ORIGINAL ARTICLE

Outcome of patients with clinical stage II or III rectal cancer treated without adjuvant radiotherapy

Shin Fujita · Seiichiro Yamamoto · Takayuki Akasu · Yoshihiro Moriya

Abstract

Background To clarify the indications for preoperative adjuvant radiotherapy for rectal cancer, the outcome of patients who underwent curative surgery without adjuvant radiotherapy was investigated.

Methods A total of 817 consecutive patients who underwent curative surgery for clinical stage II or III rectal cancer without preoperative adjuvant radiotherapy between 1988 and 2002 were reviewed.

Results The actuarial 5-year local recurrence rate in the examined patients was 6.2%. Univariate analysis showed that sex, pathological T classification (pT), clinical N classification (cN), pathological N classification (pN), tumor site, distance from the anal verge, type of surgery, pathological stage, a positive radical margin, lymphatic invasion, and venous invasion were significantly correlated with local recurrence. Multivariate analysis of preoperative factors identified cN, distance from the anal verge, and sex as statistically significant risk factors for local recurrence. In patients with rectal cancer located less than 5 cm from the anal verge and with positive cN, the local recurrence rate was more than 10%.

Conclusions Patients with rectal cancer located less than 5 cm from the anal verge and with clinically positive lymph nodes should be given preoperative adjuvant radiotherapy.

Keywords Rectal cancer · Local recurrence · Radiotherapy · Adjuvant therapy

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Introduction

Rectal cancer is one of the most common cancers worldwide. Many patients with rectal cancer have localized disease, and surgical resection has been the only treatment for such patients. Recently, however, the effectiveness of adjuvant radiotherapy or chemoradiotherapy has been demonstrated, and this has become a standard therapy for rectal cancer [1]. Preoperative radiotherapy has been shown to be more effective than postoperative therapy [2]. After the introduction of adjuvant radiotherapy and the development of total mesorectal excision (TME) [3], the local recurrence rate of rectal cancer became about 10%. However, radiotherapy increases the incidence of short-term complications [4] and late adverse effects, including bowel, anal, sexual and urinary dysfunctions, and cardiovascular morbidity [5–13], and some reports have suggested that adjuvant radiotherapy could be omitted in a subset of rectal cancer patients [14–17]. Therefore, the indications for preoperative adjuvant radiotherapy should be determined and unnecessary therapy should be avoided. In Japan, the incidence of local recurrence of rectal cancer is lower than in western countries, and adjuvant radiotherapy has not been a standard therapy for rectal cancer. The reasons for this lower local recurrence rate are considered to be that Japanese patients are generally thinner than Western patients, and that lateral pelvic lymph node dissection and tumor-specific mesorectal excision were done in Japan before the introduction of TME. In order to clarify the risk factors for local recurrence of rectal cancer and to determine the indications for preoperative adjuvant radiotherapy, we examined local recurrence rates and survival rates of patients with clinical stage II or III rectal cancer without adjuvant radiotherapy at the National Cancer Center Hospital, Tokyo.

Materials and methods

Patients

A total of 817 consecutive patients with stage II or III primary rectal cancer treated at the National Cancer Center Hospital, Tokyo, between 1988 and 2002 were reviewed. All the rectal cancers were adenocarcinoma. The patients were followed up at 3-month intervals for 2 years and at 6-month intervals thereafter. Tumor markers were examined at every patient visit. Computed axial tomography (CAT scan) of the liver and lung or abdominal ultrasonography with chest X-ray were performed at least every 6 months. Colonoscopy was performed twice within 5 years after surgery. Recurrences were clinically determined by colonoscopy or radiological images. Median follow-up time was 5.8 years, and none of the patients received adjuvant radiotherapy. Pathological stage III patients were given adjuvant chemotherapy.

Surgical resection

Patients with rectal cancer at or below the peritoneal reflection underwent TME and lateral pelvic lymph node dissection [18]. The remaining patients underwent TME or tumor-specific mesorectal excision. In patients with T4 tumors, combined resection of tissues and/or organs invaded by the cancer was performed.

Clinical and pathological analysis

Tumor sites were divided into four categories: upper rectum (RS), rectum above the peritoneal reflection (Ra), rectum below the peritoneal reflection (Rb), and anal canal (P). Standard oncological analysis was performed on all the patients and specimens in accordance with the TNM classification. Clinical T (cT) was determined before surgery by digital rectal examination, endoscopy, barium enema, CAT scan and/or magnetic resonance imaging (MRI), and, finally, confirmed by macroscopic findings of the resected specimen. In this study, T3 was divided into two subclasses: shallow cancer invasion to the mesorectum (T3a) and deep cancer invasion to the mesorectum (T3b). Clinical N (cN) was determined before surgery by CAT scan and/or MRI and finally confirmed by examination of the resected specimen. Radical margin involvement was defined as the presence of cancer cells at the resection margin on the single primary slice revealed by microscopic evaluation.

Statistical analysis

Local recurrence rates and survival rates were calculated by the Kaplan–Meier method and differences were compared statistically by the log-rank test. Cox's proportional hazards model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P < 0.05$.

Results

Patient characteristics and oncological outcome

Overall survival and actuarial local recurrence curves are shown in Fig. 1. Five-year overall survival rate was 77.9% and 5-year actuarial local recurrence rate was 6.2%. Three patients died within 30 days after surgery, and mortality was 0.4%. In Japan, lateral pelvic lymph node dissection is indicated for stage II or III tumors at or below the peritoneal reflection, and 337 patients (41.2%) underwent this procedure. The clinical and pathological characteristics and outcome of patients with clinical stage II and III rectal cancer are shown in Tables 1 and 2. Among clinical factors, sex, cN, tumor site, distance from the anal verge, and type of surgery were significantly correlated with local recurrence. Age, carcinoembryonic antigen (CEA), cT, cN,

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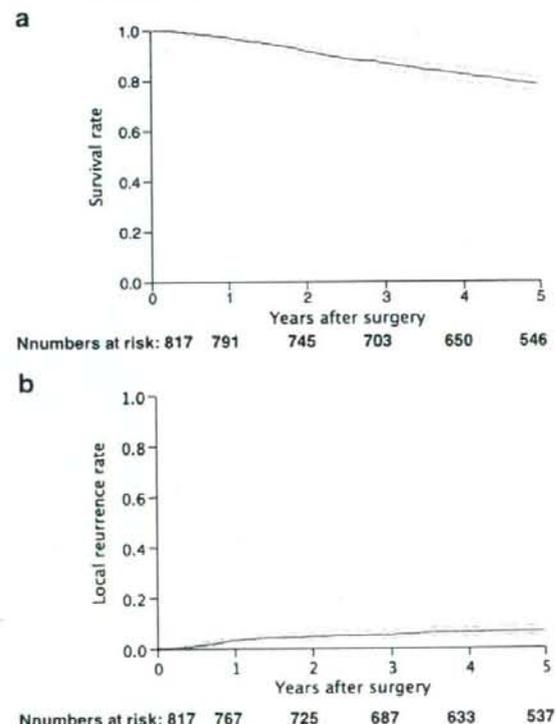
Fig. 1 Overall survival (a) and actuarial local recurrence (b) curves with 95% confidence intervals. Five-year overall survival rate was 77.9% and 5-year actuarial local recurrence rate was 6.2%

Table 1 Clinical characteristics and outcome of patients with clinical stage II or III rectal cancer

	No. of patients (%)	Local recurrence rate (%)	P value	Survival rate (%)	P value
Age (median: 60, range: 21–92)			0.096		0.013
<60	377 (46.1)	7.8		80.8	
≥60	440 (53.9)	4.9		75.4	
Sex			0.028		0.181
Male	530 (64.9)	4.9		76.8	
Female	287 (35.1)	8.8		79.9	
CEA (ng/ml)			0.841		0.001
≤5	514 (62.9)	6.2		79.6	
>5	303 (37.1)	6.3		74.9	
Clinical T (cT)			0.239		<0.001
T1, T2	47 (5.8)	4.5		84.9	
T3a	302 (37.0)	5.6		83.6	
T3b	361 (44.2)	5.8		78.2	
T4	107 (13.1)	10.4		57.6	
Clinical N (cN)			<0.001		<0.001
N0	315 (38.6)	1.7		89.3	
N1, N2	502 (61.4)	9.2		70.6	
Tumor site			<0.001		<0.001
RS	229 (27.3)	1.4		80.8	
Ra	233 (28.5)	3.2		79.9	
Rb	342 (41.9)	10.6		76.3	
P	19 (2.3)	25.6		47.3	
Distance from anal verge (cm)			<0.001		0.046
10–15	119 (14.6)	0.01		86.4	
5–10	404 (49.4)	3.4		78.8	
≤5	294 (36.0)	12.5		73.1	
Type of surgery			<0.001		<0.001
Anterior resection	571 (69.9)	4.0		83.0	
Abdomino-perineal resection	184 (22.5)	12.6		72.2	
Hartmann	27 (3.3)	12.6		42.3	
Pelvic exenteration	35 (5.0)	6.3		51.1	

tumor site, distance from the anal verge, and type of surgery were significantly correlated with survival. Among pathological factors, pathological T (pT), pathological N (pN), pathological stage, radical margin involvement, lymphatic invasion, and venous invasion were significantly correlated with local recurrence. All the examined pathological factors were significantly correlated with survival.

Multivariate analysis of preoperative factors

In order to determine the indications for preoperative therapy, preoperative clinical factors including age, sex, CEA, cT, cN, tumor site, distance from the anal verge, and tumor differentiation were examined by multivariate analysis. cN, distance from the anal verge, and sex were statistically significant risk factors for local recurrence (Table 3). For survival, cIT, cN, tumor differentiation, age, and CEA were significant risk factors.

Results of multivariate analysis of local recurrence rates in relation to the selected factors are shown in Table 4. In

patients with rectal cancer located less than 5 cm from the anal verge and with positive cN, the local recurrence rate was more than 10%. In patients with rectal cancer located between 5 and 10 cm from the anal verge and with positive cN, the rate was about 5%. In female patients with rectal cancer located less than 5 cm from the anal verge and with negative cN, the rate was 7.7%. In other patients, the rate was less than 3%.

Discussion

Our results showed that clinical lymph node status, distance from the anal verge and sex were risk factors for local recurrence of rectal cancer. The data indicated that patients with rectal cancer located less than 5 cm from the anal verge and with clinically positive lymph nodes, who showed a local recurrence rate of more than 10%, should receive preoperative radiotherapy. Similarly, preoperative radiotherapy was also considered beneficial for patients

Table 2 Pathological characteristics and outcome of patients with clinical stage II or III rectal cancer

	No. of patients (%)	Local recurrence rate (%)	P value	Survival rate (%)	P value
Pathological T (pT)			0.020		<0.001
T1, T2	148 (18.1)	2.9		91.7	
T3a	345 (42.2)	4.9		82.2	
T3b	278 (34.0)	9.5		70.6	
T4	46 (5.6)	7.4		45.6	
Pathological N (pN)			<0.001		<0.001
N0	358 (43.8)	1.8		87.9	
N1	278 (34.0)	6.1		80.3	
N2	181 (22.2)	16.0		53.8	
Pathological stage			<0.001		<0.001
Stage I	83 (9.7)	1.3		95.0	
Stage II	282 (33.0)	2.0		85.7	
Stage III	461 (53.9)	9.5		72.5	
Stage IV	29 (3.4)	20.7		24.5	
Radical margins			0.026		0.010
Negative	806 (98.7)	6.0		78.2	
Positive	11 (1.3)	30.0		54.6	
Lymphatic invasion			<0.001		<0.001
Negative	351 (43.0)	2.2		86.5	
Positive	466 (57.0)	9.4		71.4	
Venous invasion			0.001		<0.001
Negative	444 (54.3)	3.8		82.9	
Positive	373 (45.7)	9.3		71.8	
Tumor differentiation			0.056		<0.001
Well	342 (41.9)	5.0		82.3	
Moderate	433 (53.0)	6.6		76.7	
Others	42 (5.1)	13.9		54.6	

with rectal cancer located between 5 and 10 cm from the anal verge and with clinically positive lymph nodes, who showed a local recurrence rate of around 5%, and for female patients with rectal cancer located less than 5 cm from the anal verge with clinically negative lymph nodes, who showed a local recurrence rate of 7.7%. However, the

risks and benefits of preoperative radiotherapy should be explained to these patients before surgery. On the other hand, local recurrence rates for the remaining patients with rectal cancer were less than 3%, and therefore preoperative radiotherapy was considered unnecessary for them. Because preoperative radiotherapy has been reported to have many adverse effects, it should be avoided in these selected patients.

Eriksen et al. examined patients with T3 rectal cancer and demonstrated that those with a circumferential resec-

Table 3 Multivariate analysis of preoperative clinical factors affecting survival and local recurrence

	Hazard ratio (95% C.I.)	P
Local recurrence		
Clinical N (positive/negative)	2.46 (1.6–4.19)	<0.001
Distance from anal verge (≤5/> 5)	1.97 (1.15–3.68)	0.012
Sex (male/female)	0.72 (0.54–0.96)	0.026
Survival		
Clinical N (positive/negative)	1.47 (1.26–1.72)	<0.001
Clinical T (T1, 2, 3/T4)	0.71 (0.60–0.84)	<0.001
Tumor differentiation (well, moderate/others)	0.67 (0.54–0.85)	0.002
Age (<60/≥60)	0.84 (0.73–0.96)	0.011
CEA (≤5/>5)	0.86 (0.81–0.99)	0.037

C.I. Confidence interval

Table 4 Local recurrence rates in relation to the factors selected by multivariate analysis

Distance from anal verge	Clinical N	
	Negative	Positive
Male		
10–15	0%	2.4%
5–10	0%	5.5%
≤5	1.4%	13.2%
Female		
10–15	0%	0%
5–10	2.0%	4.5%
≤5	7.7%	28.2%

tion margin (CRM) of less than 3 mm or with lymph node involvement should be considered for preoperative therapy [17]. Other reports have also indicated that patients with stage II rectal cancer need not receive radiation therapy after TME surgery [14, 15]. Moreover, MacKay et al. considered that preoperative radiotherapy was unnecessary for patients with T1–T3 rectal cancer after TME surgery because of the low local recurrence rate [16]. These reports and our present results suggest that all rectal cancer patients should not receive adjuvant radiotherapy, and that indications for radiotherapy should be determined according to the local recurrence rates of rectal cancer in each hospital or surgeon.

Late side effects of radiotherapy affect sexual, urinary, bowel, and anal function. Sexual dysfunction includes ejaculation and erectile disorders in male patients and sexual inactivity in both male and female patients. These sexual dysfunctions occur at a significantly higher rate in patients after radiotherapy than in patients without radiotherapy [5, 7]. Heriot et al. proposed a nomogram for predicting sexual dysfunction in male patients, which was able to assist patients when considering treatment options for rectal cancer [7]. Urinary dysfunction caused by radiotherapy is urinary incontinence, and bowel dysfunction caused by radiotherapy includes bowel obstruction, nausea, and abdominal pain. The incidences of urinary incontinence and bowel dysfunction are also significantly higher in patients who receive radiotherapy than in those who do not . [6, 10]. Radiotherapy also worsens anal function and causes fecal incontinence, gas incontinence, soiling, and high stool frequency [6, 9–13]. Fecal incontinence rates were 45%–62% in patients with radiation and 24%–39% in patients without radiation. These differences were significant. Because these late side effects apparently impair patients' quality of life (QOL), as examined by a QOL questionnaire [5, 9, 12], the benefits of radiotherapy should be balanced against these side effects, and appropriate selection of rectal cancer patients for radiotherapy is important.

Recent data have shown an advantage of preoperative therapy compared with postoperative therapy [2, 19]. The German CAO/ARO/AIO 94 trial of preoperative versus postoperative chemoradiation using the TME technique clearly showed that preoperative radiotherapy led to marked improvements in treatment compliance, grade 3–4 toxicity, tumor downstaging, rates of sphincter preservation, and rates of local recurrence, with no improvement of overall survival [2]. Because preoperative therapy has a number of theoretical and practical advantages, it is expected to become a standard therapy for rectal cancer. Therefore, preoperative rectal cancer staging and selection of patients are important, and our results should be of help for this purpose.

Radiation with concurrent chemotherapy (chemoradiotherapy) has been evaluated in several trials. Two trials comparing chemoradiotherapy with radiotherapy alone showed that chemoradiotherapy improved local control and downstaging, although there was no difference in survival benefit between the groups [20, 21]. Bujko et al. showed that chemoradiation did not increase survival and local control compared with radiotherapy alone [22]. Because acute toxicity is increased by chemoradiotherapy and there has been no study of the late side effects of chemoradiotherapy, patient selection is more important than for radiotherapy alone. Further study is required to determine whether or not chemoradiotherapy is necessary.

In the selection of patients for preoperative therapy, correct staging is very important. MRI is very sensitive and specific for this purpose. Brown et al. demonstrated that high-spatial-resolution MRI has high sensitivity and specificity for lymph node metastasis [23]. Our preoperative diagnosis of lymph node status was done using CAT scan and/or MRI, and the sensitivity, specificity and accuracy for lymph node metastasis were 83%, 66% and 76%, respectively. Although these results are relatively good, further improvement is necessary for selection of patients for preoperative therapy.

In this study, the local recurrence rate in females was higher than in males. The reason for this was unknown, because cancer stage, tumor size, and radical margin involvement did not differ between males and females. In the Dutch TME trial, local recurrence in female patients was also significantly higher than in male patients [24]. One of the reasons for this may have been that the positivity rate at the circumferential resection margin in females who underwent abdomino-perineal resection was higher than that in males.

In our study, patients with lower rectal cancer underwent lateral pelvic lymph node dissection [18] and all the patients were Japanese and treated in a National Center Hospital. Therefore, our data could not be directly applied to other hospitals where lateral pelvic lymph node dissection is not performed or in other countries. We are currently performing a clinical trial to compare TME with TME and lateral pelvic lymph node dissection (JCOG0212; ClinicalTrials.gov Identifier: NCT00190541). If this trial shows that the local recurrence rate for TME with lateral pelvic lymph node dissection is lower than that for TME, the results of this study will only be applicable to patients treated with lateral pelvic lymph node dissection. However, if there is no significant difference in the local recurrence rate between TME alone and TME with lateral pelvic lymph node dissection, then the results may be applicable to all patients with rectal cancer.

CRM involvement is a high-risk factor for local recurrence of rectal cancer [25]. In this study, the radical

margin involvement rate was only 1.3%. Because tumors with zero clearance were assessed for radical margin involvement and only one primary slice of the tumor specimen was examined, the radical margin involvement rate was thought to be lower than the reported CRM positivity rate. Adam et al. defined CRM as positive when the tumor was located less than 1 mm from the CRM [26], and the validity of this definition was confirmed by Birbeck et al [27]. These studies showed that the CRM positivity rate was about 25% and was significantly related to local recurrence. The proportion of tumors with zero clearance was about 10% in reports including non-TME surgery [25, 27, 28] and 6–7% in reports including TME surgery[2, 29]. These rates were still higher than the rate of radical margin involvement in our study, possibly because lateral pelvic lymph node dissection is a wider form of resection than TME, thus reducing the CRM positivity rate.

In conclusion, because radiotherapy has several short- and long-term adverse effects, adjuvant radiotherapy should be applied for selected patients. Patients with rectal cancer located less than 5 cm from the anal verge and with clinically positive lymph nodes should be given preopera- tive adjuvant radiotherapy. Patients with rectal cancer located between 5 and 10 cm from the anal verge and with clinically positive lymph nodes, and female patients with rectal cancer located less than 5 cm from the anal verge and with clinically negative lymph nodes should also be considered eligible for preoperative radiotherapy. In the remaining patients with rectal cancer, preoperative radio- therapy is not indicated.

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Case Report

A Case of Lateral Pelvic Lymph Node Recurrence after TME for Submucosal Rectal Carcinoma Successfully Treated by Lymph Node Dissection with En Bloc Resection of the Internal Iliac Vessels

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In Japan, lateral lymph node dissection (LLND) is generally performed for the treatment of T3–4 lower rectal carcinoma, and not for T1 lower rectal carcinoma, because of a low positive rate in patients with T1 lesion. We experienced a rare case of lateral pelvic lymph node recurrence after total mesorectal resection for T1 lower rectal carcinoma, successfully treated by LLND with en bloc resection of the internal iliac vessels. There is no guideline for the treatment of patients with isolated lateral lymph node recurrence; however, surgery should be considered for such patients.

Key words: submucosal rectal carcinoma — isolated lateral lymph node recurrence — surgical resection

INTRODUCTION

Significant impact on survival of lateral lymph node dissection (LLND) for lower rectal carcinoma has been reported, mainly from Japan. Many reports have suggested that a beneficial effect of LLND was achieved in patients with T3–4 lower rectal carcinoma; thus, few surgeons consider T1 as an indication for LLND (1–3). Sugihara et al. (4) reported that lateral lymph node metastasis had been found in only two patients among 42 patients with T1 rectal carcinoma treated with LLND in their retrospective multicenter analysis (2/42, 4.8%), suggesting that LLND should be considered for T3 or T4 lower rectal carcinoma. Currently, in Japan, LLND is not generally performed for treatment of T1 rectal carcinoma.

There are three different patterns of pelvic recurrence of rectal carcinoma including anastomosis, residual mesorectal fat, and the pelvic wall, and it is possible to determine if pelvic wall recurrence is lateral pelvic lymph node recurrence by performing detailed evaluations using computed

tomography (CT) and MRI. Generally, if it is judged that pelvic recurrence is resectable, chemoradiation therapy plus surgery is usually indicated. Regarding surgery for pelvic recurrence, total pelvic exenteration or combined sacral resection has to be selected in a significant number of cases (5,6). Although the significance of surgical resection for isolated lymph node recurrence has been reported in several papers, there have been few reports on treatment for isolated lateral pelvic lymph node recurrence, and a general therapeutic strategy for isolated lateral pelvic lymph node recurrence has not been established (7,8).

We experienced a rare case of lateral pelvic lymph node recurrence after TME for T1 lower rectal carcinoma, successfully treated by LLND with en bloc resection of the internal iliac vessels. Isolated lateral lymph node recurrence after TME for T1 lower rectal carcinoma is rare and has not been reported previously in the literature.

CASE REPORT

A 61-year-old man was referred to the Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan, in December 2003 for the treatment of isolated lateral

A

B
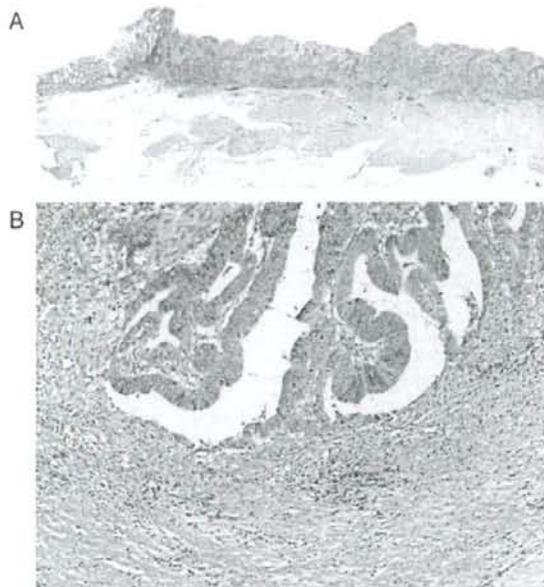
Figure 1. H & E staining of the resected specimen [the tumor had invaded the submucosa, but not the muscularis propria (a: low-power view, b: higher-power view)].

lymph node recurrence after TME for T1 lower rectal carcinoma. He had a past history of lower rectal carcinoma with low anterior resection (LAR) at another hospital in February 2002. Regarding the extent of lymph node dissection, division of the root of the inferior mesenteric artery without LLND had been performed. Macroscopically, the size of the tumor was 20 mm in maximal diameter, and the tumor was diagnosed as for the superficial type. Histopathological findings demonstrated well-differentiated adenocarcinoma, and 12 lymph nodes were harvested, but there were no detectable metastases. The tumor had invaded till the submucosa, but not the muscularis propria (Fig. 1).
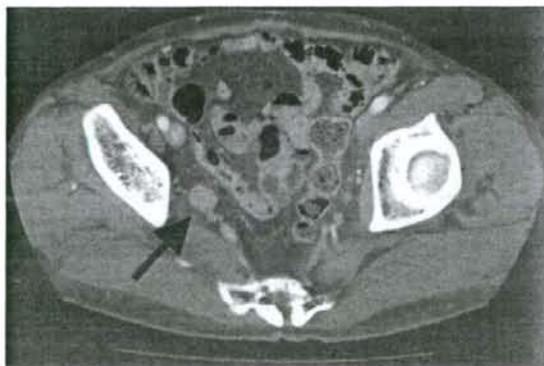
Figure 2. CT findings. A 2 cm mass was located in the right pelvic cavity. The arrow points at a tumor.

Figure 3. Surgical finding. En bloc resection with internal iliac vessels and pelvic nerve plexus.

Lymphovascular invasion was not identified. No cancer cells were observed in the margin of the resected specimen.

After the operation, periodic follow-up examinations were performed, and in December 2003, abdominal CT demonstrated a 2 cm mass located in the right pelvic cavity (Fig. 2).

While we observed him for several months, no other metastasis was found. The preoperative diagnosis was solitary lateral lymph node metastasis. In May 2004, we performed right LLND with en bloc resection of the internal iliac vessels and pelvic nerve plexus (Fig. 3).

Histologically, 10 lymph nodes were removed and, in one of them, metastasis of adenocarcinoma was found. His postoperative course was uneventful, and he was discharged on the 14th day after the operation. Fortunately, he had neither dysuria nor sexual dysfunction. Postoperative additional chemo-radiotherapy was not performed, because of the patient's refusal. Forty-four months after the second operation, the patient is alive and recurrence free.

DISCUSSION

Isolated lateral lymph node recurrence after TME for pT1 lower rectal carcinoma is rare, and has not been reported previously in the literature. Generally, lateral lymph node recurrence after TME is regarded as systemic disease, and in such cases, chemotherapy, radiotherapy or a combination of both, rather than surgery, is selected. With regard to isolated lymph node recurrence, there are some reports of resected cases (7,8), but the significance of surgical treatment remains unclear; however, this patient underwent surgical resection and has survived recurrence free for 44 months.

It is generally accepted that deep submucosal invasion, the presence of lymphovascular invasion, low grade differentiation, and tumor cell at or near the resection margin after endoscopic resection or local excision are adverse risk factors for lymph node metastasis with submucosal invasion (9–13).

Additionally, Kikuchi et al. (9) reported that tumor location in the lower third of the rectum promotes lymph node metastasis more often. Although histopathological finding of the present case demonstrated deep submucosal invasion without lymphovascular invasion, it was difficult to predict lateral lymph node recurrence based on this initial histopathological finding. However, there is a possibility that the sentinel lymph node was located in the lateral area (14).

As mentioned above, many clinical studies from Japan have suggested that a beneficial effect of LLND was achieved in patients with T3–4 lower rectal carcinoma; thus, few surgeons consider T1 as an indication for LLND (1–3). However, in reports by Western researchers on the site of recurrence after TME for advanced rectal carcinoma, as the incidence of lateral lymph node recurrence was low, they concluded that the benefit of LLND is limited (15,16). A randomized controlled trial (RCT) on the efficacy of prophylactic LLND is currently ongoing in Japan in patients with advanced lower rectal carcinoma without obvious pre- and intra-operative lateral lymph node metastasis (17). This study is receiving attention as an RCT performed by surgeons with sufficient accumulated experience in LLND.

In contrast, for patients who have lateral lymph node metastasis at the time of initial operation, or for patients with isolated lateral lymph node metastasis after TME, no therapeutic strategy has been established. Although lateral lymph node metastasis is regarded as distant metastasis in TNM classification, it is regarded as local disease in Japan (18). In our hospital, if there is no finding of metastasis/recurrence in other regions and LLND is not difficult to perform, then LLND is considered.

With regard to en bloc resection of blood vessels, it goes without saying that there is a fear of increased risk of complications; however, from the oncological viewpoint, even if the tumor does not invade blood vessels through the capsule of the lymph node, the risk of tumor cell spillage is increased if the dissection cuts into the lymph node capsule, even to a slight degree. We have reported the favorable effect of LLND with en bloc resection of the internal iliac vessels on local control in patients with lateral pelvic lymph node metastasis from lower rectal carcinoma (1). A particular aspect of en bloc resection of the internal iliac vessels is that it does not require revascularization. For lymph node recurrence near blood vessels, and if en bloc resection of the vessels requires revascularization with artificial vessels, it should be performed only if it can be justified after considering the risks associated with surgery.

In conclusion, we report the first case of lateral pelvic lymph node recurrence after TME for pT1 lower rectal carcinoma, successfully treated by lymph node dissection with en bloc resection of the internal iliac vessels. Patients with isolated lateral lymph node recurrence treated with surgery might have a favorable long-term prognosis. Therefore, for such patients, surgery is one of the choices. On the other hand, in patients with pT1N0 lower rectal carcinoma, we may rarely experience lateral lymph node recurrence, but occasionally, pelvic recurrence including anastigmatic recurrence. Although lateral lymph node recurrence was detected in the present case, we are not insisting that LLND is necessary during the initial surgery for patients with T1 lower rectal carcinoma, because of the low positive rate (4); however, follow-up examinations of the pelvis should be performed periodically.

Conflict of interest statement
None declared.

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Intersphincteric Resection for Very Low Rectal Adenocarcinoma: Univariate and Multivariate Analyses of Risk Factors for Recurrence

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Background: The aim of this study was to analyze the risk factors for local and distant recurrence after intersphincteric resection (ISR) for very low rectal adenocarcinoma.

Methods: One hundred twenty consecutive patients with T1–T3 rectal cancers located 1–5 (median 3) cm from the anal verge underwent ISR. Univariate and multivariate analyses of prospectively recorded clinicopathologic parameters were performed.

Results: Fifty patients had disease categorized as stage I, 21 as stage II, 46 as stage III, and 3 as stage IV on the basis of International Union Against Cancer tumor, node, metastasis staging system. Median follow-up time was 3.5 years. The 3-year rates of local and distant recurrence were 6% and 13%, respectively. Univariate analysis of the risk factors for local recurrence revealed pathologic T, pathologic stage, focal dedifferentiation, microscopic resection margins, and preoperative serum CA 19-9 level to be statistically significant. Multivariate analysis showed resection margin, focal dedifferentiation, and serum CA 19-9 level to be independently significant. Univariate analysis of the risk factors for distant recurrence indicated tumor location, combined resection, tumor annularity, pathologic N, lateral pelvic lymph node metastasis, pathologic stage, histologic grade, lymphovascular invasion, perineural invasion, and adjuvant chemotherapy to be significant. Multivariate analysis identified pathologic N, histologic grade, and tumor location to be independently significant.

Conclusion: Profiles of risk factors for local and distant recurrences after ISR are different. With local recurrence, the resection margin, focal dedifferentiation, and serum CA 19-9 level are important. For distant recurrence, the lymph node status, histologic grade, and tumor location need to be taken into account.

Key Words: Rectal cancer—Surgery—Intersphincteric resection—Local recurrence—Recurrence—Prognostic factor.

Standard surgery for patients with massively invasive rectal adenocarcinoma located within 5 cm

from the anal verge is abdominoperineal resection.[1] To avoid permanent colostomy for such patients, modern intersphincteric resection (ISR) was developed in the 1980s and became well established in the 1990s.[2–4] ISR is currently defined as a procedure obtaining sufficient margins by removing part or whole of the internal sphincter and restoring bowel continuity for rectal cancers involving or next to the

anal canal. ISR is usually performed in combination with total mesorectal excision. Cautious performance of this operation has been reported to allow satisfactory results with regard to both defecatory function and oncologic outcome.[4–7]

In our previous study, we showed that ISR with meticulous dissection and irrigation after closure of the distal stump does not increase risk of local or distant recurrence.[8] ISR without radiotherapy is usually sufficient for patients with T1–T2 tumors. However, with T3 tumors, neoadjuvant therapy should be considered if resection margins are estimated to be insufficient.[8]

Appropriate selection of patients who are at high risk for recurrence is essential to reduce unnecessary toxicity and costs of neoadjuvant and adjuvant therapy for those at low risk. Selection criteria are thus needed to stratify patients for neoadjuvant and adjuvant therapy and also for clinical trials. At present, however, there have been few studies addressing risk factors for recurrence after ISR. The aim of this study was thus to conduct retrospective exploratory analysis of the risk factors for local and distant recurrences after ISR for very low rectal adenocarcinoma.

PATIENTS AND METHODS

Between October 1993 and February 2007, 122 patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. Selection criteria for ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) of <2 cm; (4) no involvement of the external sphincter; and (5) no signs of disseminated disease. The patients were assessed with chest and abdominal computed tomography (CT), digital anorectal examination, and radiological studies, including endorectal ultrasound, thin-section helical CT, or high-resolution magnetic resonance imaging (MRI). Approval by the institutional review board was not required for the observational study. All patients gave informed consent for usage of their data for analysis.

Univariate and multivariate analyses of 26 prospectively recorded clinicopathologic variables were conducted for the 120 consecutive patients who did not receive neoadjuvant radiotherapy. Data from the remaining two given radiotherapy were excluded from the present analysis.

Surgical Procedures

The surgical procedures were described previously[8] and are basically similar to those originally documented by Schiessel et al.[4,7] The intersphincteric plane between the puborectalis and the internal sphincter was dissected cautiously as caudal as possible under direct vision by electrocautery. If the lower edge of the tumor was reached, the anal canal was closed just below the tumor, and then washed with povidone iodine followed by saline. A self-holding retractor was applied to the anal canal, the internal sphincter was circumferentially incised and the intersphincteric plane was dissected. A resection margin of at least 1 cm was always attempted. After removal of the rectum, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made.

Histopathologic Examination

Results of histopathologic examination were prospectively documented in the pathology report form. Evaluated variables included gross tumor morphology, pathologic depth of transmural invasion (pT), pathologic regional lymph node metastasis (pN), pathologic lateral pelvic lymph node metastasis, pathologic distant metastasis (pM), pathologic stage, histopathologic grade, lymphovascular invasion, perineural invasion, mucin production, focal dedifferentiation, and circumferential and distal resection margins. pT, pN, pM, pathologic stage, and histopathologic grade were classified according to the International Union Against Cancer tumor, node, metastasis (TNM) classification.[9] Perineural invasion was defined as the presence of cancer cells inside the perineurium.[10] Focal dedifferentiation was defined as the presence of polygonal, noncolumnar cancer cells which had a single or a solitary trabecular form with indistinct polarity and had a diffusely infiltrative pattern at the invasive front.[11,12]

Follow-up

All of the patients were followed up with a median follow-up time of 3.5 (range, .9–11.7) years for those who remained alive, and 93 patients (78%) could be followed up for more than 2 years. Patients with stage I tumors were examined by chest and abdominopelvic CT, as well as carcinoembryonic antigen measurement every year for at least 5 years. Patients with stage II tumors were examined every 6 months for 2 years, then yearly for at least 3 years. Patients with

stage III tumors were examined every 4 months for 2 years, then every 6 months for at least 3 years.

Statistical Analysis

The starting point for the recurrence-free interval was the day of surgery, and data on patients who were alive or free of recurrence were censored at the last follow-up. Local recurrence was defined as confined to the pelvis and distant recurrence as present outside of the pelvis.

Survival curves were estimated by the Kaplan-Meier method, and differences in survival were evaluated with the log rank test. Multivariate analysis was performed by Cox regression model with the forward stepwise method (likelihood ratio). All statistical analyses were conducted by SPSS for Windows, version 11.0J (SPSS-Japan, Tokyo, Japan). P values were two sided and were considered to be statistically significant at <.05.

RESULTS

Clinicopathologic Findings

Findings for 26 clinicopathologic variables related to patient and tumor characteristics, treatment, and pathology are summarized in Table 1. There were 92 male and 28 female patients with a median age of 57 (range, 26–75) years. The median distance from the anal verge to the tumor was 3 (range, 1–5) cm.

A total of 103 patients underwent partial resection of the internal sphincter and 17 underwent complete resection. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. All patients underwent total mesorectal excision. In addition to total mesorectal excision, 46 patients received extended lateral pelvic lymph node dissection. The median number of lymph nodes removed at surgery was 29 (range, 4–88), and 108 patients (90%) underwent dissection of 12 or more nodes. Combined resection of adjacent organs was performed for 12 patients. Two patients with a solitary liver metastasis and one with a solitary lung metastasis underwent complete resection of their metastases. A total of 108 patients had a protective stoma, which was closed 3 months after ISR. Postoperatively, 26 patients with stage III disease and 1 with curatively resected liver metastasis received adjuvant chemotherapy with 5-fluorouracil plus leucovorin, or uracil-tegafur plus leucovorin on the basis of the results from the National Surgical Adjuvant

Breast and Bowel Project Protocol C-06,[13] or oral uracil-tegafur on the basis of the results of the National Surgical Adjuvant Study of Colorectal Cancer 01 randomized trial.[14]

The median tumor size was 3.7 (range, 1–12) cm. Data on TNM classifications and histopathologic findings are provided in Table 1. Resection margins were macroscopically negative in all patients, but microscopically positive in four. One patient had both circumferential and distal positive margins, and the other three had a circumferential positive margin. Excluding these four patients, the median distal margin was 1.2 (range, .3–4) cm.

Of 39 patients (33%) who experienced complications, 30 were treated conservatively and 9 received surgery. Of 15 patients (13%) with anastomotic leakage, 6 underwent emergency operations. One patient who had anastomotic leakage and sepsis died on the third postoperative day (30-day mortality rate = .8%).

Survival and Recurrence

At the last follow-up in February 2008, 112 patients were alive and 8 were dead. Causes of death included rectal cancer (n = 4 patients), other cancers (n = 2), anastomotic leakage (n = 1), and cerebral contusion (n = 1). The estimated overall 3- and 5-year survival rates were 95% and 91%, respectively, including one hospital death.

A total of 20 patients (17%) experienced recurrence. Estimated 3- and 5-year cumulative rates for overall recurrence were 17% and 23%, respectively (Fig. 1). Sites of the first recurrence included the pelvis in six patients, pelvis and lung in one, inguinal lymph nodes in two, inguinal lymph nodes and lung in one, lung in four, lung and liver in one, and liver in five. The incidences of overall recurrence for stage I, II, III, and IV disease were 5%, 22%, 27%, and 50%, respectively.

In total, eight patients (6.7%) developed local recurrence, with estimated 3- and 5-year cumulative rates of 6% and 10%, respectively (Fig. 1). Detailed sites of local failure included the internal iliac or obturator nodes in three patients, circumferential resection margin in two, anastomosis in one, seminal vesicle in one, and sacrum in one. The incidences of local failure for stage I, II, III, and IV disease were 2%, 19%, 7%, and 0%, and for pathological T1, T2, and T3 tumors were 4%, 2%, and 12%, respectively.

Estimated 3- and 5-year cumulative rates for distant recurrence, found in 15 patients (13%), were 13% and 18%, respectively (Fig. 1). The incidences

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TABLE 1. *Univariate analyses of 26 clinicopathologic variables related to patient and tumor characteristics, treatment, and pathology*

Characteristic	No. of patients	3-Year cumulative local recurrence rate		3-Year cumulative distant recurrence rate	
		%	P	%	P
Sex					
Male	92	6	.87	16	.38
Female	28	7		4	
Age					
<60 y	71	10	.098	16	.57
≥60 y	49	0		9	
Distance of tumor from the anal verge					
<2.5 cm	21	0	.91	28	.034
≥2.5 cm	99	7		11	
Internal sphincter resection					
Partial	103	7	.27	11	.14
Complete	17	0		27	
Combined resection					
No	108	7	.33	11	.021
Yes	12	0		33	
Extended lateral pelvic lymph node dissection					
No	74	5	.58	10	.25
Yes	46	8		17	
Tumor size					
<3.5 cm	50	5	.86	9	.95
≥3.5 cm	70	7		15	
Tumor annularity					
<3/4	101	7	.35	10	.034
≥3/4	16	0		44	
Unknown	3				
Gross tumor contour					
Clear	117	6	.69	12	.17
Diffuse	2	0		50	
Unknown	1				
Gross anal margin					
<1 cm	28	4	.49	18	.72
≥1 cm	92	7		12	
Pathological depth of transmural invasion (pT)					
1	25	0	.027	9	.055
2	46	3		5	
3	49	13		23	
Pathological lymph node metastasis (pN)					
0	72	5	.24	5	<.0001
1	30	4		17	
2	18	0		50	
Histopathologic lateral pelvic lymph node metastasis					
Negative	112	6	.27	10	<.0001
Positive	8	13		53	
Pathological distant metastasis (pM)					
0	117	6	.73	12	.14
1	3	0		50	
Pathological UICC TNM stage					
I	50	0	.012	5	.0058
II	21	17		5	
III	46	8		25	
VI	3	0		50	
Histopathologic grade					
Well differentiated	59	5	.47	11	.029
Moderately differentiated	53	7		12	
Poorly differentiated	8	13		38	
Lymphovascular invasion					
Negative	48	3	.22	2	.0077
Positive	71	8		22	
Unknown	1				

TABLE 1. *continued*

Characteristic	No. of patients	3-Year cumulative local recurrence rate		3-Year cumulative distant recurrence rate	
		%	*P*	%	*P*
Perineural invasion					
Negative	99	6	.80	11	.022
Positive	13	8		40	
Unknown	8				
Mucin production					
Negative	108	5	.26	13	.80
Positive	12	17		18	
Focal dedifferentiation					
Negative	55	0	.018	7	.13
Positive	58	13		21	
Unknown	7				
Microscopic resection margins					
Negative	116	4	<.0001	14	.50
Positive	4	50		0	
Transfusion					
No	112	6	.47	12	.21
Yes	8	0		25	
Anastomotic leak					
No	105	7	.31	14	.55
Yes	15	0		8	
Adjuvant chemotherapy					
No	93	5	.47	8	.0008
Yes	27	8		38	
Preoperative serum CEA level					
<5 ng/mL	95	5	.73	14	.44
≥5 ng/mL	25	8		11	
Preoperative serum CA 19-9 level					
<37 U/mL	113	5	<.0001	13	.17
≥37 U/mL	7	29		25	

UICC, International Union Against Cancer; TNM, tumor, node, metastasis system; CEA, carcinoembryonic antigen.
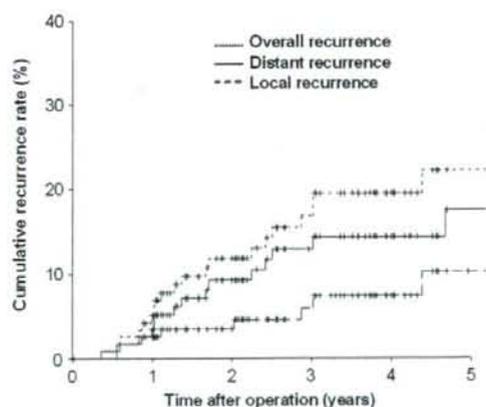
FIG. 1. Cumulative rates for overall recurrence, distant recurrence, and local recurrence among 120 patients undergoing intersphincteric resection.

of distant recurrence for stage I, II, III, and IV disease were 6%, 5%, 22%, and 33%, respectively.

Univariate Analysis

Cumulative local recurrence was statistically significantly associated with pT, pathologic stage, focal dedifferentiation, microscopic resection margins, and the preoperative serum CA 19-9 level (Table 1).

Cumulative distant recurrence was statistically significantly associated with distance of the tumor from the anal verge, combined resection, tumor annularity, pN, lateral pelvic lymph node metastasis, pathologic stage, histopathologic grade, lymphovascular invasion, perineural invasion, and adjuvant chemotherapy (Table 1).

Multivariate Analysis

Multivariate analysis was performed for those factors associating statistically significantly with cumu-

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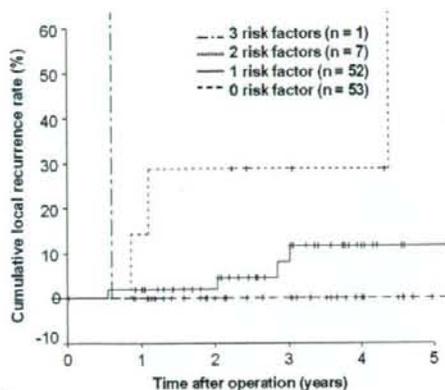
No. at risk

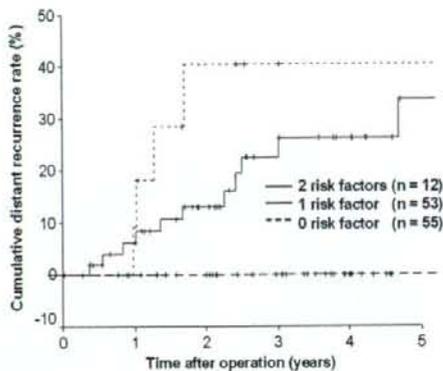|					
0 risk factor	53	50	39	32	23	14
1 risk factor	52	48	37	25	12	5
2 risk factors	7	5	4	2	1	
3 risk factors	1					

FIG. 2. Cumulative rates for local recurrence among 120 patients undergoing intersphincteric resection, according to the number of risk factors for local recurrence.

No. at risk

0 risk factor	55	52	46	38	25	15
1 risk factor	53	44	32	21	15	8
2 risk factors	12	10	5	3	2	2

FIG. 3. Cumulative rates for distant recurrence among 120 patients undergoing intersphincteric resection, according to the number of risk factors for distant recurrence.

lative local recurrence and distant recurrence on univariate analysis. The multivariate analysis of four variables, excluding pathological stage, revealed that a positive microscopic resection margin (hazard ratio, 19 [95% confidence interval, 3.3–111]; $P = .001$), positive focal dedifferentiation (22 [1.6–333]; $P = .021$), and preoperative serum CA 19-9 level of >37 U/mL (5.6 [1.1–29]; $P = .04$) were independently associated with an high local recurrence rate. The 3-year cumulative local recurrence rates for patients with zero, one, two, and three positive risk factors were estimated to be 0%, 8%, 29%, and 100%, respectively (Fig. 2).

Multivariate analysis for distant recurrence with seven variables, excluding pathological stage and lateral pelvic lymph node metastasis, revealed that pN1 or pN2 (hazard ratio, 13 [95% confidence interval, 3.0–53]; $P < .001$), poorly differentiated histology (6.4 [1.4–29]; $P = .015$), and distance of tumor from the anal verge less than 2.5 cm (3.7 [1.2–12]; $P = .026$) were independently associated with a poorer prognosis. The 3-year cumulative distant recurrence rates for patients with zero, one, and two positive risk factors were estimated to be 0%, 23%, and 40%, respectively (Fig. 3).

DISCUSSION

In the present study, we found by univariate analysis that pT, pathologic stage, focal dedifferentiation,

microscopic resection margins, and preoperative serum CA 19-9 level were statistically significantly associated with local recurrence after ISR. On multivariate analysis, resection margins, focal dedifferentiation, and serum CA 19-9 level were independently associated with local recurrence. We could stratify high-risk patients by using these three factors. With two or more factors, the 3-year local recurrence rate was estimated to be 29% or higher. Therefore, when two or more risk factors identified here become apparent, neoadjuvant chemoradiotherapy should be provided to widen resection margins, or abdominoperineal resection should be substituted for ISR.

Preoperative radiotherapy or chemoradiotherapy are generally applied as standard neoadjuvant therapy for T3 and/or lymph node positive rectal cancers in general, in addition to total mesorectal excision. This is based on evidence that radiotherapy better reduces local recurrence and prolongs disease-free and overall survival when compared with surgery alone,[15,16] and that preoperative chemoradiotherapy is more effective for local control, less toxic, and more favorable for sphincter preservation than postoperative therapy.[17]

However, neoadjuvant and adjuvant therapy strategies to prevent local and distant recurrence after ISR have yet to be established. There is great variation in application of radiotherapy as a neoadjuvant against local recurrence, with reported rates ranging from 0% to 88%. Schiessel et al.[7] never provided radiation, even for T3 tumors, like us, whereas Rullier et al.[18] irradiate

all T3 tumors and some T1 and T2 lesions. The other authors provided radiotherapy to 25% to 75% of patients.[5,6,19,20] Although there is some dependence on selected patient population, tumor stage, and staging accuracy, usage also seems to reflect surgeons' preferences.

Radiotherapy for rectal cancer in general is well known to have the potential to cause damage to anorectal[21,22] and sexual[23,24] functions. In cases with very low rectal cancer necessitating ISR, if radiation is provided, damage to the sphincter is inevitable and may be catastrophic for some patients whose sphincters are also damaged by surgery. Chamlou et al.[20] reported that functional results after ISR are statistically significantly altered by preoperative radiotherapy. Ten (42%) of 24 patients who received preoperative radiotherapy of 45 Gy were incontinent as compared with 7 (15%) of 46 without radiotherapy ($P = .02$).[20] Therefore, more selective usage of radiotherapy in case with ISR seems to be preferable than in the general rectal cancer population.

Because preoperative radiotherapy is known to be more effective and less toxic,[17] it is preferable to stratify patients preoperatively. For this purpose, high-resolution MRI is accurate at estimating the resection margin status. In a prospective study of 408 rectal cancer patients, the MERCURY Study Group found that high-resolution MRI predicted a clear circumferential resection margin with an overall accuracy rate of 88%.[25]

Focal dedifferentiation,[11,12] also known as "tumor budding,"[26] can be accurately estimated by excisional or transanal submucosal biopsy[26] before ISR. The transanal submucosal biopsy allows specimens to be removed from the boundary zone between the tumor and the normal mucosa, including the submucosal tissue with exploratory excisional forceps. On the basis of this technique, the submucosal invasive frontal region can be predicted with up to 86% accuracy.[26]

Although the exact relation between CA 19-9 and local recurrence is unclear, CA 19-9 is easily assessable. Thus, preoperative performance of high-resolution MRI, excisional/submucosal biopsy, and serum CA 19-9 measurement is recommended for every candidate for ISR and warrants further investigation and validation.

In our previous study, we observed the 3-year cumulative local recurrence rate of 0% in patients with T1–T2 tumors and thus stated that meticulous performance of ISR allows local control without radiotherapy for such lesions.[8] In the present investigation, however, we found two cases (2.8%) with local recurrence. One patient with a pT1 tumor and a microscopic positive margin developed anastomotic recurrence 4.4 years after ISR. Another with a pT2 tumor had liver metastasis 10 months after ISR and underwent partial hepatectomy. This patient subsequently developed lung, liver, arm, and brain metastases, and also experienced pelvic recurrence in a seminal vesicle 2 years after ISR. Because the former case had a disease-positive surgical margin and the latter developed pelvic recurrence after fatal disseminated diseases, these two cases should be regarded as exceptional. Therefore, we still consider ISR without radiotherapy to be sufficient treatment for T1–T2 tumors in general. However, if patients have two or more of the risk factors we identified in the present study, neoadjuvant therapy should be considered.

Of the other studies on ISR, only three mentioned risk factors for local recurrence. Schiessel et al.[7] reported that only Dukes' stage and the T stage had an impact on local failure. Chamlou et al.[20] described overall survival to be statistically significantly influenced by pathologic TNM stage and pT on univariate analysis, but found no impact of the investigated factors on local recurrence. Analyzing data of 134 patients with rectal cancer located 2 to 11 (median 6.5) cm from the anal verge, undergoing not only ISR, but also low anterior resection or coloanal anastomosis, Paty et al.[27] found that mesenteric implants, a positive microscopic resection margin, a T3 tumor, perineural invasion, blood vessel invasion, and poorly differentiated histology were statistically significantly associated with pelvic recurrence on univariate analysis. In line with the previous reports, pT and pathologic staging were identified as prognostic factors in the present study as well. In addition, these variables are regarded as category I prognostic factors.[28] Therefore, they should be included with the above-mentioned list for further validation.

To our knowledge, risk factors for distant as opposed to local recurrence have hitherto not been studied separately and sufficiently. We here found that by univariate analysis, cumulative distant recurrence was statistically significantly associated with distance of tumor from the anal verge, combined resection, tumor annularity, pN, lateral pelvic lymph node metastasis, pathologic stage, histopathologic grade, lymphovascular invasion, perineural invasion, and adjuvant chemotherapy. By multivariate analysis, pathologic lymph node involvement, histologic grade, and tumor location were independently associated with distant recurrence. For patients with one or more positive risk factors, the 3-year cumulative distant recurrence rate was estimated to be 23% or

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higher. Because adjuvant chemotherapy for stage II and III disease is believed to reduce distant recurrence by 30% to 40%, we recommend adjuvant chemotherapy for patients with one or more risk factors, in line with other authors' recommendations.[7,18,19]

As we showed, the risk factor profiles for distant and local recurrence differ, as do the prophylactic treatments. Therefore, local and distant recurrence should be analyzed separately. This is now feasible in the era of modern imaging technologies, with the availability of high-resolution MRI, multidetector row CT, and positron emission tomography-CT, which enable accurate diagnosis and differentiation of local and distant recurrence.

In conclusion, this retrospective exploratory study suggests that profiles of risk factors for local and distant recurrence after ISR may differ greatly. With local recurrence, the resection margin, focal dedifferentiation, and serum CA 19-9 level seem to be important. For distant recurrence, the lymph node status, histologic grade, and tumor location need to be taken into account. By using these factors, we may be able to stratify patients for neoadjuvant and adjuvant therapy and also for future clinical trials. These results warrant further investigation and validation with larger data sets or in future prospective trials according to the scoring system we have outlined.

ACKNOWLEDGMENTS

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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.