

Table 1 Clinical features, diagnostic examinations, and treatment of patients with postoperative coloseminal vesicle fistula

Author	Cause	Symptoms	Urine passage	Onset	Diagnostic examination	Initial treatment	Radical treatment
Goldman [4]	LAR leakage	Pneumaturia, bacteriuria testicular pain,	No	1 month	Water-soluble contrast enema	Cutaneous vasotomy	None
Kollmogen [5]	APR	Urethral discharge, fever, dysuria	No	10 days	Sinography	Antibiotics, drainage	None
Carlin [6]	Crohn's	Discharge from perineal sinus	No	15 years	CT sinography	N.S.	None
	AR	None	No	2 months	CT with rectal contrast enema	Drainage	APR
Calder [7]	Open prostatectomy	N.S.	N.S.	N.S.	Water-soluble contrast enema	N.S.	N.S.
Celebrezze [8]	Prostatic brachytherapy	Rectal ulcer	Yes	2 years	N.S.	Mucosal flap	Diversion
	Prostatic brachytherapy	Rectal bleeding	Yes	15 months	N.S.	Mucosal flap	Colostomy
Kawasaki [9]	LAR leakage	Dysuria	No	2 weeks	Water-soluble contrast enema	Conservative	Colostomy
Our cases	LAR leakage	Pneumaturia, testicular pain, fever	No	1 month	CT and vesiculography	Urinary catheter	None
	AR	Pneumaturia, testicular pain, scrotal swelling	No	2 weeks	CT and contrast enema	Urinary catheter, antibiotics	Colostomy
	LAR leakage	Fecaluria, fever, scrotal swelling	Yes	1 week	CT and vasogram	Urinary catheter, antibiotics	Muscle flap

LAR low anterior resection, AR anterior resection, APR abdominoperineal resection, N.S. not stated

may cause local tissue destruction and the formation of a fistula if this septum is resected.

The second case showed no evidence of anastomotic leakage during the postoperative course. Latent anastomotic leakage may have been present or the fragile seminal vesicle wall may have eventually collapsed, allowing passage between the seminal vesicle and anastomotic site in the outpatient follow-up period. Accidental catheter removal may have adversely affected the urinary tract, with injury of the ejaculatory duct and seminal vesicle causing fistula to the rectum. However, a seminal vesicle fistula is rarely observed in cases with accidental removal of a urethral catheter.

The third case required resection of a huge T4 mass, including the bilateral seminal vesicles. A Retzius cavity approach was selected due to the size of the tumor occupying the pelvic cavity, and the bases of the seminal vesicles were difficult to identify for ligation. Anastomotic leakage caused the abscess formed by leakage to increase in size around the remnant rectum, and become a seed of inflammation, leading to a fistula into the unclosed ejaculatory duct.

Rectoseminal vesicle fistula formation in all three cases appeared to be due to a combination of resection of Denonvilliers' fascia or the seminal vesicle itself and anastomotic leakage.

Many investigators have evaluated the safety of the double stapled technique and its role in rectal cancer

surgery. They concluded that the double stapling technique is an equivalent or even superior type of intervention with respect to speed, sterility and anastomosis safety, while also associate with fewer complications [11–20]. However, Kosugi et al. [21] reported that the incidence of rectovaginal fistula was higher in patients who were anastomosed by the double stapled technique or had concomitant resection of the vaginal wall. The current surgical reports and postoperative examinations proved no direct relationship between the double stapled technique and fistulae. However, these reports concerning rectovaginal fistula [21–23] emphasize that the double stapled technique might cause rectoseminal vesicle fistula when frustrating distal anastomosis is carelessly performed.

No diverting stoma was constructed in the first two cases. The first case recovered conservatively, but the other was treated with transverse colostomy. The third case required the construction of a diverting ileostomy, but it failed. These cases suggest that a diverting stoma cannot always prevent leakage or the formation of rectoseminal vesicle fistula. Several studies have shown the absence of a diverting stoma to be a risk factor for leakage after LAR [24–29], whereas others did not [30]. Anastomotic failure and the completion of rectoseminal vesicle fistula are thought to be influenced by an infectious environment, the viscosity of the discharge and the rectum-cavity urinary tract pressure gradient. Whether diverting the fecal stream

in itself directly prevents fistula formation between the urinary tract and fragile rectal wall remains to be proven.

The symptoms of fever, pneumaturia, scrotal swelling and testicular pain were seen in these three cases (Table 1). Some late-onset cases are described in the literature, as in the present cases. A fistula therefore needs to be considered in patients who show fever, pneumaturia, scrotal swelling or testicular pain, particularly in cases with evidence of anastomotic leakage in the postoperative period.

These three cases indicate that conservative therapy may be an option when the patients develop a rectourethral fistula arising from minor leakage. Antibiotics, urinary catheterization, and percutaneous drainage are effective in well-chosen cases. Although unsuccessful in the third patient, gracilis muscle or abdominal rectus muscle flap closure may be viable treatment options when a diverting stoma had been established in the first operation [31]. The radical diversion of either or both the urinary and fecal streams may be applicable in cases with apparent urine passage and extended infection.

Conclusions

Pneumaturia, fever, scrotal swelling and testicular pain are signs of a rectoseminal vesicle fistula in patients following anterior resection for rectal cancer. The resection of Denonvilliers' fascia and anastomotic leakage appear to represent risk factors for this complication. These symptoms may emerge within a few days or several weeks into the postoperative period. A water-soluble contrast enema and CT are effective diagnostic examinations which may lead to appropriate therapeutic options. Local medical or surgical therapy will do well in some cases. Unsuccessful fistulae should be treated with urinary or fecal diversion, or both. Selection criteria for conservative therapy include the severity of the anastomotic leakage, extent of abscess formation and passage of urine through the fistula.

Conflict of interest None of the authors have any conflicts of interest to disclose.

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ORIGINAL CONTRIBUTION

Clinical Impact of Elastic Laminal Invasion in Colon Cancer: Elastic Laminal Invasion-Positive Stage II Colon Cancer Is a High-Risk Equivalent to Stage III

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BACKGROUND: Elastic laminal invasion is defined as tumor invasion beyond the peritoneal elastic lamina. It is one of the factors affecting the prognosis of patients with colon cancer.

OBJECTIVE: This study aimed to investigate the clinical impact of elastic laminal invasion in colon cancer and the magnitude of the worse prognosis of elastic laminal invasion-positive, node-negative patients.

DESIGN: This was a retrospective cohort study.

SETTINGS: This study reviewed data from a tertiary care cancer center in Japan.

PATIENTS: The records of 436 patients with pT3 or pT4a colon cancer who underwent curative resection between January 1996 and December 2006 were reviewed.

MAIN OUTCOME MEASURES: The primary outcome measure was recurrence-free survival. Cox regression analyses established the factors associated with recurrence-free survival. Six groups formed by combining the factors were compared.

RESULTS: Of the patients with pT3 disease, those who were positive for elastic laminal invasion had a 5-year recurrence-free survival rate of 73.8% compared with a rate of 85.0% in those who were negative for elastic laminal invasion and 53.5% in patients with pT4 disease. Three unfavorable prognostic factors were identified, including lymph node metastasis, positive elastic laminal invasion, and a lack of adjuvant chemotherapy. Log-rank analysis revealed statistically significant differences in recurrence-free survival between group 1 (node negative, elastic laminal invasion negative, and no adjuvant chemotherapy) and group 3 (node negative, elastic laminal invasion positive, and no adjuvant chemotherapy). The HR for group 1 compared with group 3 was 0.49 (95% CI, 0.27–0.90). Furthermore, the HRs for group 2 (node positive, elastic laminal invasion negative, and received adjuvant chemotherapy) and group 4 (node positive, elastic laminal invasion positive, and received adjuvant chemotherapy) vs group 3 were 0.77 (95% CI, 0.35–1.69) and 1.36 (95% CI, 0.62–2.98).

LIMITATIONS: Our study has limited prediction accuracy of our prognostic stratification, and an analysis of small subgroups may not have been capable of detecting significant differences. In addition, a wide range of hematoxylin and eosin- and elastica-stained slides were examined per case.

CONCLUSIONS: Elastic laminal invasion adversely influences prognosis in pT3 and pT4a colon cancer. Although elastic laminal invasion positivity does not affect prognosis in node-positive patients receiving adjuvant chemotherapy, node-negative patients with elastic laminal invasion have a similar risk of recurrence as node-positive patients.

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1

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In 2008, 1.2 million people received a new diagnosis of colorectal carcinoma (CRC), and 608,700 patients died of the disease, making it the fourth most common cause of cancer death globally.¹ However, in the United States and Europe, it is the second leading cause of cancer death.^{2,3} In Japan, CRC is diagnosed in \approx 105,000 patients each year and accounts for 42,000 deaths, making it the third leading cause of death from cancer.⁴

CRC is staged using the TNM system of the International Union Against Cancer (UICC),⁵ in which primary tumor extension (T), regional lymph node involvement (N), and the presence of distant metastasis (M) are established to guide treatment and predict prognosis. Pathologic (p) T categories are divided into pT1 to pT4: pT3 disease is defined by subserosal tumor invasion and accounts for approximately half of all cases of CRC. The prognosis of patients with pT3 disease varies, which may be explained by differences in the depth of tumor invasion.⁶⁻⁸ Nevertheless, although it has been suggested that pT3 disease be subclassified, it currently remains 1 category.

The peritoneal elastic lamina (PEL) is a component of the normal intestinal wall and can be identified histologically by elastica staining. It is situated beneath the visceral peritoneum and invests the intestinal wall. Subclassifying pT3 tumors according to their relationship with the PEL has been suggested as another method of pT3 classification. Patients with tumor invasion beyond the PEL are classified as having elastic laminal invasion (ELI).⁹ Furthermore, the elastic lamina is used as a landmark of invasion of the visceral pleura in the TNM classification of lung cancer.⁵ These facts guide us to focus on the PEL as a landmark of the classification of tumor spread.

Our previous study of 564 patients with stage II to IV CRC suggested that ELI was one of the factors affecting the prognosis of patients with colon cancer (CC) and an independent risk factor for tumor recurrence only among CC patients with stage II disease.¹⁰ However, it is not yet clear that ELI status can be a prognostic factor under comprehensive analysis, including factors such as lymph node involvement and adjuvant chemotherapy.

The aim of this study was to investigate the clinical impact of ELI in patients diagnosed with pT3 and pT4a CC and the magnitude of the worse prognosis of patients with ELI-positive, node-negative CC (NNCC).

MATERIALS AND METHODS

Patients Selection and Follow-up

Of the 1103 consecutive patients who underwent surgery for CC at the National Cancer Center Hospital East between January 1996 and December 2006, 721 patients

had pT3 or pT4a disease. The following patients were excluded: 1) patients with multiple or metachronous CC, 2) patients simultaneously or previously diagnosed with an advanced tumor other than CC, 3) patients with distant metastasis, 4) patients who received neoadjuvant therapy, and 5) patients in whom resection was incomplete (R1 and R2). Completeness of resection was classified as R0 (negative gross and pathologic margins), R1 (negative gross and positive microscopic margins), and R2 (positive gross margins). R1 and R2 were defined as incomplete resection. After exclusions, the clinical records of 439 patients with pT3 and pT4a CC were retrospectively studied. We began routinely administering 5-fluorouracil-containing adjuvant chemotherapy for patients with stage III disease in 2003, and 3 patients with stage II CC were excluded because they had also received adjuvant chemotherapy. Each patient's prospectively collected demographic, staging, histopathology, and prognostic outcome data were recorded. All of the cases were reclassified based on the 7th edition of the UICC TNM staging system.⁵ We did not categorize isolated tumor deposits as pN1c to avoid overestimating the prognosis of patients with stage III disease. Follow-up after surgery was composed of serum tumor marker measurement every 3 months and chest and abdominal CT every 6 months for the first 3 years, then every 6 months for the next 2 years, and annually for 2 additional years. All of the patients were followed from the date of surgery to the last contact (death or last follow-up) or until December 31, 2011. Recurrence was defined as distant metastasis, local recurrence, or peritoneal dissemination; the final diagnosis was made by imaging (CT, MRI, and/or positron emission tomography CT), cytologic analysis, or biopsy, if necessary.

Written, informed consent to tissue collection and use for research was obtained. Conduct of the study was approved by our local ethics committee (National Cancer Center Hospital, No. 2012-067).

Histopathologic Analysis

We used the same histopathologic protocol as our previous study.¹⁰ The resected specimens were fixed in 10% formalin, and the entire tumor was cut into 5-mm sections. Representative slices were embedded in paraffin, cut into 3- μ m sections, and stained with hematoxylin and eosin (H&E) and elastica stain to allow evaluation of serial sections for ELI status and lymphovascular invasion (Fig. 1). We used the modified resorcin-fuchsin method for the latter.¹¹ There is a defect of the PEL at the mesenteric attachment; therefore, we undertook elastica staining on at least 1 whole section where the tumor was closest to the peritoneal surface to confirm the continuity of the PEL. The median numbers of H&E- and elastica-stained sections were 6 (range, 2–20) and 4 (range, 2–16). We defined cases with tumor invasion beyond the PEL as ELI positive (Fig. 1C

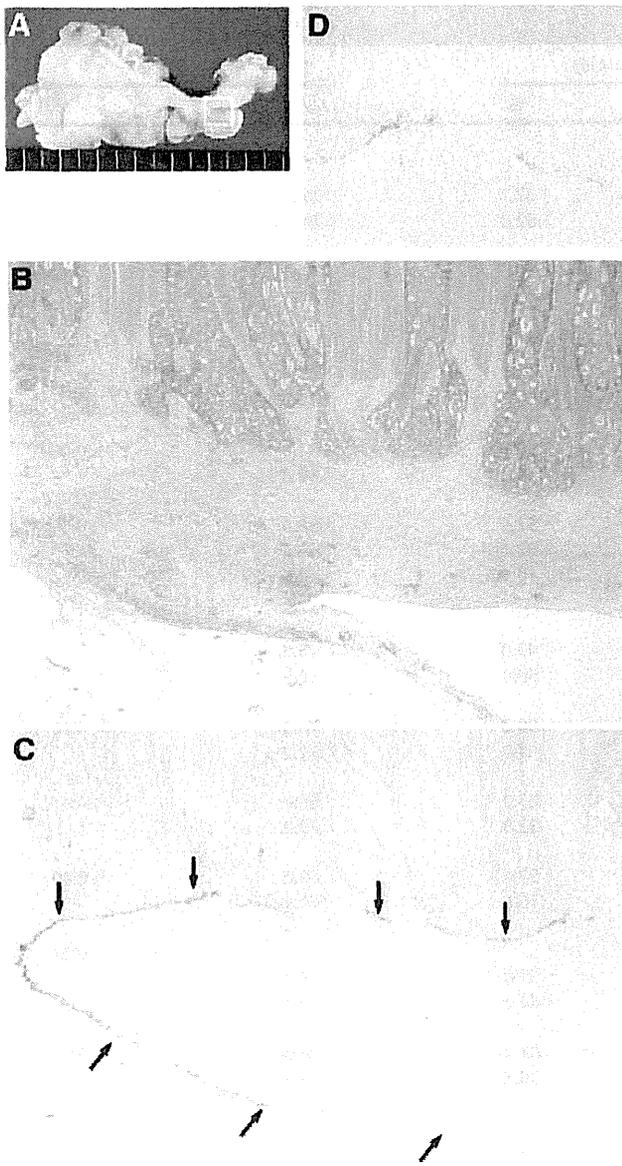


FIGURE 1. A, Cut surface of a tumor with elastic lamina invasion (ELI). Hematoxylin and eosin staining (B; $\times 40$); and elastica staining (C; $\times 40$; D, $\times 100$) of the white box area in A. The peritoneal elastic lamina (PEL; arrows in C) is situated beneath the visceral peritoneum. C and D, Tumor invasion beyond the PEL represents ELI positivity.

and 1D). Continuity of the PEL in unaffected areas was confirmed regardless of the intensity of staining near the tumor. In cases with duplication of the PEL around the invasive front of the tumor, we determined cases with tumor invasion beyond the PEL to be ELI positive only when the PEL was judged the outermost layer of elastin. In cases in which the PEL had been disrupted, its estimated course was obtained by drawing a straight line between the residual PEL; only cases with invasion beyond the line were defined as ELI positive. ELI status was retrospectively evaluated by 2 pathologists blinded to the patient outcomes.

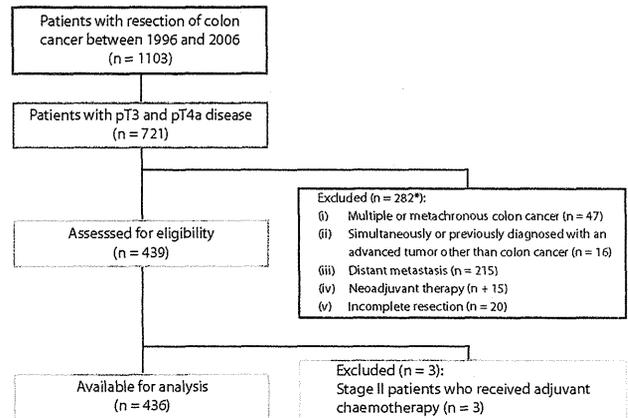


FIGURE 2. Consolidated Standards of Reporting Trials diagram of the study. *At least 1 of the criteria (i to v) was met.

Statistical Analysis

Our primary outcome measure was recurrence-free survival (RFS), defined as the time that elapsed between the date of surgery and any relapse or death from any cause. Overall survival (OS) was a secondary outcome, defined as the time from surgery to death from any cause. We chose RFS as the primary outcome to avoid the impact of treatments after recurrence on survival. Kaplan-Meier survival curves were plotted and compared using the log-rank test. Continuous variables were separated into 2 categories on the basis of their median values. All of the baseline characteristics were summarized as numbers and percentages.

To verify whether ELI status was an independent prognostic factor, we first performed multivariate Cox regression analyses for RFS. Baseline covariates included age (<65 or ≥ 65 years), sex (male or female), tumor size (<4.5 or ≥ 4.5 cm), histologic differentiation (well/moderately or poorly/mucinous), surgical technique (open or laparoscopic), lymphatic invasion (positive or negative), venous invasion (positive or negative), lymph node metastasis (positive or negative), number of lymph nodes retrieved (less than 12 or 12 or more), preoperative serum CEA level (<5 or ≥ 5 ng/mL), adjuvant chemotherapy (received or not received), and ELI (positive or negative).

The branch-and-bound algorithm of the Furnival and Wilson¹² variable selection procedure was applied to identify the risk factors using these candidate covariates. Next, we divided patients into all of the possible combinations based on the covariates identified in the Cox regression analyses so that their stratification would be meaningful. To establish the extent to which ELI adversely affected prognosis in NNCC, we compared the group consisting of patients with ELI-positive NNCC with groups composed of patients with node-positive CC (NPCC; stage III disease). We also applied the risk group to patients with pT3, because exclusion of pT4a patients might have influenced our proposed risk stratification. Furthermore, we evaluated how the risk group affected OS.

TABLE 1. Patient characteristics and univariate analysis for RFS

Variable	No. of patients (n = 436)		RFS	
	No.	%	5 y (%)	p ^a
Age, y				
Median (range)	65.0 (26.0–92.0)			0.32
<65	208	47.7	76.2	
≥65	228	52.3	80.5	
Sex				
Male	251	57.6	76.1	0.17
Female	185	42.4	81.1	
Tumor location				
Right	146	33.5	3.7	0.08
Transverse	51	11.7	71.4	
Left	239	54.8	76.3	
Tumor stage				
pT3	393	90.1	81.0	<0.0001
pT4a	43	9.9	53.5	
Nodal status				
pN0	250	57.3	88.3	<0.0001
pN1	140	32.1	68.4	
pN2	46	10.6	54.8	
Tumor size, cm				
Median (range)	4.5 (0.6–16.5)			0.09
<4.5	196	45.0	75.0	
≥4.5	240	55.0	80.9	
Histologic differentiation				
Well/moderately	396	90.8	78.8	0.38
Poorly/mucinous	40	9.2	72.2	
Lymphatic invasion				
Negative	293	67.2	80.6	0.07
Positive	143	32.8	73.2	
Venous invasion				
Negative	102	23.4	89.0	0.002
Positive	334	76.6	74.9	
CEA, ng/mL				
Median (range)	3.9 (0.2–247.7)			0.27
<5	252	57.8	79.8	
≥5	184	42.2	76.0	
Type of surgery				
Open	267	61.2	78.0	0.84
Laparoscopic	169	38.8	78.6	
No. of lymph nodes retrieval				
Median (range)	26.5 (4.0–124.0)			0.58
<12	31	7.1	76.0	
≥12	405	92.9	78.4	
Adjuvant chemotherapy				
Received	71	16.3	78.4	0.98
Not received	365	83.7	77.2	
ELI				
Negative	254	58.3	85.1	<0.0001
Positive	182	41.7	68.8	

ELI = elastic laminal invasion; RFS = recurrence-free survival.

^ap value was calculated by log-rank test (2 sided).

All of the statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All p values were reported as 2 sided, and statistical significance was defined as values <0.05.

RESULTS

Patient Characteristics

A total of 436 patients with a median age of 65.0 years were enrolled (Fig. 2). Their characteristics were shown in

Table 1. Tumors were located in the cecum in 26 patients (6.0%), the ascending colon in 120 (27.5%), the transverse colon in 51 (11.7%), the descending colon in 36 (8.3%), and the sigmoid colon in 203 (46.5%). Tumors were classified as stage IIA, IIB, IIIB, and IIIC in 236 (54.1%), 14 (3.2%), 165 (37.9%), and 21 patients (4.8%). Seventy-one patients (38.2%) with stage III CC received adjuvant chemotherapy after primary resection. Overall, 182 patients

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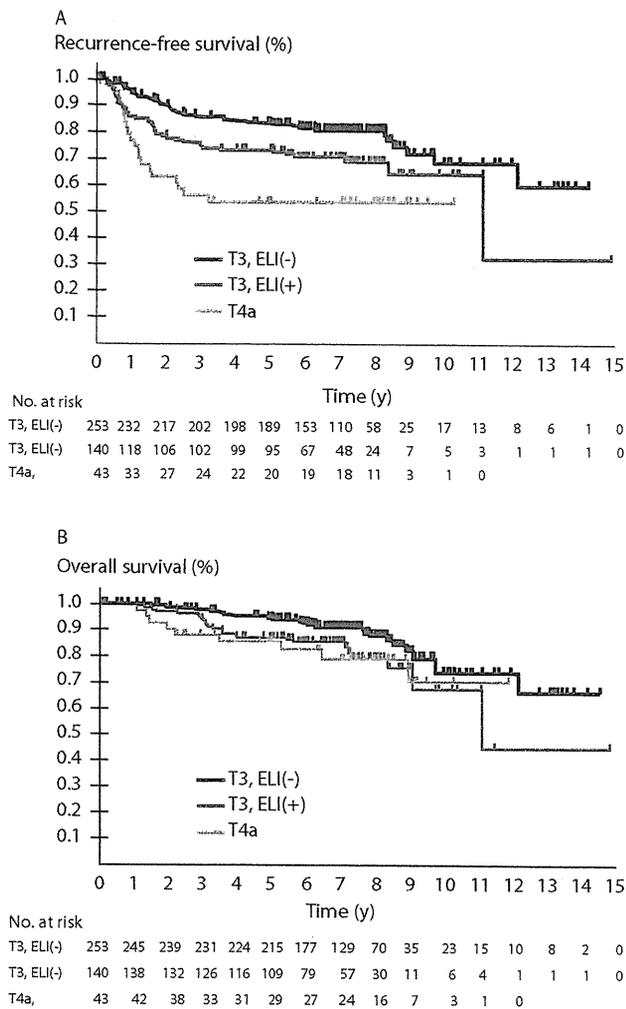


FIGURE 3. Kaplan-Meier curves depicting recurrence-free (A) and overall survival (B) based on the elastic lamina invasion status of 436 patients who underwent primary resection for colon cancer.

(41.7%) were identified as ELI positive, 140 (35.6%) of those with pT3 and 42 (97.7%) of those with pT4a disease.

Association Between ELI Status and Survival

The 5-year RFS and OS for all of the participants were 78.2% and 92.9%. The median follow-up was 7.1 years (range, 0.1–15.1 years). Of those who survived, 93.3% were followed for ≥3 years, and 88.0% were followed for ≥5 years. Tumor stage, nodal status, venous invasion, and

TABLE 2. Multivariate Cox regression analyses for RFS to assess the influence of risk factors

Variable	RFS		
	HR	p	95% CI
Lymph node metastasis (+)	2.96	<0.0001	1.95–4.49
Adjuvant chemotherapy (+)	0.50	0.01	0.29–0.85
ELI (+)	1.59	0.02	1.08–2.33

ELI = elastic lamina invasion; RFS = recurrence-free survival.

ELI status influenced RFS (Table 1). Of the patients with pT3 disease, those who were ELI positive had a 5-year RFS of 73.8% compared with 85.0% for those who were ELI negative ($p = 0.002$) and 53.5% for patients with pT4 disease ($p = 0.02$; Fig. 3A). Tumors recurred in 95 (21.8%) of the 436 patients; the most common sites of recurrence were the liver (48 patients), lung (18 patients), and peritoneum (13 patients). The 5-year OS of ELI-positive patients with pT3 disease was 87.3% compared with 94.9% if ELI status was negative ($p = 0.02$) and 85.3% in patients with pT4 disease ($p = 0.82$; Fig. 3B). Overall, 63 patients died (14.4%): of those who died of CC, 28 were ELI positive and 14 were ELI negative; of those who died of other causes, 6 were ELI positive and 15 were ELI negative.

Multivariate Analyses

We performed Cox regression analyses on all 436 patients. For RFS, the branch-and-bound algorithm identified 3 unfavorable factors, including lymph node metastasis ($p < 0.0001$), lack of adjuvant chemotherapy ($p = 0.01$), and ELI positive status ($p = 0.02$; Table 2). Patients were divided into 6 groups based on these unfavorable factors, as shown in Table 3. We chose group 3 (node negative, ELI positive, and no adjuvant chemotherapy) as the reference value to compare with node-positive patients.

Evaluation of Prognosis

Kaplan-Meier curves for RFS in each group are shown in Figure 4A. The survival curves of group 5 (node positive, ELI negative, and no adjuvant chemotherapy) and group 6 (node positive, ELI positive, and no adjuvant chemotherapy) were almost identical ($p = 0.43$), and there was not a significant difference between group 2 (node positive, ELI negative, and received adjuvant chemotherapy) and group 4 (node positive, ELI positive, and received adjuvant chemotherapy; $p = 0.15$). There was, however, a significant difference between group 1 (node negative, ELI negative, and no adjuvant chemotherapy) and group 3 ($p = 0.001$). The RFS curve of group 3 lay between those of group 2 and group 4, both of which were composed of node-positive patients. The HR for group 1 vs group 3 was 0.49 (95% CI, 0.27–0.90), corresponding with a 51% relative reduction in the risk of recurrence. Furthermore, the HRs for groups 2 and 4 vs group 3 were 0.77 (95% CI, 0.35–1.69) and 1.36 (95% CI, 0.62–2.98).

When group 3 was compared with the other groups in terms of OS, similar trends were observed (Table 3 and Fig. 4B). The estimated OS Kaplan-Meier curve of group 3 was also between those of groups 2 and 4. The HRs for groups 2 and 4 vs group 3 were 0.88 (95% CI, 0.29–2.62) and 1.81 (95% CI, 0.61–5.41).

Findings After Exclusion of Patients With pT4a Disease

The impact of ELI status was reanalyzed using the same 6 groups after patients with pT4a disease were excluded

TABLE 3. Comparison of 5-year RFS and OS of the 6 stratified groups

Group	n	RFS		OS	
		5-y % (95% CI)	HR (95% CI)	5-y % (95% CI)	HR (95% CI)
1	166	91.1 (85.4–94.6)	0.49 (0.27–0.90)	98.1 (94.2–99.4)	0.59 (0.25–1.41)
2	42	83.0 (67.7–91.5)	0.77 (0.35–1.69)	97.6 (83.9–99.7)	0.88 (0.29–2.62)
3	84	78.3 (67.8–85.7)	1.00	91.2 (82.4–95.7)	1.00
4	29	69.0 (48.8–82.5)	1.36 (0.62–2.98)	89.7 (71.3–96.5)	1.81 (0.61–5.41)
5	46	57.7 (41.9–70.6)	1.92 (1.03–3.57)	82.0 (67.1–90.5)	2.10 (0.88–5.01)
6	69	55.9 (43.3–66.7)	2.36 (1.36–4.11)	79.5 (67.3–87.6)	2.64 (1.20–5.81)

N = nodal status; ELI = elastic laminal invasion; AC = adjuvant chemotherapy; RFS = recurrence-free survival; OS = overall survival.

T4 (Table 4). The 5-year RFS for group 3 excluding those with pT4a disease (group 3') was significantly worse than that for group 1' (group 1 excluding those with pT4a disease; 81.1% vs 92.9%; $p = 0.003$). The RFS curve of group 3' was similar to that of groups 2' (group 2 excluding those with pT4a disease) and 4' (group 4 excluding those with pT4a disease; group 3' vs group 2', $p = 0.61$; group 3' vs group 4', $p = 0.83$; Fig. 5A). The OS curve of group 3' lay below that

of groups 2' and 4' (group 3' vs group 2', $p = 0.41$; group 3' vs group 4', $p = 0.98$; Fig. 5B).

DISCUSSION

ELI appears to influence outcome in patients with pT3 and pT4a CC. The RFS and OS of patients with ELI-negative NPCC (group 2) were better than those with ELI-positive NNCC (group 3). A similar trend was observed in previous reports based on the UICC 6th edition. Patients with stage IIIA (T1 to 2N1) disease had a better 5-year survival than those with stage IIA (T3N0) disease, and the Kaplan-Meier curve of patients with stage IIB (T4N0) disease lay approximately halfway between those of patients with stage IIIA and stage IIIB (T3-4N1) disease.^{13,14} Whether the favorable outcome of patients with stage IIIA disease was because of limited tumor spread or adjuvant chemotherapy is unclear; these and our results show that some patients with stage II disease have a worse outcome than some with stage III disease.

Several studies have reported a variety of poor prognostic indicators in patients with stage II CC, including tumor necrosis,¹⁵ perineural invasion,^{15,16} male sex,¹⁷ bowel obstruction,^{17–19} tumor depth,^{6,7,16–21} retrieval of less than 10 or 14 lymph nodes,^{17,19} emergency presentation,⁶ left colonic disease,⁶ venous invasion,^{20,21} lymphovascular invasion,^{16,18,19,22} margin involvement,²⁰ differentiation pattern,⁷ preoperative CEA level,¹⁶ mucinous component of >50%,¹⁸ tumor grade,²² and tumor length.²² Tumor depth and lymphovascular invasion have been identified most often. ELI status, which subdivides tumors invading beyond the muscularis propria, is also an indicator related to tumor depth. The "TNM Supplement: A Commentary on Uniform Use"²³ stated that the pT3 subclassification identified an extent of disease with a clinically relevant influence on outcome and could be used to determine the need for adjuvant chemotherapy.

There is a consensus that pT4 staging indicates a high risk of recurrence²⁴; thus, the ELI status of patients other than those with pT4a disease is also of great interest. The findings presented in Figure 5, from which patients with pT4a disease were excluded, show the poor prognosis of patients with ELI-positive NNCC with pT3 disease and indicate

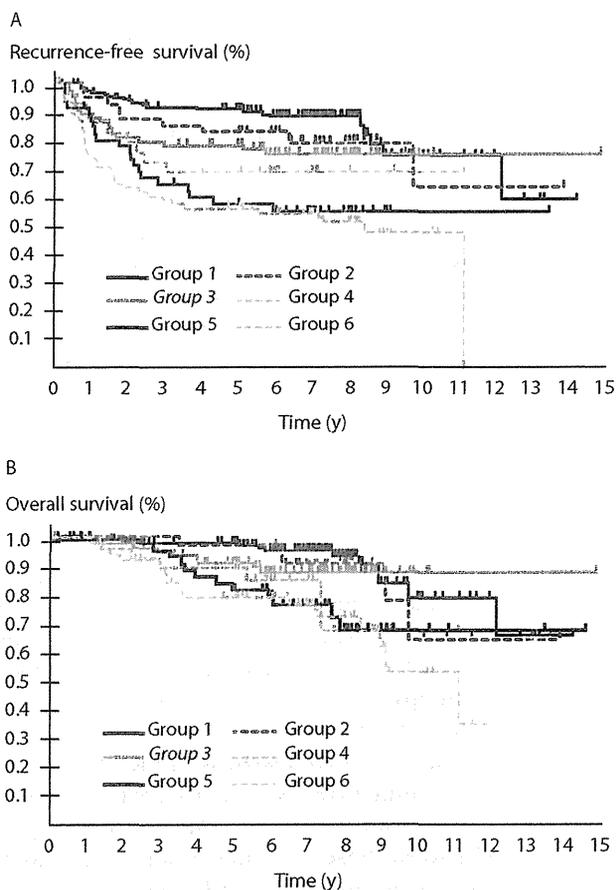


FIGURE 4. Kaplan-Meier curves depicting recurrence-free (A) and overall survival (B) of 6 groups of 436 patients who underwent primary resection for colon cancer, stratified according to elastic laminal invasion (ELI), lymph node metastasis, and adjuvant chemotherapy status. The bold line (red) represents group 3 (node negative, ELI positive, and no adjuvant chemotherapy).

TABLE 4. Comparison of 5-year RFS and OS of the 6 stratified groups excluding patients with pT4a disease

Group	n	RFS		OS		
		5-y % (95% CI)	HR (95% CI)	5-y % (95% CI)	HR (95% CI)	
1'	N0,ELI(-),AC(-)	166	92.9 (88.9-97.0)	0.34 (0.16-0.73)	98.1 (95.9-NE)	0.46 (0.20-1.10)
2'	N1-2,ELI(-),AC(+)	41	82.6 (70.9-94.3)	0.79 (0.32-1.95)	97.5 (92.7-NE)	0.70 (0.23-2.09)
3'	N0,ELI(+),AC(-)	70	81.1 (71.9-90.4)	1.00	89.6 (82.3-96.9)	1.00
4'	N1-2,ELI(+),AC(+)	21	76.2 (58.0-94.4)	1.12 (0.40-3.12)	95.2 (86.1-NE)	0.81 (0.17-3.75)
5'	N1-2,ELI(-),AC(-)	46	59.8 (45.4-74.2)	2.09 (1.04-4.20)	82.0 (70.6-93.3)	1.65 (0.69-3.93)
6'	N1-2,ELI(+),AC(-)	49	62.5 (48.8-76.2)	2.21 (1.11-4.41)	80.1 (68.4-91.8)	2.04 (0.88-4.74)

N = nodal status; ELI = elastic lamina invasion; AC = adjuvant chemotherapy; RFS = recurrence-free survival; OS = overall survival; NE = not estimated.

that subclassification by ELI status allows valid conclusions to be made about outcome independent of tumor staging. The survival of patients with stage II CRC and pT3 deep tumor invasion (which represented tumors that had invaded beyond the PEL) has been reported to be equal to that of patients with stage II CRC and pT4 disease.⁹ There-

fore, a deeply invasive pT3 tumor, which fulfills the criteria for ELI used in this study, is a poor prognostic indicator.

Comparing the prognosis of stage II and III CC may help identify high-risk stage II patients. A small number of studies have reported the prognosis of stage II alongside that of stage III disease. The 5-year survival of patients with Dukes B CC determined to be at high risk by the Peterson index (43.3%) was worse than that of patients with Dukes C disease with a single lymph node metastasis (57.9%).²⁵ Patients with stage II CC and perineural invasion had significantly worse outcomes than stage III patients (5-year disease-free survival of 29% vs 56%; 5-year OS of 43% vs 67%).²⁶ This suggests that the Peterson index and perineural invasion may also be useful means of identifying a high-risk group for whom adjuvant chemotherapy might be recommended. Likewise, the RFS and OS of patients with ELI-positive NNCC were equivalent to those of patients with NPCC and pT3 or pT4a histology, corresponding with stage IIIB disease. Thus, ELI status appears to identify patients with high-risk stage II CC.

There is considerable variability in the incidence of serosal involvement in patients with Dukes stage B CC reported in previous studies,²⁷ which may reflect diagnostic difficulties.^{28,29} One difficulty is that mesothelial cells are fragile, and the serosal surface may easily be disrupted during surgery and fixation. Another is that inflammatory and desmoplastic stromal reactions are often seen around the invasive tumor front. These problems can lead to underestimation of invasion because of the difficulty of demonstrating tumor cells on the peritoneal surface. In this regard, ELI may be advantageous because it is assessed from the inner surface of the serosa and is, therefore, not influenced by external trauma. Like vascular invasion, tumor spread might also be determined more objectively by routine elastica staining.^{30,31}

ELI is sometimes affected by the tumor-associated inflammation around the invasive tumor front. In such cases, we speculate that the use of an estimated line and multiple histologic sections might provide a more precise and objective diagnosis. Nevertheless, we could not demonstrate ELI positivity in 2.3% of patients with pT4a disease. This is likely to be a consequence of marked in-

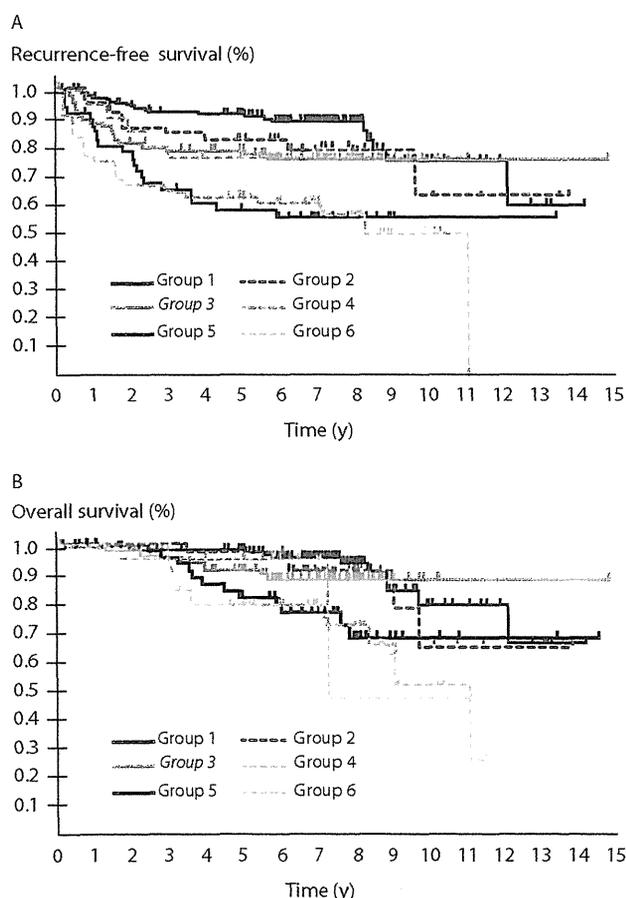


FIGURE 5. Kaplan-Meier curves depicting recurrence-free (A) and overall survival (B) of 6 groups of 393 patients who underwent primary resection for colon cancer, stratified according to elastic lamina invasion (ELI), lymph node metastasis, and adjuvant chemotherapy status after exclusion of those with pT4a disease. The bold line (red) represents group 3 excluding those with pT4a disease (group 3'; node negative, ELI positive, and no adjuvant chemotherapy).

flammation at the tumor invasion front, making it impossible to determine ELI positivity in some patients with pT4a disease.

The prediction accuracy of our prognostic stratification is a limitation of our study, because we developed the risk group based only on the training set of 436 patients. A prospective study is needed to evaluate the validity and accuracy of our conclusions. Stratifying patients with CC into 6 groups based on 3 unfavorable factors led to an analysis of small subgroups that may not have been capable of detecting significant differences. Another limitation is that there was a wide range of H&E- and elastica-stained slides examined per case, because we did not adopt the protocol with a predefined number of blocks and sections. This could cause bias in the ELI and pT4 rates.

The strength of our study was that not all of the patients with stage II CC routinely received adjuvant chemotherapy. If all of the patients predicted to have a poor outcome had received adjuvant chemotherapy, almost three quarters would have done so, making any comparison impossible.³²

CONCLUSION

ELI status predicts prognosis in patients with pT3 and pT4a CC. Patients with ELI-positive NNCC have a worse outcome than those with ELI-negative histology and a prognosis similar to patients with stage III CC who received adjuvant chemotherapy. Therefore, although ELI positivity does not affect prognosis in patients with stage III CC receiving adjuvant chemotherapy, ELI is a strong prognostic factor to identify patients with high-risk stage II CC. Further prospective studies are needed to prove the reproducibility and validity of our findings.

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AQ1—Please confirm that "invests" is what is meant, term may not be used correctly.

AQ2—Please modify figure legends as necessary because figures may have been recolored to match journal style.

AQ3—pT4a, as meant?

AQ4—Please review the typeset tables carefully to verify accuracy of editing and typesetting.

1. 局所高度進行直腸癌に対する外科治療 a) 隣接臓器合併切除を伴う拡大切除*

齋藤典男 酒井康之 駒井好信
伊藤雅昭 小林昭広 西澤雄介 杉藤正典**

【要旨】 下部直腸進行癌では、隣接臓器浸潤を示す症例もときどき存在する。男性では前立腺浸潤の場合が問題となり、従来では骨盤内臓全摘術(TPE)が標準とされてきた。しかし、下部直腸癌の手術と前立腺全摘を組み合わせることにより、TPEの回避は可能と考えられる。そして、尿路および排便路の積極的な再建手術を行うことにより、術後の機能確保と quality of life (QOL) の改善に大きく貢献するものと思われる。このような手術は理論的には可能であるが、現在までに十分なデータは示されなかった。本稿では、本手術法の現状を提示する。

はじめに

高度に進行した下部直腸癌例では、根治性を得るために臨床的に浸潤を伴う隣接臓器の合併切除を必要とする場合がある。女性では子宮・陰が存在するため、これらの臓器の合併切除で根治手術となることが大半である。しかし男性では、泌尿器系臓器(膀胱、前立腺、尿道)の切除が必要となる。特に下部尿路系臓器浸潤が認められる場合に、骨盤内臓全摘術(total pelvic exenteration: TPE)が施行されることも多い。上部尿路系臓器浸潤の場合の手術については、以前の報告を参照していただきたい。TPEでは排便・排尿路の変更のため、多くのストーマが必要となる場合も多く、quality of life (QOL) が低下することも否めない。本稿では、もっとも問題となる臨床的に前立腺浸潤を認める局所進行下部直腸癌例におい

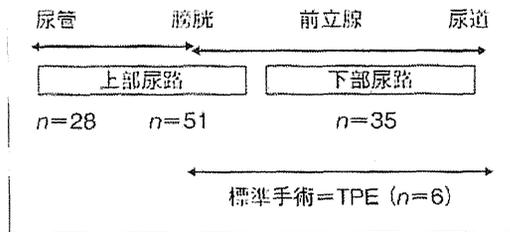


図1. 尿路系浸潤を伴う原発局所進行直腸癌 (n=114, 1997～2011年)

て、合併切除を伴う拡大手術により TPE を回避しうる手術について述べることにする

1. 臨床的前立腺浸潤を伴う直腸癌

1997～2011年の15年間に、当施設での原発直

キーワード：高度進行下部直腸癌、TPE、合併前立腺全摘、intersphincteric resection、排尿路再建、排便路再建

* Extended resection and reconstruction for low-lying rectal cancer involving adjacent organs

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表1. 前立腺全摘合併の直腸癌手術報告例 (TPEは除く)

報告者(年)	症例数	術式	膀胱尿道吻合の縫合不全
Ganemら (1957) ^{a)}	1	APR	0/1
Campbellら (1993) ^{a)}	2	conventional CAA	報告なし
Fujisawaら (2002) ^{a)}	1	APR	報告なし
Wiigら (2003) ^{a)}	6	APR: 4	3/6 (50.0%)
		LAR: 1	
		TR: 1	
Herranz Amoら (2004) ^{a)}	2	APR	報告なし
中尾ら (2005) ^{a)}	1	APR	1/1
Saitoら (2007) ^{a)}	11	APR: 6	4/11 (36.4%)
		ISR: 4	
		TR: 1	
武藤ら (2007) ^{a)}	1	APR	1/1
松崎ら (2008) ^{a)}	1	APR	1/1
Saitoら (2010) ^{a)}	20	ISR: 11	5/16 (31.3%)
		APR: 8	
		v-LAR: 1	

CAA: 肛門(窄)吻合, APR: 腹会陰式直腸切除術, LAR: 低位前方切除, TR: 腫瘍切除

腸癌手術例1,775例中114例(6.4%)に臨床的尿路浸潤を認め、そのうち35例(2%)は前立腺を主にした下部尿路系浸潤例であった(図1)。従来の適応からいえば、この35例はTPEの対象であった。しかし当施設では、2000年より下部直腸癌に対する究極的肛門温存手術が本格化し、臨床的前立腺浸潤例に対してもTPEを回避しうる手術に関する検討を始めた。これは主に前立腺を同時に合併切除し、癌浸潤を伴わない膀胱を可能な限り温存する試みである。これまでに、直腸癌手術と同時に前立腺全摘が行われた報告を表1に示す¹⁾。まとまった報告は筆者以外には少ない。

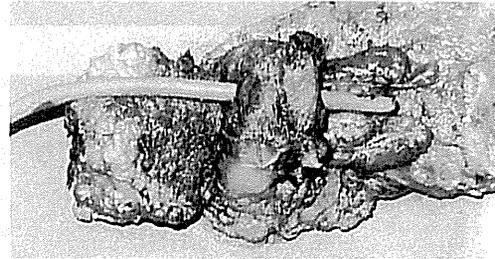
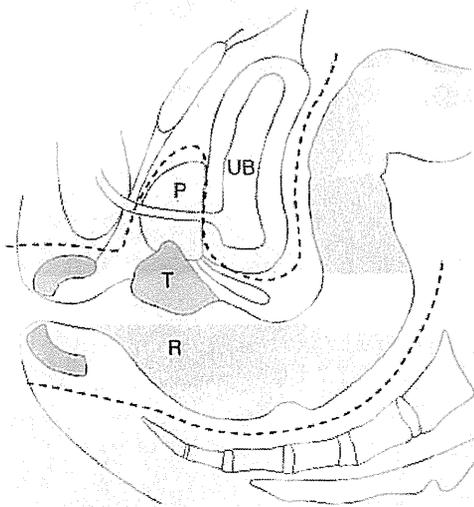
報告の主な術式は直腸切除術(APR)と前立腺全摘であり、尿路再建は膀胱・尿道吻合で行われ自然排尿路が確保されている。これらの症例の排便経路に関してはAPRによる永久人工肛門であるが、ストーマの数の減少に大きく寄与している。また従来の肛門吻合(conventional CAA)や超低位前方切除(v-LAR)、究極的肛門温存術(ISR)などによる自然排便経路の確保例も認め、これらの症例ではストーマのない状態となっている。ISRを用いた究極的肛門温存と前立腺全摘の組み合わせは、筆者以外に報告を認めない。これらのTPEを回避しえた症例の腫瘍学的予後や、

術後の機能は許容できるという報告もあるが、慎重な症例選択が必要と思われる。また、TPEや膀胱臓器合併切除の切除標本による病理組織学的検討では、実際の癌浸潤例は40~50%であることも認識しておきたい。一方、安全な外科的剥離面の確保は、外科手術において最重要事項であることはもちろんである。

II. 前立腺全摘合併の膀胱温存手術

この手術法の適応については、以下に示すように慎重でなければならない。臨床的前立腺浸潤直腸癌例において、①広範な膀胱浸潤を伴わないこと、②尿道括約筋が温存可能なこと、③著明な骨髄内リンパ節転移を伴わないことなどである。これらの条件を満たす症例において、本手術法による膀胱温存と膀胱・尿道吻合による自然排尿路の再建を考慮すべきと考えられる。そして直腸癌における本手術法は、肛門温存不可能例と温存可能例の二つの型に大別される。

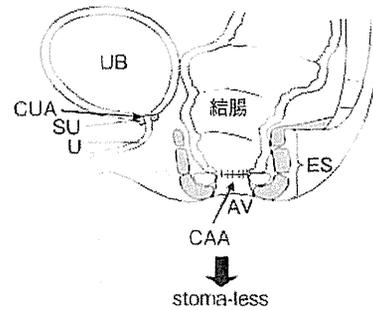
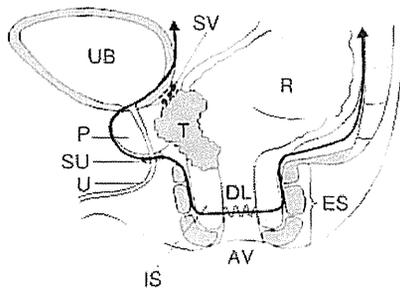
図2に肛門温存不可能な場合の手術術式を示す。APRと前立腺全摘および膀胱・尿道吻合(CUA)の組み合わせで、この場合CUAの背部は死腔となり、CUAの縫合不全が生じやすく難治性になることがある。また図3に、肛門温存型の



a. 前立腺全摘合併 APR. ----: 切除線, T: 腫瘍, P: 前立腺, R: 直腸, UB: 膀胱

b. 切除標本

図2. 膀胱温存を伴う拡大切除(文献6より引用改変)
肛門非温存型, APR+前立腺全摘(RP)



a. 切除線, SV: 貯精囊, SU: 尿道括約筋, U: 尿道, DL: 荷状線, AV: 肛門線, IS: 内括約筋, ES: 外括約筋

b. 再建法

図3. 手術法(肛門温存型)(文献8より引用改変)
ISR+RP

手術法を示す。合併の前立腺全摘およびCUAは前者と同様であるが、肛門が温存されその肛門温存法は腫瘍下縁の肛門からの距離により異なる。

つまりv-LARで再建が可能、conventional CAAで再建可能。究極的肛門温存術であるISRで排便経路の確保可能などである。図3は腫瘍下縁が

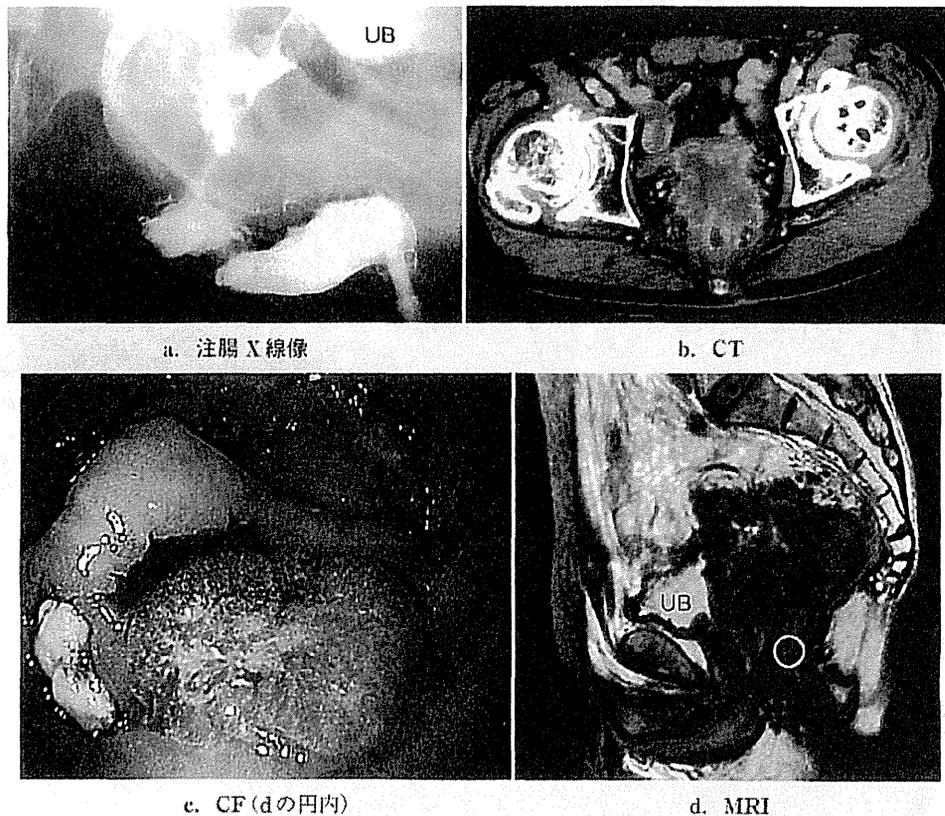


図4. 症例, 65歳, 男性
排便・排尿痛, AV 4.5 cm, 膀胱・精嚢・前立腺浸潤

もっとも肛門に近く、肛門括約筋の温存が部分的に可能な場合である。これらの術式選択には、直腸癌自体の状況、尿路系への浸潤状況、癌の骨盤内の進展状況などを十分に検討して慎重に決定すべきである。またCUAの縫合不全による難治性瘻孔形成などの面から、可能な限り排便路の確保（新直腸による再建）を行ったほうが有利と考えられる。これにより、CUAの背部の支持組織が構成されるためである。

Ⅲ. 症例提示

最近経験した、骨盤内を占居する局所高度進行直腸癌例を図4に示す。CTとMRIでは骨盤内に存在する巨大な腫瘍が描出され、膀胱、精嚢、前立腺に浸潤が及ぶ所見であった。注腸X線所見では、壁不整を伴う直腸から膀胱が造影され、口側腸管は造影されなかった。大腸内視鏡(CF)所

見で、主病変に連続すると考えられる肛門側の腫瘍性病変を肛門縁から4~5cmの位置に認めた。直腸指診でも同様の所見であった〔肛門縁(AV): 4.5cm〕。

本例は当然のことながらTPEの適応であったが、本人の強い希望もあり図5に示すような合併切除と新膀胱による尿路再建、ISRによる排便路の再建手術を実施した。TPEを回避した本手術法により、永久の排尿および排便のストーマのない状況となった。図6に切除標本所見と、再建した尿路の術後造影および排便路の新直腸造影を示す。切離面のmarginは確保され、造影所見も良好である。Stoma-lessのため、QOLの向上が期待される。またconventional CAAを用いた手術法は、以前にKodairaにより報告されている²⁾。

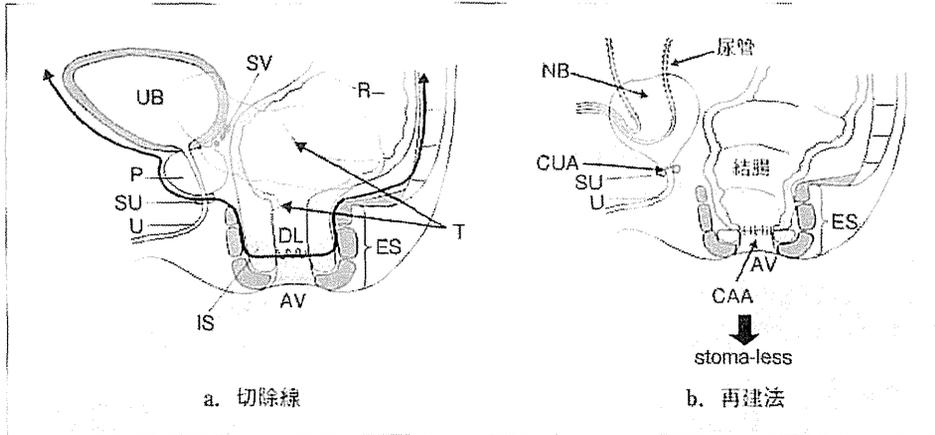
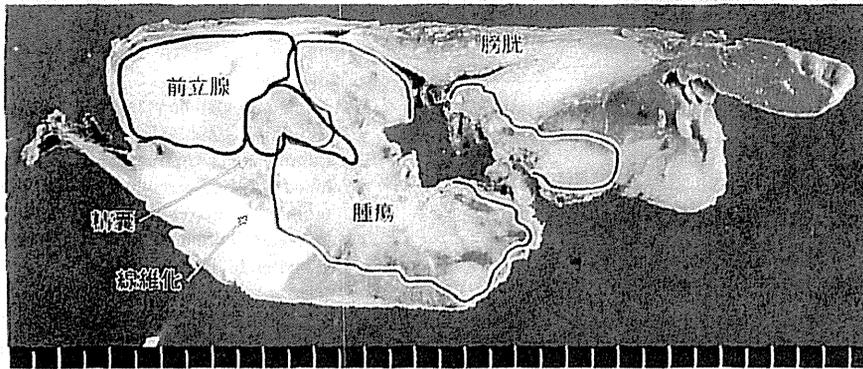
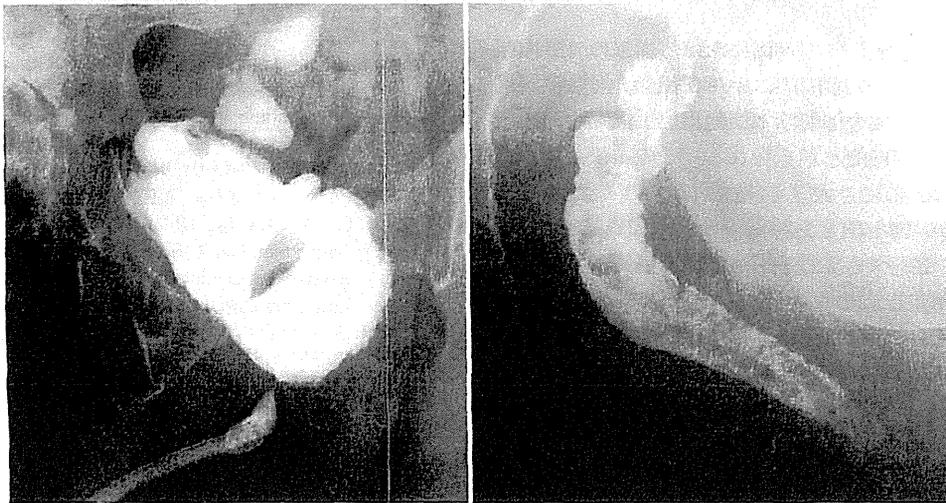


図5. 手術法
ISR + radical cystectomy



a. 切除標本剖面像



新膀胱尿道

再建直腸

b. 術後再建部造影像(7週)

図6. 切除標本および再建術後所見

IV. 予 後

このような拡大合併切除による機能温存・再建手術例では、根治性が低下しては何も意味がない。当科で施行したTPEを回避した手術例($n=30$)の予後を図7に示すが、現在のところ(観察期間中央値:約50ヵ月)、5年生存率77%,5年無再発生存率59%であった。この成績は、現在までに報告されているTPEの5年生存率43~64%¹⁾に比べ劣るものではなかった。

V. 術後機能

このようなTPEを回避した拡大合併切除・機能再建手術例では、術後機能評価は重要である。排尿路再建例では全例に自然排尿が可能で残尿も10ml程度であり、国際前立腺症状スコア(IPSS)の中央値は12(範囲4~12)、QOLスコアの中央値は2(範囲1~4)でほぼ満足であることを示した。排便路再建例(主にISRによる)の排便機能をWexnerスコアで評価すると、そのスコアの中央値は11(範囲0~16)を示した。また排便に特化したQOL評価を大腸癌研究会で認可されているmodified-fecal incontinence quality of life scale(m-FIQL)でみると、その中央値は54(範囲7~69)を示していた。これらの結果から、本手術法は機能面からも許容できるものと考えられる。

おわりに

高度進行下部直腸癌例における従来の骨盤内臓全摘(TPE)の適応例においても、慎重な症例選択により拡大合併切除と機能再建・温存手術の組み合わせが可能と考えられる。その結果、術後のQOLの改善にも大きく貢献するものと思われる。今後の症例集積と追跡調査が必要である。なお、これまで述べてきた手術法の開発研究は、厚生労働科学研究費補助金・第3次対がん総合戦略研究事業「QOLの向上をめざしたがん治療法の開発研究」(H22-3次対がん一般-033)江角班の研究の一部によるものであることを追記する。

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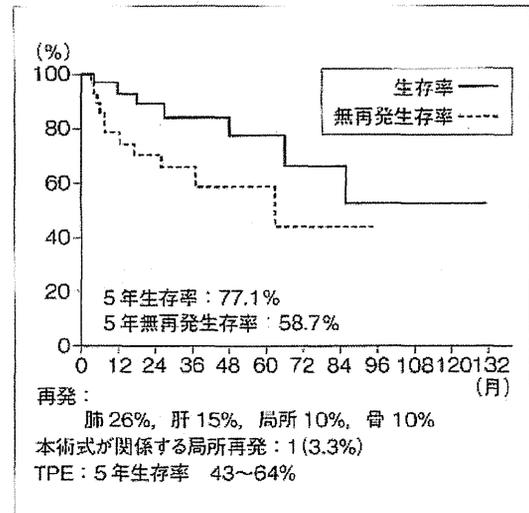


図7. 予 後

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お知らせ

◆第4回日本プライマリ・ケア連合学会

会 期 2013年5月17日(金)～19日(日)

会 場 仙台国際センター(仙台市青葉区青葉山無番地)

会 長 嶋沼信夫(東北大学医療管理学分野教授)

名誉大会長: 村井嘉浩(宮城県知事)

テ ー マ 「新しい地域医療を拓く——がんぼう日本」

開催プログラム(予定)

特別講演

「日本の覚悟」(仮) 柳田邦男(ノンフィクション作家)、「突破する力」 伊藤智也(ロンドンパラリンピック・銀メダリスト)

特別シンポジウム

「大災害で地域医療をどう守るか」 座長・石井 正(東北大学)、「総合医か総合診療医か」 座長・福井次矢(聖路加国際病院)

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そのほか Meet the Expert (6件)、ワークショップ (31件)、インタレストグループ (8件)、PCAT 活動報告会、International Session、学術セミナー (10件)、被災地視察がある

事前参加登録締切日: 2013年3月29日(金)

事前参加登録方法: 大会ホームページ <http://www.c-linkage.co.jp/ipca2013/> を交付

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