FIGURE 3 Disease-free survival curves of patients with and those without lateral lymph node dissection in stage II and stage III disease.
LLD: lateral lymph node dissection. There was no significant difference between the two groups for stage II (p=0.1815) or stage III (p=0.0896) by the log-rank test.
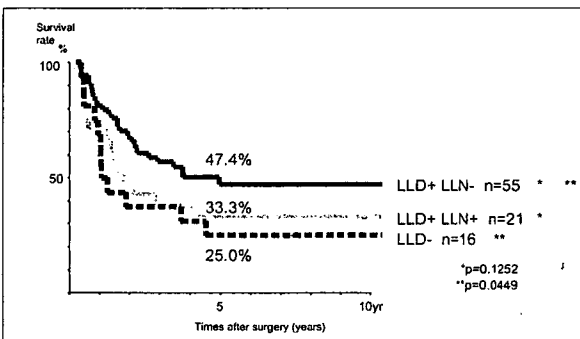

FIGURE 4 Disease-free survival curves of three groups with stage III disease: lateral lymph node metastasis group, without lateral lymph node metastasis group, and without lateral lymph node dissection group.
LLD: lateral lymph node dissection. LLN: lateral lymph node. There was a significant difference between the LLD+LLN- and LLD- groups (p=0.0449) and no significant difference between the LLD+LLN- and LLD+LLN+ groups (p=0.1252) by the log-rank test.
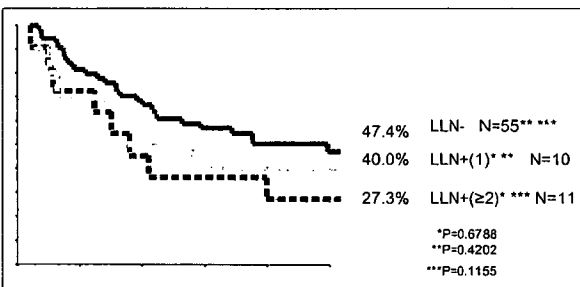

FIGURE 5 Disease-free survival curves of three groups with stage III disease: only one lateral lymph node metastasis group, two or more lateral lymph node metastases group and no lateral lymph node metastasis group.
LLN: lateral lymph node. There was no significant difference among the three groups. The survival of patients with even one lateral lymph node metastasis tended to be poorer than that of patients without lateral lymph node metastasis.

DISCUSSION

In Japan, extended operation with *en bloc* excision of both the primary tumor and superior regional lymph nodes, including the lateral nodes, was previously recommended to prevent local recurrence and improve survival in patients with advanced rectal cancer (7-9). However, this procedure disturbed urinary and sexual functions (7,10). Techniques for LLD with auto-nerve preservation were thus developed to prevent such complications (4,11-15). Surgeons at leading hospitals have introduced these techniques to Japan. We have performed LLD with auto-nerve preservation since 1990.

Many patients with advanced lower rectal cancer prophylactically undergo LLD, but the contribution of LLD to the prevention of local recurrence and improvement of survival remains unclear. The rate of lateral lymph node metastasis in advanced lower rectal cancer ranges from 13 percent to 24 percent (2,3,5,14,18). The internal iliac nodes and obturator nodes are most likely to have metastasis (6). Lateral lymph node metastasis is most often associated with 1) cancer below the peritoneal reflection, 2) mesorectal node metastasis, 3) deeply penetrating tumors, and 4) poorly differentiated adenocarcinoma (2). Patients with one or more of these conditions are thus most likely to benefit from LLD.

We studied patients who had T2 or more advanced disease because T1 tumors are usually free of lateral lymph node metastasis (18). Our analyses showed that T stage (TNM classification), N stage (TNM classification), and LLD were independently related to disease-free survival. Because LLD was one of the factors identified, we compared disease-free survival rates between patients who underwent LLD and those who did not undergo LLD. We found that LLD was associated with a better outcome than no LLD. However, this finding might have been biased by the fact that LLD was not done in patients who were elderly or had severe cardiovascular or respiratory disease. As for disease stage, there was no significant difference in the prevalence of stage II or stage III disease between patients who underwent LLD and those who did not. When we compared outcomes in stage III disease among patients without lateral lymph node metastasis, those with only one lateral lymph node metastasis, and those with two or more lateral lymph node metastases, we found that outcome was negatively affected by the presence of even one positive lateral node. Fujita *et al.* (17) reported that LLD did not improve survival in patients with stage II or III disease. However, among patients with pathological N1 (TNM classification) lymph node metastasis, those who underwent LLD had a better outcome than those who did not undergo LLD.

What is the value of LLD? The rate of local recurrence after LLD ranges from 4.8 percent to 12.5 percent (5,14,15,18,19). The difference in the rate of local recurrence rate between LLD and total mesorectal excision (TME) is minimal (16,20), and LLD has not

TABLE 6 Local recurrence Rate		
		Patients with local
	All patients	recurrence
LLD-	26	6 (23.1%)
LLD+	143	25 (17.5%)

$P=0.498$

been shown to be superior to TME. Enker *et al.* (16) reported that the local recurrence rate after TME was only 7.3 percent.

The outcomes of patients with lateral lymph node metastasis are poor owing to a high rate of relapse caused by remote metastasis. This factor may be responsible for an unbridgeable gap between potential benefits of LLD and an improvement in survival. In our study, the rate of local recurrence did not differ significantly between patients who underwent LLD (17.5 percent) and those who did not (23.1 percent). However, the rate of local recurrence among patients with lateral lymph node metastasis was 38.1 percent, implying that local recurrence was controlled in the remaining 61.9 percent. Moreover, 33.3 percent of the patients with lateral lymph node metastasis remained disease free. These patients most likely had local

rather than systemic disease. Our results suggest that LLD positively contributed to outcome in 20.6 percent of the patients with lateral lymph node metastasis.

Firm conclusions have yet to be made concerning the contribution of LLD to outcome. In Japan, randomized controlled clinical studies have been begun by the Japanese Clinical Oncology Group to clarify the role of LLD in the treatment of rectal cancer. Preoperative radiotherapy has been used to maintain sexual and urinary functions and reduce local recurrence after standard TME in patients with rectal cancer (21,22) and thereby improve their quality of life after operation. We believe that LLD and radiation therapy can substantially improve outcomes in selected patients at high risk for lateral lymph node metastasis.

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Clinical Study

Oncology

Impact of Plasma Tissue Inhibitor of Matrix Metalloproteinase-1 on Long-Term Survival in Patients with Colorectal Cancer

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Abstract

Tissue inhibitor of metalloproteinase-1 (TIMP-1) not only inhibits matrix metalloproteinases but also stimulates tumor growth. In this study, long-term follow-up results were analyzed to clarify the prognostic value of plasma TIMP-1. Preoperative plasma TIMP-1 was measured from peripheral blood samples of 87 Japanese patients with colorectal carcinoma. All the patients underwent surgical resection and were followed for 5 years prospectively. The median follow-up period was 70 months (60–79 months). The cutoff value of plasma TIMP-1 was set at 170 ng/ml based on the ROC curve. Sensitivity and specificity to predict 5-year survival was 66.7 and 55.0% with this cutoff value. In univariate analyses for overall survival, lymph node metastasis, serosal invasion, peritoneal metastasis, liver metastasis, metastasis to other distant organs and TIMP-1 were significant. In multivariate analyses, lymph node and liver metastases, metastasis to other distant organs and plasma TIMP-1 were independent prognosticators, but p values of TIMP-1 did not reach statistical significance. Our results suggested that the preoperative plasma TIMP-1 concentration could be a useful prognosticator of long-term survival in patients with colorectal carcinoma.

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Introduction

Every year, more than 945,000 people develop colorectal cancer in the world, and around 492,000 patients die [1]. Further, despite intended curative surgery, 50% of these patients experience relapse, which is invariably fatal [2]. In Japan, the westernization of lifestyle, especially dietary habits, has progressed remarkably since 1950 and is presumably directly related to the increasing incidence of colorectal cancer [3]. Colorectal cancer is the third leading cause of death due to cancer in Japan [4]. The Study Group of the Japanese Society for Cancer of the Colon and Rectum on Postsurgical Surveillance of Colorectal Cancer reported that the recurrence rates of stage I, II and III cancers were 3.7, 13.3 and 30.8%, respectively (p < 0.0001) [5, 6]. They reported that the curves of the cumulative appearance rate of recurrence in stage II and III patients showed a rapid increase for the first 3 years. Recurrence after 5 years was less than 1% in each stage [5].

A variety of new biomarkers including oncogenes, tumor suppressor genes, angiogenic factors and proteinases have been examined and discussed in relation to tumor progression and patient survival. However, none of them have proven superior to the conventional pathologic markers in determining prognosis.

Tissue inhibitor of metalloproteinase-1 (TIMP-1) not only inhibits matrix metalloproteinases but also stimulates tumor growth [7, 8]. TIMP-1 expression has been reported to correlate with disease progression in patients

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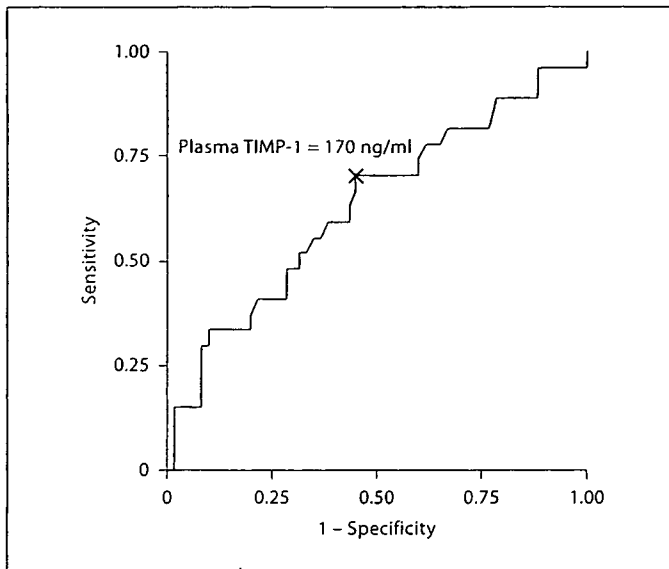Tel. +81 45 787 2645, Fax +81 45 786 0226, E-Mail nryukawa@mac.com

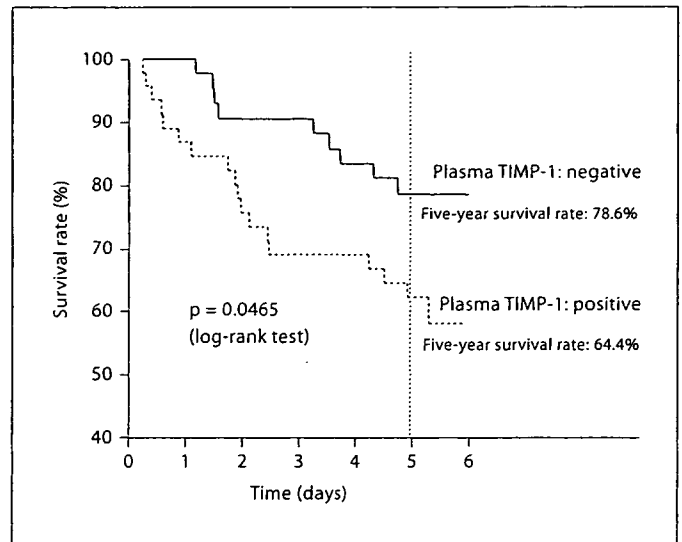Fig. 1. ROC curve for survival obtained from plasma TIMP-1.

Fig. 2. Survival curves in patients with negative or positive plasma TIMP-1.

with colorectal carcinoma [9]. Zeng et al. [10] indicated that there was a correlation between TIMP-1 mRNA level and advanced stage. TIMP-1 has been examined not only in tumor tissues but also in blood samples. Serum TIMP-1 levels have not shown any correlation with tumor progression [11]. Previously, we reported that plasma TIMP-1 could be a marker for tumor progression [12] and a prognosticator for short-term survival [13] in patients with colorectal cancer. We reported that plasma TIMP-1 could predict serosal invasion, lymph node and liver metastases, and Dukes' C with an accuracy of 68.5, 66.7, 70.4 and 68.5%, respectively, and would be a significant prognostic factor 1 year after surgery.

Generally, most recurrence has been reported to occur within 2–3 years after surgical resection for colorectal cancer [2]. To assess the prognostic value, a follow-up period of more than 5 years is recommended. However, the clinical significance of TIMP-1 for long-term survival has not been fully clarified. In this study, the results of long-term survival were analyzed to clarify the prognostic value of plasma TIMP-1.

Patients and Methods

Peripheral blood samples were collected from 87 Japanese patients with colorectal carcinoma at the Kanagawa Cancer Center, Yokohama, Japan, between June 1999 and July 2000. Concentrations of TIMP-1 protein were measured by enzyme-linked immu-

nosorbent assay in plasma samples. Clinical and pathologic classifications followed previously established rules [6]. The depth of invasion was categorized into two groups: tumors confined to the proper muscle layer and those invading the subserosal layer or deeper tissue in pathological findings. Metastases to the lymph nodes, liver, peritoneum and other distant organs were also divided into two groups: tumors with and without metastases. Subsequently, all the patients underwent surgical resection and were followed for 5 years prospectively.

Statistical Analysis

Overall survival was evaluated by univariate and multivariate analyses. Survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test. Multivariate survival analyses were performed by Cox's proportional hazard model. $p < 0.05$ was considered statistically significant, and data were expressed as means ± SD.

Results

The median follow-up period was 70 months (60–79 months). TIMP-1 was elevated in 45 patients (51.7%) when the cutoff value was set at 170 ng/ml based on the ROC curve (fig. 1).

Sensitivity and specificity to predict 5-year survival was 66.7 and 55.0%, respectively, with this cutoff value. The TIMP-1 level discriminated significantly the presence or absence of lymph node metastasis, serosal invasion and stage (table 1).

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Rino/Masuda/Imada

Table 1. Patient characteristics

Characteristics	TIMP-1 negative (n = 42)	TIMP-1 positive (n = 45)	p value
Sex, male/female	25/17	29/16	0.636
Age, years	63.17 ± 2.02	65.4 ± 1.44	0.365
Macroscopic type[a]			
Type 0 (early cancer)	4	0	0.214
Type 1	8	6	
Type 2	26	32	
Type 3	3	6	
Type 5	1	1	
Histologic type			
Well differentiated	20	16	0.254
Moderately and poorly differentiated	22	29	
Lymph node metastasis			
Negative	23	13	0.014
Positive	19	32	
Serosal invasion (ss and more)			
Negative	11	3	0.013
Positive	31	42	
Peritoneal metastasis			
Negative	41	43	0.598
Positive	1	2	
Liver metastasis			
Negative	38	36	0.171
Positive	4	9	
Metastases to distant organs			
Negative	2	4	0.448
Positive	40	41	
Remaining			
R0	40	34	0.010
R2	2	11	
Stage			
I	9	2	0.20
II	13	9	
IIIA	11	11	
IIIB	3	11	
IV	6	12	

Statistical comparisons between the two groups were performed by unpaired Student's t and χ^2 tests.

[a] Pathological measures according to the general rules of the Japanese Research Society for Cancer of the Colon and Rectum [6].

Table 2. Univariate analysis of clinicopathological factors

Factors	p value	Hazard ratio
Sex		
Male vs. female	0.9995	0.00
Age		
<59 vs. >60 years	0.2904	1.12
Histologic type		
Well vs. moderately and poorly differentiated	0.1157	2.47
Depth of invasion		
Mp vs. ss	0.0443	4.04
Lymph node metastasis[a]	0.0025	9.13
Peritoneal metastasis[a]	0.0218	5.26
Liver metastasis[a]	0.0000	47.91
Metastasis of distant organs[a]	0.0000	21.80
Plasma TIMP-1[a]	0.0465	3.96

[a] Negative versus positive.

Table 3. Multivariate analysis of clinicopathological factors

Factors	p value	Hazard ratio
Lymph node metastasis[a]	0.022	3.244
Liver metastasis[a]	0.000	9.555
Metastasis of distant organs[a]	0.003	4.483
Plasma TIMP-1[a]	0.075	2.131

[a] Negative versus positive.

In multivariate analyses for clinicopathological factors, lymph node and liver metastases, and metastases to other distant organs were significant independent prognosticators, but TIMP-1 did not reach statistical significance (table 3).

Discussion

A variety of new biomarkers, including oncogenes, tumor suppressor genes, angiogenic factors and proteinases have been examined and discussed in relation to tumor progression and patient survival. Recently, TIMP-1 expression has been reported to correlate with disease progression in patients with colorectal carcinoma [9]. Moreover, plasma TIMP-1 levels were significantly higher in patients with far-advanced colorectal cancer than in healthy controls [14]. Previously, we reported that plasma

Univariate analyses for overall survival showed significant differences in serosal invasion, lymph node, peritoneal and liver metastasis, metastases to other distant organs and TIMP-1 (table 2). Five-year survival was 64.4% in patients with positive TIMP-1 and 78.6% in those with negative TIMP-1 (fig. 2).

TIMP-1 could be a marker of tumor progression [12] and a prognosticator of short-term survival in patients with colorectal cancer [13]. To further clarify the clinical role of plasma TIMP-1 in long-term survival of patients with colorectal cancer, we classified patients into higher and lower TIMP-1 groups and attempted to follow them for >5 years prospectively, examining the prognostic value of TIMP-1 by both univariate and multivariate analyses. A cutoff value for plasma TIMP-1 was determined based on the ROC curve. Sensitivity and specificity to predict 5-year survival was 66.7 and 55.0%, respectively, with this cutoff value. In univariate analyses for overall survival, there were significant differences in preoperative plasma TIMP-1 together with other conventional clinico-pathological factors. Thus, plasma TIMP-1 was a significant prognosticator not only for short-term survival but also for long-term survival in patients with colorectal cancer. Recently, Holten-Andersen et al. [15, 16] stratified patients into four groups according to pre- and postoperative plasma TIMP-1 and demonstrated a significant association between plasma TIMP-1 and long-term survival. Moreover, they described that the combination of

postoperative plasma TIMP-1 and carcinoembryonic antigen was a significant marker for survival [16]. Our results confirm these reports in Japanese patients.

It has been generally accepted that the most important factors affecting survival are depth of tumor invasion, extent of lymph node metastasis and presence of distant metastases [17]. In our study, univariate analyses for overall survival showed significant differences in serosal invasion, lymph node, peritoneal and liver metastases, metastases to other distant organs and TIMP-1, and in multivariate analyses, lymph node and liver metastases, metastasis to distant organs and TIMP-1 were independent prognosticators. Although the p value of TIMP-1 did not reach statistical significance, its prognostic value was superior to serosal invasion and peritoneal metastasis.

Plasma measurement of TIMP-1 is simpler, easier and more reproducible than the other molecular markers examined in the tumor. Information on TIMP-1 could be available before computed tomography is performed, and the pathological findings could be examined only in the resected specimen. Thus, plasma TIMP-1 could be a useful prognosticator in patients with colorectal carcinoma.

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Rino/Masuda/Imada

Functional Outcome After Sphincter Excision for Ultralow Rectal Cancer

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This article shows a prospective study investigating bowel function after transanal rectal resection with internal and external sphincterectomy for low rectal cancer. Eight patients underwent standard low anterior resection with colonic J-pouch anal anastomosis (LARJ), and eight patients underwent transanal rectal resection with internal and external sphincter resection (IESR). Manometry, manovolumetry, transit time study, and a questionnaire were performed before and after the operation. Six and 12 months after the operation, maximum resting pressure and squeezing pressure were significantly lower in IESR group than in LARJ group, whereas there was no significant difference between the two groups in terms of constant sensation, maximum tolerable volume, or neorectal compliance. Although the functional score of the IESR group remained low at 6 months after the operation in comparison with the LARJ group, it improved at 12 months after the operation. Transanal rectal resection with internal and external sphincterectomy showed usefulness in preserving bowel function and avoiding permanent colostomy.

Key words: Rectal cancer – Anus-preserving operation – Anorectal function – Intersphincteric resection – External sphincter muscle resection

S ince Parks[1] described sphincter-saving operation for rectal cancer, low anterior resection has gained safety with improved circular staplers and has consequently decreased the number of patients with permanent colostomy. The sphincter-saving operation using a colonic J-pouch to preserve bowel function improves postoperative quality of life and has become a widespread treatment for rectal cancer.[2–4]

In 1994, Schissel *et al*[5] reported intersphincteric resection (ISR) for a rectal cancer located in the vicinity of the anal canal. Although anal sphincteric resection preserving the anus has been applied even to those with low rectal cancer or anal canal cancer to avoid permanent colostomy, those studies on postoperative anal and bowel functions are still unknown.

Curative treatment of rectal cancer requires not

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only resection of the internal anal sphincter muscle for carcinoma invading the internal anal sphincter muscle but also partial resection of the deep-superficial external anal sphincter muscles for carcinoma invading their muscles. This is the first prospective study comparing early postoperative bowel function between standard low anterior resection with colonic J-pouch anal anastomosis (LARJ) and transanal rectal resection with internal and external sphincter resection (IESR) in patients with low rectal cancer or anal canal cancer.

Patients and Methods

From January 2001 to December 2001, LARJ and IESR were performed in 16 patients with low rectal cancer or anal canal cancer. We assessed the patients by verbal and written information about the objective, importance, and procedure of the study, and we obtained their consent to examination and operations. Before surgery, the distance from the dentate line to the lower edge of tumor was measured with a rigid rectoscope. Diagnosis for whether the tumor infiltrated the internal-external anal sphincter muscles or not was made from computed tomography (CT) and ultrasonography.

Rectal cancer with its lower edge locating at 2 cm or more from the dentate line was indicated for LARJ, whereas ISR was applied if the lower edge was within 2 cm from the dentate line and the tumor invasion was limited to the internal sphincter muscle. IESR was applied if the tumor invasion was suspected beyond the internal sphincter muscle.

Operative procedure

According to the transabdominal approach, the inferior mesenteric artery was severed, and the rectum was resected including total mesorectum. Splenic flexure was completely mobilized. The anal canal was resected including the dentate line at the intramuscular groove by transanal approach. The IESR group consisted of eight patients.

Figure 1A shows the schema of ISR. The indication is applied for T1 or T2 cancer invading within the muscle layer. The dentate line is also excised, and the anal canal is removed at the intermuscular groove. The puborectal muscle and external sphincter muscles are all preserved. Figure 1B shows the schema of ESR. The indication is applied for T3 cancer invading beyond the muscle layer. The puborectal muscle is cut off. The dentate line is also excised, and the anal canal is removed at the intermus-

cular groove. The subcutaneous external sphincter muscle is preserved.

Five patients underwent ISR, and three patients underwent transanal rectal resection with IESR; however, only the subcutaneous external sphincter muscle was preserved (Fig. 1). The colonic J-pouch anoderm anastomosis including subcutaneous external sphincter muscle was performed. Temporary ileostomy was also performed in all patients. The stoma was closed 3–10 months after operation.

Physiological examination

Anorectal function test and transit time study were conducted before operation and 6 and 12 months after operation. The manometric study was performed by the pull-through procedure with an 8-Fr water-filled open-tip catheter,[4,6] which measured the maximum resting pressure (MRP), high-pressure zone (HPZ), and maximum squeezing pressure (MSP). The manovolumetric study was performed by an 8-Fr catheter attached a latex dilatation balloon to be inserted into the rectum, which measured the constant sensation (CS), the maximum tolerable volume (MTV), and compliance.[7] Biofeedback with anal manometry, digital examination, and exercises by instrumentation were performed when the patients visited.

The time transit study was performed by the Sitzmarks (ring type, double D type and Tri-chamber type; Konsyl Co.). They were orally administered after breakfast for 3 days, and abdominal radiography was taken on the fourth day. During this period, any medications or treatments that affected bowel movements were withheld. We measured the whole transit time and segmental transit time study. The whole transit time and the segmental transit time in two areas of the large bowel, i.e., transit time in the right colon (cecum, ascending colon, and transverse colon) and transit time in the left colon (descending colon, sigmoid colon, and neorectum), were calculated by the method of Arhan et al and Metcalf et al[8,9] Ten patients with colon cancer without obstruction served as preoperative controls, Their preoperative transit times were compared with the transit times of the two groups.

Questionnaire

Patients were asked to fill out a questionnaire on defecation frequency, stool consistency, dietary restriction, nocturnal defecation, distinction between stool and gas, soiling, fecal incontinence, sense of residual stool, fecal urgency, difficulty of defecation,
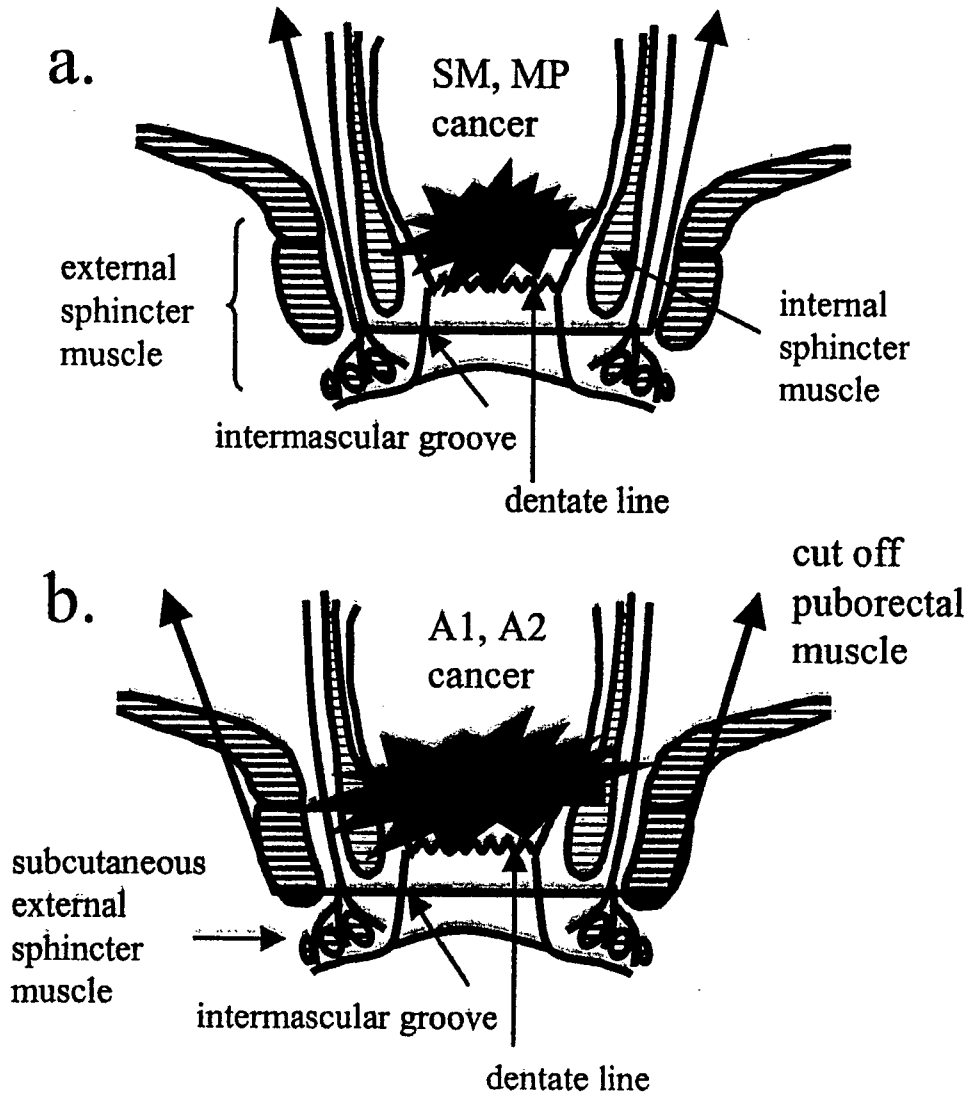
Fig. 1 (a) Schema of the internal sphincter resection line. (b) Schema of the external-internal sphincter resection line. SM, tumor invasion of submucosa; MP, tumor invasion of muscularis propria.

sense of controlling the anus, curtailment of daily activities, and limitation on outing and traveling. Bowel functional score were assessed by Komatsu's score. Three parameters (bowel frequency, soiling, and urgency) were evaluated and scored 0 (poor), 1 (fair), or 2 (good) to obtain the functional score ranging from a total of 0 to 6.[10] Continence grading was assessed by five parameters of Wexner's Continence Grading Score.[11]

Statistical analysis

The statistical analysis of quantitative variables was performed using the Mann-Whitney *U* test and Wil-

coxon signed ranks test for comparison between groups and evaluation of time-related changes. *P* < 0.05 was considered statistically significant.

Results

As Table 1 shows, there was no significant difference in male/female ratio or age between the LARJ (n = 8) and IESR groups (n = 8). The lower edge of tumor was located at 4.1 cm on average from the dentate line in the LARJ group and at 1.3 cm in the IESR group. The length of internal anal sphincter muscle removed in the IESR group measured an average of

Table 1 Patient characteristics

	LARJ group (n = 8)	IESR group (n = 8)
Sex (male/female)	6/2	5/3
Age	62 (48–84)	61 (45–74)
Dukes stage (A, B, C)	2,3,3	4,2,2
Anastomotic length from the anal verge (cm)	4.1 (3.5–5)	1.3 (0.5–2.0)
Operative time (min)	377	361
Morbidity	1 (12.5%)	2 (25%)
Postoperative ileus	0 (0%)	2 (25%)
Pouchitis	1 (12.5%)	0 (0%)
Leakage	0 (0%)	0 (0%)

14.7 ± 5.9 mm in diameter. However, the internal anal sphincter muscle in the LARJ group was not removed. Postoperative leakage was not found in the two groups. Pouchitis was found in one patient in the LARJ group. Postoperative ileus was found in two patients in the IESR group.

IESR required an average of 361 minutes in operating time. On the other hand, LARJ required an average of 377 minutes. Figure 2 summarizes the data on functional tests (manometry). MRP values in the IESR group were significantly decreased 1 month after surgery and were not significantly improved 12 months after surgery. On the other hand, MRP values in the LARJ group were improved 12 months after surgery. (Strong contraction waves in the pouch were not found in both groups.) The HPZ values were significantly decreased after IESR because the value was 1.5 ± 0.4 cm and that showed no significant improvement at 12 months after surgery. Postoperative MSP values showed a significant decrease in the IESR group compared with the value of the LARJ group. Both groups significantly decreased the MTV values at 1 month after surgery. Figure 3 shows the data on the manovolumetric study (manovolumetry). MTV in the LARJ group showed improvement at 12 months after surgery compared with the preoperative values, but in the IESR group, there was no improvement. In IESR patients, CS values were 1.5 ± 1.3 ml/cm H_2O at 6 months after surgery, indicating a significantly lower compliance; this was maintained at 12 months after surgery, with a CS value of 2.3 ± 0.8 ml/cm H_2O.

Figure 4 shows results of the transit time study. The difference in transit time through the whole colon between the two groups was not statistically significant at 6 months after surgery. The transit time in the left colon was 14.6 ± 9.2 hours in the LARJ group and 11.6 ± 5.5 hours in the IESR group at 12
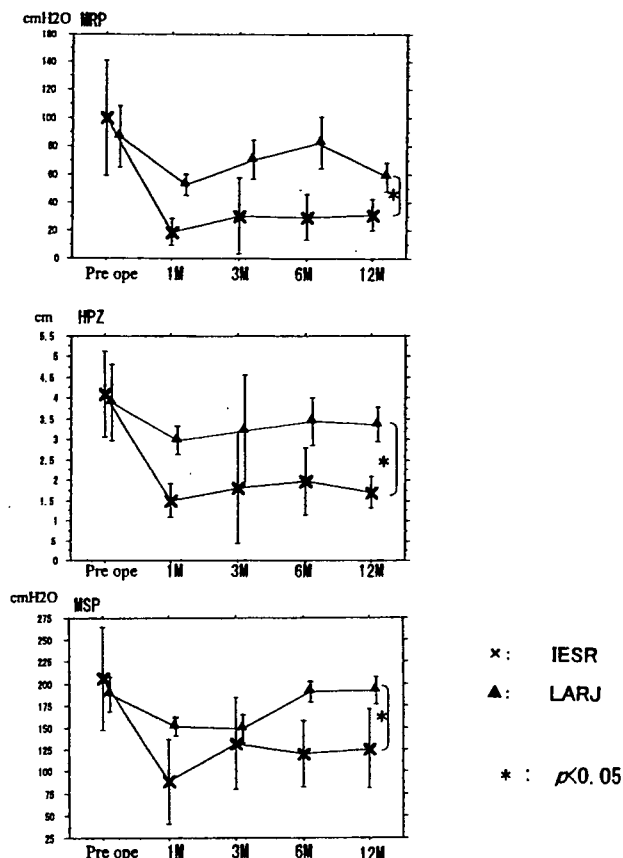

Fig. 2 Manometric examination in comparison of the IESR group with the LARJ group. M, months after surgery.

months after surgery, and this showed a trend toward delayed transit in the left colon compared with that of preoperative control patients.

As for the functional score (Table 2), it was 3.0 ± 1.3 in the IESR group at 6 months after surgery, which was significantly lower than 5.2 ± 1.0 in the LARJ group. However, the IESR group showed a trend toward improvement, with a score of 3.8 ± 1.8 at 12 months after surgery (Fig. 5). Analysis of each parameter revealed frequent defecation in the IESR group at 6 months after surgery. The number of defecations was 6.0 ± 2.8 in the IESR group compared with 4.4 ± 2.2 in the LARJ group; however, this decreased with time to 2.7 ± 1.2 in the IESR group and 3.2 ± 1.4 in the LARJ group at 12 months. Night soiling was observed in six IESR patients (three ISR patients and all three ESR patients) at 6 months after surgery, but was limited to one LARJ and two IESR patients (two ESR patients) at 12 months after surgery. Postoperative urgency was not significantly different between the two groups. According to the questionnaire, all patients felt more
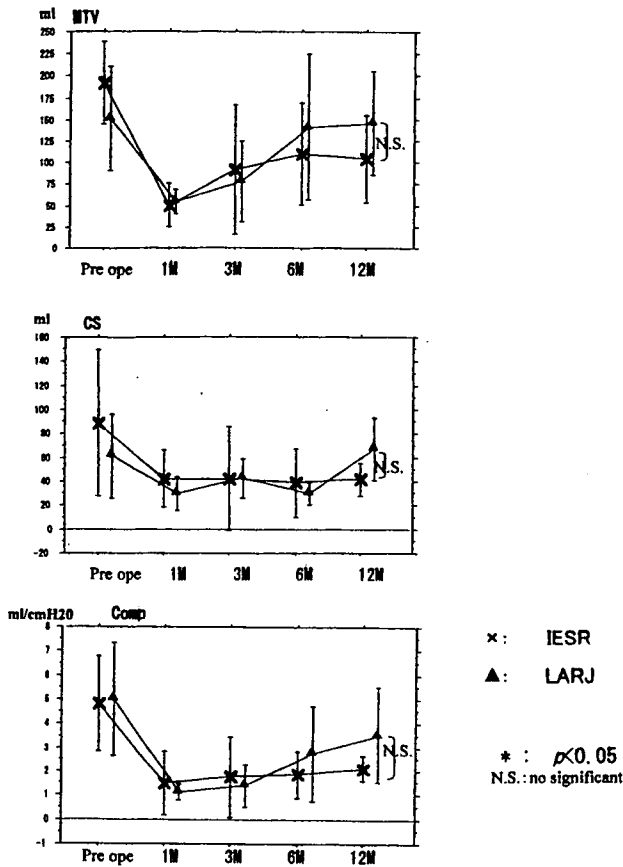
Fig. 3 Manovolumetric examination in comparison of the IESR group with the LARJ group. M, months after surgery.

Fig. 4 Transit time study in comparison of the IESR group with the LARJ group. M, months after surgery.

satisfied at 12 months after surgery than before closure of the stoma.

Table 3 shows five parameters of Wexner's Continence Grading Score. One patient in the LARJ group had incontinence at 12 months after surgery, and the IESR group also had two patients. Six of eight, patients had wearing pads at 6 months after surgery. All 3 ESR patients needed pads. However, they did not need wearing pads at 12 months after surgery. Only one ISR patient needed a pad at 12 months after surgery.

Neither anastomotic recurrence nor mortality was seen during the mean of 16.1 months of follow-up. One patient had para-aortic lymph node metastasis and died of lung metastasis. Another patient had pelvic recurrence and received abdominoperineal resection.

Discussion

Sphincter-saving operations to avoid a permanent stoma have been adopted as an operative interven-
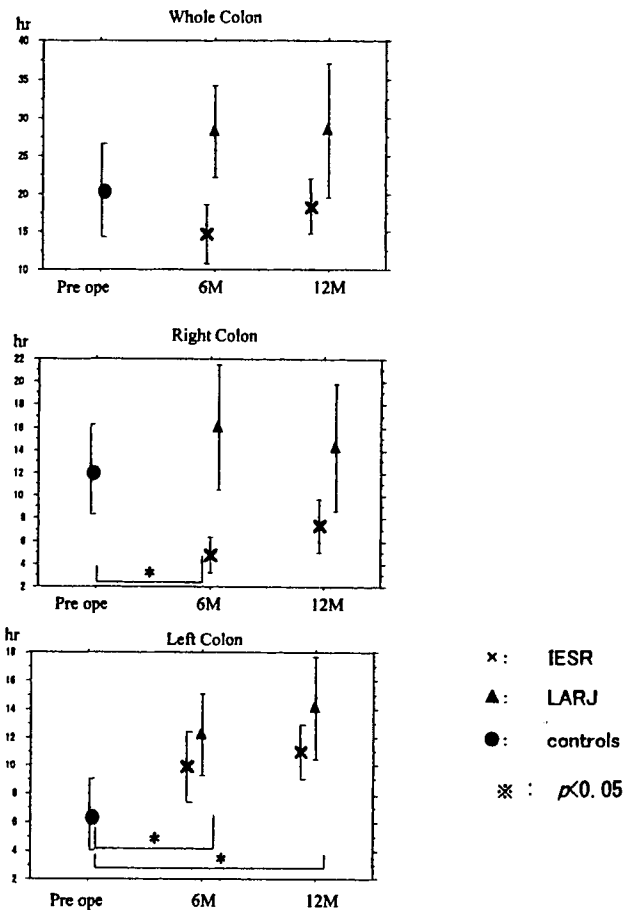
tion for low rectal cancer since the 1940s.[12,13] Since safe methods for mechanical anastomosis and transanal anastomosis were established, the sphincter-saving operations securing good anal function have gained increased popularity. ISR, an operative modality resecting the internal anal sphincter muscle

Table 2 Functional score

	Score		
	0	1	2
Bowel frequency (times/day)	>6	3–6	≤3
Fecal incontinence (times/wk)	>2	≤2	Never
Urgency (ability to defer defecation)	<10 minutes	10–30 minutes	>30 minutes

Three parameters (bowel frequency, soiling, and urgency) were evaluated and scored 0 (poor), 1 (fair), or 2 (good) to obtain the functional score ranging from a total of 0 to 6.
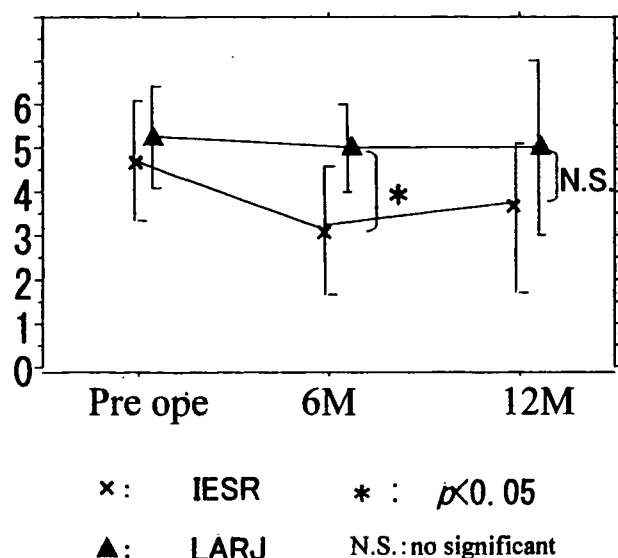
50

Fig. 5 Functional score in comparison of the IESR group with the LARJ group. M, months after surgery.

and preserving the anus, was reported to bring good anal bowel function and cure since 1994.[5,14,15] The new surgical strategy of preserving the anus with resection of the anal sphincter muscle seems to be replacing the standard sphincter-saving operation for the treatment of low rectal cancer or anal canal cancer extremely close to anus.

We retrospectively studied surgical specimens of 213 patients who underwent abdominoperineal resection for rectal cancer. According to our histological examination, we found that internal or external sphincter muscle resection could be a curative therapy for preserving the anus for low rectal cancer or anal canal cancer.[16]

In this prospective study, we compared IESR and standard low anterior resection concerning early postoperative anal and bowel function. It is well known that MRP and HPZ reflect internal anal sphincter muscle function, whereas MSP reflects external anal sphincter muscle function.[17] MRP, HPZ,

and MSP were significantly lower after IESR than those after LARJ. MTV indicating neorectal capacity[17] decreased 12 months after surgery in the IESR group compared with that of the LARJ group, although there was no significant difference between the two groups. This suggests that IESR caused sphincteric insufficiency, leading to precocious detachment of the rectal balloon and making it difficult to evaluate function of the pouch, in contrast with normal sphincter muscle function after LARJ.

Furst et al[18] noted that a short pouch of 5 cm in length was useful in decreasing defecation frequency and preventing fecal urgency caused by abolished peristaltic waves. In our study, intestinal peristalsis was measured at the oral side anastomotic portion, but the pouch was found to be devoid of peristaltic waves. Rullier et al[14] obtained better bowel function after ISR with construction of pouch than after ISR with straight anastomosis. In their ISR patients, the functional score showed a trend toward improvement despite anorectal function remaining unchanged during the course of time. Construction of a pouch may contribute to the inconsistency between physiological findings and clinical symptoms.

The postoperative transit time in the left colon determined by Arhan et al[8] was significantly increased in both groups over preoperative values of the preoperative control group. This is explained by the decrease of blood flow in the left colon after severing of the inferior mesenteric artery and by the decrease of motility of the left colon after dissection of the parasympathetic nerve. The delayed transit in the left colon seems to be a benefit for bowel function for IESR. The lack of peristaltic waves caused by construction of pouch may also contribute to maintaining good bowel function for IESR. It was reported that ISR was accompanied by frequent defecation, fecal urgency, and fecal incontinence, which tended to improve with time, and that neither major incontinence nor serious bowel dysfunction occurred to require reconstruction of the colostomy.[14] The incidence of minor incontinence after recon-

Table 3 Continence grading score in comparing the IESR group with the LARJ group

Type of incontinence	LARJ (n = 8)			IESR (n = 8)		
	Preoparative	6 months	12 months	Preoperative	6 months	12 months
Solid	0/8	1/8	1/8	0/8	1/8	0/8
Liquid	0/8	1/8	1/8	0/8	2/8	2/8
Gas	0/8	3/8	1/8	0/8	5/8	3/8
Wears pad	0/8	2/8	1/8	1/8	6/8	1/8
Life style alternation	0/8	1/8	2/8	0/8	6/8	2/8

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struction of the low anterior resection (LAR) with a colonic J-pouch was estimated to range from 11% to 60%.[19-26] We observed night soiling in two of eight IESR patients at 12 months after surgery. Daily remnant sphincter muscle training with biofeedback may be one of the helpful treatment for improving physiologic, clinical anal function. Post-LAR symptoms including frequent defecation, fecal incontinence, fecal urgency, and constipation were attributable to decreased anal sphincteric function and decreased capacity for feces.[27] Some investigators reported the usefulness of a colonic J-pouch against these complications.[23-26] Constructing a pouch that would delay the postoperative transit time in the left colon was found to be effective, at least for a year after IESR, in reducing frequent defecation, fecal urgency, fecal incontinence, and other adverse events observed in the early postoperative phases. However, a disadvantage was indicated with reconstruction of a colonic J-pouch; some patients complained of difficulty of defecation for a long time after surgery.[19,21,22] According to observation, the transit time in the left colon was prolonged after operation for rectal cancer, and this constituted one of causes of defecation trouble,[28] so we prepared a 6-cm short pouch, and none of our patients complained of difficulty of defecation. However, the patients in the IESR group may be suffered from the risk of developing difficulty of defecation in the future. It is well known that patients with permanent stoma suffer from mental stress, depression, and limited social function more frequently than those with a preserved anus.[29-31] Renner et al[15] compared quality of life (QOL) of patients receiving transanal anastomosis including ISR and those with stoma and concluded, on the basis of physical signs and objective evaluation, that the former had poorer QOL. They recommended that every patient to be subjected to transanal anastomosis should be fully informed of postoperative adverse events. In our study, all IESR patients felt satisfied after closure of ileostomy.

Even patients who underwent partial resection of the superficial-deep external sphincter muscles had relatively good bowel function at the time of this report. The maximum extent of sphincteric resection that preserves good bowel function is still unknown. Because sphincter function alone determined by anorectal function test is not predictive for bowel function after closure of stoma, additional predictable measures should be established. As to the oncologic results, long-term follow-up is required. Local recurrence including anastomotic site is one of the impor-

tant problems. However, we have not anastomotic recurrences.

In conclusion, a new procedure of transanal rectal resection with internal and external sphincterectomy showed usefulness in preserving bowel function and avoiding permanent stoma. Further research and long-term observation will be necessary to clarify the extent of resection of the external sphincter muscle that would secure good anal function and to evaluate the therapeutic effect of this surgical modality.

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直腸手術

Rectal surgery

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●要旨●　実際の直腸癌手術の流れに沿って起こり得る偶発症の病態と予防，および発生後の対処法について述べる。偶発症は偶然に起こるのではなく，発生の要因を理解し，良好な視野のもとに正しい手術操作を心がけることでその多くは予防できると思われる。また，偶発症に対する不適切な処置は術後の機能障害や根治性の低下の原因となり，場合によっては致命的となりかねない。とくに，大量出血となる血管損傷は特定の状況や操作時に発生するものであり，止血の基本操作や対処法を習熟することが大切である。

● key words：直腸癌，術中偶発症，脈管損傷，尿管損傷，神経損傷

はじめに

直腸癌手術は狭い骨盤腔内の操作であり，視野が不良となるため隣接する泌尿・生殖器の損傷や内腸骨動脈に沿うリンパ節郭清に伴う脈管や神経の損傷をきたしやすい。また，再発手術では癌の進展や術後の瘢痕・癒着により，偶発症の発生頻度と程度は格段に高くなる。これらの偶発症は，その対処法を誤ると根治性と機能性を著しく低下させる結果となり，時には致命的となりかねない。本稿では，直腸癌手術における偶発症の予防と対策について筆者らの経験をまじえ概説する。

手術操作と偶発症

術中偶発症発生後の適切な対処はいうまでもなく重要であるが，泌尿器系臓器損傷など偶発症のなかには術中には気づかず術後にはじめて判明するものもある。したがって，偶発症の発生を極力予防することが大切であり，実際の手術の流れに沿って起こり得る偶

発症とその防止のための手術操作のポイントを整理する（表1）。

1．S状結腸間膜の授動

S状結腸間膜と左側壁側腹膜との癒合（Monk's white line）を切開，さらにToldt's fusion fasciaに沿って切開を進め，S状結腸および下行結腸を後腹膜下筋膜（腎筋膜）前葉の層で後腹膜より授動する。正しい層を保てば左精巣（卵巣）動静脈，左尿管が容易に結腸間膜から剝離されるが，深い層での剝離は尿管や左精巣動静脈周囲の細い血管からの出血の原因となり，尿管や脈管損傷の危険がある。また，尿管周囲の止血に電気メスを過度に使用すると，遅発性の尿管損傷（壊死）をきたすことがあるので注意を要する。通常，直腸癌手術では脾彎曲部の授動は必要としないが，脾彎曲部の粗暴な操作では脾被膜や実質の裂傷をきたすことがある。操作時には脾臓の頭背側にタオルやガーゼなどを挿入しておくと脾結腸間膜の緊張がとれ，損傷を予防できる。

S状結腸間膜を正しい層で十分に剝離すると，左下腹神経，上下腹神経叢を確認して温存しつつ右下腹神経に達する。次に大動脈分岐部から下腸間膜動脈（IMA）根部2〜3cm頭側までの大動脈前面の腹膜を切開する。上下腹神経叢は左右の第2〜4腰部交

表1　手術操作と偶発症

手術操作	損傷臓器
Ｓ状結腸間膜の授動	脾臓，尿管，精巣動静脈，上下腹神経叢
下腸間膜動脈の処理	腰内臓神経，十二指腸，腎静脈
直腸後腔，仙骨前面の剥離	下腹神経，仙骨前静脈叢
前方の剥離	前立腺，腟
側方の切離	骨盤神経叢，尿管，内腸骨動静脈
直腸の切離	直腸壁，尿管，自律神経，脈管
会陰操作	尿道，前立腺，腟
側方郭清	尿管，骨盤神経叢，閉鎖神経，内外腸骨動静脈
閉腹およびドレーン挿入	下腹壁動静脈，膀胱，腸管

感神経節または腰部交感神経幹から分枝した腰内臓神経が大動脈前面で合流して形成されている。IMA 根部から大動脈分岐部までは大動脈前面からＳ状結腸間膜が立ち上がっており，Ｓ状結腸間膜を切除する際には背側から上下腹神経叢へ移行する左腰内臓神経分枝，左腰部交感神経幹を大動脈側に温存する必要がある。

2. 下腸間膜動脈の処理

IMA 根部周囲は，上下腹神経叢と腰内臓神経とのネットワークを形成する部位であり，IMA を根部で処理する場合のリンパ節郭清はこれら神経を可及的に温存するようサンプリングにとどめ，神経損傷を避ける。筆者らは，若年の男性患者に対してメチレンブルーによる神経染色法を用いた腰内臓神経および上下腹神経叢の確実な温存を心がけている[1]。左結腸動脈を温存する場合には，#253リンパ節郭清を同様にサンプリングするか省略するか症例によって選択することが術後の自律神経障害予防の観点から勧められる。

上方リンパ節の拡大郭清では，上下腹神経叢は切除され，IMA 根部より十二指腸水平脚下縁および左腎静脈下縁まで大動脈周囲リンパ節を郭清するが，十二指腸や腎静脈を損傷しないよう慎重な操作が必要である。下大静脈・大動脈間を郭清する際には下大静脈左前面からの数本の枝はていねいに結紮しておかないと，誤った止血操作による下大静脈からの大出血をきたす可能性がある。また，下大静脈・大動脈間のリンパ管本幹は結紮しておかないと術後乳糜腹水となることがあるので留意すべきである。

3. 直腸後腔，仙骨前面の剥離

上下腹神経叢・下腹神経を温存する場合，左右下腹神経が直腸固有筋膜に接しているので，左右下腹神経を確認しつつ，分枝する直腸枝を切離して直腸後腔の剥離を行う（いわゆる TME の層）。剥離層が深いと下腹神経や仙骨前面の静脈を損傷しやすい。とくに腫瘍が大きく骨盤腔を占めるような場合には，やむを得ず深い層での操作となり，視野も悪く仙骨静脈の損傷に注意しなければならない。

骨盤腔の再発手術では，仙骨前面への腫瘍の浸潤か瘢痕癒着か判断できない場合も多く，つい深い層での剥離となり仙骨静脈損傷が起こりやすい。ここでのポイントは，前方および側方の剥離が容易であればこれらを先行させ，後方切離は最後に剥離と圧迫止血操作を繰り返しつつ慎重に進めることである。

4. 前方の剥離

直腸膀胱窩の腹膜を切開し，Denonvilliers 筋膜を切除する層で精嚢，前立腺の後面を露出させる。女性の場合には直腸子宮窩の腹膜を切開し，直腸と腟を剥離する。剥離層が前方に偏ると前立腺や腟壁を損傷しやすく，前立腺，腟はともに血行が豊富な臓器であり，止血に難渋することがある。止血操作としての腟後壁の過度な電気凝固は遅発性の壊死をきたし，直腸腟瘻などの要因ともなるので注意したい。

5. 側方の切離

骨盤神経叢を温存する場合は，下腹神経を温存した直腸固有筋膜の層を延長して側方靱帯の切離を進める。後方から十分に剥離を行っておくと神経の位置と尿管の走行が確認しやすく損傷を避けられる。この側方の切離では，骨盤神経叢からの会陰枝（膀胱，前立腺）を傷つけないよう十分に注意する。前方から正しく直腸膀胱間隙を開き後方と連続させ，側方靱帯を挟み込むようにすると会陰枝の損傷が避けられる。

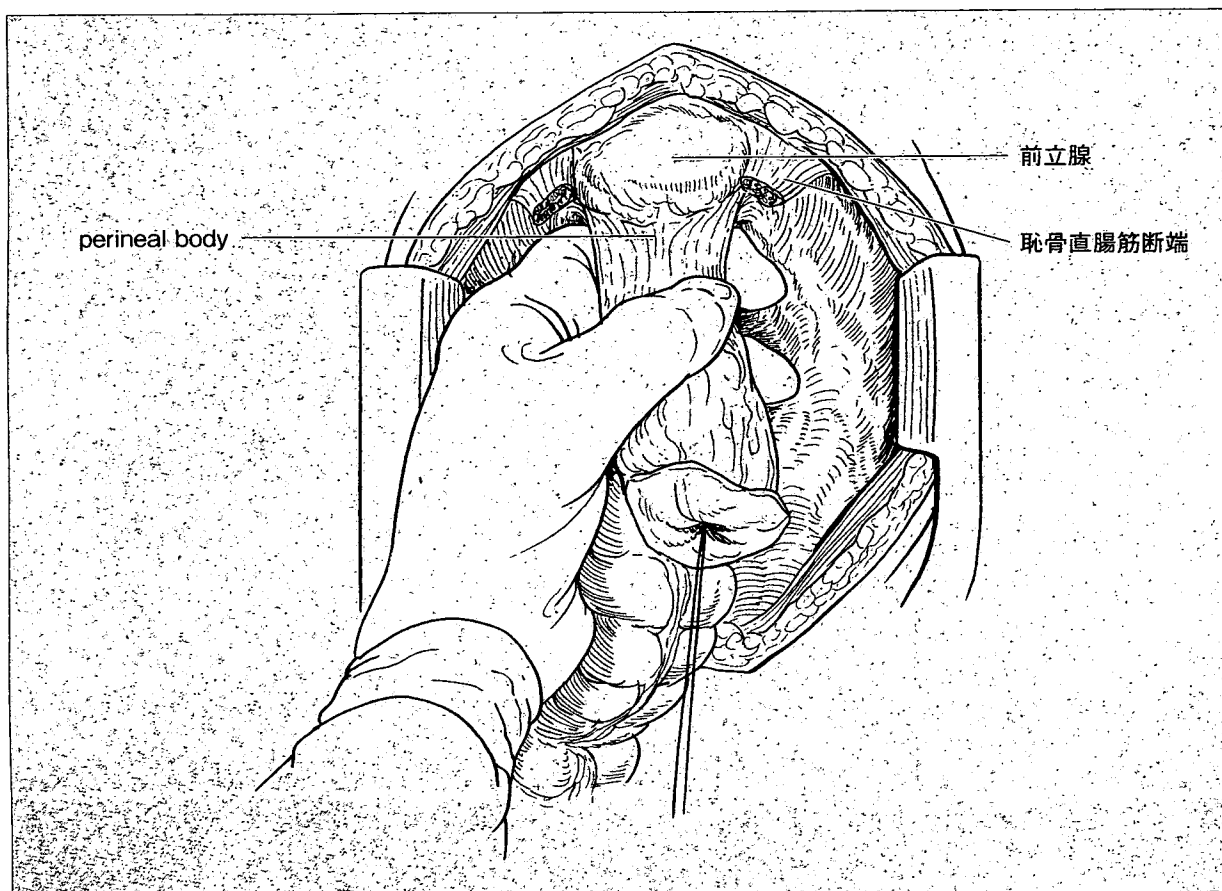初回手術で一般的な直腸癌では，側方の切離に際して内腸骨動静脈を損傷することはまれである。しかし，腫瘍が骨盤腔を占め操作が盲目的になるような場合，

図 1　直腸前面（perineal body）の剝離

あるいは再発手術においては内腸骨動静脈の損傷はもっともよく遭遇する術中偶発症であり，大量出血の原因となる。また，このような場合は尿管の走行も不明瞭なことが多く，術前の尿管ステント留置は尿管損傷予防の観点から必須である。

6.　直腸の切離

低位前方切除の場合，直腸の切離線が決定したら直腸固有筋膜を全周にわたって電気メスで切開する。次に，直腸間膜を処理するが，誤って直腸壁に切り込むと吻合の際に不具合を生じ，縫合不全の原因となる。直腸膀胱間隙を開く際はクーパー剪刀の先端を用いて鈍的に剝離すると直腸壁の損傷を避けられる。直腸の切離は linear stapler を用いるが，狭骨盤の患者では stapler で周囲組織を挟み込みやすく，尿管，神経や血管などを損傷しないよう注意する。

7.　会陰操作

直腸切断術の会陰操作では，剝離層がわかりにくい perineal body の切離に注意を要する。通常S状結腸・直腸を会陰側に脱転させてこの部位を処理するが，前方へ深く切り込むと男性では外尿道，女性では腟後壁を容易に損傷し，前立腺に切り込めば出血の原因となる。左手の親指と示指で尿道・前立腺または腟後壁を触診して確認しつつ切離を進めると損傷を回避できる（図1）。

8.　側方郭清

側方郭清は直腸を切除（切断）した後に行うのが視野展開，ひいては偶発症予防の観点からも勧められる。自律神経を温存する場合には，下腹神経および骨盤神経叢にテーピングし，鑷子などで神経を強く把持しないことが術後の性機能障害を起こさないためのコツである。閉鎖孔リンパ節の郭清では，閉鎖動静脈は細いため損傷をきたしやすいが，動静脈を切除して郭清することも可能である。一方，閉鎖神経は愛護的に扱い，損傷がないよう注意しなければならない。

側方郭清でもっとも慎重な操作が必要な部位は内腸骨静脈の剝離である。とくに，リンパ節転移巣が血管壁に接して存在する場合や再発手術の際には損傷をきたしやすい。このような場合には，むしろ内腸骨動静脈の合併切除（図2）が血管損傷防止の点からも勧め
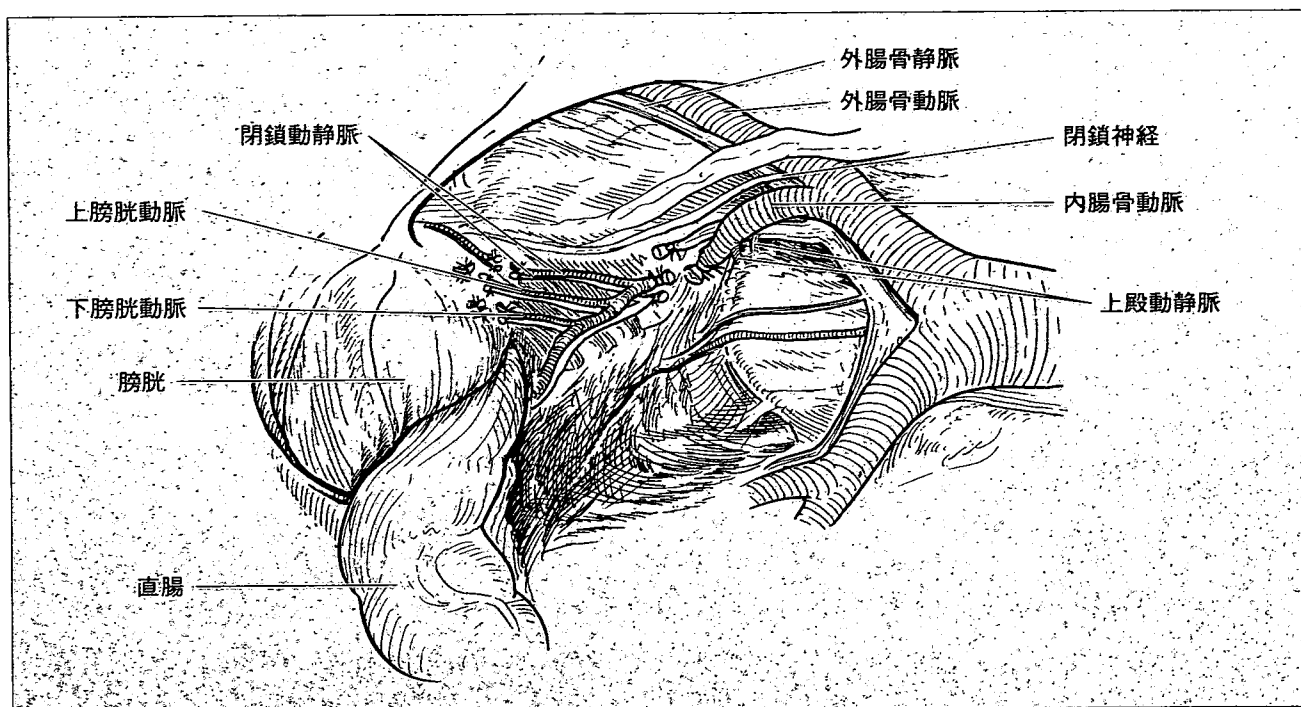
図2　内腸骨動静脈結紮切除

ラベル:
外腸骨静脈
外腸骨動脈
閉鎖神経
内腸骨動脈
上殿動静脈
閉鎖動静脈
上膀胱動脈
下膀胱動脈
膀胱
直腸

られる。

9.　閉腹およびドレーン挿入

　ドレーンの挿入で気をつけなければならない点は，腹壁の血管損傷である。とくに下腹壁動静脈を損傷すると止血が大変である。ドレーン挿入後は挿入部からの出血がないことを確認する必要がある。また，筆者らは下腹壁からのドレーン挿入の際，膀胱壁を貫通した症例を経験した。下腹部からのドレーン挿入時に腹膜，腹壁を頭側へ過度に牽引すると膀胱壁を損傷する恐れがあるので注意を要する。

　閉腹にあたっては，縫合針による腸管損傷に注意が必要である。腹壁の牽引とヘラ型の圧排鉤を用いて腸管を避けつつ運針に努めなければならない。

偶発症の対処法

1.　尿管損傷

　尿管損傷を確認したら，まず尿管ステントカテーテルを腎盂まで挿入する。損傷部が直接縫合可能であれば針付4-0のモノフィラメント吸収糸を用いて狭窄しないよう縫合する。縫合が不可能な場合には，腹膜や筋膜パッチ，大網を用いた充填などにより可及的に閉鎖する方法もある。術後2週間以上のステント留置が必要である。また，遅発性の尿管損傷が予測される場合にも術中に尿管ステントを挿入，留置することが

勧められる。

2.　尿道損傷

　会陰操作の際に損傷する尿道は前立腺部または膜様部である。術中に尿道バルールカテーテルが留置されているので，損傷は多くの場合，完全断裂とはならない。しかし，損傷尿道の背側は会陰創の死腔となるためきわめて難治性であり，可及的に縫合閉鎖したうえでバルーンカテーテルの長期継続留置による尿道の開通を維持しなければならない。術後の治療は泌尿器科専門医に相談する。カテーテル抜去後に起こる尿道狭窄に対しては，定期的なブジーを実施する。ブジーで開通が悪い場合は，直視下内尿道切開術を実施する。狭窄や閉塞による尿道の修復が必要であれば，損傷部が瘢痕化した3～6カ月後に二期的に修復する（炎症の沈静化，組織の瘢痕化を待つ）。2cm以下の尿道閉塞に関しては，内視鏡下手術が有用である。

3.　膀胱損傷

　膀胱損傷に対する処置は難しくない。むしろ損傷あるいはその可能性を認識することが重要である。損傷を認めたら，損傷部位の確実な縫合を心がける。とくに，粘膜を確認することが大切である。膀胱腹膜や筋層の部分的な損傷は，気づかず放置すると膀胱壁が皮薄化し遅発性の穿孔をきたすことがあるので注意を要する。膀胱腹膜や筋層の損傷に対しては，しっかり縫
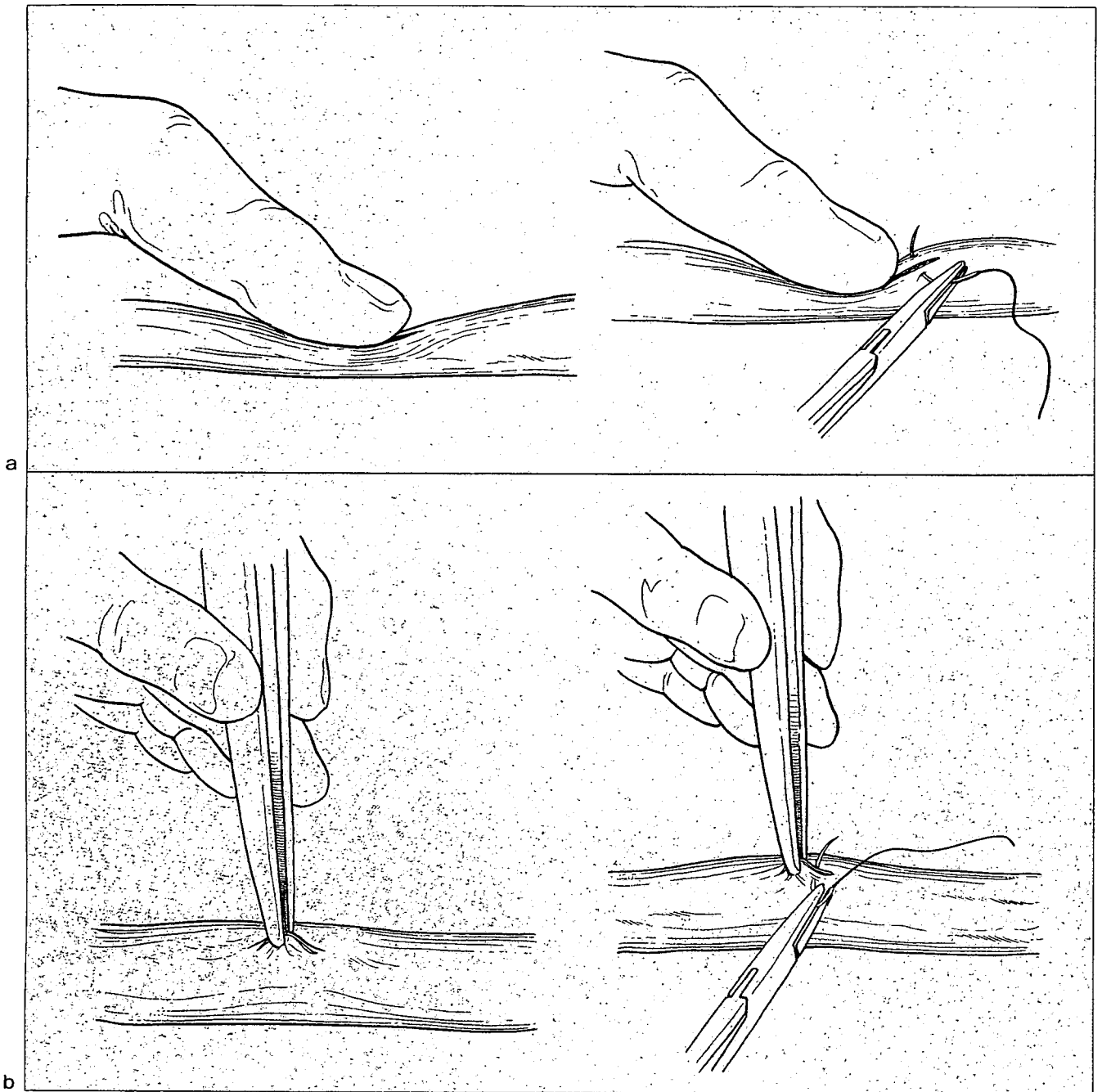
図3　止血操作の基本手技

a：手指による圧迫と側壁縫合；大・中口径動静脈に発生した比較的小さな穿孔，裂創が対象で，大きめの針付き血管縫合針を使用して必ずしも全層に針を通す必要はなく，外膜を確実に拾えればよい

b：鑷子によるつまみと側壁縫合；大・中口径の動静脈の比較的小さな損傷に適応できる。鑷子を用いて損傷部位を把持し，縫合止血する。選択する鑷子は，DeBakey タイプの無傷性血管鑷子の類，超硬チップ付無傷性ピンセットなどが安全でかつ外膜のからみ付きもよく，把持が容易である

合補強しておく必要がある。尿道バルーンは術後2週間の留置が必要で，膀胱造影後に抜去することが勧められる。

4.　血管損傷

　術中の血管損傷は本来の手術操作で予想していない事態であり，冷静さを欠いて適切な処置が行われない場合には，大量出血となる。直腸癌手術では，初回手術，再発手術問わず内腸骨静脈系と仙骨前静脈損傷に対する止血処置を習熟しておく必要がある。

　出血を認めたら，まず手指やガーゼなどの圧迫で出血を制御することが重要である。輸血の準備や循環動

表2　術中血管損傷に対する処置法

止血処置
　　1.　手指またはガーゼによる圧迫と側壁縫合
　　2.　鑷子によるつまみ
　　3.　バルーンカテーテルによる血流遮断

欠損部の修復
　　1.　部分欠損　　　側壁縫合，パッチ形成
　　2.　全周欠損　　　端々吻合，代用血管による再建

態の安定を待ってから落ち着いて止血処理を行う。出血部位を確認することが大切で，まず用指的に圧迫した部位から徐々に指をずらして出血部位を確認するが，大量に噴出して吸引器を用いても確認できない場合には，その中枢側と末梢側をツッペルガーゼなどで圧迫して観察する。出血部位への処置が困難な場合には，周囲を十分に剝離して術野を良好な視野に展開することが結果的に止血操作を容易にすることがある

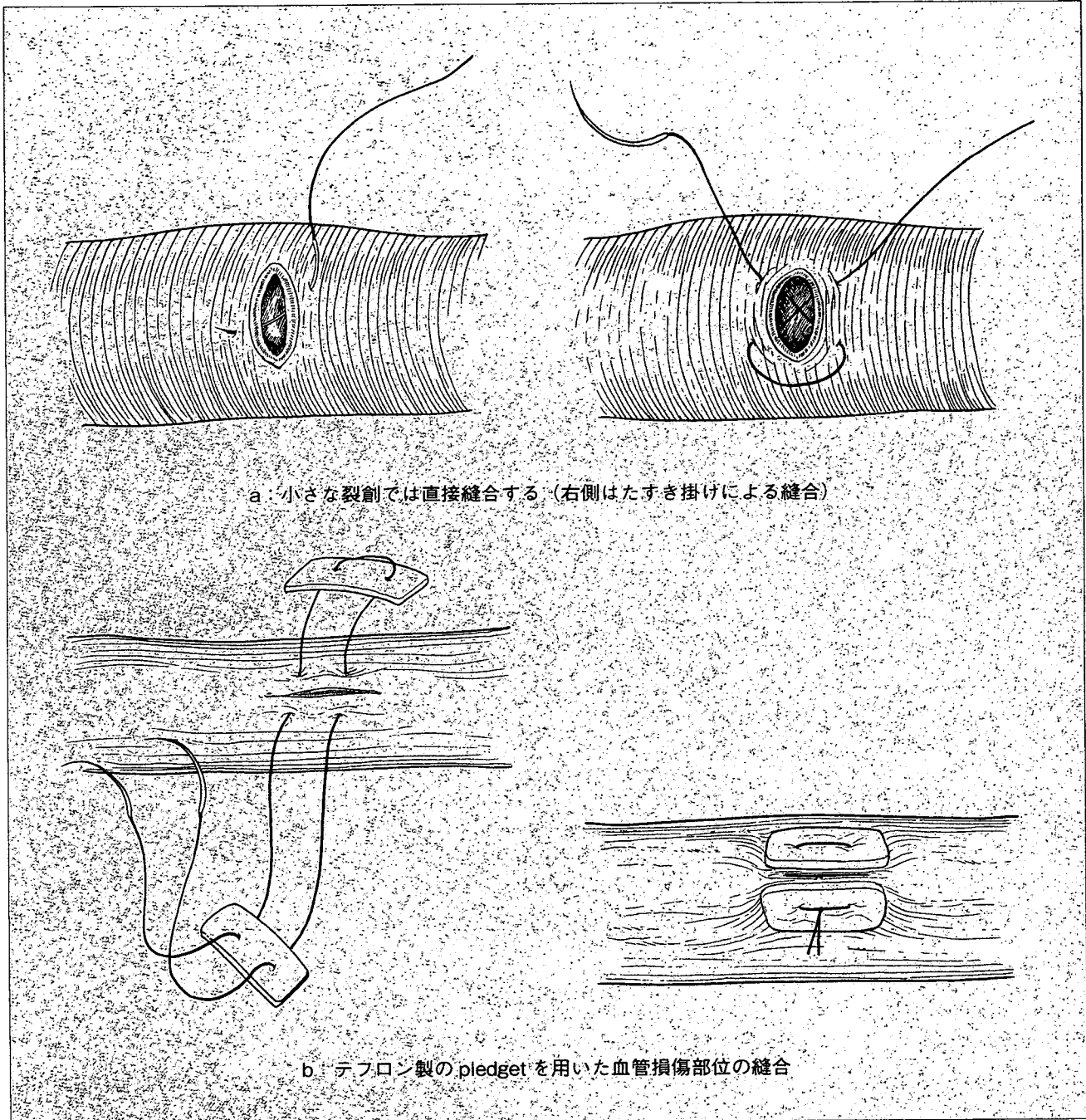a：小さな裂創では直接縫合する（右側はたすき掛けによる縫合）

b：テフロン製のpledgetを用いた血管損傷部位の縫合

図4　血管損傷に対する直接縫合による修復法
　血管壁が脆弱または緊張がかかる場合の静脈損傷に有効である。筆者らは，腹直筋膜などの自家組織をpledgetとして用いることがある