TABLE 3. *Univariate predictors of positive resection margin*

Variable	Microscopic resection margin Negative	Positive	P
Gender			
Female	5	3	1.0
Male	19	14	
Age, years			
< 60	19	10	.18
≥60	5	7	
Primary cancer stage			
I/II/III	23	12	.066
IV	1	5	
Initial surgery			
Local excision, anterior resection	13	8	.76
Abdominoperineal resection	11	9	
Lymphadenectomy at initial surgery			
Conventional	20	13	.70
Extended	4	4	
Local-disease-free interval (month)			
≤12	7	9	.20
> 12	17	8	
Preoperative CEA level (ng/ml)			
≤10	16	6	.062
> 10	8	11	
Extent of preoperative pain			
None, perineum	21	9	.029
Buttock, thigh, leg	3	8	
Tumor extent			
Solitary pelvic tumor	17	7	.11
Pelvic metastasis, distant metastasis	7	10	
Largest tumor diameter (cm)			
≤5	15	9	.75
> 5	9	8	
Sacral involvement			
Adhesion	14	11	.75
Periosteum, marrow	10	6	
Pathological grade			
Well, moderate, mucinous, adenosquamous	21	16	.63
Poor, signet-ring cell	3	1	
Macroscopic growth pattern			
Solitary expanding	12	2	.018
Multiple expanding, infiltrating	12	15	
Preoperative radiation			
Yes	8	3	.31
No	16	14	

CEA, carcinoembryonic antigen.

went palliative-intent resection as a result of gross residual lung metastases were excluded from this study. Univariate analysis revealed that the incidences of microscopic positive margins were significantly higher in patients with multiple expanding or diffuse infiltrating growth (56% vs. 14%; P = .018) and in patients with pain extending to the buttock or further (72% vs. 30%; P = .029; Table 3). On multivariate analysis of the 14 dichotomized variables, excluding resection margin, multiple expanding or diffuse infiltrating growth was independently associated with positive margin (hazard ratio, 7.5 [95% confidence interval, 1.4–40]; P = .019).

TABLE 4. *Sites of first recurrence after abdominal sacral resection in 37 patients undergoing macroscopic curative resection*

Site	No. Patients (%)
Local	
Local alone	6 (24)
Local, lung	3 (12)
Local, adrenal gland	1 (4)
Local, lung, liver	1 (4)
Local, lung, pancreas	1 (4)
Local, liver, para-aortic lymph node	1 (4)
Lung	
Lung alone	5 (20)
Lung, para-aortic lymph node	2 (8)
Liver, lymph node	1 (4)
Para-aortic lymph node	1 (4)
Peritoneum	1 (4)
Brain	1 (4)
Unknown	1 (4)

Recurrence Patterns

Of the 37 patients who underwent macroscopic curative resection, 25 (68%) experienced further recurrence. Sites of their first recurrence after ASR are listed in Table 4. Of them, 13 patients (52%) had local failure, 7 (28%) had lung metastasis, and 14 (56%) had failures confined locally or to the lung. Sites of local failure were the cut end of the sacrum in five, the sacral cut end and buttock in one, and the pelvic side wall or ischium in 3. None of the 25 patients with recurrence was treatable by surgery, so these patients were given chemotherapy, radiotherapy, and/or best supportive care.

Of the 13 patients who developed local failure, 9 had positive margins, and 4 had negative margins on histological analysis. Of the 24 patients without local failure, 20 had microscopic negative margins, and 4 had microscopic positive margins. The rate for local failure was significantly higher in patients with microscopic positive margins than in those with microscopic negative margins (69% [9 of 13] vs. 17% [4 of 20]; P = .003). When the accuracy of the microscopic status of surgical margins in prediction of local failure was evaluated, the sensitivity was 69% (9 of 13), the specificity was 83% (20 of 24), the positive predictive value was 69% (9 of 13), the negative predictive value was 83% (20 of 24), and the overall accuracy rate was 78% (29 of 37). Of the 13 patients with microscopic positive margins, 9 developed local recurrence that corresponded well to histological findings, 1 experienced local failure at a different site with a positive margin, and 3 had no obvious local failure at the last follow-up.

DISCUSSION

The most effective treatment for PPR of rectal carcinoma is a curative resection, that is, complete resection with microscopic negative margins.[13,15,17–19,22] Because the tumor involves contiguous organs, including the sacrum, retained rectum, internal iliac vessels, and genitourinary organs, by either invasion or dense adhesion, combined resection of these organs—that is, ASR—is mandatory for clear surgical margins and possible cure. The overall 5-year survival rate after ASR is reported to be 25% to 31% in the largest series[13,14] and was 34% in this study. Such results have never been achieved with other therapeutic modalities, including chemotherapy and radiotherapy.[4–9]

However, morbidity and mortality after ASR are reported to be 26% to 82%[13,15–18,21,22] and 0% to 9%,[13–22] respectively. In our series, they were 61% and 2%, and 23% of our patients experienced major complications resulting in reoperation or death, and their mean hospital stay was 135 days. In addition, most patients lose genitourinary functions and must endure permanent stomas. These costs are very high and sometimes even catastrophic for those who nevertheless do not obtain long-term survival. Therefore, appropriate patient selection based on survival benefit determined on the basis of prognostic factors is necessary. Also, efforts toward seeking effective adjuvant therapy aiming at the most common sites of recurrence are mandatory. Thus, we analyzed prognostic factors and recurrence patterns after ASR in this study.

Several factors that can be estimated before surgery have been reported to be significantly associated with prognosis on either univariate or multivariate analysis. These include residual tumor extent,[13,15,17–19,22] distant metastasis,[14] initial operation,[13] disease-free interval,[14] preoperative CEA level,[13,14] preoperative CEA doubling time,[14] and proliferating cell nuclear antigen labeling index.[24] In addition, whether significant or not, there are factors definitely indicative of a poor prognosis. Wanebo et al.[13,25] reported that patients with positive margins, bone marrow involvement, or pelvic lymph node involvement had a median survival of only 10 months. Strong suspicion of such factors thus contraindicates ASR. However, the number of patients so far studied is still not sufficiently large to allow definitive patient selection criteria to be established.

We tested 15 factors in multivariate analysis because previous studies indicated their potential relationship to survival after ASR.[13–15,17–19,22,24,25] Of these, microscopic positive margins, LDFI < 1 year, and preoperative pain exceeding the buttock showed a significant independent association with a poor prognosis. Microscopic margin status is the most significant, as reported so far.[13,15,17–19,22] Of our patients with microscopic positive margins, 69% developed local recurrence, and this caused persistent pain and a poor prognosis. Although some previous studies claimed a benefit of palliative resection for both survival and pain,[26] it usually leads to a very poor prognosis and fails to relieve pain, as previously reported.[25,27] Therefore, palliative resection leaving a gross residual tumor should not be attempted. In addition to conventional imaging,[28,29] recent advances in radiological imaging, including thin-section magnetic resonance imaging[30] and multidetector row CT,[31] allow us to accurately evaluate tumor extent so that cautious interpretation can preclude such unnecessary surgery.

The extent of preoperative pain corresponds well with tumor extent and invasiveness and therefore predicts survival.[17] In this study, the survival of the patients with buttock pain was significantly worse than that of patients without pain or with perineal pain and was significantly better than that of patients with thigh or leg pain. Thigh or leg pain, caused by involvement of the first or second sacral nerves, indicates lateral and/or cephalad extension of the tumor, which usually renders curative resection impossible. Indeed, in our series, the affected patients died within 1.2 years. In contrast, if the pain remains within the buttock, there is the possibility of curative resection.

The factors relating to tumor growth rate can predict prognosis only if patients have residual tumors after ASR. Maetani et al.[14] and Onodera et al.[24] reported a significant association of disease-free interval[14] and preoperative CEA doubling time[14] with survival. These parameters reflect not only the growth rate of locally recurrent tumors, but also that of distant metastases. The proliferating cell nuclear antigen labeling index[24] can reflect a growth rate specific to local recurrence, so it may predict prognosis more accurately. Although LDFI has not been studied so far, it is easier to measure than the labeling index, and it is also specific to local recurrence. As this study showed, patients with an LDFI of > 12 months and clear surgical margins are the best candidates for ASR, and a 5-year survival of 67% can be expected. Conversely, if the LDFI is < 12 months, thus indicating rapid tumor growth, and resection is palliative, a 2-year survival of only 11% is expected. In such cases, ASR should not be attempted. Palliative resection is indicated only for patients with an LDFI of > 12 months and preferably > 18 months.[11]

Primary cancer stage, preoperative CEA level, and macroscopic growth pattern were prognostically significant only in univariate analysis in this study. Thus, they are related to any of the previously described independent factors, but they are worth considering to a certain degree when decisions are made. Macroscopic growth pattern, which has not been investigated so far, especially influences the surgical margin status and is important when deciding the extent of resection.

As our logistic regression model showed, multiple expanding or diffuse infiltrating growth is independently associated with positive resection margins. The curative resection of the tumors with multiple expanding or infiltrating growth (44%) is clearly more difficult than with solitary expanding growth (86%). Therefore, cautious evaluation of both growth pattern and tumor extent by magnetic resonance imaging or CT is needed to determine a correct line of resection.

Although tumor extent (distant and pelvic metastases)[14,25] and initial operation type[13,25] have been reported to be significant prognostic factors, this was not confirmed here, presumably at least partly because of differences in patient backgrounds and selection criteria. As described previously,[11] the presence of pulmonary, multiple liver, peritoneal, and extrapelvic lymph node metastases leads to a very poor prognosis, with a median survival of only 1.6 years in our cases, so these patients should not undergo ASR. However, solitary liver metastasis may be an exception. Indeed, in our series, two patients with solitary liver metastases survived disease free for 7.6 and 2.7 years after ASR and liver resection. In such cases, aggressive surgery seems justified.

Because adjuvant external beam radiotherapy has been reported to be beneficial for local control and prolongation of survival in primary rectal carcinoma,[32,33] many surgeons have recommended its application for ASR.[13,15–18,20] In this multivariate study, however, a prognostic benefit of preoperative radiotherapy could not be detected. This may be at least partly caused by the small number of patients, so further investigation is necessary. Marijnen et al.[34] reported that preoperative radiotherapy for primary rectal cancer has a beneficial effect in patients with more than 1-mm resection margins but that it cannot compensate for microscopically nonradical resection resulting in positive margins. Therefore, preoperative radiation should be given only to patients for whom surgical margins are expected to be attained but insufficient.

The situation with intraoperative radiotherapy may be different.[13,15–17] Hahnloser et al.[17] reported that the overall 5-year survival rate of patients undergoing palliative resection and intraoperative radiotherapy with or without external beam radiotherapy was 21%. Survival rates for their patients with no fixation, one fixation, two fixations, and three or more fixations were 43%, 24%, 20%, and 0%, respectively. Although candidates for ASR usually have two or more fixations and the expected survival of those with positive margins is not good, intraoperative radiotherapy may benefit those undergoing ASR despite a positive margin.

As to recurrence patterns after ASR, this study showed that, in 56% of our patients, recurrence was confined locally or to the lung. Wanebo et al.[13] reported this to be the case for 68% of their series, in line with other previous studies.[35,36] Thus, in addition to precise resection based on precise evaluation of tumor extent with thin-section magnetic resonance imaging or multidetector row CT, adjuvant therapies aiming at local and lung recurrences may be necessary. For local control, preoperative and intraoperative radiotherapy may be helpful. For lung metastases, systemic adjuvant chemotherapy using 5-fluorouracil–based chemotherapy or newly developed drugs (or their combination) may be effective.[5,6]

Although this retrospective exploratory study featured only a relatively small number of patients, we conclude that ASR is beneficial for a selected subset of patients in terms of survival prolongation and even cure. To select appropriate patients, evaluation of resection margin, LDFI, pain extent, and growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

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Impact of Upward Lymph Node Dissection on Survival Rates in Advanced Lower Rectal Carcinoma

Keisuke Uehara Seiichiro Yamamoto Shin Fujita Takayuki Akasu Yoshihiro Moriya

Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

Key Words
Lymph node dissection · Upward lymph node dissection · Lower rectal carcinoma

Abstract
Background/Aims: This study investigated appropriate level of upward lymph node (LN) dissection in advanced lower rectal carcinoma. ***Methods:*** A total of 285 consecutive patients with stage II/III lower rectal carcinoma were analyzed. LN dissection was classified as follows: division of the root of the superior rectal artery (UD2), division of the root of the inferior mesenteric artery (UD3) and UD3 with para-aortic LN dissection (UD4). ***Results:*** LN metastases at the root of the inferior mesenteric artery were found in 4 patients. Their prognoses were worse than those of the other stage III patients ($p = 0.011$). On the other hand, LN metastases along the superior rectal artery were discovered in 14 patients, whose 5-year overall survival rate was 61.2%. By removing the LNs either UD2 or UD3/4, a similar survival rate was achieved in stage III patients with LN metastases along the superior rectal artery. ***Conclusion:*** Survival of a minority with metastatic LNs at the root of the inferior mesenteric artery was poor. Additionally, survival is no worse in patients with positive LN along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Low ligation is adequate for advanced lower rectal carcinoma.

Introduction

It is well known that lower rectal carcinoma has two routes of lymphatic spread, i.e. upward and lateral spread. There have been many reports that discuss the significance of lateral pelvic lymph node dissection for advanced lower rectal carcinoma [1–4]. However, there have not been any definitive conclusions and various opinions have been expressed around the world. On the other hand, the impact of upward lymph node dissection for sigmoid colon or upper rectal carcinoma has been discussed in several reports [5–7], and yet few studies have focused on this issue in advanced lower rectal carcinoma. Although Pezim et al. [8] reported that high ligation of the inferior mesenteric artery had no survival advantage for rectal carcinoma patients, no counterarguments have been published and it remains difficult to generalize about the impact of upward lymph node dissection. The appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma remains an unsolved issue and guidelines need to be established.

This study presents a detailed estimation of how the level of upward lymph node dissection affects survival rates following curative resection in advanced lower rectal carcinoma.

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Seiichiro Yamamoto
Division of Colorectal Surgery, National Cancer Center Hospital
5-1-1, Tsukiji, Chuo-ku
Tokyo 104-0045 (Japan)
Tel. +81 3 3542 2511, Fax +81 3 3542 3815, E-Mail seyamamo@ncc.go.jp

Patients and Methods

Between 1990 and 2002, a series of 303 consecutive patients at the National Cancer Center Hospital, Tokyo, underwent curative surgery for stage II or III lower rectal carcinoma. Lower rectal carcinoma was defined as a tumor with a distal margin 7 cm or less from the dentate line by digital examination and/or proctoscopy. Five patients with a history of malignancy (sigmoid colon carcinoma in 3 and bladder carcinoma in 2), who previously underwent lymph node dissection along the inferior mesenteric artery or in the lateral pelvis, were excluded, because the routes of lymphatic spread seemed to be changed in these cases. Two patients with synchronous advanced rectosigmoid carcinoma were excluded. Three stage II patients and 8 stage III patients did not undergo lymph node dissection along the inferior mesenteric artery but only in the mesorectum (UD1), because of preoperative underestimation. These 11 patients were also excluded. Consequently, 285 patients were eligible for this study. The mean (SD) distance from the dentate line of the tumor was 2.4 (1.0) (range 0.0–7.0) cm. No patients received preoperative radiotherapy and/or chemotherapy. All patients were evaluated before surgery by total colonoscopy, barium enema and computed tomography. To evaluate comorbid conditions, cardiopulmonary function and renal function tests were performed. In our study, lateral pelvic lymph nodes were regarded as regional lymph nodes according to the Japanese classification of colorectal carcinoma [9], although lateral pelvic lymph node metastases are regarded as distant metastases in the TNM classification system [10]. Clinical stage II or III middle or lower rectal carcinoma, located at or below the peritoneal reflection, is an indication for lateral pelvic lymph node dissection in our hospital [2, 3]. Postoperative adjuvant chemotherapy using oral or intravenous fluoropyrimidines was administered for 6 months to 27 stage III patients. Two stage III patients received postoperative radiotherapy and another underwent concomitant chemoradiotherapy.

The incidence of upward lymph node metastases based on histopathological data from the resected specimen, recurrence sites and survival rate were retrospectively analyzed and the appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma was evaluated.

Classification of the Level of Upward Lymph Node Dissection

Standard surgical procedures at our institution were previously reported in detail [11, 12]. The extent of upward lymph node dissection was classified as follows: UD1 is defined as resection of the mesorectum, UD2 as division of the root of the superior rectal artery with lymph node dissection below that level, UD3 as division of the root of the inferior mesenteric artery with lymph node dissection below that level and UD4 as UD3 with the addition of para-aortic lymph node dissection (fig. 1) [12]. The level of upward lymph node dissection was determined by preoperative and intraoperative findings. When a patient was diagnosed as stage I, UD1 to UD2 lymph node dissection was performed. UD2 to UD4 lymph node dissection was performed for patients with stage II or III tumor. UD4 was performed until the first half of the 1990s, but has not been performed thereafter because of excessive operative time, blood loss and a high incidence of postoperative sexual dysfunction, especially in males [11, 13, 14].

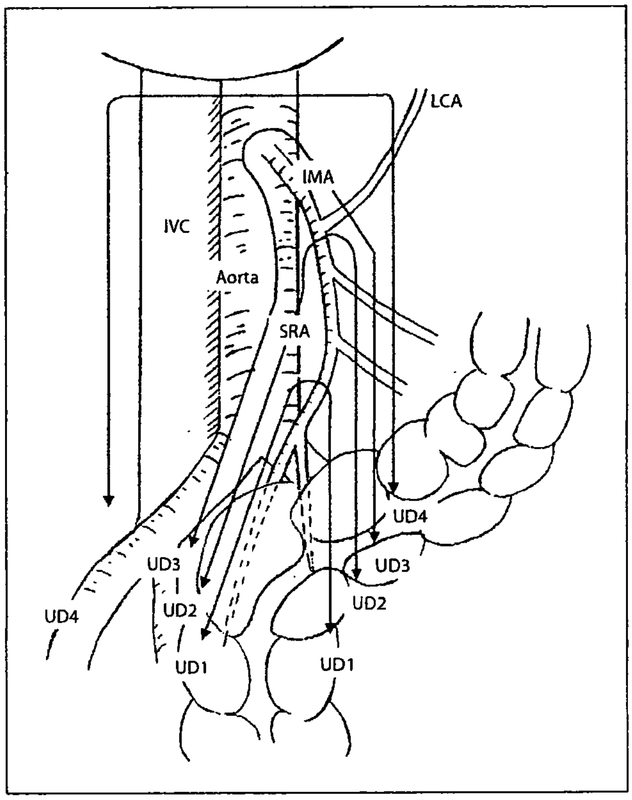

Fig. 1. Classification of the level of upward lymph node dissection. UD1 is defined as resection of the mesorectum; UD2 as division of the root of the superior rectal artery (SRA) and lymph node dissection below this level; UD3 as division of the root of the inferior mesenteric artery (IMA) and lymph node dissection below this level; and UD4 as UD3 with para-aortic lymph node dissection. IVC = Inferior vena cava; LCA = left colic artery.

Statistical Analysis

Survival curves were traced using the Kaplan-Meier method. The differences between curves were tested using the log-rank test. Comparisons between groups were performed using χ^2 test. $p < 0.05$ was considered significant. All statistical calculations were made using SPSS computer software (SPSS 11.0, SPSS Inc., Chicago, Ill., USA).

Results

The characteristics of 285 patients according to the UD classification are shown in table 1. There were 78 (27.4%), 133 (46.7%) and 74 (26.0%) patients who underwent UD2, UD3 and UD4, respectively. All patients were followed up until death or for at least 3 years with a mean follow-up period of 66 months. The rate of sphincter-pre-

Table 1. Patient characteristics according to the UD classification

	Total (n = 285)	UD2 (n = 78)	UD3 (n = 133)	UD4 (n = 74)
Age, years (mean)	58.2	58.1	58.2	58.4
Sex ratio (male:female)	191:94	53:25	90:43	48:26
Follow-up period (mean)	66	59	57	88[a, c]
Surgical procedure				
Sphincter-preserving surgery	143 (50.2)	53 (67.9)	64 (48.1)	26 (35.1)[a, b]
Non-sphincter-preserving surgery	142 (49.8)	25 (23.1)	69 (51.9)	48 (64.9)
Lateral LNs dissection				
No	68 (23.9)	32 (41.0)	31 (23.3)	5 (6.8)[d]
Yes	217 (76.1)	46 (59.0)	102 (76.7)	69 (93.2)
Evaluated LN, n (mean)	42	31	39	57[d]
Metastatic LN, n (mean)	3	2	3	3
TNM classification				
Stage II	94 (33.0)	29 (37.2)	38 (28.6)	27 (36.5)
Stage III	191 (67.0)	49 (62.8)	95 (71.4)	47 (63.5)

Values in parentheses are percentages.
[a] $p < 0.05$ UD2 vs. UD3, [b] $p < 0.05$ UD2 vs. UD4, [c] $p < 0.05$ UD3 vs. UD4, [d] $p < 0.05$ between each UD classification.

serving surgery was higher in UD2 patients than in those who underwent UD3 or UD4. The rate of undergoing lateral lymph node dissection and the number of evaluated lymph nodes increased significantly with the extension of upward lymph node dissection. However, there were no significant differences in the number of metastatic lymph nodes and the ratio of stage II to III among UD classifications.

In each TNM stage, the overall survival curves in relation to the extent of upward lymph node dissection were evaluated and there were no significant differences according to the extent of upward lymph node dissection (fig. 2). Recurrence sites after curative resection are demonstrated in table 2. In both groups with or without lymph node dissection at the root of the inferior mesenteric artery, the lung was the most common site of recurrence followed by the liver. Recurrence sites did not significantly differ between the groups, including para-aortic or mediastinal lymph node metastases.

Table 3 summarizes the characteristics and outcomes of 4 patients with lymph node metastases at the root of the inferior mesenteric artery. They accounted for 1.9% of the 207 patients who underwent UD3 or UD4. Recurrences developed in all cases and their prognoses were significantly worse than those of the other stage III patients who underwent UD3 or UD4 ($p = 0.011$) (fig. 3). None of 4 patients survived for 5 years.

Table 2. Recurrent sites after curative resection

Recurrent site	UD2 (n = 78)	UD3/UD4 (n = 207)	p value
Lung	16 (20.5)	36 (17.4)	0.543
Liver	6 (7.7)	19 (9.2)	0.692
Pelvic cavity	7 (9.0)	15 (7.2)	0.626
Para-aortic or mediastinal LNs	3 (3.8)	4 (1.9)	0.352

Values in parentheses are percentages.

On the other hand, lymph node metastases along the superior rectal artery were discovered in 14 patients, excluding 3 patients with metastatic lymph nodes at the root of the inferior mesenteric artery, and table 4 shows their characteristics. They accounted for 4.9% of all patients. Ten patients developed recurrence and the lung was the most common site (6 patients), followed by the liver (2 patients). The 5-year overall survival rate was 61.2% in this group and there were no significant differences in overall survival among the patients with and without lymph node metastases along the superior rectal artery ($p = 0.338$) (fig. 4a). In addition, there were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) ($p = 0.642$) (fig. 4b).

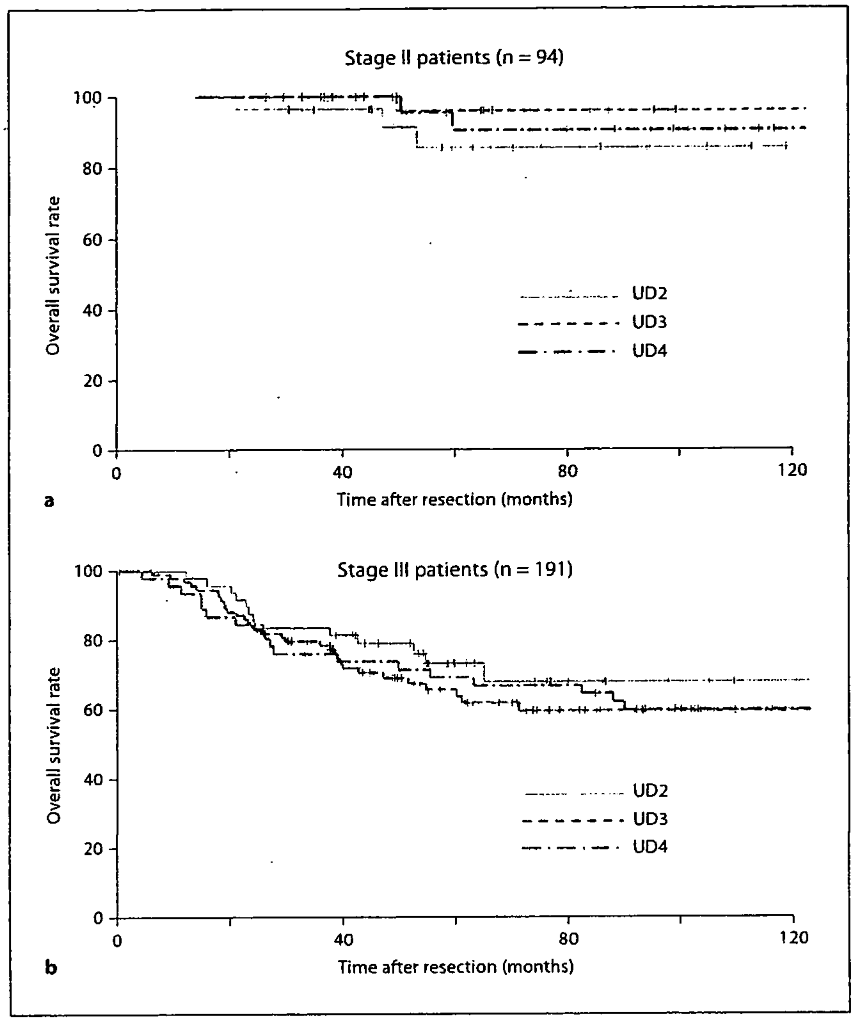

Fig. 2. Overall survival curves in relation to the extent of upward lymph node dissection at each stage: (**a**) stage II and (**b**) stage III. There were no significant differences in each stage.

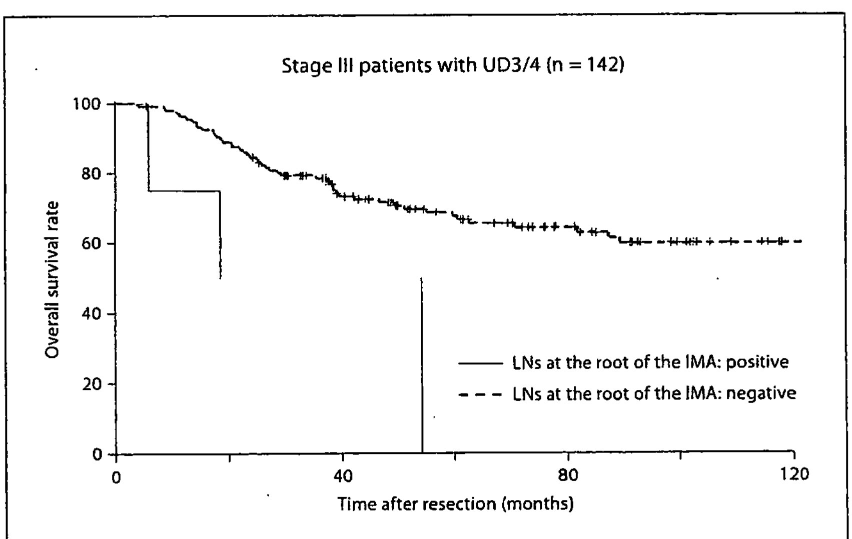

Fig. 3. Overall survival curves for the stage III patients with or without metastatic lymph nodes at the root of the inferior mesenteric artery (IMA). The former was significantly worse than the latter (p = 0.011).

Table 3. Characteristics of the patients with metastatic LNs at the root of the inferior mesenteric artery

Age	Sex	UD	Histology	pT	Metastatic LNs, n	Recurrent site	Disease-free time, months	Outcome months
33	F	3	well-differentiated adenocarcinoma	pT3	3	lung, bone	25	died (54)
64	F	3	moderately differentiated adeno-carcinoma	pT3	4	lung	22	alive with recurrent tumor (39)
51	M	3	poorly differentiated adenocarcinoma	pT3	25	pelvic cavity	11	died (19)
57	M	3	poorly differentiated adenocarcinoma	pT3	16	pelvic cavity, peritonium	4	died (6)

Discussion

Surgical decisions regarding upward lymph node dissection for advanced lower rectal carcinoma remain controversial. In our study, patients with metastatic lymph nodes at the root of the inferior mesenteric artery comprised a small minority (4 patients, 1.9%) and their prognoses were very poor. Their prognoses seemed to be almost equal to those of patients who underwent UD4 dissection and were pathologically proven to have metastatic para-aortic lymph node, although such patients are classified as stage IV in TNM classification and were excluded from this study. Furthermore, we could not demonstrate an effect of prophylactic lymph node dissection at the root of the inferior mesenteric artery in patients with any stage of disease. Moreover, lymph node dissection without the root of the inferior mesenteric artery did not result in increased para-aortic or mediastinal lymph node metastases, which we had thought might be caused by failing to perform lymph node dissection. We conclude that lymph node dissection at the root of the inferior mesenteric artery does not provide any survival advantage for patients with advanced lower rectal carcinoma and metastatic lymph nodes at this level have systematic disease.

Likewise, there were also a small number of patients with metastatic lymph nodes along the superior rectal artery (14 patients, 4.9%) and the positive rate was far below the rate of lateral lymph nodes (55 of 217 patients who underwent lateral lymph node dissection, 25.3%) in this series. However, the 5-year overall survival rate in this group was 61.2% and there were no significant differences among stage III patients with and without lymph node metastases along the superior rectal artery. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. We conclude that UD2 lymph node dissection is adequate even for stage III patients with lymph node metastases along the superior rectal artery.

Table 4. Characteristics of the patients with metastatic LNs along the SRA (exception for three with metastatic LNs at the root of the IMA)

Patients		14
Age, years (mean)		58.8
Sex ratio (male:female)		12:2
Upward LNs dissection	UD2	4
	UD3	6
	UD4	4
Lateral LNs dissection	no	5
	unilateral pelvic	2
	bilateral pelvic	7
pT category in TNM classification	pT1	2
	pT2	2
	pT3	7
	pT4	3
pN category in TNM classification	pN1	7
	pN2	7
Recurrence	yes	10
	no	4

SRA = Superior rectal artery; IMA = inferior mesenteric artery.

There are some problems with the existing classifications of rectal carcinoma. TNM classification considers lymph nodes at the root of the inferior mesenteric artery as regional lymph nodes for colorectal carcinoma without regard to the location of the tumors, as well as lymph nodes along the superior rectal artery [10]. Under this classification, patients with metastatic regional lymph nodes are regarded as stage III and are subcategorized into three groups by the depth of tumor invasion and number of metastatic lymph nodes, not by the location of metastatic lymph nodes. The problem with this classification is that we cannot distinguish whether stage III patients have lymph node metastases at the root of the inferior mesenteric artery.

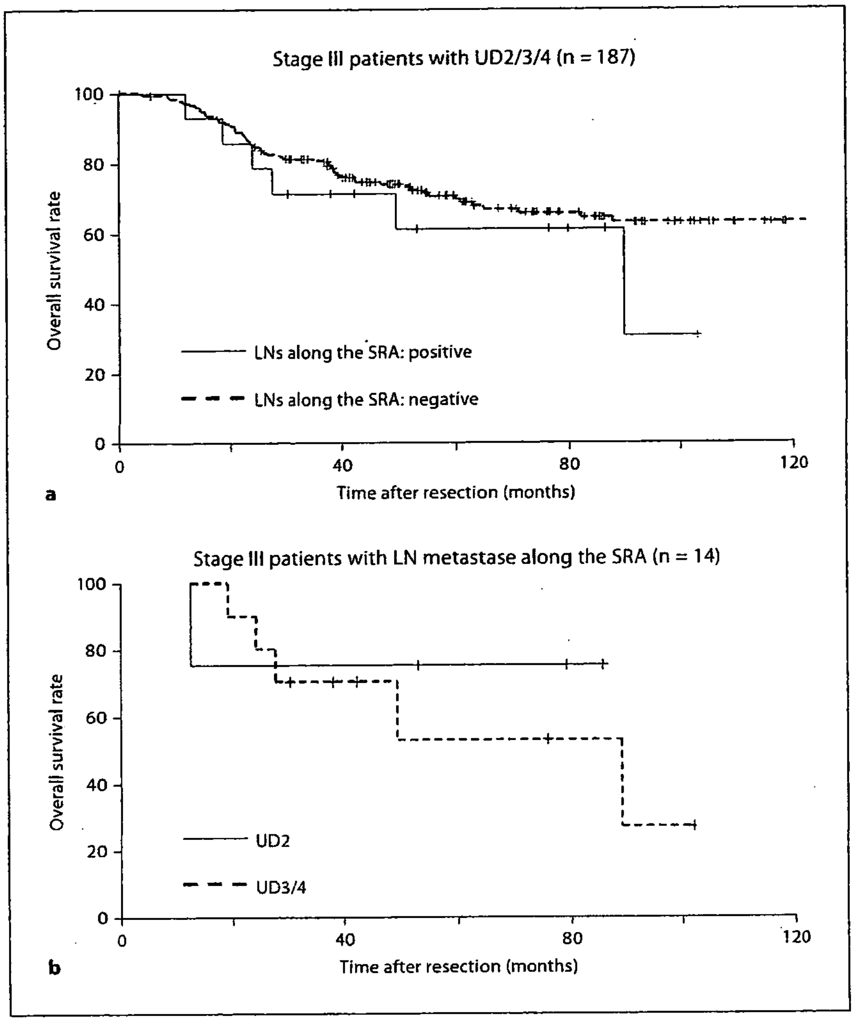

Fig. 4. a Overall survival curves for stage III patients with or without metastatic lymph nodes along the superior rectal artery, excluding 4 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in overall survival between both groups (p = 0.338). **b** Overall survival curves in relation to the extent of upward lymph node dissection for stage III patients with metastatic lymph nodes along the superior rectal artery, excluding 3 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) (p = 0.642).

In comparison, the Japanese classification of colorectal carcinoma [9] treats regional lymph nodes in rectal carcinoma as follows: pararectal lymph nodes are defined as group 1, lymph nodes along the superior rectal artery as intermediate lymph nodes (group 2) and lymph nodes at the root of the inferior mesenteric artery as the main lymph nodes (group 3). However, this classification defines patients with metastatic lymph nodes in group 2 and/or group 3 as same stage (stage IIIb). Based on the results of this study, these criteria should be reevaluated.

In recent years, sphincter-preserving surgery has been increasingly adopted in patients with lower rectal carcinoma [15, 16]. The most important postoperative complication in this procedure is anastomotic leakage. To avoid this complication, all colorectal surgeons pay attention to blood flow in the remnant colon, together with the tension of the anastomosis. Therefore, Western surgeons perform mobilization of the splenic flexure for most patients [17], but the position of the splenic flexure in Japanese is usually very deep in the left upper subphrenic area and it is sometimes rather difficult to mobilize the left side colon. However, Japanese patients usually have a long sigmoid colon, and if the surgeon preserves 1 or 2 arcades of marginal vessels of the sigmoid colon by dividing the sigmoid artery between the superior rectal artery and these marginal vessels, mobilization of the splenic flexure becomes unnecessary. In this situation, arterial blood flow is not being compensated. Preservation of the blood flow of the left colic artery is one solution to this problem, because the appropriate extent of upward lymph node dissection for lower rectal carcinoma is considered to be UD2. When the length of the vascular pedicle for lower anastomosis is short, we can cut the periphery of the left colic artery. Some surgeons choose left colic artery-preserving lymph node dissection at the root of the inferior mesenteric artery, but this increases the risk of damaging the lumbar splanchnic nerve.

Another problem encountered with lymph node dissection for lower rectal surgery is lateral lymph node dissection. Some reports mainly from Japan have supported the effectiveness of lateral pelvic lymph node dissection, and it is well established as the standard procedure in leading hospitals in Japan. However, in Western countries, the survival benefits of lateral pelvic lymph node dissection are regarded as doubtful. Instead, preoperative chemoradiotherapy is widely performed [18, 19]. To resolve this disparity, a multicentric randomized clinical trial that compares lateral pelvic lymph node dissection with autonomic nerve preservation to total mesenteric excision (JCOG-0212) is underway in Japan and data regarding this issue will become available in the near future [20].

In conclusion, survival of a minority with metastatic lymph nodes at the root of the inferior mesenteric artery was very poor. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Surgeons should take these data into consideration and recognize that low ligation is adequate for advanced lower rectal carcinoma.

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Incidence and Patterns of Recurrence after Intersphincteric Resection for Very Low Rectal Adenocarcinoma

Takayuki Akasu, MD, Masashi Takawa, MD, Seiichiro Yamamoto, MD, Shin Fujita, MD, Yoshihiro Moriya, MD

BACKGROUND: The aim of this study was to evaluate the incidence and patterns of recurrence, or oncologic safety, after intersphincteric resection (ISR) without radiotherapy for very low rectal adenocarcinoma.

STUDY DESIGN: One hundred eight consecutive patients with T1–T3 rectal cancers located 1 to 5 cm (median 3 cm) from the anal verge underwent ISR. A retrospective analysis of prospectively recorded data from the 106 patients not receiving radiotherapy was performed.

RESULTS: There were 23 T1, 40 T2, and 43 T3 tumors. Morbidity and mortality rates were 33% and 1%, respectively. The 3-year rates of overall local recurrence and survival were 5.7% and 95%, respectively. The 3-year cumulative local recurrence rate was 0% for the patients with T1–T2 tumors as compared with 15% for those with T3 tumors ($p = 0.0012$). In T3 tumors, the 2-year local recurrence rate was 5% for patients with negative surgical margins as compared with 33% for those with positive margins ($p = 0.0001$). The incidences of distant recurrence for stages I, II, III, and IV disease were 4%, 5%, 18%, and 33%, respectively.

CONCLUSIONS: ISR does not increase local or distant recurrences. For T1–T2 tumors, meticulous dissection and irrigation after closure of the distal stump allows local control without radiotherapy. With T3 tumors, preoperative therapy should be considered if resection margins are estimated to be insufficient. (J Am Coll Surg 2007;205:642–647. © 2007 by the American College of Surgeons)

Standard surgical treatment for massively invading rectal adenocarcinoma located within 5 cm from the anal verge is abdominoperineal resection.[1] This is because the length of the anal canal is 3 to 5 cm,[2] and a distal margin of at least 1 cm, but preferably 2 cm, should be taken to ensure local control.[1,3,4]

To avoid permanent colostomy for such patients, intersphincteric resection (ISR) was devised in the 1980s, and a modern concept of ISR was established in the 1990s.[4] ISR is now defined as a procedure obtaining sufficient margins by removing part or all of the internal sphincter and restoring bowel continuity for patients with rectal cancers involving or neighboring the anal canal. With meticulous performance of this operation, satisfactory early results on defecatory functions and oncologic outcomes were reported.[4,5]

But with ISR, there is a potential risk of increasing recurrence, especially local recurrence, because preservation of the anal canal, external sphincter, and levator ani muscles for such low tumors may compromise distal or circumferential resection margins. There have been only limited studies on longterm oncologic outcomes after ISR.[6-8] The purpose of this study was to review our results of ISR for rectal adenocarcinoma within 5 cm from the anal verge and to evaluate the incidence and patterns of recurrence, as parameters of oncologic safety, after ISR without radiotherapy.

METHODS

Between October 1993 and November 2005, 108 patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. During the same

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From the Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan.

Correspondence address: Takayuki Akasu, MD, Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

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period, 201 patients underwent abdominoperineal resection for rectal cancer located within 5 cm from the anal verge. The proportions of ISR were 18% (28 of 157) until 2001 and 52% (78 of 150) thereafter. Selection criteria for ISR were sufficient medical fitness; normal sphincter function; distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) of less than 2 cm; no involvement of the external sphincter; and no signs of disseminated disease. Patients were routinely assessed with chest and abdominal CT, digital anorectal examination, and radiologic studies, including endorectal ultrasonography[9] until 1997, thin-section helical CT until 2000, and thin-section MRI with a phased-array coil[10] from 2001 on. Written informed consent was obtained from all patients.

Retrospective analysis of clinicopathologic data from the prospective database and medical records of the 106 consecutive patients who did not receive adjuvant radiotherapy was conducted. Data from the remaining two patients given radiotherapy were excluded from this analysis. There were 83 men and 23 women, with a median age of 55 years (range 26 to 75 years). The median distance from the tumor to the anal verge was 3 cm (range 1 to 5 cm).

Treatment

Ninety patients underwent partial ISR and 16 had complete ISR. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. Extent of lymph node dissection included total mesorectal excision in 63 patients and total mesorectal excision plus extended lateral pelvic lymph node dissection in 43. Combined resection was performed for six patients (vagina, two; uterus, one; pelvic plexus, two; internal iliac vessels, one).

ISR was carried out through a laparotomy in 101 patients and laparoscopically in 5. A J pouch was made in 24 patients, a transverse coloplasty pouch in 35, and a straight anastomosis in 47, according to the operator's preference. Ninety-five patients had covering ileostomy, two had colostomy, and nine had no stoma. Two patients with a solitary liver metastasis and one with a solitary lung metastasis underwent complete resection of their metastases. Postoperatively, 19 patients received adjuvant chemotherapy with a 5-fluorouracil–based regimen.

Surgical procedure

The surgical procedures were basically similar to those originally described by Schiessel and colleagues[4,7] The patient was placed in a supine position with flexed and abducted thighs. The sigmoid colon and rectum were mobilized down to the levator ani. The intersphincteric plane, between the puborectalis and the external sphincter, and the internal sphincter were dissected cautiously as far as possible under direct vision, using electrocautery. If the lower edge of the tumor was reached, a vertical stapler was applied just below the tumor to close the rectum or anal canal, and then the anal canal was washed with povidone iodine followed by saline.

A Gelpi retractor or a self-holding retractor (Lone Star Retractor; Lone Star Medical Products Inc) was applied to the anal canal, the internal sphincter was circumferentially incised, and the intersphincteric plane was dissected with electrocautery under direct vision. A resection margin of at least 1 cm was always attempted. If the rectum was not closed in the abdominal phase, it was closed using sutures after per-anal dissection. After removal of the rectum, the pelvic cavity and anal canal were irrigated with povidone iodine and then with saline. Then a coloanal anastomosis was made using vertical mattress sutures.

Followup

All patients were followed for a median of 3.5 years (range 0.9 to 11.7 years) for those who remained alive, and 83 patients (78%) could be followed for more than 2 years. Patients with stage I tumors were examined with chest and abdominopelvic CT and 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

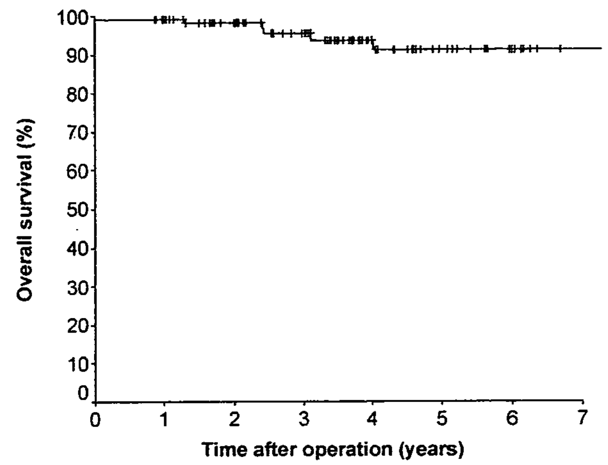
The starting point for survival and recurrence-free intervals was the day of operation, and data on patients who were alive or free of recurrence were censored at the last followup. Overall survival was defined as the time from ISR until death from any cause. Local recurrence was defined as that confined 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. The significance of differences in proportions was calculated with the chi-square test. All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc). All p values were two sided, and a p value of less than 0.05 was considered statistically significant.

RESULTS

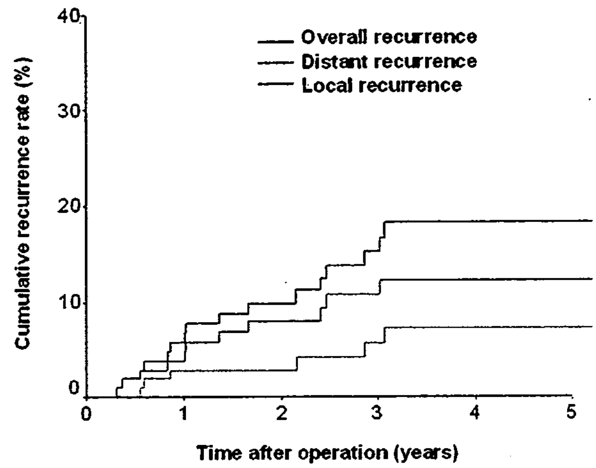
Pathologic findings

Histologic diagnoses were well, moderate, and poorly differentiated adenocarcinomas in 52, 46, and 5 patients, respectively, and mucinous carcinoma in 3. The median tu-



No. at risk 106 100 82 62 35 19 11

Figure 1. Overall survival among 106 patients undergoing intersphincteric resection.



No. at risk						
Overall	106	94	75	56	30	16
Distant	106	96	75	57	32	18
Local	106	97	81	60	33	17

Figure 2. Rates of overall recurrence, distant recurrence, and local recurrence among 106 patients undergoing intersphincteric resection.

mor size was 3.7 cm (range 1 to 12 cm). Resection margins were microscopically negative in 103 patients and positive in 3. One patient had both circumferential and distal positive margins and the other two had a circumferential positive margin. Excluding these 3 patients, the median distal margin was 1.2 cm (range 0.3 to 4 cm). Histologic depth of invasion included T1 in 23 patients, T2 in 40, and T3 in 43. All T1 tumors had massive invasion, lymphatic invasion, venous invasion, or poor differentiation. Lymph node statuses were N0 in 66, N1 in 25, and N2 in 15. Seven patients (7%) had lateral pelvic lymph node metastasis and 3 had distant metastases (liver, 2; lung, 1). Histologic staging included stage I in 45 patients, II in 20, III in 38, and IV in 3.

Morbidity and mortality

Of 35 patients (33%) who suffered from complications, 26 were treated conservatively and 9 had operations. Of 13 patients (12%) with anastomotic leakage, 6 underwent operations. The incidence of anastomotic leakage in the patients without covering stoma was not higher than that in the patients with covering stoma (11% [1 of 9] versus 12% [12 of 97], respectively). Other complications included wound infection, bowel obstruction, urinary tract infection, anal pain, anastomotic stenosis, anal prolapse, peristomal hernia, thrombocytopenia, and cholecystitis. One patient who had anastomotic leakage and sepsis died on the third postoperative day (mortality = 1%). Seven patients had a permanent stoma because of complications (six patients) or local recurrence (one patient).

Survival

At the last followup in December 2006, 100 patients were alive and 6 were dead. Causes of death included rectal cancer (two patients), gastric cancer (one), pancreatic cancer (one), anastomotic leakage (one), and cerebral contusion (one). The estimated overall 3- and 5-year survival rates were 95% and 91%, respectively, including 1 hospital death (Fig. 1).

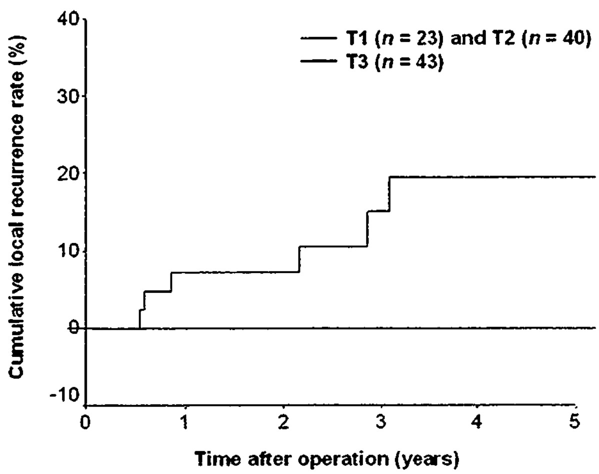
Incidence and patterns of recurrence

A total of 16 patients (15%) developed recurrence. Estimated 3- and 5-year cumulative rates for overall recurrence were 15% and 18%, respectively (Fig. 2). Sites of the first recurrence included the pelvis in five patients, pelvis and lung in one, inguinal lymph nodes in two, lung in four, lung and liver in one, and liver in three. The incidences of overall recurrence for stages I, II, III, and IV disease were 4%, 25%, 21%, and 33%, respectively.

Estimated 3- and 5-year cumulative rates for distant recurrence, found in 11 patients (11%), were 11% and 12%, respectively (Fig. 2). The incidences of distant recurrence for stages I, II, III, and IV disease were 4%, 5%, 18%, and 33%, respectively.

In total, 6 patients (5.7%) developed local recurrence, with estimated 3- and 5-year cumulative recurrence rates of 5.7% and 7.3%, respectively (Fig. 2). Detailed sites of local failure included the circumferential resection margin in two patients, internal iliac or obturator nodes in three, and sacrum in one. The incidences of local failure for stages I, II, III, and IV disease were 0%, 20%, 5%, and 0%, and those for pathologic T1, T2, and T3 tumors were 0%, 0%, and 14%, respectively.

Estimated cumulative rate of local recurrence with T1–2 tumors was significantly less than that with T3 tumors



No. at risk

T1–T2	63	60	50	41	20	9
T3	43	36	30	18	12	7

Figure 3. Rates of local recurrence among 106 patients undergoing intersphincteric resection, according to the pathologic depth of transmural invasion (T stage).

($p = 0.0012$; 3-year rates of local recurrence, 0% versus 15%, respectively; Fig. 3). All 6 patients developing local failure had T3 tumors. Of the 100 patients without local failure, 37 had T3 tumors, and 63 had T1–2 tumors. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy rate for T3 tumors in prediction of local failure were 100% (6 of 6), 63% (63 of 100), 14% (6 of 43), 100% (63 of 63), and 65% (69 of 106), respectively.

In T3 tumors, the estimated cumulative rate of local recurrence for patients with negative surgical margins was significantly less than that with positive margins ($p = 0.0001$; 2-year rates of local recurrence, 5% versus 33%, respectively). Of the six patients developing local failure, two had positive margins, but the other four had negative margins. Of the 37 patients without local failure, 36 had negative margins, and 1 had a positive margin. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy rate for the positive margin in prediction of local failure were 33% (2 of 6), 97% (36 of 37), 67% (2 of 3), 90% (36 of 40), and 88% (38 of 43), respectively.

Other evaluated factors, including age, gender, tumor size, pathologic TNM stage, pathologic N stage, histologic grade, distance between the tumor and anal verge, extended lateral lymph node dissection, and adjuvant chemotherapy, had no association with local recurrence.

One patient with local recurrence at the circumferential resection margin could undergo curative abdominoperineal resection, but the other five received chemoradiotherapy (three) or chemotherapy (two) alone.

DISCUSSION

This study confirmed the longterm oncologic safety of ISR for rectal adenocarcinoma located within 5 cm from the anal verge, in addition to acceptable morbidity and mortality. In this study, local recurrence and 5-year overall survival rates after ISR were 5.7% and 91%, respectively. In a large series with 117 patients, Schiessel and associates[7] reported a similar favorable local failure rate of 5.3%. There were no substantial differences in oncologic outcomes between the two studies; because our surgical procedures are based on theirs, the stage distributions were almost the same, and radiotherapy was not used in either study. In another large series with 92 patients, Rullier and coworkers[8] reported a better local recurrence rate (2%) and a slightly worse distant recurrence rate (19%), with a 5-year overall survival of 81%. These differences were attributable to the background of their patients, 85% of whom had T3 or T4 tumors and 88% of whom received preoperative radiotherapy. Considering duration of followup and prevalence of site and stage, these local recurrence rates after ISR compared favorably with the 6% to 9% reported in population-based data for anterior resection or abdominoperineal resection with total mesorectal excision.[11-13]

This study showed that invasion through the muscularis propria (T3) and positive microscopic resection margin were significantly associated with local recurrence after ISR. Although data were not shown, Schiessel and colleagues[7] reported that only Dukes stage and T stage had an impact on local failure. Paty and associates[14] analyzed data of 134 patients with rectal cancer located 2 to 11 cm (median 6.5 cm) from the anal verge, undergoing not only ISR, but also low anterior resection or coloanal anastomosis; they found that mesenteric implants, positive microscopic resection margin, T3 tumor, perineural invasion, blood vessel invasion, and poorly differentiated histology were significantly associated with pelvic recurrence in a univariate analysis. Among these factors, only T3 and positive resection margin were reproducible, so these 2 can currently serve as indicators of high risk for local failure. In this study, positive margins had better positive predictive value and overall accuracy rate than T3.

Our study clearly showed that there was no local recurrence after ISR for T1 and T2 tumors, despite the absence of adjuvant radiotherapy. So far, there have been few studies mentioning oncologic safety of ISR without radiotherapy for such tumors.[4,7] Although longterm preoperative radiotherapy is known to reduce tumor volume and change protruding tumors into ulcerative scars, facilitating operations and decreasing tumor spillage,[15] radiotherapy, in both short and long courses, has the potential to cause damage to anorectal[16,17] and sexual[18,19] functions. So, identification of a subset of patients for whom radiotherapy is not necessary is valuable.

To select patients with T1 or T2 tumors, both transrectal ultrasonography and high-resolution MRI are sufficiently accurate, with overall accuracy rates of around 85%.[9,10] Although the frequency of overstaging of T2 tumors may be a little high with both examinations,[9] this should not increase the risk of local recurrence, because overstaging generally leads to overtreatment, rather than undertreatment.

But caution is necessary to interpret these results because in our series, total mesorectal excision with meticulous pelvic and per-anal dissection was performed, and closure of the distal stump and irrigation of raw surfaces of the pelvic cavity and anal canal were carried out for all patients. Without such procedures, favorable outcomes may not be expected.

On the other hand, local treatment has been regarded recently as an alternative option for T1 and T2 tumors, with the advantages of sphincter preservation and minimal morbidity. According to a current massive literature review,[20] low-risk T1 tumor with invasion confined to the superficial submucosa, well to moderate differentiation, and lack of lymphatic and venous invasion make a patient suitable for local excision alone; high-risk T1 or T2 tumors require radical operations or adjuvant treatment. Although the recent integration of potent chemotherapeutic agents into chemoradiotherapy has been steadily improving efficacy, the role of local excision with chemoradiotherapy in curative treatment of high-risk T1 and T2 tumors still remains to be clarified.

For T3 tumors, our local recurrence rate of 14% without radiotherapy is much higher than the 2% reported with radiotherapy,[8] so adjuvant therapy should be considered for T3 tumors, as Rullier and coauthors[8] recommended. But because 86% of our patients with T3 tumors can achieve local control without radiotherapy, it should be given only to high-risk patients, considering its toxicity to anal and sexual functions.

This study showed microscopic involvement of the circumferential resection margin to be significantly associated with local recurrence, in line with results of other studies.[13] In addition, tumor presence within 1 mm of the circumferential resection margin is reported to be a major significant risk factor for local recurrence.[13] Because preoperative radiotherapy can increase the margin,[15] this should be applied for patients with predicted insufficient margins. High-resolution MRI is useful for selecting such patients, predicting a clear circumferential resection margin with a specificity of 92% in a large prospective study of 408 patients.[21]

Although a positive distal margin caused local failure in only one of our patients, the distal margin has long been reported to be a significant risk factor of local failure.[22] MRI is useful for predicting distal margin and assigning preoperative therapy to high-risk patients. Urban and colleagues[23] used double-contrast, material-enhanced MRI with a flexible surface coil for 61 patients with rectal cancer and reported a specificity of 98% and a sensitivity of 100% in assessment of anal sphincteric infiltration.

But distal intramural spread that is microscopic invasion beyond the macroscopic tumor edge has been reported to occur in 4% to 24% of patients undergoing curative operations and to reach nearly 2 cm.[24] Although distal intramural spread has been suggested to be associated with lymph node involvement, transmural invasion depth, annularity, gross tumor appearance, and unfavorable histology,[24] clear prediction criteria have yet to be established and these warrant further investigation.

It is controversial whether lateral pelvic lymph node metastasis has a significant role in local recurrence. In our study, three of six local failures appeared to be caused by lateral node metastasis. But analyses of radiologic findings by Syk and associates[25] revealed that only 2 of 33 local failures originated from lateral node metastases among 880 rectal cancer patients undergoing total mesorectal excision. The incidence of lateral node metastasis was 7% in this study and was estimated to be between 6.5% and 9.4% in a large series with 1,977 rectal cancer patients,[26] suggesting a certain influence on local failure. So, the real incidence of lateral node metastasis and its role in determining prognosis should be investigated further in a prospective fashion.

The 3-year rate for distant recurrence in our study was 11%, and this compared favorably with the 2-year distant recurrence rate of 14% in the Total Mesorectal Excision (TME) project of the Stockholm Colorectal Cancer Study with 447 patients.[11] The Stockholm study contained slightly more advanced but more cephalad tumors than our study did. Considering this, ISR seems not to increase distant recurrence. But caution is necessary so as not to overlook inguinal lymph node recurrence. It is very rare with usual sphincter-preserving operations but can occur in patients undergoing ISR.

We concluded that ISR, in general, does not increase local or distant recurrences. With T1 and T2 tumors, if meticulous dissection and irrigation after closure of the distal stump are performed, local control is assured and radiotherapy is not necessary. For T3 tumors, if resection margins are estimated to be insufficient, preoperative therapy should be considered to reduce the risk of local failure.

Author Contributions

Study conception and design: Akasu
Acquisition of data: Akasu, Takawa, Yamamoto, Fujita, Moriya
Analysis and interpretation of data: Akasu
Drafting of manuscript: Akasu
Critical revision: Takawa, Yamamoto, Fujita, Moriya

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Original article

Clinicopathological significance of fibrous tissue around fixed recurrent rectal cancer in the pelvis

K. Uehara[1,2], T. Shimoda[2], Y. Nakanishi[3], H. Taniguchi[2], T. Akasu[1], S. Fujita[1], S. Yamamoto[1] and Y. Moriya[1]

[1]Colorectal Surgery Division, [2]Clinical Laboratory Division and [3]Pathology Division, National Cancer Centre Hospital and Research Institute, Tokyo, Japan

Correspondence to: Dr T. Shimoda, Clinical Laboratory Division, National Cancer Centre Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan (e-mail: tshimoda@ncc.go.jp)

Background: Fibrous tissue around a locally recurrent rectal tumour is an interesting histological feature, but its clinicopathological significance has not been investigated.

Methods: This retrospective study examined clinicopathological findings in 48 patients who underwent curative total pelvic exenteration with distal sacrectomy (TPES) between 1992 and 2004. Data were analysed with respect to fibrosis around the recurrent tumour, categorized into one of three groups: no fibrosis (f0), partial fibrosis (f1) or circumferential fibrosis (f2).

Results: Ten, 17 and 21 patients had f0, f1 and f2 fibrosis respectively, with 5-year survival of none, four and eight patients respectively. The overall survival of patients with circumferential fibrosis was significantly better than that in patients with no fibrosis ($P = 0.003$). Univariable analysis showed that a high level of sacrectomy ($P = 0.036$), absence of lymphatic invasion ($P = 0.031$) and circumferential fibrosis ($P = 0.039$) were significantly associated with better overall survival. In multivariable analysis, circumferential fibrosis ($P = 0.031$) and low serum carcinoembryonic antigen levels ($P = 0.044$) were independent factors for a favourable outcome.

Conclusion: The outcome of patients with locally recurrent rectal cancer after curative TPES appears to be better when circumferential fibrosis is present around the tumour.

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Introduction

Local recurrence after rectal excision for cancer is common, with reported rates of 4–33 per cent, even after curative resection[1,2]. Total pelvic exenteration with distal sacrectomy (TPES), originally described by Wanebo and Marcove[3], consists of extended surgical resection of the recurrent tumour and affected neighbouring organs, including the bladder, prostate, uterus, vagina, pelvic wall and sacrum, along with urinary tract reconstruction using an ileal conduit. In a previous study[4,5], the present authors found that TPES with complete (R0) resection achieved a 5-year relapse-free survival rate of 49 per cent in patients with local relapse fixed in the pelvis. These local recurrences are sometimes surrounded by thick fibrous tissue, although the significance of this fibrosis is unknown. The aim of this study was to evaluate the clinicopathological significance of fibrous tissue related to recurrent rectal cancer in the pelvis.

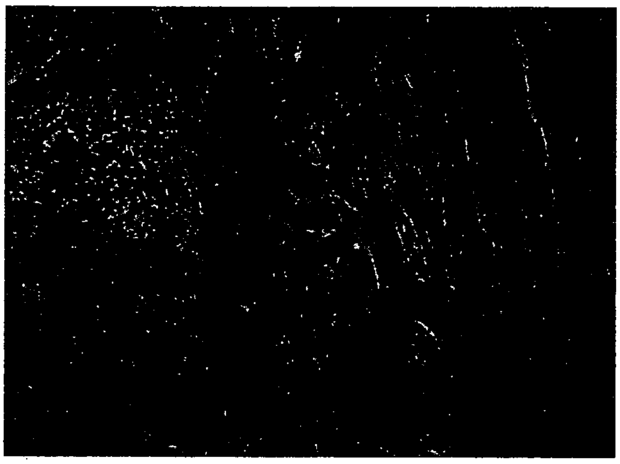
The Editors have satisfied themselves that all authors have contributed significantly to this publication

Methods

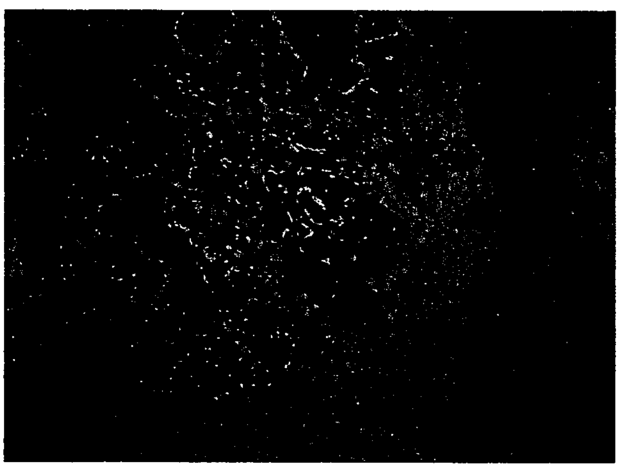
The study included patients who had undergone curative TPES. All had localized, fixed, recurrent cancer in the pelvis without distant metastases, with the exception of concomitant liver metastases amenable to surgical resection. Between 1992 and 2004, 56 patients had TPES for fixed recurrent rectal cancer in the pelvis. Of these, eight had a non-curative resection (R1 or R2) and were excluded, leaving 48 patients who underwent R0 resection, including five who had simultaneous hepatic resection for metastases. There were 35 men and 13 women, with a median age of 57·5 (range 32–76) years.

Initial resection of the primary rectal tumour had been performed in the authors' institution in two patients and elsewhere in 46. All patients had computed tomography (CT) of the thorax and abdomen, pelvic CT and magnetic resonance imaging; positron emission tomography was not available during the study interval.

As the first step in treatment of the recurrent tumour, three patients had chemotherapy and 12 had radiotherapy. The surgical technique for TPES has been described in detail previously[4,5]. No patient received adjuvant chemotherapy or radiotherapy after TPES.

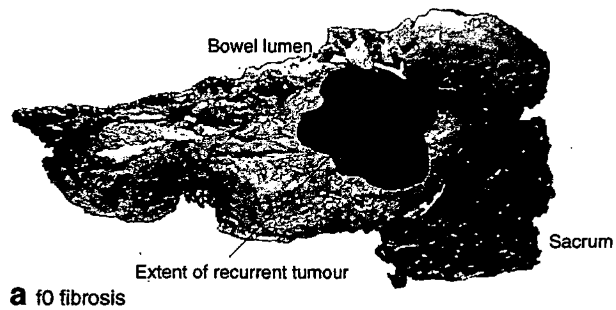


a Fibrotic stroma

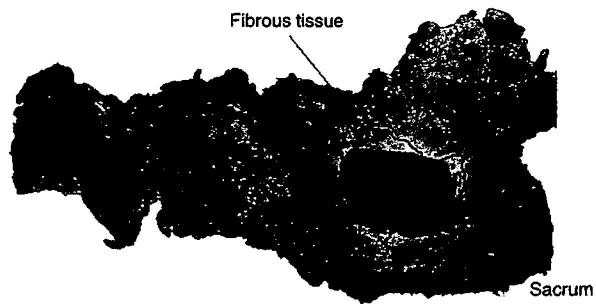


b No fibrous tissue

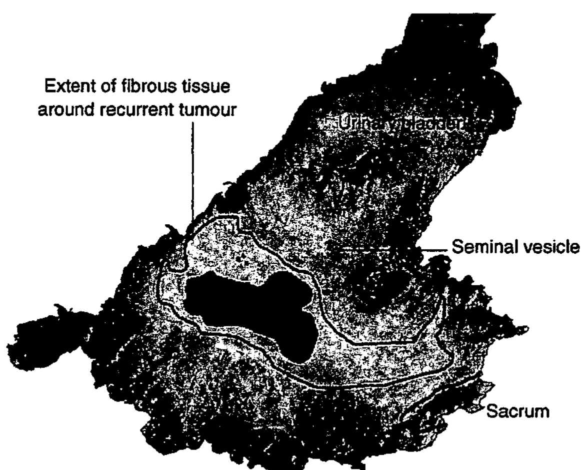
Fig. 1 **a** Mature fibrotic stroma (thick and thin fibres with fibrocytes stratified into multiple layers) evident around the recurrent tumour. **b** No fibrous tissue visible between cancer cells and surrounding soft tissue. (Haematoxylin and eosin stain, original magnification × 40)



a f0 fibrosis



b f1 fibrosis



c f2 fibrosis

Fig. 2 Classification of fibrous tissue around the recurrent tumour. **a** f0 fibrosis was defined as absence of fibrous tissue around the tumour, **b** f1 as partial presence and **c** f2 as circumferential fibrosis enclosing the tumour together with any of the surrounding organs

Histopathological examination

All surgical specimens were fixed in 10 per cent formaldehyde solution. After macroscopic examination, a section including the maximum diameter of the tumour was cut, embedded in paraffin, and stained with haematoxylin and eosin. Microscopic examination determined the histological type according to the Japanese classification of colorectal carcinoma[6], invasion to surrounding organs, perineural, venous and lymphatic invasion, fibrous tissue and abscess formation around the recurrent tumour.

Fibrous tissue was regarded as present when mature fibrotic stroma (thick and thin fibres with fibrocytes stratified into multiple layers) was evident around the recurrent tumour (*Fig. 1*)[7]. The fibrous tissue was classified as follows: f0, no surrounding fibrous tissue present; f1, fibrous tissue present but not surrounding the tumour completely; and f2, circumferential fibrosis (*Fig. 2*). The clinicopathological features of each tumour were correlated with this classification.

Statistical analysis

Patient survival was measured from the date of TPES to the date of the last follow-up examination. Survival curves (not shown) were constructed using the Kaplan–Meier method and differences between the curves compared with the log rank test. The prognostic significance of the selected factors on overall survival was evaluated with the Cox proportional hazards regression model. Comparisons between groups were performed using the χ^2 test. All statistical calculations were made using SPSS® version 11.0 (SPSS, Chicago, Illinois, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

Of the 48 patients, ten were classified as having f0 fibrosis, 17 as f1 and 21 as f2. Clinical characteristics in relation to the fibrosis classification are shown in *Table 1*. Significantly more patients with f2 fibrosis had a high level of sacrectomy compared with patients with f0 fibrosis ($P = 0{\cdot}007$).

Table 2 shows the pathological features of the 48 patients. The predominant histological type was moderately differentiated adenocarcinoma in patients with

Table 1 Clinical characteristics of 48 patients with recurrent rectal cancer

	Total (n = 48)	f0 (n = 10)	f1 (n = 17)	f2 (n = 21)
Median (range) age (years)	57·5 (32–76)	52·0 (38–65)	57·0 (37–76)	58·0 (32–68)
Sex ratio (M : F)	35 : 13	9 : 1	10 : 7	16 : 5
Median (range) time between initial surgery and TPES (months)	30 (10–122)	21 (10–54)	38 (11–119)	29 (10–121)
Serum CEA level (ng/ml)				
< 20	38	7	14	17
≥ 20	10	3	3	4
Initial surgery				
Sphincter-preserving operation	30	8	10	12
Abdominoperineal resection	18	2	7	9
Dukes' classification for primary growth				
A	5	0	4	1
B	14	1	5	8
C	29	9	8	12
Preoperative radiotherapy				
Yes	12	1	4	7
No	36	9	13	14
Preoperative chemotherapy				
Yes	3	0	1	2
No	45	10	16	19
Surgery for recurrent tumour				
Yes	11	4	2	5
No	37	6	15	16
Level of distal sacrectomy				
S3 superior margin or high	26	2	9	15*
S3 inferior margin or low	22	8	8	6*
Simultaneous hepatectomy				
Yes	5	3	1	1
No	43	7	16	20
Median (range) follow-up (months)	38 (8–157)	30 (10–57)	30 (8–157)	49 (8–142)

TPES, total pelvic exenteration with distal sacrectomy; CEA, carcinoembryonic antigen. *$P < 0{\cdot}050$ *versus* f0 (χ^2 test).