

Because it was thought that the radical cure operation was able to be performed, the patient underwent abdominoperineal resection of the rectum on September 26, 2006. Massive lymph-node swelling around the aorta was noted in the operative findings (Figure 2). Histological analysis of a frozen section revealed metastases, which extended to the cranial site of the bilateral renal veins. Palliative resection was thus performed. Histological analysis of the surgical specimen revealed moderately-differentiated adenocarcinoma (stage pT2), lymphatic invasion, vascular invasion, and lymph-node metastases (12/35).

We initially considered two alternative chemotherapy combinations for this patient: FOLFOX, which comprises folinic acid (FOL), 5-FU, and oxaliplatin (OX); and FOLFIRI, which comprises FOL, 5-FU, and irinotecan (IRI). When we explained the method of treatment, regimen, and the adverse event to the patient in postoperatively, he refused it. He hoped for chemotherapy with few possibilities of ruining QOL even if the effect was weak because he was aged. Therefore, UFT/LV therapy was eventually selected based on the patient's age and the requirement to maintain his QOL. UFT/LV therapy was eventually selected based on the patient's age and the requirement to maintain his QOL. Each course of chemotherapy comprised 400 mg/day UFT and 75 mg/day LV administered for 28 days every 35 days.

## RESULTS

The therapy began on postoperative day 48. After 10 courses, a good partial response (PR) was achieved according to abdominal CT. After 17 courses, the para-aortic lymph-node swelling had disappeared, indicating a CR (Figure 3). During this period, no AEs were noted and the treatment proceeded without changing the dosage. The treatment was continued and no recurrence had been noted 4 months after the CR was confirmed.

## DISCUSSION

FOLFOX and FOLFIRI are now widely used in Japan, and the main choices for second-line chemotherapy are bevacizumab and cetuximab. However, the AEs associated with these new medicines can significantly decrease a patient's QOL. With FOLFIRI the reported incidence of grade 3/4 neutropenia was 21.8% and that of diarrhea was 12.9%, whereas with FOLFOX the reported incidence of grade 3/4 neutropenia was 40%, that of neurological disorder was 30.9%, and that of diarrhea was 10% (6,7). Moreover, the drug disposition differed between elderly and non-elderly patients (12). It is therefore necessary to select the appropriate type of chemotherapy for elderly patients. The UFT/LV therapy regimen is based on the concept of biochemical modulation. Two large-scale phase III studies showed that, in comparison with conventional intravenous 5-FU/LV therapy for metastatic colorectal cancer, UFT/LV therapy had similar therapeutic

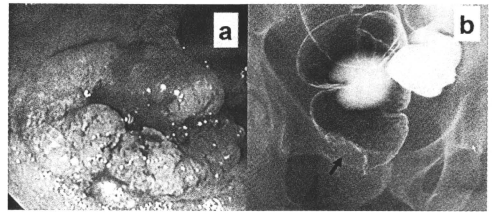


FIGURE 1 Local recurrence 29 months after endoscopic mucosal resection. (a) Colonofiberscopy showed an elevated lesion with an ulcer. (b) A shadow defect could be seen in the lower rectum in a double-contrast roentgenogram.

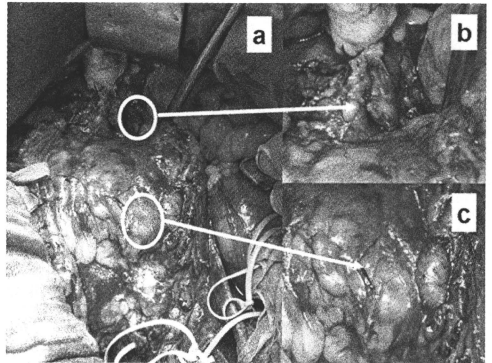
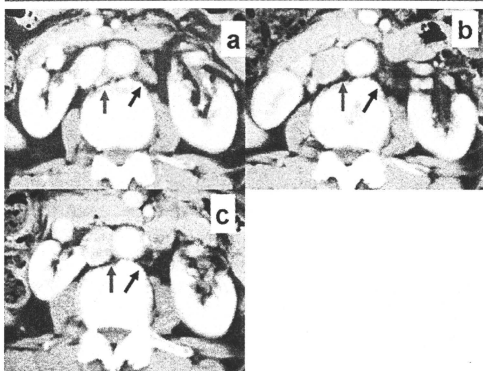


FIGURE 2 Operative findings. (a) Massive lymph-node swelling was noted from the mesorectum to the para-aortic site. (b) The para-aortic lymph node below the left renal vein was revealed to be an adenocarcinoma according to a frozen section. (c) Massive para-aortic lymph-node metastases to the aortic bifurcation were recognized.

effects and fewer AEs, with the exception of a bilirubin rise; the incidence of diarrhea of grade 3/4 was 21% and 18%, respectively, in these two studies; these figures were high compared with intravenous 5-FU/LV therapy, although the difference was not statistically significant (9, 10). The National Surgical Adjuvant Breast and Bowel Project Trial (NSABP) C-06 reported an incidence of diarrhea of 28.3%, which significantly differed from the incidence of intravenous 5-FU/LV therapy (16.6%). In a bridging phase II study, the incidence of grade 3/4 diarrhea was 22.2% in the United States compared with 9% in Japan; the response rates in the two countries were similar (36.4% and 34.1%, respectively) (13). Another Japanese study reported that the response rate of previously untreated patients was 33.3% and the incidence of diarrhea of grade 3/4 was 3.7% (14). This suggests that the drug disposition of UFT/LV might differ among populations, and that previously untreated patients in Japan might benefit from UFT/LV therapy. The effects of UFT/LV therapy on the QOL were evaluated in the NSABP C-06 report (11). The convenience-of-care score was significantly higher for UFT/LV therapy



**FIGURE 3** CT findings. (a) CT findings on October 5, 2006, before UFT/LV therapy. The maximum diameter of the lateral para-aortic lymph node was 22 mm (black arrow). Inter-lymph-node swelling was seen between the aorta and the vena cava (gray arrow). (b) CT findings on January 23, 2008, after 10 courses of UFT/LV therapy. The lateral para-aortic lymph node had shrunk to a maximum diameter of 14 mm, with a reduction of 36.4% (black arrow). The inter-lymph-node swelling had disappeared (gray arrow). (c) CT findings on October 20, 2008, after 17 courses of UFT/LV therapy. The para-aortic lymph-node metastases had disappeared, indicating a CR (black and gray arrows).

than for intravenous 5-FU/LV therapy, because the need for outpatient care was lower and central venous port management was unnecessary with the former approach.

Some previous studies have reported on UFT/LV therapy in elderly patients. In a phase II study of patients aged 75 years or above, the response rate was 22%, the median survival time was 13.0 months, and the median progression-free survival

time was 4.6 months; regarding AEs of grade 3/4, the incidence of diarrhea was 25%, and the GI toxicity was 36% (15). In studies of patients aged 70 years or above, the response rate was 11–28.6%, no AEs of grade 3/4 were reported, and the efficacy was equivalent to that in non-elderly patients (16,17). However, these studies included small numbers of patients (7–55). A well-controlled study on the safety of UFT/LV therapy in the elderly is required.

The CR rate of UFT/LV therapy alone for the treatment of metastatic colorectal cancer has been reported to range from 0 to 2% (9,10,13,14). Some case reports of CR after UFT/LV therapy have been published, as listed in **Table 1** (18–23). The patients ranged in age from 57 to 81 years, and two cases were aged 75 years or above. Another study reported a case of long-term survival after UFT monotherapy and lymph-node removal to treat lymph-node recurrence after colectomy with para-aortic lymph-node dissection. However, the CR was achieved by the oral administration of an anti-cancer agent alone in this case, because para-aortic lymph-node metastasis was absent. Moreover, the CR was recognized early in the course of the therapy (24). Three of the previously reported cases involved two courses of treatment, and all involved seven courses or fewer (18–23). However, in the current case, the CR was recognized late in the course of treatment; this might have been due to the difference in the method of drug delivery, as it would be expected to take longer for the metastatic lymph nodes to be metabolized and absorbed, and to be absent from the diagnostic images. Body weight loss, anorexia, pigmentation, and grade 1 pruritus were reported in one 78-year-old female patient. However, the other patients in the reported cases did not experience any AEs.

**TABLE 1** Case Reports of CR after UFT/LV Therapy Alone for Metastatic Colorectal Cancer

Author	Age (years) and gender	Primary site	Metastatic site	UFT/LV therapy regimen	Number of courses until CR	Total number of courses	Outcome
Mukai (18)	81, Female	Ascending colon	Liver	UFT 300 mg + LV 15 mg for 28 days every 35 days	2	8	Liver recurrence 7 months after CR; death due to brain infarction
Okabayashi (19)	70, Male	Transverse colon	Peritoneum	UFT 450 mg + LV 75 mg for 28 days every 35 days	2	3 (discontinued)	Lymph-node recurrence 7 months after CR; living in the TS-1
Asai (20)	57, Female	Transverse colon	Liver and Peritoneum	UFT 450 mg + LV 75 mg for 28 days every 35 days	5	11 (continued)	Living with no recurrence 8 months after CR
Mizushima (21)	78, Female	Cecum	Local recurrence	UFT 400 mg + LV 75 mg for 28 days every 35 days	6	7 (discontinued)	Living with no recurrence 5 months after CR
Hosotaki (22)	65, Female	Rectum	Lung	UFT 450 mg + LV 75 mg for 21 days every 28 days	7	8 (discontinued)	Living with no recurrence 9 months after CR
Okamura (23)	78, Male	Sigmoid colon	Lung	UFT 300 mg + LV 75 mg for 28 days every 35 days	2	23	No recurrence 28 months after CR; death due to pneumonia

Whether therapy should be continued after CR remains an important issue. Recurrence was reported in one of the three cases in which the therapy was continued (18,20,23). Early recurrence was reported in one of the three cases in which the treatment was discontinued (19,21,22). There is currently no consensus on whether the treatment of colorectal cancer should be continued after a CR. In a phase III study, the continuance of chemotherapy after remission in cases of recurrent breast cancer had no effect on the survival time (25). It is not clear whether the effect on colorectal cancer is similar. In the current case, we continued therapy because of the early recurrence after discontinuation (19). Five courses of UFT/LV therapy were performed as an adjuvant therapy after CR, although evidence to support this approach is lacking. It will be necessary to evaluate the effect of the continuance of chemotherapy after CR in the future.

It is expected that there is a criticism that it is necessary to select not the operation but chemoradiotherapy or neoadjuvant chemoradiotherapy for the local recurrence in this case. Some excellent result

of chemoradiotherapy in nonresectable rectal cancer was reported (26,27). However, we had selected the operation because we expected that the radical cure was able to be excised preoperatively. Consequently, correct staging was performed though the radical surgery was impossible because of para-aortic lymph node metastasis. The point that had to be reflected was not to be able to diagnose para-aortic lymph node metastasis preoperatively. Some reports of the para-aortic lymph node metastasis diagnosis by PET are seen in cervical cancer (28-30), but it is few in the colorectal cancer (31). The improvement of the diagnostic performance of PET/CT in the colorectal cancer will be hoped for in the future.

## CONCLUSION

We report a case who obtained complete remission by the UFT/LV oral therapy without adverse event to the rectal cancer with the para-aortic lymph node metastasis in 77-year-old male. UFT/LV therapy can be selected as regimen of chemotherapy in elderly or high risk patient.

## REFERENCES

- Braun AH, Achterrath W, Wilke H, Vanhoefler U, Harstrick A, Preusser P: New systemic frontline treatment for metastatic colorectal carcinoma. *Cancer* 2004; 100:1558-1577
- de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papatmichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-2947
- Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer. *Lancet* 2000; 355:1041-1047
- Komatsu Y: Current organ topics: Advancement of colorectal cancer drug therapy (in Japanese). *Jpn J Cancer Chemother* 2007; 34:1771-1776
- Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirota N, Elfring GL, Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; 343:905-914
- Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22:223-230
- Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A: FOLFIRI followed by FOLFOX 6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 2004; 22:229-237
- Tanaka F: UFT (tegafur and uracil) as postoperative adjuvant chemotherapy for solid tumors (carcinoma of the lung, stomach, colon/rectum, and breast): clinical evidence, mechanism of action, and future direction. *Surg Today* 2007; 37:923-943
- Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE: Multicenter Phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; 20:3605-3616
- Carmichael J, Popiela T, Radstone D, Falk S, Bornier M, Oza A, Skovsgaard T, Munier S, Martin C: Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; 20:3617-3627
- Kopec JA, Yothers G, Ganz PA, Land SR, Cecchini RS, Wieand HS, Lembersky BC, Wolmark N: Quality of life in operable coloncancer patients receiving oral compared with intravenous chemotherapy: results from National Surgical Adjuvant Breast and Bowel Project Trial C-06. *J Clin Oncol* 2007; 25:424-430
- Greenblatt DJ, Sellers EM, Shader RI: Drug disposition in old age. *N Engl J Med* 1982; 306:1081-1088
- Shirao K, Hoff PM, Ohtsu A, Loehrer PJ, Hyodo I, Wadler S, Wadleigh RG, O'Dwyer PJ, Muro K, Yamada Y, Boku N, Nagashima F, Abbruzzese JL: Comparison of the efficacy, toxicity, and pharmacokinetics of a uracil/tegafur (UFT) plus oral leucovorin (LV) regimen between Japanese and American patients with advanced colorectal cancer: Joint United States and Japan study of UFT/LV. *J Clin Oncol* 2004; 22:3466-3474
- Sato Y, Inaba Y, Yamaura H, Shimamoto H, Nishiofuku H, Oyama T, Kanemitsu Y, Sawaki A, Arai Y, Muro K: Analysis of tegafur/uracil (UFT) plus oral leucovorin (LV) regimen in patients with advanced colorectal cancer. *Jpn J Cancer Chemother* 2006; 33:887-890. (in Japanese with English abstract)
- Hochster HS, Luo W, Papa EC, Lyman BT, Mulcahy M, Beatty PA, Benson AB: Phase II study of uracil-tegafur with leucovorin in elderly (75 years old) patients with colorectal cancer. *ECOG* 1299. *J Clin Oncol* 2007; 25:5397-5402
- Tsutsumi S, Yamaguchi S, Tsuboi K, Fukasawa T, Yamaki S, Asao T, Kuwano H: Oral regimen consisting of UFT/UZEL for elderly patients with colorectal cancer. *Hepato-Gastroenterology* 2006; 53:209-212

17. Mizushima T, Mizuno H, Ito T, Hoki M, Souma Y, Iwamoto T, Ozawa H, Kanou T, Nakamori Y, Iwase K: Efficacy of uracil/tegafur (UFT) plus oral leucovorin (LV) therapy for colorectal cancer in elderly patients. *Jpn J Cancer Chemother* 2006; 33:941-944. (in Japanese with English abstract)
18. Mukai M, Moriya H, Himeno S, Oida Y, mukohyama S, Nishi T, Nakasaki H, Satoh S, Makuuchi H: Efficacy of oral UFT plus leucovorin for colon cancer with ovarian and multiple liver metastases: report of two cases. *Oncol Rep* 2001; 8:1079-1083
19. Okabayashi K, Hasegawa H, Kawano Y, Kawano S, Nishibori H, Ishii Y, Yamauchi T, Kawano T, Kitajima M: A case of colorectal cancer effectively treated with UFT/LV. *Jpn J Cancer Chemother* 2005; 32:1343-1345. (in Japanese with English abstract)
20. Asai K, Fujita T, Nakamura Y, Tokuda E, Hiyoshi M, Aoki F, Sugizaki K, Masaki Y: A case of multiple hepatic and peritoneal metastases from colon cancer responding to oral UFT+Leucovorin chemotherapy. *Jpn J Cancer Chemother* 2005; 32:1959-1961. (in Japanese with English abstract)
21. Mizushima T, Ito T, Mizuno H, Souma Y, Kainuma S, Yamanaka H, Ozawa H, Kanou T, Nakamori Y, Iwase K: A case of recurrent colon cancer responding completely to uracil/tegafur (UFT) plus oral Leucovorin (LV) Therapy. *Jpn J Cancer Chemother* 2005; 32:2129-2131. (in Japanese with English abstract)
22. Hosotaki K, Tabira Y, Shimamoto M, Tamori Y: Two cases of recurrent colorectal cancer treated successfully with Folinat/Tegafur/Uracil chemotherapy on an outpatient basis. *Jpn J Cancer Chemother* 2005; 35:661-664. (in Japanese with English abstract)
23. Okamura M, Kmiizumi Y, Kawamura N, Yokoyama R, Itoh K, Abe K, Nakajima Y: A patient in whom oral UFT/ Leucovorin therapy proved markedly effective for lung metastasis after surgery for colon cancer. *Jpn J Cancer Chemother* 2005; 35:1205-1207. (in Japanese with English abstract)
24. Ogino T, Ohue M, Noura S, Seki Y, Goto K, Motoori M, Kishi K, Eguchi H, Yamada T, Miyashiro I, Tomita H, Ohigashi H, Yano M, Ishikawa O, Imaoka S: A long-term case of advanced sigmoid colon cancer with massive metastases to para-aortic lymph nodes (in Japanese). *Jpn J Cancer Chemother* 2007; 34:2056-2058. (in Japanese with English abstract)
25. Muss HB, Case LD, Richards F 2nd, White DR, Cooper MR, Cruz JM, Powell BL, Spurr CL, Capizzi RL: Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. *N Engl J Med* 1991; 325:1342-1348
26. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pählman L, Wiig JN, Byström P, Bujko K, Glimelius B: Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008; 26:3687-3694
27. Lim SB, Choi HS, Jeong SY, Kim DY, Jung KH, Hong YS, Chang HJ, Park JG: Optimal surgery time after preoperative chemoradiotherapy for locally advanced rectal cancers. *Ann Surg* 2008; 248:243-251
28. Esthappan J, Chaudhari S, Santanam L, Mutic S, Olsen J, Macdonald DM, Low DA, Singh AK, Grigsby PW: Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2008; 72:1134-1139
29. Yen TC, See LC, Lai CH, Tsai CS, Chao A, Hsueh S, Hong JH, Chang TC, Ng KK: Standardized uptake value in para-aortic lymph nodes is a significant prognostic factor in patients with primary advanced squamous cervical cancer. *Eur J Nucl Med Mol Imaging* 2008; 35:493-501
30. Yildirim Y, Sehirali S, Avci ME, Yilmaz C, Ertopcu K, Tinar S, Duman Y, Sayhan S: Integrated PET/CT for the evaluation of para-aortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings. *Gynecol Oncol* 2008; 108:154-159
31. Stelzner F, Ruhlmann J: PET studies of recurrent rectal carcinoma. Fundamental aspects of lymphatic metastasis of visceral and somatic carcinomas. *Chirurg* 2001; 72:537-546



## Prediction of Residual Disease or Distant Metastasis After Resection of Locally Recurrent Rectal Cancer

Yukihide Kanemitsu, M.D.<sup>1</sup> • Takashi Hirai, M.D.<sup>1</sup> • Koji Komori, M.D.<sup>1</sup>  
Tomoyuki Kato, M.D.<sup>1,2</sup>

<sup>1</sup> Department of Gastroenterological Surgery, Aichi Cancer Center, Nagoya, Japan

<sup>2</sup> Department of Surgery, Kamiida Daiichi General Hospital, Nagoya, Japan

**PURPOSE:** It is important to preoperatively identify patients at high risk of relapse at extrapelvic sites or residual disease after salvage surgery for locally recurrent rectal cancer to maximize the survival benefit by indicating whether a surgical approach might be successful.

**METHODS:** Data from 101 consecutive patients who underwent exploration with curative intent for local recurrence after radical resection of rectal cancer were retrospectively collected. Preoperative factors were examined in univariate and multivariate analyses for their ability to predict resectability and distant disease-free survival.

**RESULTS:** The 5-year disease-specific survival rates of R0, R1, and R2 resection were 43.3%, 19.5%, and 10.0%, respectively ( $P < .001$ ). In a logistic regression analysis, upper sacral (above the inferior margin of the second sacrum)/lateral invasive type and high-grade lymphatic invasion of the primary tumor were associated with palliative surgery. A Cox regression analysis revealed that upper sacral/lateral invasive type, extrapelvic disease, hydronephrosis at recurrence, and high-grade lymphatic or venous invasion of the primary tumor were associated with a lower distant disease-free survival rate. Patients with one or more of these risk factors had a 3-year distant

disease-free survival rate of 6.2% compared with 54.1% for those with none of these risk factors.

**CONCLUSION:** It was possible to preoperatively identify patients at high risk of relapse or residual disease. This system might be used on an individual basis to select patients with locally recurrent rectal cancer for chemotherapy or radiotherapy before surgical intervention with curative intent.

**KEY WORDS:** Rectal cancer; Recurrence; Surgery.

In patients who undergo radical surgery for rectal cancer, 4% to 30% develop locoregional relapse.<sup>1-4</sup> Since the 1990s, several studies have reported 5-year survival rates favorably ranging from 22% to 58% after resection of locally recurrent rectal cancer (LRRC).<sup>5-10</sup> These observations strongly support the view that surgery is the most effective therapy for selected patients with LRRC, because it offers a potential for long-term survival that is not possible with other treatment modalities. However, these advantages are tempered by the high incidence of postoperative complications and the early development of a second distant recurrence.<sup>9,11-13</sup> Without complete resection (R0), these patients have a short life expectancy<sup>7,9,12-18</sup> and tend to experience unpleasant symptoms, especially pain, and their quality of life becomes extremely poor.<sup>19</sup> The patients who present with metastatic disease soon after a curative resection of their local recurrence may experience delays in systemic treatment secondary to complications from surgery. Optimal patient selection and multimodality treatment strategies are desirable but difficult. We conducted a retrospective study of patients with isolated pelvic recurrences who underwent exploration with curative intent to determine predictors of resectability and distant disease-free survival after surgery. It may contribute greatly to the development of methods for the

**Financial Disclosures:** None reported.

Presented at the meeting of the Japanese Society of Gastroenterological Surgery, Sapporo, Japan, July 17, 2008.

**Correspondence:** Yukihide Kanemitsu, M.D., Department of Gastroenterological Surgery, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681 Japan. E-mail: ykanemit@aichi-cc.jp

Dis Colon Rectum 2010; 53: 779-789  
DOI: 10.1007/DCR.0b013e3181cf7609  
©The ASCRS 2010

DISEASES OF THE COLON & RECTUM VOLUME 53: 5 (2010)

779

**TABLE 1.** PATTERNS OF PELVIC INVASION OF LOCALLY RECURRENT CANCER

Anastomotic site invasive type Visceral/lower sacral invasive type	<p>Recurrent tumor is localized to the anastomotic site</p> <ul style="list-style-type: none"> <li>• Recurrent tumor is localized to adjacent pelvic organs or connective tissue without contact onto or invasion into bone</li> <li>• Recurrent tumor invades or abuts the lower sacrum (S3, S4, S5) or coccyx</li> </ul>
Upper sacral/lateral invasive type	<ul style="list-style-type: none"> <li>• Recurrent tumor invades or abuts the structures on the lateral pelvic sidewall, including the greater sciatic foramen, sciatic nerve through to piriformis, gluteal region or cortex above the inferior margin of the second sacrum (S1, S2)</li> </ul>

preoperative identification of patients likely to benefit from surgery.

## MATERIALS AND METHODS

### Patients Included in the Study

Between January 1981 and December 2006, a total of 101 consecutive patients (57 men and 44 women) underwent surgical exploration with curative intent for LRRC at Aichi Cancer Center Hospital. The patients' ages ranged from 36 to 78 (median, 57) years. All of the patients had previously undergone radical resection of the primary rectal adenocarcinoma. Fifty-five patients (54.5%) underwent surgical treatment of their primary tumors elsewhere and were referred to our institution for treatment of their recurrences. Details of the primary tumor and management were obtained from the hospitals in which the patients were originally treated. This included date of surgery, type of operation, tumor (T) stage, node (N) stage, Dukes classification, lymphatic invasion, venous invasion, and histologic grade of the primary tumor. The clinicopathological features were retrospectively reviewed by use of case charts and written pathological reports. The degree of lymphovascular invasion was classified according to the criteria of the "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus,"<sup>20</sup> in which lymphatic and venous invasions are classified as follows: no invasion (grade 0), minimal invasion (grade 1), moderate invasion (grade 2), and marked invasion (grade 3). This classification was dichotomized, ie, classed as low (grade 0-1) or high (grade 2-3) for analysis. Local recurrence was defined as tumor recurrence in the previous operative field, and was classified according to the pattern of pelvic invasion of the recurrent tumor (Table 1, Fig. 1). The extent of the locally recurrent tumor was classified by the 3 patterns of pelvic invasion on CT or MRI as follows: anastomotic site invasive type, visceral/lower sacral invasive type, and upper sacral/lateral invasive type. This classification was based on modified criteria from the previous reported pelvic invasive pattern of local recurrence (localized, sacral, or lateral), which influenced prognosis after resection.<sup>21</sup> Local recurrence occurred at a median of 17.9 months (range, 2.2-111.6 mo) after the initial operation. Details of the operation for local recurrence, and of preoperative radiotherapy and chemotherapy were recorded.

Before the surgery for locoregional recurrence, 6 patients had undergone liver resection, 3 had pulmonary resection, one had both; one had peritonectomy, and one had inguinal lymphadenectomy for distant metastases. At salvage surgery for LRRC, 4 patients had liver metastases, 2 had lung metastases, 1 had both, 1 had para-aortic nodal metastasis, and 2 had localized peritoneal metastases. Metastatic tumors in 3 of 10 patients with concurrent distant metastases were resected simultaneously. In the remaining 7 patients, the initial plan for staged surgery was abandoned because the disease rapidly progressed to multiple metastases after salvage surgery for the pelvic local disease. These patients were entered into a group of incomplete resections with gross residual disease for the analysis. Including the patients who had evidence of distant metastatic disease before or at the time of resection of their local recurrence, a total of 22 patients included in the study were defined as having extrapelvic disease. The entire cohort of 101 patients was followed up completely, with a median follow-up time for live patients of 53.7 months (range, 3.2-140.0 mo).

### Preoperative Evaluation

All patients underwent clinical assessment and preoperative imaging to determine tumor resectability, to exclude metastatic disease outside the pelvis, and to assess the general fitness of the patient and ability to withstand major surgery. Each patient underwent CT of the thorax and abdomen to exclude distant metastases and to assess involvement of the bony pelvis. The presence of extensive abdominal or thoracic metastases was considered to be a contraindication to resection of the pelvic recurrence. Patients also underwent MRI of the pelvis to assess the location of the tumor, its direction of invasion, and involvement of local viscera and the pelvic sidewall structures. Contraindications to locally curative surgery as determined by imaging included extensive pelvic sidewall involvement or adherence, tumor encasement of the iliac vessels, extension of the tumor into the sciatic notch, and proximal sacral invasion above the level of the S1-S2 junction. Patients who had had surgery since 2000 in the study underwent whole-body positron emission tomography (PET) or PET-CT scans as part of their preoperative evaluation. Although PET-CT scans are now a standard component of preoperative assessment through improved diagnostic accuracy, still, a 10% of false-positive rates in the detection of

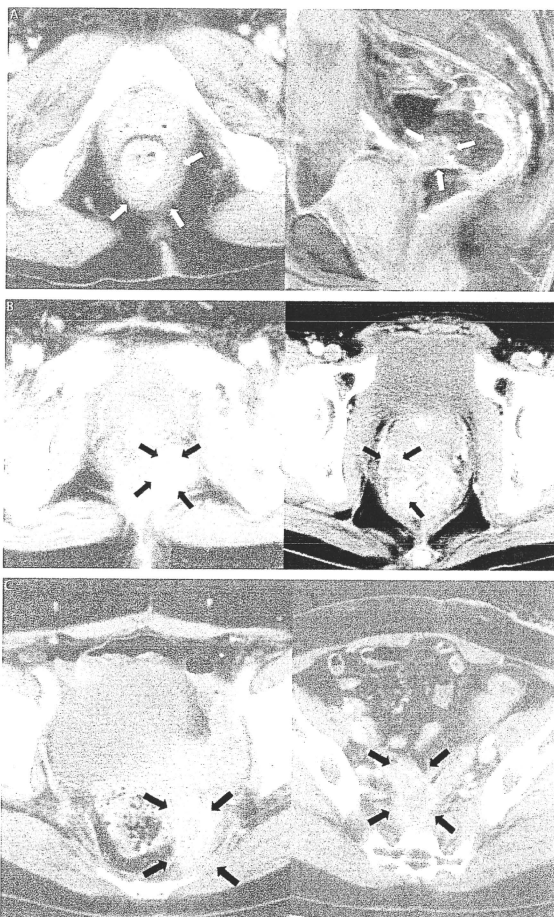


FIGURE 1. A, Anastomotic site invasive type. B, Visceral/lower sacral invasive type. C, Upper sacral/lateral invasive type. Arrows reveal a recurrent tumor.

pelvic recurrence in patients with colorectal cancer has been reported.<sup>22</sup> Therefore, histologic confirmation of malignancy by CT-directed fine-needle aspiration or biopsy per rectum was obtained for all patients before surgical intervention. Serum CEA concentration was measured in most patients as part of their preoperative workup.

#### Stage and Treatment of Primary Tumors

The initial tumor stage according to Dukes classification was A in 18 patients (17.8%), B in 21 patients (20.8%), C in 52 patients (51.5%), D in 5 patients (5.0%), and unknown in 5 patients (5.0%). All the metastatic tumors in patients with Dukes stage D were resected simultaneously or

**TABLE 2.** Clinical and pathological characteristics of patients who underwent resection of locally recurrent rectal cancer

	n	%
Age (y) <sup>a</sup>	57 (36-78)	(58)
Sex		
Female	44	43.6
Male	57	56.4
Interval to recurrence (mo) <sup>a</sup>	17.9 (2.2-111.6)	(24.2)
Recurrent disease		
Pelvic invasive pattern		
Anastomotic invasive type	18	17.8
Visceral/lower sacral invasive type	41	40.6
Upper sacral/lateral invasive type	27	26.7
Unknown	15	14.9
CEA		
Normal	42	41.6
Elevated	54	53.5
Unknown	5	4.9
Extrapelvic disease		
Yes	22	21.8
No	79	78.2
Hydronephrosis		
Yes	5	4.9
No	83	82.2
Unknown	13	12.9
Primary disease		
Dukes stage		
A	18	17.8
B	21	20.8
C	52	51.5
D	5	5.0
Unknown	5	5.0
Histology		
Well	21	20.8
Moderately	72	71.3
Mucinous or poorly	7	6.9
Unknown	1	1.0
Lymphatic invasion		
Grade 0-1	54	53.5
Grade 2-3	33	33.7
Unknown	14	12.8
Venous invasion		
Grade 0-1	70	69.3
Grade 2-3	17	17.9
Unknown	14	12.8
Surgical procedure		
Local resection	4	4.0
HAR	15	14.9
LAR	46	45.5
APR	32	31.7
Hartmann procedure	4	4.0

HAR = high anterior resection; LAR = low anterior resection; APR = abdominoperineal resection.

<sup>a</sup>Values are median (range) (mean).

metachronously. Primary cancers had been surgically treated by transanal or transsacral resection (n = 4, 4.0%), high anterior resection (n = 15, 14.9%), low anterior resection (n = 46, 45.5%), abdominoperineal resection (APR) (n = 32, 31.7%), or Hartmann procedure (n = 4, 4.0%) (Table 2). Adjuvant chemotherapy, using 5-fluorouracil plus leucovorin or 5-fluorouracil prodrugs (ura-

**TABLE 3.** Surgical procedure and additional therapy performed for recurrent disease

Procedure	Total	With sacrectomy	%
Operation			
Local resection	10	0	9.9
APR	22	9	21.8
Hartmann procedure	8	0	7.9
LAR	12	0	11.9
TPE	36	16	35.6
Posterior pelvic exenteration	13	6	12.9
Margins at recurrent resection			
R0	62		61.4
R1	20		19.8
R2	19		18.8
Radiotherapy for recurrence			
Yes	43		42.6
External-beam radiation	43		42.6
IORT	18		17.8
No	57		56.4
Unknown	1		0.9
Chemotherapy for recurrence			
Yes	41		40.6
No	59		58.4
Unknown	1		1.0

APR = abdominoperineal resection; LAR = low anterior resection; TPE = total pelvic exenteration; IORT = intraoperative radiotherapy.

cil and tegafur) was administered to 33 patients and radiotherapy was given to 3 patients with tumors deemed to be at high risk for metastasis.

#### Clinical Presentation of Recurrent Disease

Fifty-one patients (50.5%) exhibited symptoms caused by their local recurrences, such as pelvic pain, rectal bleeding, or changes in bowel habits. CEA levels on presentation were available for 96 patients: 54 had elevated levels and 42 had normal levels (Table 2). The median CEA level on presentation for the salvage surgery was 6.6 ng/mL (normal level, <5 ng/mL).

**TABLE 4.** Description of surgery for recurrent disease

	n	% of 101 patients
Operative time (min) <sup>a</sup>	495 (32-1101)	(509)
Blood loss (mL) <sup>a</sup>	2500 (0-24300)	(4005)
Hospital stay (d) <sup>a</sup>	62 (6-466)	(79)
In-hospital mortality	5	5.0
Morbidity	82	81.2
Pelvic abscess	38	37.6
Fistula	24	23.8
Bowel obstruction	21	20.8
Leakage of ileal conduit	10	9.9
Wound infection	8	7.9
Leakage of intestines	3	2.9
Septicemia	2	2.0

<sup>a</sup>Values are median (range) (mean).

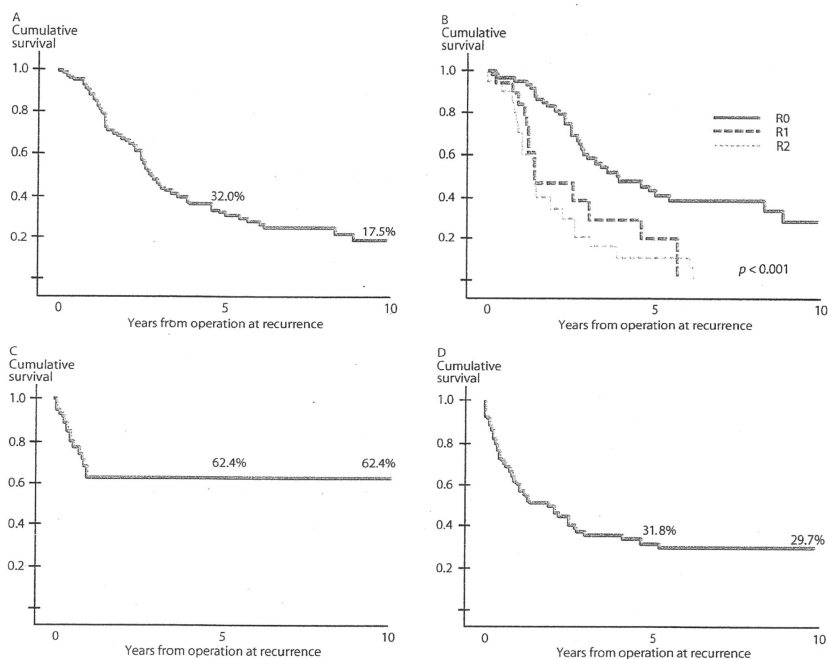


FIGURE 2. Kaplan-Meier estimates. A, Disease-specific survival after resection in the entire cohort ( $n = 101$ ). B, Disease-specific survival after resection by margin status of resected specimen. C, Local disease-free survival after resection in the entire cohort ( $n = 101$ ). D, Distant disease-free survival after resection in the entire cohort ( $n = 101$ ). R0 = negative for disease; R1 = microscopically positive for disease; R2 = gross residual disease.

#### Treatment of Recurrence

Two patients received preoperative adjuvant radiation of 50 Gy during 5 weeks because preoperative imaging indicated frank invasion of adherent structures. All 101 patients underwent a potentially curative resection of the local recurrence. This included a local resection in 10 patients, APR in 13, APR with sacral resection in 9, Hartmann procedure in 8, low anterior resection in 12, total pelvic exenteration (TPE) in 20, TPE with sacral resection in 16, posterior pelvic exenteration in 7, and posterior pelvic exenteration with sacral resection in 6 (Table 3). TPE was accompanied by urinary reconstruction by use of an ileal conduit. Levels of sacral transection included S2 to S3 in 9 patients, S3 in 3 patients, S3 to S4 in 10 patients, S4 in 3 patients, and S4 to S5 in 6 patients. The extent of sacral resection was limited to the distal sacrum below S2. Fro-

zen-section analysis was performed of the resected specimen and of the closest margins. On detection of any positive margins, further tissue was resected until negative margins were achieved or until it was not possible to resect further. Sixty-two of the patients underwent curative (R0) resections with negative microscopic margins. Marginal (R1) resections with positive microscopic margins were performed for 20 patients, and incomplete (R2) resections with gross residual disease were performed for 19 patients. Eighteen patients (17.8%) with suspected or confirmed microscopic residual disease in the pelvis received intraoperative radiotherapy (10–20 Gy). When the outcome of frozen sections taken during surgery was positive with macroscopic or gross residual disease, external beam radiotherapy (45–50 Gy) was delivered postoperatively in 41 patients (40.6%). Forty-one patients received preoperative

TABLE 5. Factors Associated With Palliative vs Curative Resection\*

Variable	Univariate		Multivariate (logistic)	
	OR	P	OR	P
Age				
$\geq 60$ vs $< 60$	0.8 (0.4–2.1)	0.770	–	–
Sex				
Male vs female	1.3 (0.5–2.9)	0.577	–	–
Pelvic invasive pattern				
Upper sacral/lateral vs anastomotic invasive type	7.0 (1.8–27.5)	0.005	54.6 (3.2–2,194.0)	0.005
Visceral/lower sacral vs anastomotic invasive type	1.3 (0.3–4.7)	0.708	3.3 (0.3–38.4)	0.331
CEA				
Normal vs elevated	0.5 (0.2–1.1)	0.079	–	–
Extrapelvic disease				
Yes vs no	3.0 (0.7–2.1)	0.002	3.9 (0.7–20.9)	0.112
Hydronephrosis				
Yes vs no	3.0 (0.5–18.7)	0.251	–	–
Primary disease				
Lymph node metastasis				
Yes vs no	4.8 (1.6–13.8)	0.004	3.6 (0.6–19.8)	0.140
Histology				
Well vs moderately	0.5 (0.2–1.8)	0.311	–	–
Mucinous or poorly vs moderately	1.8 (0.2–14.1)	0.561	–	–
Lymphatic invasion <sup>b</sup>				
Grade 2–3 vs grade 0–1	5.9 (2.2–15.4)	<0.001	11.7 (1.6–85.4)	0.015
Venous invasion <sup>b</sup>				
Grade 2–3 vs grade 0–1	4.5 (1.4–13.8)	0.008	1.5 (0.2–14.1)	0.741

OR = odds ratio.

\*Values in parentheses are 95% confidence intervals.

<sup>b</sup>The degree of invasion was divided into 4 grades according to the Japanese criteria.<sup>20</sup> Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderate invasion; grade 3 = marked invasion.

chemotherapy, usually 5-fluorouracil-based, for the locally recurrent tumor, most frequently concurrent with external beam radiotherapy.

#### Statistical Analysis

Survival time was calculated from the date of surgery for local recurrence of rectal cancer until the last follow-up visit, or the occurrence of the defined events. Survival rates were estimated using the Kaplan-Meier method. Comparisons of survival rates between groups were made using the log-rank method. Multivariate survival analyses were performed by use of a Cox proportional hazards model. Univariate and multivariate analyses of factors influencing curative (R0) vs palliative (R1 or R2) resections were performed by use of logistic regression. Multivariate models were constructed based on variables known to be predictive of risk of events in univariate models.<sup>23</sup> Among the significant prognostic characteristics, variables measured during preoperative investigations were chosen to establish a prediction model. Missing variables occupying more than 20% of the data set were omitted from the model. For all tests, a *P* value of 0.05 was considered significant.

#### RESULTS

Descriptive statistics regarding the surgeries are shown in Table 4. The median operating time was 495 minutes (range, 32–1101 min). Median blood loss was 2500 mL (range, 0–24,300 mL). The median length of hospital stay was 62 days (range, 6–466 d) with an in-hospital mortality rate of 5.0%. The postoperative complication rate was 81.2% with the most common major complications being pelvic abscess (37.6%), enterocutaneous or colovesical fistula (23.8%), and bowel obstruction (20.8%).

The 1-, 3-, 5-, and 10-year disease-specific survival rates for the 101 patients that underwent surgery for LRRC were 87.9%, 47.5%, 32.0%, 17.5%, respectively, whereas the median survival time for these patients was 33.6 months (Fig. 2A). Completeness of resection correlated strongly with survival rates, as shown in Figure 2B. The 5-year disease-specific survival rates of curative (R0), R1, and R2 resection were 43.3%, 19.5%, and 10.0%, respectively (*P* < .001).

#### Predictors of Curative Resection

Table 5 compares the characteristics of patients who underwent curative and palliative resection. The pattern of

**TABLE 6.** Univariate and multivariate regression of factors related to local disease-free survival

Variable	Univariate		Multivariate (Cox)	
	HR	P	HR	P
Age				
$\geq 60$ vs $< 60$	0.5 (0.3–1.2)	0.118	–	–
Sex				
Male vs female	0.6 (0.3–1.2)	0.148	–	–
Pelvic invasive pattern				
Anastomotic vs upper sacral/lateral invasive type	0.2 (0.0–0.8)	0.028	0.2 (0.0–0.9)	0.045
Visceral/lower sacral vs upper sacral/lateral invasive type	0.5 (0.2–1.2)	0.124	0.5 (0.2–1.1)	0.083
CEA				
Normal vs elevated	0.6 (0.3–1.2)	0.170	–	–
Extrapelvic disease				
Yes vs no	1.3 (0.6–2.7)	0.542	–	–
Hydronephrosis				
Yes vs no	1.0 (0.2–4.3)	0.991	–	–
Interval to recurrence (mo)				
$< 12$ vs $\geq 12$	1.1 (0.5–2.2)	0.811	–	–
Margins at recurrent resection				
R0 vs R2	0.5 (0.2–1.2)	0.115	–	–
R1 vs R2	0.9 (0.3–2.5)	0.882	–	–
Chemotherapy for recurrent disease				
Yes vs no	1.3 (0.7–2.6)	0.387	–	–
Radiotherapy for recurrent disease				
Yes vs no	2.0 (1.5–3.9)	0.078	–	–
Primary disease				
Lymph node metastasis				
Yes vs no	2.1 (1.1–4.7)	0.046	2.0 (0.8–5.0)	1.110
Histology				
Moderately vs well	2.2 (0.7–6.3)	0.157	–	–
Mucinous or poorly vs well	3.2 (0.3–28.6)	0.306	–	–
Lymphatic invasion <sup>b</sup>				
Grade 2–3 vs grade 0–1	0.9 (0.4–1.9)	0.705	–	–
Venous invasion <sup>b</sup>				
Grade 2–3 vs grade 0–1	0.6 (0.2–1.7)	0.328	–	–

HR = hazard ratio.

<sup>a</sup>Values in parentheses are 95% confidence intervals.<sup>b</sup>The degree of invasion was divided into 4 grades according to the Japanese criteria.<sup>20</sup> Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

pelvic invasion of the recurrent tumor ( $P = .005$ ) and grade of lymphatic invasion of the primary tumor ( $P = .015$ ) had significant effects on the possibility of curative resection. The proportion of patients undergoing palliative resection was much higher in upper sacral/lateral invasive type (66.7%) than in viscera/lower sacral invasive type (26.8%) or anastomotic site invasive type (22.2%).

#### Factors Affecting Local Disease-Free Survival After Resection

The 1-, 3-, 5-, and 10-year local disease-free survival rates of the entire cohort were 68.2%, 62.4%, 62.4%, and 62.4%, respectively (Fig. 2C).

Univariate analyses suggested that the pattern of pelvic invasion of the recurrent tumor ( $P = .028$ ) and lymph node metastasis of the primary tumor ( $P = .046$ ) were independently associated with local disease-free survival after salvage surgery. Multivariate analyses of fac-

tors identified as significant by univariate analyses revealed that only the pattern of pelvic invasion of the recurrent tumor ( $P = .045$ ) retained statistical significance (Table 6).

#### Factors Affecting Distant Disease-Free Survival After Resection

The 1-, 3-, 5-, and 10-year distant disease-free survival rates of the entire cohort were 59.5%, 36.8%, 31.8%, and 29.7%, respectively (Fig. 2D).

Univariate analyses suggested that margins at recurrent resection ( $P < .001$ ), high-grade lymphatic ( $P = .004$ ) or venous ( $P = .004$ ) invasion of the primary tumor, presence of hydronephrosis with recurrent tumor ( $P = .031$ ), presence of extrapelvic disease before or at resection ( $P < .001$ ), and the pattern of pelvic invasion of the recurrent tumor ( $P = .001$ ) were independently associated with distant disease-free survival after salvage surgery. Multivariate analyses of factors identified as significant by univariate

TABLE 7. Univariate and multivariate resection risk factors related to distant disease-free survival

Variable	Univariate		Multivariate (Cox)	
	HR	P	HR	P
Age				
$\geq 60$ vs $< 60$	1.3 (0.7-2.1)	0.432	-	-
Sex				
Male vs female	1.1 (0.7-2.0)	0.675	-	-
Pelvic invasive pattern				
Anastomotic vs upper sacral/lateral invasive type	0.4 (0.2-0.9)	0.019	0.5 (0.2-1.5)	0.228
Visceral/lower sacral vs upper sacral/lateral invasive type	0.4 (0.2-0.7)	0.001	0.4 (0.2-0.9)	0.040
CEA				
Normal vs elevated	0.7 (0.4-1.3)	0.259	-	-
Extrapelvic disease				
Yes vs no	2.7 (1.5-4.8)	$< 0.001$	2.3 (1.1-5.2)	0.044
Hydronephrosis				
Yes vs no	3.2 (1.1-9.1)	0.031	3.4 (0.9-12.3)	0.063
Interval to recurrence (mo)				
$< 12$ vs $\geq 12$	0.9 (0.5-1.7)	0.971	-	-
Margins at recurrent resection				
R0 vs R2	0.2 (0.1-0.4)	$< 0.001$	0.4 (0.1-0.8)	0.031
R1 vs R2	0.6 (0.3-1.2)	0.150	0.8 (0.3-2.5)	0.761
Chemotherapy for recurrent disease				
Yes vs no	0.9 (0.6-1.6)	0.805	-	-
Radiotherapy for recurrent disease				
Yes vs no	1.4 (0.8-2.3)	0.206	-	-
Primary disease				
Lymph node metastasis				
Yes vs no	1.8 (0.9-3.3)	0.065	-	-
Histology				
Moderately vs well	1.3 (0.7-2.7)	0.433	-	-
Mucinous or poorly vs well	0.7 (0.1-5.4)	0.725	-	-
Lymphatic invasion <sup>b</sup>				
Grade 2-3 vs grade 0-1	2.3 (1.4-3.9)	0.004	3.1 (1.3-7.5)	0.009
Venous invasion <sup>b</sup>				
Grade 2-3 vs grade 0-1	2.6 (1.3-5.1)	0.004	0.7 (0.2-1.8)	0.418

HR = hazard ratio.

\*Values in parentheses are 95% confidence intervals.

<sup>b</sup>The degree of invasion was divided into 4 grades according to the Japanese criteria.<sup>20</sup> Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

analyses revealed that margins at recurrent resection ( $P = .031$ ), lymphatic invasion of the primary tumor ( $P = .009$ ), extrapelvic disease ( $P = .044$ ), and the pattern of pelvic invasion of the recurrent tumor ( $P = .040$ ) retained statistical significance. Hydronephrosis showed borderline significance ( $P = .063$ ) (Table 7).

#### Relationship Between Pattern of Recurrence and Curability

The incidence rates of distant and local diseases at 2 years after resection of LRRC were shown according to the curability in Figure 3. Patients with R2 demonstrated an incidence rate of distant diseases higher than that of the patients with R1, and almost twice that of the patients with R0 (R2, 77.0%; R1, 67.1%; R0, 38.7%). However, patients with R1 and R2 had identical 2-year incidence rate of local diseases after resection of LRRC (R2, 45.5%; R1, 47.0%; R0, 30.9%).

#### Establishment of a Model Predicting Treatment Failure After Surgery

Among the significant prognostic factors by univariate analyses (Table 7), lymphatic or venous invasion of the primary tumor, hydronephrosis with recurrent tumor, extrapelvic disease before or at resection, and the pattern of pelvic invasion of the recurrent tumor were chosen as the factors that could be detected before an operation for LRRC. Multivariate analyses of these factors revealed that lymphatic invasion of the primary tumor ( $P < .001$ ), hydronephrosis ( $P = .043$ ), extrapelvic disease ( $P = .016$ ), and the pattern of pelvic invasion of the recurrent tumor ( $P = .001$ ) retained statistical significance. Venous invasion of the primary tumor showed borderline significance ( $P = .079$ ) (Table 8).

We assigned the patients to 2 groups based on the 5 preoperative investigated risk factors identified for systemic failure after treatment: those with no risk factors and



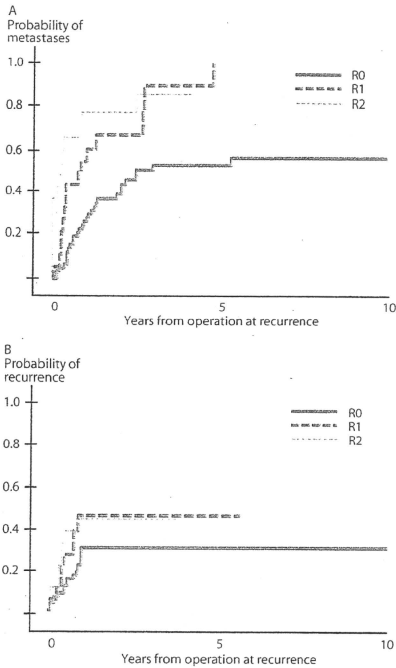


FIGURE 3. A, Time to distant metastases by curability. B, Time to local diseases by curability. R0 = negative for disease; R1 = microscopically positive for disease; R2 = gross residual disease.

those with at least one risk factor. We found a statistically significant difference in the distant disease-free survival curves for the 2 risk groups ( $P < .001$ ). The 3-year distant disease-free survival rate decreased from 54.1% in patients with no risk factors to 6.2% for those with one or more risk factors (Fig. 4).

**DISCUSSION**

In studies that have analyzed factors affecting the survival of patients after resection of LRRC, the possibility of performing curative resection has been consistently reported as a significant determinant of survival. The reported 5-year survival rates vary from 22% to 58% after obtaining R0 resection.<sup>5-10</sup> Although the validity of an R0 resection has been established, this can only be achieved in approximately 45% of cases, ranging from 10% to 67% in the

**TABLE 8.** Multivariate regression of preoperative investigated factors related to distant disease-free survival

Variable	Multivariate (Cox)	
	HR	P
Pelvic invasive pattern		
Anastomotic vs upper sacral/lateral invasive type	0.4 (0.1-1.1)	0.072
Visceral/lower sacral vs upper sacral/lateral invasive type	0.2 (0.1-0.6)	0.001
Extrapelvic disease		
Yes vs no	2.9 (1.2-6.8)	0.016
Hydronephrosis		
Yes vs no	3.7 (1.1-14.3)	0.043
Primary disease		
Lymphatic invasion*		
Grade 2-3 vs grade 0-1	4.9 (1.9-12.5)	<0.001
Venous invasion*		
Grade 2-3 vs grade 0-1	2.1 (0.7-5.9)	0.079

Values in parentheses are 95% confidence intervals.

HR = hazard ratio.

\*The degree of invasion was divided into 4 grades according to the Japanese criteria.<sup>20</sup> Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

published literature.<sup>24-28</sup> Negative resection margins were achieved in 61% of the patients in our study. The limitations of preoperative diagnosis are reflected by the fact that there were a number of palliative resections in locally recurrent diseases that had been considered resectable. On the other hand, the majority of patients with recurrence after resection for LRRC developed extrapelvic disease before or at the time of resection.<sup>9,12,13</sup> In the present study, which is the first to analyze prognostic predictors of systemic failure after treatment, the distant disease-free survival curve had a steep decline within one year after resection, indicating a high frequency of residual or subclinical

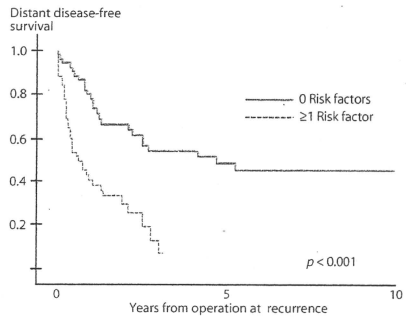


FIGURE 4. Distant disease-free survival after resection based on the number of risk factors.

metastatic disease outside the pelvis in patients with isolated LRRC. It is essential to predict failure patterns accurately in patients with treatable LRRC so that appropriate therapy can be selected as an adjunct to extensive surgery for the local recurrence. The incidence of treatment failure could be reduced by specific prophylactic measures including adjuvant radiotherapy and chemotherapy. Multimodality treatment of LRRC is essential. The aim of the present study was to identify predictors of local and systemic failure after surgery.

This study identified several variables that affect curative surgery. In the multivariate analysis, the pattern of pelvic invasion of the recurrent tumor visualized by only preoperative imaging, which needed no histopathological confirmation, had the greatest impact on a curative resection. We obtained the highest probability of curative resection for patients with recurrent disease limited to the anastomosis. This group has been reported previously to represent a small but favorable subset of local recurrences.<sup>5,21,29,30</sup> In contrast, a high frequency of the recurrent tumors of the upper sacral/lateral invasive type were not amenable to curative resection. We found that pelvic recurrences involving or attaching to the lateral pelvic sidewalls were less likely to be curatively resected than those involving axial or anterior lesions, which has led to a higher incidence rate of distant diseases after resection; disseminated spread might be the major reason for not undertaking curative resection. In addition, sacral involvement above the S2 narrows the therapeutic window because of the functional sequelae of higher resections and the small likelihood of obtaining clear margins, making these recurrences difficult to control. The biological aggressiveness of the primary tumor, represented by the lymphatic invasion, was also a significant predictor of curative resection. Although imaging studies provide valuable information, the ability to predict margins preoperatively would be of great value.

Although some reports deal with factors that potentially influence survival after reoperation in cases of LRRC,<sup>7,8,21</sup> high-grade lymphatic or venous invasion of the primary tumor, presence of hydronephrosis with recurrent tumor, presence of extrapelvic disease before or at resection, and the pattern of pelvic invasion of the recurrent tumor were first established as predictors of systemic failure after reoperation. Hydronephrosis does not necessarily preclude a curative resection,<sup>31</sup> but all 5 patients with hydronephrosis (2 in R0, 3 in R1) in this study manifested systemic diseases within 2 years after surgery. Hydronephrosis occurring under circumstances of sidewall involvement or ureteral obstruction at the bladder, requiring more extended resections, may portend a poor outcome. In cases of distant metastasis, we extended the indications to 22 patients with one or 2 metastases. This group achieved a curative resection rate of 41%, a 2-year distant disease-free survival rate of 11%, and a 3-year disease-specific survival rate of 18%. However, none survived 5 years.

The presence of extensive abdominal or thoracic metastases is considered to be a contraindication to resection of the pelvic recurrence. However, our experience has demonstrated that highly selected patients with this traditional adverse factor can experience medium-term survival following reoperation for LRRC. Therefore, we did not delete extrapelvic disease from the analysis.

Preoperative selection of patients at a high risk for failure after reoperation is particularly important given the high morbidity, as shown in our study, that can be incurred by an aggressive surgical approach to LRRC. The classification system based on variables selected by multivariate analysis assigned patients undergoing resection for LRRC to 2 groups, each with a different probability of developing relapse at extrapelvic sites or residual disease. This system was able to define a group of patients with a 3-year distant disease-free survival rate of only 6.2%. The majority of patients with at least one risk factor developed extrapelvic disease within one year; none of these patients had an operable recurrence. They would not benefit from surgery alone. Multimodality treatment strategies are critical for selecting and supporting these patients perioperatively and over the long term. With the development of new and more effective chemotherapeutic regimens for the treatment of colorectal cancer, strong consideration should be given to preoperative adjuvant treatment for LRRC to maximize the chance of clear margins, and to suppress residual or subclinical metastatic disease outside the pelvis. There is still much room for improvement, in particular, for patients at a high risk for treatment failure after reoperation.<sup>32</sup> Our predictive model may help to delineate patients who will subsequently benefit from addition of chemotherapy or radiotherapy before operating with curative intent for LRRC. This model should be validated in a larger, unselected population.

## CONCLUSION

The ability to obtain a negative margin, highly predicted by the pattern of pelvic recurrence on imaging, is critical for avoiding local and systemic failure. Our results suggest that, in addition to preoperative imaging, certain biologically related tumor factors of the patients, ie, high-grade lymphatic or venous invasion of the primary tumor, presence of hydronephrosis with recurrent tumor, and presence of extrapelvic disease, will be important in their selection for pelvic resections. Preoperative treatments for a selected LRRC have the potential to downsize bulky disease, optimize the ability to perform an R0 resection, and optimize long-term patient outcomes. This system might be used on an individual basis to determine when surgery would be most beneficial and to select patients with LRRC for chemotherapy or radiotherapy before surgical intervention with curative intent.

## REFERENCES

- Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg.* 1982;69:613–616.
- MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet.* 1993;341:457–460.
- Law WL, Chu KW. Resection of local recurrence of rectal cancer: results. *World J Surg.* 2000;24:486–490.
- Moore E, Heald RJ, Cecil TD, Sharpe GD, Sexton R, Moran BJ. Almost all five year disease free survivors are cured following rectal cancer surgery, but longer term follow-up detects some late local and systemic recurrences. *Colorectal Dis.* 2005;7:403–405.
- Salo JC, Paty PB, Guillem J, Minsky BD, Harrison LB, Cohen AM. Surgical salvage of recurrent rectal carcinoma after curative resection: a 10-year experience. *Ann Surg Oncol.* 1999;6:171–177.
- Lindell K, Willett CG, Shellito PC, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. *Radiation Oncol.* 2001;58:83–87.
- Shoup M, Guillem JG, Alekhtiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum.* 2002;45:585–592.
- Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg.* 2003;237:502–508.
- Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. *Dis Colon Rectum.* 2004;47:2047–2053.
- Bakx R, van Tinteren H, van Lanschot JJ, Zoetmulder FA. Surgical treatment of locally recurrent rectal cancer. *Eur J Surg Oncol.* 2004;30:857–863.
- Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. *Cancer.* 1992;69:2876–2883.
- Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. *Ann Surg Oncol.* 2007;14:390–395.
- Bedrosian I, Giacco G, Pederson L, et al. Outcome after curative resection for locally recurrent rectal cancer. *Dis Colon Rectum.* 2006;49:175–182.
- Boyle KM, Sagar PM, Chalmers AG, Sebag-Montefiore D, Cairns A, Eardley I. Surgery for locally recurrent rectal cancer. *Dis Colon Rectum.* 2005;48:929–937.
- Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol.* 2007;14:447–454.
- Henry LR, Sigurdson E, Ross EA, et al. Resection of isolated pelvic recurrences after colorectal surgery: long-term results and predictors of improved clinical outcome. *Ann Surg Oncol.* 2007;14:1081–1091.
- Asoglu O, Karanlik H, Muslumanoğlu M, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. *Eur J Surg Oncol.* 2007;33:1199–1206.
- Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. *Dis Colon Rectum.* 2008;51:284–291.
- Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. *Eur J Surg Oncol.* 2001;27:349–353.
- Japanese Research Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus.* 7th ed. Tokyo, Japan: Kanahara Shuppan; 2006.
- Yamada K, Ishizawa T, Niwa K, Chuman Y, Akiba S, Aikou T. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. *Br J Surg.* 2001;88:988–993.
- Even-Sapir E, Parag Y, Lerman H, et al. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resection. *Radiology.* 2004;232:815–822.
- Cox DR. Regression models and life tables. *J R Stat Soc.* 1972;34:187–220.
- Caricato M, Borzomati D, Ausania F, Valeri S, Rosignoli A, Coppola R. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. *Eur J Surg Oncol.* 2006;32:126–132.
- Huguier M, Houry S. Treatment of local recurrence of rectal cancer. *Am J Surg.* 1998;175:288–292.
- García-Aguilar J, Cromwell JW, Marra C, Lee SH, Madoff RD, Rothenberger DA. Treatment of locally recurrent rectal cancer. *Dis Colon Rectum.* 2001;44:1743–1748.
- Cheng C, Rodriguez-Bigas MA, Petrelli N. Is there a role for curative surgery for pelvic recurrence from rectal carcinoma in the presence of hydronephrosis? *Am J Surg.* 2001;182:274–277.
- Wiggers T, Mannaerts GH, Marinelli AW, Martijn H, Rutten HJ. Surgery for locally recurrent rectal cancer. *Colorectal Dis.* 2003;5:504–507.
- Pihl E, Hughes ES, McDermott FT, Price AB. Recurrence of carcinomas of the colon and rectum at the anastomotic suture line. *Surg Gynecol Obstet.* 1981;153:495–496.
- Vassilopoulos PP, Yoon JM, Ledesma EJ, Mittelman A. Treatment of recurrence of adenocarcinoma of the colon and rectum at the anastomotic site. *Surg Gynecol Obstet.* 1981;152:777–780.
- Henry LR, Sigurdson E, Ross E, Hoffman JP. Hydronephrosis does not preclude curative resection of pelvic recurrences after colorectal surgery. *Ann Surg Oncol.* 2005;12:786–792.
- Austin KK, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. *Dis Colon Rectum.* 2009;52:1223–1233.

# 腹会陰式直腸切断術

愛知県がんセンター中央病院消化器外科

平井 孝 金光幸秀 小森康司

- 開腹および会陰操作では、術野の展開が最も重要である。骨盤内直腸の剥離には、各種の幅および長さの鉤を使い分けて、術野を展開し、剥離を進める層と切離する組織を直視下に視認して操作を進めることが最も重要である。
- 骨盤臓側筋膜、自律神経の含まれる尿管下腹筋膜、壁側筋膜、Denonvilliers 筋膜、直腸仙骨筋膜、挙筋上腔、perineal body、恥骨直腸筋、neurovascular bundle を解剖のポイントとして、出血の少ない、層に沿った切除を行うことで、癌遺残の少ない手術が期待できる。

## はじめに

直腸癌手術では、近年、肛門温存術式が発展し、gold standardであった Miles 手術と通称される腹会陰式直腸切断術 (abdominoperineal resection: APR) の割合が減少している。しかしながら、肛門縁から 5 cm 以内の進行直腸癌、肛門管癌に対しては、いまだに標準手術である。骨盤内や会陰操作は、ある程度は数をこなせばできるようになるのであるが、機能温存や癌の根治性を求めていくと、骨盤内、肛門部の解剖学の複雑さは手術をするたびに新たな疑問を投げかけてくる。現時点での解剖学の理解に沿った手術手技の工夫を詳述する。

## 適 応

腫瘍下縁から 2 cm の DM (distal margin) を確保するうえで、外科的肛門管の長さがおよそ 3 cm とすると、MP 以深癌では肛門縁から 5 cm 未満に腫瘍下縁をもつ癌が対象となる。下部直

腸から肛門管癌では MP 以深例に対して側方リンパ節廓清を行い、自律神経への直接浸潤や側方リンパ節転移を認めない症例には神経全温存を行っている。

## 術前準備

本術式に対する病名告知による説明と同意を得る。Mechanical preparation (前日:流動食、マグコロール®250 ml+ラキソベロン®10 ml) を行う。ストーマサイトマーキングはクリーブランドクリニックの基準を原則に医師、看護師で臥位、坐位で行う。正中からストーマ左縁を 4~5 cm 離す。ただし、太鼓腹の症例には下腹部はケア不良ストーマになる可能性が高く、臍レベルかそれより頭側にマーキングする。

## 手術手技

### ① 体位

レビテーターにより碎石位とする。容易に足

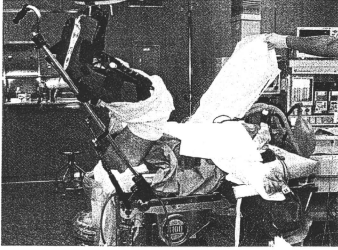


図1 会陰操作時体位

の位置を変更できることと腓骨神経麻痺を予防できるメリットがある。腹部操作では股関節は軽度屈曲，開脚位とする。会陰操作では，強い屈曲位で頭低位とする（図1）。

## ② 開腹操作

術者（右利き）は，骨盤側操作で手が逆手にならないよう患者左側に立つ。第一助手は右側，第二助手は股間に立つ。まず，正中切開をする前に，皮膚と腹直筋の位置がずれないように，サイトマーキング部にストーマのための皮膚切開（縦2.5 cm，横2 cmの楕円）を行う。腹直筋前鞘を縦切開し，腹直筋を分け，後鞘は外側にずらして縦切開してガーゼを挿入しておく。

人工肛門を左側腹部に造設するため，臍を右に回る正中切開を行う。頭側はCTで下腸間膜動脈根部の位置を確認し，その高さまで切開する。尾側は恥骨上縁まで切る（図2）。開腹後は，病変の進行度（肝・腹膜転移，リンパ節腫大）の評価を行う。

Applied wound retractor を創縁にかけた後，Codman 社製 Bookwalter 開創器にて術野を展開し，視野を確保する。小腸は厚手の大きなガーゼで頭側に納め，術野に出てこないようにブ

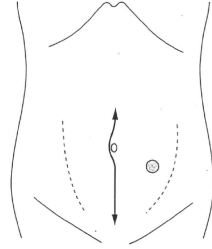


図2 腹部皮膚切開

ストーマの皮膚切開をまず行う。

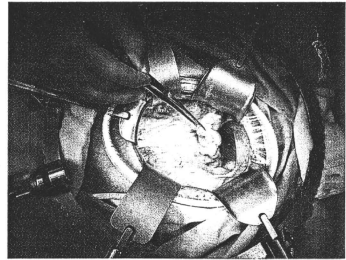


図3 開腹創の展開

左が頭側。S状結腸（鉗子把持）。鉤が4葉以上のものを使い，頭側から尾側まで十分に開創する。操作術野ごとに鉤の引き具合を調整し，広い視野を得る。

レードで押さえておく（図3）。

## ③ 中極側郭清，口側結腸処理（図4）

広い視野でS状結腸を左傍結腸溝から授動。授動の層は，癒合筋膜（S状結腸間膜後葉と背側腹膜の癒着）を剥離する層で行う。この層では，尿管，gonadal vessels，上下腹神経叢が自然と背側に温存される。S状結腸間陥凹周辺を行う。そして，大動脈右縁に沿って頭側に下腸間膜動脈分岐まで腹膜切開を延長する。上下腹

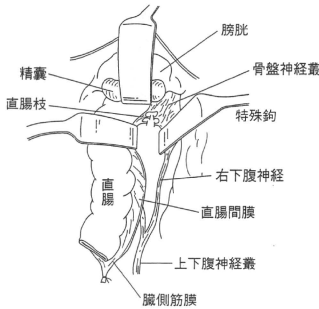


図6 骨盤神経叢の剝離

男性狹骨盤腔でも、特殊鉤での展開で適切な層での剝離を視認しながら行う。

で切開できないこともある。挙筋上腔はそれまでの間隙より一層疎であり、容易に鉤で空間が展開できる間隙なので、空間の展開が容易でなく、肛門挙筋の筋腹が確認できなければ、まだ直腸仙骨筋膜が切離できていないと判断し、残っている仙骨前面の筋膜を思いきって切開しなければならぬ<sup>2,3)</sup>。尾骨までの剝離が指で確認できれば最もよいが、肛門挙筋の確認は必須である。

②骨盤底腹膜切開を奥に進め、直腸膀胱窩、直腸子宮窩で切開線を合流させる。左右の腹膜切開の目安は直腸間膜脂肪と周囲の脂肪組織は境界があるので、注意深くこれを追う。直腸膀胱・子宮窩では、いったん精囊、腔壁につき当たり、Denonvilliers 筋膜を切除側につけて剝離する。経産婦は、正中中部で腔壁と癒着があることが多いので、このような場合は最初に正中を剝離することにこだわらない。

③前方と後方を見ながら、途中に残っている骨盤神経叢からの直腸枝を切離する。梨状筋の奥から立ち上がる骨盤内臓神経を見ながら直腸を反対側に牽引すると、テント状に持ち上がる

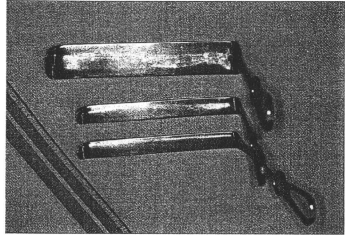


図7 骨盤内用特殊鉤

3×23 cm, 1.5×18 cm (90°, 110°の2種類の開き角)を男性用に使用する。

骨盤神経叢から出ている直腸枝が確認でき、1本ずつ切離する。切離するたびに直腸が授動される感触を得る(図6)。奥に入れれば入るほど、特に男性では視野が狭くなる。細身の長い特殊鉤(図7)を直腸側、神経側にかけて、この間隙だけに展開を絞ると、直視下に直腸枝が切離できる。最後に、神経叢下縁で折り返す壁側筋膜を切開すると、挙筋上腔まで一望できるようになる。

④精囊下縁で Denonvilliers 筋膜上では剝離ができなくなるので、これを切開し、直腸臓側筋膜上を剝離層に変更する。男性は Denonvilliers 筋膜は厚いが、女性は薄い。直腸壁に切り込まないようにきらきらと光る膜一枚(臓側筋膜)を温存する。臓側筋膜上、正中では肛門管上縁まで鈍的に剝離が可能である。正中を剝離すると、直腸前側方部分に骨盤神経叢から精囊/前立腺あるいは子宮/腔に向かう neurovascular bundle と連続する結合組織が残っていることがわかる。ここには副中直腸動静脈とされる血管群があり、最も出血しやすい<sup>4)</sup>。剝離してある正中から鉗子を通し、vessel sealing sys-

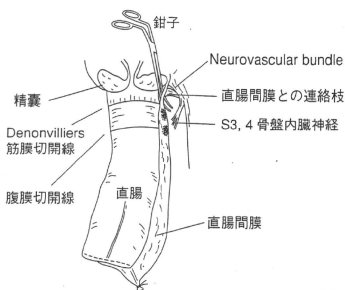


図8 直腸前側方での剥離

Denonvilliers 筋膜を切開し、neurovascular bundle と直腸間膜の連絡枝を切離。

tem や超音波振動メスにて凝固して切離していく(図8)。奥にいくと視野が悪くなるが、肛門管上縁までできれば会陰側の操作が楽になる。

#### ⑤ 会陰側操作

会陰側操作の際は、強い砕石位、頭低位とする。臀部、肛門部の皮膚がピンと張った状態にすることが切離操作、視野の展開に重要である。2-0 絹糸を折り返し2本とし、肛門を巾着縫合(刺入部は0, 6時の2点のみ、細かくするとヒダの隙間から便が漏れる)にて閉鎖する。

皮膚切開は、肛門括約筋外縁、前方は陰囊下縁、陰下縁で後方は尾骨近くまで行う。ローンスターリトラクターをかけ、術野を広く展開する。坐骨直腸窩は外括約筋外縁を垂直に肛門挙筋まで、脂肪を電気メスにて切開していく(図9)。腫瘍が外括約筋を超えているようであれば、外科的剥離面の確保のため、大臀筋、坐骨結節を目安とした剥離を行う。肛門挙筋直上下直腸動静脈は存在するので、確認して切離する。会陰側での内陰部動静脈の郭清は行わない。前方は浅会陰横筋下縁を剥離の上縁とする。こ

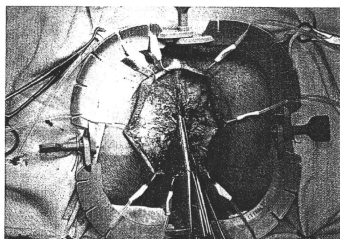


図9 会陰側皮膚切開

ローンスターリトラクターで術野を展開し、坐骨直腸窩脂肪を切開していく。

れ以上、上方に進むと内陰部動静脈の枝が正中に寄ってきて、一挙に出血しやすくなる。下方では、尾骨を指で触れながら、尾骨直腸靭帯を切離する。尾骨前面に沿うと、壁側筋膜下に入るの、この壁側筋膜も切開して骨盤腔と交通させる。さらに左右に回り込んで肛門挙筋を切離する(図10)。2/3ほど挙筋を切開したら、口側断端をつかみ、直腸を会陰側に引き抜く。鉤で展開しながら、直腸を恥骨側に吊り上げている恥骨直腸筋を切開していく。電気メスで筋の攣縮を見ながら、前立腺、腔寄りで行う(図11)。恥骨直腸筋が切開できても、肛門管上縁では直腸と前立腺、腔とが両側で結合織によりまだ連続している。腹側正中での剥離層を確認しながら、頭側から尾側(会陰小体:横紋筋の合流部)に向かって電気メスで切離する。会陰小体の頭側、尿道の背側で、直腸尿道筋(平滑筋で、静脈が多い)<sup>5-7)</sup>が直腸を前方に引っ張っており、この部は出血しやすく、横紋筋のように電気メスによる攣縮がみられないので直腸筋層と区別がつきにくく、直腸壁筋層に入り込みやすいとされている(図12, 13)。特に前壁にある腫瘍ではよく層を見きわめながら、必要であれば直腸尿道筋を切除し、外科的剥離面を確

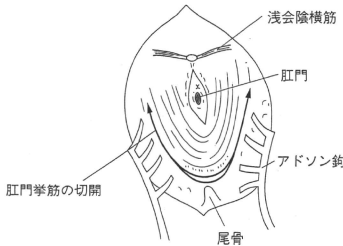


図 10 坐骨直腸窩，肛門挙筋の切開

前方は浅会陰横筋まで，後方は尾骨先端を目安にして，坐骨直腸窩脂肪，肛門挙筋を切開する。

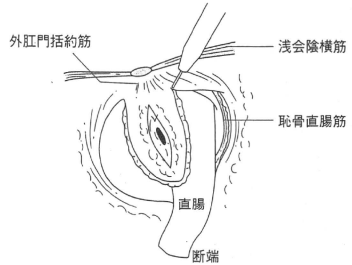


図 11 前方での恥骨直腸筋の切離。

直腸断端を脱肛，肛門挙筋切開を連続して，恥骨直腸筋を切離，前立腺，膈外側に至る。

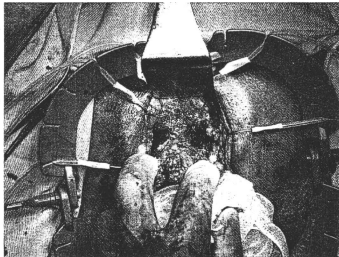


図 12 会陰小体，直腸尿道筋

直腸，肛門を下方に引いて，会陰小体および，その後ろにある直腸尿道筋を切離しようとしている。

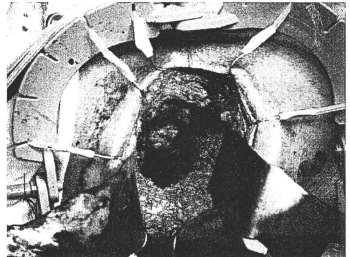


図 13 直腸切断後の会陰創

前方には浅会陰横筋，前立腺，精囊が見えている。仙骨前面からは前立腺尾側に向かって八の字状に neurovascular bundle が走行する。

保する。女性では陰に指を挿入して厚さを確認できる。前立腺に浸潤が疑われれば，前立腺全摘に変更する。膈壁は後壁を合併切除し，縫合あるいは開放とする。

骨盤腔を 50 ml 注射器を使い，合計生食 1 l で洗浄する。皮下を 4-0 PDS，皮膚を 4-0 Nylon にて結節縫合する。ドレーンは原則会陰側からは挿入しない。座るとドレーンが触り痛みが強いこと，清潔度が保てない欠点があるからで

ある。

#### ⑥ 再腹腔操作

側方郭清の術式は，本稿では省略する<sup>8)</sup>。人工肛門は原則として，後腹膜経路としている。内ヘルニアによる腸閉塞の予防，ストーマ傍ヘルニアの予防効果を期待している<sup>9)</sup>。上腹部にマーキングされた場合，非常に間膜内脂肪が厚い場合，腹腔経路としている。腹膜トンネル作