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.

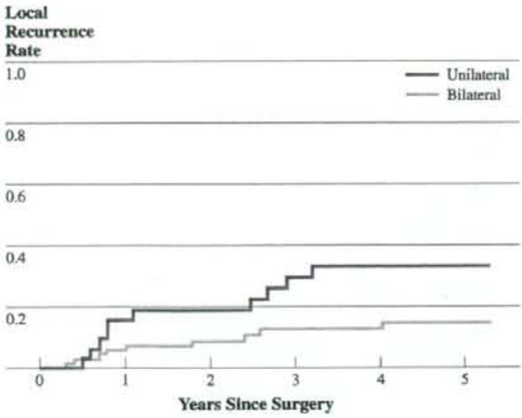

FIG. 1 Local recurrence in N+ patients

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	

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.

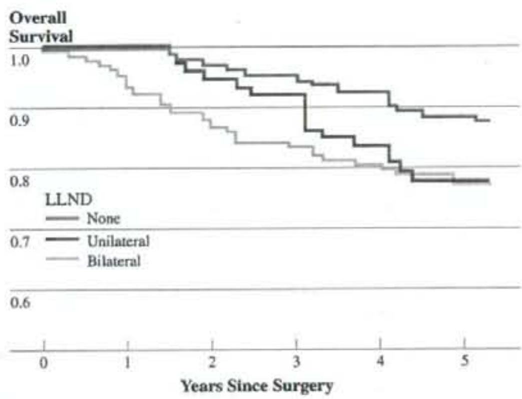

FIG. 2 Overall survival in all patients

TABLE 4 Sites of local recurrence

Site of local recurrence	All patients: Unilateral LLND ($n = 73$)	All patients: Bilateral LLND ($n = 133$)	*p*	Only N+ patients: Unilateral LLND ($n = 32$)	Only N+ patients: 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.

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

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

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Original Paper

Digestive Surgery

Dig Surg 2008;25:319–324
DOI: 10.1159/000158597

Received: April 23, 2008
Accepted: July 30, 2008
Published online: September 26, 2008

Doubling Time of Carcinoembryonic Antigen Is a Significant Prognostic Factor after the Surgical Resection of Locally Recurrent Rectal Cancer

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Key Words

Local recurrence · Rectal cancer · Carcinoembryonic antigen · Doubling time

Abstract

Background: Patients undergoing a curative rectal cancer resection have a risk of developing locoregional recurrence. A curative resection for local recurrence is the option of improvement in prognosis. However, a curative resection is sometimes too invasive and should be considered in selected patients. ***Methods:*** A total of 43 patients with locally recurrent rectal cancer who had been treated by operation between 1989 and 2007 were retrospectively reviewed and the factors, including doubling time of carcinoembryonic antigen (CEA-dt), were analyzed. ***Results:*** The 5-year overall survival rate after the operation for local recurrence was 50.8%. Gender, presence of distant metastasis, tumor size, CEA-dt and curability were found to be significant prognostic factors. A multivariate analysis demonstrated the presence of distant metastasis, CEA-dt and tumor size to be significant prognostic factors for overall survival. The 5-year overall survival rates of patients with a CEA-dt ≥150 days and a tumor size <5 cm were 76.9%. ***Conclusions:*** The tumor size and CEA-dt were useful prognostic factors that were recognizable before surgery. Patients with locally recurrent rectal cancer with a CEA-dt ≥150 days and a recurrent tumor size <5 cm are considered to be good candidates for surgery.

Introduction

Patients undergoing a potentially curative rectal cancer resection have a risk of up to 35% of developing a locoregional recurrence, with 30–50% of these occurring in the absence of distant metastasis [1–7]. Locally recurrent rectal cancer is associated with a poor prognosis. Without treatment, patients with recurrent rectal cancer have a short life expectancy, a median survival of 3.5–11 months [1, 8, 9], and tend to experience unpleasant symptoms such as pain and bleeding. Considerable variations have been reported in the effect of treatment for local recurrence. The 5-year survival rates vary between 0 and 81% for patients treated with a curative approach [10–13]. Radiotherapy, either alone or in combination with chemotherapy, allows symptomatic improvement in most patients, but the 5-year survival is usually less than 5% [14].

A surgical resection of recurrent cancer is performed both to avert the morbidity of local tumor growth and

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prolong survival. Generally, a radical resection of the locally recurrent tumor is the only option that offers a significant improvement in prognosis [9, 11, 15, 16]. However, a radical resection, which may involve total pelvic exenteration and/or distal sacrectomy, is sometimes too invasive. The quality of life sometimes dramatically deteriorates due to the postoperative complications and aftereffects such as pain, difficulty in walking, infection and double stoma due to urinary tract diversion. The prognosis of noncurative surgical cases is as poor as that of inoperable cases [3]. Therefore, these invasive procedures should only be considered in carefully selected patients. Although significant prognostic factors influencing the outcome of surgery for local recurrence have been identified, such as postoperative tumor marker levels and pathological curativity of surgical margins [17, 18], recognizable factors after surgery are not useful in determining the indications for surgery. As a result, factors which can be found preoperatively must be identified.

Tumor growth rate plays an important role in the prognosis of patients with cancer. Collins et al. [19] introduced the concept that malignant tumor growth in humans was exponential, and that the rate of growth could be described by the tumor doubling time. Tanaka et al. [20] reported that the tumor doubling time of a liver metastasis from colorectal cancer was the most reliable risk factor for postoperative recurrence in the remnant liver and poor prognosis. Staab et al. [21] stated that doubling time of carcinoembryonic antigen (CEA-dt) was strongly correlated with tumor doubling time. Koga et al. [22] reported that CEA-dt is a prognostic factor after a hepatectomy of liver metastasis from colorectal cancer. However, there have been no reports addressing the prognostic factors including CEA-dt after a surgical resection of locally recurrent rectal cancer.

In this study, patients with locally recurrent rectal cancer were retrospectively reviewed, and the factors associated with their prognosis, including the CEA-dt, were analyzed.

Table 1. Characteristics of patients

	n
Primary lesion	
pTNM (stage I/II/III/IV/unknown)	5/11/24/3
Histological differentiation (well/mod./muc./unknown)	17/18/4/4
Adjuvant therapy (done/not done)	30/13
Local recurrence lesion	
Gender (male/female)	23/20
Age (<60/≥60 years)	20/23
Distant metastasis (+/–)	8/35
DFI (<2/≥2 years)	17/26
Size (<5/≥5 cm)	24/19
CEA-dt (<150/≥150 days)	17/21
Curability (curative/noncurative + palliative)	27/16
Preoperative therapy (done/not done)	6/37
Postoperative therapy (done/not done)	32/11

Well = Well-differentiated adenocarcinoma; mod. = moderately differentiated adenocarcinoma; muc. = mucinous adenocarcinoma; DFI = disease-free interval.

Patients and Methods

A total of 43 patients with locally recurrent rectal cancer were treated by operation in this surgical department in the period between January 1989 and January 2007. Local recurrence was defined as any tumor recurrence in the pelvis or perineum with or without distant metastasis. Distant metastasis was defined as any tumor recurrence outside the pelvis, including multiple metastases to the abdominal cavity, liver, lung, brain or bone.

The CEA-dt was calculated using the following equation: $\text{CEA-dt} = \Delta t \log 2/(\log C2 - \log C1)$, where Δt is the CEA measured between 2 voluntary points, C1 is the value of CEA measured the first time and C2 the value measured the second time [22].

The clinicopathological and postoperative follow-up data were also retrospectively collected from the ongoing database in this hospital. Follow-up data were available for all cases. A curative resection was defined as no residual cancer at the local site after surgery even if distant metastasis was found. The overall survival period was defined as the period between surgery for local recurrence and cancer- or surgery-related death. The postoperative overall survival rates were calculated using the Kaplan-Meier method and then compared using the log rank test. A Cox proportional hazards model was used to assess the risk ratio under the simultaneous contribution of several covariates.

The differences in each group were analyzed by the χ^2 or Fisher's exact test. The statistical analysis was performed using the Statview software program (version 5.0; SAS Institute Inc., Cary, N.C., USA). $p < 0.05$ was considered to be statistically significant. This study was approved by the Human Ethics Review Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

Results

Factors Associated with Primary Surgery

The characteristics of the 43 patients are summarized in table 1. The procedures employed for the primary tumor included a sphincter-preserving operation in 21 cases, an abdominoperineal resection in 18 cases and a local excision in 4 cases. All cases were pathologically diagnosed to have adenocarcinoma. None of the patients received neoadjuvant therapy. Overall, 30 patients received prior adjuvant chemotherapy consisting of 5-fluorouracil and its derivatives for their primary tumor.

Factors Associated with Surgery for Local Recurrence

There were 23 men and 20 women, and their median age was 58.6 years (range 32–80). The procedures employed for the local recurrences were a pelvic exenteration in 17 cases, an abdominoperineal resection in 8 cases, a wide local resection in 4 cases and a low anterior resection in 6 cases. Of the 43 patients, 8 were found to have evidence of extrapelvic disease during an evaluation just before or at the time of surgery for recurrence (3 liver, 3 lung, 2 peritoneal dissemination). Eight patients underwent surgery with a curative intent and, as a result, 3 patients received a palliative operation (2 bowel bypass, 1 colostomy), while the other 5 patients received either a curative or noncurative operation. The mean interval between surgery for the primary tumor and the diagnosis of the local recurrence (disease-free interval) was 26.3 months (2.7–99.8). Local recurrences were diagnosed within 3 years in 33 patients (76.7%). Of the 43 patients, 27 (62.8%) received a pathologically curative resection, 8 (18.6%) received a noncurative resection because of gross or microscopic residual cancer cells, and 8 (18.6%) received only a palliative operation (2 diagnostic laparotomy, 3 bowel bypass, 2 colostomy, 1 other). No patients died of postoperative complications. Six patients received neoadjuvant therapy for a local recurrence. Thirty-two patients received postoperative chemotherapy and/or radiotherapy for local recurrence. The follow-up was complete for all patients. The median postoperative follow-up period for all patients was 44 months (range 0.9–146).

Outcome after Surgery

The 3- and 5-year overall survival rates after the operation for local recurrence were 54.7 and 50.8%, respectively (fig. 1). Table 2 shows a summary of the prognostic univariate analysis using various tumor-related variables on overall survival after the surgery for the local recurrence. Gender (male vs. female: $p = 0.0079$), recurrence pattern (local recurrence with distant metastasis versus local recurrence without distant metastasis: $p = 0.0041$), tumor size (<5 vs. ≥5 cm: $p < 0.0001$), CEA-dt (<150 vs. ≥150 days: $p = 0.0081$) and curability (curative vs. noncurative and palliative: $p = 0.0025$) were found to be significant prognostic factors. Disease-free interval was not a significant factor. Neoadjuvant and adjuvant therapy did not influence survival. In addition, a multivariate analysis was conducted by using preoperatively recognized factors (gender, presence of distant metastasis, tumor size and CEA-dt). The multivariate analysis demonstrated the presence of distant metastasis, CEA-dt and tumor size to be significant prognostic factors for overall survival (table 3). The 3-year overall survival rates of patients with distant metastasis (n = 8) and patients without distant metastasis (n = 35) were 14.3 and 64.6%, respectively ($p = 0.0041$). There was only 1 patient with distant metastasis surviving more than 3 years. Next, the pa-

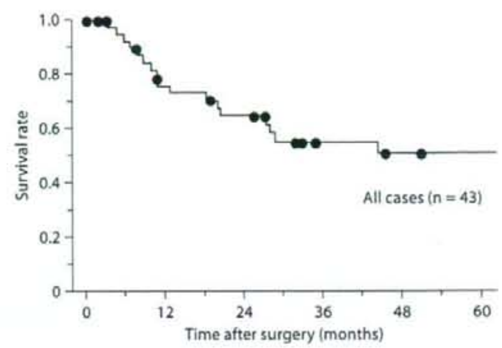

Fig. 1. The overall survival rate of patients with locally recurrent rectal cancer.

Table 2. Univariate analysis of the prognostic factors for overall survival

	p
Gender (male/female)	0.0079
Distant metastasis (+/–)	0.0041
DFI (<2/≥2 years)	0.6454
Size of local recurrence lesion (<5/≥5 cm)	<0.0001
CEA-dt (<150/≥150 days)	0.0081
Curability (curative/noncurative + palliative)	0.0025
Preoperative therapy for local recurrence (done/not done)	0.4579
Postoperative therapy for local recurrence (done/not done)	0.2354

DFI = Disease-free interval.

Table 3. Multivariate analysis of the prognostic factors for overall survival

	OR	95% CI	p
Gender (female/male)	0.282	0.078–1.121	0.0735
Distant metastasis (+/–)	4.242	1.305–13.790	0.0163
CEA-dt (≥150/<150 days)	0.268	0.084–0.861	0.0270
Size of local recurrence lesion (≥5/<5 cm)	9.850	2.504–38.742	0.0011

OR = Odds ratio; 95% CI = 95% confidence interval.

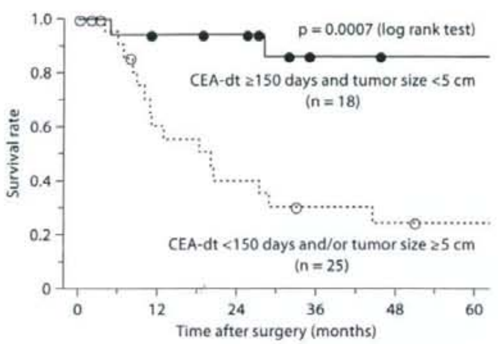

Fig. 2. The overall survival rate of patients with a CEA-dt of ≥150 days and tumor size of <5 cm (solid line) in comparison to that of patients with a CEA-dt of <150 days and/or tumor size of ≥5 cm (dotted line).

tients were divided into 2 groups based on the CEA-dt and tumor size. When the CEA-dt was ≥150 days and recurrent tumor size was <5 cm (n = 18), the 3- and 5-year overall survival rates of patients after the resection were both 86.3% (fig. 2). On the contrary, when the CEA-dt was <150 days and/or the recurrent tumor was ≥5 cm in diameter (n = 25), the 3- and 5-year overall survival rates of patients after the resection were 30.3 and 24.2%, respectively (p = 0.0007).

There were 6 cases of distant metastasis alone and 8 cases of local recurrence with or without distant metastasis even after a curative operation for local recurrence. In addition, there were 13 cases (48.1%) without recurrence.

Discussion

A number of prognostic factors affecting survival after a surgical resection of a local recurrence of rectal cancer have been reported by many investigators, including maximum tumor size [17], interval between the primary surgery and surgery for recurrence [23], curability of the surgery for recurrence [24, 25], procedure of primary surgery [26, 27], absence of severe symptoms [28], fixity of the recurrent tumor [28], gender [29] and the preoperative serum CEA level [11, 27, 30]. However, the survival in relation to the prognostic factors varied among the institutions, and the factors which are the best indicators for a surgical resection remain unclear.

The tumor doubling time was initially reported as a way to estimate when pulmonary metastasis from colorectal cancer might become apparent, with a short tumor doubling time thus indicating a rapid tumor growth [19]. Thereafter, serum CEA-dt level was also reported to strongly correlate with the survival of patients with recurrent colorectal cancer [21]. Onodera et al. [31] reported that CEA-dt reflects the rate of growth and is the most powerful determinant, while it also correlates with survival, more closely than the CEA level. In this study, a CEA-dt cutoff point of 150 days was used because the median value of CEA-dt was 158 days (mean 343 days; range 28.8–2,453). The CEA-dt was selected as an independent prognostic factor, presumably because a short CEA-dt may reflect adverse tumor characteristics including a high potential for spread.

The tumor size as a prognostic factor still remains controversial. Cunningham et al. [32] demonstrated that tumor size is not statistically related to survival. Gagliardi et al. [17] reported that the recurrent tumor diameter (5 cm) was the only independent prognostic factor. In this study, the mean of tumor diameter was 4.6 cm and we used 5 cm as the cutoff line. A tumor diameter <5 cm was determined to be an independent prognostic factor, and the tumor diameter may thus reflect the curability of a resection.

The presence of distant metastases at the time of surgery for local recurrence remains an unresolved problem. Most reports consider distant metastases to be a criterion for excluding the resectability of recurrent tumors. However, Hashiguchi et al. [33] analyzed the presence of distant metastases at the time of resection of a local recurrence and did not find any statistical significance, suggesting that not even the intraoperative discovery of a liver metastasis should be considered a contraindication to surgery for a local recurrence. Gagliardi et al. [17] showed that resection of metastases at the time of the recurrence excision is an independent prognostic factor. Based on this result, no surgical limitation is presented by the presence of distant metastases. The current study revealed distant metastasis to be an independent prognostic factor according to a multivariate analysis. However, 1 patient with distant metastasis whose CEA-dt was 523 days received an operation for distant metastasis and local recurrence at the same time and is presently alive without recurrence for 75 months. This may be due to a slow rate of tumor progression. The prognosis of patients with distant metastasis is not always poor, and surgery for those patients may be considered when the distant metastasis can be controlled and the CEA-dt is long.

Considering the results of this study, patients with locally recurrent rectal cancer should therefore receive a surgical resection when the CEA-dt is ≥150 days and recurrent tumor is <5 cm in diameter. In contrast, patients with locally recurrent rectal cancer with either distant metastasis or with a CEA-dt of <150 days and/or recurrent tumor measuring ≥5 cm in diameter may undergo neoadjuvant and/or adjuvant therapy, because surgery alone does not result in a good prognosis. Even after a curative operation, 8 of 27 cases developed local recurrences. This result suggests that local control for local recurrence is difficult. A true curative surgical approach can be obtained only when the microscopic margins are negative. A pathologically true negative margin can be achieved in about 45% of cases, ranging from 10 to 67% [34]. In the current study, 27 of 43 patients (62.8%) received a pathologically curative resection. The involvement of the pelvic side wall and/or adjacent organs makes a curative resection a very ambitious target. Preoperative chemoradiation and intraoperative radiation may improve local control and survival in patients with locally recurrent disease with acceptable morbidity. Vermaas et al. [35] reported that preoperative radiotherapy for recurrent rectal cancer results in a higher number of complete resections and improved local control in comparison to patients treated without radiotherapy. High-dose rate interstitial brachytherapy delivers high-dose, highly controlled and focused radiation to specific sites of disease, thereby minimizing the degree of injury to normal tissues. It was reported that high-dose rate interstitial brachytherapy was useful for increased local control, better palliation and increased salvage of patients [36, 37]. Recently, carbon ion radiotherapy was reported to be effective in terms of improved local control and less risk of normal tissue damage in comparison to traditional radiotherapy. Tsujii et al. [38] reported that the 3- and 5-year overall survival rates of patients with locally recurrent rectal cancer treated by carbon ion radiotherapy were 65% and 55%, respectively. The patients with unresectable local recurrence may receive high-dose rate interstitial brachytherapy or carbon ion radiotherapy. In our study, there was no survival benefit with either neoadjuvant or adjuvant therapy. However, the regimen of chemotherapy and the quality of radiation in this study were different from the modalities we use today, and we also could not deny the benefit of either neoadjuvant or adjuvant therapy. However, due to the small number of patients investigated in these studies and the short follow-up, no definitive conclusions could be made.

Based on the findings of this study, the presence of distant metastasis, tumor size and CEA-dt were all identified to be useful prognostic factors before surgery. Patients with locally recurrent rectal cancer with a CEA-dt ≥150 days and a recurrent tumor measuring <5 cm in diameter are therefore considered to be good candidates for surgery.

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Evaluation of the lateral sentinel node by indocyanine green for rectal cancer based on micrometastasis determined by reverse transcriptase-polymerase chain reaction

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Received April 17, 2008; Accepted May 27, 2008

DOI: 10.3892/or_00000069

Abstract. The significance of dissecting the lateral pelvic lymph node (LN) for lower rectal cancer remains controversial. We detected the lateral sentinel node (SN) by indocyanine green (ICG) and micrometastases using carcinoembryonic antigen (CEA)-specific reverse transcriptase-polymerase chain reaction (RT-PCR). Twenty-five patients who underwent curative surgery with a dissection of the lateral pelvic LNs between 2003 and 2005 were examined. We investigated the existence of lateral SNs and any associations between pathological metastases and micrometastases by RT-PCR. Lateral SNs were detected in 7 (28%) of the 25 patients. The number of lateral SNs was 13 LNs, or 1.9 nodes per case. Of the 25 cases, 7 had lateral LN metastases based on pathological examinations in dissected lateral LNs. Three cases had massive lateral LN swelling by pre-operative pelvic CT and the SNs were not detected in them. The SNs were detected in two cases and were negative based on pathological examinations and positive according to a genetic diagnosis. SNs were detected in one case, which was positive based on pathological examinations and a genetic diagnosis. SN was not detected in one case. There were five SNs in which CEA was positive by RT-PCR, though only one of them was positive based on pathological examinations. No SNs were observed that were negative based on a genetic diagnosis, but were positive according to the pathological diagnosis. We detected the lateral SNs using ICG. The sensitivity of identifying lateral LN metastasis was improved by the use of a genetic diagnosis. However, the detection rate was still low, therefore we need to develop a new method for detecting SNs.

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Key words: rectal cancer, lateral sentinel node, indocyanine green, micrometastasis, reverse transcriptase-polymerase chain reaction

Introduction

Metastasis to the regional lymph node (LN) is an important prognostic factor, which is used for clinical decision-making regarding the selection of the most appropriate cancer treatment. The development of locoregional recurrences and distant metastases accounts for most of the deaths. Adequate tumor staging, including an evaluation of the presence of regional LN metastases at the time of diagnosis, is essential, since it constitutes the most important prognostic factor (1-5). Local recurrence develops in about half of all patients with advanced rectal cancer, especially in the lower rectum, who underwent a potentially curative resection (6). Although many trials consisting of extended surgery, adjuvant chemotherapy and radiotherapy were carried out to prevent local recurrence after curative surgery, no significantly favorable results have yet been reported. Since the early 1980s, the results of a lateral pelvic LN dissection (LPLD) for rectal cancer have improved steadily, although LPLD performed in Japan at that time often caused urinary and sexual dysfunction (7,8). Since the beginning of the mid 1980s, colorectal surgeons in Japan have sought to improve their surgical techniques to either alleviate or prevent functional disturbances and to individualize the operative procedures according to the local extent of the cancer without increasing the risk of local recurrence. These efforts have led to the development of various procedures developed with the goal of pelvic autonomic nerve preservation (9).

The sentinel node (SN) concept was first advocated by Morton *et al* (10) in patients with melanoma. Sentinel node navigation surgery (SNNS) for breast cancer and malignant melanoma can accurately assess LN dissection areas (11,12). The SN concept was recently applied to cancers of the gastrointestinal tract (13-16). If SNNS can be applied to lower rectal cancer, unnecessary LPLD can be omitted and personalized lymphadenectomy may be possible.

Some authors reported the clinical significance of LN micrometastasis detected by either immunohistochemistry (IHC) or reverse transcriptase-polymerase chain reaction (RT-PCR) (17-20). The aim of this study was to investigate whether the SN concept by indocyanine green (ICG) is a useful indicator of lateral region lymph node involvement in lower rectal cancer patients. In addition, we investigated the significance of the lateral SNs for lower rectal cancer based on micrometastasis as determined by RT-PCR.

Patients and methods

Patients. In our hospital, Stage II or III [clinically staged according to the tumor node metastasis (TNM) classification of UICC (Union International Contre le Cancer) (21)] middle or lower rectal cancer, located at or below the peritoneal reflection, is an indication of LPLD. Twenty-five patients with lower rectal cancer, who were preoperatively diagnosed to have Stage II or III of the disease, were investigated. The patients were clinically diagnosed before surgery based on the findings of a colonoscopy, Ba-enema, CT and MRI. All underwent curative surgery with LPLD at our department of surgery between January 2003 and April 2005. These patients (n=25) included 12 (48%) males and 13 (52%) females, with a mean age of 58.8±10.5 years (±SD, range, 41 to 77 years). The tumor lower levels were located at or below the peritoneal reflection. None of the patients had undergone either preoperative chemotherapy or irradiation (Table I). This study was approved by the Human Ethics Review Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases and a signed informed consent form was obtained from each patient.

Detection of the lateral SNs. Before laparotomy, a fine needle (26-gauge) was inserted into the submucosal layer via the anus at three sites anal sides of the tumor circumferentially, and dye, indocyanine green (ICG) (Diagnogreen; Dai-Ichi Pharm Co Ltd, Tokyo, Japan) was then gently injected. The total amount of injected dye was 5 ml (25 mg) for each patient. After the laparotomy, the lateral vesical and obturator spaces were opened between the lateral aspect of the internal iliac vessels and the pelvic wall. In addition, we observed the lateral pelvic adipose tissue around the internal iliac arteries and the obturator spaces with macroscopic observation. Sixty minutes after the ICG injection, we were able to identify the SNs around a lateral lesion and then performed a rectal resection and lateral pelvic LN dissection with autonomic nerve preservation. Even though we could not detect the lateral SN, we performed the same operation.

Tissue preparations. Each SN was immediately cut into halves individually to prevent RNA cross-contamination between specimens. One half of the node was fixed with 10% buffered formalin and was then embedded in paraffin for H&E staining. The other half was stored in RNA*Later* solution (Ambion, Austin, TX) at -20˚C until RNA extraction.

RNA extraction from SN specimens and RT-PCR. Tissue specimens were minced with RNase-free disposable pellet pestles (Kimble Kontes, Vineland, NJ) in TRIzol Reagent (Invitrogen, Carlsbad, CA). RNA extraction was carried out according to the protocol recommended by the manufacturer. Purified RNA was quantified and assessed for purity by UV spectrophotometry. Complementary DNA (cDNA) was generated with a transcriptor first-strand cDNA synthesis kit (Roche Diagnostics, Mannheim, Germany) according to the protocol provided by the manufacturer. The RT reaction was performed in a total of 20 μl at 50˚C for 60 min, followed by heating at 85˚C for 5 min.

All PCR analyses were performed using LightCycler (Roche Diagnostics) and a real-time monitoring thermal cycler, for the rapid and quantitative detection of cancer cells. The integrity of the RNA samples was verified by the amplification of ß-2-microglobulin (B2M) mRNA.

The primer sequences used for CEA detection were 5'-ccc gcagtattcttggcgtatc-3' and 5'-tgcaaatgctttaaggaagaagc-3'. The primer sequences used for B2M detection were 5'-gctatgtgtct gggtttc-3' and 5'-tacatgtctcgatcccac-3'.

For each PCR amplification, a reaction mixture was prepared containing 2 μl of a cDNA template, 10X PCR buffer, 3 mM $MgCl_2$, 0.25 μM of primer pairs and FastStart DNA Master SYBR-Green I (Roche Diagnostics). The PCR cycling conditions were set as follows: an initial denaturing step at 95˚C for 10 min and 40 cycles at 95˚C for 15 sec, 62˚C for 10 sec and 72˚C for 5 sec. The quantification data were analyzed using the Light Cycler analysis software program (Roche Diagnostics GmbH) as recommended by the manufacturer. The standard curves for the quantification of CEA or B2M mRNAs were drawn using 10-fold dilutions of cDNA from the human pancreatic cancer cell line CaPan1.

Cell lines and cell culture conditions. The human pancreatic cancer cell line, CaPan1, was obtained from the Health Science Research Resources Bank (Tokyo, Japan). It was grown in Dulbecco's modified Eagle's medium plus 10% fetal bovine serum, 100 U/ml penicillin and 100 μg/ml streptomycin and 0.25 μg/ml amphotericin B, in 5% CO_2 at 37˚C.

Statistical analysis. Statistical analysis was performed with the software package StatView version 5.0 (Abacus Concepts, Inc. Berkeley, CA). The associations between the discrete variables were assessed using the Fisher exact test, the Chi-square test or Student's t-test as appropriate. P-values of <0.05 denoted the presence of a statistically significant difference.

Results

RT-PCR sensitivity in detecting cancer cells. Serial dilutions of CaPan1 cancer cells [$1x10^0$ (=1) -$1x10^4$] were mixed with lymphocytes ($1x10^7$) obtained from healthy volunteers (that did not express CEA mRNA). Total RNA was extracted from each mixture and subjected to a quantitative RT-PCR assay. One hundred cancer cells mixed with 10^7 normal lymphocytes were detected by RT-PCR with a CEA marker (Fig. 1).

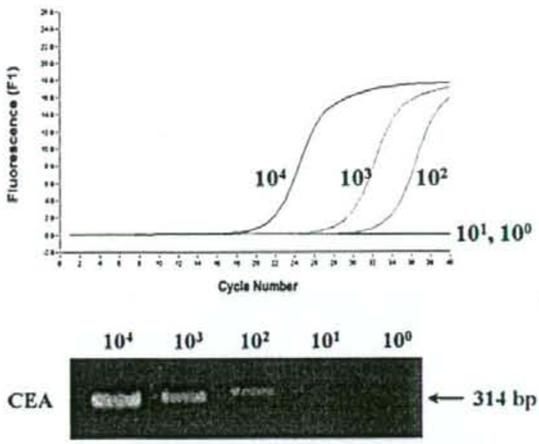

Figure 1. Real-time RT-PCR for CEA (carcinoembryonic antigen) mRNA. We used a LightCycler to detect various ratios of CaPan1 cells mixed with lymphocytes. Upper panel: fluorescence vs. PCR cycles. CaPan1 cells were sequentially diluted 10-fold and mixed with lymphocytes to give 10^4 to 10^0 CaPan1 cells per 10^7 lymphocytes. Lower panel: ethidium bromide-stained agarose gels following electrophoresis of CEA RT-PCR products. The RT-PCR products for CEA were resolved as 314 base pair fragments. bp, base pairs.

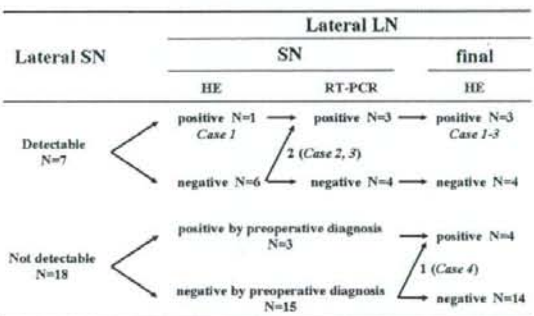

Figure 2. Distribution of lateral lymph node metastasis and micrometastasis in the sentinel and other nodes.

Detection of lateral SNs. With macroscopic observations, we detected the green-stained SNs in the lateral pelvic adipose tissue around the internal iliac arteries and the obturator spaces. We identified the lateral SNs in seven patients (28%), a mean number of 1.9 (range, 1-4). The detection rates were 20% (1/5) in T2 and 30% (6/20) in T3 rectal cancer. No significant differences were observed in age, gender, tumor size, histological grade, LN stage, TNM stage, lymphatic invasion or venous invasion between the two groups (Table I).

Comparison of the histological and genetic diagnoses. In lateral SNs detectable cases (N=7), only one case (Case 1) demonstrated metastasis by HE in the lateral SNs. Another six cases demonstrated no metastasis by HE in the lateral SNs. Two cases (Case 2, 3) had no metastasis by HE in the lateral SNs. However, these cases had micrometastasis by RT-PCR in the lateral SNs. Three cases (Cases 1-3) had metastasis by

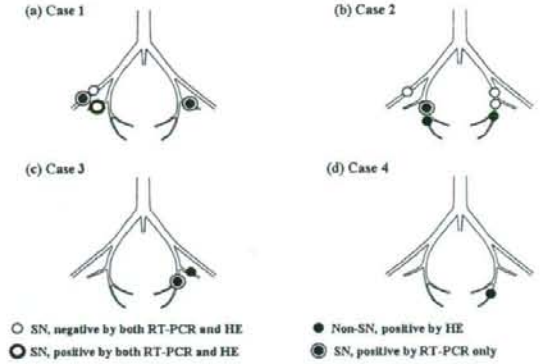

Figure 3. Anatomical mapping of the lateral LN detected by RT-PCR and histological examinations in four representative cases. (a) Case 1 had four lateral SNs. One SN was positive according to RT-PCR and HE. (b) Case 2 had four lateral SNs. One SN was positive based on RT-PCR only. (c) Case 3 had one lateral SN. One SN was positive according to RT-PCR only. One dissected lateral non-SN was found to have metastasis by HE. (d) Case 4 had no SNs. However, one lateral LN had metastasis based on HE.

HE in dissected lateral LNs. The status of dissected lateral LN metastasis is completely consistent with the diagnosis of the lateral SNs according to RT-PCR. Case 1 has four lateral SNs. One SN is positive by RT-PCR and HE. However, the other SN was negative according to RT-PCR and HE. Further two SNs were positive by RT-PCR only. In addition, the dissected lateral non-SNs demonstrated no metastasis by HE. Case 2 had four lateral SNs. One SN was positive according to RT-PCR only. However, the other three SNs were negative by RT-PCR and HE. In dissected lateral LN, two non-SNs had metastasis by HE. Case 3 had one lateral SN. One SN is positive by RT-PCR only. In the dissected lateral LN, one non-SN had metastasis according to HE.

In cases where the lateral SNs were not detectable (N=18), three out of 18 patients had massive lateral pelvic LN swelling based on pre-operative pelvic CT and the SN was not detected macroscopically. Another patient had no lateral LN swelling by pre-operative diagnosis. In case 4, only one lateral LN along the internal iliac artery had metastasis by HE. This LN could not be detected by either pre-operative CT or MRI and could not be found by intra-operative observations (Figs. 2 and 3).

The number of lateral SNs was 13 LNs. There were five SNs in which CEA was positive by RT-PCR, though there was only one that was positive based on pathological examinations. In contrast, no SNs that were negative based on a genetic diagnosis were found to be positive according to a pathological diagnosis.

Discussion

One of the most common sites of recurrence after a curative resection of rectal cancer is the pelvis (22) and local control is a major goal of surgical treatment. Appropriate dissection in order to eliminate residual cancer foci, such as any involved LNs, is therefore necessary to achieve local control. However, the target region for local recurrence remains controversial. Some Japanese surgeons place great emphasis

Table I. Clinicopathological findings of 25 patients with rectal cancer.

	Lateral SN (+) (N=7)	Lateral SN (-) (N=18)	P-value
Age (yrs)	55.9±10.9	59.9±10.5	0.3950
Gender			
Male	3 (43%)	9 (50%)	0.9999
Female	4 (57%)	9 (50%)	
Tumor size (cm)	5.8±1.6	5.8±1.9	0.9534
Histological grade			
Well	1 (14%)	6 (33%)	0.3418
Moderate	6 (86%)	10 (56%)	
Mucinous	0 (0%)	2 (11%)	
Primary tumor			
pT2	1 (14%)	4 (22%)	0.9999
pT3	6 (86%)	14 (78%)	
Regional lymph nodes			
pN0	1 (14%)	5 (28%)	0.1316
pN1	5 (71%)	5 (28%)	
pN2	1 (14%)	8 (44%)	
pTNM stage			
I	1 (14%)	2 (11%)	0.3962
II	0 (0%)	4 (22%)	
III	6 (86%)	12 (67%)	
Lymphatic invasion			
No	1 (14%)	4 (22%)	0.9999
Yes	6 (86%)	14 (78%)	
Venous invsion			
No	1 (14%)	1 (6%)	0.4900
Yes	6 (86%)	17 (94%)	

not only on a total mesorectal excision, but also on intrapelvic lateral LN dissection, whereas the latter procedure is performed only rarely in Western countries. There are several possible reasons for this difference of opinion regarding the clinical significance of an iliac lymphadenectomy. The clinical importance of the lateral spread of lower rectal cancer was first demonstrated in the 1950s (23). Since then, LPLD was performed for middle or lower rectal cancer in Japan, because the incidence of lateral LN metastasis in patients with lower rectal cancer is high (13-18%) (7,24,25). This procedure is associated with a lower local recurrence rate than conventional surgery. However, due to the high incidence of complications with LPLD, including sexual and urinary dysfunction (8), and the poor prognosis of patients with lateral LN metastasis (5-year survival rate, 38-42%) (7,24,25), this operation has only been performed in Japan. As a result, it is necessary to restrict the indications of LPLD for advanced lower rectal cancer.

The SN is defined as the first node in the regional lymphatic basin that drains the primary tumor and either a radionucleotide tracer or vital dye has been used to detect it. The clinical applicability of SNNS and radio-guided SN detection to gastrointestinal tract cancer has been extensively investigated (13-16). The usefulness of dye-guided SN detection in colon cancer has already been reported (26). These studies demonstrated the high efficacy (70-99%) of SN. However, we were able to identify SNs in only 7 of the 25 patients (success rate, 28%). In comparison to these studies, our detection rate of SNs is very low. One of the reasons for this is the degree of TNM stage. We investigated the SNs in advanced rectal cancer and therefore the detection rate may be low. Another reason may be that the use of dye followed by intraoperative tracing was impracticable, because of the close vicinity of the pelvic region and the narrow space around the mesorectal tissue (27). A final reason, may be due to the method used to detect SNs, namely, we detected SNs macroscopically.

The presence of LN metastasis is usually assessed by hematoxylin and eosin staining. Micrometastasis is generally evaluated by IHC or RT-PCR. Several investigators have emphasized the significance of LN micrometastasis as diagnosed by RT-PCR in colorectal cancer (CRC) (20,22). In the present study, we used RNA rather than DNA to investigate the existence of micrometastases. DNA-based methods have the limitation that mutations of K-*ras* and/or *p53* are found in subsets of CRC, but not in all cases, whereas CEA is expressed exclusively by primary CRC tissues (20,28). Another reason for using this technique is that tumor cells detected by RT-PCR are very likely to be viable since mRNA is extremely unstable. In contrast, there is concern that mutated DNA found in regional LNs might represent a fraction of free tumor DNA rather than being derived from viable cancer cells (29,30). Although special techniques, which act as a supplement to light microscopy, such as IHC and RT-PCR analyses, may improve the accuracy of the pathological staging, these modalities tend to be rather expensive, labor intensive and time-consuming for each LN of the operative specimens. Consequently, the possibility of a focused analysis of one or a few LNs which can reliably predict the regional nodal status is certainly attractive (31).

In the present study, we designed an original CEA primer, since CEA is an epithelial-specific antigen that is expressed in most cancers and in normal gastrointestinal tissue (32). Many studies have detected LN micrometastasis in CRC using RT-PCR of CEA mRNA (19,20,28). Our method was thus able to detect 100 cancer cells mixed with 10^7 normal lymphocytes. However, this rate is not so high. This may be attributable to differences in the system of reverse transcription and the PCR conditions. The CEA transcripts used as a target for the amplification of PCR is expressed in both normal epithelial and CRC cells and, therefore, it is possible that the detection rate would increase with an increasing number of PCR cycles. It has been reported that the nested PCR technique, which can achieve a high sensitivity by the two-step amplification of CEA cDNA, results in a 100% detection rate in node-negative CRC patients (33).

Lateral LN metastasis is generally considered to be a sign of systemic disease due to its poor prognosis in affected patients. However, some patients survived >5 years without adjuvant therapy, thus suggesting that the spread to the lateral LNs may not always represent systemic disease and that some patients may be cured by extended surgery. Although extensive preoperative and intraoperative investigations for lateral LN spread were performed, its incidence is thought to be low. Therefore, we need to develop a method to accurately select the patients who should undergo LPLD. From the viewpoint of detecting LN metastasis, minimally invasive surgery with a personalized lymphadenectomy can be performed if SNNS is introduced to patients with advanced lower rectal cancer. We can detect the lateral SNs using ICG. The sensitivity of lateral LN metastasis was found to improve using a genetic diagnosis. However, the detection rate of SNs was very low, as a result we still have to develop a new method for detecting SNs.

The present study investigated the adequacy of the SN concept based on LN micrometastasis as determined by RT-PCR. No definitive conclusion was made as to whether micrometastasis by RT-PCR/IHC or macrometastasis by HE is a more effective diagnostic modality for SNs. However, if we judge SN metastasis by HE only, we may miss metastatic non-SNs. As a result, we consider RT-PCR to be better than HE in making a final decision regarding the SNs.

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Original Paper

Positron Emission Tomography for Preoperative Staging in Patients with Locally Advanced or Metastatic Colorectal Adenocarcinoma in Lymph Node Metastasis

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KEY WORDS:
Positron emission tomography; Colorectal carcinoma; Lymph node metastasis

ABBREVIATIONS:
Positron Emission Tomography (PET); 18(F)-fluoro-deoxyglucose (FDG); Lymph Nodde (LN); Computed Tomography (CT)

ABSTRACT

Background/Aims: The impact of positron emission tomography was prospectively evaluated using 18 (F)-fluoro-deoxyglucose (FDG-PET) for the detection of lymph node (LN) metastasis in preoperative locally advanced colorectal adenocarcinoma, compared with computed tomography (CT) and pathologic findings.

Methodology: Fifty-three patients who were suspected of LN involvement by CT were staged preoperatively for LN metastasis using FDG-PET and CT. Regional LNs were classified into 3 groups, N1, N2-3, and N4, according to the Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (6th Edition). A comparison of pathologic findings with CT and FDG-PET findings was used to calculate sensitivity, specificity, and accuracy.

Results: The sensitivity, specificity and accuracy of CT/FDG-PET were 91.3%/52.2%, 91.7%/75.0% and 65.9%/72.3%, respectively, for N1, 91.7%/75.0%, 72.2%/94.4% and 77.1%/89.6%, respectively, for N2-3, and 100%/100%, 17.6%/100% and 41.7%/100%, respectively, for N4. The detection rate of the number of metastatic N1 LNs by CT was significantly higher than by FDG-PET, and not significantly in the N2-4 area. LNs hidden by strong halation of the primary tumor were not detected by FDG-PET.

Conclusions: While FDG-PET is markedly more sensitive than CT for detection of N4 LN involvement, the number of metastatic LNs is difficult to determine.

INTRODUCTION

The most important determinants of survival for colorectal carcinoma patients that are suitable candidates for curative surgery are the presence of hepatic metastasis, lymph node (LN) involvement, and extent of tumor invasion through the bowel wall. Preoperative clinical staging in colorectal cancer patients is generally decided by computed tomography (CT) focused on the abdomen and pelvis to detect LN involvement and liver metastasis.

[18](F)-fluoro-deoxyglucose (FDG), like glucose, is phosphorylated intracellularly. Positron emission tomography (PET) using FDG has recently been recognized as a new method of non-invasive evaluation for the staging of colorectal carcinoma. FDG-PET is able to visualize the increased metabolism (glycolysis) often observed in malignant tissues, and several reports have shown that FDG-PET is invaluable for the study of management of primary rectal cancer, local recurrence and liver metastasis in colorectal carcinoma (1-7).

Recently, CT, magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) and FDG-PET have been performed for the evaluation of LN metastasis in patients with colorectal carcinoma. However, few investigators have used FDG-PET to detect LN metastasis and locations of metastatic LNs in colorectal carcinoma for preoperative staging (3-5). Generally, CT is used for detection of LN metastasis. If para-aortic LN swelling is visualized by CT preoperatively, many surgeons perform sampling of para-aortic LNs with laparotomy and recommend pathological examination to detect LN involvement, obviously with a view to curability. The aim of this prospective study was to evaluate the impact of FDG-PET for the preoperative detection of LN metastasis and associated locations, in patients with diagnosed locally advanced and/or para-aortic LN metastatic

Hepato-Gastroenterology 2008; 55:398-402