TABLE I. Patients and Clinical Characteristics, 2001–2008 (n = 20)

Mean age, years (range)	64 (43–76)
Mean distance from AV, cm (range)	3.0 ± 1.1 (0–4.2)
Depth of invasion (clinical)	cT3, 2[a]; cT4, 18
Involving organs	P, n = 11; P + SV, n = 3; P + SU, n = 4; combined with prostatic cancer, n = 2[a]
Node involvement (clinical)	cN (−), n = 5; cN (+), n = 15

AV, anal verge; P, prostate; SV, seminal vesicle; SU, sphincter urethrae muscle.
[a]Rectal cancer with synchronous primary prostatic cancer.

patients agreed to undergo preoperative radiochemotherapy according to our previous protocol [6]. During the same period of time, we performed only five TPEs for locally advanced primary rectal cancer involving a wide-ranging area of the urinary bladder and prostate in male patients.

Rectal tumor was staged according to the 6th UICC TNM staging system. Age, level of tumor, and clinical tumor stage for the 20 patients are given in Table I. Although two of these patients displayed cT3 tumors with synchronous primary prostatic cancer, adequate margins were not clinically evident between the rectal tumor and the prostate. Therefore, these two patients were included in this study. Mean patient age was 64 years (range: 43–76 years), and mean distance from tumor to anal verge was 3.0 cm (range: 0–4.2 cm). To determine the distance of the rectal tumor to the anal verge, rigid proctoscopy with measurement, and/or digital examination were used.

Preoperative staging was conducted using transanal digital examination, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, colonoscopy, and barium enema. Position emission tomography was also performed preoperatively to exclude multiple metastatic disease. All patients in this study showed localized rectal tumor involving the prostate and seminal vesicle, or combined with carcinoma of the prostate, without distant metastases evident preoperatively. Clinicopathological findings were examined in all resected specimens. Involvement of adjacent organs and surgical margins, perioperative morbidity and mortality, locoregional control, overall survival (OS), and disease-free survival (DFS) were investigated. Urinary and anal functions were also evaluated postoperatively by monitoring continence and voiding habits. Fecal evacuation functions were investigated using both Wexner score [18] and Kirwan grade [19].

Indications and Surgical Procedure

Bladder-sparing extended en bloc rectal resection combined with radical prostatectomy was considered if the cancer was clinically fixed to the prostate or bladder, or if an adequate margin between the tumor and these organs seemed impossible to achieve as judged from MRI and CT. Patients undergoing this surgical procedure had a residual urinary bladder with available capacity ≥50 ml and with the possibility of cysto-urethra anastomosis (CUA). Distant metastasis, wide-ranging involvement of the urinary bladder and prostate, or marked pelvic lymph node metastasis were generally considered contraindications for this operation, as preservation of the available urinary bladder was impossible in patients with wide-ranging involvement of the urinary bladder. If the patient showed wide-ranging involvement of the urinary bladder and prostate, TPE was performed.

Surgical technique was as follows. The patient was placed in the lithotomy position. Total mesorectal excision with lateral pelvic node dissection was performed, although lateral node dissection is not standard care outside of Japan. Ureters were visualized and carefully protected throughout the procedure, and the superior vesical artery was preserved bi- or unilaterally. At this time, the status of involvement between the rectum and the base of the bladder was investigated. After confirming the absence of wide-ranging involvement of the urinary bladder, bladder-sparing surgery was deemed possible. The rectal cancer, prostate and seminal vesicles were resected en bloc as a cooperative venture between colorectal and urological surgeons using the usual methods for radical prostatectomy and ISR or APR. APR was performed when safe surgical margins could not be obtained by ISR. Confirmation of cancer-free radial and distal margins was then performed in the resected specimen using frozen sections to evaluate the extent of pelvic invasion, and to determine whether limited resection was possible. If tumor invasion was suspected in surgical margins from intraoperative histological examination, the operative procedure was converted to TPE. After confirming preservation of the membranous urethra and bladder, the bladder neck was reconstructed and a CUA was created by urological surgeons. When the sphincter urethrae muscle was sacrificed due to probable tumor invasion, a cystostomy was created for voiding through a catheter. Finally, a CAA with diverting stoma or permanent colostomy was established by colorectal surgeons.

The bladder catheter was left for 2 or 3 weeks and removed after cystography revealed an intact anastomosis. The diverting stoma was closed 3 months after radical surgery.

Adjuvant Therapy

Four patients (clinical T4, N2: n = 3; clinical T4, N1: n = 1) agreed to undergo preoperative radiochemotherapy according to our old-fashioned protocol between 2001 and 2002, although preoperative radiochemotherapy for resectable rectal cancer, even in those patients undergoing TPE, is not standard in Japan. These patients received 45 Gy in the whole pelvis over a 5-week period, followed by resection after ≥2 weeks. In addition, 5-fluorouracil (5-Fu) was administered as a continuous infusion at 250 mg/m^2/day during radiotherapy to enhance radiotherapeutic efficacy. Postoperative chemotherapy (5-Fu/leucovorin therapy) was offered to patients with pathological stage III.

Follow-Up

Mean duration of follow-up was 40 months (range: 4–106 months). Follow-up examinations were performed every 3 or 4 months for 2 years postoperatively, then every 6 months thereafter. Patients underwent clinical examination, laboratory tests including tumor marker levels, and lung, liver, and pelvic CT. Investigation of functional status for voiding and evacuation was also performed using our questionnaire on the status of voiding and bowel functions based on continence, frequency, soiling, urgency, and discrimination. These functions were evaluated at 3, 6, 12, and 24 months postoperatively using Wexner score [18] and Kirwan classification [19]. Physiological assessment was also performed using anal manometry and uroflowmetry.

Statistical Analysis

The starting point for survival and recurrence-free intervals was the day of operation, and data on patients who were alive or free of recurrence were censored at the last follow-up. OS was defined as the time from radical surgery until death from any cause. Local recurrence was defined as recurrence confined to the pelvis and distant recurrence as recurrence present outside of the pelvis. Statistical evaluations were undertaken using the SPSS for Windows version 11.0J software (SPSS-Japan, Tokyo, Japan). OS and DFS curves were calculated using the Kaplan–Meier method.

RESULTS

Operation Type

Eighteen patients showed localized tumors clinically involving the prostate, two had clinical T3 lower rectal tumors with synchronous primary prostatic cancer. No procedures were converted to TPE because of inadequate margins during the period of this study. Twelve patients underwent anal SPOs (ISR, n = 11; U-LAR, n = 1) with radical prostatectomy, and 8 patients received APR with radical prostatectomy because the lower edge of the tumor was very close to the anal verge or the tumors clinically involved the external anal sphincter. Urinary reconstruction was performed in 16 patients using CUA, while cystostomy was established in four patients because of intraoperative histological probability of cancerous invasion to the sphincter urethrae muscle. As a result, 12 patients were without stoma, four patients had a single stoma, and a fecal stoma and cystostomy were used in four patients (Table II).

Median operative time was 495 min (range: 416–628 min), and median intraoperative blood loss was 2,200 ml (range: 1470–6172 ml). Median duration of hospitalization was 25 days (range: 21–38 days).

Pathological Findings

All resected margins were examined pathologically and confirmed as cancer-free. Final pathological examination revealed pT4 in eight patients (40.0%). Histological cancerous invasion of the prostate was revealed in seven patients. Nine patients showed pT3 tumor with fibrosis or inflammatory changes surrounding the tumor, and three patients displayed pT2 tumor with the same histological changes. Two of three patients with pT2 tumor had synchronous primary prostatic cancer (pT1c). It seemed to be difficult to separate the rectal tumors safely from the prostate during operation in these patients with pT3 or pT2 tumors. Curative resection was achieved in all 20 patients by bladder-preserving surgery.

Morbidity and Mortality

Morbidity for this series is shown in Table III. No postoperative complications were seen in 13 patients. Of the seven patients (35.0%) who suffered from some form of complication, cysto-urethral anastomotic leak was identified in five patients, requiring catheterization through the anastomosis site for 3–24 weeks postoperatively. However, none of these cases developed urethral stricture. Incidence of cysto-urethral anastomotic leak was significantly higher in patients with APR (75.0%, 3 of 4) than in patients with SPO (16.7%, 2 of 12; $P < 0.05$). In particular, anastomotic urethral leak was a major complication in patients undergoing APR with CUA (Fig. 1), requiring special care during the long postoperative course. Colo-anal anastomotic leak was only observed in 1 of the 12 patients with SPO. This patient suffered from colo-anal anastomotic stenosis before closure of the diverting ileostomy. Additional plastic surgery for anastomotic stricture was thus performed by plastic surgeons. After that, the diverting stoma was closed at 14 months after initial operation. Other complications included pelvic abscess (20.0%, 4 of 20), wound infection (15.0%, 3 of 20), and bowel obstruction (5.0%, 1 of 20). No postoperative mortality was encountered in hospital or within 30 days postoperatively.

TABLE II. Operation Type and Pathological Findings

Surgery types	ISR with RP, n = 11; APR with RP, n = 8; V-LAR with RP, n = 1
Reconstruction	Urinary...CUA, n = 16; CS, n = 4 Fecal...CAA, n = 11; CACA, n = 1; stoma, n = 8
Depth of invasion (pT)	pT4, n = 8 (40.0%); pT3, n = 9; pT2, n = 3
Involving organs	P, n = 7; ES, n = 2; SV, n = 1 (prostatic cancer, n = 2)
Node involvement (pN)	pN0, n = 11; pN1, n = 4; pN2, n = 3
Surgical margins	Negative, n = 20; positive, n = 0

No stomas, n = 12; single stoma, n = 4; CS + stoma, n = 4.
ISR, intersphincteric resection; APR, abdominoperineal resection; PR, radical prostatectomy; SPO, sphincter-preserving operation; CUA, cysto-urethral anastomosis; CS, cystostomy; CAA, colo-anal anastomosis; CACA, colo-anal canal anastomosis; ES, external anal sphincter.

TABLE III. Postoperative Complications (n = 20)

Anastomotic leakage	5/16 (31.3%) CUA: 5/16 SPO with CUA: 2/12 (16.7%)* APR with CUA: 3/4 (75.0%)* CAA, CACA: 1/12
Pelvic abscess	4/20 (20.0%)
Wound infection	3/20 (15.0%)
Ileus (small bowel)	1/20 (5.0%)
Overall morbidity	7/20 (35.0%)
Mortality	0/20 (0%)

*$P < 0.05$.

Survival

As of the last follow-up in December 2009, 15 patients were alive and 5 were dead. Causes of death included multiple bone metastases (n = 2), multiple lung metastases (n = 1), multiple liver metastases (n = 1), and multiple liver and lung metastases (n = 1). Estimated 5-year overall and DFS rates were 83.6% and 42.0%, respectively (Fig. 2).

Local and Overall Recurrence

A total of 10 patients (50.0%) developed recurrence (Table IV). Incidence of recurrence was 10.0% for local recurrence, 35.0% for lung metastases, 15.0% for liver metastases, and 10.0% for bone metastases. These local recurrences developed in the presacral area, and in the perianastomotic site of the CUA. Patients with local recurrence successfully underwent tumor resection with sufficient surgical margins. Intraoperative radiotherapy was therefore not administered. One of these patients was alive with no evidence of disease after resection of local recurrence, and 2 of 3 patients with liver metastasis were also alive and disease-free after hepatic resection. Cumulative 5-year local recurrence rate was 20.0% in this series.

Postoperative Urinary and Anal Functions

Urinary function was evaluated in 16 patients with CUA and anal functions were also investigated in 11 patients with SPO who were followed for ≥12 months after stoma closure (Table V). All 16 patients with CUA were able to void via the urethra, with little or no residual urine (range: 0–70 ml) and without the need for intermittent self-catheterization. All patients also showed complete daytime urinary continence. Median voiding volume at one time was 245 ml (range: 150–350 ml). Overflow incontinence at night was occasionally experienced over the course of 2 years postoperatively.

The four patients who underwent catheter-cystostomy passed urine via an inserted catheter. Voiding style was similar to that of patients with an ileal conduit. Unfortunately, erectile function could not be preserved in any of the 20 patients.

Of the 12 patients who underwent SPO with radical prostatectomy, 11 received closure of a diverting stoma and 1 died of multiple liver metastases before stoma closure. Anal functions were evaluated in

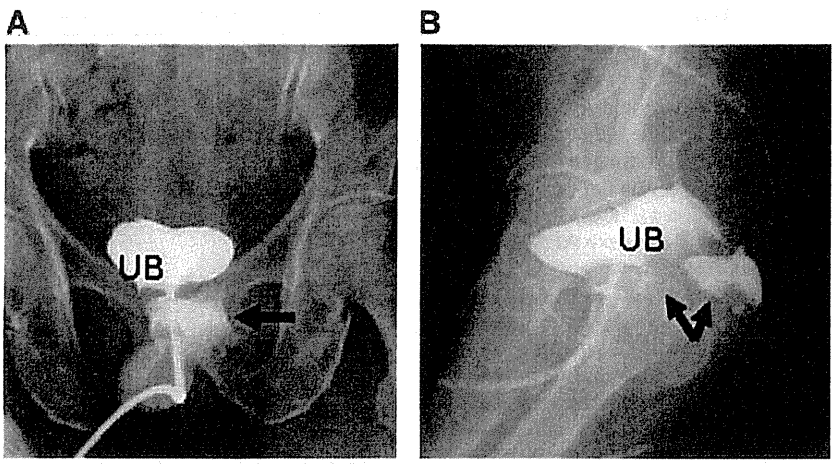

Fig. 1. Cysto-uretheral anastomotic leak in a patient undergoing APR with CUA. A: Front of view in postoperative retrograde cystogram. B: Lateral of view in postoperative retrograde cystogram. Arrow indicates collection of leakage. UB, urinary bladder.

these 11 patients. Wexner scores and Kirwan classification for the 11 patients are shown in Table V. None experienced complete incontinence, although one patient suffered occasional major soiling (Kirwan grade 4) for about 1 year after closure of the diverting stoma. Five of the 11 patients experienced minor soiling, particularly at night. These patients passed fewer than 6 bowel movements per day, 2 patients had incontinence of flatus, and 8 patients wore pads. Median Wexner score in the 11 patients was 11.5 (range: 0–15). Anal functions tended to improve gradually during the second year after stoma closure.

DISCUSSION

Orthotropic neobladder surgery is often attempted as an alternative for patients undergoing radical cystectoprostatectomy for bladder cancer, to enable voiding via the urethra with urinary continence [14,15]. Patients undergoing radical prostatectomy with CUA for carcinoma of the prostate can also void with continence via the urethra. On the other hand, SPOs for lower rectal cancer have been becoming more common with the introduction of improved surgical techniques such as ISR, which was devised in the 1980s, and these modern concepts were established in the 1990s. ISR is now defined as a procedure obtaining sufficient surgical margins by removing part or all of the internal anal sphincter and restoring bowel continuity for patients with rectal cancer located within 5 cm from the anal verge. Fixation to the lower urinary tract organs in primary locally advanced rectal cancer is not uncommon in male patients. Standard therapy for such patients with the absence of extra-pelvic metastases has traditionally been pelvic exenteration, to ensure negative surgical margins. However, this procedure sometimes requires urinary and fecal diversion. Double stomas are therefore sometimes needed.

In 1966, separate prostatectomy was suggested as a routine additional procedure to prevent voiding problems after APR for rectal cancer. More recently, three patients with synchronous rectal and prostate cancer who underwent separate dissections were reported [10]. Other reports have described combined radical retropubic prostatectomy and proctosigmoidectomy en bloc in 11 selected patients with the cancer fixed only to the prostate [11–13,16].

We believe that even more limited excision is feasible and preferable if the tumor can be removed en bloc. We also think some of these patients may be allowed preservation of the prostate if they had significant tumor shrinkage by neoadjuvant therapy such as preoperative chemoradiation or chemotherapy. However, preoperative radiochemotherapy for advanced rectal cancer, even in those patients undergoing TPE, is not a standard option in Japan. Moreover, preoperative radiotherapy or radiochemotherapy may affect postoperative complications and various functions. Since 2001, we have used a combined approach in 20 patients with primary rectal cancer involving lower urinary tract organs or combined with synchronous prostatic cancer. In our series, the bladder was preserved in all patients, and anal SPOs using ISR techniques were performed wherever possible, obtaining cancer-free margins in all patients. These procedures without ISR were first reported by Campbell et al. [11]. In their report of two patients, en bloc excision yielded negative surgical margins with no evidence of local recurrence at 1-year follow-up

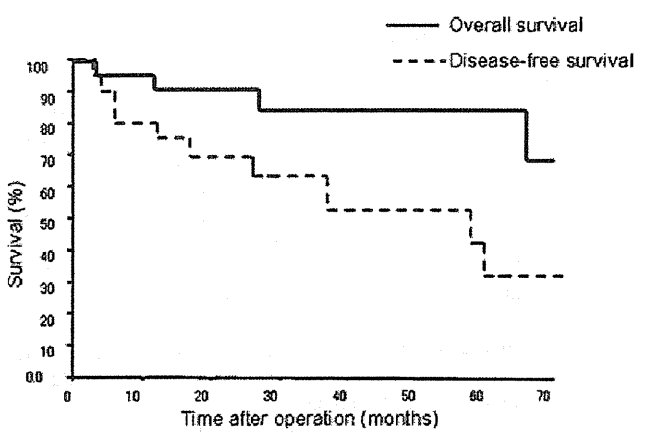

Fig. 2. Overall and disease-free survival rates among 20 patients who underwent bladder-preserving surgery.

TABLE IV. Patients With Recurrence (n = 20)

Recurrences	Number of patients (n = 10)	Salvage operation
Lung	7 (35.0%)	
Liver	3 (15.0%)	Resection, n = 3 → ANED; 2
Bone	2 (10.0%)	
Loco-regional	2 (10.0%)	Resection, n = 2 → ANED; 1
Distant lymph node	1 (5.0%)	AWD; 1
Median follow-up, months (range): 40 (4–106)		

ANED, alive with no evidence of disease; AWD, alive with disease.

TABLE V. Postoperative Functions (12 Months After Operation)

Reconstruction	Voiding	VV (ml), median (range)	RV (ml), median (range)
Urinary function			
CUA, n = 16	Spontaneous continence	245 (150–350)	5 (0–70)
CS, n = 4	Incontinence	Catheterization	
Anal function (SPO, n = 11)			
Kirwan grade[a]	I, n = 3; II, n = 2; III, n = 5; IV, n = 1; V, n = 0		
Wexner score	11.5 (0–15), median (range)		

VV, voided volume; RV, residual volume; Grade I, perfect; Grade II, incontinence of flatus; Grade III, occasional minor soiling; Grade IV, frequent major soiling; Grade V, incontinent (requiring colostomy).
[a]Kirwan classification.

examination, and patients displayed satisfactory control of bowel and voiding function. In a report by Wiig et al. [16], six patients underwent en bloc radical prostatectomy for locally advanced or recurrent rectal cancer involving the prostate. During 10–50 months of follow-up, none of these patients developed local recurrence, 4 of the 5 patients with CUA showed good quality of life and none wanted an ileal conduit.

In our previous report with a median follow-up period of 26 months, no sign of local recurrence was seen in 11 patients who underwent the same operation for locally advanced or recurrent rectal cancer involving the prostate and seminal vesicles [17]. Few patients with long-term follow-up were examined in these previous reports [11,16,17]. Deciding whether these procedures represent a reasonable operation was thus difficult, due to a lack of published reports with long-term follow-up.

However, the present study showed that two patients (10.0%) developed local recurrence during follow-up. In one of these patients, recurrence occurred in the presacral area. Local recurrence does not seem likely to have been prevented if the patient had undergone TPE. This patient underwent successful resection of the recurrent tumor. However, this patient died of multiple lung metastases at 85 months after initial operation. Another local recurrence developed at the perianastomotic site of CUA. This patient also received resection of the recurrent tumor and underwent cystostomy. The patient remains alive and disease-free at follow-up (106 months). An acceptable 5-year OS (83.6%) was obtained in patients undergoing the same operation for primary locally advanced very low-lying rectal cancer during a mean follow-up of 40 months (range: 4–106 months), although 5-year DFS was not so good. Despite our concerns about the risk of local recurrence after limited excision to preserve the urinary bladder, local recurrence rate in this series was relatively low. We think that a remaining problem is the prevention of distant metastases. To date, these procedures appear oncologically safe in selected patients with rectal cancer involving the prostate.

Moreover, patients with CUA reported satisfactory control of voiding function. Voiding style resembled that of patients with an ileal neobladder. Unfortunately, four patients required cystostomy because the sphincter urethrae muscle was sacrificed due to the probability of cancerous invasion. These patients voided via an inserted catheter that was exchanged once a month, much like patients with an ileal conduit. An obvious difference between neobladder and bladder-sparing surgery is that the neobladder is made using intestine, which results in inevitable long-term complications such as mucus production, nutritional abnormalities, metabolic acidosis, skeletal demineralization, and the risk of malignant transformation in the intestinal segment [20,21]. No such problems are associated with bladder-sparing surgery.

Patients with SPO using ISR also reported satisfactory control of anal function, even though they experienced occasional minor soiling, urgency, fragmentation, and frequent bowed movements. In patients undergoing ISR for lower rectal cancers, almost all patients were able to achieve acceptable anal function according to our and other reports [4,6,7,22–24]. Status was Grade I, II, or III in the Kirwan classification, and few patients showed incontinence (Kirwan Grade V). In the present series, acceptable anal function was achieved using these procedures, and permanent colostomy was not required.

Conversely, the complication rate was relatively high in terms of leakage from CUA. In the present series, anastomotic urethral leak was observed in 5 (31.3%) of 16 patients with CUA. Wiig et al. [16] also reported that 3 of 6 patients with CUA had anastomotic urethral leak with one major leakage. In particular, the frequency of anastomotic leaks was significantly high in patients undergoing APR with CUA. However, urethral anastomotic leak rate was less in patients undergoing ISR or ultra-LAR with CUA, as the neorectum was present behind the CUA. Some reports have examined the leakage rate from CUA in patients undergoing radical retropubic prostatectomy only [25,26], finding no evidence of extraversion in 135 (75%) of 179 cystograms, and a clinical prolonged leakage rate of 0.6% (11/1796). All of these patients had the rectum behind the CUA. Urethral anastomotic leaks are thus probably due to a lack of supporting tissue behind the anastomosis when the rectum has been removed in patients who have received APR. Measures to prevent urethral anastomotic leakage by introducing a flap of greater omentum behind the anastomosis or other additional flap operations such as gracilis flap thus appear warranted.

CONCLUSION

In this series, en bloc rectal resection combined with radical prostatectomy was successfully performed in 20 men, even though these patients had been considered as candidates for standard TPE. Acceptable curability and postoperative urinary and/or anal functions could be achieved with this procedure, although the complication rate was relatively high. More experience and longer follow-up evaluations are necessary to define the operative morbidity, risk of recurrence, and functional results associated with these procedures. However, if the bladder and anal sphincter are spared, the procedures described offer several advantage over TPE.

We conclude that en bloc rectal resection combined with radical prostatectomy may produce acceptable curability and good functional results in selected patients with lower rectal cancer involving the lower urinary tract organs. These procedures may become an option for selected patients who would otherwise need TPE for locally advanced rectal cancer involving the prostate.

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ORIGINAL ARTICLE

Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

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Abstract
Background A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

Patients and methods This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.

Results The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively (p=0.04).

Conclusions LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

Keywords Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

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Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A

temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

Patients and method

Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess

and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a p value$\leq$0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All p values <0.05 were considered statistically significant.

Table 1 Patient characteristics

Gender	
Male	215
Female	114
Age(years)	59.0±10.5 (23–87)
Tumor location (cm)	6.1±1.7 (4.0–12.0)
Bowel obstruction	
No	305
Yes	18
Missing	6
Tumor invasion	
T1,T2	108
T3,T4	215
Missing	6
Neoadjuvant chemo Tx	
No	324
Yes	5
Anastomosis	
SST	15
DST	314
High ligation	
No	142
Yes	183
Missing	4
LLND	
No	197
Yes	132
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)
Intraoperative bleeding (ml)	598±590 (10–3723)
Operating time (min)	240±104.1 (90–620)
BMI (k/m^2)	22.6±3.1 (14.1–31.2)
Tumor size (cm)	4.4±2.3 (0–12.0)
Simultaneous resection	
No	292
Yes	37
DS construction	
No	209
Yes	120

Values are number or mean±standard deviation (ranges)

DS diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Results

Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neo-

adjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

Table 2 Univariate analysis of factors related with DS construction

	Diverting stoma		Rate	*p*-value
	DS(−)	DS(+)		
Gender				
Male	130	85	39.5	0.11
Female	79	35	30.7	
Age (years)	58.8±10.7 (23–87)	59.4±10.2 (29–75)		0.42
Tumor location (cm)	6.4±1.6 (4.0–12.0)	5.9±1.7 (4.0–12.0)		0.001
Bowel obstruction				
No	195	110	36.1	0.76
Yes	11	7	38.9	
Tumor invasion				
T1,T2	71	37	34.6	0.50
T3,T4	133	82	38.1	
Neoadjuvant chemo Tx				
No	204	120	37.0	0.10
Yes	5	0	0.0	
Anastomosis				
SST	8	7	46.7	0.40
DST	201	113	36.0	
High ligation				
No	125	58	31.7	0.12
Yes	82	60	42.3	
LLND				
No	146	51	25.9	<0.0001
Yes	63	69	52.3	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	3.8±1.4 (1.0–9.5)		0.002
Intraoperative bleeding (ml)	505±524 (10–2985)	760±662 (17–3723)		<0.0001
Operating time (min)	231±90.6 (90–559)	318±102.7 (130–620)		<0.0001
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.3±3.2 (15.8–30.8)		0.07
Tumor size (cm)	4.4±2. (0–12.0)	4.4±2.3 (1.0–10.0)		0.97
Simultaneous resection				
No	192	100	34.2	0.02
Yes	17	20	54.1	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

Table 3 Univariate analysis of leakage risk factors

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	190	25	11.6	0.19
Female	106	8	0.7	
Age(years)	58.8±10.6 (23–87)	61.1±10.0 (40–76)		0.20
Tumor location (cm)	6.2±1.7 (4.0–12.0)	6.5±1.7 (4.0–10.0)		0.31
Bowel obstruction				
No	276	29	9.5	0.16
Yes	14	4	22.2	
Tumor invasion				
T1,T2	101	7	6.5	0.12
T3,T4	189	26	12.1	
Neoadjuvant chemo Tx				
No	291	33	10.2	0.59
Yes	5	0	0.0	
Anastomosis				
SST	13	2	13.3	0.66
DST	283	31	9.9	
High ligation				
No	135	7	4.9	0.02
Yes	157	26	14.2	
LLND				
No	177	20	10.1	0.93
Yes	119	13	9.8	
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)	4.4±1.3 (1.9–7.0)		0.13
Intraoperative bleeding (ml)	573±559 (10–3365)	817±791 (40–3723)		0.06
Operating time (min)	261±102 (90–616)	273±118 (113–620)		0.70
BMI (k/m^2)	22.7±3.1 (14.1–31.2)	22.5±3.2 (16.1–27.0)		0.87
Tumor size (cm)	4.4±2.3 (0–12.0)	5.0±2.3 (2.0–11.0)		0.18
Simultaneous resection				
No	266	26	8.9	0.06
Yes	30	7	18.9	
DS construction				
No	185	24	11.5	0.25
Yes	111	9	7.5	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Table 4 Univariate analysis of leakage risk factors (without DS patients)

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	114	16	12.3	0.63
Female	71	8	10.1	
Age(years)	58.7±10.8 (23–87)	59.7±10.1 (40–76)		0.65
Tumor location (cm)	6.4±1.6(4.0–12.0)	6.3±1.6 (4.0–10.0)		0.61
Bowel obstruction				
No	173	22	11.3	0.64
Yes	9	2	18.2	
Tumor invasion				
T1,T2	65	6	8.5	0.28
T3,T4	115	18	13.5	
Neoadjuvant chemo Tx				
No	180	24	11.8	0.54
Yes	5	0	0.0	
Anastomosis				
SST	7	1	12.5	0.63
DST	178	23	11.4	
High ligation				
No	108	17	13.6	0.47
Yes	75	7	8.5	
LLND				
No	130	16	11.0	0.72
Yes	55	8	12.7	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	4.2±1.1(2.2–7.0)		0.89
Intraoperative bleeding (cm)	480±502 (10–2985)	703±650 (40–2720)		0.07
Operating time (cm)	228±88 (90–552)	248±108(113–559)		0.60
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.7±3.1 (16.1–27.0)		0.82
Tumor size (cm)	4.3±2.3 (0–12.0)	5.0±2.4 (2.0–11.0)		0.26
Simultaneous resection				
No	171	21	10.9	0.31
Yes	14	3	17.6	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively ($p=0.04$).

Table 5 Multivariate analysis of leakage risk factors

	p-value	Odds ratio (95% CI)
High ligation	0.17	1.9 (0.77–4.54)
Intraoperative bleeding	0.78	1.0 (0.99–1.00)
Simultaneous resection	0.12	2.2 (0.82–6.09)

Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

Table 6 Clinical course affected by diverting stoma

DS in initial LAR		Leakage		Conservative therapy	Urgent operation	Rate of urgent operation	
			%			%	
DS(+)	120	9	7.5	8	1	11.1	p=0.04
DS(−)	209	24	11.5	11	13	54.2	

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or non-randomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS (p<0.001). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma (n=116) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma (n=118). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were

comparable to those in previous reports. In the present investigation, due to the retrospective nature of the study design, the level of anastomosis was calculated from the tumor location and distal resection margin when data were not available. And in some patients, tumor location was measured only by digital examination and not by rectoscopy, these might introduce bias. Although the anastomotic level was not associated with leakage, this data should be evaluated with caution.

High ligation of IMA was the only leakage risk factor on univariate analysis in the present study. Lange et al. [24] systematically reviewed the literature concerning the level of ligation and concluded that preserving IMA and left colic artery was anatomically less invasive with respect to circulation and autonomous innervations of the proximal limb of anastomosis. Seike et al. [25] measured the colonic blood flow at the proximal site of the anastomosis by laser Doppler flowmetry to evaluate the influence of high ligation. They proved a significant reduction of colonic blood flow at the proximal site after clamping IMA. Our result also suggested the possibility that blood flow reduction on anastomotic sites leads to more leakage.

In the present study, we reported our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1]. This may have some association with our patient population that neoadjuvant radiotherapy or chemo-radiotherapy was not performed in this series. Neoadjuvant radiation therapy is considered to be a risk factor by some authors [13, 14]. Although randomized multicenter trials have shown that neoadjuvant radiation does not increase postoperative morbidity [26–28], Peeters et al. [18] retrospectively analyzed risk factors from the database of the Dutch Colorectal Cancer Group, and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate.

We also reported our low mortality. This reflects our low leakage rate in cases without DS and our appropriate decision of reoperation for peritonitis in cases without DS. We considered that our appropriate decision lead to low mortality rate and high reoperation rate (54.2%). In the present study, a DS constructed at the time of initial surgery obviously reduced the necessity of an urgent reoperation after overt leakage, proving the clinical benefits of DS in this regard. The important objective of DS was not to eliminate leakage but to decrease the risk of reoperation. However, DS construction did not guarantee the complete safety of LAR. In fact, we experienced one mortality in a patient with DS in this series, so complete elimination of leakage and severe septic complications was not feasible.

In conclusion, we clearly demonstrated the outstanding safety of LAR with very low mortality and acceptable leakage rate in our group. Although this retrospective study could not prove whether DS can prevent leakage itself, we found that it could mitigate the need for urgent abdominal reoperation for leakage. To define clear criteria for DS construction, a well-designed randomized control study is genuinely needed in the future.

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Postoperative Lymphocyte Percentage Influences the Long-term Disease-free Survival Following a Resection for Colorectal Carcinoma

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Objective: The aim of this study is to examine the relationship between postoperative laboratory parameters of inflammation and the disease-free survival in patients undergoing resection for colorectal cancer.
Methods: Six hundred seventy-five consecutive patients who underwent an elective resection for primary colorectal cancer from October 1999 to March 2004 were included in this study. We examined the associations between cancer recurrence and white blood cell count, lymphocyte percentage, neutrophil percentage and C-reactive protein.
Results: Lymphocyte percentage on postoperative days 3 and 7 was significantly higher in patients without recurrence than in those with recurrence. Lymphocyte percentage on postoperative day 7 differed the most between the two groups. On postoperative day 7, Stage II patients with lymphocyte percentage >15% had significantly longer survival compared with the patients with lymphocyte percentage ≤15%. A multivariate analysis showed lymphocyte percentage ≤15% on postoperative day 7 to be an independent prognostic factor, along with lymph node metastases and serosal invasion. Logistic regression analysis showed that blood loss (>250 ml) and postoperative complications were significant independent predictors of lymphocyte percentage ≤15% on postoperative day 7.
Conclusions: Lymphocyte percentage ≤15% on postoperative day 7 is an independent prognostic factor for the patients undergoing a resection for colorectal cancer.

Key words: colorectal carcinoma – lymphocyte percentage – less invasive surgery

INTRODUCTION

Surgery remains the definitive treatment for advanced colorectal cancer. However, major surgery causes significant alterations in metabolic, immune and endocrine functions. It has been well documented that major surgery alters multiple immune parameters and accelerates tumor growth (1–4). Links between cancer and inflammation have not been elucidated. In some types of cancer, inflammatory conditions are present before a malignant change occurs. The mediators and cellular effectors of inflammation are important constituents of the local environment of tumors (5). Some studies show that the presence of inflammation is correlated with poor prognosis in the patients with malignancies (6,7). However, the impact of the postoperative inflammatory response on the recurrence of cancer has not been elucidated.

Laparoscopic surgery has led to great progress in the treatment of colorectal cancer. Recently, published randomized trials comparing laparoscopic and open surgery do not show inferior oncologic results in patients who undergo laparoscopic surgery (8,9). Lacy et al. (10) report significant improvement in 3-year survival in patients with advanced stage cancer who undergo laparoscopic surgery. The better survival might be attributed to the favorable immunologic response and lower stress response in patients who have undergone laparoscopic surgery.

The prognostic value of biological markers in patients with advanced cancer has been investigated in palliative care. There is some evidence that abnormalities in certain laboratory parameters [e.g. leukocytosis, lymphocytopenia and an elevated C-reactive protein (CRP) level] have prognostic values (11). However, the prognostic values of these

parameters in the perioperative period have not yet been examined in patients undergoing potentially curative surgery.

We examined the preoperative and postoperative white blood cells (WBCs), neutrophil percentage (NEUTRO%), lymphocyte percentage (LYMPH%) and level of CRP. The aim of this study is to clarify the impact of these parameters on the recurrence of cancer.

PATIENTS AND METHODS

Patients

Patients with histologically proven colorectal cancer who had undergone a potentially curative resection and had routine laboratory findings were included in this study. We retrospectively reviewed a database of 675 patients between August 1999 and March 2004 at the National Cancer Center East. Demographic and clinical data (age, sex, tumor location, tumor stage, differentiation, carcinoembryonic antigen (CEA) level, surgical approach, operating time, blood loss and postoperative complication) were collected. Patients with an emergency operation, non-curative resection, no laboratory data or preoperative chemoradiotherapy were excluded. The surgical approach was decided with the consent of the patients after thorough discussion on the advantages and disadvantages of the approaches. Patients with large, fixed tumors with invasion to other organs were advised against laparoscopic resection.

Data Collection

Routine laboratory measurements were taken before the operation and on postoperative days (PODs) 1, 3 and 7. In all blood samples, WBC, LYMPH%, NEUTRO% and CRP were measured.

Statistical Analysis

The statistical analysis was performed using the SPSS 11.0.1 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Comparisons of categorical ordinal variables were performed using the Pearson χ^2 test. The Mann–Whitney *U*-test was used to compare laboratory data at each time point between two groups. Survival rates were calculated with the Kaplan–Meier method, and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model. Logistic regression analysis was used to estimate the odds ratio with 95% confidence intervals for LYMPH% $\leq$ 15%. A *P* value of <0.05 was considered to be statistically significant.

RESULTS

The median follow-up duration was 46.3 months. Within the observation period, 124 patients developed recurrence. We compared laboratory data (WBC, LYMPH%, NEUTRO% and CRP) from patients with recurrence and those without recurrence. WBC and NEUTRO% on PODs 3 and 7 in patients without recurrence were significantly lower than in those with recurrence (Fig. 1a and c). LYMPH% on PODs 3 and 7 in the patients without recurrence was significantly higher than in patients with recurrence (Fig. 1b). The difference in LYMPH% on POD 7 (LYMPH%7POD) was most evident between the two groups. We compared clinicopathological factors and disease-free survival according to LYMPH%7POD. The patients with $\leq$15% LYMPH%7POD were classified in the low group and those with more than 15% LYMPH%7POD were classified in the high group. The median of LYMPH%7POD was 15.8%.

The correlation between clinicopathological factors and LYMPH%7POD are shown in Table 1. LYMPH%7POD was significantly correlated with gender ($P = 0.01$), tumor location ($P < 0.01$) and tumor stage ($P < 0.01$). Disease-free survival was significantly higher ($P < 0.01$) in the LYMPH%7POD $>$ 15% group than in the LYMPH% 7POD $\leq$ 15% group (Fig. 2). Three-year survival rates in patients with LYMPH%7POD $\leq$ 15% and in those with LYMPH%7POD $>$ 15% were 70.7 and 85.1%, respectively. More patients with advanced stage cancer had LYMPH%7POD $\leq$ 15%; therefore, disease-free survival was compared according to TMN tumor stage. As shown in Fig. 3, patients with LYMPH%7POD $>$ 15% had longer survival compared with those with LYMPH%7POD $\leq$ 15% in Stage II. Only three patients with Stage I tumors had recurrence, and there was no significant difference between the two groups in Stage I. Disease-free survival in the patients with Stage III and VI tumors was longer in the LYMPH%7POD $>$ 15% group, but the difference was not statistically significant. To determine the importance of the LYHPH%7POD as a predictor of disease recurrence, a multivariate analysis using the Cox proportional hazards model was performed. The analysis identified LYMPH%7POD $\leq$ 15% as an independent prognostic factor, along with lymph node metastases and serosal invasion (Table 2).

To identify the meaning of LYMPH%7POD, we performed logistic regression analysis with adjustments for operating time, blood loss, CEA, differentiation, lymph node metastases, serosal invasion, postoperative complications and laparoscopic surgery. Table 3 shows that blood loss ($>$250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD $\leq$ 15%. The extent of tumor spread, such as lymph node metastases and serosal invasion, was not a significant predictive factor.

DISCUSSION

To date, laboratory parameters, such as CRP (6,7), lymphocytopenia and leukocytosis (12,13), have been described as significant prognostic factors in patients with advanced

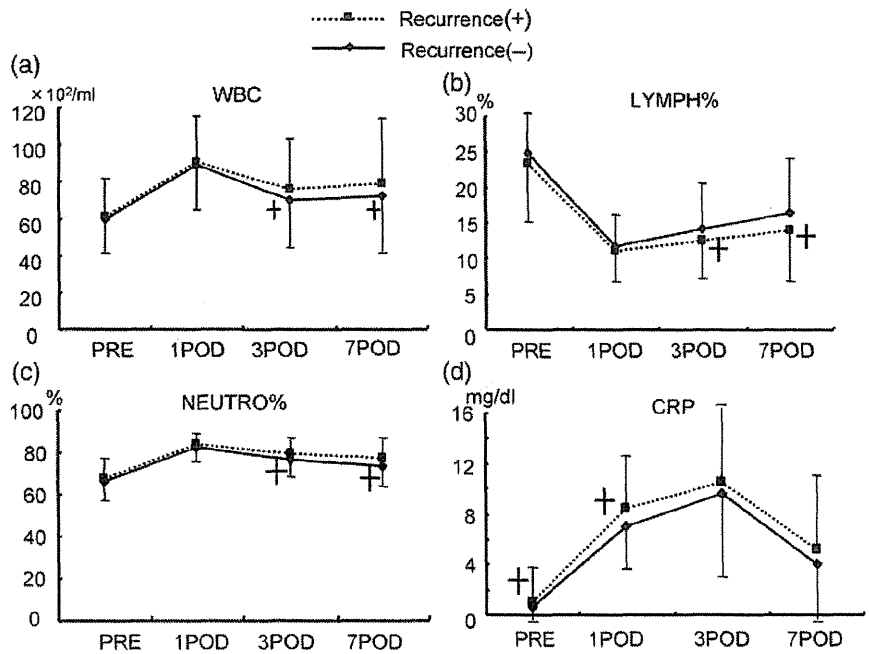

Figure 1. White blood cell (WBC), lymphocyte percentage (LYMPH%), neutrophil percentage (NEUTRO%) and C-reactive protein (CRP) in patients undergoing resection for colorectal carcinoma. Sample points were taken preoperative (PRE) and on postoperative days 1 (1POD), 3 (3POD) and 7 (7POD) ($^{+}P < 0.05$).

Table 1. The correlation between clinicopathological factors and LYMPH%7POD

	Lymph%7POD		*P* value
	>15% ($n = 248$)	≤15% ($n = 258$)	
Median age	63.6	62.6	0.31
Sex (M/F)	143/105	178/80	0.01
Tumor location			
Right side	52	39	<0.01
Transverse	23	17	
Left side	11	9	
Sigmoid	81	41	
Rectum	81	152	
Stage			
I	68	39	<0.01
II	88	81	
III	80	100	
IV	11	37	
Differentiation well or moderately	233	236	0.52
Poorly and others	9	13	

LYMPH%7POD, lymphocyte percentage on postoperative day 7.

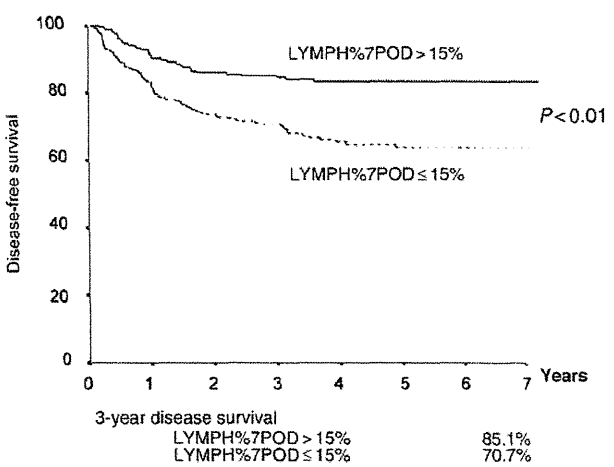

Figure 2. The disease-free survival rates of the patients with LYMPH%7POD > 15% and those with LYMPH%7POD ≤ 15%.

cancer. However, little information is available regarding the prognostic role of postoperative laboratory parameters in patients undergoing a resection of colorectal carcinoma. In this study, we evaluated whether postoperative laboratory data, such as WBC, LYMPH%, NEUTRO% and CRP, are associated with recurrence of colorectal carcinoma. This study demonstrated LYMPH%7POD ≤ 15% to significantly correlate with the recurrence of carcinoma as well as lymph node metastases and serosal invasion.

The LYMPH% is an important parameter in patients with advanced cancer (11,14,15). Some reports demonstrated that the neutrophil–lymphocyte ratio predicts survival in patients with colorectal cancer (16–18). Our results suggest that decreased LYMPH% may indicate an impaired host immune response to the tumor or inflammatory conditions that are

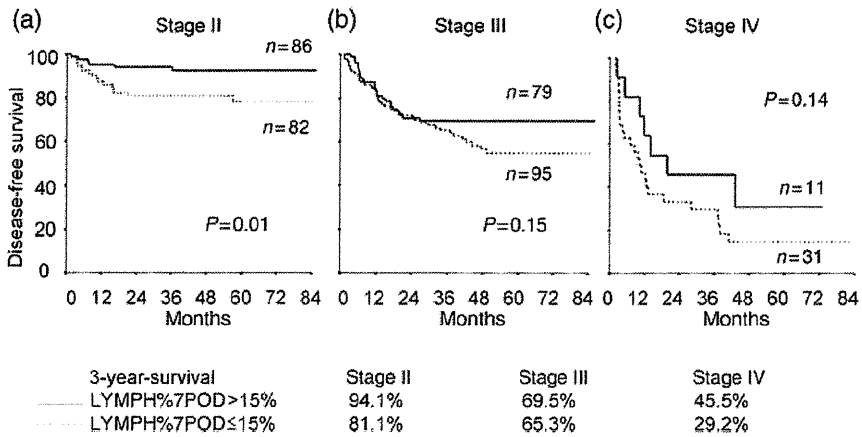

Figure 3. Comparison of disease-free survival between the patients with LYMPH%7POD > 15% and those with LYMPH7POD ≤ 15% according to TMN tumor stage.

Table 2. Multivariate analysis of risk factors affecting disease-free survival

	Hazard ratio	95% CI	*P* value
CEA >5 ng/dl	1.36	0.93–1.98	0.11
Differentiation	1.91	0.92–3.95	0.08
Lymph node metastases	5.7	2.47–13.1	<0.01
Serosal invasion	3.78	2.47–5.79	<0.01
LYMPH%7POD ≤ 15%	2.11	1.43–3.11	<0.01

CI, confidence interval; CEA, carcinoembryonic antigen.

Table 3. Multivariate analysis of clinicopathological variables for LYMPH%7POD

	Hazard ratio	95% CI	*P* value
Operating time (more than 3 h)	1.37	0.87–2.16	0.18
Blood loss (>250 ml)	2.82	1.62–4.88	<0.01
CEA >5 ng/dl	0.95	0.62–1.46	0.81
Differentiation (poorly and mucinous)	1.73	0.62–4.78	0.29
Lymph node metastases	0.75	0.47–1.20	0.23
Serosal invasion	1.34	0.89–2.03	0.17
Postoperative complication	2.89	1.90–4.39	<0.01
Laparoscopic surgery	0.64	0.37–1.11	0.11

associated with recurrence of the tumor. It is well known that lymphocytes are the most important factor in the antitumor immune system. Patients with decreased LYMPH% may exhibit a poorer lymphocyte-mediated immune response to malignancy, thereby increasing the risk of tumor recurrence. There is no correlation between LYMPH% and mode of recurrence. This study showed the difference in LYMPH% between the recurrent group and the non-recurrent group was evident on POD 7. During postoperative course, the condition of patients on POD 7 may be the most symbolic state of the recovery after surgery.

The LYMPH% shows a relative decrease in cases with inflammation. The connection between inflammation and cancer is now generally accepted. In some types of cancer, inflammatory conditions are present before a malignant change occurs.

However, it is not clear whether postoperative inflammation increases the recurrence of cancer. The relationship between surgical stress and host resistance to cancer was demonstrated in a murine model. Eggermont et al. (19) showed that a surgical procedure with entry into the abdominal cavity resulted in augmented tumor growth; conversely, a surgical incision on the animal's back did not promote tumor growth. Some authors show that anastomotic leak is associated with poor survival or local recurrence (20,21). These results suggest that acute inflammatory response may promote tumor spread and metastases. The LYMPH% may be a good indicator of systemic inflammatory response.

We demonstrated that LYMPH%7POD was significantly correlated with gender, tumor location and tumor stage. The reason for the association is speculative at present. The surgery for the patients with these variables may be more invasive and postoperative inflammatory response for these patients may be increased. We also demonstrated that blood loss (>250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD ≤ 15%. Surgical techniques that minimize blood loss and postoperative complications may be associated with improved postoperative immune and nutritional status that promote long-term disease-free survival. In this study, laparoscopic surgery tented to show a decreasing LYMPH%7POD, but the decline was not significant. The LYMPH% may also be a good indicator of the immune and nutritional status in the postoperative period.

In conclusion, our data demonstrated an association between LYMPH% on POD 7 and cancer recurrence. The postoperative

LYMPH% may be a good anti-inflammatory marker and a sensitive predictor of cancer recurrence in colorectal cancer.

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Conflict of interest statement

None declared.

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