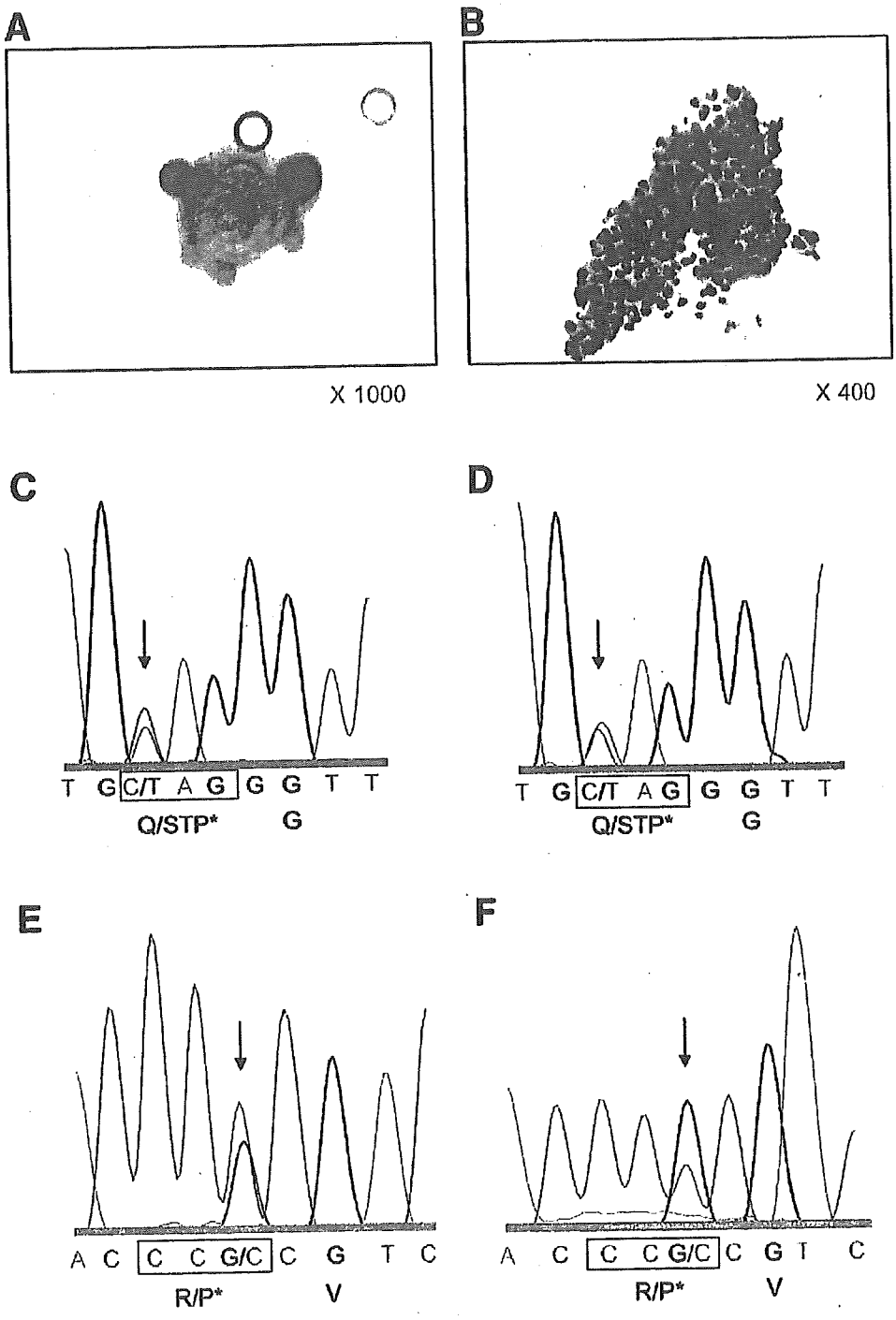

Figure 3. Cytology and DNA sequencing. Papanicolaou staining of colonocytes isolated from the feces of patients with colorectal cancer. (*A*) A patient with ascending colon cancer, Dukes' stage A. (*B*) A patient with rectal cancer, Dukes' stage C. Detection of mutations in tumor tissues and colonocytes 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.

References

1. The Editorial Board of the Cancer Statistics in Japan. Cancer statistics in Japan—2003. Available at: http://www.fpcr.or.jp. Accessed 2003.
2. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993;328:1365–1371.
3. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–1477.
4. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomized study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–1471.
5. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer

using the faecal occult blood test, hemoccult. BMJ 1998;317:559–565.
6. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology 2003;124:544–560.
7. Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, Snover DC, Schuman LM. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603–1607.
8. Sidransky D, Tokino T, Hamilton SR, Kinzler KW, Levin B, Frost P, Vogelstein B. Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. Science 1992; 256:102–105.
9. Hasegawa Y, Takeda S, Ichil S, Koizumi K, Maruyama M, Fujii A, Ohta H, Nakajima T, Okuda M, Baba S, et al. Detection of K-*ras* mutations in DNAs isolated from feces of patients with colorectal tumors by mutant-allele-specific amplification (MASA). Oncogene 1995;10:1441–1445.
10. Smith-Ravin J, England J, Talbot IC, Bodmer W. Detection of c-Ki-ras mutations in faecal samples from sporadic colorectal cancer patients. Gut 1995;36:81–86.
11. Eguchi S, Kohara N, Komuta K, Kanematsu T. Mutations of the p53 gene in the stool of patients with resectable colorectal cancer. Cancer 1996;77:1707–1710.
12. Nollau P, Moser C, Weinland G, Wagener C. Detection of K-*ras* mutations in stools of patients with colorectal cancer by mutant-enriched PCR. Int J Cancer 1996;66:332–336.
13. Ratto C, Flamini G, Sofo L, Nucera P, Ippoliti M, Curigliano G, Ferretti G, Sgambato A, Merico M, Doglietto GB, Cittadini A, Crucitti F. Detection of oncogene mutation from neoplastic colonic cells exfoliated in feces. Dis Colon Rectum 1996;39:1238–1244.
14. Deuter R, Muller O. Detection of APC mutations in stool DNA of patients with colorectal cancer by HD-PCR. Hum Mutat 1998;11: 84–89.
15. Ahlquist DA, Skoletsky JE, Boynton KA, Harrington JJ, Mahoney DW, Pierceall WE, Thibodeau SN, Shuber AP. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroenterology 2000;119:1219–1227.
16. Dong SM, Traverso G, Johnson C, Geng L, Favis R, Boynton K, Hibi K, Goodman SN, D'Allessio M, Paty P, Hamilton SR, Sidransky D, Barany F, Levin B, Shuber A, Kinzler KW, Vogelstein B, Jen J. Detecting colorectal cancer in stool with the use of multiple genetic targets. J Natl Cancer Inst 2001;93:858–865.
17. Rengucci C, Maiolo P, Saragoni L, Zoli W, Amadori D, Calistri D. Multiple detection of genetic alterations in tumors and stool. Clin Cancer Res 2001;7:590–593.
18. Traverso G, Shuber A, Olsson L, Levin B, Johnson C, Hamilton SR, Boynton K, Kinzler KW, Vogelstein B. Detection of proximal colorectal cancers through analysis of faecal DNA. Lancet 2002; 359:403–404.
19. Traverso G, Shuber A, Levin B, Johnson C, Olsson L, Schoetz DJ Jr, Hamilton SR, Boynton K, Kinzler KW, Vogelstein B. Detection of APC mutations in fecal DNA from patients with colorectal tumors. N Engl J Med 2002;346:311–320.
20. Boynton KA, Summerhayes IC, Ahlquist DA, Shuber AP. DNA integrity as a potential marker for stool-based detection of colorectal cancer. Clin Chem 2003;49:1058–1065.
21. Yamao T, Matsumura Y, Shimada Y, Moriya Y, Sugihara K, Akasu T, Fujita S, Kakizoe T. Abnormal expression of CD44 variants in the exfoliated cells in the feces of patients with colorectal cancer. Gastroenterology 1998;114:1196–1205.
22. Davies RJ, Freeman A, Morris LS, Bingham S, Dilworth S, Scott I, Laskey RA, Miller R, Coleman N. Analysis of minichromosome maintenance proteins as a novel method for detection of colorectal cancer in stool. Lancet 2002;359:1917–1919.
23. Winter MJ, Nagtegaal ID, van Krieken JH, Litvinov SV. The epithelial cell adhesion molecule (Ep-CAM) as a morphoregulatory molecule is a tool in surgical pathology. Am J Pathol 2003;163: 2139–2148.
24. Balzar M, Prins FA, Bakker HAM, Fleuren GJ, Warnaar SO, Litvinov SV. The structural analysis of adhesions mediated by Ep-CAM. Exp Cell Res 1999;246:108–121.
25. Salem RR, Wolf BC, Sears HF, Lavin PT, Ravikumar TS, DeCoste D, D'Emilia JC, Herlyn M, Schlom J, Gottlieb LS. Expression of colorectal carcinoma-associated antigens in colonic polyps. J Surg Res 1993;55:249–255.
26. Iyengar V, Albaugh GP, Lohani A, Nair PP. Human stools as a source of viable colonic epithelial cells. FASEB J 1991;5:2856–2859.
27. Davidson LA, Lupton JR, Miskovsky E, Fields AP, Chapkin RS. Quantification of human intestinal gene expression profiles using exfoliated colonocytes: a pilot study. Biomarkers 2003;8:51–61.
28. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal cancer screening in an average-risk population. N Engl J Med 2004;351:2704–2714.
29. Matsumura Y, Tarin D. Significance of CD44 gene products for cancer diagnosis and disease evaluation. Lancet 1992;340: 1053–1058.
30. Matsumura Y, Hanbury D, Smith J, Tarin D. Non-invasive detection of malignancy by identification of unusual CD44 gene activity in exfoliated cancer cells. BMJ 1994;308:619–624.

Received May 24, 2005. Accepted August 31, 2005.

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.

Supported in part by a grant for research on advanced medical technology from the Ministry of Health, Welfare, and Labor and a research and development project of the Industrial Science and Technology Program supported by the New Energy and Industrial Technology Development Organization (NEDO) of Japan.

ELSEVIER
SAUNDERS

Surg Oncol Clin N Am
14 (2005) 225–238

SURGICAL
ONCOLOGY CLINICS
OF NORTH AMERICA

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).

1055-3207/05/$ - see front matter
doi:10.1016/j.soc.2004.11.014 *surgonc.theclinics.com*

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

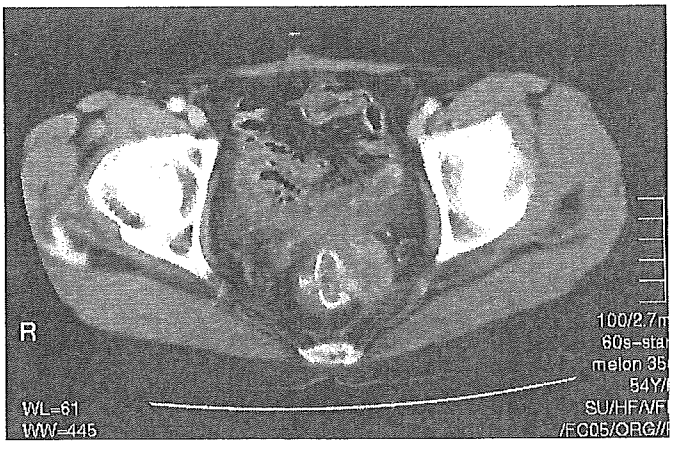

Fig. 1. Perianastomotic recurrence. A 54-year-old female patient underwent TPES for her FRT with 556 mL blood loss and no complication. At initial surgery 4 years ago, she received low anterior resection with D3 lymph node dissection and postoperative 60 Gy radiotherapy.

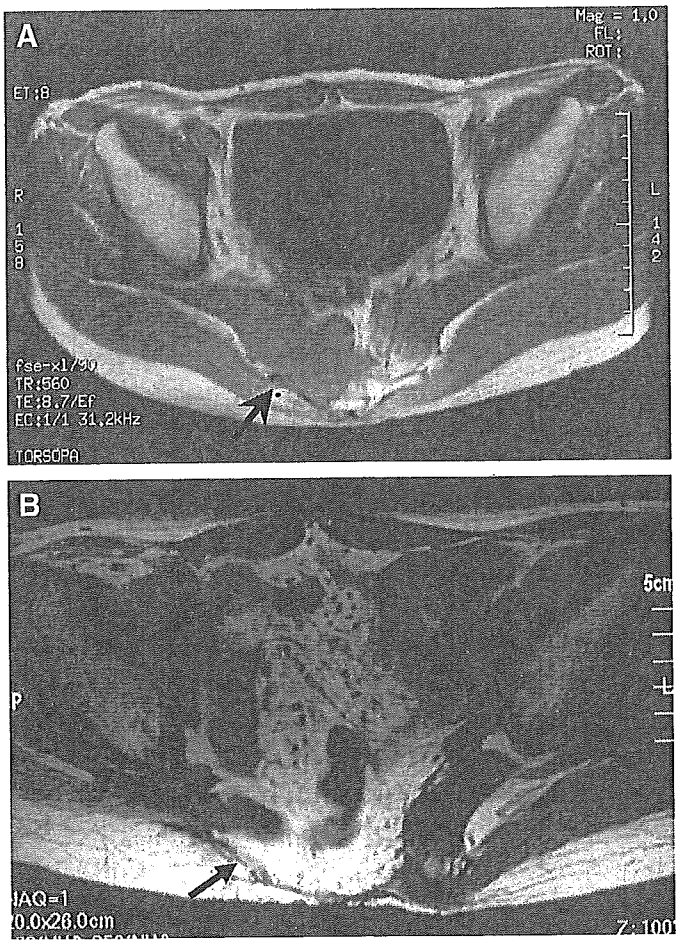

Fig. 2. (*A*) Dorsolateral pelvic recurrence with sacral bone invasion. A 47-year-old male patient underwent TPES for his FRT (*arrow*) with 673 mL blood loss and no complication. At initial surgery 1.5 years ago, he received low anterior resection. (*B*) Postoperative MRI. The patient is alive without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

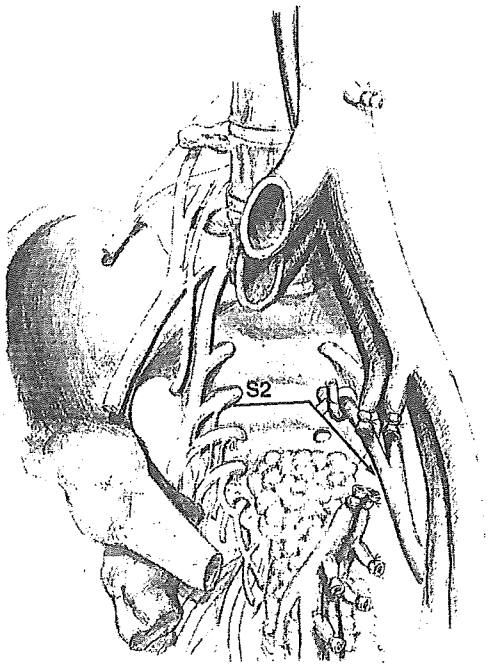

Fig. 3. Line of sacrectomy and marked second sacral nerve.

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

is used to prevent an increase in abdominal or vertebral venous pressure. Bleeding caused by the increase of vertebral venous pressure makes sacral amputation complicated. The median incision is made approximately 10 cm longer toward the head from the planned line of sacral amputation. The gluteus maximus muscle is detached from the sacrum so that the posterior surface of the sacrum can be exposed fully. The next step of this phase involves detaching the sacrotuberous and sacrospinous ligaments and piriform muscle that fix the sacrum. After dissecting these structures, the sacral nerve plexus also can be checked.

The surgeon inserts an index finger into the pelvic cavity from the lower edge of the sacroiliac joint and checks the dissected level of the anterior surface of the sacrum to determine the level of sacral amputation. The medial sacral crest is scraped, laminectomy is performed, and the root of the second sacral nerve is identified. The caudal end of the dura usually extends to around the lower edge of the S2. The dura, together with the cauda equine, is tied and divided. The surgeon performs sacral amputation using chisel and hammer at a stretch (Fig. 4). Hemostasis is performed quickly using electric cautery and bone wax. In men, after checking the stump of the urethra, the urethra is closed tightly to prevent transurethral infection. The origins of the gluteus maximus muscle, the subcutis, and the skin are closed tightly.

Urinary diversion, prevention of pelvic sepsis, and wound closure

The patient is placed in the lithotomy position. Reconstruction of the urinary tract using ileal conduit and colostomy is performed. Mobilization of the right colon from the cecum to the hepatic flexure enables construction of a high urostoma. After constructing the ileal conduit, an ileoileostomy

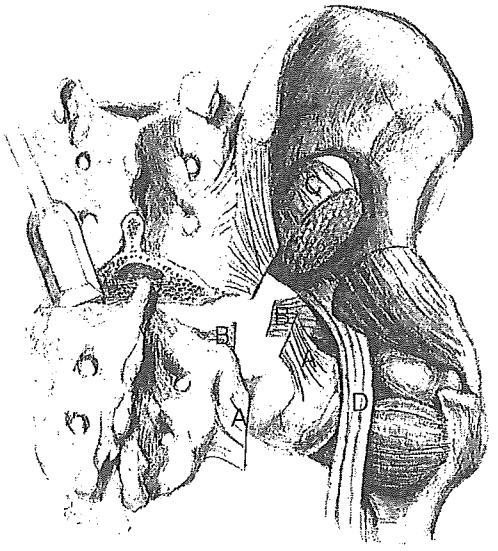

Fig. 4. Sacral amputation in prone position. (*A*) Sacrotuberous ligament. (*B*) Sacrospinous ligament. (*C*) Piriform muscle. (*D*) Sciatic nerve.

should be lifted up above the pelvic brim and fixed to the mesentery so that it will not fall in the pelvic cavity. This procedure is invariably required to prevent anastomotic leakage secondarily caused by pelvic sepsis, especially after radiotherapy. If the greater omentum is long enough with favorable blood flow, omentoplasty into the pelvic cavity should be performed. In patients who have recurrent tumor invading the perineal skin, it is necessary to combine a wide resection of the perineal skin. In such cases, reconstruction should be performed with a musculocutaneous flap [20,30]. It is appropriate that gastrostomy be performed before closing the abdomen, because enteroparalysis continues for a while after TPES. A thick drain is placed in the pelvis, and then the abdomen is closed.

Surgical invasiveness and oncologic outcomes after total pelvic exenteration with distal sacrectomy

Margins were microscopically negative in 57 patients (83%) and positive in 12. A comparison between two periods (1983–1992 and 1993–2003) showed a mean blood loss decrease from 4229 to 2102 mL ($P < 0.001$), with a favorable learning curve (Table 2). There was no difference in operative time and hospital stay. The most common level of sacral amputation was the S3 superior margin in 26 cases, followed by the S3 inferior margin and S2 inferior margin (Table 3). Overall mortality and complication rates were 3% and 58%, respectively. There was no hospital death in the latter period. The most frequent complication was sacral wound dehiscence in 51%, followed by pelvic sepsis in 39%. The incidence of pelvic sepsis in the latter period decreased significantly to 27%, compared with 72% in the former period ($P = 0.038$). Enteroperineal fistulae were observed in four cases.

Survival curves show overall 3- and 5-year disease-specific survival rates of 58% and 40%, respectively. In 57 patients with R0, including 5 patients with hepatic metastasis, 3- and 5-year disease-specific survival rates were 67% and 49%, respectively, whereas there was no 4-year survivor in patients with margin-positive, which showed significantly poor prognosis ($P < 0.001$) (Fig. 5). There was no survival difference between patients with and without radiotherapy before re-resection. Fourteen patients had lateral node metastases around the internal iliac vessels. Of these 14 patients, 6 are alive and 3 were long-term survivors for 64, 71, and 141 months, respectively.

Table 2
Surgical invasiveness and hospital stay

Operative burden	Former period (1983–1992) mean $n = 18$	Latter period (1993–2003) mean $n = 51$	P-value
Operative time (min)	769 (370–990)	702 (480–1100)	NS
Blood loss (mL)	4229 (1800–16,300)	2102 (673–8468)	$P < 0.0001$
Hospital stay (d)	37.5 (23–200)	34 (21–257)	NS

Table 3
Level of distal sacrectomy and complications

Level of sacrectomy	Sepsis in pelvis	Ileus	Fistula[a]
Middle amputation			
S2 inferior margin (n = 12)	6	2	1
S2-3 (n = 26)	9	1	1
Low amputation			
S3 inferior margin (n = 16)	8	1	2
S3-4 (n = 10)	2	1	
S4 inferior margin (n = 5)	2		

[a] Fistula: enteroperineal fistula caused by anastomotic leakage.

Of 57 patients with R0 resection, 34 developed re-recurrence. The most common site was the lung (18 patients) followed by the pelvis (12 patients).

Oncologic outcomes reported in the literature

Factors such as type of surgery, combined therapy, and postoperative follow-up period are diversified, and comparison of reported oncologic outcomes for LRRC is of small significance. For example, a study that includes patients with recurrence after local excision naturally should show favorable outcome, whereas in a study conducted only with cases of FRT, unfavorable outcome can be predicted. Lopez-Kostner et al [33] reported a 5-year survival rate of 32% in 43 patients who underwent surgical treatment, 11 of whom developed recurrence after local excision. On the other hand, Bozzetti et al [18] showed a 5-year survival rate of less than 10% in patients who underwent surgery alone and pointed out a limitation of outcome after surgical treatment alone. Regarding 5-year survival after

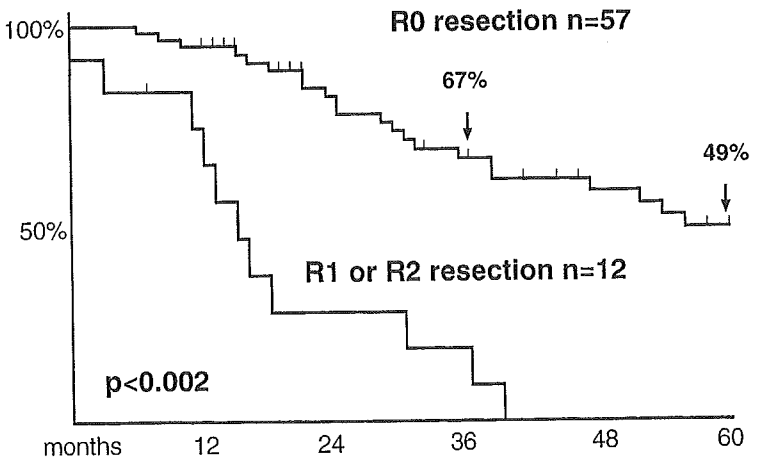

Fig. 5. Disease-specific survival curve. The difference between the two groups was significant ($P < 0.001$).

composite resection, Wanebo et al [19] reported a rate of 31%, Maetani et al [10] reported a rate of 25%, and Yamada et al [21] reported a rate of 18%. Those are not satisfactory outcomes. Incidence of local re-recurrence ranges from 27% to 61% [10,19,31].

As for outcome after multimodality therapy, there are many reports in which the ordinary dosages of radiation used preoperatively were 45 to 50 Gy. Intraoperative dosages of 10 to 15 Gy in R0 cases and 15 to 20 Gy in R-positive cases also were reported [24–29]. Valentini et al [24] reported a 5-year survival rate of 22%, and Mannaerts et al [23] reported a 3-year survival rate of 60%. In the series by Shoup et al [25], who investigated outcomes after resection plus intraoperative radiotherapy, patients with R0 had a median disease-free survival of 31 months and a median disease-specific survival of 66 months.

Lung metastasis and local re-recurrence account for nearly 90% of all re-recurrence patterns [31], and measures to prevent these two types of re-recurrence are important. Compared with 20 years ago, when the only effective antitumor agent was 5-fluorouracil, some effective antitumor agents (eg, CPT-11, UFT, capecitabine, and oxaliplatin) have become available. We think that surgical treatment, combined with composite resection and intraoperative radiotherapy, is indispensable for improving local control rates and that an effective chemotherapy regimen after re-resection is indispensable for inhibiting lung metastasis.

Prognostic factors and staging system

Several factors, such as type of initial surgery, tumor size, presence of symptoms, and serum carcinoembryomic antigen level, have been regarded as significant prognostic indicators, although a consensus has not been reached yet. Willet et al [11] and Wanebo et al [19] found improved resectability in patients who underwent initial low anterior resection compared with patients who had initial APR. If FRT developed after low anterior resection, however, there was no difference in resectability and survival between them [31]. Shoup et al [25] indicated that vascular invasion and R1/R2 resection are factors for poor prognosis. In either report, the most important factor is whether R0 resection was attained [19,24,25,27,31]. Researchers already have shown that in surgical treatment for primary rectal cancer, surgery-related and biologic factors are crucial [34]. Surgical margin status and complications are exclusively determined by a surgeon's technical skills. Complicated surgeries, such as TPES or abdominosacral resection, should be undertaken only in specialized centers with an experienced complex treatment team.

Suzuki et al [14] judged the degree of fixation to surrounding structures according to surgical and pathologic findings and proposed their own staging method. Valentini et al [24] also reported a similar staging system in

which they judged from CT scan imaging. They mentioned that degree of fixation is an independent prognostic factor. Wanebo et al [19] proposed a new staging system for stages TR1-2 to TR5, which are determined by extent of invasion. A staging system that uses degree of fixation or other prognostic factors is constructed so that treatment modalities for LRRC, especially surgical treatment, are placed in an appropriate position.

Summary

For primary rectal cancer, there is a difference in therapy between Western countries and Japan. In Western countries, initial surgery is total mesorectal excision or less limited surgery plus radiotherapy. For this reason, fibrosis caused by radiation occurs in the pelvis. On the other hand, in Japan, although preoperative radiotherapy is not given, total mesorectal excision or more extended surgery is performed as initial surgery, and the intrapelvic spaces are covered with postoperative scar tissue. In identifying an anatomic index and doing hemostasis, this scar tissue brings the surgeon more difficulty than the fibrosis caused by radiotherapy. Approximately half of our patients are irradiated preoperatively for recurrence. In those patients, operation is performed under an unfavorable condition because the fibrosis caused by radiation is added to the scar tissue caused by dissection. Composite resection, such as TPES, has been thought to be demanding and formidable because of high mortality and morbidity rates. Improvement of surgical techniques has allowed TPES to be completed with a blood loss of approximately 2000 to 3000 mL, however, which has resulted in a favorable learning curve with low morbidity and mortality rates.

We have excluded tumors that grow into the sacral promontory or sciatic notch from surgical indications. If high sacral amputation is performed, increased surgical invasiveness, more serious complications, and inevitable walking disorders are observed; as a result, a patient may have a remarkably deteriorated quality of life [6,9,12,19]. We have limited the level of sacral amputation in TPES to the S2 lower edge or below to preserve the second sacral nerve. Consequently, patients were able to have favorable quality of life after TPES, except for living with double stomas and temporary pain caused by resection of sacral nerves, and they were able to return to their original occupations [31,35].

If oncologic outcome obtained is superior to that after multimodality treatment, composite resection for FRT also may become an acceptable treatment. Finally, it should be noted that when extended surgeries, such as TPES, are performed for FRT, each of the departments concerned should review surgical indications and the surgeries must be worked on in the form of team medicine. One must realize that only through such process can negative resection margins be obtained as a great boon to patients.

References

[1] Gunderson LL, Sosin H. Area of failure found at reoperation following curative surgery for adenocarcinoma of the rectum. Cancer 1974;34:1278–92.

[2] McDermott FT, Hughes ES, Pihl E, et al. Local recurrence after potentially curative resection for rectal cancer in a series of 1008 patients. Br J Surg 1985;72:34–7.

[3] Pilipshen SJ, Heilweil M, Quan SH, et al. Patterns of pelvic recurrence following definitive resection of rectal cancer. Cancer 1984;53:1354–62.

[4] McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. Int J Colorectal Dis 1995;10:126–32.

[5] Wong CS, Cumming BJ, Brierly JD, et al. Treatment of locally recurrent rectal carcinoma: results and prognostic factors. Int J Radiat Oncol Biol Phys 1998;40(2):427–35.

[6] Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. Ann Surg 1981;194(4):458–71.

[7] Pacini P, Cionini L, Pirtoli L, et al. Symptomatic recurrences of carcinoma of the rectum and sigmoid: the influence of radiotherapy on the quality of life. Dis Colon Rectum 1986;29: 865–8.

[8] Takagi H, Morimoto T, Hara S, et al. Seven cases of pelvic exenteration combined with sacral resection for locally rectal cancer. J Surg Oncol 1986;32:184–8.

[9] Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. Cancer 1992;69:2876–83.

[10] Maetani S, Onodera H, Nishikawa T, et al. Significance of local recurrence of rectal cancer as a local or disseminated disease. Br J Surg 1998;85:521–5.

[11] Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for recurrent locally advanced rectal or rectosigmoid carcinoma. Cancer 1991;67:1504–8.

[12] Temple WJ, Ketcham AS. Sacral resection for control of pelvic tumors. Am J Surg 1992;163: 370–4.

[13] Wanebo HJ, Koness J, Vezeridis MP, et al. Pelvic resection of recurrent rectal cancer. Ann Surg 1994;220(4):586–97.

[14] Suzuki K, Gunderson LL, Devine RM, et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer 1995;75(4):939–52.

[15] Suzuki K, Dozois RR, Devine RM, et al. Curative reoperation for locally recurrent rectal cancer. Dis Colon Rectum 1996;39(7):730–6.

[16] Wiggers T, de Vries MR, Veeze-Kuypers B. Surgery for local recurrence of rectal carcinoma. Dis Colon Rectum 1996;39(3):323–8.

[17] Goes RN, Beart RW, Simons AJ, et al. Use of brachytherapy in management of locally recurrent rectal cancer. Dis Colon Rectum 1997;40(10):1177–9.

[18] Bozzetti F, Bertario L, Rossetti C, et al. Surgical treatment of locally recurrent rectal carcinoma. Dis Colon Rectum 1997;40(12):1421–4.

[19] Wanebo HJ, Antoniuk P, Koness J, et al. Pelvic resection of recurrent rectal cancer. Dis Colon Rectum 1999;42(11):1438–48.

[20] Mannaerts GHH, Rutten HJT, Martijn H, et al. Abdominosacral resection for primary irresectable and locally recurrent rectal cancer. Dis Colon Rectum 2001;44(6):806–14.

[21] Yamada K, Ishizawa T, Niwa K, et al. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. Br J Surg 2001;88:988–93.

[22] Magrini S, Nelson H, Gunderson LL. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. Dis Colon Rectum 1996;39:1–9.

[23] Mannaerts GHH, Martijn H, Crommelin MA, et al. Intraoperative electron beam radiation therapy for locally recurrent rectal carcinoma. Int J Radiat Oncol Biol Phys 1999;45(2): 297–308.

[24] Valentini V, Morganti A, De Franco A, et al. Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma. Cancer 1999; 86(12):2612–24.

[25] Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. Dis Colon Rectum 2000;45(5):585–92.
[26] Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. Surg Oncol Clin N Am 2003;12:993–1013.
[27] Kuehne J, Kleisli T, Biernacki P, et al. Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. Dis Colon Rectum 2003;46(79):895–9.
[28] Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg 2003;237(4):502–8.
[29] Rodel C, Grabenbauer GG, Matzel K, et al. Extensive surgery after high-dose preoperative chemoradiotherapy for locally advanced recurrent rectal cancer. Dis Colon Rectum 2000; 43(39):312–9.
[30] Temple WJ, Saettler EB. Locally recurrent rectal cancer: role of composite resection of extensive pelvic tumors with strategies for minimizing risk of recurrence. J Surg Oncol 2000; 73:47–58.
[31] Moriya Y, Akasu T, Fujita S, et al. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. Dis Colon Rectum, in press.
[32] Moriya Y, Hojo K, Sawada T, et al. Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 1989;32(4):307–15.
[33] Lopez-Kostner F, Fazio VW, Vignali A, et al. Locally recurrent rectal cancer: predictors and success of salvage surgery. Dis Colon Rectum 2001;44(2):173–8.
[34] Porter GA, Soskolne CL, Yakimets WW, et al. Surgeon-related factors and outcome in rectal cancer. Ann Surg 1998;227(2):157–67.
[35] Guren MG, Wiig JN, Dueland S, et al. Quality of life in patients with urinary diversion after operation for locally advanced rectal cancer. Eur J Surg Oncol 2001;27(7):645–51.

Original Paper

Postsurgical Surveillance for Recurrence of UICC Stage I Colorectal Carcinoma: Is Follow-up by CEA Justified?

Seiichiro Yamamoto MD, Takayuki Akasu MD, Shin Fujita MD, Yoshihiro Moriya MD
Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan
Corresponding Author: Seiichiro Yamamoto, MD, Division of Colorectal Surgery, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo, 104-0045, Japan
Tel: +81 3 3542 2511, Fax: +81 3 3542 3815, E-mail: seyamamo@ncc.go.jp

KEY WORDS: UICC stage I colorectal carcinoma; Follow-up; Surveillance; CEA

ABBREVIATIONS: Carcinoembryonic Antigen (CEA)

ABSTRACT

Background/Aims: This study was undertaken to investigate whether it will be possible to reduce the times and types of postoperative examinations for surveillance in patients with UICC stage I colorectal carcinoma. In addition, the value of CEA in postoperative surveillance is discussed.

Methodology: A review was performed of 541 patients who underwent curative resection for UICC stage I colorectal carcinoma between January, 1985 and December, 1998. Periodic check-up was routinely conducted to identify recurrence.

Results: The median follow-up was 82 months. The recurrence rate was 2.9% in the UICC stage Ia (pT1N0M0) group, and 5.6% in the Ib (pT2N0M0) group. Cancer-specific survival rates at 5 years were 99.3% and 97.6%, respectively ($p=0.0354$). Recurrences occurred more frequently in patients with lower rectal carcinoma ($p=0.0415$). Curative-intent salvage surgery was performed in 61.9% (13/21) for recurrent lesions. Between the patients who were CEA positive (13/21; 61.9%) and those who were CEA negative at the time of recurrence, there was no significant difference in the prognosis.

Conclusions: The incidence of recurrence was low after curative surgery in patients with UICC stage I colorectal carcinoma, and it is therefore possible to reduce times and types of postoperative examinations. CEA measurement alone appears to be sufficient.

INTRODUCTION

Currently, a main topic for discussion with regard to the surveillance after colorectal carcinoma surgery is whether intensive follow-up for detecting recurrence earlier and initiating the treatment of it practically contributes to the improvement in prognosis for colorectal carcinoma patients. In nonrandomized cohort studies and randomized studies, significant differences in the time of confirming recurrence, the surgical resectability of recurrent lesion, and the 5-year survival rate between intensive follow-up group and control group (traditional follow-up or no follow-up group) were reported (1-5). At the same time, there are other studies that have reported no significant difference in these points (6-12). However, in those previous studies, the numbers of cases that were reviewed ranged from 98 to 1247, and there were a variety of disease stages from UICC stages I through IV. One study reported that although the resectability after recurrence was higher by more than 10% in an intensive follow-up group than in the control group, no significant difference was obtained, probably due to the small number of cases (13). In two studies using meta-analysis that were reported lately, the 5-year survival rates were 9% to 14% greater in the intensive follow-up group than in the control group (14,15).

Recently, advances in diagnostic techniques have enabled the detection of colorectal carcinoma at earlier stages in Japan (16). At our institution, the proportion of UICC stage I cases in all colorectal carcinoma patients receiving the first-line treatment was 14% (12/86) in 1980, but it increased to 25% (71/284) in 2000. It is important to conduct a cost-effective follow-up in view of the risk for recurrence (17,18). In fact, for UICC stage I colorectal carcinoma patients, the rate of recurrence is lower, and hence fewer times and screening examinations may be reasonable and warranted for the postoperative surveillance, compared with UICC stages II-IV colorectal carcinoma patients (19).

In the present study, we utilized the prospective follow-up database at a single institution to analyze the long-term outcomes of UICC stage I colorectal carcinoma patients, and to investigate whether it will be possible to reduce the times and types of screening examinations for postoperative surveillance. In addition, the present study discusses the value of CEA (carcinoembryonic antigen) in performing surveillance after curative surgery for UICC stage I colorectal carcinoma.

METHODOLOGY

Between January, 1985 and December, 1998,

Hepato-Gastroenterology 2005; 52:444-449

2,550 primary colorectal carcinoma patients were treated at our institution. Patient information and follow-up data were prospectively collected and added to the department database. Of those patients, the present study selected 541 (21.2%) cases of UICC stage I colorectal carcinoma undergoing curative resection combined with surgical lymph node clearance, in order to review the time and form of recurrence, the changes in CEA levels at recurrence, and the rate of re-resectability. For analysis, the 541 cases of UICC stage I colorectal carcinoma were divided into two groups: 313 patients with stage Ia colorectal carcinoma (pT1N0M0) and 228 patients with stage Ib colorectal carcinoma (pT2N0M0).

In terms of the follow-up of a patient with stage I colorectal carcinoma, we routinely conducted a periodic check-up every six months until two years after the operation, and subsequently once per year from the 3rd to 5th postoperative year. Clinical examination, abdominal ultrasound, and CEA measurement were performed at each visit, and chest X-ray was performed once per year. CEA was defined as positive when the level was increased above the cut-off value. Colonoscopy or barium enema was conducted once within one year of the first surgery, and was repeated at intervals of one to two years depending on the findings of the prior examination. When a patient complained of a symptom that suggested recurrence or had an increased level of CEA without symptoms, we employed other types of examinations in addition to the periodic check-up.

The clinicopathologic parameters were compared using Student's t test and the Fisher's exact test as appropriate. Cancer-specific survival curves and disease-free survival curves were estimated using the Kaplan-Meier technique and were compared by means of the log-rank test. For cancer-specific survival, only cancer-related deaths were considered; data on the patients who died from other causes or who were still alive at the end of the study were censored. A P value of less than 0.05 was considered significant.

TABLE 1 Patient's Characteristics

		UICC stage Ia patients	UICC stage Ib patients	P value
Number of patients		313	228	
Sex ratio (Male:Female)		201:112	129:99	0.0750
Age (yr; mean and range)		60.7 (33-88)	62.0 (23-91)	0.1641
Location	Cecum	16	14	0.0003*
	Ascending colon	23	15	
	Transverse colon	18	7	
	Descending colon	7	5	
	Sigmoid colon	122	53	
	Upper rectum	28	23	
	Middle rectum	34	31	
	Lower rectum	65	80	
Operative procedures	Partial resection	45	4	
	Ileocecal resection	11	4	
	Right hemicolectomy	15	25	
	Transverse colectomy	3	5	
	Descending colectomy	7	2	
	Left hemicolectomy	0	4	
	Sigmoid colectomy	105	49	
	Anterior resection	91	93	
	Abdominoperineal resection	14	35	
	Abdominosacral resection with coloanal anastomosis	4	2	
	Transsacral partial resection	17	0	
	Hartmann's operation	1	4	
	Total pelvic exenteration	0	1	
Follow-up time (mo; range and median)		3-189 (80)	1-201 (85)	
Recurrence	Positive	9	12	0.1793
	Negative	304	216	
Sites of First Tumor Recurrence	Liver	7	5	
	Lung	1	6	
	Local			
	Pelvis	1	2	
	Anastomosis	1	1	
	Para-aortic lymph node	0	1	
Oncologic outcome	5-Year disease-free survival (%)	96.9	94.9	0.1575
	5-Year cancer-specific survival (%)	99.3	97.6	0.0354

*colon and upper/middle rectum *vs.* lower rectum.

RESULTS

The patient demographics are summarized in **Table 1**. Compared with the UICC stage Ia group, the UICC stage Ib group included significantly more patients with lower rectal carcinoma ($p=0.0003$). Recurrence occurred in 9 of 313 (2.9%) UICC stage Ia group, and in 12 of 216 (5.6%) UICC stage Ib group. However, the difference between the two groups was not significant ($p=0.1793$). Disease-free survival rates at 5 years were 96.9% for the UICC stage Ia group and 94.9% for the UICC stage Ib group **(Figure 1a)**, with no significant difference between the two groups ($p=0.1575$). Cancer-specific survival rates at 5 years were 99.3% for the UICC stage Ia group and 97.6% for the UICC stage Ib group **(Figure 1b)**; there was a significant difference between the two groups ($p=0.0354$).

The performance rate of curative-intent salvage surgery for recurrent lesions in these recurrent carcinoma patients was 61.9% (13/21) **(Table 2)**. Recurrence was found at a median time of 19 months (range 6-66) after primary carcinoma resection. Only one patient with pelvic and hepatic recurrence was found after five-year routine follow-up.

Since the proportion of lower rectal carcinoma patients was significantly elevated in the UICC stage Ib group, we divided the sites of carcinoma into the lower rectum and other parts to evaluate recurrence rates and prognoses **(Table 3)**. Recurrences occurred in 10 of 145 (6.9%) patients with lower rectal carcinoma, and in 11 of 396 (2.8%) patients with colon or upper/middle rectal carcinoma. Between these two groups, the difference in the recurrence rate was significant ($p=0.0415$). Disease-free survival rates at 5

years in patients with lower rectal carcinoma were 92.6%, and 97.3% in patients with colon or upper/middle rectal carcinoma (**Figure 2a**), with the difference between the two groups significant ($p=0.0304$). However, the cancer-specific survival rates at 5 years were not significantly different between the groups ($P=0.2402$) (**Figure 2b**).

Among the 21 recurrent cases, 13 (61.9%) individuals were CEA positive at the time of recurrence (**Table 4**). With regard to the recurrent site and CEA positive rate, patients with hepatic recurrence showed a significantly higher rate of CEA positivity, compared with the patients with recurrence at other sites ($p=0.0272$). Between the patients who were CEA positive and those who were CEA negative at the time of recurrence, no significant difference in the prognosis after the detection of recurrence was found (**Figure 3a**), in addition to in the prognosis after the first surgery (**Figure 3b**).

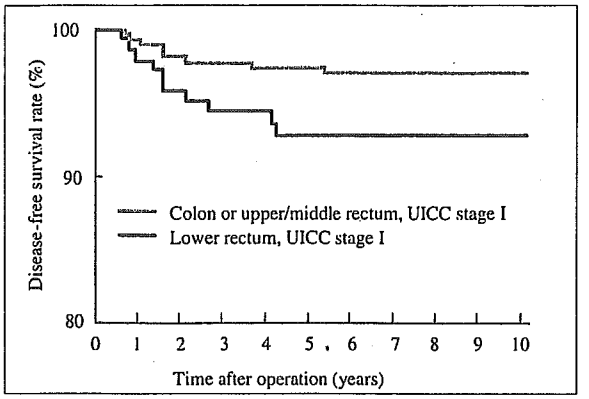

FIGURE 2a Cumulative disease-free survival curves for patients with lower rectal carcinoma and colon or upper/middle rectal carcinoma. The difference between the two groups was significant ($p=0.0304$).

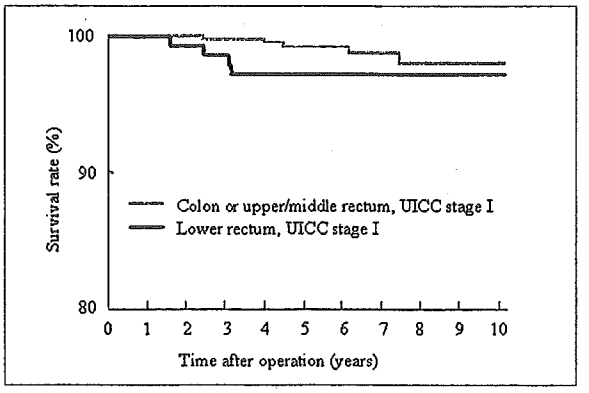

FIGURE 2b Cancer-specific survival curves for patients with lower rectal carcinoma and colon or upper/middle rectal carcinoma. The difference between the two groups was not significant ($p=0.2402$).

FIGURE 1a
Cumulative disease-free survival curves for UICC stage Ia group and UICC stage Ib group. The difference between the two groups was not significant ($p=0.1575$).

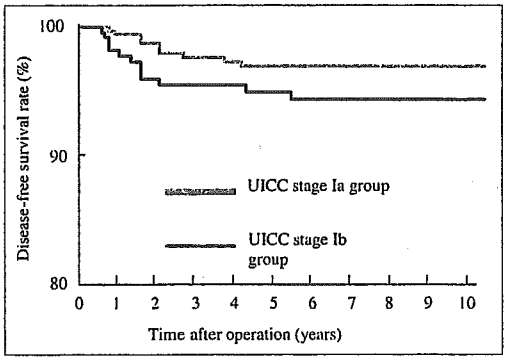

FIGURE 1b
Cancer-specific survival curves for UICC stage Ia group and UICC stage Ib group. The difference between the two groups was significant ($p=0.0354$).

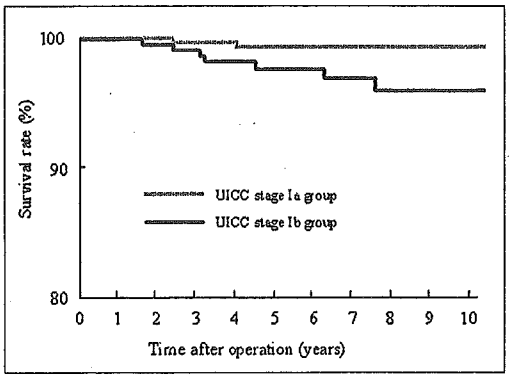

TABLE 2 Treatment of Recurrent Cancers

Treatment	No. of patients
Resection	
APR+radiation	3 (2*)
TPE+combined resection of sacrum	1 (1)
hepatic resection	9 (7*)
lung resection	5 (5)
Systemic chemotherapy	2
Hepatic artery infusion	2
Pelvic radiotherapy	1

( ), number of patients having curative-intent salvage surgery. *two patients underwent curative-intent salvage surgery for pelvic and hepatic recurrences.

DISCUSSION

For surveillance after curative surgery for colorectal carcinoma, a cost-effective method of follow-up should be established for consideration of the risk for recurrence. The probable subjects that the numbers of times and follow-up examinations can be reduced are UICC stage I patients. In the present study, we carried out follow-up examinations of a large number of UICC stage I patients over a long period at a single institution, and analyzed the data to clarify an appropriate method of surveillance. The present findings demonstrated that compared with the UICC stage Ia group, the UICC stage Ib group had a significantly lower rate of 5-year cancer-specific survival. In addition, lower rectal carcinoma involved a significantly higher incidence of recurrence. A recent study by Wichmann *et al.* (19) reported that between UICC stages Ia and Ib, there was an approximately 10% difference in the 5-year survival rate, although the difference did not achieve significance due to the small number of study patients. In the present study, however, the number of UICC stage I patients who were investigated was