there have been few long-term follow-up studies, this aggressive operation provides pain control, prolongation of survival, and possibly cure.[13–22] However, reported morbidity and mortality are significantly high,[13–22] and survival is still low.[13–22] Therefore, appropriate selection of patients, especially with reference to the probable prognosis, is necessary. In addition, adjuvant therapy based on recurrence patterns may be required. The purpose of this study was to evaluate the results of ASR for PPR of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

PATIENTS AND METHODS

Between March 1983 and May 2000, 44 patients with PPR of rectal carcinoma that involved the sacrum on computed tomography (CT) were considered candidates for ASR and admitted to the National Cancer Center Hospital, Tokyo. There were 35 men and 9 women, with a median age of 55 years (range, 32–73 years). Of these, 40 patients underwent initial operation at other hospitals. Selection criteria for curative-intent ASR were as follows: (1) medical fitness for ASR; (2) no signs of disseminated disease on preoperative imaging; (3) tumors involving the sacrum but not the first sacral bone and the bony lateral walls; and (4) tumors anatomically confined within the pelvis, with or without resectable solitary liver metastasis. The imaging studies routinely performed before resection were abdominal and pelvic CT, abdominal ultrasonography, and chest roentgenogram until 1989; pelvic magnetic resonance imaging and chest CT were added thereafter.

Of the 44 patients for whom ASR was attempted, 40 received curative-intent ASR, and 4 received palliative-intent ASR because of 1 or 2 lung metastases in 3 and 3 liver metastases in 1. Of the 40 who received curative-intent ASR, 33 patients underwent macroscopic curative ASR, 2 with solitary liver metastasis underwent macroscopic curative ASR with complete resection of liver metastasis, 1 with 4 peritoneal metastases adjacent to the main tumor underwent macroscopic curative ASR with complete resection of peritoneal metastases, and the remaining 4 underwent palliative ASR because of macroscopic residual local tumor in 3 and residual lymph node metastases in 1. Of the four who received palliative-intent ASR, three with lung metastases underwent palliative ASR leaving only residual lung metastases in two and both residual lung and local tumors in one, and one with three liver metastases underwent macroscopic curative ASR with complete resection of liver metastases. Conseuently, 37 underwent macroscopic curative resection, and 7 underwent macroscopic palliative resection. Of them, 27 patients received no radiation, 13 received preoperative adjuvant radiation of 30 to 73 Gy (median, 44 Gy), and 4 received 44 to 50 Gy (median, 50 Gy) as previous treatment.

Data for these patients were collected and entered prospectively into the database of the Colorectal Surgery Division. They included the following: (1) patient demographics; (2) treatment and pathology of the primary rectal cancer; (3) presentation of PPR; (4) treatment and pathology of recurrent tumor; (5) operative details; (6) hospital course, including complications; and (7) outcome. Of these, 15 variables were selected for prognostic factor analysis (Table 1) by consideration of their potential relationship to survival after ASR, as indicated by previous studies.[13–15,17–19,22] The local disease–free interval (LDFI) was defined as the interval between the initial curative operation and the occurrence of symptoms or detection of asymptomatic PPR by CT.

Surgical Procedure

Our surgical procedure was basically similar to that originally described by Wanebo and Marcove[11] and Wanebo et al.;[13] however, it was slightly modified.[23] Our sacral resection was performed immediately after the abdominal phase as a one-stage procedure instead of a two-stage procedure.[13] The presence of liver metastasis did not preclude continuation of the procedure if it was solitary and if the disease-free interval was sufficiently long. Solitary liver metastasis was resected simultaneously. We did not make full-thickness fascial myocutaneous flaps for sacroperineal wound closure but sutured the wound simply because there were no patients with large exposed tumors at the perineum.

After the patient was placed in a supine position with flexed and abducted thighs, dissection was started at the aortic bifurcation, and the common and external iliac vessels were dissected. The internal iliac vessels were divided at their root or beyond the superior gluteal artery. Adipose tissue, lymphatics, and the nodes surrounding these vessels, including obturator nodes, were removed completely, and the muscular pelvic side walls and the sacral nerve roots were exposed. The upper limit of the tumor was identified, and the anterior surface of the sacrum was dissected down to the planned level of sacral transection. When the tumor adhered or invaded into

TABLE 1. *Univariate Predictors of Adverse Outcome*

Variable	No. of Patients	Overall survival (%)			*P*
		1-yr	3-yr	5-yr	
Overall	44	90	47	34	
Gender					
Female	9	87	45	45	.41
Male	35	91	48	32	
Age					
< 60 years	30	96	55	40	.10
≥ 60 years	14	92	31	23	
Primary cancer stage					
I, II	2, 13	93	64	48	.046
III	22	90	39	31	(I, II, III vs. IV)
IV	7	85	28	14	
Initial surgery					
Local excision, anterior resection	1, 20	90	51	36	.83
Abdominoperineal resection	23	90	44	34	
Initial lymphadenectomy					
Conventional	33	93	55	41	.25
Extended	11	81	27	18	
Local-disease-free interval (months)					
≤ 12	17	75	20	20	.0042
> 12	27	96	62	43	
Preoperative CEA level (ng/ml)					
≤ 10	23	91	70	49	.025
> 10	21	90	25	20	
Extent of preoperative pain					
None, perineum	15, 17	93	55	43	.0006
Buttock	7	85	35	0	(none, perineum vs. buttock, more)
Thigh, leg	3, 2	50	0	0	
Tumor extent					
Solitary pelvic tumor	24	95	55	40	.17
Pelvic metastasis	12	75	43	29	(solitary tumor vs. others)
Distant metastasis	8	85	28	28	
Largest tumor diameter (cm)					
≤ 5	26	92	50	40	.086
> 5	18	88	40	24	
Sacral involvement					
Adhesion	27	84	56	37	.85
Periosteum, marrow	11, 6	94	32	32	
Resection margin					
Microscopic negative	24	95	81	62	< .0001
Microscopic positive	13	91	16	8	(microscopic negative vs. others)
Gross positive, residual	7	71	0	0	
Pathological grade					
Well, moderate	4, 29	90	40	35	.49
Mucinous, adenosquamous	6, 1	85	57	42	(poor, signet vs. others)
Poor, signet-ring cell	3, 1	75	75	0	
Macroscopic growth pattern					
Solitary expanding	15	92	70	70	.0027
Multiple expanding	5	80	40	20	(solitary vs. others)
Diffuse infiltrating	24	87	34	13	
Preoperative radiation					
Yes	13	91	55	46	.55
No	31	90	44	29	

CEA, carcinoembryonic antigen.

urogenital organs, the remaining rectum, pelvic nerves or muscles, and involved organs were all resected en bloc to avoid incomplete resection and cancer cell spillage. To facilitate resection and hemostasis and to shorten operating time, a combined abdominal and perineal approach was used.

After dissection of the lateral, cephalad, anterior, and caudal aspects of the tumor with surrounding organs to be resected was accomplished, the patient was placed in a prone position with flexed and abducted thighs. A posterior sacral incision including the perineal lesion was made, and the sacrum and

gluteal muscles were exposed. The gluteal muscles, sacrotuberous ligament, sacrospinous ligaments, and pyriformis muscles were divided as far from the tumor as possible. After the level of abdominal dissection and the extent of the tumor were confirmed by hand in the pelvic cavity, a laminectomy proximal to the planned level of sacral transection was performed to preserve the noninvolved sacral nerve roots and ligate the dura. The sacrum was transected by an osteotome, and en-bloc resection of the tumor with the sacrum and the surrounding organs was accomplished. The gluteal muscles and skin were closed primarily. Again, the patient was placed in a supine position with flexed and abducted thighs. A colostomy and an ileal conduit were made.

Extent of Resection

Levels of sacral transection included S2 in 6 patients, S2–3 in 19, S3 in 5, S3–4 in 11, S4 in 1, and S4–5 in 2. Thirty-nine patients underwent total pelvic exenteration, one underwent posterior pelvic exenteration, and four underwent abdominoperineal resection. En-bloc resection of entire pelvic lymph nodes with the bilateral internal iliac arteries and veins was performed for all patients. Resected organs included the rectum in 20 cases, the urinary bladder in 39, the uterus and vagina in 8, the external genitalia in 2, the obturator internis muscle in 12, the gluteus maximus muscle in 5, and the small intestine in 7. Urinary diversions were an ileal conduit in 37 patients and a ureterocutaneostomy in 2. Three patients underwent complete resection of one, one, and three synchronous liver metastases. In addition, one patient underwent complete resection of four peritoneal metastases.

Follow-Up

One patient returned to Indonesia and was lost to follow-up. The other 43 were followed up completely, with a median follow-up time for live patients of 4.7 years (range, 1.2–15.8 years). They were examined with abdominal and pelvic CT, chest roentgenogram or CT, and carcinoembryonic antigen (CEA) measurement every 4 months for 0 to 1 years, every 6 months for 2 to 4 years, and annually for 5 to 10 years.

Statistical Analysis

Survival, disease-free survival, and local disease–free survival distributions were estimated by using the Kaplan-Meier product-limit method. Univariate comparisons of survival were made by using the log-rank test, and multivariate analysis was performed by using the Cox regression model with the forward stepwise method (likelihood ratio). All variables were dichotomized for analysis. Differences in proportions were analyzed by Fisher's exact test and by multivariate analysis with the logistic regression model and the forward stepwise method (likelihood ratio). All statistical analyses were performed with SPSS for Windows, version 10.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two sided, and a P value of $< .05$ was considered to be statistically significant.

RESULTS

Pathologic Findings

Histological diagnoses of the PPR cases are listed in Table 1. The bone marrow or periosteum of the sacrum was histologically involved in 17 patients. The remaining 27 had no sacral invasion, but dense fibrotic tissues adhered extensively to the sacrum, and cancer cells were found within them. Of 13 patients with pelvic lymph node involvement, 12 had intrapelvic metastases alone, and 1 had both intrapelvic and extrapelvic metastases. Eight patients had distant metastasis, including liver metastasis in three, lung metastasis in three, peritoneal metastasis in one, and distant lymph node metastasis in one.

Resection margins were microscopically negative in 24 patients, microscopically positive in 13, macroscopically positive in 3, and grossly residual in 4 (lung, n = 2; lung and local, n = 1; lymph node, n = 1; Table 1). The sites of macroscopic positive margins included cut ends of the sacrum and/or presacral connective tissue in two, cut ends of the sacral nerves and the external iliac artery in one, and the lateral pelvic sidewall in one. The major artery was involved only in one patient with prior extended lateral pelvic lymph node dissection. The sites of microscopic positive margins included the cut end of the sacrum in two, the cut end of the presacral connective tissue in three, the cut ends of the sacrospinous ligament and sacrotuberous ligament in one, the cut ends of the sacrospinous ligament and obturator internis muscle in one, the cut end of the obturator lymph node in one, and the cut ends of the sacral nerves in one.

Macroscopic growth patterns were based on macroscopic views of sections of resected specimens and were classified as solitary expanding growth, multiple expanding growth, and diffuse infiltrating growth (Fig. 1; Table 1). Expanding growth featured smooth

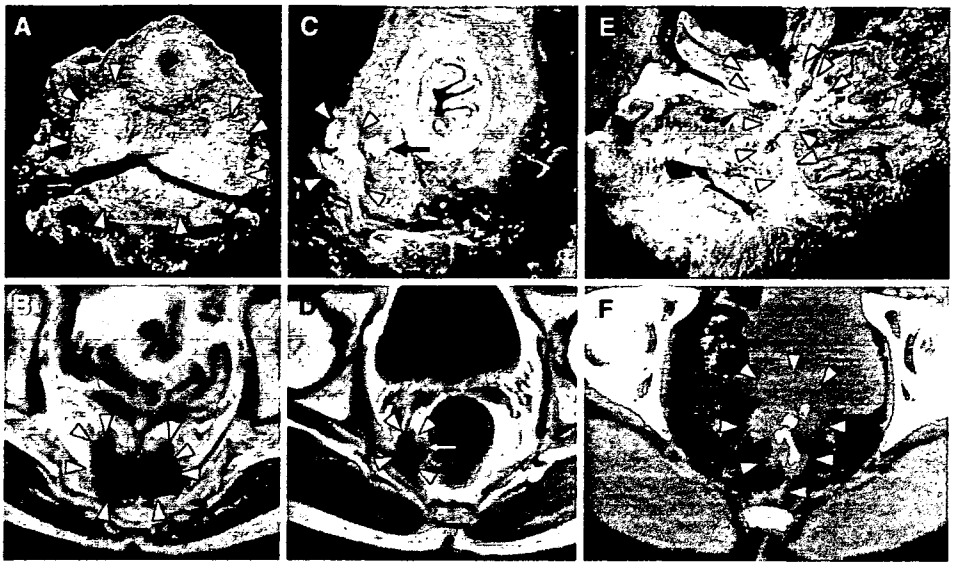

FIG. 1. (A) A section after abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. This tumor was macroscopically classified as solitary expanding growth. (B) Corresponding magnetic resonance image of (A). (C) A section of tumor macroscopically classified as multiple expanding growth. (D) Corresponding magnetic resonance image of (C). (E) A section of tumor macroscopically classified as diffuse infiltrating growth. (F) Corresponding computed tomography of (E). Arrowheads, main tumor; arrow, satellite tumor. *Sacrum.

and clear margins. Any tumors showing irregular or obscure margins were therefore classified into the diffuse infiltrating category.

Morbidity and Mortality

The median operating time was 751 minutes (range, 263–1377 minutes). The median blood loss was 3208 mL (range, 856–26160 mL), and all of the patients underwent transfusion. Of the 27 patients with postoperative complications (morbidity, 61%), 10 (23%) had major complications that necessitated surgical interventions or resulted in hospital death, and 17 (38%) had minor complications that could be managed conservatively (Table 2). The number of complications per patient was as follows: 4 in 1 patient, 3 in 5 patients, 2 in 10 patients, and 1 in 11 patients. One patient who had pelvic sepsis, residual tumor regrowth, bowel obstruction, and renal failure died on the 66th postoperative day (mortality, 2%).

Eleven (65%) of 17 patients who had received adjuvant or previous radiation had postoperative complications, compared with 16 (59%) of 27 who had not received radiation ($P = .76$). In contrast, 7 (41%) of 17 with adjuvant or previous radiation experienced major complications, compared with 3 (11%) of 27 without irradiation ($P = .03$). The median hospital stay was 38 days (range, 22–316 days).

TABLE 2. *Complications*

Complication	No. Patients
Major complications	
Pelvic sepsis	8
Bowel obstruction	3
Intestinal fistula	2
Ureteroileostomy leakage	2
Ureterocutaneostomy stenosis	1
Ileal conduit necrosis	1
Renal failure	1
Uncontrollable bleeding	1
Postoperative bleeding	1
Tracheal stenosis	1
Minor complications	
Wound dehiscence/infection	6
Bowel obstruction	12
Urinary tract infection	10
Ureteroileostomy stenosis	1
Neurogenic bladder	2

Survival

The median survival for all the patients undergoing ASR was 2.3 years (range, .1–15.8 years). The estimated overall 1-, 3-, and 5-year survival rates were 90%, 47%, and 34%, respectively, including one hospital death (Fig. 2). Of the 15 patients who survived >4 years, 9 were disease free, and 5 survived >8 years. The disease-free 1-, 3-, and 5-year survival rates were 44%, 26%, and 24%, respectively. The local disease-free 1-, 3-, and 5-year survival rates were 63%, 47%, and 47%, respectively (Fig. 2).

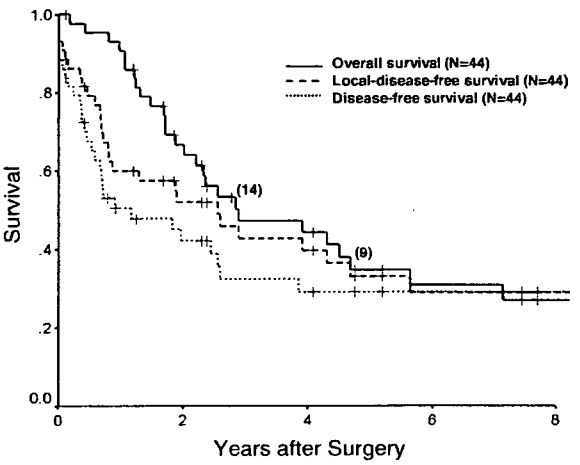

FIG. 2. Overall, disease-free, and local disease–free survival distributions for the 44 patients undergoing abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. The numbers in parentheses for the overall survival curve indicate the patients alive at 3 and 5 years.

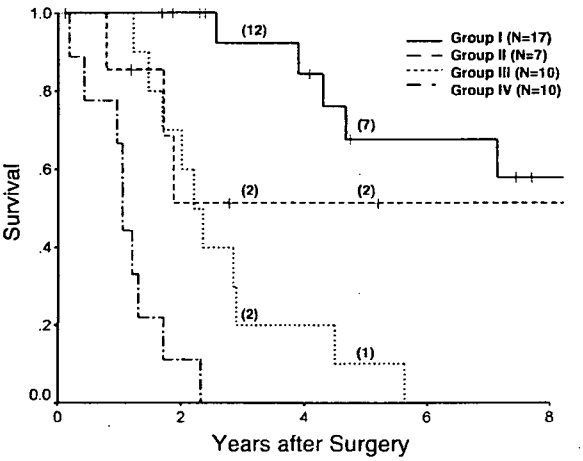

FIG. 3. Overall survival curves for group I (microscopic negative margin and local disease–free interval [LDFI] of > 12 months), group II (microscopic negative margin and LDFI < 12 months), group III (positive margin and LDFI > 12 months), and group IV (positive margin and LDFI < 12 months). The numbers in parentheses for each curve indicate the patients alive at 3 and 5 years.

Prognostic Factors

Results of univariate analysis of prognostic factors are summarized in Table 1. The overall survival of the patients with microscopic positive resection margins was significantly worse than that of those with microscopic negative margins ($P < .0001$) but was not significantly better than that of those with macroscopic positive margins or macroscopic residual tumor ($P = .11$). Patients with macroscopic positive margins or macroscopic residual tumor did not survive > 2.3 years.

The survival of patients with buttock pain was significantly worse than that of those without pain or with perineal pain ($P = .043$) and was significantly better than that of those with thigh or leg pain ($P = .0046$). The latter died within 1.2 years.

Of the eight patients with distant metastasis, two undergoing resection of solitary liver metastasis were alive and disease free for 7.6 and 2.7 years, one undergoing resection of three liver metastases died of disease at 1.3 years, one undergoing resection of four peritoneal metastases was alive with disease at 1.1 years, three with one or two lung metastases died of disease at 2.3, 2.0, and 1.6 years, and one with paraaortic lymph node metastasis died at 1.7 years.

The univariate analysis of the 15 variables (Table 1), when dichotomized, showed a positive resection margin, pain extending to the buttock or further, multiple growths or diffuse infiltrating growth, LDFI of < 12 months, a preoperative CEA level > 10 ng/mL, and primary cancer stage IV to be associated with significantly worse survival. The other nine factors did not show any significant association with outcome.

The multivariate analysis of the 15 dichotomized variables revealed that only a positive resection margin (hazard ratio, 10 [95% confidence interval, 3.8–28]; $P < .001$), an LDFI of < 12 months (4.2 [1.8–9.8]; $P = .001$), and pain radiating to the buttock or further (4.2 [1.6–11]; $P = .004$) were independently associated with worse survival.

When the most significant independent factors were considered together, the 5-year overall survival rates of the 17 patients with microscopic negative margins and an LDFI > 12 months (group I), the 7 with microscopic negative margins and an LDFI < 12 months (group II), the 10 with positive margins and an LDFI > 12 months (group III), and the 10 with positive margins and an LDFI < 12 months (group IV) were 67%, 51%, 10%, and 0%, respectively (Fig. 3). There were significant survival differences between group I and group III ($P < .0001$), group III and group IV ($P = .0014$), and group II and group IV ($P = .01$). Group IV patients did not survive > 2.3 years.

Risk Factors for a Positive Resection Margin

To clarify the risk factors for a positive resection margin, the most significant prognostic factor on multivariate analysis, univariate and multivariate analyses were conducted. Three patients who under-

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. Pallia-

tive 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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REFERENCES

1. Stearns MWJ. Diagnosis and management of recurrent pelvic malignancy following combined abdominoperineal resection. *Dis Colon Rectum* 1980; 23:359–61.
2. Wanebo HJ, Whitehill R, Gaker D, Wang GJ, Morgan R, Constable W. Composite pelvic resection, an approach to advanced pelvic cancer. *Arch Surg* 1987; 122:1401–6.

3. Wanebo HJ, Koness RJ, Turk PS, Cohen SI. Composite resection of posterior pelvic malignancy. *Ann Surg* 1992; 215:685–95.
4. Pearlman NW, Stiegmann GV, Donohue RE. Extended resection of fixed rectal cancer. *Cancer* 1989; 63:2438–41.
5. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ* 2000; 321:531–5.
6. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; 352:476–87.
7. Hoffman JP, Riley L, Carp NZ, Litwin S. Isolated locally recurrent rectal cancer: a review of incidence, presentation, and management. *Semin Oncol* 1993; 20:506–19.
8. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 1997; 38:785–90.
9. Wong CS, Cummings BJ, Brierley JD, et al. Treatment of locally recurrent rectal carcinoma: results and prognostic factors. *Int J Radiat Oncol Biol Phys* 1998; 40:427–35.
10. Cohen AM, Minsky BD. Aggressive surgical management of locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 1990; 33:432–8.
11. Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. *Ann Surg* 1981; 194:458–71.
12. Brunschwig A, Barber HR. Pelvic exenteration combined with resection of segments of bony pelvis. *Surgery* 1969; 65:417–20.
13. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. *Dis Colon Rectum* 1999; 42:1438–48.
14. Maetani S, Onodera H, Nishikawa T, et al. Significance of local recurrence of rectal cancer as a local or disseminated disease. *Br J Surg* 1998; 85:521–13.
15. Mannaerts GH, Rutten HJ, Martijn H, Groen GJ, Hanssens PE, Wiggers T. Abdominosacral resection for primary irresectable and locally recurrent rectal cancer. *Dis Colon Rectum* 2001; 44:806–14.
16. Magrini S, Nelson H, Gunderson LL, Sim FH. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. *Dis Colon Rectum* 1996; 39:1–9.
17. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg* 2003; 237:502–8.
18. Pearlman NW, Stiegmann GV, Donohue RE. Extended resection of fixed rectal cancer. *Cancer* 1989; 63:2438–41.
19. Schiessel R, Wunderlich M, Herbst F. Local recurrence of colorectal cancer: effect of early detection and aggressive surgery. *Br J Surg* 1986; 73:342–4.
20. Temple WJ, Ketcham AS. Sacral resection for control of pelvic tumors. *Am J Surg* 1992; 163:370–4.
21. Takagi H, Morimoto T, Hara S, Suzuki R, Horio S. Seven cases of pelvic exenteration combined with sacral resection for locally recurrent rectal cancer. *J Surg Oncol* 1986; 32:184–8.
22. Yamada K, Ishizawa T, Niwa K, Chuman Y, Aikou T. Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 2002; 45:1078–84.
23. Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. *Dis Colon Rectum* 2004; 47:2047–53.
24. Onodera H, Maetani S, Kawamoto K, Kan S, Kondo S, Imamura M. Pathologic significance of tumor progression in locally recurrent rectal cancer: different nature from primary cancer. *Dis Colon Rectum* 2000; 43:775–81.
25. Wanebo HJ, Koness RJ, Vezeridis MP, Cohen SI, Wrobleski DE. Pelvic resection of recurrent rectal cancer. *Ann Surg* 1994; 220:586–95.
26. Deckers PJ, Olsson C, Williams LA, Mozden PJ. Pelvic exenteration as palliation of malignant disease. *Am J Surg* 1976; 131:509–15.
27. Cunningham JD, Enker W, Cohen A. Salvage therapy for pelvic recurrence following curative rectal cancer resection. *Dis Colon Rectum* 1997; 40:393–400.
28. de Lange EE, Fechner RE, Wanebo HJ. Suspected recurrent rectosigmoid carcinoma after abdominoperineal resection: MR imaging and histopathologic findings. *Radiology* 1989; 170:323–8.
29. Farouk R, Nelson H, Radice E, Mercill S, Gunderson L. Accuracy of computed tomography in determining resectability for locally advanced primary or recurrent colorectal cancers. *Am J Surg* 1998; 175:283–7.
30. Brown G, Richards CJ, Newcombe RG, et al. Rectal carcinoma: thin-section MR imaging for staging in 28 patients. *Radiology* 1999; 211:215–22.
31. Fletcher JG, Johnson CD, Krueger WR, et al. Contrast-enhanced CT colonography in recurrent colorectal carcinoma: feasibility of simultaneous evaluation for metastatic disease, local recurrence, and metachronous neoplasia in colorectal carcinoma. *AJR Am J Roentgenol* 2002; 178:283–90.
32. Gastrointestinal Tumor Study Group Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985; 312:1465–72.
33. Påhlman L. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336:980–7.
34. Marijnen CA, Nagtegaal ID, Kapiteijn E, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003; 55:1311–20.
35. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum* 2002; 45:585–92.
36. Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. *Cancer* 1992; 69:2876–83.

Original article

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

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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 ($P = 0{\cdot}003$). Univariable analysis showed that a high level of sacrectomy ($P = 0{\cdot}036$), absence of lymphatic invasion ($P = 0{\cdot}031$) and circumferential fibrosis ($P = 0{\cdot}039$) were significantly associated with better overall survival. In multivariable analysis, circumferential fibrosis ($P = 0{\cdot}031$) and low serum carcinoembryonic antigen levels ($P = 0{\cdot}044$) 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.

Methods

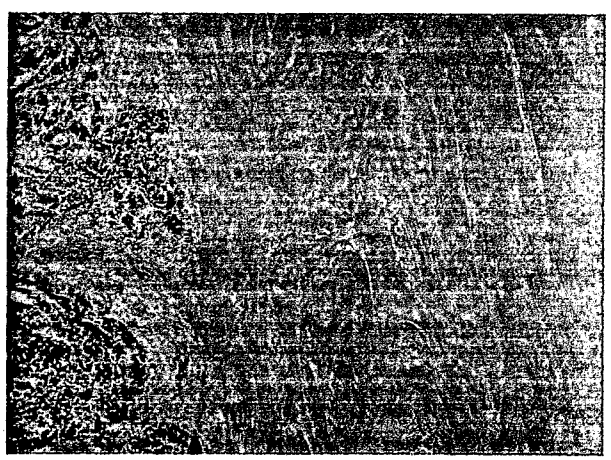
The study included patients who had undergone curative TPES. All had localized, fixed, recurrent cancer in the pelvis without distant metastases, with the exception of concomitant liver metastases amenable to surgical resection. Between 1992 and 2004, 56 patients had TPES for fixed recurrent rectal cancer 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

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

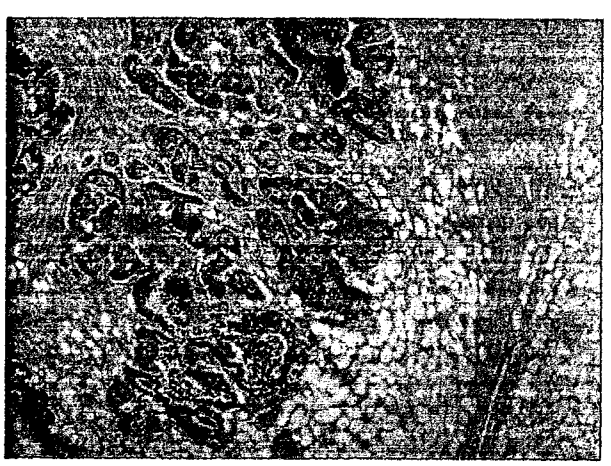
metastases. There were 35 men and 13 women, with a median age of 57·5 (range 32–76) years.

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)

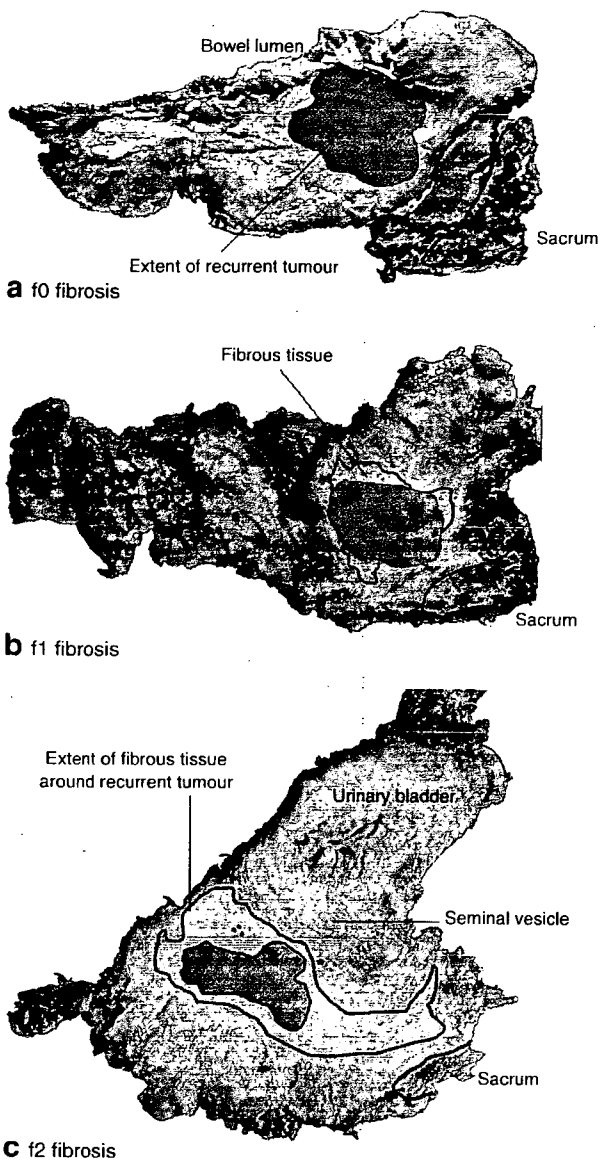


Fig. 2 Classification of fibrous tissue around the recurrent tumour. **a** f0 fibrosis was defined as absence of fibrous tissue around the tumour, **b** f1 as partial presence and **c** f2 as circumferential fibrosis enclosing the tumour together with any of the surrounding organs

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).

Table 2 Pathological findings

	Total ($n = 48$)	f0 ($n = 10$)	f1 ($n = 17$)	f2 ($n = 21$)
Histological type				
Well differentiated adenocarcinoma	16	3	1	12*
Moderately differentiated adenocarcinoma	29	6	14	9*
Poorly differentiated adenocarcinoma	3	1	2	0
Invasion to surrounding organs				
Yes	21	5	11	5*
No	27	5	6	16*
Perineural invasion				
Yes	20	6	9	5†
No	28	4	8	16†
Venous invasion				
Yes	12	5	7	0*†
No	36	5	10	21*†
Lymphatic invasion				
Yes	10	3	6	1*
No	38	7	11	20*
Abscess formation around recurrent tumour				
Yes	8	1	3	4
No	40	9	14	17

*$P < 0.050$ *versus* f1, †$P < 0.050$ *versus* f0 (χ^2 test).

f0 or f1 fibrosis, and well differentiated adenocarcinoma in those with f2 fibrosis. Patients with f2 fibrosis had significantly lower rates of perineural ($P = 0.049$) and venous ($P < 0.001$) invasion than those with f0 fibrosis, and significantly lower rates of invasion to surrounding organs ($P = 0.011$) and venous ($P = 0.001$) and lymphatic ($P = 0.016$) invasion than patients with f1 fibrosis.

The overall 5-year survival rate was 52 per cent (25 of 48 patients), with 5-year survival of none, four and eight patients with f0, f1 and f2 fibrosis respectively. The overall survival of patients with f2 fibrosis was significantly greater than that of patients with f0 fibrosis ($P = 0.003$).

To simplify the analysis, the histological type (well *versus* moderately or poorly differentiated) and degree of fibrous tissue (f2 *versus* f0–1) were grouped into two categories. A favourable overall survival after TPES correlated significantly with a higher level of sacrectomy ($P = 0.036$), absence of lymphatic invasion ($P = 0.031$) and circumferential fibrosis ($P = 0.039$). In multivariable analysis, circumferential fibrosis ($P = 0.031$) and low serum carcinoembryonic antigen levels ($P = 0.044$) were independent factors for a favourable outcome (*Table 3*).

Table 3 Univariable and multivariable analysis for overall survival using the Cox proportional hazards regression model

	Univariable analysis	Multivariable analysis	
	P	Odds ratio	*P*
Dukes' classification for primary growth (A, B *versus* C)	0·059	2·86 (1·00, 8·17)	0·050
Surgery for recurrent tumour (no *versus* yes)	0·066		0·614
Serum CEA level (< 20 *versus* ≥ 20 ng/ml)	0·131	2·87 (1·03, 7·97)	0·044
Simultaneous hepatectomy (no *versus* yes)	0·944		0·845
Level of distal sacrectomy (< S3 *versus* > S3)	0·036		0·295
Histological type (well *versus* moderately, poorly differentiated)	0·187		0·624
Perineural invasion (no *versus* yes)	0·117		0·725
Venous invasion (no *versus* yes)	0·079		0·947
Lymphatic invasion (no *versus* yes)	0·031		0·915
Degree of fibrous tissue (f2 *versus* f0–1)	0·039	3·19 (1·11, 9·12)	0·031

Values in parentheses are 95 per cent confidence intervals. CEA, carcinoembryonic antigen. Odds ratios given only for significant variables.

Discussion

Tumours surrounded by fibrous tissue in locally recurrent rectal cancer are associated with a better 5-year survival rate than those with no surrounding fibrosis.

Several factors have been suggested as prognostic indicators after surgical resection of recurrent rectal cancer fixed in the pelvis. The most important single factor has generally been accepted to be the achievement of an R0 resection[8–10]. The present authors have reported previously that TPES with R0 resection resulted in a 5-year relapse-free survival rate of 49 per cent, although no patient who had R1 or R2 resection survived for 4 years[4].

Although fibrotic tissue around a recurrent tumour sometimes makes it difficult to determine the preoperative extent of the disease[11], it is an interesting histological feature. This tissue is distinct from the stromal or desmoplastic reaction to tumour invasion, which has been reported to be a prognostic predictor in primary rectal cancer[12]. The fibrotic area that extends widely around the fixed recurrent tumour appears to lack cancer cells. A similar 'fibrous tissue-encapsulating tumour' is

often encountered in hepatocellular carcinoma[13–15] and in metastatic liver tumours from colorectal primary cancers[16,17]. It has been reported that the fibrous tissue is related to decreased tumour invasiveness and is an indicator of improved survival after resection[13–17]. There have been no reports of the clinical significance of fibrous tissues in locally recurrent rectal tumours.

The pathogenesis of fibrosis surrounding the recurrent fixed tumour has not been elucidated. It is unclear whether this fibrous tissue formation is promoted by radiotherapy, chemotherapy or previous pelvic surgery, and there were insufficient patients in the present series to justify multivariable analyses to examine the influence of these factors. Alternatively, fibrous tissue might be formed around the tumour by an active host response[18]. Inflammatory cell infiltration at the border between the tumour and non-cancerous tissue has been demonstrated to be a favourable prognostic indicator in primary gastric and colorectal cancers[19,20], and the fibrous tissue surrounding fixed recurrent tumours may represent part of a defensive immune inflammatory mechanism.

Previous studies have suggested staging systems for locally recurrent rectal cancer according to the degree of fixation to surrounding structures[8,21–23], but none has been universally adopted[8,9]. As indicated by the present data, the degree of fibrosis may be an important prognostic factor and perhaps valuable in the selection of high-risk patients who would benefit from adjuvant treatment after TPES.

References

1 Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following 'curative surgery' for adenocarcinoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. *Cancer* 1974; **34**: 1278–1292.

2 Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resection of rectal cancer. *Cancer* 1984; **53**: 1354–1362.

3 Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. *Ann Surg* 1981; **194**: 458–471.

4 Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer. *Surg Oncol Clin N Am* 2005; **14**: 225–238.

5 Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. *Dis Colon Rectum* 2004; **47**: 2047–2054.

6 Japanese Society for Cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma* (1st edn). Kanehara: Tokyo, 1997.

7 Ueno H, Jones AM, Wilkinson KH, Jass JR, Talbot IC. Histological categorisation of fibrotic cancer stroma in advanced rectal cancer. *Gut* 2004; **53**: 581–586.

8 Willett CG, Shellito PC, Tepper JE, Eliseo R, Convery K, Wood WC. Intraoperative electron beam radiation therapy for recurrent locally advanced rectal or rectosigmoid carcinoma. *Cancer* 1991; **67**: 1504–1508.

9 Wanebo HJ, Antoniuk P, Koness RJ, Levy A, Vezeridis M, Cohen SI *et al.* Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. *Dis Colon Rectum* 1999; **42**: 1438–1448.

10 Shoup M, Guillem JG, Alektiar KM, Liau K, Paty PB, Cohen AM *et al.* Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum* 2000; **45**: 585–592.

11 Robinson P, Carrington BM, Swindell R, Shanks JH, O'dwyer ST. Recurrent or residual pelvic bowel cancer: accuracy of MRI local extent before salvage surgery. *Clin Radiol* 2002; **57**: 514–522.

12 Hasebe T, Sasaki S, Sugitoh M, Ono M, Saitoh N, Ochiai A. Highly proliferative intratumoral fibroblasts and a high proliferative microvessel index are significant predictors of tumor metastasis in T3 ulcerative-type colorectal cancer. *Hum Pathol* 2001; **32**: 401–409.

13 Ng IO, Lai EC, Ng MM, Fan ST. Tumor encapsulation in hepatocellular carcinoma: a pathologic study of 189 cases. *Cancer* 1992; **70**: 45–49.

14 Franco D, Capussotti L, Smadja C, Bouzari H, Meakins J, Kemeny F *et al.* Resection of hepatocellular carcinomas: results in 72 European patients with cirrhosis. *Gastroenterology* 1990; **98**: 733–738.

15 Okuda K, Musha H, Nakajima Y, Kubo Y, Shimokawa Y, Nagasaki Y *et al.* Clinicopathologic features of encapsulated hepatocellular carcinoma: a study of 26 cases. *Cancer* 1977; **40**: 1240–1245.

16 Okano K, Yamamoto J, Kosuge T, Yamamoto S, Sakamoto M, Nakanishi Y *et al.* Fibrous pseudocapsule of metastatic liver tumors from colorectal carcinoma. Clinicopathologic study of 152 first resection cases. *Cancer* 2000; **89**: 267–275.

17 Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H. Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. *Br J Surg* 1999; **86**: 332–337.

18 van Ravenswaay Claasen HH, Kluin PM, Fleuren GJ. Tumor infiltrating cells in human cancer. On the possible role of CD16+ macrophages in antitumor cytotoxicity. *Lab Invest* 1992; **67**: 166–174.

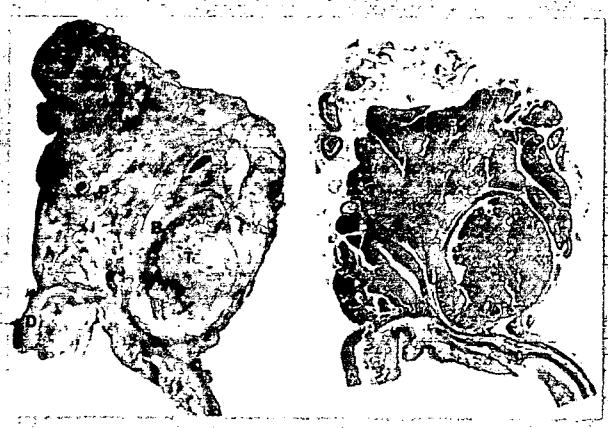
19 Watanabe H, Enjoji M, Imai T. Gastric carcinoma with lymphoid stroma: its morphologic characteristics and prognostic correlations. *Cancer* 1976; **38**: 232–243.

20 Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. *J Pathol* 1997; **182**: 318–324.

21 Suzuki K, Gunderson LL, Devine RM, Weaver AL, Dozois RR, Ilstrup DM *et al.* Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. *Cancer* 1995; **75**: 939–952.
22 Valentini V, Morganti AG, De Franco A, Coco C, Ratto C, Battista Doglietto G *et al.* Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma: prognostic factors and long term outcome. *Cancer* 1999; **86**: 2612–2624.
23 Yamada K, Ishizawa T, Niwa K, Chuman Y, Akiba S, Aikou T. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. *Br J Surg* 2001; **88**: 988–993.

Papillary tumour of the common bile duct

A 77 year old man with obstructive jaundice had a polypoidal mass occupying the lumen of the distal common bile duct on ERCP and intraductal ultrasound. Biopsies revealed papillary proliferation with excessive mitotic activity. He underwent a pylorus preserving pancreaticoduodenectomy. There was a 40 × 30 × 20 mm tumour within the lumen of the common bile duct, extending across the papilla into the duodenum (T: tumour, B: bile duct, P: pancreas, D: duodenum). Microscopy (H&E stain × 1) revealed a well-circumscribed intraductal papillary tumour with focal intestinal metaplasia and clear cell change. There was marked nuclear pleomorphism, but no stromal invasion. Papillary carcinomas of the extrahepatic bile ducts behave as in-situ carcinomas, invasion is a late event and prognosis is excellent.



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Original article

Clinicopathological significance of microscopic abscess formation at the invasive margin of advanced low rectal cancer

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Background: The aim of this study was to evaluate the clinicopathological significance of microscopic abscess formation (MAF) at the invasive front of advanced low rectal cancer.

Methods: The clinicopathological features of 226 consecutive patients with low rectal cancer, who underwent curative resection between May 1997 and December 2002, were analysed.

Results: Fifty-seven (25·2 per cent) of the 226 tumours had MAF and 169 (74·8 per cent) did not. Patients with tumours showing MAF were more likely to have extended surgery than those without MAF: 47 *versus* 31·4 per cent respectively underwent non-sphincter-preserving surgery ($P = 0·029$) and 82 *versus* 60·9 per cent underwent lateral lymph node dissection ($P = 0·003$). The incidence of lymph node metastases was lower in patients with MAF (30 *versus* 53·3 per cent; $P = 0·002$). Univariable analysis of disease-free survival revealed that depth of invasion ($P < 0·001$), lymph node status ($P < 0·001$), histological type ($P = 0·035$), lymphatic invasion ($P < 0·001$), venous invasion ($P < 0·001$), perineural invasion ($P < 0·001$), focal dedifferentiation ($P < 0·001$) and MAF ($P < 0·001$) were significant prognostic factors. Multivariable analysis showed that lymph node status ($P < 0·001$), perineural invasion ($P = 0·002$), venous invasion ($P = 0·033$) and MAF ($P = 0·012$) remained independent prognostic factors.

Conclusion: MAF may reflect indolent tumour behaviour and a more favourable outcome in patients with advanced low rectal cancer.

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Introduction

In Japan, the incidence of colorectal cancer has been increasing, reflecting the trend in Western countries. Colorectal cancer has become the most common cause of cancer death in women and the fourth most common cause in men[1]. Even after curative resection, there is a risk of recurrence within 5 years of initial diagnosis. In addition to the tumour node metastasis (TNM) classification[2], various attempts have been made to derive prognostic indicators based on conventional histopathological features[3–7]. Focal dedifferentiation and perineural invasion have been described as significant prognostic factors in colorectal cancer[8,9].

Microscopic abscess formation (MAF) due to neutrophil infiltration is one of the characteristic features of colorectal cancer. The presence of MAF and accompanying fibrosis at the invasive margin of the tumour sometimes make it difficult to diagnose the extent of tumour invasion before surgery[10–12]. There have been few previous reports on the clinicopathological significance of MAF in low rectal cancer[13]. The aim of this prospective study was to clarify the significance of MAF in low rectal cancer.

Patients and methods

Between May 1997 and December 2002, a series of 283 consecutive patients underwent curative surgery for rectal cancer located at or below the peritoneal reflection, at the National Cancer Centre Hospital, Tokyo. Of these, 53 patients with pT1 tumour were excluded. Four patients who had previous pelvic surgery for cancer (bladder cancer in two and rectosigmoid cancer in two) were also excluded. Consequently, 226 patients who had pathological (p)T2 or deeper tumour invasion according to the TNM

classification were eligible for this study. They comprised 151 men (66·8 per cent) and 75 women (33·2 per cent) with a mean age of 59 (range 27–91) years. In this study, the lateral pelvic lymph nodes were regarded as regional nodes according to the Japanese Classification of Colorectal Carcinoma[14], although lateral pelvic lymph node metastases are regarded as distant metastases in the TNM classification system[2].

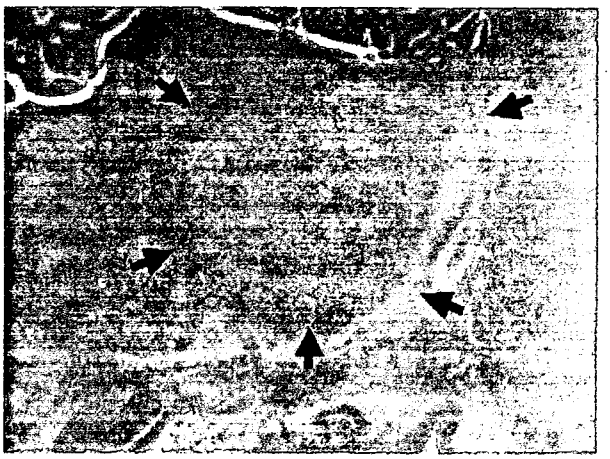
All patients were evaluated before surgery by total colonoscopy, barium enema and computed tomography (CT). None of the patients underwent preoperative radiotherapy and/or chemotherapy. One hundred and forty-six patients had sphincter-preserving surgery, 67 had abdominoperineal resection and 13 needed total pelvic exenteration. Patients with stage II or III tumours underwent lateral lymph node dissection based on the preoperative or intraoperative findings. Lateral lymph node dissection was performed bilaterally in 107 patients and unilaterally in 43. Median follow-up was 50 (range 1–98) months.

Histopathological examination

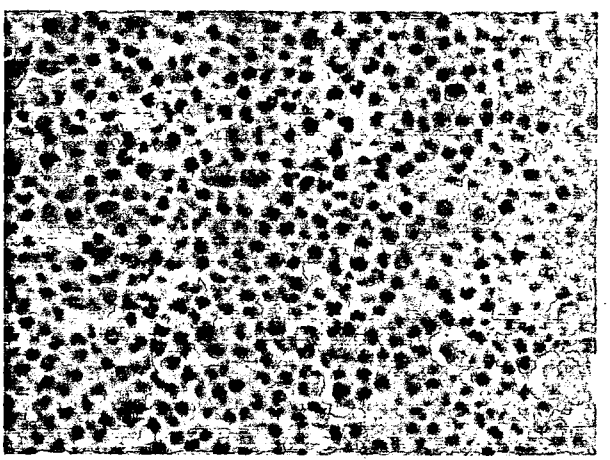
The resected tissue specimens were subjected to conventional processing. Histological sections containing the deepest site of cancer invasion were stained with haematoxylin and eosin, and were reviewed by three pathologists who had no previous knowledge of the clinical parameters and outcomes for each patient. All discrepancies were resolved by joint review. Focal dedifferentiation was defined as the presence of a polygonal (not columnar) cancer cell morphology that had a single or a solitary trabecular form with indistinct polarity and an infiltrative pattern at the invasive front[8]. MAF was judged to be present when liquefied masses formed by debris and leucocytes, mainly neutrophils, were evident at the invasive margin of the tumour in the section containing the deepest site of cancer invasion (*Fig. 1*).

Statistical analysis

Comparisons between groups were performed using the χ^2 test. Deaths from causes other than rectal cancer were treated as censored cases. Survival curves were traced using the Kaplan–Meier method and differences between curves were tested using the log rank test. The prognostic significance of selected factors to disease-free survival was evaluated using the Cox proportional hazards regression model. $P < 0{\cdot}050$ was considered statistically significant. All statistical calculations were made using SPSS® version 11.0 computer software (SPSS, Chicago, Illinois, USA).



a MAF, × 20 magnification



b MAF, × 400 magnification

Fig. 1 **a** Microscopic abscess formation (MAF) was usually found at the invasive margin of the tumour (arrows). **b** MAF was formed by debris and leucocytes, mainly neutrophils (haematoxylin and eosin stain, original magnification **a** × 20, **b** × 400)

Results

Of the 226 tumours, 57 (25·2 per cent) had MAF and 169 (74·8 per cent) did not. MAF was usually found at the invasive margin of the tumour. The mean size of microscopic abscesses was 2·2 (range 0·4–13·0) mm. The clinical characteristics of the 226 patients in relation to MAF are shown in *Table 1*. There was no significant difference in the distance from the dentate line to tumours with or without MAF. Patients with tumours showing MAF were more likely to need extended surgery than those without; 47 *versus* 31·4 per cent respectively

Table 1 Clinical characteristics of 226 patients who had resection of rectal cancer

	No. of patients	Microscopic abscess formation: No ($n = 169$)	Microscopic abscess formation: Yes ($n = 57$)	P*
Age (years)				0·193
< 60	114	81 (47·9)	33 (58)	
≥ 60	112	88 (52·1)	24 (42)	
Sex				0·978
M	151	113 (66·9)	38 (67)	
F	75	56 (33·1)	19 (33)	
Level of CEA (ng/ml)				0·388
< 5	157	120 (71·0)	37 (65)	
≥ 5	69	49 (29·0)	20 (35)	
Tumour distance from DL (cm)				0·068
< 3	141	100 (59·2)	41 (72)	
≥ 3	85	69 (40·8)	16 (28)	
Surgical procedure				0·029
SPS	146	116 (68·6)	30 (53)	
Non-SPS	80	53 (31·4)	27 (47)	
Lateral lymph node dissection				0·003
No	76	66 (39·1)	10 (18)	
Yes	150	103 (60·9)	47 (82)	
TNM classification				0·002†
Stage I	59	43 (25·4)	16 (28)	
Stage II	60	36 (21·3)	24 (42)	
Stage III	107	90 (53·3)	17 (30)	

Values in parentheses are percentages. CEA, carcinoembryonic antigen; DL, dentate line; SPS, sphincter-preserving surgery; TNM, tumour node metastasis. *χ^2 test; †stage I and II *versus* stage III.

underwent non-sphincter-preserving surgery ($P = 0·029$) and 82 *versus* 60·9 per cent had lateral lymph node dissection ($P = 0·003$). However, the proportion of stage III tumours in the MAF group was lower than that in the non-MAF group (30 *versus* 53·3 per cent; $P = 0·002$).

There were few histological differences in the 226 tumours in relation to MAF (*Table 2*). Five patients had a pT4 tumour, but only one of these had MAF. MAF rates were lower in tumours with lymph node metastases, focal dedifferentiation and

Table 2 Histological characteristics of 226 rectal tumours in relation to microscopic abscess formation

	No. of tumours	Microscopic abscess formation: No ($n = 169$)	Microscopic abscess formation: Yes ($n = 57$)	P*
Depth of invasion (pT)				0·549
pT2	86	66 (39·1)	20 (35)	
pT3 or pT4	140	103 (60·9)	37 (65)	
Lymph node status (pN)				0·002
Negative	119	79 (46·7)	40 (70)	
Positive	107	90 (53·3)	17 (30)	
Histological type				0·796
Well differentiated	84	62 (36·7)	22 (39)	
Non-well differentiated	142	107 (63·3)	35 (61)	
Lymphatic invasion				0·013
No	135	93 (55·0)	42 (74)	
Yes	91	76 (45·0)	15 (26)	
Venous invasion				0·146
No	120	85 (50·3)	35 (61)	
Yes	106	84 (49·7)	22 (39)	
Perineural invasion				0·184
No	185	135 (79·9)	50 (88)	
Yes	41	34 (20·1)	7 (12)	
Focal dedifferentiation				0·003
No	150	103 (60·9)	47 (82)	
Yes	76	66 (39·1)	10 (18)	

Values in parentheses are percentages. *χ^2 test.

Table 3 Univariable and multivariable analysis of disease-free survival using the Cox proportional hazards regression model in 226 patients with rectal cancer

	Univariable analysis*: P	Multivariable analysis†: Odds ratio	Multivariable analysis†: P
Surgical procedure (SPS *versus* non-SPS)	0·232		0·157
Lateral lymph node dissection (no *versus* yes)	0·429		0·736
Depth of invasion (pT2 *versus* pT3/4)	< 0·001		0·371
Lymph node status (pN0 *versus* pN1/2)	< 0·001	4·84 (2·27, 10·31)	< 0·001
Histological type (well *versus* non-well differentiated)	0·035		0·779
Lymphatic invasion (no *versus* yes)	< 0·001		0·288
Venous invasion (no *versus* yes)	< 0·001	1·84 (1·05, 3·21)	0·033
Perineural invasion (no *versus* yes)	< 0·001	2·35 (1·36, 4·07)	0·002
Focal dedifferentiation (no *versus* yes)	< 0·001	1·64 (0·98, 2·75)	0·058
Microscopic abscess formation (yes *versus* no)	< 0·001	4·48 (1·38, 10·47)	0·012

Values in parentheses are 95 per cent confidence intervals. SPS, sphincter-preserving surgery *χ^2 test; †Cox regression.

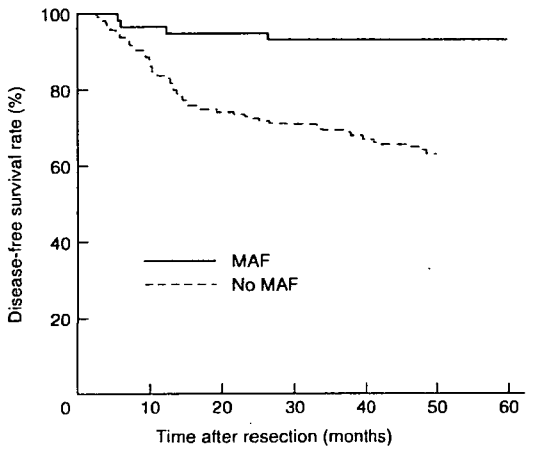


Fig. 2 Disease-free survival curves in relation to microscopic abscess formation (MAF). $P < 0{\cdot}001$ (log rank test)

lymphatic invasion ($P = 0{\cdot}002$, $P = 0{\cdot}003$ and $P = 0{\cdot}013$ respectively).

The 3- and 5-year disease-free survival rates were both 95 per cent for patients with MAF, and 68·8 and 62·6 per cent respectively for patients without MAF (*Fig. 2*). Patients with tumours showing MAF had significantly better disease-free survival ($P < 0{\cdot}001$). Univariable analysis showed that depth of invasion ($P < 0{\cdot}001$), lymph node status ($P < 0{\cdot}001$), histological type ($P = 0{\cdot}035$), lymphatic invasion ($P < 0{\cdot}001$), venous invasion ($P < 0{\cdot}001$), perineural invasion ($P < 0{\cdot}001$), focal dedifferentiation ($P < 0{\cdot}001$) and MAF ($P < 0{\cdot}001$) were significant prognostic indicators of disease-free survival. In multivariable analysis lymph node status ($P < 0{\cdot}001$), perineural invasion ($P = 0{\cdot}002$), venous invasion ($P = 0{\cdot}033$) and MAF ($P = 0{\cdot}012$) remained independent prognostic factors (*Table 3*).

Discussion

Microscopic abscesses formed by neutrophil infiltration at the invasive margin are one of the interesting features of colorectal cancer. Although it has not been clear why a local inflammatory response is common, it is conceivable that various amounts of bacteria in the colorectal lumen could be the cause. Despite its unique nature, there have been few previous reports about the clinicopathological significance of MAF in colorectal cancer[13]. In the present study patients with pT2 or deeper tumour invasion were selected, and MAF was found to be one of the independent factors indicative of a favourable outcome after curative resection for low rectal cancer. Because the operative methods in this series included various types of surgical procedure and lymph node dissection, multivariable analysis including these operative methods was used to confirm that MAF was an independent prognostic factor. In fact, lymph node metastases were found more often in patients without tumours showing MAF than in those with. The presence of MAF is easily judged by conventional haemotoxylin and eosin staining, and does not require special staining such as in immunohistochemistry. MAF could be evaluated as a prognostic indicator in each patient with colorectal cancer.

The ability to invade and metastasize is dependent on both the intrinsic characteristics of the tumour cells and the environment surrounding a tumour[15]. There have been many reports about prognostic indicators that are based on tumour morphology, such as neurovascular invasion and tumour budding[3–9]. However, there are few data on prognostic indicators related to the stroma surrounding a tumour. Inflammation is one of the factors associated with the peritumoral environment, although the functional relationship between inflammation and cancer is complex and controversial[16]. In previous studies, infiltration by leucocytes at the margin between the tumour and non-cancerous tissue has been associated with a favourable prognosis in gastric and colorectal cancer[17–20]. It is suggested that polymorphonuclear neutrophils play a key role in cytokine-induced tumour rejection, often in cooperation with T lymphocytes[21,22]. High levels of neutrophil and/or monocyte infiltration can be associated with cytotoxicity, angiostasis and tumour regression[15]. The present study demonstrated a significant association between MAF and possible prognostic factors including lymph node status, lymphatic invasion and focal dedifferentiation. Moreover, irrespective of the operative method, MAF was a useful indicator of a favourable prognosis after curative surgery. Thus, MAF at the invasive margin of a tumour could represent a defensive immunoinflammatory mechanism.

In contrast, it is well known that chronic inflammation can have powerful effects on tumour development[15,20,23]. The strongest association between chronic inflammation and malignancy is found in inflammatory bowel disease. There are reports that a preoperative systemic inflammatory response, evidenced by raised C-reactive protein levels or an increased neutrophil-to-lymphocyte ratio, predicts a poor prognosis in patients with colorectal cancer[24,25].

Although the clinical relevance of MAF is minimal, its presence can sometimes make it difficult to assess the extent of tumour invasion both before and during surgery[10–12]. Surrounding fibrosis can be difficult to distinguish from

tumour invasion on CT or magnetic resonance imaging, and the depth of invasion may be overestimated. The degree of tumour invasion is a critical factor in determining whether sphincter-saving surgery is feasible, and in the present study patients whose tumours showed MAF underwent more extended surgery, although they actually had less invasive tumours than those without MAF.

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References

1 Editorial Board of Cancer Statistics in Japan. *Cancer Statistics in Japan 2005*. Foundation for Promotion of Cancer Research: Tokyo, 2005.
2 Sobin LH, Wittekind C (eds) *International Union Against Cancer. TNM Classification of Malignant Tumours* (6th edn). Wiley-Liss: New York, 2002.
3 Ueno H, Hase K, Mochizuki H. Criteria for extramural perineural invasion as a prognostic factor in rectal cancer. *Br J Surg* 2001; **88**: 994–1000.
4 Shirouzu K, Isomoto H, Kakegawa T. Prognostic evaluation of perineural invasion in rectal cancer. *Am J Surg* 1993; **165**: 233–237.
5 Bentzen SM, Balslev I, Pedersen M, Teglbjaerg PS, Hanberg-Sorensen F, Bone J *et al.* Time to loco-regional recurrence after resection of Dukes' B and C colorectal cancer with or without adjuvant postoperative radiotherapy. A multivariate regression analysis. *Br J Cancer* 1992; **65**: 102–107.
6 Horn A, Dahl O, Morild I. Venous and neural invasion as predictors of recurrence in rectal adenocarcinoma. *Dis Colon Rectum* 1991; **34**: 798–804.
7 Hase K, Shatney C, Johnson D, Trollope M, Vierra M. Prognostic value of tumor 'budding' in patients with colorectal cancer. *Dis Colon Rectum* 1993; **36**: 627–635.
8 Ono M, Sakamoto M, Ino Y, Moriya Y, Sugihara K, Muto T *et al.* Cancer cell morphology at the invasive front and expression of cell adhesion-related carbohydrate in the primary lesion of patients with colorectal carcinoma with liver metastasis. *Cancer* 1996; **78**: 1179–1186.
9 Fujita S, Shimoda T, Yoshimura K, Yamamoto S, Akasu T, Moriya Y. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *J Surg Oncol* 2003; **84**: 127–131.
10 Kuo LJ, Chern MC, Tsou MH, Liu MC, Jian JJ, Chen CM *et al.* Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. *Dis Colon Rectum* 2005; **48**: 23–28.
11 Akasu T, Iinuma G, Fujita T, Muramatsu Y, Tateishi U, Miyakawa K *et al.* Thin-section MRI with a phased-array coil for preoperative evaluation of pelvic anatomy and tumor extent in patients with rectal cancer. *AJR Am J Roentgenol* 2005; **184**: 531–538.
12 Moriya Y, Akasu T, Fujita S, Yamamoto S. Aggressive surgical treatment for patients with T4 rectal cancer. *Colorectal Dis* 2003; **5**: 427–431.
13 Halvorsen TB, Seim E. Association between invasiveness, inflammatory reaction, desmoplasia and survival in colorectal cancer. *J Clin Pathol* 1989; **42**: 162–166.
14 Japanese Society for Cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma* (1st edn). Kanehara: Tokyo, 1997.
15 Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860–867.
16 McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. *Br J Surg* 2003; **90**: 215–219.
17 Watanabe H, Enjoji M, Imai T. Gastric carcinoma with lymphoid stroma: its morphologic characteristics and prognostic correlations. *Cancer* 1976; **38**: 232–243.
18 Ostberg JR, Ertel BR, Lanphere JA. An important role for granulocytes in the thermal regulation of colon tumor growth. *Immunol Invest* 2005; **34**: 259–272.
19 Caruso RA, Bellocco R, Pagano M, Bertoli G, Rigoli L, Inferrera C. Prognostic value of intratumoral neutrophils in advanced gastric carcinoma in a high-risk area in northern Italy. *Mod Pathol* 2002; **15**: 831–837.
20 Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. *J Pathol* 1997; **182**: 318–324.
21 Di Carlo E, Forni G, Lollini P, Colombo MP, Modesti A, Musiani P. The intriguing role of polymorphonuclear neutrophils in antitumor reactions. *Blood* 2001; **97**: 339–345.
22 Musiani P, Allione A, Modica A, Lollini PL, Giovarelli M, Cavallo F *et al.* Role of neutrophils and lymphocytes in inhibition of a mouse mammary adenocarcinoma engineered to release IL-2, IL-4, IL-7, IL-10, IFN-α, IFN-γ, and TNF-α. *Lab Invest* 1996; **74**: 146–157.
23 Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539–545.
24 Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil–lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 2005; **91**: 181–184.
25 Nozoe T, Matsumata T, Sugimachi K. Preoperative elevation of serum C-reactive protein is related to impaired immunity in patients with colorectal cancer. *Am J Clin Oncol* 2000; **23**: 263–266.