately also unilateral LLND has been performed. The purpose of this study was to evaluate the treatment between 1993 and 2002 at the National Cancer Center Hospital for rectal carcinoma, at or below the peritoneal reflection, looking at the patterns of local recurrence and the risk factors for local recurrence. To our knowledge, there are no published results of unilateral lymph node dissection in rectal carcinoma.

The results of this study show 5-year local recurrence rate of 6.6% in rectal cancer at or below the peritoneal reflection by Japanese surgery. This primarily surgical approach compares favorably with results in Western countries, where neoadjuvant treatment is adopted as the standard in order to reduce local recurrence rates. Therefore, the Japanese concept of removing the lateral basins of lymph nodes spread can be considered successful. However, some questions still remain to be answered. The etiology of locally recurrent disease is not completely understood yet.

This study, although retrospective, provides further evidence of disease outside the TME envelope in higher-stage tumors. Bilateral LLND (5-year local recurrence rate 14%) resulted in better local control than unilateral LLND (5-year LR rate 33%) in N+ patients. Persistent disease in lateral lymph nodes that is left behind may account for some of the local recurrences, as would occur in standard TME surgery. However in that case, it would be expected that most of the recurrences would occur originating in this lateral basin. In this study we noted that only a part of the local recurrences was present in the lateral side walls. Most of the recurrences could not be explained by the anatomical position of the lateral lymph nodes. One can only speculate about other mechanisms of how tumor cells seed into the surgical resection volume. Maybe removal of the lateral lymph nodes also removes (microscopic) tumor cells which are in transit in the lateral lymph flow route, which could otherwise leak back into the surgical wound. This would explain why unilateral dissection is inferior to bilateral dissection, having more local recurrence in also the presacral, perineal, and anastomotic subsite, not only the lateral.

The rationale behind the unilateral LLND is that the contralateral autonomic nervous system stays untouched, decreasing the chance of autonomic nerve injury. Studies report that, after LLND with nerve-sparing surgery, urinary function is maintained. Between 50% and 100% of males are sexually active, however with compromised ejaculation.[16,18,19,23] This is ascribed to traction and injury to nerves during the mobilization and electrocautery required for LLND.[18] Unfortunately we have no data on urinary and sexual function of this cohort, being unable to report on the results after unilateral LLND with nerve preservation. Therefore, the question of whether functional results are truly better remains unanswered.

The tumors of the patients who had TME without LLND were smaller and less advanced compared with those of LLND patients. This better staging is reflected in better survival. That only one patient who had standard TME surgery had local relapse (5-year local recurrence 0.8%) is striking. The selection for low-risk disease by pre- and intraoperative evaluation has obviously been accurate. Interesting however, is that pathology (Tables 1 and 2) showed that about 30% of the patients operated by TME had T3-stage or N-positive disease. Pathology seems to filter out more metastatic lymph nodes than preoperative imaging, but these (micro)metastases obviously have no oncologic consequences. Jump metastases (mesorectal negative, lateral positive) occurred in only 3% of the LLND patients, thus when mesorectal lymph nodes are unsuspected, risk for lateral lymph node recurrence is very low.

Preoperative evaluation in advanced disease is difficult. In this study local recurrence developed on the contralateral side after unilateral lymph node dissection, while these contralateral lymph node metastases were not suspicious on preoperative CT imaging. Meta-analysis report that assessment of lymph node status by CT is unreliable for clinical decision making, because the radiologist can only look at lymph node size.[24,25] Since 2002 in the NCCH magnetic resonance imaging (MRI) has been used, which is reported to be superior to CT because it can rely on additional morphological criteria, such as signal intensity and border contour.[26–28] Furthermore, lymph-node-specific contrast agents or molecular imaging might play a role in detecting micrometastases in the near future.[29]

In the West, (chemo)radiation is used instead of LLND. There are no (randomized) studies comparing preoperative

(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.

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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.

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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

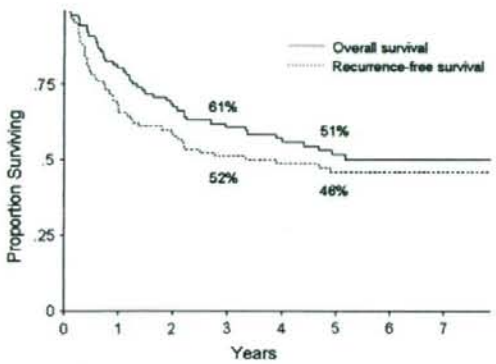

Fig 1. OS and RFS after PE in patients with clinical T4 rectal cancer. Estimated 3- and 5-year survival rates were 61% and 52%, respectively. Estimated 3- and 5-year RFS rates were 51% and 46%, respectively.

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

		N0 (n = *53*)	*Upper LN involvement* (n = *18*)	*Lateral LN involvement* (n = *22*)
	All (n = *93*)	*No. (%)*	*No. (%)*	*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.

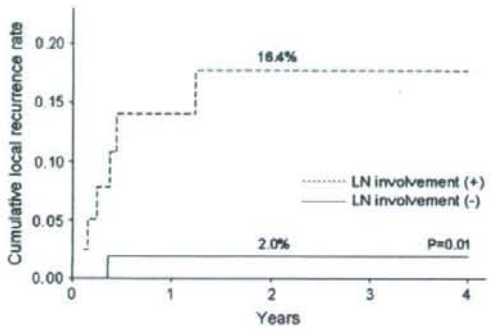

Fig 2. Cumulative local recurrence rate after PE in patients with clinical T4 rectal cancer stratified by LN involvement. Estimated 2-year local recurrence rate was 2.0% in patients without LN involvement (LN involvement [−]) and 16.4% in those with involvement (LN involvement [+]). The difference was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

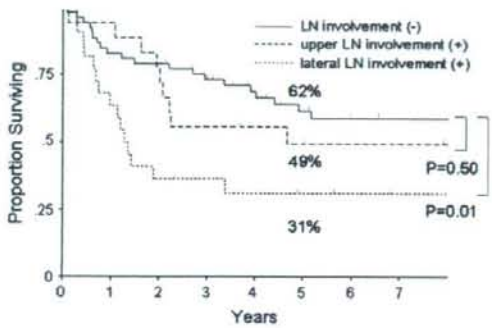

Fig 3. OS after PE in patients with clinical T4 rectal cancer stratified by the direction of LN involvement. Compared with patients without LN involvement (LN involvement [−]), those with lateral LN involvement (lateral LN involvement) had significantly decreased survival ($P = .01$), whereas those with 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

Variable	*OS*			*RFS*		
	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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Prevention of Postoperative Pancreatic Fistula After Total Gastrectomy

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Abstract
Background Pancreatic fistula (PF) is still one of the serious complications after total gastrectomy (TG). The purpose of this study was to identify risk factors for PF after TG and to evaluate our attempts to prevent PF.
Methods From August 1992 to July 2006, 740 consecutive patients with gastric neoplasm underwent TG at the National Cancer Center Hospital East. Univariate and multivariate analyses of potential risk factors for the development of PF and the effectiveness of operative procedures to prevent PF were performed.
Results Postoperative PF was identified in 130 patients (18%). On multivariate analysis, body mass index ($P < 0.001$) and the operative procedure (TG with pancreaticosplenectomy) ($P = 0.001$) were independent risk factors. In TG with splenectomy (pancreas-preserving method), total preservation of the splenic artery was significantly correlated with a lower incidence of PF ($P < 0.001$). In TG with pancreaticosplenectomy, the use of a linear stapling device was an effective surgical technique for closure of the cut end of the pancreas, but there was no significant difference from conventional methods. Recently, the incidence decreased significantly for TG overall and TG with splenectomy.
Conclusions PF after TG is more likely to occur in obese patients undergoing TG with pancreaticosplenectomy. When TG with splenectomy (pancreas-preserving method) is performed, the splenic artery should be totally preserved. If TG with pancreaticosplenectomy is performed, the use of a linear stapling device for closure of the cut end of the pancreas should be suggested. These improvements in surgical techniques are useful to prevent PF.

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Introduction

Although gastric surgery has been performed with lower morbidity and mortality rates in recent years [1], pancreatic fistula (PF) remains a serious complication after total gastrectomy (TG) [2]. In a Japanese major clinical trial (JCOG9501) that included 523 patients with advanced gastric cancer, PF was the most frequent complication after gastrectomy [3]. The incidence of PF after TG has been reported to range from 9–19% [2, 4, 5].

Once PF develops, it sometimes contributes to other major complications, such as bleeding, anastomotic leakage, and intra-abdominal abscess. In fact, PF was the factor most strongly linked with death in most series [6, 7]. Therefore, every effort should be made to avoid the catastrophe of PF. The purpose of this study was to identify risk factors for PF after TG and to evaluate the effectiveness of our attempts to prevent PF.

Patients and methods

From August 1992 to July 2006, 740 consecutive patients with gastric neoplasm underwent TG at the National Cancer Center Hospital East. Of these patients, 512 were men and 228 were women (age range, 24–92 (median, 64) years). Among these 740 patients, 728 had gastric cancer and 12 had malignant lymphoma. Data for these patients were analyzed to identify risk factors for PF, using a multivariate logistic regression model.

Operative procedures

At our institution, TG with splenectomy (so-called pancreas-preserving method [8]), Japanese-style D2 lymph node dissection, and reconstruction with Roux-en-Y esophagojejunostomy has been the standard surgical procedure for the treatment of advanced gastric cancer located in the upper third of the stomach. TG without splenectomy is performed for patients with early gastric cancer or far advanced gastric cancer that requires palliative resection. TG with pancreaticosplenectomy is performed for patients with direct invasion to the pancreas or evident macroscopic lymph node metastasis along the splenic artery.

Perioperative management

All patients received prophylactic antibiotics intraoperatively and for at least 1 day postoperatively. Prophylactic somatostatin analogues were not administrated to prevent PF. All drains were removed on postoperative day 7 or 8 when there was normal discharge. Preoperative total parenteral nutrition (TPN) was used only for patients who could not take a regular diet.

Pancreatic fistula

Postoperative PF was diagnosed when there was purulent discharge containing necrotic debris from the drainage tube for more than 7 days after operation. We included cases of intra-abdominal abscess that might have occurred from pancreatic juice leakage. On diagnosis, we referred to the amylase levels of drainage fluid measured on postoperative days 1, 3 or 4, and 7, but we had no diagnostic criterion for amylase concentration.

We usually treat PF by maintenance of the drains and intermittent irrigation. We need very little radiological guided drainage because we do not remove drains at an early postoperative day. If the patient's general condition is good, without signs of sepsis, oral food intake is continued and neither TPN nor enteral nutrition is adopted. Administration of somatostatin analogues is limited to the patient with large amount of pancreatic juice discharge. Thus, in our institution, the basic principle of treatment is adequate drainage.

Mortality

Mortality was defined as postoperative death due to any cause within 30 days, or death within the same hospital admission.

Statistical methods

Mann-Whitney U test and χ^2 test were used for univariate analyses. A multiple logistic regression model was used to determine the effect of all of the potential variables. Differences were considered significant at $P < 0.05$.

Results

Among 740 patients, TG without splenectomy was performed in 171 patients (23%), TG with splenectomy in 494 (67%), and TG with pancreaticosplenectomy in 75 (10%).

Postoperative complications were identified in 271 patients (37%) and PF in 130 patients (18%). Seven patients (1%) died as a result of serious postoperative complications (Table 1). Among these seven patients, three patients died as a result of PF and secondary hemorrhage, two as a result of acute renal failure, and two as a result of pneumonia.

Table 2 shows the results of 12 parameters subjected to univariate analysis as potential risk factors in the 130 patients with PF versus the 610 patients without PF. Three preoperative factors (sex, $P = 0.011$; body mass index (BMI), $P < 0.001$; diabetes, $P = 0.015$) and five perioperative factors (operative procedure, $P < 0.001$; operative time, $P < 0.001$; intraoperative bleeding, $P < 0.001$; curability, $P = 0.001$; lymph node dissection, $P < 0.001$) differed significantly between these two groups. There was no significant difference in pathological factors between these two groups.

Multivariate logistic regression analysis revealed that BMI ($P < 0.001$) and the operative procedure (TG with pancreaticosplenectomy; $P = 0.001$) were significant independent risk factors for PF (Table 3).

Figure 1 shows the sites of division of the splenic artery in the case of TG with splenectomy. The splenic artery was divided at the root in no patient (Group A), divided at the midpoint of the line between the root and the end in 98 patients (Group B), and totally preserved in 273 patients (Group C). Data were not available for 123 patients. There was a significant difference in the incidence of PF between group B and C ($P < 0.001$; Table 4).

Table 1 Operative morbidity and mortality (n = 740)

Morbidity	271 (37%)
Pancreatic fistula[a]	130 (18%)
Anastomotic leakage	42 (6%)
Wound abscess	26 (4%)
Pneumonia	20 (3%)
Paralytic ileus	20 (3%)
Cholecystitis	16 (2%)
Postoperative bleeding	10 (1%)
Anastomotic stenosis	10 (1%)
Mortality	7 (1%)

[a] Including intra-abdominal abscess

Table 2 Univariate analysis of risk factors influencing pancreatic fistula

	Pancreatic fistula		*P* value
	(+) (n = 130)	(−) (n = 610)	
Preoperative factors			
Sex			0.011
Male	102 (20%)	410 (80%)	
Female	28 (12%)	200 (88%)	
Age (yr)	64 (24–92)[a]	64 (27–88)[a]	0.521
Body mass index (kg/m^2)	22.7 (14.5–32.3)[a]	21.5 (14.3–32.4)[a]	<0.001
Diabetes			0.015
Yes	19 (28%)	48 (72%)	
No	111 (16%)	562 (84%)	
Neoadjuvant chemotherapy			0.474
Yes	9 (14%)	54 (86%)	
No	121 (18%)	556 (82%)	
Perioperative factors			
Operative procedure			<0.001
TG without splenectomy	9 (5%)	162 (95%)	
TG with splenectomy	85 (17%)	409 (83%)	
TG with pancreaticosplenectomy	36 (48%)	39 (52%)	
Operative time (min)	285 (154–678)[a]	245 (95–596)[a]	<0.001
Intraoperative bleeding (ml)	841 (213–4,750)[a]	598 (45–14,410)[a]	<0.001
Curability			0.001
Curative operation	124 (19%)	516 (81%)	
Palliative operation	6 (6%)	94 (94%)	
Lymph node dissection			<0.001
D0,1	11 (6%)	174 (94%)	
D2,3	119 (21%)	436 (79%)	
Pathological factors			
Primary tumor[b]			0.285
pT1	17 (14%)	103 (86%)	
pT2,3,4	113 (18%)	507 (82%)	
Regional lymph nodes[b]			0.968
pN0	46 (18%)	214 (82%)	
pN1,2,3	84 (18%)	396 (82%)	

TG—total gastrectomy

[a] Median value, with range in parentheses

[b] Japanese classification of gastric carcinoma

Figure 2 shows the surgical techniques for transection and closure of the cut end of the pancreas in the case of TG with pancreaticosplenectomy. The cut end of the pancreas was transected and closed by conventional methods in 50 patients (Group D) and using a linear stapling device in 12 patients (Group E). Data were not available for 13 patients. The incidence of PF in group E was lower than that in group D, but the difference was not significant (Table 4).

The incidence of PF is presented in Table 5. Recently, the incidence of PF decreased significantly for TG as a whole and TG with splenectomy. The ratio of cases with new operative procedures is presented in Table 6. We have adopted new operative procedures more frequently in second half period.

The postoperative outcomes of the patients with and without PF were compared (Table 7). The patients with PF had a longer postoperative hospital stay ($P < 0.001$) and higher postoperative mortality rate ($P = 0.001$).

Discussion

Until recently, there had been no universally acknowledged definition of PF. The incidence of PF after TG has been reported to range from 9–19% according to the different definitions applied [2, 4, 5]. Because these different definitions could lead to misleading discrepancies on the basis of only differences in terminology, a unifying definition of PF was necessary for us to compare the different surgical

Table 3 Multivariate analysis of risk factors influencing pancreatic fistula

	P value	Odds ratio	95% confidence interval
Sex : Male	0.118	1.475	0.906–2.402
Body mass index (continuous)	<0.001	1.142	1.063–1.227
Diabetes	0.06	1.836	0.974–3.459
Operative procedure			
TG with splenectomy	0.288	2.07	0.541–7.929
TG with pancreaticosplenectomy	0.001	10.06	2.506–40.381
Operative time (continuous)	0.163	1.002	0.999–1.005
Intraoperative bleeding	0.381	1	1–1
Curability: curative operation	0.355	1.564	0.248–1.65
Lymph node dissection: D2,3	0.585	1.43	0.396–5.169

TG—total gastrectomy

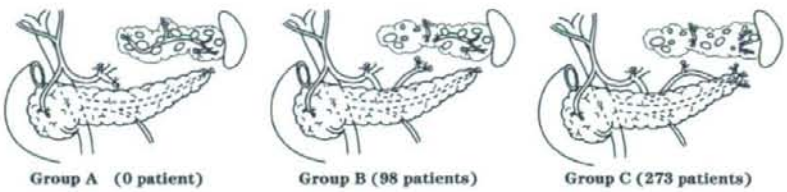

Fig. 1 Sites of division of splenic artery in cases of splenectomy. Group A (0 patient): the splenic artery was divided at the root. Group B (98 patients): the splenic artery was divided at the midpoint of the line between the root and the end. Group C (273 patients): the splenic artery was totally preserved

Table 4 Effectiveness of preservation of splenic artery and use of linear stapling device

	Pancreatic fistula		*P* value
	(+)	(−)	
TG with splenectomy[a]			<0.001
Group A ($n = 0$)	–	–	
Group B ($n = 98$)	36 (37%)	62 (63%)	
Group C ($n = 273$)	32 (12%)	241 (88%)	
TG with pancreaticosplenectomy[b]			0.124
Group D ($n = 50$)	29 (58%)	21 (42%)	
Group E ($n = 12$)	4 (33%)	8 (67%)	

TG—total gastrectomy

[a] Data were not available for 123 patients

[b] Data were not available for 13 patients

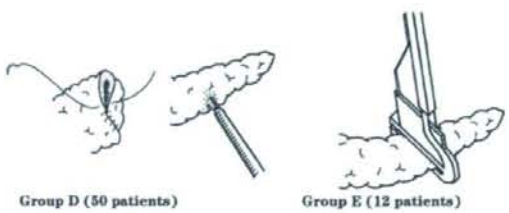

Fig. 2 Surgical techniques for transection and closure of cut end of pancreas in cases of pancreaticosplenectomy. Group D (50 patients): closure by conventional methods; the pancreas was transected with a knife and sutured, or transected with an ultrasonically activated scalpel. Group E (12 patients): closure using a stapling device; the pancreas was transected with a linear stapling device

experiences accurately. In July 2005, the International Study Group on Pancreatic Fistula (ISGPF) developed and published a universal definition and clinical grading for postoperative PF, as follows: an all-inclusive definition of PF is a drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content >3 times the serum amylase activity [9]. At our institution, we have made a diagnosis of PF mainly by the appearance of drainage fluid. In this study, the incidence of PF in patients in which TG without splenectomy, TG with splenectomy, and TG with pancreaticosplenectomy were performed was 5%, 17%, and 48%, respectively. The incidence must be lower if the ISGPF definition is used. However, the purpose of this study was to evaluate the operative procedures and the surgical techniques to reduce postoperative complications associated with the pancreas. Therefore, we included intra-abdominal abscess that might have resulted from pancreatic juice leakage as PF. Katai et al. [4] used the term "pancreas-related abscess" for the condition that was similar to ours.

Table 5 Incidence of pancreatic fistula

	No. of patients (%) with PF			*P* value
	First half (during 1992–1999)	Second half (during 2000–2006)	Total	
Overall	79/359 (22)	51/381 (13)	130/740 (18)	0.002
TG without splenectomy	2/ 62 (3)	7/109 (6)	9/171 (5)	0.368
TG with splenectomy	54/252 (21)	31/242 (13)	85/494 (17)	0.011
TG with pancreaticosplenectomy	23/ 45 (51)	13/ 30 (43)	36/75 (48)	0.509

PF—pancreatic fistula, TG—total gastrectomy

Table 6 Ratio of cases with new operative procedures

	No. of patients (%) with new operative procedures		*P* value
	First half (during 1992–1999)	Second half (during 2000–2006)	
Splenic artery preservation (Group C) in the case of TG with splenectomy	107/169[a] (63)	166/202[b] (82)	<0.001
Transection with a stapling device (Group E) in the case of TG with pancreaticosplenectomy	0/34[c] (0)	12/28[d] (43)	<0.001

TG—total gastrectomy

[a] Data were not available for 83 patients

[b] Data were not available for 40 patients

[c] Data were not available for 11 patients

[d] Data were not available for 2 patients

Table 7 Relationship of postoperative outcomes to pancreatic fistula

	Pancreatic fistula		*P* value
	(+) ($n = 130$)	(−) ($n = 610$)	
Postoperative hospital stay (days)	43 (21–114)[a]	20 (11–173)[a]	<0.001
Mortality	5 (4%)	2 (0.3%)	0.001

[a] Median value, with range in parentheses

A previous report confirmed that risk factors for PF after TG were age, BMI, and dissection of lymph nodes along the distal splenic artery [4]. Especially, being overweight increases the risk of surgical complications in patients undergoing gastrectomy [10]. Our study also showed that obesity and pancreatic transection were correlated with the risk of PF.

Maruyama et al. [8] reported that when performing splenectomy, the splenic artery should be divided at the root for complete removal of lymph nodes along this artery. At our institution, we formerly ligated and divided the splenic artery at the midpoint of the line between the root and the end. To preserve the blood supply to the pancreatic tail and to prevent PF, we have totally preserved the splenic artery in recent years. Maruyama et al. demonstrated that the preserved pancreas received a good blood supply through the dorsal pancreatic artery and the transverse pancreatic artery, even after removal of the splenic artery; however, we think that blood supply is insufficient with the Maruyama method, and the great pancreatic artery and caudal pancreatic artery should be preserved, too. With advanced surgical skill, we can perform complete lymph node dissection along the upper border of the pancreas, even preserving the splenic artery. We demonstrated that preserving the splenic artery was effective in preventing PF after splenectomy in this study.

When performing pancreaticosplenectomy, we formerly used a knife or ultrasonically activated scalpel (Harmonic Scalpel; Johnson & Johnson Medical, Ethicon, Tokyo, Japan) for transection of the cut end of the pancreas. In an attempt to reduce the incidence of PF, we have used a linear stapling device in recent years. Our study suggested that closure of the cut end of the pancreas with a stapler may have reduced the incidence of PF, whereas a previous study suggested that it was associated with a significantly higher PF rate [11]. It is important that the indications for use of a linear stapling device might be limited to soft and thin pancreatic parenchyma. A randomized, controlled trial to determine the best closure technique is now being planned [12], and we are awaiting the results.

Conclusions

PF after TG is more likely to occur in obese patients undergoing TG with pancreaticosplenectomy. When splenectomy is performed, the splenic artery should be totally preserved. When pancreaticosplenectomy is performed, the use of a linear stapling device for closure of the cut end of the pancreas is suggested. It has been shown that these improvements in surgical techniques for TG are useful to prevent PF.

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Low Serum Level of Cholinesterase at Recurrence of Pancreatic Cancer Is a Poor Prognostic Factor and Relates to Systemic Disorder and Nerve Plexus Invasion

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Objectives: Systemic disorder is a characteristic of advanced pancreatic cancer. Clinical prognostic factors in earlier disease state than terminal stage are expected to be sensitive markers for the foresight of systemic disorder. This study aimed to find the associations between these sensitive markers and morphological factors of primary tumor that may indicate finding a way of pathogenesis of systemic disorder.

Methods: The current study examined 75 patients who received macroscopic curative resection for pancreatic cancer in our institution as follows: (1) identification of clinical prognostic factors at initial recurrence after resection of primary tumor and (2) analysis of correlations between clinical prognostic factors and histological findings in primary tumor.

Results: Important prognostic factors were peritoneal dissemination and serum levels of carbohydrate antigen 19-9 and cholinesterase. Only low levels of serum cholinesterase correlated to nerve plexus invasion in histological findings of primary tumor. Patients with low cholinesterase levels show systemic disorder, including poor performance status, anemia, and hypoalbuminemia.

Conclusions: Nerve invasion may thus result in low functional state of the liver followed by systemic disorder. This mechanism may be useful for elucidating cancer cachexia in future studies.

Key Words: pancreatic cancer, cholinesterase, nerve plexus invasion, nerve invasion, systemic disorder, cachexia

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Systemic disorder is a characteristic of patients with invasive ductal carcinoma (IDC) of the pancreas[1] and includes anemia, worsened performance status, hypoalbuminemia, and weight loss,[1–3] all of which represent prognostic factors for end-stage cancer patients.[2–4] Predictive recognition of systemic disorder may be useful for judgement of suitable treatment and prevention of rapid general deterioration. This foresight for patients' conditions needs sensitive clinical markers for systemic disorder, and these markers are expected to be prognostic factors in earlier disease state than terminal stage. On analysis of clinical data, choosing clinical points to extract clinical data is important. Preoperative clinical condition of patients with IDC of the pancreatic head is affected by obstruction of the bile and pancreatic ducts.[5,6] Conversely, patients who undergo pancreatectomy for IDC of the pancreatic head are released from those obstructions by the reconstruction. After surgery for pancreatic IDC, recurrence is a common event that most patients experience.[7] Initial recurrence is thus considered a suitable point to investigate clinical data. Patients after surgery give us resected specimen as histological information of tumor. Many studies report morphological findings of pancreatic IDC as predictive of prognosis. Some histological factors in pancreatic IDCs may relate to systemic disorder. Sensitive histological factor for systemic disorder may be important tumoral information for choice of appropriate treatment and elucidation of pathogenesis. On the basis of the above context, the present study was planned to identify important clinical factors for predicting prognosis at initial recurrence and correlations to histological factors in patients with pancreatic IDC.

MATERIALS AND METHODS

Patients

This study reviewed 73 consecutive patients (32 women, 41 men) who displayed recurrent pancreatic IDC after macroscopic curative resection at National Cancer Center Hospital East. Inclusion criteria were as follows: (1) macroscopic curative resection for IDC of the pancreas performed between September 1992 and January 2004 in our institution; (2) pathologically confirmed pancreatic IDC from a resected specimen by 2 authors (S.M. and T.H.); (3) sufficient follow-up at our institution, comprising computed tomography (CT), complete blood cell counts, serum biochemistries, and physical examinations at intervals of at least once every 3 to 6 months after resection; and (4) clear recognition of date of initial recurrence on the basis of CT or cytology, enabling review. Median patient age at diagnosis of initial recurrence was 62 years (range, 25–81 years). None of the patients received neoadjuvant or adjuvant therapy. Pancreaticoduodenectomy (PD) had been performed for 55 patients, and distal pancreatectomy (DP) had been performed for 18 patients. Regional lymph node dissection had been performed in all

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