Movie 2

下部直腸癌に対する内肛門括約筋部分切除術

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症例

40歳代女性．歯状線から約2cmの直腸前壁に存在するIs癌に対して，すでに内科でESD（内視鏡的粘膜下層剝離術）がなされている．病理の結果“SM massive，垂直断端陽性疑い”のため，今回外科で追加切除となった．術前診断は，Rb，Is，20mm，cSM，cN0，cH0，cP0，cM0，cStageIである．

手術のポイント

本症例では，歯状線から前壁2cmのESD後瘢痕を腹腔側から確実に切除，吻合することは困難であり，肛門側から直視下に歯状線で切除，吻合する内肛門括約筋部分切除術（partial ISR）とした．またリンパ節郭清はSM，N0癌であり，上方はD2郭清，側方は非郭清とした．

腹腔側操作

上方D2郭清とS状結腸全温存

D2郭清であり臍下正中切開（00:23）とした．腹腔内は著変なし．内側アプローチを原則としている（00:33）．IMA（下腸間膜動脈）を剝離してLCA（左結腸動脈）を確認し，その末梢側でSRA（上直腸動脈）を結紮切離（00:56）．同レベルでIMV（下腸間膜静脈）を切離する（01:09）．経肛門吻合に備えてほぼ全S状結腸を温存するように腸間膜を処理し結腸を切離する（01:32）．

直腸剝離

癌の浸潤がない限りTME（全直腸間膜切除）の層での直腸剝離を原則とする．まずは後壁の剝離から開始（01:41）．内側アプローチの際の後腹膜下筋膜の層を骨盤に延長し上下腹神経叢，左右下腹神経を温存する．さらに骨盤深部に向かうが，仙骨前面の静脈叢を損傷しないように仙骨の彎曲に注意する．腹膜翻転部で左右からの切離ラインを一致させ，腟後壁を露出し（02:35），さらにDenonvillier筋膜を確認する（03:14）．以降の操作ではどうしても術者や助手の頭が画像の視野を妨げることが多いため，第1助手がサブスクリーンのように腹腔鏡で撮影を行っている（03:31）．直腸後方の骨盤深部に肛門挙筋が確認される．後壁以外にも，前壁，左壁，右壁と全周性に直腸を剝離していく．腟直腸靱帯はできるだけ直腸側で切離する（04:50）．直腸を後側方で十分に剝離すると恥骨直腸筋が観察される（07:11）．この筋肉は通常結紮切離しているが，今回は肛門操作で使用するLigaSure™を用いて切離した（07:27）．露出した肛門挙筋を直腸近傍で後方から側方に向かい剝離する．側方はやや出血しやすく右，左ともにLigaSure™で処理した（07:42，07:46）．この操作により，肛門側操作の外肛門括約筋から恥骨直腸筋にかけての剝離がスムーズになる．最後に，Denonvillier筋膜の延長である直腸前壁の剝離を可及的に行うが，次第に出血しやすくなり剝離が困難になる（08:03）．この時点で，腫瘍やクリッピングなどのマーキングを触診し，直腸の剝離が十分であることを確認する．

骨盤内操作のできあがり

直腸は全周性に十分に剝離され，前方からでも肛門挙筋が十分に露出していることが確認される（08:16）．また後方では，自律神経が温存され，肛門挙筋が露出している（08:41）．

肛門側操作

直腸前壁のESD後瘢痕にクリップが確認される（09:13）．操作中は癌のimplantationと骨盤内感染の予防として生理食塩水を用いて頻回に洗浄している．まず，切離ラインの歯状線に電気メスでマーキング（09:24）．6時で粘膜，粘膜下層，輪状な線維からなる内肛門括約筋を認識しながら切離し（09:33），外肛門括約筋前面に至る．内肛門括約筋を含めて直腸を縫合閉鎖する（09:48）．閉鎖に用いた糸で直腸を牽引しながら，内外括約筋間の縦走筋を確認し，LigaSure™で側方に向かって剝離を進める（10:00）．さらにこの剝離を前方に向かって連続する（10:20）．

骨盤内との開通

腹腔側の助手の補助が重要である．通常は6時の開通が最も容易で，助手が恥骨直腸筋と直腸のあいだ（08:55）に手指を挿入し会陰側に押すことで，外肛門括約筋前面から骨盤内の恥骨直腸筋前面に至る切離ラインが明瞭となる．この後，2時，10時に向かってこの開通を切り広げる．以上の操作は比較的容易である．しかしながら，残りの前壁の処理はMiles手術と同様に容易ではなく，直腸を摘出するまでに2つの方法が存在する．①切除側直腸を後方から反転し，肛門外に引き出してから前壁の剝離を行う．②直腸はそのままで，0時を開通した後に残りの2時と10時を剝離する．Miles手術では直腸の反転・引き出しは容易であるが，内肛門括約筋切除術（ISR）では直腸（直腸間膜も含む）が厚い症例や，肛門管が狭い症例では，この操作が困難である．そこで本症例では以下のように，　の直腸はそのままで，0時を開通する方法を選択した．

腹腔側から剝離したDenonvillier筋膜の最先端部に置かれた助手の手指を目安に，肛門側から同筋膜を切開して0時で骨盤内と開通する（10:28）．6時における骨盤内との開通は容易である（10:47）．この開通を後方から側方に向かって外肛門括約筋から肛門挙筋前で切り上げる（11:04）．この際も腹腔側の助手の直腸牽引によるカウンタートラクションが有効であり，最後に2時と10時が残る．2時を切離（11:26）．10時を切離（11:35）．本法では，直腸を肛門側に反転・引き出しする必要はなく，*in situ*での直腸切除が可能であり，直腸が厚い症例や肛門管が狭い症例にも有用である（12:03）．洗浄，止血の後にS状結腸を肛門側に誘導（12:20）し，肛門吻合は，3-0 Vicryl®で垂直マットレス縫合を8針行った後に結節縫合を追加して計20～24針としている（12:29）．術直後は肛門が腫脹するが（12:42），次第に改善していく．回腸を用いた一時的なdiverting stomaを造設し，腹腔側から骨盤をよく洗浄しドレーンを2本留置して手術を終了する（12:51）．

切除標本では，ESD後瘢痕内の肛門側にクリッピングがされており，AW（腫瘍下縁から肛門側切離端までの距離）は1.5cm（13:01）．術後経過は良好で第14病日に退院．約6か月後に，ストーマを閉鎖する予定である．

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Quantification of CD10 mRNA in Colorectal Cancer and Relationship between mRNA Expression and Liver Metastasis

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Abstract. *CD10 mRNA expression in colorectal cancer and its relationship with cancer progression and prognosis were investigated. Patients and Methods: CD10 mRNA was quantified in 167 colorectal cancer and matched normal tissue samples using real-time polymerase chain reaction (RT-PCR). The tumor to normal tissue (T/N) CD10 mRNA ratio was compared with clinicopathological factors and prognosis. Results: CD10 mRNA was overexpressed in 138 of the 167 tumors in comparison with the matched normal tissues. T/N was higher in colon, pN1/pN2, stage III and IV, and well- or moderately-differentiated adenocarcinoma than in rectum, pN0, stage I and II, and poorly-differentiated or mucinous adenocarcinoma, respectively. However, these differences were not significant. T/N was not associated with prognosis. Conclusion: CD10 mRNA showed significantly higher expression in tumor tissues than in matched normal tissues. Although CD10 mRNA was associated with invasion depth, lymph node status and TNM stage, it was not associated with prognosis.*

CD10 is a 100 kDa cell surface zinc metalloendopeptidase that was initially identified as the common acute lymphoblastic leukemia antigen. Although CD10 is commonly expressed on hematopoieteic cells and tumors, it is also expressed in a variety of normal and tumor tissues. Recently, several studies have shown an association between CD10 expression and progression of various kinds of tumors including gastric cancer (1-5), colorectal cancer (6-10), pancreatic endocrine tumor (11), ovarian cancer (12), cervical carcinoma (13), renal cell carcinoma (14, 15), prostate cancer (16), breast cancer (17), non-small cell lung cancer (18), melanoma (19, 20), nasopharyngeal carcinoma (21), oral cavity squamous cell carcinoma (22) and B-cell lymphoma (23). Therefore, CD10 is considered to play an important role in both normal and tumor tissues. We recently demonstrated that CD10 protein expression in colorectal cancer was significantly associated with liver metastasis (10). This result prompted us to examine the association between CD10 mRNA expression and liver metastasis. In the present study, CD10 mRNA in colorectal cancer tissues was quantified by real-time PCR in comparison with matched normal tissues, and the relationship between CD10 mRNA expression and clinicopathological characteristics was examined.

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Key Words: Colorectal cancer, CD10, liver metastasis, prognosis.

Patients and Methods

Patients and tissues. Tumor tissue and adjacent normal tissues (10 cm away from the tumor) were obtained from 175 patients with colorectal cancer between January 1995 and September 1996 at the National Cancer Center Hospital, Tokyo, Japan, after informed consent had been obtained. Among these, a total of 167 samples in which CD10 expression was examined using the avidin-biotin-peroxidase method with mouse monoclonal antibody 56C6 (Novocastra, Newcastle, UK) in our previous study (10) were investigated for CD10 mRNA quantification. Although in our previous study >5% staining of tumor cells had been judged as positive, in the present study we considered staining of >5% of tumor and/or stromal cells as positive, because CD10 is also expressed in stromal cells (7). Tissues had been obtained immediately after surgery and stored frozen in liquid nitrogen until RNA extraction. All surviving patients had been followed up for more than 5 years, initially at 3-month intervals for 2 years and then at 6-month intervals thereafter. Median follow-up time was 7.9 years, and no adjuvant chemotherapy was given in this period.

RNA extraction and relative mRNA quantification. Total RNA was extracted from the frozen tissues according to the procedure described by Chomczyski and Sacchi (24). Randomly primed cDNA was synthesized from 1 μg of total RNA using a High-Capacity cDNA Archive Kit in accordance with the manufacturer's instructions (Applied Biosystems, CA, USA). CD10 mRNA expression was quantified using TaqMan gene expression assay and

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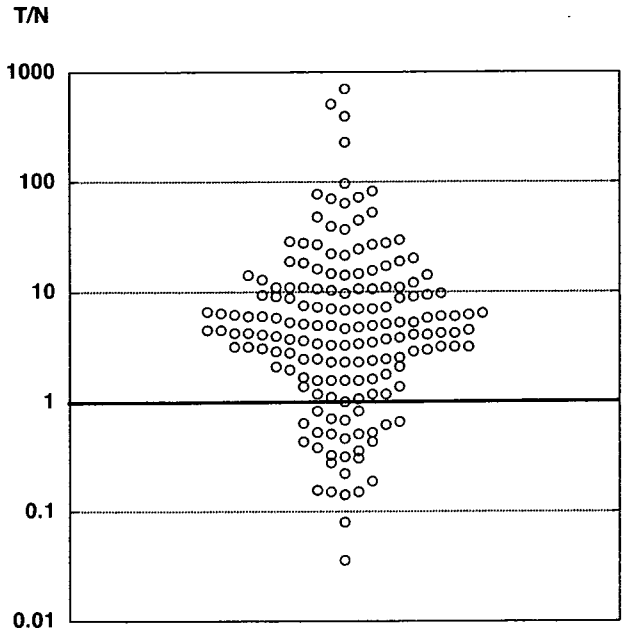

Figure 1. *Distribution of CD10 mRNA T/N. Mean T/N±standard deviation was 20.89±75.80, range was 0.036 to 709.176.*

a 7300 Real-Time PCR System (Applied Biosystems) in accordance with the manufacturer's instructions. The CD10 mRNA level in the tumor was compared with that in matched normal mucosa after standardization against 18S rRNA as an internal control gene (25). The CD10 mRNA level was calculated using the formula: – Δ Δ Ct (cycle threshold) (Δ Ct of tumor (CD10 Ct - 18S rRNA Ct) – Δ Ct of matched normal tissue (CD10 Ct – 18S rRNA Ct)) to the power two ($2^{-\Delta\Delta Ct}$). This value is the ratio of CD10 mRNA in the tumor relative to that in matched normal tissue (T/N).

Statistical analysis. T/N was compared statistically using Mann-Whitney *U*-test. Survival rates were calculated by the Kaplan-Meier method and survival curves were compared by the log-rank test. Data differences between groups were considered statistically significant at $p<0.05$.

Results

Patient characteristics and CD10 mRNA. The distribution of CD10 mRNA T/N is shown in Figure 1. Mean T/N±standard deviation was 20.89±75.80, and the range was 0.036 to 709.176. In 138 (83%) of the 167 tumors, T/N was more than one, which meant that CD10 was overexpressed in the tumor tissue compared with the matched normal tissue. Patient characteristics and T/N are shown in Table I. T/N was higher in colon, pN1/pN2, stage III and IV, and well or moderately-differentiated adenocarcinoma than in rectum, pN0, stage I and II, and poorly-differentiated or mucinous adenocarcinoma, respectively. However, these differences were not significant. Because CD10 protein expression had been examined in our previous study (10), T/N was compared with CD10 protein expression, and was found to be significantly associated.

Table I. *Patient clinicopathological characteristics and CD10 mRNA (T/N).*

Characteristic	No. (n=167)	CD10 mRNA (T/N±S.D.)	*P*
Age (yr)			
≤ 60	71	25.39±79.97	0.645
60 <	96	17.57±72.81	
Gender			
Male	99	19.77±64.88	0.881
Female	68	22.52±89.88	
Tumor site			
Colon	100	29.31±96.56	0.156
Rectum	67	8.33±14.04	
Depth of invasion (pT)			
pT1/pT2	1/27	11.98±17.37	0.333
pT3/pT4	105/34	22.68±82.66	
Lymph node status			
pN0	76	9.81±14.88	0.847
pN1/ pN2	54/37	30.14±101.11	
Stage			
I/II	19/49	9.60±15.16	0.996
III/IV	67/32	28.64±97.09	
Tumor differentiation			
Well/Moderate	70/85	22.21±78.53	0.063
Poor/Mucinous	9/3	3.86±4.30	
Lymphatic invasion			
Negative	60	19.03±66.30	0.643
Positive	107	21.94±80.92	
Venous invasion			
Negative	80	18.55±62.41	0.859
Positive	87	23.05±86.62	
CD10 protein expression			
Negative	83	5.33±5.65	0.003
Positive	84	36.64±105.35	

Relationship between CD10 mRNA and liver metastasis. Among the 167 patients, 32 had synchronous metastasis: liver metastasis in 22 cases, peritoneal dissemination in 4, lung metastasis in one, and distant lymph node metastasis in 5. The remaining 135 patients who had no synchronous metastasis underwent curative resection. Among these patients, 41 suffered cancer recurrence, 20 of them developing liver metastasis. The relationship between CD10 mRNA and metastasis is shown in Table II. There was no significant relationship between CD10 mRNA and metastasis including liver metastasis. Because the median T/N was 4.55, the survival curves of patients with T/N ≥5 and of patients with T/N <5 were analyzed (Figure 2), but

Table II. *Relationship between CD10 mRNA and metastasis in colorectal cancer patients.*

	No. (n=167)	CD10 mRNA (T/N±S.D.)	*P*
Liver metastasis			
Negative	125	18.65±61.20	0.873
Positive	42	27.56±108.96	
All metastases			
Negative	94	20.13±69.11	0.886
Positive	73	21.87±84.12	

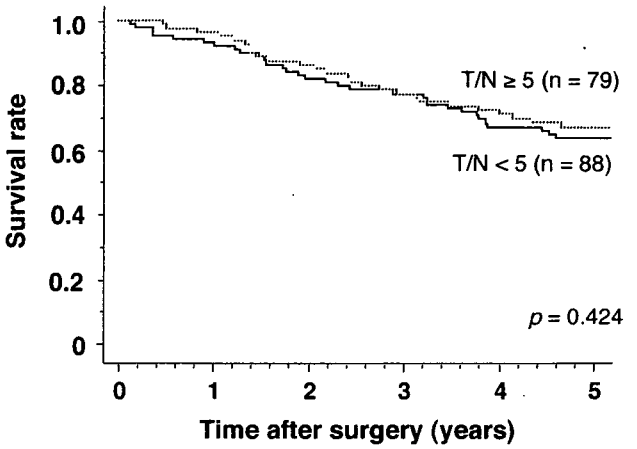

Figure 2. *Survival curves for patients with T/N≥5 or T/N<5. There was no significant difference between the groups.*

there was no significant difference between the groups. There were also no significant survival differences according to clinical stage (data not shown).

Discussion

We have recently demonstrated that CD10 protein expression in colorectal cancer cells was significantly associated with liver metastasis and that CD10 protein expression was an independent predictor of liver metastasis (10). Yao *et al.* have also demonstrated a significant association between CD10 protein expression and liver metastasis from colorectal cancer (8), and other reports have indicated a relationship between CD10 protein expression and the development and progression of colorectal cancer (7, 9). These results prompted us to examine the association between CD10 mRNA expression level and liver metastasis using real-time PCR. Although CD10 mRNA in tumor tissues was higher than that in matched normal tissues in more than 80% of colorectal cancers and was associated with tumor progression, there was no significant relationship between the level of CD10 mRNA expression and metastasis, including liver metastasis. This suggested that CD10 might play an important role in tumorigenesis and tumor progression and that measurement of CD10 mRNA in colorectal cancer tissues is not useful as a predictor of liver metastasis.

In this study, the level of CD10 mRNA was higher in pN1and pN2 tumors than in pN0 tumors, and was also higher in stage III and IV tumors than in stage I and II tumors. These facts suggested that the CD10 mRNA level was associated with tumor progression. Many previous studies have demonstrated that overexpression of CD10 protein is associated with tumor progression (1-5, 7-11, 15, 17, 19-22) and with tumor proliferation and microvascular density (11), thus indicating that CD10 plays an important role in tumor progression. Although the actual function of CD10 in tumors is not known, it is a cell surface metalloendopeptidase with structural similarity to matrix metalloprotease, and is capable of degrading a number of bioactive peptide and cytokines. Therefore, CD10 at the tumor cell surface and in the areas adjacent to tumor glands is considered to activate or inactivate tumor-related substances and to create a microenvironment that facilitates tumor cell invasion and metastasis. On the other hand, several studies have demonstrated an association between reduced expression of CD10 and tumor progression in lymphoma (23), and renal cell (14), lung (18), prostate (16), ovarian (12) and cervical cancer (13). Tumorigenesis and proliferation are inhibited (12,13), and apoptosis is induced, by CD10 (23). When CD10 expression is reduced in a tumor, loss of these functions of CD10 was considered to promote tumor progression. Because these tumors arise from tissues that normally express CD10, loss of CD10 in an advanced cancer may be explained in terms of dedifferentiation during tumorigenesis. On the other hand, CD10 expression in tumors that arise from normal tissues without CD10 expression probably represent a phenomenon acquired during tumorigenesis and is considered to be associated with tumor progression. Colorectal cancer acquires CD10 expression during tumorigenesis because it is not expressed in normal colorectal mucosa or stroma.

CD10 protein is reportedly expressed even in tumor stroma (5 , 7, 11, 17, 20-22). In colorectal cancer, CD10 protein is expressed both in tumor and stromal cells (6, 7). A similar pattern has been reported in gastric cancer (1, 5), melanoma (19, 20) and pancreatic endocrine tumor (11). CD10 expression in tumor and/or stromal cells was associated with tumor progression, except in pancreatic endocrine tumor. In the present study, because CD10 mRNA was extracted from both tumor and stroma, it was quantified in both tissues as a whole, and there was no clear relationship between CD10 mRNA expression and

liver metastasis. CD10 protein expression in tumor cells has been shown to be significantly associated with liver metastasis (8, 10). Therefore, CD10 mRNA in tumor cells might be associated with liver metastasis. Further investigation will be necessary to clarify the relationship between CD10 mRNA in tumor cells and colorectal cancer liver metastasis.

CD10 mRNA expression was higher in colon cancer than in rectal cancer. Because CD10 is expressed in the brush border of the small intestine (6), colon cancer is considered to have a higher tendency to differentiate to the small intestine than rectal cancer. In gastric cancer, phenotypic differences have been associated with prognosis and the pattern of recurrence (1, 3). These facts suggest that there are biological and oncological differences between colon and rectal cancer.

The level of CD10 mRNA was higher in well- or moderately-differentiated adenocarcinoma than in poorly differentiated or mucinous adenocarcinoma. However, CD10 mRNA expression in poorly differentiated or mucinous adenocarcinoma is still higher than in normal mucosa. On the other hand, CD10 protein is reportedly undetectable in poorly-differentiated adenocarcinoma (6, 26). This suggests that the expression of CD10 mRNA is not directly associated with protein production and that post-transcriptional regulation plays an important role in protein expression in cancer cells. This is one of the reasons why liver metastasis was associated with CD10 protein expression and not with CD10 mRNA

In conclusion, CD10 mRNA shows significantly higher expression in tumor tissue than in matched normal tissue. Although CD10 mRNA is associated with depth of invasion, lymph node status and TNM stage, it is not associated with liver metastasis, any type of metastasis, or prognosis. Therefore it seems that CD10 mRNA extracted from tumor tissues might not be useful as a predictor of liver metastasis or a prognostic marker.

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Diseases of the Colon & Rectum

Cancer Invasion to Auerbach's Plexus is an Important Prognostic Factor in Patients with pT3-pT4 Colorectal Cancer

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PURPOSE: By defining perineural invasion of colorectal cancer as invasion to Auerbach's plexus, we examined the usefulness of this pathologic finding as a prognostic factor. METHODS: A total of 509 consecutive patients who underwent curative surgery for pT3 or pT4 colorectal cancer between May 1997 and December 2001 were reviewed. All the surviving patients were followed for more than five years. All the pathologic findings, including perineural invasion, were described prospectively in the pathology report forms. RESULTS: Perineural invasion was detected in 132 of 509 patients (26 percent) and was significantly associated with lymph node status, lymphatic invasion, and venous invasion. Incidences of local and systemic recurrence were significantly higher in patients with perineural invasion than in those without perineural invasion. The disease-free survival of the perineural invasion-positive group was significantly poorer than that of the perineural invasion-negative group for Stages II and III colon cancer, irrespective of the use of adjuvant chemotherapy. This improved disease-free survival also was seen in patients with Stage II rectal cancer not treated with adjuvant chemotherapy. There was a nonsignificant difference in disease-free survival for Stage II rectal cancer and Stage III rectal cancer treated with chemotherapy, that of the perineural invasion-positive group being poorer. Multivariate analysis showed that lymph node status, perineural invasion, depth of invasion, and cancer site were significant prognostic factors. CONCLUSIONS: Perineural invasion defined as cancer invasion to Auerbach's plexus is an important prognostic factor for colorectal cancer. [Key words: Colorectal cancer; Perineural invasion; Auerbach's plexus; Prognostic factor]

Several reports have shown that perineural invasion (PNI) is an important prognostic factor in colorectal cancer[1–5] and rectal cancer.[6–17] Therefore, the colorectal working group of the American Joint Committee on Cancer (AJCC) prognostic factors consensus conference has classified PNI as category IIA, which means that PNI has been extensively studied biologically and/or clinically and is considered to have sufficient predictive value for outcome to be noted in pathology reports.[18] However, because many reports on PNI have been based on retrospective studies, and PNI has not been clearly defined, there is still no definitive conclusion about the degree to which PNI is a prognostic factor, especially in colon cancer. Therefore, in pathology reports compiled at the National Cancer Center Hospital from May 1997, we defined PNI as cancer invasion to Auerbach's plexus, because this feature is a prominent and easily detectable type of PNI, and

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PNI was reported prospectively. Although we had already reported that PNI was an important prognostic factor,[19] follow-up time in the previous study was short and the number of patients examined was small. In the present study, all surviving patients were followed for more than five years and the number of examined patients was larger than in our previous study. Moreover, only pT3 or pT4 tumors were examined in the present study, because PNI was not found in pT1 tumors and was rare in pT2 tumors.

PATIENTS AND METHODS

Consecutive patients who underwent curative surgery for pT3 or pT4 colorectal cancer at the National Cancer Center Hospital between May 1997 and Dec 2001 were reviewed. Synchronous or metachronous multiple cancers were excluded from the analysis. One patient who died four days after surgery because of anastomotic leakage and sepsis also was excluded. A total of 509 patients were examined. The patients were followed up at three-month intervals for two years and at six-month intervals thereafter. Tumor markers were examined at every patient visit. CT scans of the liver and lung or abdominal ultrasonography with chest x-ray were performed at least every six months. Colonoscopy was performed twice within five years after surgery. All the surviving patients were followed for more than five years. Fifty-one of 266 patients with Stage III tumors received postoperative adjuvant chemotherapy as part of a clinical trial. Adjuvant radiotherapy was not used for rectal cancer during the study period.

Pathologic Examination

All the specimens were reviewed by two pathologists (TS and YN). Perineural invasion was defined as the presence of cancer cells inside the perineurium in Auerbach's plexus adjacent to the tumor front, and the results and other pathologic findings were described prospectively in the pathology report forms.

Statistical Analysis

Statistical analysis was performed by using the chi-squared test. Survival rates were calculated by the Kaplan-Meier method and survival curves were compared by using the log-rank test. Cox proportional hazards model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P < 0.05$.

RESULTS

PNI and Clinicopathologic Characteristics

A representative case of PNI is shown in Figure 1. Cancer cells invaded the perineurium in Auerbach's plexus. PNI was detected in 132 of 509 patients (26 percent). PNI and clinicopathologic characteristics of the patients are shown in Table 1. PNI was significantly associated with lymph node status, lymphatic invasion, and venous invasion ($P < 0.01$).

PNI in Relation to Recurrence and Survival

In colon cancer, the incidence of liver metastasis in the PNI-positive group was significantly higher than that in the PNI-negative group ($P < 0.01$; Table 2). In rectal cancer, the incidences of liver and lung metastasis and local recurrence in the PNI-positive group were significantly higher than in the PNI-negative group ($P \leq 0.01$). The five-year, disease-free survival rate in the PNI-positive group was 53 percent and that in the PNI-negative group was 80 percent (Fig. 2). Outcome was significantly poorer in the PNI-positive group than in the PNI-negative group ($P < 0.01$). Disease-free survival rates were examined according to tumor site (colon and rectum) and Stage (Stages II and III). Disease-free survival in the PNI-positive group was significantly poorer than that in the PNI-negative group for Stage II and III colon cancer ($P = 0.02$, 0.03, respectively) and Stage III rectal cancer ($P < 0.01$; Table 3, Fig. 3). Although disease-free survival in the PNI-positive group also was poorer than that of the PNI-negative group for Stage II rectal cancer, the difference was not statistically significant ($P = 0.21$). Because 51 of 266 patients with Stage III tumors received adjuvant chemotherapy, which is known to affect survival, the effect of adjuvant chemotherapy on disease-free survival was analyzed (Table 3). Patient survival in the PNI-positive group was poorer than that in the PNI-negative group, irrespective of whether adjuvant chemotherapy was given. Multivariate analysis of PNI, lymph node status, depth of invasion, tumor differentiation, lymphatic invasion, venous invasion, tumor site, preoperative CEA, gender, age, and adjuvant chemotherapy showed that lymph node status, PNI, depth of invasion, and tumor site were significant prognostic factors ($P < 0.01$; Table 4).

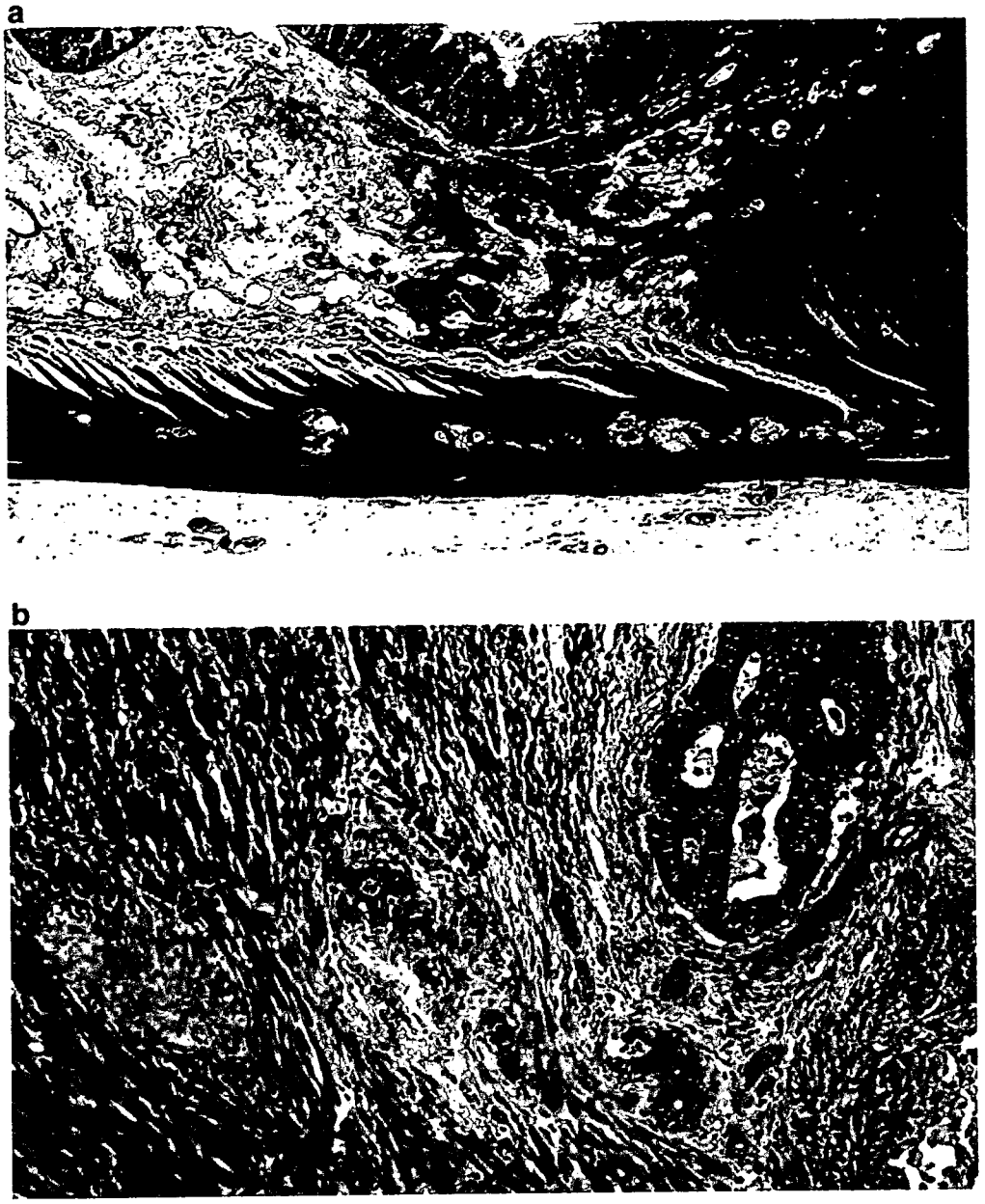

Figure 1. Representative PNI. a. Arrows shows cancer cells inside the perineurium in Auerbach's plexus. This is a case of massive PNI. b. Eighty percent of cases of PNI involve only slight invasion to Auerbach's plexus. In this case, one or two plexuses adjacent to the tumor front were invaded by cancer cells (arrow). Arrowhead shows Auerbach's plexus without cancer invasion. PNI = perineural invasion.

DISCUSSION

PNI has been reported to be a prognostic factor in colorectal cancer,[1–5] colon cancer,[20–22] and rectal cancer.[6–17] However, there is still no definitive conclusion about the degree to which PNI is a prognostic factor, especially in colon cancer, because many of the previous studies of PNI were retrospective, and PNI was not clearly defined. Although many of the reports did not define PNI, PNI was considered to be perineural cancer invasion within and outside the bowel wall in some of them,[1,6,9,12] and only extramural PNI was examined in other studies.[7,10,14] We defined PNI as cancer invasion to Auerbach's plexus, and on this basis prospectively examined more than 500 patients. Our findings clearly demonstrated that PNI was a significant prognostic factor in pT3 or pT4 colorectal cancer. Therefore, this study provides strong evidence that cancer invasion to Auerbach's plexus is a prognostic factor for colorectal cancer.

Table 1.
PNI and Clinicopathologic Characteristics of the Examined Patients

	PNI-negative (n=377)	PNI-positive (n=132)	*P* Value
Age (yr)			0.68
<60	155	57	
≥60	222	75	
Male/female ratio	225/152	75/57	0.56
Tumor site			0.16
Colon	229	71	
Rectum	148	61	
Preoperative CEA (ng/ml)			0.34
<5	257	84	
≥5	120	48	
Depth of invasion (pT)			0.08
pT3	329	107	
pT4	48	25	
Lymph node status (pN)			<0.01
pN0	209	34	
pN1	120	57	
pN2	48	41	
Tumor differentiation			0.99
Well/moderate	354	124	
Poor/mucinous	23	8	
Lymphatic invasion			<0.01
Negative	255	37	
Positive	122	95	
Venous invasion			<0.01
Negative	234	53	
Positive	143	79	

PNI = perineural invasion.

The outcome of patients with Stage II colorectal cancer with cancer invasion to Auerbach's plexus was poor, and the survival rate was similar to that of patients with Stage III colorectal cancer. Because adjuvant therapy is recommended for patients with Stage III colorectal cancer, patients with Stage II colorectal cancer with invasion to Auerbach's plexus also are thought to be candidates for such therapy. On the other hand, the outcome of patients with Stage III colon cancer without invasion to Auerbach's plexus was good, and therefore these patients may not require adjuvant chemotherapy. These findings suggest that cancer invasion to Auerbach's plexus could be used to facilitate the selection of patients with colorectal cancer for adjuvant chemotherapy. However, among patients with Stage III colon cancer without invasion to Auerbach's plexus, those who received adjuvant chemotherapy showed better survival than those who did not, although the difference was not statistically significant. Further investigations of cancer invasion to Auerbach's plexus and the need for adjuvant chemotherapy are necessary.

Cancer invasion to Auerbach's plexus is a significant prognostic factor even in patients with colon cancer. Only three studies have examined the relationship between PNI and the prognosis of colon cancer patients.[20–22] These demonstrated that PNI was associated with recurrence and poor survival, although multivariate analysis showed that this association was not significant. Therefore, our study is the first to report a significant association between PNI and survival of colon cancer patients based on multivariate analysis.

Although cancer invasion to Auerbach's plexus is a significant prognostic factor in patients with rectal cancer, the difference in disease-free survival between the PNI-positive group and the PNI-negative group was not statistically significant for Stage II rectal cancer. This may have been the result of the small number of patients with Stage II rectal cancer included in this study (n = 89), and thus any apparent difference would have had low statistical power. Because the difference in five-year, disease-free survival rate between the groups was large (14 percent in this study) and the hazard ratio between the survival curves seemed to be constant over time, statistical significance may have been achieved by analyzing a larger number of patients with Stage II rectal cancer.

Table 2.
Pattern of Recurrence

	PNI-negative	PNI-positive	*P* Value
Colon	n=229	n=71	
Liver	12 (5.2)	14 (19.7)	<0.01
Lung	9 (3.9)	5 (7)	0.28
Peritoneum	6 (2.6)	2 (2.8)	0.93
Local	1 (0.4)	0	0.58
Others	5 (2.2)	1 (1.4)	0.68
Rectum	n=148	n=61	
Liver	9 (6.1)	13 (21.3)	<0.01
Lung	22 (14.9)	18 (29.5)	0.01
Peritoneum	0	1 (1.6)	0.12
Local	4 (2.7)	8 (13.1)	<0.01
Others	10 (6.7)	3 (4.9)	0.62

PNI = perineural invasion.
Data are numbers with percentages in parentheses unless otherwise indicated.

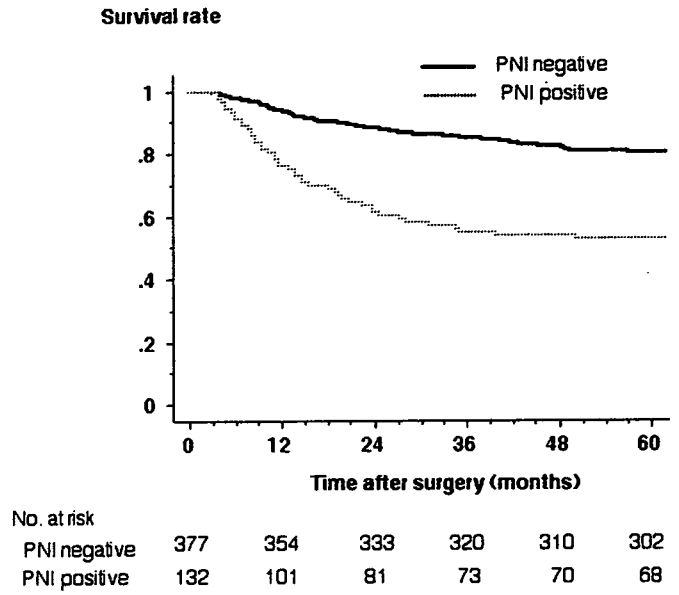

Figure 2. Disease-free survival curves according to PNI status. The prognosis of the PNI-positive group was significantly poorer than that of the PNI-negative group ($P < 0.01$). PNI = perineural invasion.

In this study, the incidence of PNI in pT3 or pT4 colorectal cancer was 26 percent. The reported incidence of PNI has differed among previous studies, and in patients with advanced cancer, the incidence has ranged between 14 and 50 percent.[7–11,14] These differences are thought to have been the result of the different definitions of PNI employed. Therefore, a clear definition of PNI is very important for clinical use, and we consider our present definition to be a candidate.

Table 3.
Five-Year Disease-Free Survival Rate According to Tumor Site and Stage

	PNI negative	PNI-positive	*P* Value
Colon			
Stage II	94 (134)	80 (20)	0.02
Stage III	75.8 (95)	52.9 (51)	0.03
Adjuvant chemotherapy +	93.3 (15)	61.5 (13)	0.04
Adjuvant chemotherapy −	72.5 (80)	50 (38)	0.01
Rectum			
Stage II	78.7 (75)	64.3 (14)	0.21
Stage III	63 (73)	38.3 (47)	<0.01
Adjuvant chemotherapy +	71.4 (14)	44.4 (9)	0.08
Adjuvant chemotherapy −	61 (59)	36.8 (38)	0.01

PNI = perineural invasion.
Data are percentages with numbers in parentheses unless otherwise indicated.

Immunohistochemical evaluation can be used to confirm the presence of PNI.[23] Use of an antibody against S-100 protein showed that the incidence of PNI was 70 percent, which was more than four times the incidence revealed by routine staining. This PNI positivity rate was very high, and patients with a poor prognosis were not selected using that method and immunohistochemistry was not always used for routine pathology because of the labor, time, and cost involved.

Venous invasion and lymphatic invasion are considered to be poor prognostic factors in patients with colorectal cancer.[18] In our study, venous invasion and lymphatic invasion were significant prognostic factors in univariate analysis but were not significant in multivariate analysis, and cancer invasion to Auerbach's plexus was selected as an indicator of poor prognosis. Our data suggest that cancer invasion to Auerbach's plexus is considered to be a more important prognostic factor than venous and lymphatic invasion.

Although many molecular markers for colorectal cancer have been studied, and some, such as p53 and DCC, have been considered to indicate prognosis, some of the evidence is conflicting,[24] and these markers are still not used in routine pathology. Moreover, these techniques are labor-intensive, time-consuming, and expensive. Because PNI can be easily detected by routine pathologic examination, it is easy to add this simple finding to pathology reports.

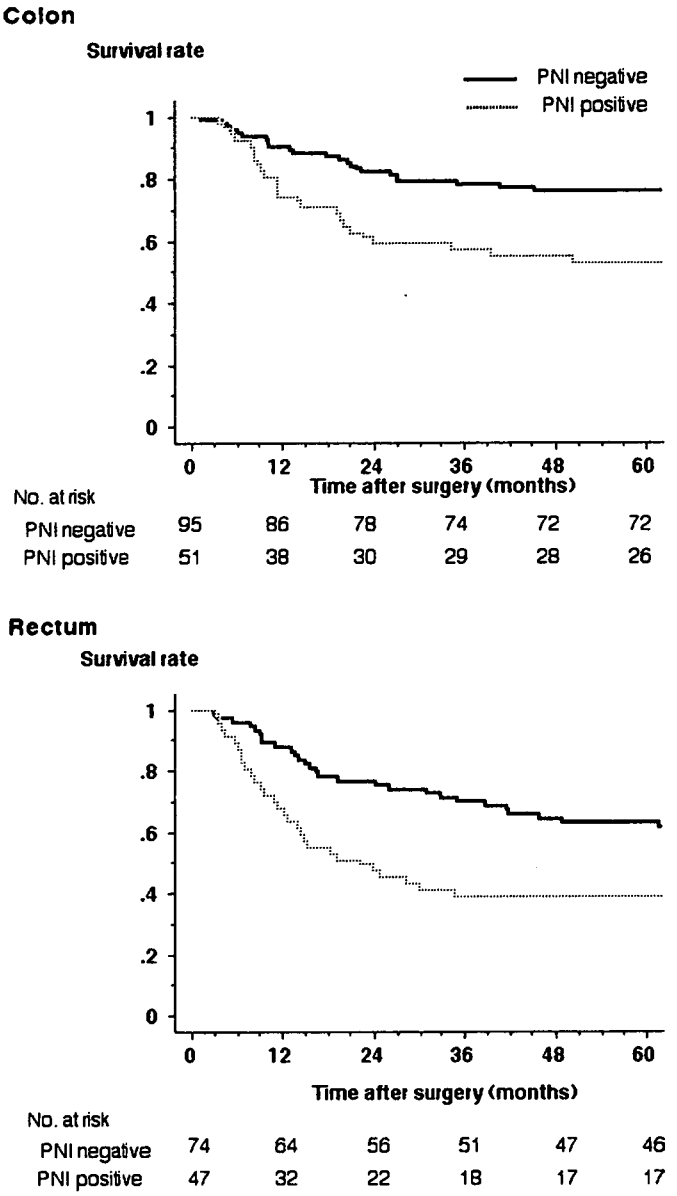

Figure 3. Disease-free survival curves of Stage III patients according to PNI status and cancer site. For both colon and rectal cancer, disease-free survival in the PNI-positive group was significantly poorer than that in the PNI-negative group ($P=0.03$ and $P<0.01$, respectively). PNI = perineural invasion.

Table 4.
Multivariate Analysis of the Prognostic Factors

Prognostic Factors	*P* Value	Hazards Ratio (CI)
Lymph node status (pN0/pN1, 2)	<0.0001	0.37 (0.25–0.57)
Tumor (colon/rectum)	<0.0001	0.44 (0.3–0.64)
PNI (negative/positive)	<0.0001	0.47 (0.32–0.68)
Depth of invasion (pT3/pT4)	0.0004	0.44 (0.28–0.69)

PNI = perineural invasion; CI = confidence interval.

Several reports have indicated that PNI is associated with local recurrence of rectal cancer.[6,9,10,14,25] Our study also showed that local recurrence of rectal cancer was significantly associated with invasion to Auerbach's plexus, and that such invasion was significantly associated with liver metastasis in colon cancer and with liver and lung metastasis in rectal cancer. These results suggest that cancer invasion to Auerbach's plexus is an important factor not only for local recurrence but also distant metastasis.

The PNI grading system has been used in our pathology reports. Slight invasion to Auerbach's plexus is classified as PNI1, massive invasion as PNI3, and

intermediate invasion as PNI2. However, only 20 percent of PNI cases were classified as PNI2 and 3, and there were no significant differences in outcome among these grades (data not shown). This indicates that the presence, rather than the extent, of cancer invasion to Auerbach's plexus is important for prognosis.

CONCLUSIONS

Cancer invasion to Auerbach's plexus is an important prognostic factor for colorectal cancer, and this should form the basis for defining PNI.

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Abdominal Sacral Resection for Posterior Pelvic Recurrence of Rectal Carcinoma: Analyses of Prognostic Factors and Recurrence Patterns

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Background: Local recurrence of rectal cancer presents challenging problems. Although abdominal sacral resection (ASR) provides pain control, survival prolongation, and possibly cure, reported morbidity and mortality are still high, and survival is still low. Thus, appropriate patient selection and adjuvant therapy based on prognostic factors and recurrence patterns are necessary. The purpose of this study was to evaluate the results of ASR for posterior pelvic recurrence of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

Methods: Forty-four patients underwent ASR for curative intent in 40 and palliative intent in 4 cases. All but one could be followed up completely. Multivariate analyses of factors influencing survival and positive surgical margins were conducted.

Results: Morbidity and mortality were 61% and 2%, respectively. Overall 5-year survival was 34%. The Cox regression model revealed a positive resection margin (hazard ratio, 10 [95% confidence interval, 3.8–28]), a local disease–free interval of < 12 months (4.2 [1.8–9.8]), and pain radiating to the buttock or further (4.2 [1.6–11]) to be independently associated with poor survival. The logistic regression model showed that macroscopic multiple expanding or diffuse infiltrating growths were independently associated with a positive margin (7.5 [1.4–40]). Of the patients with recurrence, 56% had failures confined locally or to the lung.

Conclusions: ASR is beneficial to selected patients in terms of survival. To select patients, evaluation of the resection margin, the local disease–free interval, pain extent, and macroscopic growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

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

Posterior pelvic recurrence[1–3] (PPR) of rectal carcinoma, which involves the sacrum and/or sacral nerves, presents challenging clinical problems. It may cause sacral nerve pain, perineal ulcers, fistula formation, bleeding, bowel and/or urinary tract obstruction, sepsis, and, finally, death.[4] These conditions are difficult to treat, and chemotherapy provides only minimal benefits at present.[4–6] Radiotherapy may give pain relief, but its effectiveness is limited and temporary.[4,7–9] Conventional abdominoperineal resection or local excision is only palliative.[10,11]

In 1981, Wanebo and Marcove[11] reported the advantage of the abdominal sacral resection (ASR), which was first described by Brunschwig and Barber[12] in 1969, for PPR of rectal carcinoma. Although published data on this operation are still limited and

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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

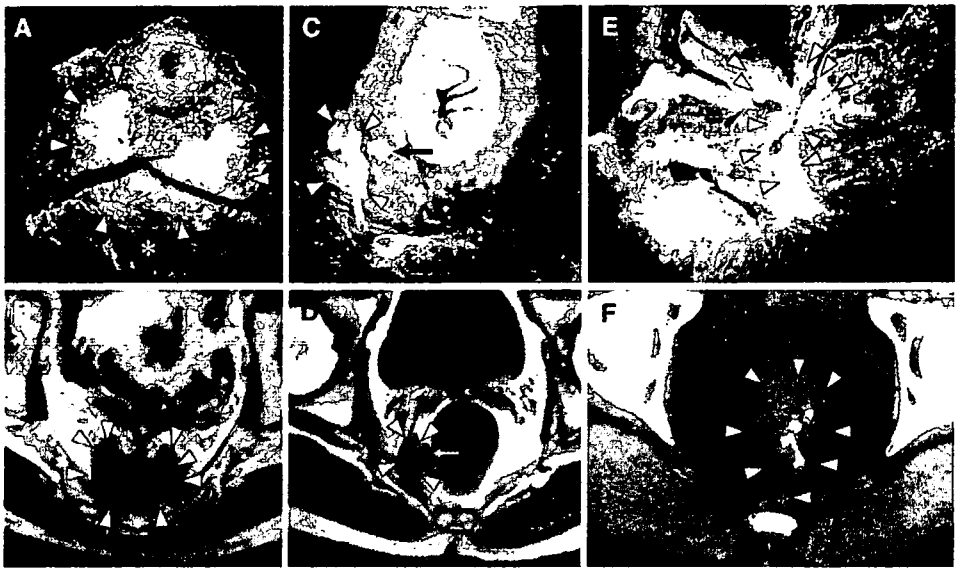

FIG. 1. (A) A section after abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. This tumor was macroscopically classified as solitary expanding growth. (B) Corresponding magnetic resonance image of (A). (C) A section of tumor macroscopically classified as multiple expanding 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).

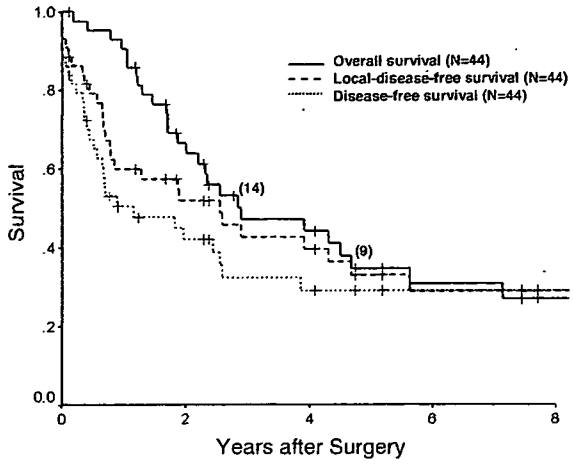

FIG. 2. Overall, disease-free, and local disease–free survival distributions for the 44 patients undergoing abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma. The numbers in parentheses for the overall survival curve indicate the patients alive at 3 and 5 years.

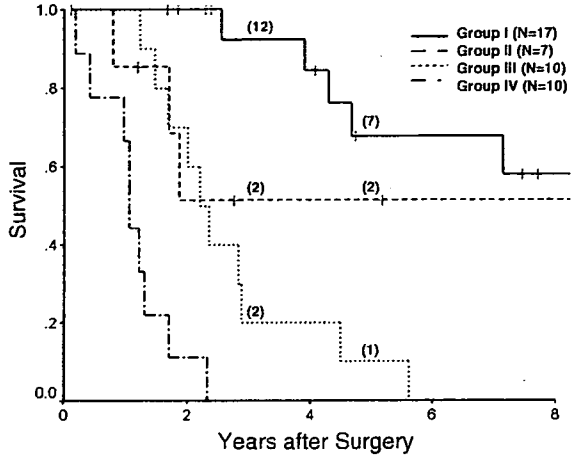

FIG. 3. Overall survival curves for group I (microscopic negative margin and local disease–free interval [LDFI] of > 12 months), group II (microscopic negative margin and LDFI < 12 months), group III (positive margin and LDFI > 12 months), and group IV (positive margin and LDFI < 12 months). The numbers 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-