survival (7,8). Therefore adjuvant radiotherapy has been recommended as the standard treatment. However, this approach was challenged by the results of a randomized trial which revealed no additional survival benefit from radiotherapy when chemotherapy was administered (9). Furthermore, radiotherapy entails risks of morbidity and mortality (6,7,10–12).

We started the National Surgical Adjuvant Study of Colorectal Cancer 01 randomized trial at the same time as the Dutch trial started (6). The aim of our trial was to evaluate the efficacy of postoperative adjuvant chemotherapy with a combination of uracil and tegafur (a prodrug of fluorouracil) taken orally after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in stage III rectal cancer. Selective lateral pelvic lymphadenectomy is defined as selective application of extended lateral pelvic lymph node dissection, to resect the iliac and obturator lymph nodes when lateral pelvic lymph node involvement is clinically suspected (5,13–15).

We adopted mesorectal excision with selective lateral pelvic lymphadenectomy alone as the control treatment because it was the standard for stage III rectal cancer in Japan (13–15). We did not choose adjuvant radiotherapy because, in addition to the reasons mentioned above, local recurrence rate after mesorectal excision with selective lateral pelvic lymphadenectomy in Japan had been 7–15% in high-volume centers (14,15). Instead, we used oral uracil–tegafur, which was reported to be effective as adjuvant therapy for lung cancer in recent studies (16), because previous studies suggested efficacy of uracil–tegafur for prolonging disease-free survival in rectal cancer (17,18). Bolus fluorouracil and folinic acid, the present world standard for stage III colon cancer, was not used, because folinic acid was not approved in Japan until 1999. We present the results of the planned interim analysis at a median follow-up of 3 years.

METHODS

Patients and Study Design

Enrollment began in October 1996. Eligible patients had undergone a microscopically verified complete resection of pathological stage III adenocarcinoma of the rectum according to the 1992 Tumour Node Metastasis (TNM) Classification of Malignant Tumours (International Union Against Cancer) (19), by standardized mesorectal excision with selective lateral pelvic lymphadenectomy. Other inclusion criteria were the center of the tumor being located between the levels of the first sacral bone and the anal canal; an age of 20–75 years; the absence of preoperative anticancer treatment, previous cancer and synchronous multiple cancers; an Eastern Cooperative Oncology Group performance status of 0, 1 or 2; a leukocyte count of at least 4000/mm^3; a platelet count of at least 100 000/mm^3; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; a serum total bilirubin level of at most 1.2 mg/dl; a blood urea nitrogen level of at most 25 mg/dl; a serum creatinine level of at most 1.5 mg/dl; normal electrocardiogram; and an absence of severe postoperative complications uncontrolled by the time of registration.

An open-label study design was used. After written informed consent had been obtained, we randomly assigned the patients to postoperative adjuvant treatment with uracil–tegafur or to surgery alone. Randomization was performed by telephone or fax at the central trial office within 42 days after operation. Patients were allocated by the minimization method with Zelen's adjustment for inter-institutional imbalance. The factors used for balancing were the site of the primary tumor (above versus below the rectovesical fossa or rectouterine fossa), primary tumor stage (pT1 or pT2 versus pT3 or pT4) and N stage (pN1 or pN2 versus pN3). The primary endpoint was relapse-free survival and the secondary endpoint was overall survival. The trial was approved by the institutional review board of each participating center.

TREATMENT

Quality Control for Surgery and Pathology

All of the 28 participating centers are the high-volume centers which treated more than 100 colorectal cancer patients per year and institutional members of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (13). The JSCCR has held a general assembly and sessions intended to improve treatment of colorectal cancer twice every year, and has standardized treatment. The JSCCR has provided guidelines for standardized surgical treatment and pathological evaluation (13). All procedures and pathological evaluations were in accordance with the fifth edition of the guidelines published in 1994 (13).

Mesorectal excision was the baseline procedure for all patients. The definitions of the mesorectum and mesorectal excision were the same as those from the Guidelines 2000 (5,13–15). In addition, extended lateral pelvic lymph node dissection (5,13–15) was performed in cases with clinically suspected lateral lymph node disease, as recommended by the JSCCR guidelines (13–15).

The quality of surgery was monitored by the surgeon's report on the location and clinical stage; extent of the resection of the bowel; mesorectum; and lymph nodes, and the pathologist's documentation of the pathological stage; number of resected and positive lymph nodes in each lymph node group; extent of bowel resection; and anal, oral and radial margin status (13).

Adjuvant Chemotherapy

In the treatment group, uracil–tegafur (UFT®, Taiho Pharmaceutical Co., Tokyo, Japan; 400 mg/m^2 tegafur per day) in the form of 100 mg units (100 mg of tegafur plus

224 mg of uracil) was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. All patients but one received 3 units of uracil–tegafur (300 mg of tegafur and 672 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the units as prescribed.

Adverse events were graded according to the toxicity grading criteria of the Japan Clinical Oncology Group, which consist of the Common Toxicity Criteria of the National Cancer Institute with minor modifications (20). Grades range from 0 (none) to 5 (fatal) (20). If a moderate (grade 2) adverse event occurred, the dose of uracil–tegafur was reduced to 250 mg/m^2 per day of tegafur. Treatment was stopped if, despite dose reduction, there was anything of the following: a grade 2 or higher adverse event, a leukocyte count of <3000/mm^3, an aspartate aminotransferase or alanine aminotransferase level of more than 2.6 times the upper limit of the normal range, a total bilirubin level of more than two times the upper limit of the normal range, moderate or severe anorexia, one or more vomitings per day or four or more bowel movements per day.

Follow-up

All the patients were evaluated every 4 months for the first 2 years after surgery and every 6 months for the next 3 years. The evaluation included a physical examination, a complete blood count, blood chemical tests, serum tumor markers, chest roentgenography, and abdominal ultrasonography or computed tomography. A pelvic computed tomography was performed every 6 months. In addition, patients receiving uracil–tegafur had a physical examination, a complete blood count and blood chemical tests every month during the first year.

Statistical Analysis

The sample size was calculated by the method of Schoenfeld and Richter. The study was designed to detect a hazard ratio for relapse or death of 0.67 in the uracil–tegafur group compared with the control group with 80% power at a two-sided α-level of 0.05. Assuming a 5-year relapse-free survival rate of 50% in the surgery-alone group, a 2-year accrual period and a 5-year follow-up, the targeted sample size was 400. In April 2000, the accrual period was extended to 5 years based on the actual accrual rate.

Interim analysis was planned 2 years after accrual termination. Early termination would be considered at the time of the interim analysis if the one-sided P-value of the log-rank test for the primary endpoint was below 0.005, according to the Lan-DeMets spending function method.

Relapse-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, or death from any cause, and overall survival was defined as the time from surgery until death from any cause. All comparisons between the treatment groups were made on the intention-to-treat principle. Survival curves were estimated by the Kaplan–Meier method, and differences in survival were evaluated with the log-rank test.

RESULTS

Accrual and Interim Analysis

From October 1996 to April 2001, 276 patients were enrolled and randomly assigned to one of the two treatment groups (Fig. 1). The study group decided to stop recruitment in April 2001, because a rapid, further enrollment could not be expected and evaluation of the treatment would be possible through a meta-analysis including the data obtained from this study and existing data (17,18,21). Planned interim analysis was conducted by the data and safety monitoring committee on 13 December 2003. Sufficient results favoring the treatment arm caused the committee to recommend a prompt disclosure of the results. This report is based on the results presented to the data and safety monitoring committee.

Patient Population

Of the 276 enrolled patients 2 (one in each group) proved to be ineligible so that data from 274 patients (139 in the uracil–tegafur group and 135 in the surgery-alone group) were included in the analysis (Fig. 1). The characteristics of the patients are shown in Table 1 and were well balanced in the two groups.

Quality of Surgery

The quality of the surgical procedures (Table 2) was similar in both groups. All patients underwent at least mesorectal excision. Extended lateral pelvic lymph node dissection was added in 38% of the patients, most of whom had a tumor

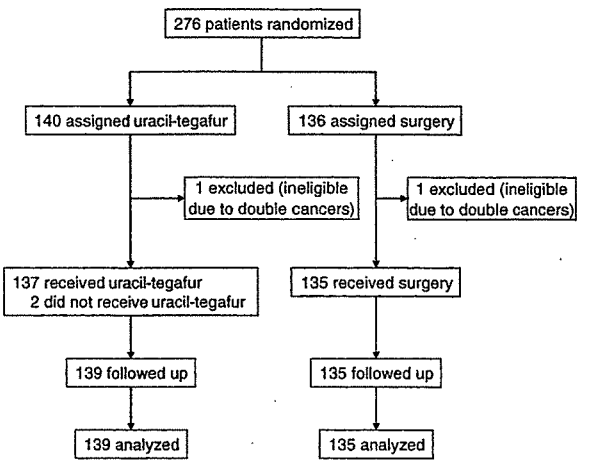

Figure 1. Study profile.

Table 1. Characteristics of the patients

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Age (years, mean [range])	58 (32–75)	57 (30–75)
Sex		
Female	56	53
Male	83	82
Location of the center of the tumor		
Below the promontrium	43	39
Below the lower edge of the second sacral bone	39	43
Below the rectouterine fossa or rectovesical fossa	57	53
Pathological tumor stage*		
T1	8	11
T2	21	16
T3	94	90
T4	16	18
Pathological nodal stage*		
N1	88	89
N2	22	22
N3	29	24
Positive lateral pelvic lymph node	11	7
Type of resection		
Anterior resection	113	109
Hartmann operation	1	0
Abdominoperineal resection	24	25
Other	1	1

*The 1997 TNM Classification of malignant tumors (International Union Against Cancer).

Table 2. Quality of surgery

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Lymph node dissection		
Mesorectal excision	89	81
Mesorectal excision plus extended lateral pelvic lymphadenectomy	50	54
Distal margin of the mesorectum		
2–4 cm	7	2
≥4 cm or total mesorectal excision	132	133
Distal margin of the bowel (cm)		
Median (range)	3 (0.3–10.5)	3.5 (0.5–8)
Number of resected lymph nodes		
Median (range)	21 (1–80)	20 (2–108)

locating below the rectovesical fossa or rectouterine fossa. Distal margins of the mesorectum and rectum were sufficient in both groups. Anal, oral and radial margins were microscopically negative in all the patients. More than 12 lymph nodes were resected in 80% of the patients. The rate of positive lateral pelvic lymph node metastasis was 17% (18/104) in the patients who underwent extended lateral pelvic lymph node dissection.

Table 3. Adverse events

Adverse event	Uracil–tegafur Grade of Toxicity*			Surgery alone Grade of Toxicity*		
	2	3	4	2	3	4
	% of patients					
Leukopenia	5	0	0	1	0	0
Thrombocytopenia	1	0	0	0	0	0
Anemia	4	0	0	2	0	0
Increase in bilirubin	51	9	0	17	2	0
Increase in aspartate aminotransferase	4	2	0	2	0	0
Increase in alanine aminotransferase	10	3	0	6	1	0
Anorexia	7	1	0	1	1	0
Nausea or vomiting	3	1	0	1	1	0
Diarrhea	5	1	0	1	1	1
Skin eruption	6	1	0	0	0	0
Alopecia	0	0	0	0	0	0

*Adverse events were graded according to the toxicity criteria of the Japan Clinical Oncology Group, which consists of the Common Toxicity Criteria of the National Cancer Institute with minor modifications. Grades range from 0 (none) to 5 (fatal).

Adverse Events and Compliance

Of the 139 patients assigned to the uracil–tegafur group, 137 actually took uracil–tegafur and two withdrew from the trial before drug administration (Fig. 1). Moderate (grade 2) and severe (grade 3) events were observed in 65 and 17% of the patients in the uracil–tegafur group and in 39 and 4% of the patients in the surgery-alone group, respectively. Observed adverse events are listed in Table 3. A life-threatening (grade 4) event occurred only in one patient in the surgery-alone group. There was no fatal event.

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence and those who died. The rate of compliance, with or without dose reduction, was 93% at 3 months, 88% at 6 months, 83% at 9 months and 80% at 12 months. The reasons for discontinuation of uracil–tegafur were a cancer recurrence (18 patients), an adverse event (8 patients), patient withdrawal due to adverse events (10 patients) and patient withdrawal due to other causes (4 patients).

Relapse-free Survival

The median follow-up among surviving patients was 3.0 years. At the last follow-up, 32 patients in the uracil–tegafur group

and 53 in the surgery-alone group had recurrence or had died (Table 4). The 3-year estimate of relapse-free survival for the uracil–tegafur group was 78% (95% CI 71–86%). That for the surgery-alone group was 60% (95% CI 51–69%) (Fig. 2). Patients receiving uracil–tegafur had significantly better relapse-free survival than those undergoing surgery alone ($P = 0.0014$). The hazard ratio for any recurrence in the uracil–tegafur group as compared with the surgery-alone group was 0. 52 (95% CI 0. 33–0. 81).

Table 4. Pattern of the first recurrence

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Local alone	6 (4%)	9 (7%)
Anastomotic recurrence	3	4
Pelvic recurrence	3	5
Distant alone	23 (17%)	39 (29%)
Liver metastasis	11	21
Lung metastasis	7	15
Liver and lung metastases	1	0
Others	4	3
Local plus distant recurrences	2	4
Death from other diseases	1	1
Overall events	32 (23%)	53 (39%)

Overall Survival

At the last follow-up, 12 patients in the uracil–tegafur group and 27 in the surgery-alone group had died. The 3-year estimate of overall survival for the uracil–tegafur group was 91% (95% CI 86–97%). That for the surgery-alone group was 81% (95% CI 73–88%) (Fig. 2). Thus patients with uracil–tegafur

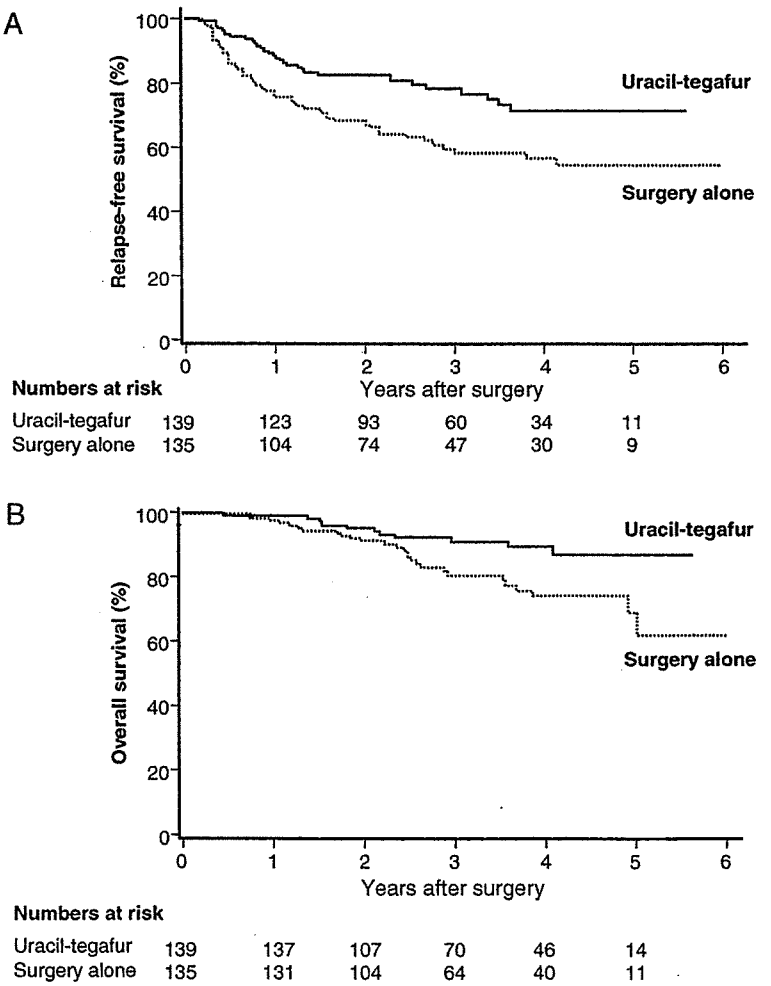

Figure 2. (A) Kaplan–Meier estimates of relapse-free survival. (B) Kaplan–Meier Estimates of overall Survival. At 3 years, the rate of relapse-free survival was 78% in the uracil–tegafur group and 60% in the surgery-alone group ($P = 0.0014$). The rate of overall survival was 91% in the uracil–tegafur group and 81% in the surgery-alone group ($P = 0.0048$).

had significantly better overall survival than those with surgery alone ($P = 0.0048$). The hazard ratio for death in the uracil–tegafur group compared with the control group was 0.42 (95% CI 0. 21–0.83).

Pattern of Recurrence

Details of the pattern of first recurrence are shown in Table 4. At the last follow-up, the rates of overall local recurrence were 5.8% (8/139) for the uracil–tegafur group and 9.6% (13/135) for the surgery-alone group. Adjuvant uracil–tegafur reduced the rates of distant metastases. The rates of overall distant metastases were 18% (25/139) for the uracil–tegafur group and 32% (43/135) for the surgery-alone group. Liver and/or lung metastases composed the majority of distant metastases in both treatment groups.

DISCUSSION

This trial demonstrated the efficacy of postoperative adjuvant chemotherapy with uracil–tegafur after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in pathological stage III rectal cancer. At the planned interim analysis, we found that the 3-year estimate of both relapse-free survival (78%) and overall survival (91%) of the uracil–tegafur group were significantly better than the surgery-alone group (60 and 81%, respectively). The data and safety monitoring committee concluded that the results confirmed the findings of previous studies (17,18) and a recent meta-analysis (21) which showed the effectiveness of uracil–tegafur for rectal cancer.

Rates of local recurrence have been reported to be 20–36% in series of non-standardized, conventional surgery for stage III rectal cancer, with a follow-up of 5 years (3,7,8). For experienced surgeons in mesorectal excision, however, they are 7.5–12% (22,23). At a median follow-up of 3 years, the local recurrence rate was 9.6% in the surgery-alone group of our trial. Although comparisons of such figures should be interpreted cautiously, this shows that a standardized mesorectal excision with selective lateral pelvic lymphadenectomy may achieve good results even in a multicenter setting. Moreover, it may possibly be better than the 2-year local recurrence rate of 8.2% in the mesorectal-excision-alone group of the Dutch trial (6), considering that 56% of patients of the Dutch trial had stage 0–II tumors (6).

Lateral pelvic lymph node metastases from rectal cancer occur outside the mesorectum and appear to account for a major cause of local recurrence. The incidence of lateral pelvic lymph node metastases was reported to be 9–14% (14,15). If the patients have such metastases and undergo only mesorectal excision, the patients have apparent residual tumor in case of recognizable metastases or develop local recurrence after seemingly curative surgery in unrecognizable metastasis cases. Extended lateral pelvic lymph node dissection is a surgical procedure to resect such macroscopic or microscopic metastases (5,14,15). Therefore, this procedure potentially has a similar local-control effect to adjuvant radiotherapy. Whether lateral dissection can be an alternative to radiotherapy should be tested in a randomized controlled trial assessing local control, survival, mortality and morbidity. To conduct such trials, accuracy for detection of lateral pelvic metastases may be a problem. Indeed, in our trial, only 17% of the patients who underwent lateral dissection actually had lateral metastases. To avoid such over-treatment, an accurate diagnostic modality detecting metastasis is necessary.

Between 1990 and 1994, the JSCCR registered 25 224 patients with colorectal cancer. (24) Among them, 2789 patients had curative resection of stage III rectal cancer and their 3-year overall survival rate was 75% (24). In the surgery-alone group of our trial, the 3-year overall survival was 81%. Introduction of revised guidelines, standardized surgical procedures assured by precise documentation and participation of colorectal specialists from high-volume centers may have contributed to this improvement. Quality of surgery is already known as an independent prognostic factor for survival in rectal cancer (1,2), and case volume per surgeon also influences the outcome (3,25).

However, the quality of surgery has no influence on the initial occurrence of distant metastases (1). Even when better-quality surgery reduces local recurrence, occult distant metastases necessitate further treatment to improve survival. We found that, in addition to the efficacy of mesorectal excision with selective lateral pelvic lymphadenectomy, uracil–tegafur further decreased the rate of local recurrence from 9.6 to 5.8%. The rate of distant metastasis was almost halved from 32 to 18%, including a substantial reduction in the rates of liver and lung metastases. Uracil–tegafur appears to improve survival mainly through reduction of distant metastases when applied along with such operations.

The recent meta-analysis assessing randomized controlled trials using oral fluorouracil-based adjuvant chemotherapy for stage I–III colorectal cancer revealed that 1-year chemotherapy reduced the risk of death by 11% ($P = 0.04$) and the risk of recurrence or death by 15% ($P < 0.001$) as compared with surgery alone (21). However, of the three previous randomized trials that compared uracil–tegafur adjuvant therapy with surgery alone in rectal cancer, two revealed significantly improved relapse-free survivals, but none demonstrated an advantage in overall survival (17,18). In these trials, eligible stages were I–III, the dosage of tegafur was 400 mg per day, the compliance was 48–70% and local recurrence rates in surgery-alone group were 19–34% (17,18,21). The significantly better relapse-free and overall survivals in our uracil–tegafur group may be attributable to a selection of stage III patients, a higher dosage of 600 mg per day, better compliance and better quality of surgery. In the meta-analysis, hazard reduction was more marked in early-stage disease (21). In contrast, our results show that a higher dosage may also be effective for advanced-stage disease.

We found that 1-year treatment with uracil–tegafur was safe and well tolerated. Grade 3 events occurred in 16.5% of the patients and consisted mainly of increases in bilirubin

and aminotransferases. No grade 4 or grade 5 events were observed. Previous colon cancer adjuvant trials showed that the overall incidences of grade 3 or more events in patients treated with different regimens were 38% or more for fluorouracil plus folinic acid (26,27), 38% for uracil–tegafur plus folinic acid (27), 30% for capecitabine (26) and more than 41% for oxaliplatin with fluorouracil plus folinic acid (28). The most frequent events included neutropenia, diarrhea, vomiting and hand-foot syndrome. Therefore, the safety profile of uracil–tegafur compares favorably with those of the previous regimens. Consequently, 80% of our patients completed 1 year of treatment, including dose modification. A study using a therapy preference questionnaire demonstrated that, after having experienced both oral and intravenous fluorouracil regimens, most patients preferred an oral regimen (29). The most important reasons for their preference included the convenience of taking the medication at home, less stomatitis and diarrhea, and preference of pills over injections (29). In addition, we should mention that uracil–tegafur is less expensive than the other regimens in this country, where medical costs are becoming an increasingly important issue.

Thus the most significant findings of our trial can be summarized as follows. Peroral monotherapy using uracil–tegafur achieved survival prolongation of stage III rectal cancer patients, without an addition of any other active agents, including folinic acid. This makes it possible to provide less toxic, yet effective, and convenient adjuvant chemotherapy for such patients.

However, several issues may limit the wider applicability of our findings. The numbers of patients recruited were smaller than those of recent rectal cancer adjuvant trials (6,7), although our trial was aimed solely at stage III tumor. The median follow-up time of our study was only 3 years, though disease-free survival with 3-year follow-up is suggested to be an appropriate primary endpoint to replace overall survival with 5-year follow-up (30). We used mesorectal excision with selective lateral pelvic lymphadenectomy that is a standard treatment only in Japan, and did not use mesorectal excision with radiotherapy, a world-standard combination. We could not use fluorouracil plus folinic acid, a standard adjuvant chemotherapy for stage III colon cancer, and neither the recently reported effective regimens including capecitabine and oxaliplatin (26–28). While the standard adjuvant chemotherapy course for colorectal cancer is 6 months (26–28), we opted for chemotherapy of 1 year. Therefore, the appropriateness of our approach should be tested further through comparison with recent standard adjuvant radiotherapy and chemotherapy.

In conclusion, radiotherapy has been considered to be standard adjuvant therapy worldwide for stage III rectal cancer. The present study indicates that uracil–tegafur treatment improves relapse-free survival and overall survival after mesorectal excision with selective lateral pelvic lymphadenectomy. This approach may become one of the treatment options for stage III rectal cancer and may deserve comparison with other treatment approaches.

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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].

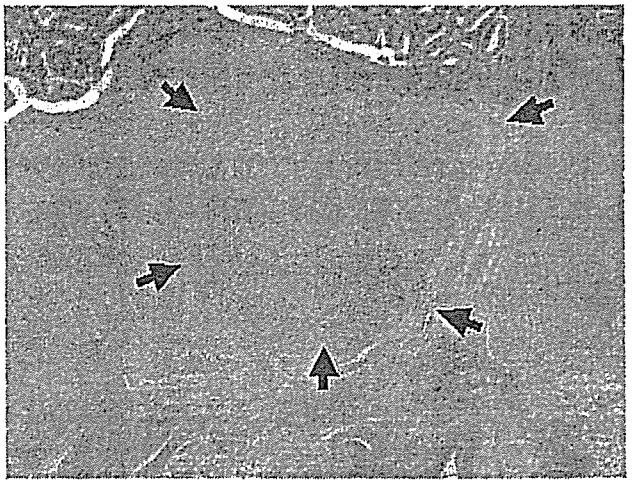
All patients were evaluated before surgery by total colonoscopy, barium enema and computed tomography (CT). None of the patients underwent preoperative radiotherapy and/or chemotherapy. One hundred and forty-six patients had sphincter-preserving surgery, 67 had abdominoperineal resection and 13 needed 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

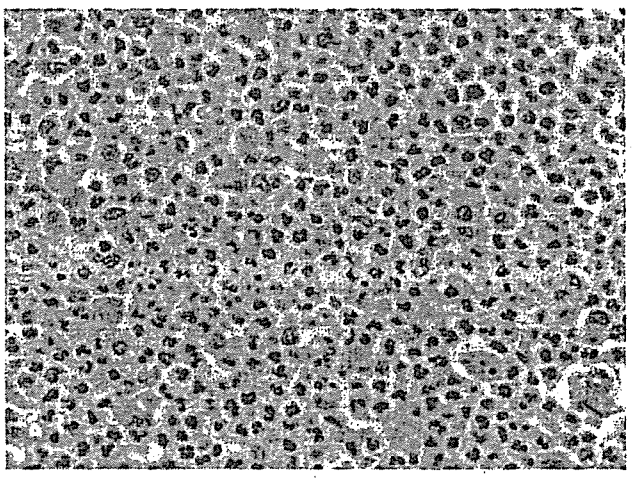
The resected tissue specimens were subjected to conventional processing. Histological sections containing the deepest site of cancer invasion were stained with haematoxylin and eosin, and were reviewed by three pathologists who had no previous knowledge of the clinical parameters and outcomes for each 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

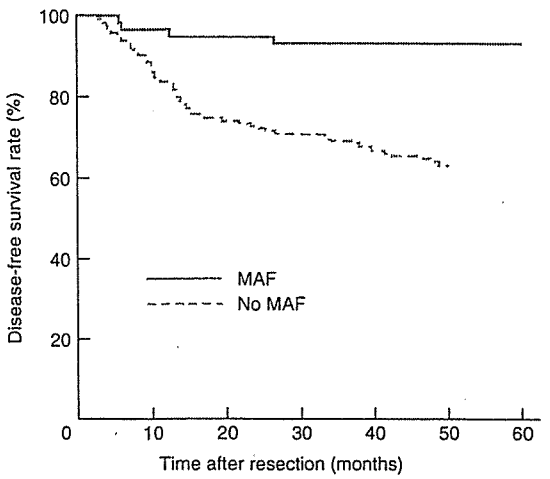
	No. of tumours	Microscopic abscess formation: No ($n = 169$)	Microscopic abscess formation: Yes ($n = 57$)	P*
Depth of invasion (pT)				0·549
pT2	86	66 (39·1)	20 (35)	
pT3 or pT4	140	103 (60·9)	37 (65)	
Lymph node status (pN)				0·002
Negative	119	79 (46·7)	40 (70)	
Positive	107	90 (53·3)	17 (30)	
Histological 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.



No. at risk

MAF	57	56	54	51	33	27	20
No MAF	169	143	122	114	90	68	

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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直腸癌局所再発に対する拡大手術
仙骨合併骨盤内臓全摘術

Total pelvic exenteration with distal sacretomy for fixed recurrent rectal cancer

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●要旨●仙骨合併骨盤内臓全摘術（TPES）は骨盤壁に浸潤の及ぶ局所再発直腸癌に対して，仙骨を含む隣接臓器とともに腫瘍を *en bloc* に摘出し，free surgical margin が確保できる根治的治療である。71例の再発直腸癌に対して TPES を行ってきた。本稿では TPES の手術適応，手術手技，合併症の実際を概説した。R0切除率は84.5％で，R0切除症例の５年生存率は48.1％，10年生存率は40.6％と比較的良好な成績を得ている。手術侵襲は過大なゆえ，その手術適応は厳格でなくてはならず，骨盤外科に精通した外科チームのみが行うべき術式である。

● key words：仙骨合併骨盤内臓全摘術，直腸癌，局所再発

はじめに

局所再発直腸癌患者の QOL は低く，長期にわたり出血，疼痛，腸閉塞，会陰潰瘍などの難治性合併症を患い，悲惨な経過をたどる症例も少なくない。欧米では主に放射線化学療法を中心に集学的な治療が広く行われているが，いまだ満足のいく治療法は確立されていない。一方，当院では局所再発直腸癌に対して積極的に外科的切除を行ってきた。

仙骨合併骨盤内臓全摘術（total pelvic exenteration with distal sacretomy；TPES）は骨盤壁に浸潤の及ぶ局所再発直腸癌（fixed recurrent tumor；FRT）に対して，仙骨を含む隣接臓器とともに腫瘍を *en bloc* に摘出し，free surgical margin を確保する根治的治療である。本術式は1981年の Wanebo らの報告に始まり，当院では1983年から積極的に導入し，これまでに71例に対して施行してきた。現在では安定した手術手技となり，FRT に対する基本術式と位置づけている。

本稿では TPES の手術手技の実際，手術適応，合併症および遠隔成績について述べる。

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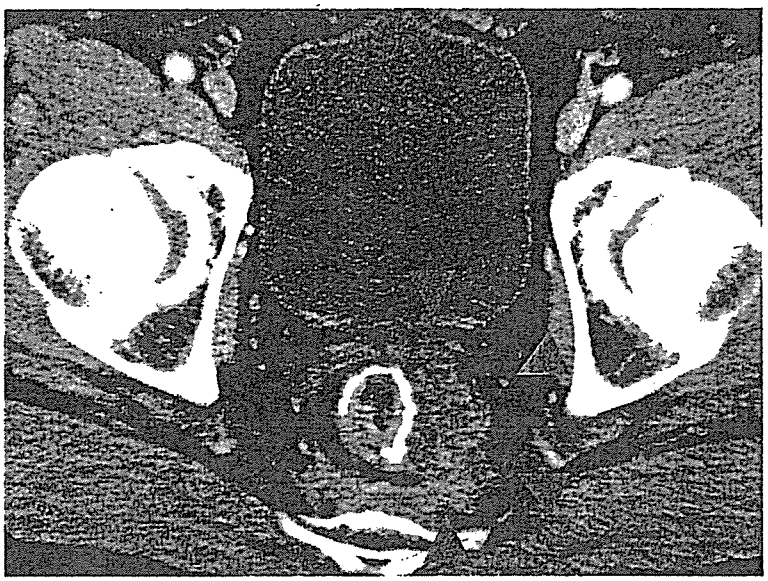
表１ 手術適応条件

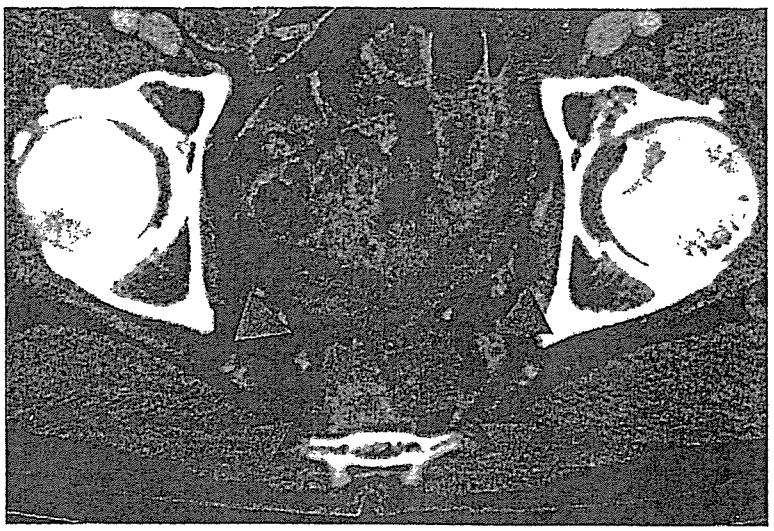
絶対的禁忌条件	
	切除可能な肝転移以外に遠隔転移を認める
相対的禁忌条件	
	仙骨岬角までの進展（S2 温存不可）
	外腸骨血管周囲への浸潤
	下肢に放散する疼痛
	腸骨静脈・リンパ管閉塞による下肢の浮腫
	側方リンパ節転移
	75 歳以上の高齢者
	初回手術で側方郭清が行われている
	高度な動脈硬化
	低分化腺癌または印環細胞癌

手術適応

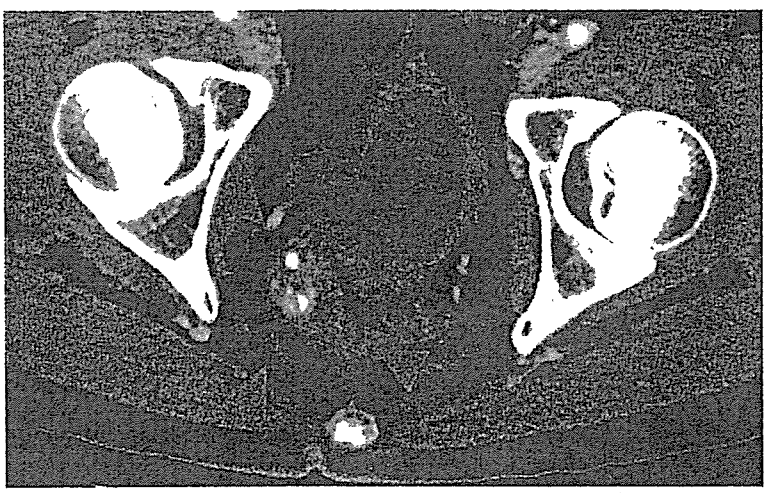
TPES は過大な侵襲を伴う術式のため，手術適応は厳格でなくてはならない。当院における手術適応を表１に示す。原則的に切除可能な１～２個の肝転移を除き，遠隔転移がなく，骨盤内に限局した局所再発癌のみを適応としている。下肢の浮腫，坐骨神経痛などをきたす症例は癌の神経，リンパ組織への広範な浸潤が予測され，また初回手術時に側方郭清施行症例や側方



a：吻合部および吻合部近傍再発



b：後方骨盤壁再発



c：側方骨盤壁再発

図1　TPESの適応となる再発形式

リンパ節転移を認める症例も原則的に適応外としている。

局所再発は再発の原因とその進展状況から図1のごとく分類できる。吻合および吻合部近傍再発は吻合部断端へのimplantationや直腸間膜の切除不足が主な原因である。しかし進展が進めば骨盤壁再発との区別は困難となる。後方・側方骨盤壁再発は側方リンパ節転移などのリンパ系進展や剝離面での腫瘍遺残が主な

原因である。

TPES において R0手術を行うためにもっとも重要なのが上方および側方断端である。腹側には泌尿器系臓器，背側には仙骨が存在するのに対し，側方では骨盤壁に直接浸潤する。このためとくに側方骨盤壁再発症例では側方剝離断端を free にすることが手術の山場となる。術前の画像，とくに MRI による進展所見の詳細な検討と術中の内閉鎖筋や棘突起などの積極的合併切除が肝要となる。

仙骨切断レベルは術前 MRI 所見を参考に決定する。切断レベルは原則として術後歩行障害や脊髄液瘻をきたすことのない S2下縁までとしている。これより高位での仙骨切断が必要となる症例は仙骨前面の表層切除あるいは Waldeyer 筋膜のみの切除に留めている。仙骨高位での切断は原発性仙骨腫瘍に対して行われることもあるが，根治性と重篤な術後障害を天秤にかければ，再発癌に対して行うべき術式ではない。仙骨 S2以下の切断を含む本術式において合併切除可能な非骨性骨盤壁は仙棘靱帯，仙結節靱帯，尾骨筋，内閉鎖筋の一部，梨状筋および S3以下の仙骨神経となる。

手術手技

手術手順を表2に示す。

表2　手術手順

1. 腹腔操作
   - ①前方（Retzius 腔）の展開と DVC（dorsal vein complex）の処理
   - ②仙骨前面の展開
   - ③側方郭清および内腸骨血管の処理と仙骨切断レベルの決定
2. 会陰操作
   - ①肛門挙筋の切離
   - ②尿道の切離
3. 体位変換，仙骨部操作
   - ①大殿筋の仙骨からの切離
   - ②椎弓切除，仙骨神経の確認
   - ③仙骨切断
4. 体位変換，再建操作
   - ①回腸導管，人工肛門の作成
   - ②ドレーン挿入と閉腹

1. 腹腔操作

体位は砕石位とし，剣状突起 5 cm 下から恥骨結合までの正中切開で開腹する。肝転移，腹膜播種，大動脈周囲リンパ節転移などの遠隔転移がなく，再発巣が骨盤内に限局していることを確認し，手術遂行の是非を決定する。

まず膀胱前腔（Retzius 腔）の展開を行う。膀胱前面を恥骨に沿って疎な組織の剝離を進めると，前立腺の前側方で恥骨前立腺靱帯と内骨盤筋膜（endopelvic fascia）が現れる。前立腺の両側で endopelvic fascia

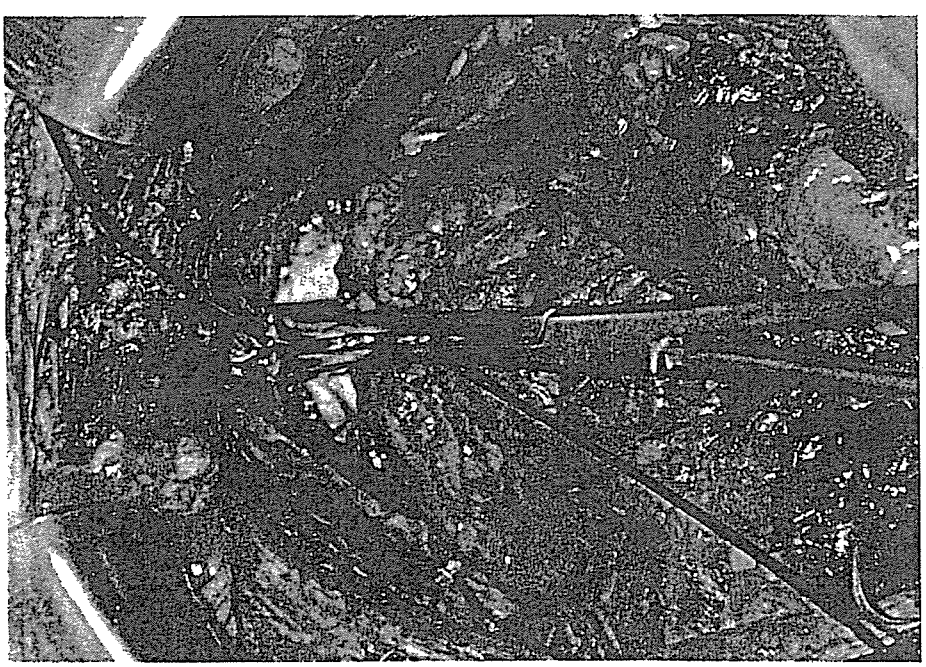


図2　bunching method
鳶巣式 bunching 鉗子で DVC を集束し，2-0 Ti-cron で二重結紮，切離する

を電気メスで切開し肛門挙筋を露出する。続いて，前立腺表面を走行する深陰茎背静脈の深枝である dorsal vein complex (DVC) の処理を行う。鳶巣式 bunching 鉗子を用い，左右の endopelvic fascia 断端から前立腺前面に沿って組織を集束させると，この中にDVC が含まれることになる (bunching method) (図2)。鉗子の前後で二重結紮，切離する。尿道の切離は会陰操作時に行うとよい。

大動脈分岐部より仙骨骨膜を露出する層で仙骨切断予定部位まで剝離をすすめる。この操作では瘢痕組織に埋もれる仙骨前面静脈叢の確認が困難なために多少の出血を伴うが，出血部位をしっかりと確認し，吸引しながら電気凝固を行えば止血可能である。それでも止血できない場合は，綿球で圧迫し，術野の展開を十分に行った後，再度止血を試みる。

次に内腸骨血管系の処理を行う。左右総腸骨動脈から内外腸骨動脈分岐部を露出し，外腸骨血管に沿い内閉鎖筋を露出しながら内下方に剝離操作を進める。閉鎖動静脈は切離し，閉鎖神経は温存する。この操作の過程で腰仙骨神経および第1，第2仙骨神経の同定ができる。可能であれば温存すべき第2仙骨神経にテーピングを行うと，仙骨切断時の神経誤認を回避できる。内腸骨動脈は上殿動脈が分岐した後で，二重結紮切離する。上殿動脈の温存は必須ではないが，会陰創の血流が悪くなるため，できるだけ温存する。内腸骨静脈本幹の切離に先立ち，骨盤壁を貫通する下殿動静脈，陰部動静脈などの末梢分枝を丁寧に結紮切離し，最後に内腸骨静脈本幹を結紮切離する。内腸骨静脈の切離を先行すれば，骨盤内静脈系のうっ血を招き，後の操作で思わぬ大出血につながる可能性がある。骨盤内静脈系からの出血コントロールがきわめて大切な本術式において，重要なポイントの1つである。

尿管は瘢痕組織のなかに埋もれているため，周囲の結合織，栄養血管をできるだけ温存しながら慎重に剝離し，左右総腸骨血管との交叉部より可及的膀胱側で切離する。一側または両側にシングルJカテーテルを挿入し，術中の尿量モニタリングを行う。

2. 会陰操作

会陰の皮膚切開は男性では直腸切断術に準じ，女性では外性器を含めた切離線で腹部創につなげる。会陰部に再発巣の浸潤が及ぶ場合には広範な会陰皮膚の切除が必要となる場合もある。

この操作での出血は骨盤底筋群のうっ血した静脈が主な原因であり，出血を減らすためには内腸骨静脈本幹の結紮前に会陰操作を行っておくとよい。

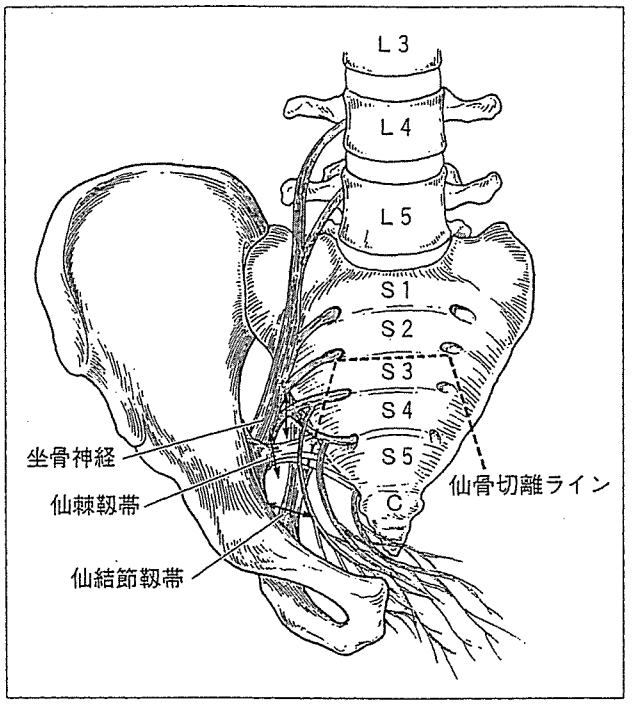


図3　仙骨の切離ライン

3. 仙骨操作

仙骨切断操作は整形外科医の協力が必要である。腹部および会陰創の仮閉鎖を行った後，体位を砕石位から腹臥位へ変更する。注意すべき点は腹圧の上昇を避けることで，腹圧が上昇すると静脈還流が悪くなり，椎骨静脈叢の圧が上昇して仙骨切断時の出血量が増加する。われわれは椎弓切除用の4点支持架台を使用し腹圧上昇を防止している。

皮膚切開は会陰創の背側端から仙骨切断予定部位より約10cm 頭側までの正中切開とする。大殿筋は後の骨盤底形成時に使用するため，仙骨骨膜に沿って剝がし，仙骨背側面を十分に露出する。ついで仙骨を固定する靱帯および筋肉の切離を行う。坐骨結節を確認後，仙結節靱帯を切離する。次いで会陰より示指を挿入し，仙棘靱帯の走行を確認後，これを坐骨棘近傍で切離する (図3)。これらの靱帯を切離した後，梨状筋の切離を行うが，梨状筋腹側には坐骨神経および仙骨神経が走行しており，損傷しないよう注意が必要である。この際，腹腔操作で行った第2仙骨神経のテーピングが非常に有用となる。切離が進んだら示指で仙骨前面の剝離層を確認し，仙骨切断レベルの最終確認を行う。

仙骨切断は，まず正中仙骨稜を削り，仙骨管を開放

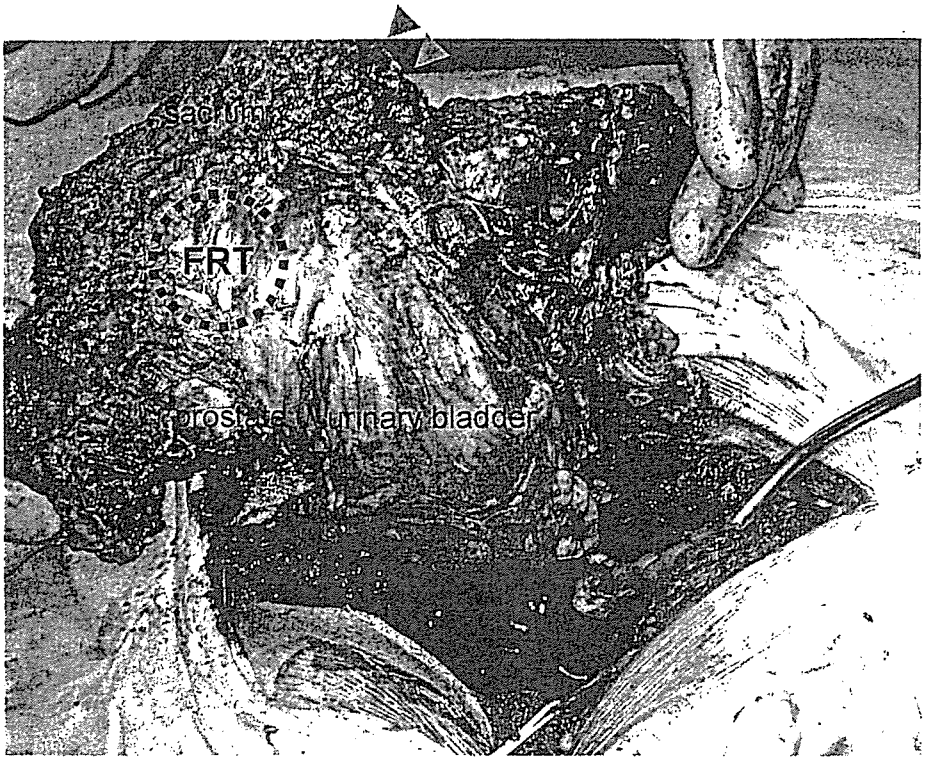


図4　標本摘出
仙骨を切断するとFRTを取り巻く骨盤内臓器が *en bloc* に摘出される。矢頭が仙骨断端

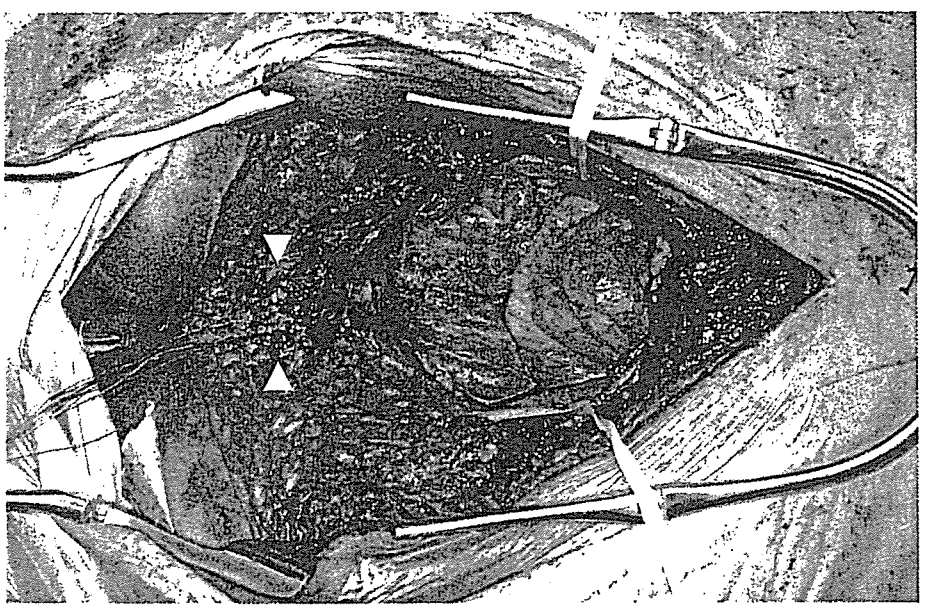


図5　標本摘出後
左右のS2神経は温存されている（黄色テープ）。尿道の縫合閉鎖はこの視野で行うとよい（矢頭）

する。硬膜の尾側端はS1下縁あたりとされており，S2下縁以下での仙骨切除では通常，硬膜の結紮処理は不要である。左右の示指を挿入し，腹腔側剝離層との交通を再度確認し，ノミと鎚を用いて迅速に仙骨切断を行う（図4）。腫瘍，仙骨を一塊として摘出後，視野は良好となり，電気メス・骨蝋ですばやく止血する（図5）。

男性では尿道断端を確実に閉鎖する。怠れば経尿道的に骨盤死腔炎を起こす原因となる。十分に止血を確認後，大殿筋起始部，皮下，皮膚をwater-tightに3層で縫合閉鎖する（図6）。

4.　再建と閉腹

体位を仰臥位とし，洗浄・止血確認を行った後，尿路変向および人工肛門造設を行う。尿路変向には回腸導管を用いる。回腸末端より約20cm口側で，2本の栄養血管を含む約15cmの回腸を使用する。長すぎる導管は尿の再吸収をきたすため避けるべきである。導管内を生理食塩水にて洗浄後，尿管回腸吻合を行い，シングルJカテーテルをスプリントカテーテルとする（図7）。高さのあるurostomaを作るため，上行結腸を肝彎曲まで十分に授動し，右側結腸全体を頭側へよける。この操作によって回腸導管間膜の過度の緊張を

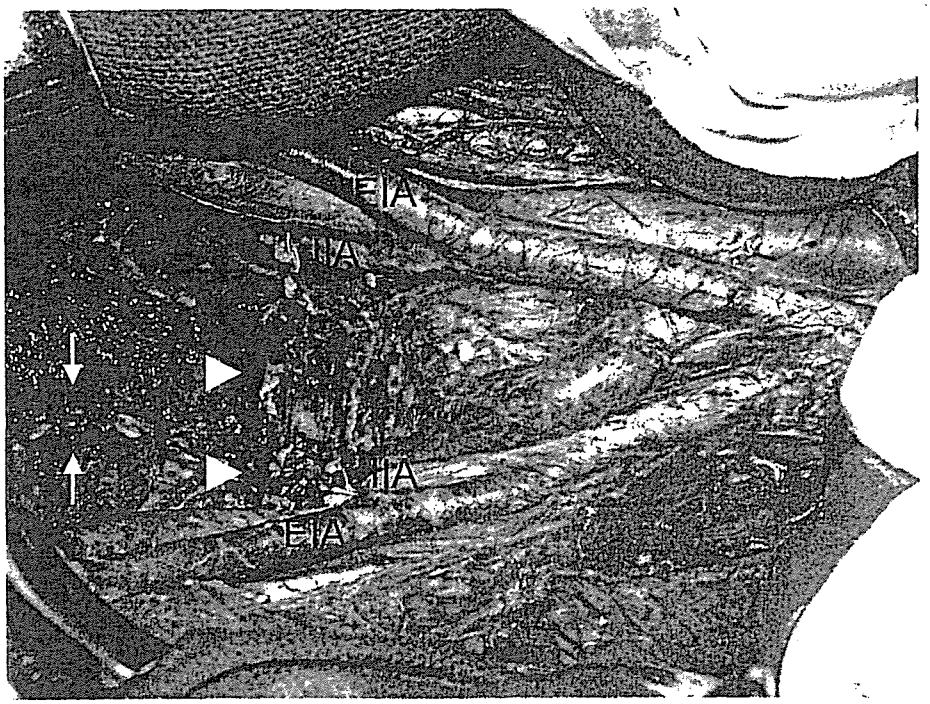


図6　標本摘出後の骨盤内
矢頭は仙骨断端，矢印は3層に閉鎖形成後の骨盤底。左右のIIAは上殿動脈分岐部末梢で二重結紮，切離されている
(IIA：internal iliac a.，EIA：external iliac a.)

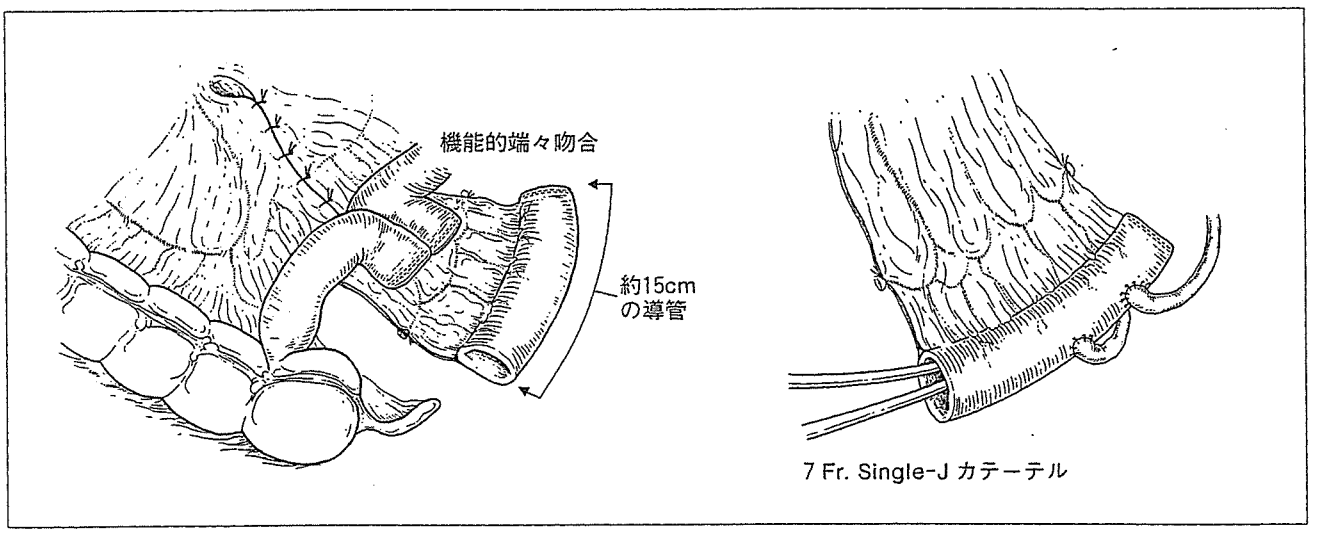


図7　回腸導管による尿路再建
a：導管は約15cmとし，回腸回腸吻合は機能的端々吻合を行う
b：尿管回腸吻合を5-0 Vicryl™で行う

回避できる。低いurostomaは患者のQOLを損なうため避けなければならない。

回腸回腸吻合は機能的端々吻合で行っている。吻合部が骨盤内に落ち込むと，骨盤死腔炎から2次的に縫合不全をきたし，小腸会陰瘻を形成する可能性がある。小腸会陰瘻は患者のQOLを著しく損なうため，吻合部が骨盤底に落ち込まぬように，腸間膜を固定するとよい。この操作は術前放射線照射例では必須である。

骨盤死腔炎の防止のためには術中汚染の防止や完全な止血が必要なことはいうまでもないが，血流の良好な大網の充填も感染防止に有用である。骨盤底に10mmプリーツドレーンを留置し，術後は10mmH_2Oで持続吸引を行っている。また広範な癒着剝離や長時間手術のため術後腸管運動の回復が遅れるため，胃瘻

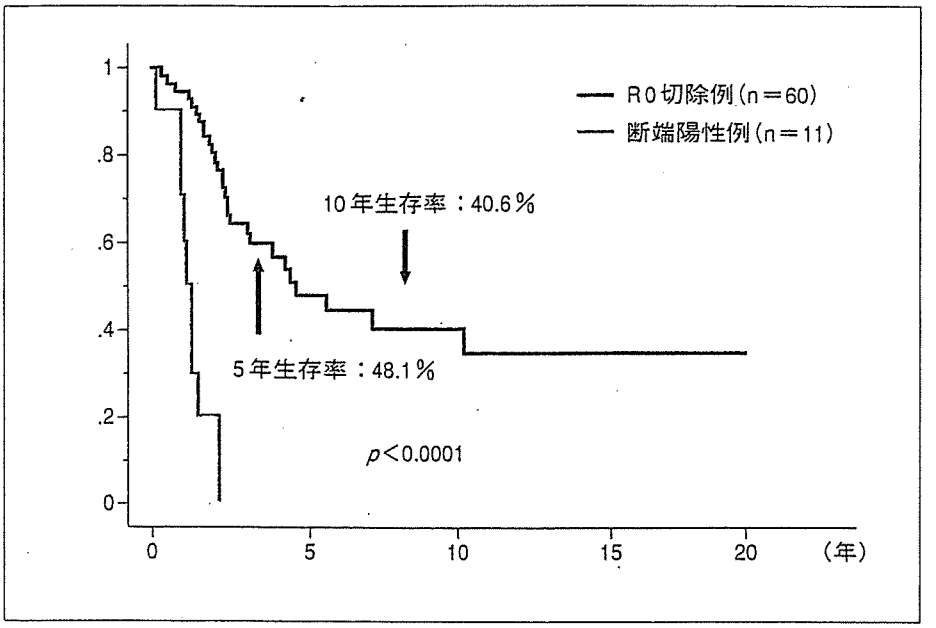


図8　TPES後，累積生存率
R0切除例 vs. 断端陽性例

表3　仙骨切断レベル（n＝71）

S2下縁	14例（19.7%）
S2～3	26例（36.6%）
S3下縁	16例（22.5%）
S3～4	10例（14.1%）
S4以下	5例（ 7.1%）

を造設し，術直後のQOLの向上を図っている。

手術成績

1983年から2005年の23年間に71例のTPESを行い，60例（84.5%）にR0手術が可能であった。切除断端陽性症例の予後は不良であったが，R0手術が可能であった60例の5年，10年累積生存率はそれぞれ48.1%，40.6%と比較的良好な成績を得ている（図8）。手術時間，出血量の中央値はそれぞれ720分，2580mlで，これが本術式の標準的手術侵襲である。しかしながら前期症例（1983～1992年）と後期症例（1993年～2005年）を比較すると平均出血量は4229mlから2500mlへ有意（$p=0.002$）に減少し，良好なlearning curveを示していると考えられる。在院死も前期には2例認めるも，後期では経験していない。

仙骨切断レベルはS3上縁が26例（36.6%）ともっとも多く，次いでS3下縁，S2下縁の順であった（表3，図9）。

合併症は全体の58%で認め，仙骨創の哆開が52%ともっとも多く，次いで骨盤死腔炎が39%であった。しかし骨盤死腔炎の頻度は前期の72%から後期の23%へ有意（$p=0.046$）に減少を認めている。イレウスは5例で認めたが，すべて保存的に改善した。また晩期合併症として小腸会陰瘻5例認め，全例でバイパス手術が必要であった。回腸導管会陰瘻の1例は両側腎瘻が必要となったが術後15年の長期生存が得られた。術後の殿部の疼痛は不可避で，MSコンチン® の内服が効果的である。

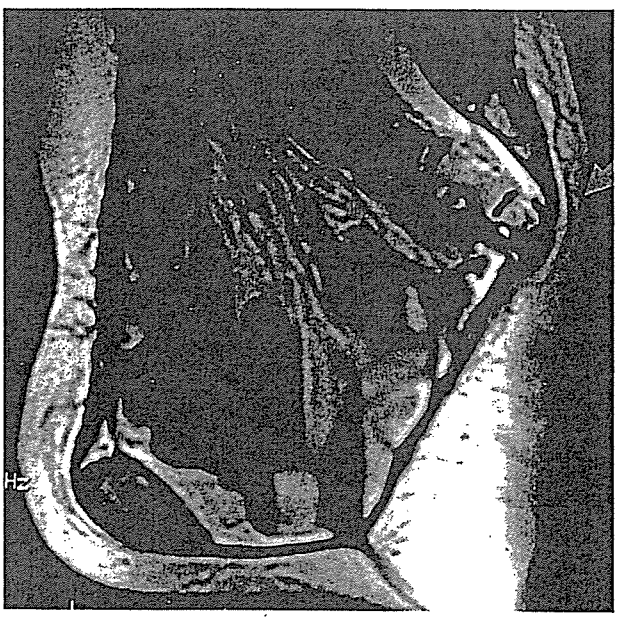


図9　TPES術後の骨盤MRI
仙骨切断レベルはS2～3（矢印）

おわりに

骨盤壁に浸潤するFRTに対しTPESはR0切除を行う最後のチャンスであり，長期生存の期待もできる。手術手技が確立され，比較的安全に行える治療となった現在，FRTに対する基本治療と考える。しかしながら手術適応は厳格でなくてはならず，骨盤外科に精通した外科チームのみが行うべき術式である。

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