ples were also obtained from 83 healthy volunteers a few weeks after they had undergone a total colonoscopy. Naturally evacuated feces from subjects who had not taken laxatives were used as stool samples. Each patient was instructed to evacuate into a polystyrene disposable tray (AS one, Osaka, Japan) measuring 5 × 10 cm in size at home and bring the sample to the reception counter at the outpatient clinic or the Cancer Prevention and Screening Center of the National Cancer Center. The samples were collected and transferred to a laboratory at which they were allowed to stand at room temperature. Preparation of the stool samples for examination was conducted within 1–6 hours after the evacuation.

Magnetic Beads

Dynabeads Epithelial Enrich are uniform, superparamagnetic, polystyrene beads (4.5-μm diameter) coated with a mouse IgG1 monoclonal antibody (mAb Ber-EP4) specific for the glycopolypeptide membrane antigen Ep-CAM, which is expressed on most normal and neoplastic human epithelial tissues (Dynal, Oslo, Norway). Ep-CAM is widely expressed in the highly proliferative cells of the intestinal epithelium, from the basal cells to cells throughout the crypts at the basolateral membranes, and only the apical membrane facing the lumen is negative. The development of adenomas has been reported to be associated with increased Ep-CAM expression, and Ep-CAM over expression (mAb GA733) has frequently been demonstrated in colorectal carcinomas.[23–25]

Simulation Studies

A series of simulation studies were conducted to establish the optimal conditions for retrieving HT-29 colorectal cancer cells from feces. Feces from healthy volunteers were divided into several portions, each of which was seeded with 100 μL HT-29 cells (1 × 10^6/approximately 5 g feces). The cells were retrieved under several different conditions as follows: use of a Hank's solution and 25 mmol/L Hepes buffer (pH 7.35); processed feces of 5, 10, or 30 g volume; filter with a pore size of 48, 96, 512, or 1000 μm; incubation of homogenized solution with magnetic beads at 4°C or room temperature; application of 20, 40, 80, 200, or 400 μL magnetic beads; incubation of homogenized solution with magnetic beads under gentle rolling at 15 rounds/minute in a mixer for 10, 20, 30, or 40 minutes; and the reaction time between the cell-magnetic bead complexes and a magnet on a shaking platform for 0, 2, 10, 20, 30, 40, 50, or 60 minutes. Finally, the cell retrieval rate calculated for the magnetic beads method under the conditions determined to be the most suitable for this simulation study was compared with that calculated for the Percoll centrifugation method. The retrieval rate was calculated by dividing the number of cells that bound to the retrieved beads by the number of cells initially added to the feces. The cells were counted using a NucleoCounter (ChemoMetec A/S, Allerød, Denmark).

Isolation of Exfoliated Cells From Feces

The procedure was conducted using the most suitable and optimal conditions determined by the simulation study (Figure 1). Approximately 5–10 g of naturally evacuated feces were used to isolate exfoliated cells. Feces were collected into Stomacher Lab Blender bags (Seward, Thetford, United Kingdom). The stool samples were homogenized with a buffer (200 mL) consisting of Hank's solution, 10% fetal bovine serum (FBS), and 25 mmol/L Hepes buffer (pH 7.35) at 200 rpm for 1 minute using a Stomacher (Seward). The homogenates were then filtered through a nylon filter (pore size, 512 μm), followed by division into 5 portions (40 mL each). Subsequently, 40 μL of magnetic beads were added to each homogenized solution portion, and the mixtures were incubated for 30 minutes under gentle rolling in a mixer at room temperature. The samples on the magnet were then incubated on a shaking platform for 15 minutes at room temperature. Colonocytes isolated from 5 tubes were smeared onto slides and then stained using the Papanicolaou method. The remainder of the samples was centrifuged, and the sediments were stored at −80°C until DNA extraction.

Extraction of DNA

Fresh tissue samples were obtained from the surgically resected specimens of 116 patients with colorectal cancer. The samples were snap frozen in liquid nitrogen within 20 minutes of their arrival at the pathologic specimen reception area and were stored in liquid nitrogen until analysis.

Genomic DNA was extracted from each tumor tissue specimen using a DNeasy kit (QIAGEN, Valencia, CA). Genomic DNA was also extracted from colonocytes isolated from feces using the SepaGene kit (Sanko-Junyaku, Tokyo, Japan).

Direct Sequence Analysis

Direct sequencing was conducted to identify mutations in the APC codon 1270–1594, in codons 12 and 13 of the K-*ras* gene, and in exons 5, 6, 7, and 8 of the p53 gene.

The PCR primers used in this study were as follows: APC (5′-AAACACCTCAAGTTCCAACCAC-3′, 5′-GGTAATTTTGAAGCAGTCTGGGC-3′); K-*ras* (5′-CTGGTGGAGTATTTGATAGTG-3′, 5′-CCCAAGGAAAGTAAAGTTC-3′); p53 exon 5 (5′-GCCGTCTTCCAGTTGCTTTAT-3′, 5′-CCAAATACTCCACACGCAAAT-3′); p53 exon 6 (5′-CATGAGCGCTGCTCAGATAG-3′, 5′-TGCACATCTCATGGGGTTATAG-3′); p53 exon 7 (5′-CTTGGGCCTGTGTTATCTCCTA-3′, 5′-AAGAAAACTGAGTGGGAGCAGT-3′); and p53 exon 8 (5′-ACCTCTTAACCTGTGGCTTC-3′, 5′-TACAACCAGGAGCCATTGTC-3′).

The sequence primers used in this study were as follows: APC (5′-CAAAAGGCTGCCACTTGCAAAG-3′, 5′-AAAATAAAGCACCTACTGCTG-3′, 5′-GAATCAGCCAGGCACAAAGC-3′); K-*ras* (5′-CTGGTGGAGTATTTGATAGTG-3′); p53 exon 5 (5′-CCAAATACTCCACACGCAAAT-3′); p53 exon 6 (5′-CATGAGCGCTGCTCAGATAG-3′); p53 exon 7 (5′-AAGAAAACTGAGTGGGAGCAGT-3′); and p53 exon 8 (5′-

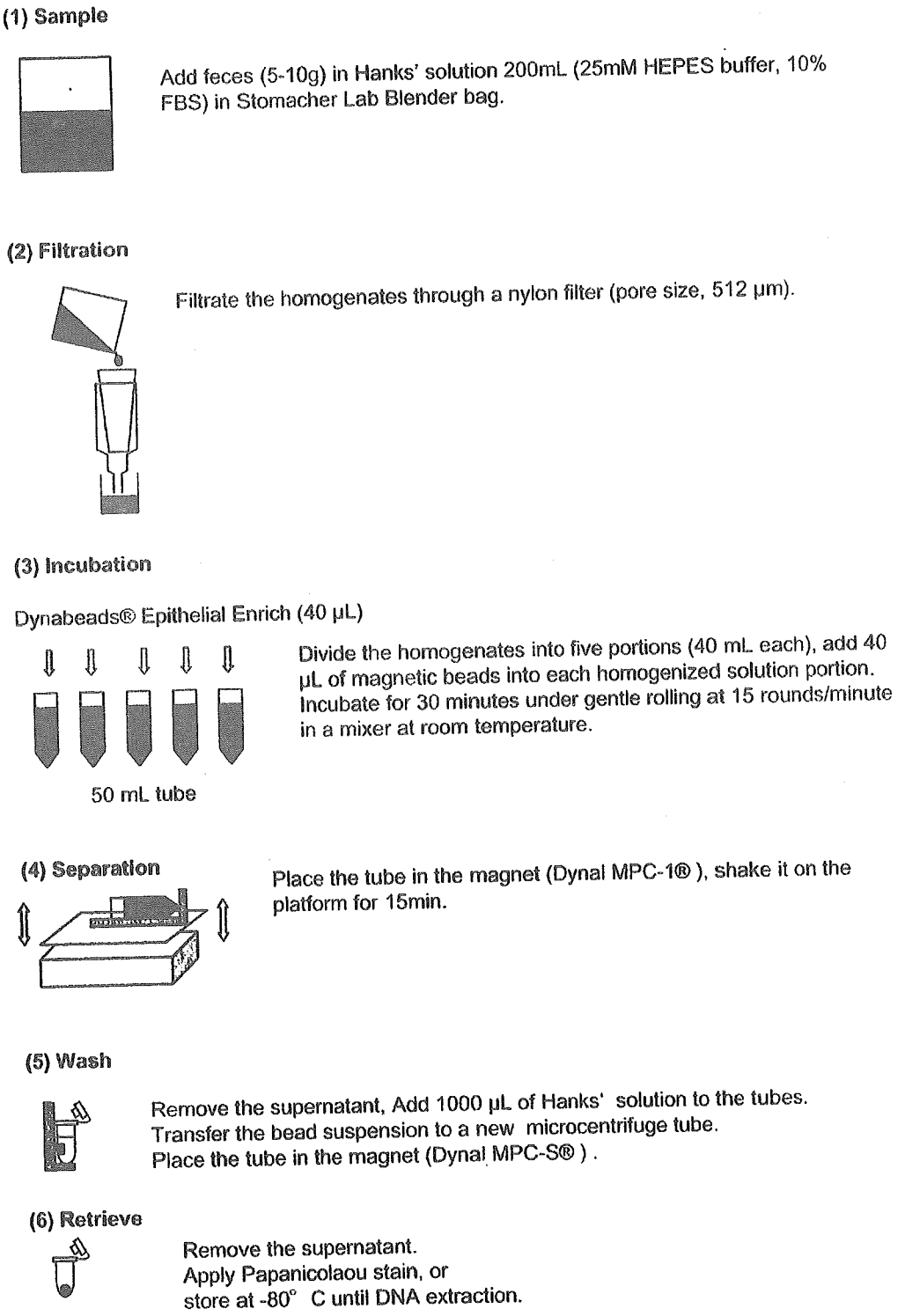

Figure 1. Schematic of procedure for isolating colonocytes from feces.

ACCTCTTAACCTGTGGCTTC-3′). Each fragment was sequenced by direct sequencing using the Big Dye Terminator v 3.1/1.1 cycle kit (Applied Biosystems, Forester City, CA).

All obtained sequences were aligned with previously published sequences (National Center for Biotechnology Information [NCBI] Genbank accession No. M74088 [APC], M54968 [K-*ras*], and X54156 [p53]) for each of the target genes and were analyzed using Phred/Phrp/DNASIS pro (Hitachi Software Engineering, Tokyo, Japan). The presence and nature of each mutation were confirmed by repeated PCR and sequencing.

BAT26

The BAT26 gene, an indicator of microsatellite instability (MSI), was amplified by PCR. Each fragment was elec-

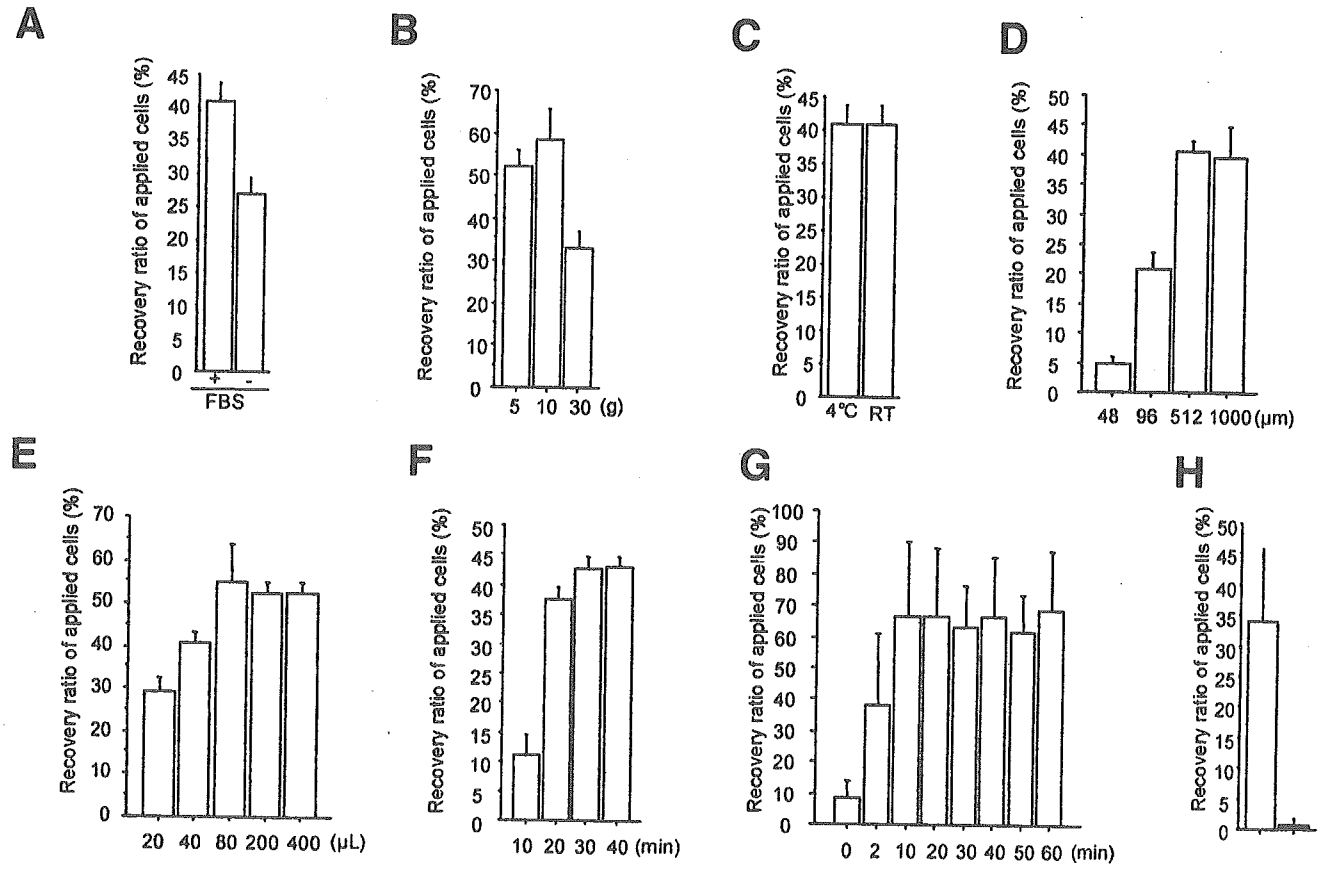

Figure 2. Simulation study to establish the optimal conditions for retrieving HT-29 colorectal cancer cells from feces and to compare the cell retrieval rates for the magnetic beads methods and the Percoll centrifugation method. Feces from healthy volunteers were divided into several portions, each of which was seeded with 100 μL HT-29 colorectal cancer cells (1×10^6/approximately 5 grams of feces). The procedure for retrieving the HT-29 cells was conducted under various conditions as follows: (*A*) homogenizing buffer with or without FBS; (*B*) stool weight (5, 10, or 30 g); (*C*) temperature during the cell-yielding procedure (4°C or room temperature); (*D*) filter pore size (48, 96, 512, or 1000 μm); (*E*) volume of applied magnetic beads (20, 40, 80, 200, or 400 μL); (*F*) incubation time of the homogenized solution with the magnetic beads under gentle rolling in a mixer (10, 20, 30, or 40 minutes); and (*G*) reaction time for the cells-magnetic bead complexes and the magnet on the shaking platform (0, 2, 10, 20, 30, 40, 50, or 60 minutes). The cell retrieval ratio (%) was calculated using the following formula: 100 × number of HT-29 cells retrieved/number of applied HT-29 cells. (*H*) Comparison of cell retrieval rates for the magnetic beads methods (*open column*) and the Percoll centrifugation method (*solid column*).

trophoresed using an ABI PRISM 3100 Genetic Analyser (Applied Biosystems) and then analyzed by GeneScan v 3.7 (Applied Biosystems). The PCR primers used in this study were 5′-TGACTACTTTTGACTTCAGCC-3′ and 5′-AACCATTCAACATTTTTAACCC-3′.

Cytology

Colonocytes isolated from feces were examined by 2 experienced cytotechnologists after Papanicolaou staining.

Study Blinding

We followed the guidelines of our medical institution for preparing blinded samples. Technicians processed the stool samples and prepared the slides for cytology and the cell pellets for DNA extraction. The samples were blinded to prevent the identification of individuals and the samples' origins. Two cytologists assessed the blinded samples, and the Life Science Group of Hitachi, Ltd, analyzed the DNA sequences.

Statistical Analysis

A Fisher exact test was used to compare all proportions. All reported P values are 2-sided. A value of $P < .05$ was considered statistically significant.

Results

Simulation Studies

The cell retrieval rate was found to decrease when Hank's solution without FBS was used, thus indicating the effectiveness of adding serum to the homogenizing buffer (Figure 2*A*). The cell retrieval rate was found to decrease when more than 30 g of feces were processed (Figure 2*B*). The cell retrieval rates were similar when incubation was conducted at room temperature and at 4°C (Figure 2*C*). Filtering of the stool suspension with the 48- or 96-μm filter resulted in significant clogging and thus hampered cell retrieval. However, a lot of fecal

residue remained after filtering with the 1000-μm filter, hindering the handling of the stool suspension thereafter. We therefore decided to use the 512-μm filter (Figure 2*D*). The dose of the magnetic beads applied was also examined. The cell retrieval rate increased in a dose-dependent manner up to 80 μL. In reality, a sufficient amount of genomic DNA derived from exfoliated colonocytes was obtained, even when 40 μL of magnetic beads were used (Figure 2*E*). Regarding the optimal incubation time of the magnetic beads for the complete binding of HT-29 cells to the beads, 30 minutes of incubation was found to be sufficient for the satisfactory binding of HT-29 cells to the beads (Figure 2*F*). For the retrieval of the cell-magnetic bead complexes on the magnet, a 10-minute reaction period was sufficient (Figure 2*G*).

The cell retrieval rates were 0.8% and 33.5% using the Percoll centrifugation method and the magnetic beads method, respectively, thus underscoring the advantage of the magnetic beads method (Figure 2*H*).

Cytology

Atypical cells were observed in colonocytes isolated from the feces of 32 of 116 patients with colorectal cancer, with a sensitivity rate of 28% (95% CI: 20–37; Table 2, Figure 3*A* and 3*B*). No atypical cells were observed in any of the 83 healthy volunteers, with a specificity rate of 100% (95% CI: 96–100). A significant difference ($P < .0001$) was found in the positivity rate between the patient group and the healthy volunteer group. The sensitivity rates for Dukes' A, B, and C or D colorectal cancers were 23% (7 of 30; 95% CI: 10–42), 32% (10 of 31; 95% CI: 17–51), and 27% (15 of 55; 95% CI: 16–41), respectively. No significant differences in the positivity rates were found among any of the stages. Furthermore, the sensitivity rates for cancers on the right side of the colon, including the cecum, ascending colon, and transverse colon, and for those on the left side of the colon, including the descending colon, sigmoid colon, and rectum, were 9% (3 of 35; 95% CI: 2–23) and 36% (29 of 81; 95% CI: 25–47), respectively. Therefore, the positivity rate was significantly higher for cancers on the left side of the colon ($P < .01$).

DNA Analysis

Overall analysis of stool samples. Sequence analysis showed distinct mutations in each of the analyzed genes in the tumor tissue and colonocytes isolated from feces (Figure 3*C–F*). Genetic alterations were observed in the colonocytes isolated from the feces of 82 of the 116 patients with colorectal cancer, yielding a sensitivity rate of 71% (95% CI: 62–79; Table 2). However, 10 of the 83 healthy volunteers were also positive for genetic alterations, producing a specificity value of 88% (95% CI: 79–94). A significant difference ($P < .0001$) was noted in the positivity rates of the patient group and the healthy volunteer group.

Genetic alterations were observed in 18 of the 30 patients with Dukes' A colorectal cancer, yielding a sensitivity rate of 60% (95% CI: 41–77). Furthermore, genetic alterations were observed among 26 of the 31 patients with Dukes' B colorectal cancer (84%; 95% CI: 66–95) and 38 of the 55 patients with Dukes' C or D colorectal cancer (69%; 95% CI: 55–81). No significant difference in sensitivity was found among any of the stages.

Genetic alterations were observed in colonocytes isolated from feces in 20 out of 35 patients with cancers originating on the right side of the colon (57%; 95% CI: 39–74) and in 62 out of 81 patients with cancers originating on the left side of the colon (77%; 95% CI: 66–85). No significant differences in the sensitivity rates were observed, although the sensitivity rate tended to be higher for cancers on the left side of the colon.

DNA analysis limited to colonocytes isolated from the feces of patients with colorectal cancer tissue involving genetic alterations. We assessed the performance of the present methodology for isolating cancer cells by examining the positivity rate of genetic alterations in colonocytes isolated from the feces of patients who showed alterations in their cancer tissues (Table 3). Among the 116 patients, a total of 93 (80%; 95% CI: 72–87) exhibited genetic alterations in the APC, K-*ras*, or p53 genes or BAT26 positivity in their cancer tissue: 51 patients exhibited APC mutations (44%, 95% CI: 35–53), 33 patients exhibited K-*ras* mutations (28%; 95% CI: 20–38), 62 patients exhibited p53 mutations (53%; 95% CI: 44–63), and 6 patients exhibited BAT26 positivity (5%; 95% CI: 2–11). Among the 93 patients with genetic alterations in their cancer tissues, the alterations were also successfully detected in colonocytes isolated from the feces of 80 patients (86%; 95% CI: 77–92). Among the 39 patients with Dukes' C or D advanced cancer who exhibited a genetic alteration in their cancer tissues, 36 patients exhibited genetic alterations in colonocytes isolated from their feces (92%; 95% CI: 79–98). Furthermore, genetic alterations were detected in colonocytes isolated from the feces of 18 of 24 patients with Dukes' A cancer (75%; 95% CI: 53–90) and 26 of 30 patients with Dukes' B cancer (87%; 95% CI: 69–96). No statistically significant difference was found among these 3 groups. In addition, genetic alterations could be detected in colonocytes isolated from the feces of 20 of 27 patients with cancers originating on the

Table 2. Incidences of Genetic Alterations of the APC, K-*ras*, p53, and MSI (BAT26) Genes as Well as Results From Cytology in all Patients and Healthy Volunteers

		Patient				Healthy volunteer	
		Tumor tissue		Isolated cell		Isolated cell	
	Marker	No.	Positivity (%) (95% CI)	No.	Sensitivity (%) (95% CI)	No.	Specificity (%) (95% CI)
Overall Patients (n = 116), healthy volunteers (n = 83)	Combined marker	93	80 (72–87)	82	71 (62–79)	10	88 (79–94)
	APC	51	44 (35–53)	47	41 (32–50)	1	99 (93–100)
	K-*ras*	33	28 (20–38)	33	28 (20–38)	1	99 (93–100)
	p53	62	53 (44–63)	45	39 (30–48)	6	93 (85–97)
	BAT26	6	5 (2–11)	4	3 (1–9)	3	96 (90–99)
	Cytology			32	28 (20–37)	0	100 (96–100)
Dukes' stage A (n = 30)	Combined marker	24	80 (61–92)	18	60 (41–77)		
	APC	14	47 (28–66)	11	37 (20–56)		
	K-*ras*	6	20 (77–39)	5	17 (6–35)		
	p53	6	20 (77–39)	9	30 (15–49)		
	BAT26	1	3 (1–17)	1	3 (1–17)		
	Cytology			7	23 (10–42)		
Dukes' stage B (n = 31)	Combined marker	30	97 (83–100)	26	84 (66–95)		
	APC	17	55 (36–73)	17	55 (36–73)		
	K-*ras*	10	32 (17–51)	9	29 (14–48)		
	p53	18	58 (39–75)	13	42 (25–61)		
	BAT26	2	6 (1–21)	1	3 (1–17)		
	Cytology			10	32 (17–51)		
Dukes' stages C and D (n = 55)	Combined marker	39	71 (57–82)	38	69 (55–81)		
	APC	20	36 (24–50)	19	35 (22–49)		
	K-*ras*	17	31 (19–45)	19	35 (22–49)		
	p53	27	49 (35–63)	23	42 (29–56)		
	BAT26	3	5 (1–15)	2	4 (0–13)		
	Cytology			15	27 (16–41)		
Right-sided colon cancer (n = 35)	Combined marker	27	77 (60–90)	20	57 (39–74)		
	APC	11	31 (17–49)	8	23 (10–40)		
	K-*ras*	16	46 (29–63)	12	34 (19–52)		
	p53	17	49 (31–66)	11	31 (17–49)		
	BAT26	2	6 (1–19)	1	3 (1–15)		
	Cytology			3	9 (2–23)		
Left-sided colon cancer (n = 81)	Combined marker	66	81 (71–89)	62	77 (66–85)		
	APC	40	49 (38–61)	39	48 (37–60)		
	K-*ras*	17	21 (13–31)	21	26 (17–37)		
	p53	45	56 (44–67)	34	42 (31–53)		
	BAT26	4	5 (1–12)	3	4 (1–10)		
	Cytology			29	36 (25–47)		

right side of their colon (74%; 95% CI: 54–89) and 60 of 66 patients with cancers originating on the left side of their colon (91%; 95% CI: 81–97). A statistically significant difference was found between the right- and left-side colon cancer patient groups ($P = .03$).

Discussion

We have devised a simple, highly reliable methodology for isolating colorectal cancer cells from nonlaxative-induced, naturally evacuated feces from most patients with colorectal cancer. To date, several methods of isolating colorectal cancer cells from feces have been reported.[21,22,26,27]

Our new funnel-shaped filter system extensively improved the filtration efficiency of the stool suspension by enlarging the filtration area and selecting the optimal pore size; the system was capable of filtrating the entire stool suspension without filter clogging. These properties permit the omission of centrifugation and simplify the overall process because all steps can be performed at room temperature. Furthermore, the use of serum successfully increased the cell retrieval rate. We presume that this increase may be attributed to the suppression of protease activity or the inhibition of nonspecific reactions of the antibodies on the bead surface. Consequently, our new methodology also allows the extraction of high-quality DNA or RNA from exfoliated colonocytes. Very recently, Imperiale et al compared a panel of fecal DNA markers and Hemoccult II as screening tests for colorectal cancer. It is worth noting that, in their study, colonoscopy as a reference standard was used

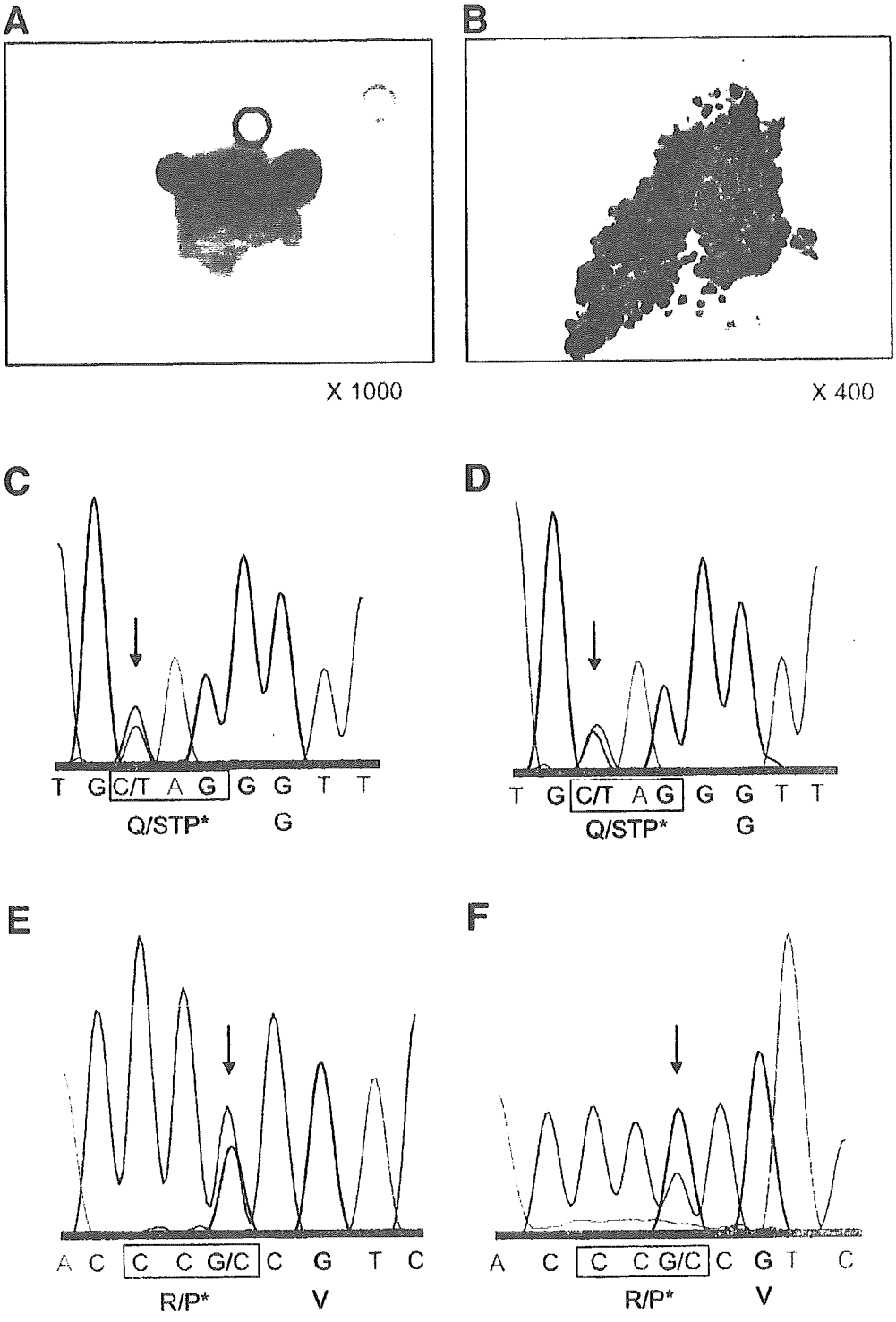

Figure 3. Cytology and DNA sequencing. Papanicolaou staining of colonocytes isolated from the feces of patients with colorectal cancer. (*A*) A patient with ascending colon cancer, Dukes' stage A. (*B*) A patient with rectal cancer, Dukes' stage C. Detection of mutations in tumor tissues and colonocytes isolated from the feces of patients with colorectal cancer. (*C*) A point mutation of the APC gene in a tumor tissue specimen obtained from a patient with rectal cancer, Dukes' stage B. (*D*) An identical mutation was detected in colonocytes isolated from the feces of the patient. (*E*) A point mutation of the p53 gene in a tumor tissue specimen obtained from a patient with ascending colon cancer, Dukes' stage A. (*F*) An identical mutation was detected in colonocytes isolated from the feces of the patient. *Wild/mutant.

in all subjects. They conducted those tests in a blinded fashion and showed that sensitivity of DNA analysis was 4-fold higher than that of Hemoccult test.[28] We believe that this report may prompt a study of fecal DNA test for colorectal cancer screening.

The idea to isolate cancer cells from feces originally derived from a study that described the abnormal expression of the CD44 gene in many tumors, including colon cancer and bladder cancer.[21,29,30] In the course of a series of studies, we predicted that normal mucous cells would die and be exfoliated during turnover and that the cancer cells would likely survive for a long time in the feces.

Although cytology is highly specific compared with direct sequence analysis, its sensitivity, especially for cancers on the right side of the colon is relatively low. From a technical aspect, our cytology method does not allow the

Table 3. Incidences of Genetic Alterations in Colonocytes Isolated From the Feces of Patients With Colorectal Cancer Tissue Involving Genetic Alterations of the APC, K-*ras*, p53, or MSI (BAT26) Gene

	Combined marker		APC		K-ras		p53		BAT 26	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Overall	80/93	86% (77–92)	46/51	90% (79–97)	29/33	88% (72–97)	42/62	68% (55–79)	4/6	67% (22–96)
Dukes' stage A	18/24	75% (53–90)	11/14	79% (49–95)	5/6	83% (36–100)	5/6	83% (36–100)	1/1	100% (3–100)
Dukes' stage B	26/30	87% (69–96)	16/17	94% (71–100)	9/10	90% (56–100)	12/18	67% (41–87)	1/2	50% (1–99)
Dukes' stages C and D	36/39	92% (79–98)	19/20	95% (75–100)	15/17	88% (64–99)	21/27	78% (58–91)	2/3	67% (9–99)
Right-sided	20/27	74% (54–89)	8/11	73% (39–94)	12/16	75% (48–93)	11/17	65% (38–86)	1/2	50% (1–99)
Left-sided	60/66	91% (81–97)	38/40	95% (83–99)	17/17	00% (81–100)	31/45	69% (53–82)	3/4	75% (19–99)

NOTE. Number of positive cases in tumor tissue and colonocytes isolated from feces/number of positive cases in tumor tissue, with 95% confidence interval.

observation of cells unless there are 5×10^4 cells per slide. Technical improvements might increase the benefits of feces cytology. However, we believe that cytology is not suitable as a method for identifying cancer because of its low sensitivity, at least at present. From a practical point of view, we have conducted a study to determine the effect of the time and temperature after evacuation on the recovery rates of fecal colonocytes, and we have found that we can obtain almost the same number of colonocytes from stool materials 3 days after evacuation in comparison with 6 hours after evacuation if fecal material is kept at 4°C (data not shown). This observation may be important for the potential clinical application of this method.

Direct sequence analysis of colonocytes isolated from the feces of 83 healthy volunteers revealed mutations in 8 subjects (9%; 95% CI: 4–18), the breakdown of which was as follows: 1 APC1 mutation, 1 K-*ras* mutation, and 6 p53 mutations. Points of mutations identified of the p53, APC, and K-*ras* genes observed in the 83 healthy volunteers in this study were identical to that reported previously in tumors. These mutations of p53, APC, and K-*ras* in tumors are recorded in the database of OMIM. PCR errors were unlikely because multiple PCR reactions and sequence reactions were separately conducted. However, genetic alterations in precancerous lesions may have been present, although endoscopy findings macroscopically verified the absence of adenoma and carcinoma. The individuals in whom the present methodology revealed genetic alterations should be monitored to assess whether these findings were false-positive results or a predictor of tumorigenesis.

Oncogenes in feces are presumably derived from cancer cells exfoliated from the cancer tissue, and genetic alterations would not be detected in colonocytes isolated from feces if the original cancer tissue did not contain genetic alterations. In fact, among the 93 patients who exhibited genetic alterations in their cancer tissues, alterations were detected in colonocytes from the stools of 80 patients, producing a true sensitivity rate of 86% (80 of 93), although the present overall sensitivity was 71%. Furthermore, our methodology allows the isolation and retrieval of colorectal cancer cells from both early stage cancer and right-side colon cancer. Because the methodology allows processing at room temperature, we are currently constructing an automated, mechanized processing system on a commercial basis. A problem of our test was its relatively low specificity for a screening test as described previously. We consider that mutations observed in the healthy subjects might be attributable to the fact that they belonged to a high-risk group for colorectal cancer because these 83 volunteers were selected from among colonoscopy examinees recruited by the newly established National Cancer Center Research Center for Cancer Prevention and Screening, and the detection rate of cancers appeared to be considerably higher in the all examinees at the center than in the general population in Japan (unpublished observation). Therefore, we speculate that precancerous lesions with mutations of the genes tested might have been present in the colorectal epithelium of some of these healthy volunteers. We think that a prospective randomized study would be needed to determine the actual specificity of our method in a real screening population and to verify its clinical usefulness.

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Address requests for reprints to: Yasuhiro Matsumura, MD, PhD, National Cancer Center Research Institute East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. e-mail: yhmatsum@east.ncc.go.jp; fax: (81) 4-7134-6866.

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Safety of Laparoscopic Intracorporeal Rectal Transection With Double-Stapling Technique Anastomosis

Seiichiro Yamamoto, MD, PhD, Shin Fujita, MD, PhD, Takayuki Akasu, MD, PhD, and Yoshihiro Moriya, MD, PhD

Abstract: To assess the feasibility and analyze the short-term outcomes of laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis, a review was performed of a prospective registry of 67 patients who underwent laparoscopic sigmoidectomy and anterior resection with intracorporeal rectal transection and double-stapling technique anastomosis between July 2001 and January 2004. Patients were divided into 3 groups: sigmoid colon/rectosigmoid carcinoma, upper rectal carcinoma, and middle/lower rectal carcinoma. A comparison was made of the short-term outcomes among the groups. The number of cartridges required in bowel transection was significantly increased in patients with middle/lower rectal carcinoma, and significant differences were observed in the length of the first stapler cartridge fired for rectal transection. Furthermore, mean operative time and blood loss were also significantly greater in the middle/lower rectum group; however, complication rates and postoperative course were similar among the 3 groups. No anastomotic leakage was observed. Laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis can be performed safely without increased morbidity or mortality.

Key Words: laparoscopic low anterior resection, rectal transection, double-stapling technique, complication, colorectal carcinoma

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More than 10 years have passed since the first report of laparoscopic colectomy by Jacobs et al[1] in 1991. With regard to long-term oncological safety, which is the most important concern for laparoscopic surgery (LS) for malignancies, there have been no reports indicating that LS is inferior to conventional open surgery (OS).[2–5] On the other hand, because LS requires surgical techniques that are different from those of OS, even a surgeon with considerable experience in OS cannot readily perform LS.

In particular, LS for rectal carcinoma is very difficult surgery from a technical standpoint, and consequently many randomized, controlled trials have excluded patients with middle/lower rectal carcinoma. This is because of concerns over the safety of the procedure, ie, the risk of complications associated with the laparoscopic procedure and the risk of tumor cell spillage because of traumatic manipulation of the tumor. Previous studies have reported an anastomotic leakage rate of 5.7% to 21% in patients who underwent laparoscopic low anterior resection (Lap-LAR), and some authors have recommended a covering ileostomy as a routine in Lap-LAR cases.[6–12] It remains uncertain which cases of rectal carcinoma are appropriate for laparoscopic surgery.

Since our first laparoscopic colectomy for colorectal carcinoma in 1993, approximately 280 laparoscopic resections for colorectal malignancies have been carried out at our institution. Most of our early experience was confined to early (Tis or T1) colorectal cancer located at the cecum, ascending colon, sigmoid colon, or rectosigmoid due to technical problems and concerns regarding port site and peritoneal recurrences. In June 2001, we unified our surgical and postoperative management procedures and expanded our indications for laparoscopic colectomy to include advanced colorectal cancers (ie, T2 lesions and beyond) located anywhere in the colon and/or rectum.

In 1980, Knight and Griffen[13] described the double-stapling technique (DST), which offered great advantages in that it permitted low rectal anastomoses to be performed with great ease. The aim of the present study was to assess the feasibility and analyze the short-term outcomes of laparoscopic intracorporeal rectal transection with DST anastomosis, one of the most demanding and stressful techniques in laparoscopic colorectal surgery, in selected patients with sigmoid colon and rectal carcinoma, who all underwent LS at our hospital after June 2001.

PATIENTS AND METHODS

Patients

At the Division of Colorectal Surgery of the National Cancer Center Hospital in Japan, 156 nonrandomized consecutive patients underwent laparoscopic colorectal resections between July 2001 and January 2004. During this period, 67 patients were treated by laparoscopic sigmoidectomy and anterior resection with DST anastomosis. Because the safety of LS in cancer patients remains to be established, candidates for laparoscopic surgery were patients who were preoperatively diagnosed with T1 or T2. Additionally, LS cases also included patients with sigmoid colon or upper rectal carcinoma who were preoperatively diagnosed with T3 but wished to undergo LS, as well as those for which palliative resection was

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From the Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan.
Reprints: Seiichiro Yamamoto, MD, PhD, Division of Colorectal Surgery, National Cancer Center Hospital 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan (e-mail: seyamamo@ncc.go.jp).

considered necessary. Exclusion criteria for LS were tumors larger than 6 cm, a history of extensive adhesions, severe obesity (body mass index >32 kg/m^2), intestinal obstruction, and refusal to undergo LS. The preoperative workup consisted of a clinical investigation, barium enema, total colonoscopy, chest x-ray, abdominal ultrasonography, and computed tomography.

LS was contraindicated for patients with preoperative diagnoses of T3 and T4 tumors in the middle and lower rectum because, with the current instrumentation, it was difficult to perform laparoscopic procedures without grasping and manipulating the bowel or mesorectum near the tumor; our concern was that this would result in accidental tumor spillage. Furthermore, lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with T3 and T4 lower rectal carcinoma in Japan, and lateral lymph node dissection by laparoscopy is still an unexplored frontier.[14–16] As a result, some patients were found to have T3 cancer only after histopathological examination of the surgical specimens. Preoperative or postoperative radiation therapy was not performed in this series because of the low local recurrence rate in patients with T1–T3 lower rectal carcinoma without preoperative radiation.[14,16]

Patients were divided into 3 groups: sigmoid colon/rectosigmoid carcinoma, upper rectal carcinoma, and middle/lower rectal carcinoma. For the patients with rectal carcinoma, a primary rectal carcinoma was defined according to its distance from the anal verge as determined by colonoscopy. The tumors were grouped into lower rectum (0–7 cm), middle rectum (7.1–12 cm), and upper rectum (12.1–17 cm). We combined patients with middle and lower rectal carcinoma as a group because laparoscopic techniques for rectal transection and DST anastomosis were almost same: anastomosis located below peritoneal reflection.[7] Patients with lesions located within 2 cm of the dentate line who underwent laparoscopic intersphincteric rectal resection and hand-sewn coloanal anastomosis were excluded from the present study. This surgical technique has been described previously.[17] Conversion to open surgery was defined as any incision greater than 7 cm, excluding cases in which the incision was enlarged due to a large specimen size that could not be removed with a 7-cm incision.

Laparoscopic Technique

Laparoscopic resection techniques have previously been described, with minor modifications.[7,17] Initial port placement was performed using the open technique, and pneumoperitoneum was induced using carbon dioxide. Two 5-mm ports were then inserted in the left lower midabdominal and the left lower quadrant regions, and 2 other 12-mm ports were inserted in the mid-lower and the right midabdominal regions under laparoscopic guidance.

The left colon was initially mobilized laterally to medially until the left ureter and superior hypogastric nerve plexus were identified. The mobilization of splenic flexure was performed if necessary. Usually, Japanese patients have a long sigmoid colon, and if the surgeon preserves 1 or 2 arcades of marginal vessels of sigmoid colon by division of sigmoidal arteries between superior rectal artery and marginal vessels, mobilization of splenic flexure becomes unnecessary; thus, splenic mobilization was performed in only about 20% of our patients. Then, a window was made between the mesocolon containing the arch of the inferior mesenteric vessels and the superior hypogastric nerve plexus, starting at the bifurcation, with support from an assistant holding the sigmoid mesocolon ventrally under traction and to the left using a 5-mm bowel grasper through the left lower quadrant port. After the dissection, proceeding to the origin of inferior mesenteric artery, taking care not to injure the superior hypogastric nerve plexus and the roots of the sympathetic nerves, intracorporeal high ligation of the inferior mesenteric artery was performed. After cutting the inferior mesenteric vein and left colic artery, mobilization of the rectum and mesorectum was performed. The avascular plane between the intact mesorectum anteriorly and the superior hypogastric nerve plexus, right and left hypogastric nerves, and Waldeyer fascia posteriorly was entered by sharp dissection and extended down to the level of the levator muscle for middle and lower rectal carcinomas, taking care to protect the pelvic nerves. For proximal sigmoid colon carcinoma, the mesentery at the promontory was excised routinely using ultrasonic shears (laparoscopic coagulating shears [LCS], Ethicon Endo-Surgery Inc, Cincinnati, OH) or an endolinear stapler (Endo GIA Universal, Tyco Healthcare, Auto Suture Co, US Surgical Corp, Norwalk, CT). For rectosigmoidal and upper rectal lesions, mesorectal tissue extending down to 5 cm below the tumor was excised routinely using LCS. Middle and lower rectal tumors were treated by total mesorectal excision. Immediately before rectal transection, laparoscopic rectal clamping was performed just above the anticipated point of rectal transection, using a bowel clamping device (Fig. 1) introduced through the 12-mm mid-lower port. A distinct advantage of this device is that the bowel clamp at the head of the device can be easily bent intraabdominally without reducing the grasping strength. Rectal washout was performed routinely using 1000 mL of a 5% povidone-iodine solution. Rectal transection was then performed by a multiple-firing technique, using Endo GIA Universal staples, introduced through the 12-mm right midabdominal port.[18] If the rectal transection was not completed after the first cartridge, the stapler line for the second cartridge was carefully positioned on the anal side stapler line of the first cartridge. The third and fourth firings were performed in the same way. A 4- to 5-cm incision was then made over the mid-lower 12-mm port site, and the bowel was exteriorized under wound protection and divided with appropriate proximal clearance. After inserting the anvil head of the circular stapler into the end of the proximal colon, the proximal colon was internalized and the incision was closed. Intracorporeal anastomosis under a laparoscopic view was performed by means of the DST, using a circular stapler (ECS 29 or 33 mm, Ethicon Endo-Surgery Inc). After the insertion of the body of the circular stapler into the anus, the puncturing cone was pushed through the midpoint of the linear staple line. In patients in whom 2 or more linear stapler cartridges were used for rectal transection, the puncturing cone was pushed near the crossing point of the first and second stapler lines.

The anastomotic air leakage test was performed if the "doughnuts" were incomplete. Patients with a low anastomosis within 1 cm from the dentate line and incomplete doughnuts

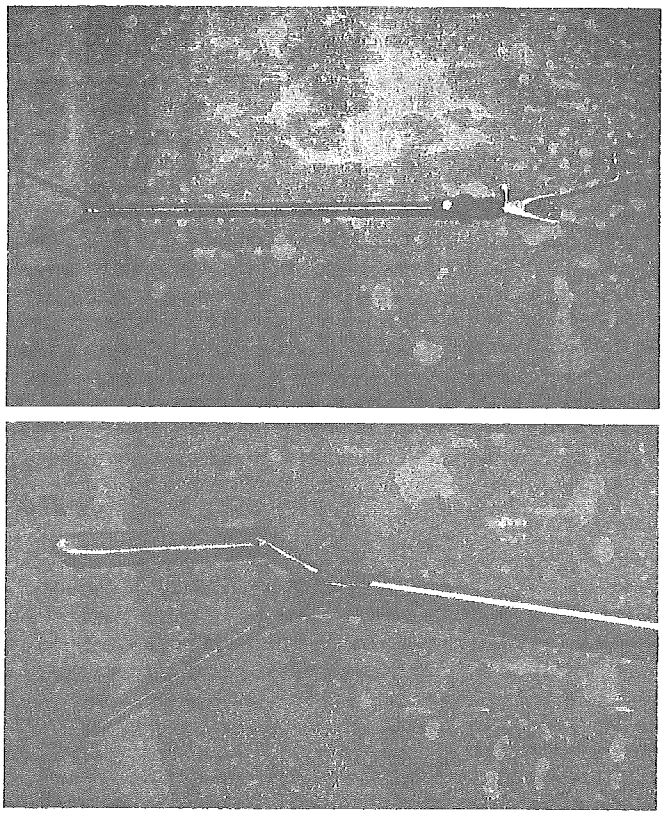

FIGURE 1. Bowel clamping device. A distinct advantage of this device is that the bowel clamp at the head of the device can be easily bent intraabdominally without reducing the grasping strength.

underwent a covering ileostomy. However, the decision to perform a protective ileostomy in this series was based on much looser criteria than those used in OS to avoid major anastomosis complications that could lead to a permanent stoma or a fatal outcome, especially in the early LS cases of lower rectal carcinoma.

Study Parameters

The parameters analyzed included gender, age, body mass index, prior abdominal surgery, operative time, operative blood loss, number of stapler cartridges fired and the length of the first stapler cartridge for rectal transection, conversion rate, days to resume diet, length of postoperative hospital stay, and both intraoperative and postoperative complications within 30 days of surgery. Pathologic staging was performed according to Duke's stage.

Statistical Analysis

Statistical analysis was performed using the χ^2 test, Kruskal-Wallis test with Bonferroni correction, and repeated-measure analysis of variance (ANOVA) with the Scheffe method when appropriate. A P value of <0.05 was considered significant.

RESULTS

The patient demographics are summarized in Table 1. No significant differences were observed in baseline characteristics among the 3 groups. In the middle/lower rectum group, anastomosis was performed <3 cm from the dentate line in 7 patients and >3 cm but below the peritoneal reflection in 3 patients. We performed an anastomotic air leakage test in 2 patients with lower rectal carcinoma and did not find any sign of air leakage; however, both patients underwent a protective ileostomy. Overall, a protective ileostomy was required in 4 patients, and a transverse coloplasty pouch was created in 1 patient.

The number of patients in relation to the number of stapler cartridges used for rectal transection in each group is shown in Table 2. The number of cartridges required during bowel transection was significantly increased in patients with middle/lower rectal carcinomas compared with the other groups. Similarly, significant differences were observed in the length of the first stapler cartridge fired for rectal transection (Table 3). In patients with middle/lower rectal carcinomas, the length of the first stapler cartridge was 45 or 30 mm, and it was 45 or 60 mm for proximal lesions.

Operative and postoperative results are shown in Table 4. Mean operative time and blood loss were significantly greater in the middle/lower rectum group. All the operations were completed laparoscopically. We did not experience any accidental intestinal perforations at or near the tumor site. Liquid and solid food was started at a median of 1 and 3 postoperative days in all groups. The median length of postoperative hospitalization was 8–9 days. No significant differences were observed in the postoperative course among the 3 groups. All patients were discharged home.

The postoperative complications are listed in Table 5. There were no perioperative mortality and no anastomotic leakage. Reoperation of a laparoscopic division of an adhesive band for a postoperative small bowel obstruction was necessary in 1 patient with sigmoid colon carcinoma. No significant differences were observed in complication rates among the 3 groups.

TABLE 1. Patient's Characteristics*

	Sigmoid Colon/ Rectosigmoid	Upper Rectum	Middle/Lower Rectum
No. of patients	36	21	10
Sex ratio (male:female)	22:14	10:11	8:2
Age (y)	59 (30–79)	59 (37–73)	60 (47–76)
Body mass index (kg/m^2)	23.5 (18.9–29.0)	24.1 (17.5–32.4)	23.8 (19.5–26.4)
Prior abdominal surgery (%)	6 (17)	5 (24)	5 (50)
Duke's stage			
A	27	16	7
B	1	0	0
C	7	3	3
D	1	2	0

*Values are means (range), $P > 0.05$.

TABLE 2. Number of Patients in Relation to the Number of Stapler Cartridges Fired for Rectal Transection*

No. of Stapler Cartridges Fired	Sigmoid Colon/Rectosigmoid†	Upper Rectum†	Middle/Lower Rectum
1	25	8	0
2	9	12	2
3	2	1	6
4	0	0	2

*$P < 0.01$ between groups, Kruskal-Wallis test.
†$P < 0.01$ versus middle, lower rectum/Boneferroni test.

DISCUSSION

In the present study, short-term outcomes were compared among different tumor sites in patients who underwent laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis. The closer the tumor site was to the anus, the more the number of stapler cartridges needed for rectal transection increased and the use of a longer Endo GIA Universal stapler cartridge was significantly restricted, suggesting that rectal transection for Lap-LAR in patients with middle/lower rectal carcinomas may be a difficult and stressful procedure. In the present study, however, the complication rate did not increase despite lower anastomotic sites. With thorough and careful intracorporeal rectal transection and DST anastomosis, the safety of Lap-LAR may be established.

Minimum invasiveness is often noted as one of the merits of LS in comparison with OS for colorectal cancer.[19–23] But even recently, some studies have reported that minimal or no short-term benefits were found with LS compared with standard OS.[24–26] Reviewing these reports raises a question about the conversion rate. Even granting that LS has a lower surgical invasiveness than OS, there is a possibility that the treatment outcomes of LS will be contaminated by the treatment outcomes of OS, when the conversion cases are included in the LS group, based on the intention-to-treat principle. In the study by Weeks et al,[26] who reported a conversion rate of 25%, LS showed only minimal short-term quality-of-life benefits compared with OS in an intention-to-treat analysis, probably due to the high conversion rate. Moreover, they pointed out that patients assigned to laparoscopy-assisted colectomy who required intraoperative conversion to open colectomy had slightly poorer quality-of-life outcomes than patients who successfully underwent minimally invasive resection, and that the length of postoperative hospital stay in the LS group requiring conversion was longer than that in patients assigned to OS (7.4 vs. 6.4 days), although statistical analysis was not performed regarding these points. If the conversion patients did not show a worse outcome than those undergoing OS, patients who might benefit from LS should be considered as candidates for LS. Further studies are necessary to evaluate postoperative and oncological outcomes of patients assigned to laparoscopy-assisted colectomy who then require intraoperative conversion.

The results of the current study suggested that laparoscopic approaches to middle/lower rectal carcinoma do not compromise early postoperative recovery, such as days to oral feeding and length of hospitalization. Previous studies reported an anastomotic leakage rate of 5.7% to 21% in patients undergoing Lap-LAR.[6–12] Some authors have recommended a covering ileostomy as a routine step in Lap-LAR.[6,10,27] At present, patients with a preoperative diagnosis of T1–T2, middle/lower rectal carcinoma are required to decide whether they prefer to undergo OS or LS, after being given full information at our institution.

TABLE 3. Length of the First Stapler Cartridge Fired for Rectal Transection*

Length of the First Stapler Cartridge (mm)	Sigmoid Colon/Rectosigmoid†	Upper Rectum†	Middle/Lower Rectum
60	34	16	0
45	2	5	7
30	0	0	3

*$P < 0.01$ between groups, Kruskal-Wallis test.
†$P < 0.01$ versus middle/lower rectum, Boneferroni test.

TABLE 4. Operative and Postoperative Results

	Sigmoid Colon/Rectosigmoid	Upper Rectum	Middle/Lower Rectum
Operative time,* min (range)	221 (135–348)†	244 (190–328)‡	315 (190–392)
Blood loss,* mL (range)	29 (6–161)†	24 (10–198)†	124 (17–265)
Conversion	0	0	0
Liquid intake, d (range)	1 (1–4)	1 (1–3)	1 (1)
Solid food, d (range)	3 (2–5)	3 (3–4)	3 (2–4)
Hospital stay, d (range)	8 (7–12)	8 (7–11)	9 (7–17)

*$P < 0.01$ between groups, repeated-measure analysis of variance.
†$P < 0.01$ versus middle/lower rectum, Scheffe test.
‡$P < 0.05$ middle/lower rectum, Scheffe test.

TABLE 5. Morbidity and Mortality*

	Sigmoid Colon/ Rectosigmoid	Upper-Rectum	Middle/Lower Rectum
Mortality	0	0	0
Morbidity			
Wound sepsis	2	1	0
Bowel obstruction	1	0	1
Urinary tract infection	1	0	0
Abscess	0	0	1
Neurogenic bladder	0	1	0
Anastomotic leakage	0	0	0
Total	4	2	2

*$P > 0.05$.

In this study, the authors evaluated the safety of laparoscopic rectal transection using an endolinear stapler, which is one of the most technically difficult procedures in Lap-LAR. To date, we have not observed serious complications, such as anastomotic leakage. However, this surgical procedure remains technically difficult. We consider that this method should not be attempted if it is not performed by a laparoscopic surgical team with sufficient experience in LS. Regarding a surgical procedure that can be placed between OS and Lap-LAR, Vithiananthan et al[28] reported a hybrid method. In their procedure, they mobilized the left-sided colon and completed high ligation of the inferior mesenteric vessels with the use of the pneumoperitoneum, and then, from the inferior midline incision measuring 8 cm or longer, they performed rectal mobilization, mesorectal division, rectal transection, and anastomosis by DST using the OS tools. They noted that the mean incision length was 11.1 cm, which is longer than in Lap-LAR but shorter than in OS and that the patients treated with this method showed a significantly faster postoperative recovery than those treated with OS. Hand-assisted laparoscopic surgery may also be another treatment option.[29] However, compared with the standard Lap-LAR technique evaluated in this study, both of these methods may need a larger incision. With the surgeon's proficiency in the surgical procedure and the improvement in and development of instruments, the safety of standard Lap-LAR will probably be established; however, it is important to remember that this surgical technique cannot be employed at an early stage of the learning curve of laparoscopic surgery.

In conclusion, the findings of the present study demonstrate that laparoscopic intracorporeal rectal transection with DST anastomosis can be performed safely without increased morbidity or mortality. Even at present, there are few prospective, randomized trials investigating the short-term and oncological outcomes in patients with middle/lower rectal carcinoma, perhaps mainly because Lap-LAR has not been widely performed compared with LS for colon/upper rectal carcinoma due to the technical difficulties. The radical resection of middle/lower rectal cancers is a procedure that requires advanced technical skills in OS, to say nothing of Lap-LAR; however, we believe that use of Lap-LAR for middle/lower rectal carcinoma will expand with improvements in technology and surgeons' experience in the near future.

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Total Pelvic Exenteration with Distal Sacrectomy for Fixed Recurrent Rectal Cancer

Yoshihiro Moriya, MD, PhD*, Takayuki Akasu, MD, Shin Fujita, MD, PhD, Seiichirou Yamamoto, MD

Department of Surgery, National Cancer Center Hospital, 1-1 Tsukiji 5-chome, Chuo-Ku, Tokyo 104-0045, Japan

Four percent to 33% of patients with rectal cancer develop locoregional relapse after undergoing radical surgery with curative intent. Without treatment, the mean survival time for patients with local recurrence is only approximately 8 months, an associated severe symptomatic disease—especially pain—occurs, and their quality of life becomes remarkably deteriorated, probably with a miserable prognosis [1–4].

For cases with locally recurrent rectal cancer (LRRC), external beam radiotherapy, intraoperative radiotherapy, chemotherapies, and surgical treatments have been used singly or as part of a multimodality approach over the last several decades, resulting in certain outcomes that are not yet satisfactory [5–21]. For the purpose of attaining thorough margin-free resection, what we have been performing actively as our standard curative approach for fixed recurrent tumor (FRT) is radical resection with removal of affected neighboring organs and pelvic walls, including the sacrum, as originally reported by Wanebo and Marcove [6]. This article describes the surgical indications, contraindications, surgical techniques, oncologic outcomes, and complications of total pelvic exenteration with distal sacrectomy (TPES).

Patterns of growth in the pelvis

By cause and growth pattern of local recurrence, LRRC can be classified into three main categories.

* Corresponding author.
E-mail address: ymoriya@ncc.go.jp (Y. Moriya).

Anastomotic recurrence and perianastomotic recurrence

These suture line recurrences after low anterior resection are caused by implantation of cancer cells into the stump of anastomosis or insufficient resection of the rectal wall or mesorectum (Fig. 1). In the case of extramural invasion, however, it is difficult to distinguish between these two recurrences. When there is no extramural invasion or neighboring organ invasion, the basic surgical procedure is abdominoperineal resection (APR).

Perineal recurrence

Perineal recurrence is a recurrence that occurs after APR near the pelvic floor or perineal wound. From its early stage, perineal recurrence invades the coccyx, gluteal maximus muscle, or pelvic wall. Surgical margin-free resection seldom can be obtained by local excision alone. Many patients need resection of the pelvic wall or intrapelvic organs.

Pelvic recurrence

By occupied site, pelvic recurrence (Fig. 2) can be subdivided into anterior, lateral, and dorsal recurrences. Anterior pelvic recurrence is an LRRC that invades the anterior organs (ie, urogenital organs). For resecting this recurrent tumor, the basic surgical procedure is total pelvic exenteration (TPE). In women, if there is no obvious bladder invasion, it is possible to preserve urinary organs. This recurrence frequently is caused by insufficient resection for T4 rectal cancer. Lateral pelvic recurrence occurs because of lateral lymph node metastasis after total mesorectal excision or insufficient lateral node dissection. It begins to infiltrate the pelvic wall in its early stage. Dorsal pelvic recurrence is presacral extramural recurrence after APR or low

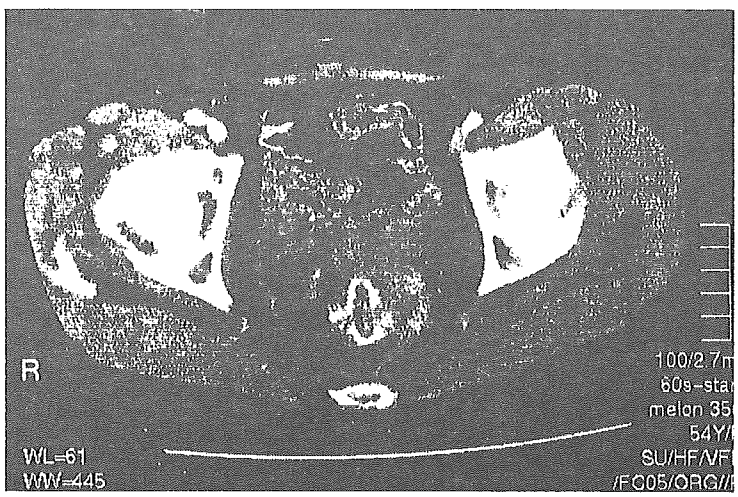

Fig. 1. Perianastomotic recurrence. A 54-year-old female patient underwent TPES for her FRT with 556 mL blood loss and no complication. At initial surgery 4 years ago, she received low anterior resection with D3 lymph node dissection and postoperative 60 Gy radiotherapy.

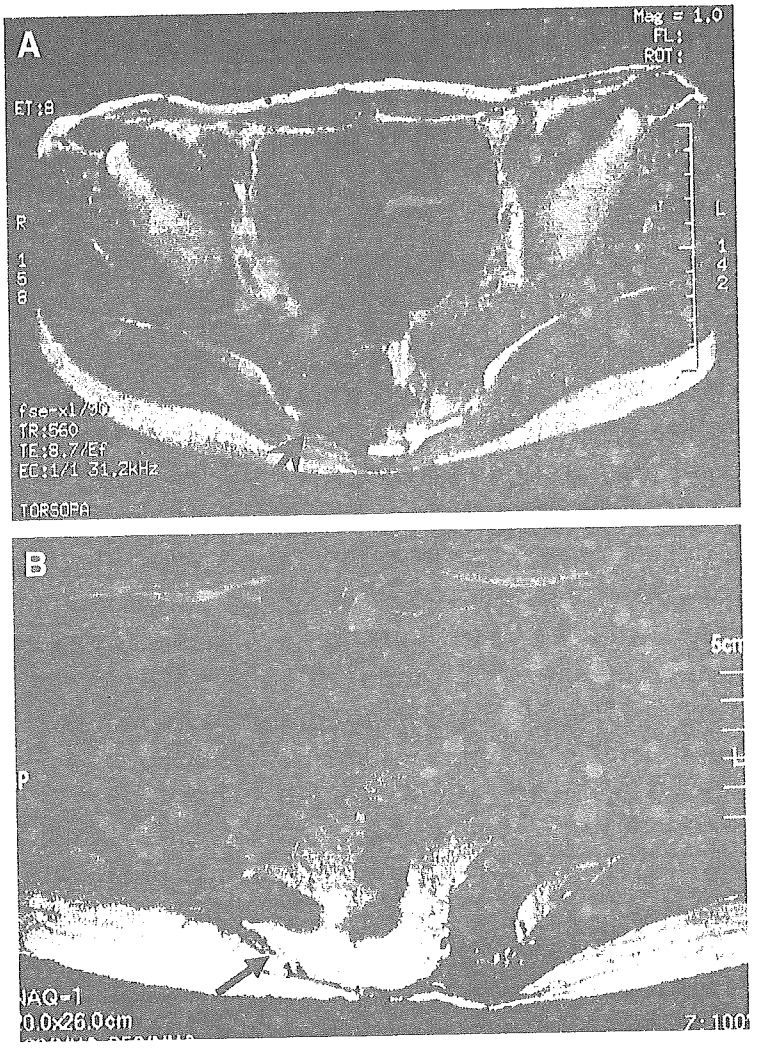

Fig. 2. (*A*) Dorsolateral pelvic recurrence with sacral bone invasion. A 47-year-old male patient underwent TPES for his FRT (*arrow*) with 673 mL blood loss and no complication. At initial surgery 1.5 years ago, he received low anterior resection. (*B*) Postoperative MRI. The patient is alive without re-recurrence 4 years after TPES.

anterior resection that invades the pelvic wall. It forms itself into FRT from its early stage. The cause of this recurrence may be extramesenteric lymphatic spread, insufficient resection of the mesorectum, or a cut into the mesorectum during operation. This pattern of recurrence is common patterns.

Why total pelvic exenteration with distal sacrectomy is the standard surgery for fixed recurrent tumor

Therapeutic policies for LRRC vary remarkably. The probable reasons for this are as follows: (1) there are various LRRCs, ranging from mobile recurrences to huge masses that occupy the pelvis, (2) an inappropriate surgical intervention may cause an iatrogenic cancer spread, leading to impaired quality of life, and (3) although treatments other than complete resection may not bring cure, the invasiveness of surgeries such as TPES is

considered excessive. In non-fixed recurrent tumors, complete resection can be achieved more often with limited surgery, such as APR or low anterior resection, and the outcomes are relatively favorable. LRRC grows within the narrow pelvis, and when the tumor size becomes larger to some extent, it can invade the pelvic wall easily and appear in the form of FRT. A challenge for the surgeon is the surgical treatment for FRTs with lateral or dorsal involvement, which comprises a larger percentage.

Such fixation is infrequently confined to one site and is of small range; many of those cases show fixations to the components surrounding the LRRC (eg, bony pelvis, including sacrum and coccyges; non-bony pelvis, including coccygeus muscle, piriform muscle, internal iliac vessels, inferior hypogastric plexus, sacral nerve plexus, obturator internus muscle, and sacrospinous and sacrotuberous ligaments; and residual anterior organs in the pelvis). Their anatomic planes are distorted, and it is difficult to determine and hold uninvolved margins during resection. For FRT cases, composite resection is inevitably required to encompass potentially involved pelvic walls, especially the distal sacrum. Only this strategy enables the R0 extirpation en bloc. Especially after APR, the LRRC grows while being sandwiched between the anterior organs and sacrum. Wanebo and Marcove [6] tackled this difficult problem using the new technique of abdominosacral resection, followed by several surgeons in 1980s [8,9,10,12].

Techniques to preserve the anterior organs and inferior hypogastric plexus for surgical treatment of FRT have been reported [16]. Those approaches, however, are likely to reduce local radicality, because the anatomic pathway around the autonomic nerve plexuses and ureter disappears and is replaced by scar tissue caused by initial surgery, especially after extended surgery. FRT in the deep pelvis also is often fixed more extensively than expected before surgery, which also justifies our experience-based strategy that TPES is positioned as the standard surgery for FRT. This technique is considered to be demanding and formidable because of high rates of mortality and morbidity [6,12,13,19]; consequently, combination of limited resection and intraoperative radiotherapy is likely to become standard in the treatment of FRT [17,22–29]. Whether an emphasis is placed on composite resection or multimodality treatment, surgeons have the same view that the key treatment to obtain local control and survival benefit is R0 surgery [22,28–31]. Is it really possible to carry out R0 resection for FRT by conventional surgery? Having been able to ensure R0 resection for FRT and develop secure surgical techniques, we consider that there are no therapies superior to TPES in treating FRT.

Evaluation by imaging and patient selection

Once the diagnosis of LRRC is made, detailed study should be conducted in terms of surgical indication from two aspects: (1) whether distance metastasis

is present and (2) to what extent the tumor spreads within the pelvis. Extrapelvic disease is searched for by the whole body CT scan. MRI and F-18-fluorodeoxy glucose position emission tomography (FDG-PET) are also useful in detecting extrapelvic disease and distinguishing between recurrent disease and scar tissue. CT, MRI, and FDG-PET are useful in distinguishing between solitary and multifocal recurrences in the pelvis and between anterior organ involvement and dorsolateral pelvic wall involvement.

We investigated a total of 196 consecutive patients who underwent laparotomy to remove LRRC between 1983 and 2003. The study excluded patients whose recurrent rectal cancer developed after local excision. We performed a limited surgery, such as APR, in 62 patients, TPE in 41, and TPES in 69. The remaining 24 patients had unresectable LRRC. Clinical and pathologic characteristics of 69 patients are listed in Table 1.

Patients with documented distant metastasis are not candidates for surgical treatment, because the curative potential is low and their life expectancy is not long enough to evaluate treatment outcome. With regard to surgical indication, we conducted TPES for FRT localized in the pelvis. Locally unresectable diseases include tumors that grow into sciatic notch,

Table 1
Clinical and pathologic characteristics of 69 patients

Characteristics	Number
Median age (range) (y)	57 (29–73)
Sex	
Male	55
Female	14
Body mass index (range)	22.9 (15.0–28.7)
Median time to local recurrence (range) (mo)	23 (7–118)
Liver metastasis	
No	65
Yes	5
Initial surgery	
Sphincter-preserving surgery; SPS	33
Abdominoperineal resection; APR	36
Radiotherapy for primary rectal cancer	
Yes	4
No	65
Radiotherapy for local recurrence before re-resection	
Yes	32 (median, 50 Gy; range, 30–80 Gy)
No	37
Dukes classification for primary growth	
A	4
B	18
C	47
Histologic type	
Well-differentiated adenocarcinoma	26
Moderately	34
Poorly	9

encase the external iliac vessels, extend to the sacral promontory, obstruct the bilateral ureters, and cause leg edema secondary to lymphatic or venous obstruction [30,31]. For patients with one or two liver metastases amenable to surgical resection, however, concomitant hepatectomy with surgical treatment of LRRC may be warranted. Lung metastasis and other extrapelvic diseases are excluded from surgical indications.

Surgical technique

TPE for primary pelvic malignancy is performed by first dividing loose connective tissues, such as the Retzius, retrorectal, and obturator spaces, and then dissecting along the parietal pelvic fascia. In recurrent cancer cases, however, those spaces disappear and are replaced by dense scar tissue. Because of this condition, TPES for FRT is a challenging procedure. The operation is performed in the following order.

Abdominal phase

The patient is placed in the lithotomy position. After detaching adhesions caused by initial surgery, the surgeon confirms the localization of the recurrent tumor within the pelvis and the absence of extrapelvic diseases and then makes a final decision to proceed to TPES. First, the Retzius space is opened. The endopelvic fascia and pubo-prostatic ligaments can be identified bilaterally and divided using electric cautery to expose the levator ani muscle. The dorsal vein complex together with the divided endopelvic fascia is bunched with the forceps and doubly tied and divided.

Next, the level of sacral amputation is determined. The anterior area from the aortic bifurcation to the sacral promontory is exposed to enter the anterior surface of the sacrum. The dissection is made using electric cautery down to the distal sacrum, at which point sacral amputation is planned, as is resection of the thickened Waldeyer's fascia with the presacral venous plexuses and scar tissue. During this process, bleeding occurs more or less; however, hemostasis can be obtained using combination of electric cautery and gauze pack. The area from the common iliac artery to the bifurcation between the internal and external iliac arteries is exposed. During dissection of the obturator space while preserving the obturator nerve, components of the sacral nerve plexus, such as the lumbosacral nerve and S1 and S2 sacral nerves, can be identified. Marking the S2 sacral nerve with a rubber loop ensures recognition of sacral nerves during sacrectomy (Fig. 3).

The next step is resection of the internal iliac vessels. The way to manipulate the internal iliac vessels is as follows. First, the trunk of the internal iliac artery is doubly tied and divided at the distal portion of the branching of the superior gluteal artery. Second, several branches that perforate the pelvic wall are divided. Finally, the trunk of the internal iliac vein is doubly tied and divided. Blood loss during TPES mostly occurs from

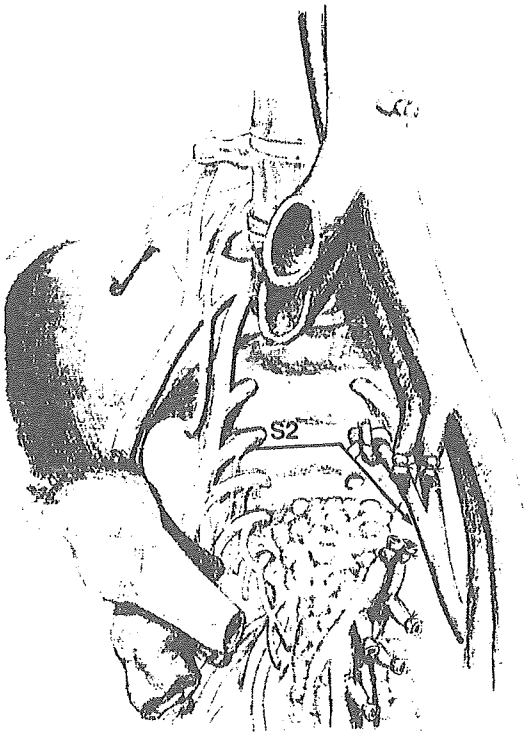

Fig. 3. Line of sacrectomy and marked second sacral nerve.

the venous plexus [31]. By taking the appropriate steps to avoid congestion of the venous plexus at the earliest possible opportunity, the operation can be performed with a minimum amount of blood loss from the venous plexus. Resection of the internal iliac veins is the most important part of this operation, and it requires advanced technical skills and careful maneuvers. FRT extends along the internal iliac vessels more frequently than the primary rectal cancer [32]; bilateral resection of the internal iliac vessels is one of the pivotal steps in TPES. Combined resection of the internal iliac vessels during the abdominal phase greatly contributes to reducing blood loss during sacrectomy.

Perineal phase

Incision of the perineal skin conforms to APR. The levator ani muscle is divided at its attachment and a connection is made through to the pelvic cavity. If the perineal phase is performed after the venous plexus is resected, a considerable amount of blood loss will occur from congested veins around the urogenital diaphragm. The perineal phase should occur before ligation of the trunk of the internal iliac veins so that the phase can be performed with less blood loss.

Sacral phase

The patient is placed in the prone position after temporary closure of abdominal wound. At that point, the padded operating frame for laminectomy