Table 3 Univariate and multivariate Cox regression analysis for tumor recurrence in all patients

		Univariate	Multivariate		
		P value	Hazards ratio	95% CI	*P* value
Age		0.159			
	≤70 years				
	>70 years				
Gender		0.764			
	Male				
	Female				
Papillary type		0.706			
	Yes				
	No				
Tumor stalk		0.011			
	Yes				
	No				
Multiplicity		<0.001			<0.001
	No		1		
	Yes		1.69	1.50–1.92	
Size		<0.001			<0.001
	≤3 cm		1		
	>3 cm		1.52	1.28–1.80	
Pathological T category		<0.001			<0.001
	Ta		1		
	T1		1.32	1.17–1.50	
Grade		<0.001			
	G1/2		1		0.002
	G3		1.28	1.10–1.50	
Intravesical instillation		<0.001			<0.001
	no Tx		1		
	chemoTx		0.65	0.57–0.74	<0.001
	BCG		0.41	0.33–0.51	<0.001

BCG, Bacillus Calmette-Guérin.

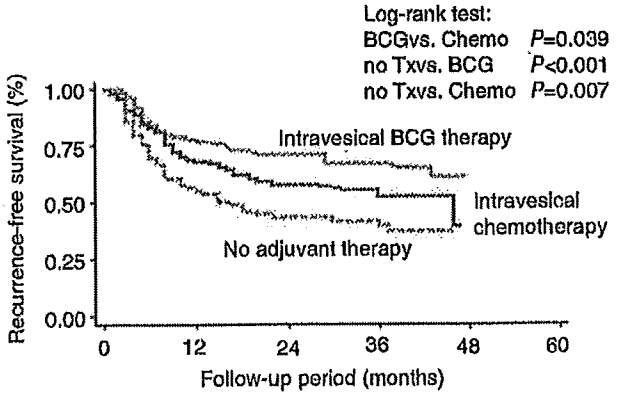

Fig. 2 Kaplan–Meier curve for tumor recurrence in patients with T1G3 ($n = 481$) comparing no instillation ($n = 163$), Bacillus Calmette-Guérin (BCG) instillation ($n = 154$), and intravesical chemotherapy ($n = 164$).

Tumor recurrence in patients treated with intravesical chemotherapy and BCG instillation

We next evaluated the prognostic indicators for tumor recurrence, particularly in patients treated with intravesical chemotherapy, which accounted for 76.8% of the intravesical adjuvant therapy. Intravesical chemotherapy consisted of adriamycin (doxorubicin) in 41, epirubicin in 468, pirarubicin in 680, mitomycin C (MMC) in 120, peplomycin in seven, and tiotepa in one. Overall, an anthracycline chemo-agent was used in 90.5% of the cases of intravesical chemotherapy. When patients treated with an anthracycline chemo-agent were compared with those receiving MMC treatment, Kaplan–Meier curve analysis revealed that the differences among the groups were not significant (Fig. 3).

Kaplan–Meier analysis (Table 5) and univariate Cox proportional hazards regression analysis (Table 6) revealed gender, presence or absence of tumor stalk, tumor multiplicity, tumor size, pathological stage, and tumor grade were significant predictors for tumor recurrence. In multivariate analysis, male gender, multiple bladder tumors, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Female patients had a recurrence risk 0.7 times lower than male patients. Recurrence risk was 1.7 times higher for multiple tumors, and 1.3 times higher for tumors greater than 3 cm compared with those equal to or smaller than 3 cm. Patients with T1 tumor had a recurrence risk 1.3 times higher than those with Ta.

In patients treated with BCG instillation, no clinicopathological factors were associated with tumor recurrence in uni- and multivariate analysis (data not shown).

Table 4 Clinicopathological characteristics in patients treated with intravesical chemotherapy (IVI), Bacillus Calmette-Guerin (BCG) instillation, and no adjuvant therapy

Patients	IVI chemotherapy No. patients (%)	BCG instillation No. patients (%)	No IVI treatment No. patients (%)	P-value
	1314	396	1527	
Age				0.853
<=70	671 (51.1)	199 (50.3)	790 (51.7)	
>70 years	643 (48.9)	197 (49.8)	737 (48.3)	
Gender				0.257
Male	1038 (79.0)	323 (81.6)	1239 (81.1)	
Female	276 (21.0)	73 (18.4)	288 (18.9)	
Papillary type				<0.001
Yes	1224 (93.2)	325 (82.1)	1389 (91.0)	
No	69 (5.3)	57 (14.4)	86 (5.6)	
Unknown	21 (1.6)	14 (3.5)	52 (3.4)	
Tumor stalk				<0.001
Yes	925 (70.4)	225 (56.8)	1101 (72.1)	
No	316 (24.1)	143 (36.1)	326 (21.4)	
Unknown	73 (5.6)	28 (7.1)	100 (6.55)	
Multiplicity				<0.001
Yes	588 (44.8)	242 (61.1)	482 (31.6)	
No	690 (52.5)	132 (33.3)	988 (64.7)	
Undetected	14 (1.1)	10 (2.5)	9 (0.6)	
Unknown	22 (1.7)	12 (3.0)	48 (3.1)	
Tumor size				<0.001
<1 cm	369 (28.1)	101 (25.5)	543 (35.6)	
1–3 cm	716 (54.5)	197 (50.0)	768 (50.3)	
>3 cm	180 (13.7)	68 (17.2)	126 (8.25)	
Uncountable	15 (1.1)	13 (3.3)	17 (1.1)	
unknown	34 (2.6)	17 (4.3)	73 (4.8)	
Pathological T category				<0.001
pTa	672 (51.1)	120 (30.3)	859 (56.3)	
pT1	642 (48.9)	276 (69.7)	668 (43.8)	
Grade				<0.001
G1	287 (21.8)	37 (9.3)	458 (30.0)	
G2	817 (62.2)	178 (45.0)	855 (56.0)	
G3	210 (16.0)	181 (45.7)	214 (14.0)	

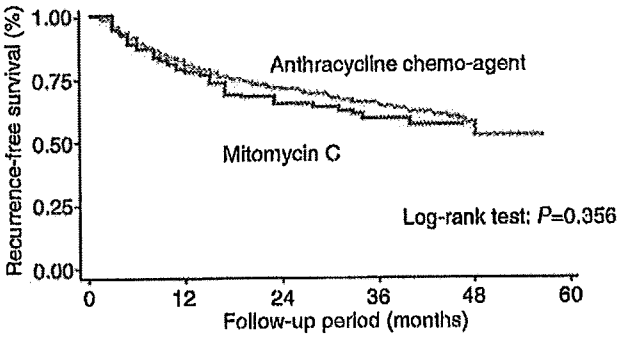

Fig. 3 Kaplan–Meier curve for tumor recurrence in patients treated with adjuvant intravesical chemotherapy comparing an anthracycline chemo-agent and mitomycin C treatment.

Discussion

In the present study, we characterized the clinical outcome of newly diagnosed non-muscle invasive bladder cancer in a large contemporary series of patients from a Japanese bladder cancer registry and determined the predictors for tumor recurrence. Overall, bladder tumor multiplicity, a tumor size greater than 3 cm, pathological stage T1, tumor grade G3, and the absence of adjuvant intravesical instillation were found to independently increase the risk of tumor recurrence. Numerous publications have reported the same prognostic indicators as ours for tumor recurrence in non-muscle invasive bladder cancer.[1–3] Recently, a combined analysis was carried out using data from 2596 non-muscle invasive bladder cancer patients collected from seven European Organization for Research and Treatment of Cancer (EORTC) trials.[4] In the analysis, six clinicopathological risk factors, namely multiplicity, tumor size, prior recurrence rate, pathological stage, concomitant CIS, and tumor grade were determined. Four of the six predictors for tumor recurrence in the present study were shared with their indicators; however, the big difference between their study

Table 5 The 1-year and 3-year recurrence-free survival rates according to clinicopathological characteristics in patients treated with intravesical chemotherapy

		1-Year (mean ± SE)	3-Year (mean ± SE)	*P* value
Age				0.695
	≤70 years	79.2 ± 0.02	64.7 ± 0.02	
	>70 years	81.6 ± 0.02	63.4 ± 0.02	
Gender				0.025
	Male	79.2 ± 0.01	62.7 ± 0.02	
	Female	84.6 ± 0.02	69.7 ± 0.03	
Papillary type				0.209
	Yes	80.7 ± 0.01	64.7 ± 0.02	
	No	74.5 ± 0.05	57.6 ± 0.06	
Tumor stalk				0.016
	Yes	82.0 ± 0.01	68.4 ± 0.02	
	No	76.2 ± 0.02	58.9 ± 0.03	
Multiplicity				<0.001
	No	85.6 ± 0.01	69.6 ± 0.02	
	Yes	73.8 ± 0.02	57.5 ± 0.02	
Size				0.004
	≤3 cm	81.8 ± 0.01	65.6 ± 0.02	
	>3 cm	70.7 ± 0.04	55.8 ± 0.04	
Pathological T category				0.002
	pTa	84.0 ± 0.02	68.1 ± 0.02	
	pT1	76.4 ± 0.02	60.1 ± 0.02	
Grade				0.001
	G1/2	82.1 ± 0.01	66.1 ± 0.02	
	G3	71.1 ± 0.03	54.5 ± 0.04	

and ours is that their population has included both primary and recurrent cases. A more homogenous population of patients who initially diagnosed non-muscle invasive bladder tumor was evaluated in our current study.

Overall, 12.2% received BCG instillation in our study. In the subgroup of patients treated with BCG instillation, no clinicopathological factors were associated with tumor recurrence. Kaplan–Meier analysis demonstrated that the recurrence-free survival in the BCG instillation group was significantly higher than that in the intravesical chemotherapy group especially in pT1G3 patients ($P = 0.039$), which was confirmed by others.[11] Furthermore, BCG instillation was significantly selected in patients with multiple, larger, and higher pathological stage tumors, compared with intravesical chemotherapy. These results suggested that BCG instillation was carried out for the prevention of recurrence in a relatively smaller percentage of high risk patients than would have been expected from the current clinical situation.[12,13] One reason for the difference in the percentage of BCG instillations carried out between 1999–2001 and the present is that the current clinical management for non-muscle invasive bladder cancer is highly affected by the guidelines.[14,15]

In our subgroup consisting of the 1314 patients treated with adjuvant intravesical chemotherapy, multivariate analyses demonstrated that male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Only about 10% of the patients were treated with MMC intravesical chemotherapy. Au *et al.* reported that intravesical chemotherapy using a modified 40 mg dose of MMC accompanied by a decrease in urine volume during the procedure and urine alkalinization significantly improved the therapeutic benefit of traditional MMC treatment for the prevention of tumor recurrence.[16] Meanwhile, Huncharek *et al.* have showed that maintenance intravesical chemotherapy reduced tumor recurrence, when compared with a single course of induction chemotherapy.[17] Further study is warranted to prove the therapeutic benefit with these modalities, especially in Japanese patients who have these risk factors for recurrence. In our multivariate analyses, gender is an independent predictor for tumor recurrence in patients treated with adjuvant intravesical chemotherapy but not in overall patients. There has been no study to evaluate the influence of gender for tumor recurrence in a large series of bladder cancer patients treated with intravesical chemotherapy. The exact reason why female patients have better outcome for tumor recurrence than male patients has to be elucidated in a future study.

Frydenberg *et al.* conducted a survey of a population cancer registry that included about 700 newly diagnosed non-muscle invasive bladder cancers between 1990 and 1995 in Victoria of Australia. Logistic regression analysis revealed that tumor grade and pathological T stage were independent factors affecting the risk of recurrence. Less than 10% of the patients received adjuvant intravesical chemotherapy or immunotherapy.[18] Gårdmark *et al.* analyzed the clinical characteristics of about 10 000 newly diagnosed cases of bladder cancer obtained from the Swedish National Bladder Cancer Register between 1997 and 2001.[19] A large number of the patients, even in the high risk group, were still undertreated and they concluded that the survival rate of bladder cancer in Sweden during this period seemed to remain at the levels previously reported for the 1980s. The accumulation of data provided by a large cancer registry is of great importance to understanding the

Table 6 Univariate and multivariate Cox regression analysis for tumor recurrence in patients treated with intravesical chemotherapy

		Univariate	Multivariate		
		P value	Hazard ratio	95% CI	*P* value
Age		0.660			
	≤70 years				
	>70 years				
Gender		0.030			0.008
	Male		1		
	Female		0.71	0.55–0.91	
Papillary type		0.706			
	Yes				
	No				
Tumor stalk		0.023			
	Yes				
	No				
Multiplicity		<0.001			<0.001
	No		1		
	Yes		1.67	1.37–2.03	
Size		0.005			0.028
	≤3 cm		1		
	>3 cm		1.34	1.03–1.73	
Pathological T category		0.009			0.004
	Ta		1		
	T1		1.33	1.09–1.62	
Grade		0.002			
	G1/2				
	G3				

CI, confidence interval.

trends in the clinical characteristics of the disease and its treatment management, and to providing an opportunity for analysis of the indicators predicting prognosis.[20]

The present study has several limitations. First, the results were obtained from a dataset created by data only from centers participating in the bladder cancer registry. Since all of the centers in Japan do not participate in the cancer registry, the dataset does not include data for all bladder cancers in Japan. However, approximately 180 institutions participate in the cancer registry in Japan and the dataset contained data for approximately 6000 patients so we believe that the results represent an accurate reflection of the characteristics of patients with newly diagnosed bladder cancer and its clinical outcome in the period from 1999 and 2001.[21] Another limitation is that the follow-up period was short. Median follow-up was 24 months and this bias might affect the understanding of true risk factors and the natural course of non-muscle invasive bladder cancer and make us unable to analyze the prediction of tumor progression and survival. In fact recurrence-free survival in our study was somewhat better than that reported in another large series.[3] Several papers pointed out the importance of the use of data from long-term follow-up of non-muscle invasive bladder cancer.[22,23] Further study would be warranted to accumulate long-term follow-up data in the bladder cancer registry.

In conclusion, patients with multiple tumors, a tumor size greater than 3 cm, tumor grade G3, or pathological T1 tumors were at greater risk, whereas those treated with intravesical BCG instillations had a decreased risk of tumor recurrence in the overall patient population. In patients treated with intravesical chemotherapy, male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Further study of datasets created from longer follow-up data is warranted in order to analyze tumor progression and disease survival.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Patterns of Local Recurrence in Rectal Cancer: A Single-Center Experience

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ABSTRACT A cohort of patients operated at the National Cancer Center Hospital in Tokyo for rectal carcinoma, at or below the peritoneal reflection, was reviewed retrospectively. The purpose was to study the risk factors for local relapse and the patterns of local recurrence. Three hundred fifty-one patients operated between 1993 and 2002 for rectal carcinoma, at or below the peritoneal reflection, were analyzed. One hundred forty-five patients, with preoperatively staged T1 or T2 tumors without suspected lymph nodes, underwent total mesorectal excision (TME). Lateral lymph node dissection (LLND) was performed in suspected T3 or T4 disease, or when positive lymph nodes were seen; 73 patients received unilateral LLND and 133 patients received bilateral LLND. Of the 351 patients 6.6% developed local recurrence after 5 years. TME only resulted in 0.8% 5-year local recurrence. In lymph-node-positive patients, 33% of the unilateral LLND group had local relapse, significantly more ($p = 0.04$) than in the bilateral LLND group with 14% local recurrence. Local recurrence in the lateral, presacral, perineal, and anastomotic subsites was lower in the bilateral LLND group as compared with in the unilateral LLND group. We conclude that, in selected patients, surgery without LLND has a very low local recurrence rate. Bilateral LLND is more effective in reducing the chance of local recurrence than unilateral LLND. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

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For rectal cancer, surgery is the principal treatment in order to cure. Total mesorectal excision (TME) removes the primary tumor with its surrounding mesorectum as an intact package, preventing residual tumor cells in the mesorectum from developing into local recurrence.[1,2] In advanced lesions neoadjuvant (chemo)radiotherapy can downstage tumors, but good surgical quality is still essential in order to achieve total clearance of tumor cells.[3]

The Japanese concept of surgical treatment of rectal cancer has evolved from anatomical studies in which three lymphatic flow routes were identified.[4,5] The upper route is along the superior rectal artery to the inferior mesenteric artery; the lateral route reaches from the middle rectal artery to the internal iliac and obturator basins; and the downward route extends to the inguinal lymph nodes. The upper and lateral routes were shown to be the main two routes of rectal cancer spread, with the peritoneal reflection as the limitation between the two lymphatic areas.[6] Consequently, lateral lymph node dissection (LLND) was developed in Japan in order to resect the tumor with the primary locoregional lymph node basins beyond the mesorectal plane.[7] LLND has resulted in better survival and lower recurrence rates than conventional surgery.[8,9]

A problem is that the lateral lymph node routes are anatomically close to the pelvic autonomic nerve plexus, requiring challenging surgery to preserve these during LLND.[10] In order to prevent damage to autonomic nerves, nowadays case-oriented policy is practised in Japan, adopting LLND only in advanced disease at or below the peritoneal reflection.

The aim of this study is to evaluate the treatment of rectal cancer between 1993 and 2002 at the National Cancer Center Hospital (NCCH), looking at patterns of local recurrence and the risk factors for local recurrence.

PATIENTS AND METHODS

Patients

From 1993 to 2002, 923 patients were operated for confirmed primary adenocarcinoma of the rectum at the National Cancer Center Hospital (NCCH) in Tokyo. Surgery was performed according to the guidelines of the Japanese Research Society for Cancer of the Colon and Rectum.[11,12] The rectum was defined as located below the lower border of the second sacral vertebra. 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.[13]

For this analysis the following patients were excluded: metastasis at the time of surgery ($n = 134$) and in situ carcinoma ($n = 22$). Of the remaining 767 patients, only patients with rectal carcinoma at or below the peritoneal refection were selected, resulting in 360 patients.

Neoadjuvant chemotherapy was given to some patients with suspicion of stage T4 disease ($n = 3$) in other hospitals, before referral to the NCCH. Neoadjuvant radiotherapy was not routinely given, so no patients received preoperative radiotherapy. Sometimes in the case of positive lymph nodes, adjuvant radiotherapy ($n = 5$) or chemoradiotherapy ($n = 1$) was given. The nine patients who received neoadjuvant chemotherapy and adjuvant (chemo)radiation were excluded, leaving 351 patients for analysis.

Methods

Until 2002 preoperative evaluation at the NCCH consisted of computed tomography (CT) imaging and endoscopic ultrasonography for all patients. Based on preoperative imaging and intraoperative findings, standard total mesorectal excision (TME) was performed in T1 or T2 stage disease without suspected lymph nodes. Lateral lymph node dissection (LLND) was added to TME in stage T3 or T4 rectal cancer at or below the peritoneal reflection, or when positive mesorectal lymph nodes were suspected. Unilateral LLND was performed when the tumor was located lateral in the low rectum, bilateral LLND when the tumor was located centrally. When the lateral lymph nodes were 1 cm or larger on preoperative imaging or intraoperative findings, bilateral extended lymph node dissection was performed, consisting of dissection of the complete internal iliac artery and the autonomic nerve system. When there was no suspicion on positive lateral lymph nodes, autonomic nerve preservation (ANP) was carried out.

Accurate documentation of lymph node status and localization is obtained because all lymph nodes are harvested and recorded from the fresh specimen. The definition of mesorectal lymph nodes is pararectal location or in the direction of the mesentery. Lateral lymph nodes are located along the iliac or obturator arteries.

Follow-up of all patients consisted of thorax, abdominal, and pelvic CT imaging every 6 months. Median follow-up of patients alive was 7.9 years.

All patients who developed local recurrence, defined as any recurrence of rectal cancer in the lesser pelvis, were identified. Local recurrence was diagnosed clinically, radiologically or histologically.

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.G.H.B.-T.) reviewed the images. 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.[14] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In one patient insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using the SPSS package (SPSS 12.0 for Windows; SPSS Inc., Chicago, IL) and R version 2.5.1. *T*-tests and chi-square tests were used to compare individual variables. Survival and cumulative recurrence incidences were estimated using the Kaplan–Meier method. Differences between the groups were assessed using the log-rank test. All *p*-values were two-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[15] 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. Multivariate analyses of local recurrence and overall survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects (p-value < 0.10) were then selected for multivariate Cox regression. The following variables were studied for local recurrence and overall survival: age, sex, operative procedure, degree of lateral lymphadenectomy, T-stage, mesorectal lymph node N-stage, lateral lymph node positivity, maximum tumor diameter, differentiation, and autonomic nerve preservation.

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.

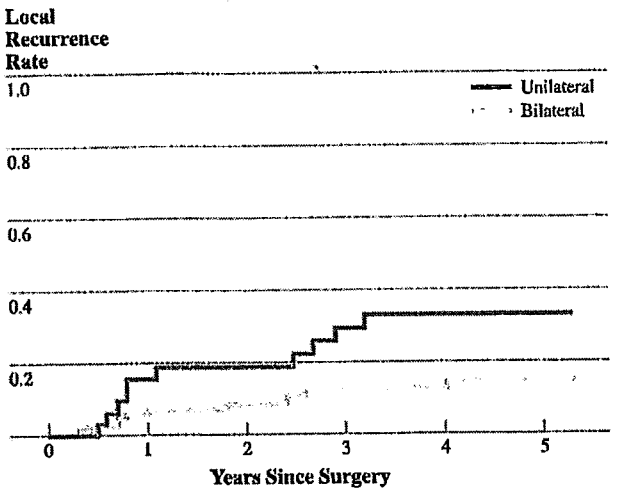

FIG. 1 Local recurrence in N+ patients

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	

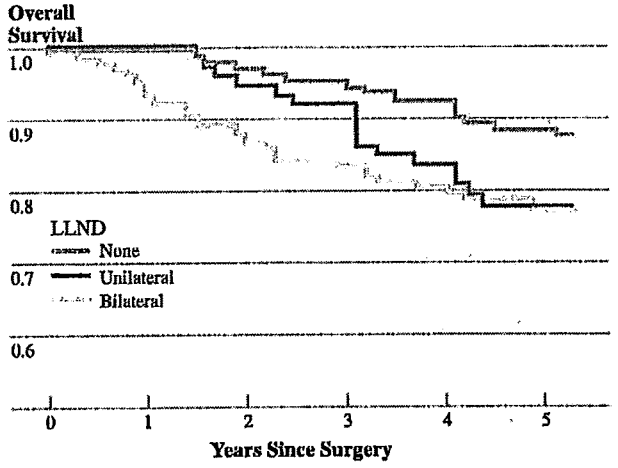

FIG. 2 Overall survival in all patients

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 lympho-vascular 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

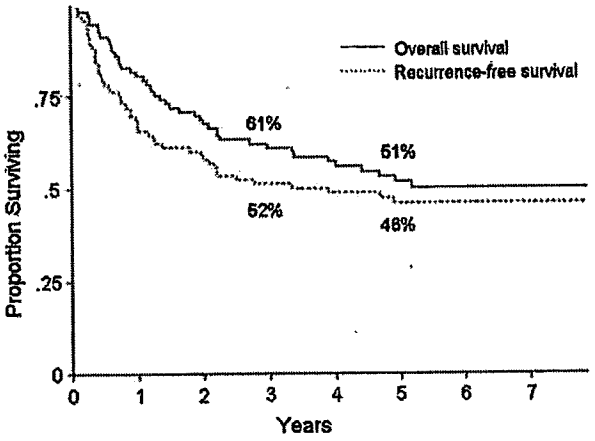

Fig 1. OS and RFS after PE in patients with clinical T4 rectal cancer. Estimated 3- and 5-year survival rates were 61% and 52%, respectively. Estimated 3- and 5-year RFS rates were 51% and 46%, respectively.

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

	All (n = 93)	*N0 (n = 53)*	*Upper LN involvement (n = 18)*	*Lateral LN involvement (n = 22)*
		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.

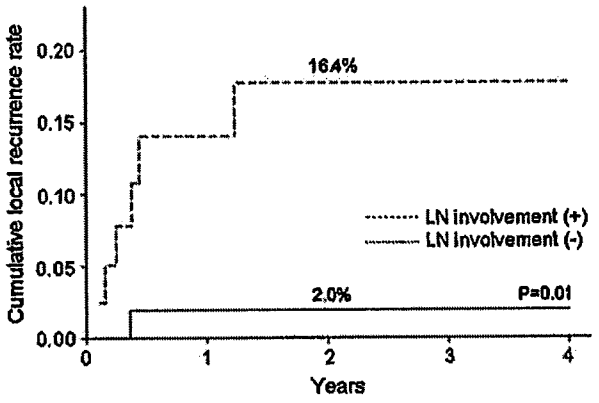

Fig 2. Cumulative local recurrence rate after PE in patients with clinical T4 rectal cancer stratified by LN involvement. Estimated 2-year local recurrence rate was 2.0% in patients without LN involvement (LN involvement [−]) and 16.4% in those with involvement (LN involvement [+]). The difference was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

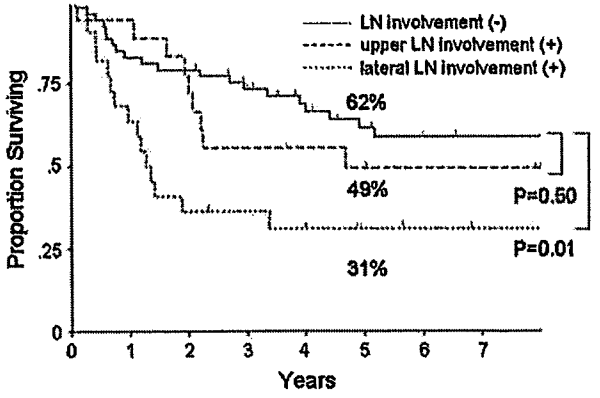

Fig 3. OS after PE in patients with clinical T4 rectal cancer stratified by the direction of LN involvement. Compared with patients without LN involvement (LN involvement [−]), those with lateral LN involvement (lateral LN involvement) had significantly decreased survival ($P = .01$), whereas those with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