TABLE IV. Univariate and Multivariate Analyses of 169 Patients With T4 Esophageal Cancers

		Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age	>70	1.26	0.83–1.91	0.269			
Gender	Male	1.31	0.775–2.22	0.320			
Tumor location	Lower third	1.03	0.65–1.65	0.874			
T4 organ	Trachea	1.35	0.92–2.00	0.133	1.032	0.69–1.54	0.877
Response	Non-responder	3.90	2.66–5.73	<0.0001	3.81	2.54–5.71	<0.0001
Surgical resection	Not performed	3.29	2.28–4.75	<0.0001	3.13	2.13–4.59	<0.0001
M1lym	Present	1.31	0.91–1.91	0.150	1.13	0.77–1.65	0.540
Induction therapy	Chemotherapy	0.81	0.57–1.17	0.260			

HR, hazard ratio; 95% CI, 95% confidence interval.

reported pathological CR rates for resectable esophageal cancers of 15–32% in patients who received neoadjuvant chemoradiotherapy, although a small number of patients with T4 disease were included in those previous studies [32–35,39,40]. However, the pathological CR rate was only 2.7–16.7% in patients with T4 esophageal cancer who received neoadjuvant chemoradiotherapy [3,4,6,17,19,20]. It therefore seems that the pathological CR rate is lower in T4 esophageal cancers than in resectable non-T4 esophageal cancers. The current result that surgical resection may offer survival benefit for both non-responders and responders could be due to the low incidence of pathological CR in T4 esophageal cancers. In fact, in the 19 patients who achieved clinical CR, there was no significant difference in survival between those who underwent chemoradiotherapy followed by surgery and those who underwent chemoradiotherapy alone.

In this study, there was no significant difference in patient survival across the 169 study patients between the induction chemotherapy group and the chemoradiotherapy group in spite of higher rate of surgical resection in the induction chemotherapy group patients, compared with those in the chemoradiotherapy group. Sub-analysis according to surgical resection also showed that the survival curves were almost similar between the two groups in both patients with surgical resection and those without surgical resection. One possible explanation for this result is that patient background differed between the two groups. Induction chemotherapy group included patients with more advanced disease compared with the chemoradiotherapy group in this retrospective study. Therefore, we think that prospective randomized-controlled trials are necessary to rigorously compare the patient survival between the patients who are treated with induction chemotherapy and those who are treated with chemoradiotherapy for T4 esophageal cancer.

This retrospective study had several limitations by allowing selection bias, in terms of decisions about treatment course. One limitation was that indication for surgical resection depended not only on respectability, but also sometimes on patient selection (several patients refused surgical resection when CR was achieved by preoperative treatment). Another limitation lay in the selection of induction chemotherapy versus chemoradiotherapy. Induction chemotherapy for T4 esophageal cancer is only relatively recent as an option, being introduced in April 2000. Therefore, the induction chemotherapy group included more recent cases, compared with chemoradiotherapy group. Moreover, patients sometimes selected chemoradiotherapy in place of chemotherapy as initial treatment because those patients were willing to receive short-term therapy. Despite this drawback, the current results that induction chemotherapy using multidrug may be as effective or more effective by combining second-line chemoradiotherapy than induction chemoradiotherapy in terms of local tumor control and the resectability rate should be considered in developing a treatment strategy for esophageal cancers invading adjacent organs (T4 esophageal cancers). Until now, T4 esophageal cancer with distant lymph node metastasis is usually excluded from indication for surgical resection even though down-staging is achieved by induction therapy. This study indicated that induction chemotherapy offers high respectability rates and prolonged survival for patients who have T4 tumors with distant lymph node metastasis, and that this strategy might provide the chance of curative resection.

In conclusion, the present study demonstrated that induction triplet chemotherapy reduced esophageal perforation and increased the resectability of T4 esophageal cancer by combining second-line chemoradiotherapy. Prospective randomized-controlled trials are necessary to confirm the clinical relevance of induction multidrug chemotherapy for patients with T4 esophageal cancers and to confirm the need for surgical resection in such patients.

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Laparoscopic Bladder-Preserving Surgery for Enterovesical Fistula Complicated with Benign Gastrointestinal Disease

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Key Words
Intestinal fistulas · Surgical techniques · Minimally invasive surgery · Colorectal and small bowel · Diverticular disease · Crohn's disease

Abstract
Enterovesical fistula (EVF) is a relatively uncommon condition that is associated with severe morbidity. Minimally invasive and organ-preserving surgery should be performed in the case of EVF caused by benign diseases. We applied laparoscopic bladder-preserving surgery (LBPS) for EVF caused by benign gastrointestinal disease. Here, we report a surgical technique for LBPS. Patient and instrument port positioning are similar to those used in laparoscopic colorectal surgery. Dissection around the fistula is performed along the intestine as distant from the bladder as possible. If there is sufficient area around the intestinal portion of the fistula, it is isolated and resected using a linear stapler. If this approach is not possible, the intestinal fistula is sharply dissected as far away from the bladder as possible. LBPS for EVF was performed in 4 patients and included 3 direct sharp dissections and 1 stapling dissection. Three of the 4 patients did not require any further treatment for the bladder, and all procedures were feasibly accomplished under laparoscopic conditions. In conclusion, LBPS is feasible in cases of EVF caused by benign gastrointestinal disease, and we suggest that it should be the first choice of intervention in such cases.

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Introduction

Enterovesical fistula (EVF) is a relatively uncommon condition; however, it is associated with a high incidence of morbidity. In the majority of cases, the symptoms of EVF are associated with a decrease in the patient's quality of life. It represents a rare complication of inflammatory or neoplastic diseases in the gastrointestinal and urinary tracts, but may also be caused by traumatic or iatrogenic injuries [1]. In cases of EVF caused by neoplastic disease, extensive surgery with multivisceral resection, including bowel resection and partial/total cystectomy, is needed. Conversely, for EVF caused by benign diseases, minimally invasive and organ-preserving surgery should be performed. We performed laparoscopic bladder-preserving surgery (LBPS) for EVF caused by benign gastrointestinal disease. We report a surgical technique and concept of LBPS for EVF caused by benign gastrointestinal disease. For a video of the procedure carried out in case 1 and case 2, see online supplementary material (www.karger.com/doi/10.1159/000339202).

Surgical Techniques

The diagnosis of EVF is not difficult. Most affected patients present with pathognomonic features of pneumaturia, fecaluria and recurrent urinary tract infections. A computed tomography scan can detect air in the bladder in the majority of patients. However, cystography, swallowing studies and enemas cannot be used to confirm the presence of a fistula. In order to minimize the likelihood of infection, surgery should be conducted after a course of antibiotic therapy or following total parenteral nutrition. Informed consent was obtained before operation in all cases. Patient and instrument port positioning are performed in a way similar to laparoscopic colorectal surgery.

First, malignancy is ruled out by laparoscopic examination. The relationship between the intestine, EVF and bladder is consequently confirmed. Then a mobilization approach of medial-to-lateral and lateral-to-medial is made for laparoscopic dissection and vessel ligation. Vessel ligation should be performed as distant from the root of the feeder arteries as possible. The identification and confirmation of the ureter must be ascertained and meticulous dissection is important for avoiding ureteral injury. Lymphadenectomy is not indicated because of the benign cause.

The fistula along the diseased intestine is dissected as distant from the bladder as possible. If isolation is not possible, the fistula is sharply dissected along the diseased intestine (fig. 1). If there is sufficient area around the intestinal fistula, it is isolated and resected using a linear stapler (fig. 2).

Following LBPS, the bladder is filled with saline (100–200 ml) to check for any leakage. In the event of a leak, curettage and suturing around the bladder fistula is undertaken to close the fistula. Neither partial cystectomy nor trimming of the bladder has further practical benefit. A Foley catheter is inserted into the bladder after the procedure.

Following fistula removal, the diseased intestine is resected and the tissue is reconstructed using stapling techniques (functional end-to-end anastomosis for the small intestine or right colon, and double-stapling technique for the left colon or rectum). The resected fistula site at the bladder is covered with omentum to prevent adhesion between the anastomotic site and the bladder. A drainage tube is inserted to assess any bleeding or urine leakage.

Postoperative oral intake is permitted as with conventional colorectal surgery. One week after the procedure, the Foley catheter is removed once cystography confirms the absence of any leakage from the bladder.

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Results

LBPS was performed on 4 patients with EVF caused by benign gastrointestinal disease. The demographics of the patients are given in table 1. Median age was 48 years. Primary disease included diverticulitis of the sigmoid colon (3 patients) and Crohn's disease (1 patient). We employed the same surgical procedure in all cases, as described before. In the male patients with diverticulitis of the sigmoid colon, 2 direct sharp dissections and 1 stapling dissection of the fistula were performed. In the female patient with Crohn's disease, direct sharp dissection of the fistula was performed. The water leak test was positive in 1 patient after the direct sharp dissection, and this patient underwent suturing around the bladder fistula. The procedures for the diseased intestines included 3 sigmoidectomies with the double-stapling technique and 1 ileocecal resection with functional end-to-end anastomosis. The median operation time and blood loss were 234 min and 225 g, respectively. All patients underwent cystography 1 week after the operation, and the Foley catheter was removed. The median postoperative follow-up period was 25 months. Neither dysuria nor recurrence of EVF was observed on follow-up.

Discussion

EVF is usually complicated by subsequent gastrointestinal diseases, such as diverticulitis, colorectal cancer and inflammatory bowel diseases. EVF caused by urologic disease is rare [2, 3]. EVFs caused by gastrointestinal diseases are mostly resistant to medical therapy and often require surgical correction. In cases of EVF caused by gastrointestinal malignancy, not only bowel resection with regional lymphadenectomy for the primary lesion, but also extensive surgery with multivisceral resection, such as total pelvic exenteration, is needed to complete en bloc resection. Construction of diverting stoma without bowel resection is common for palliation. In contrast, in cases of EVF caused by benign gastrointestinal disease, resection of the diseased portion of the intestine is fundamental to surgical treatment. However, a standard treatment for the bladder in patients with EVF caused by benign gastrointestinal disease has not been established.

Recent technological advances and development of new equipment have promoted the use of laparoscopic surgery as standard treatment for gastrointestinal diseases. The indications for laparoscopic surgery are expanding. However, laparoscopic surgery for internal fistula caused by benign gastrointestinal disease is still uncommon. Historically, partial cystectomy and formal repair of the bladder wall were performed as the typical treatment [4]. Therefore, the complicated procedures for bladder surgery, such as deciding upon an area and extent of resection or suturing a defect of the bladder wall, were considered difficult under laparoscopic surgery. Furthermore, partial cystectomy, if the area or extent of bladder resection is inadequate, may lead to dysuria. Successful surgical management of EVF from diverticulitis or Crohn's disease has recently been reported; the procedure involves only resection of the diseased bowel with minimal need for repair or resection of the bladder side of the fistula [5]. It is commonly believed that partial cystectomy should be considered only when major water leakage is detected after the repair of overt full-thickness defects in the bladder. During LBPS, we put this concept to practical use under laparoscopic surgery. The LBPS

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procedures carried out for EVF included 3 direct sharp dissections and 1 stapling dissection. The water leak test was positive in 1 patient who underwent direct sharp dissection, and this patient received subsequent suturing around the resection site to seal the bladder. In all patients the laparoscopic procedure was successfully performed. It cannot be denied that open conversion is necessary in cases with dense adhesion or with difficulties in identification and dissection of the ureter. However, we conclude that LBPS can be completed in most cases of EVF caused by benign gastrointestinal disease and should be the first choice of intervention.

Table 1. Patient characteristics

	Case			
	1	2	3	4
Age	80	40	44	51
Sex	male	male	male	female
Primary disease	diverticulitis	diverticulitis	diverticulitis	Crohn's disease
Enteric fistula	sigmoid colon	sigmoid colon	sigmoid colon	ileum
Bladder fistula	base	trigone	body	base
Fistula treatment	direct sharp dissection	stapling dissection	direct sharp dissection with additional suturing	direct sharp dissection
Operating time, min	325	235	233	100
Blood loss, g	190	200	520	250
Complication	wound infection	none	none	none

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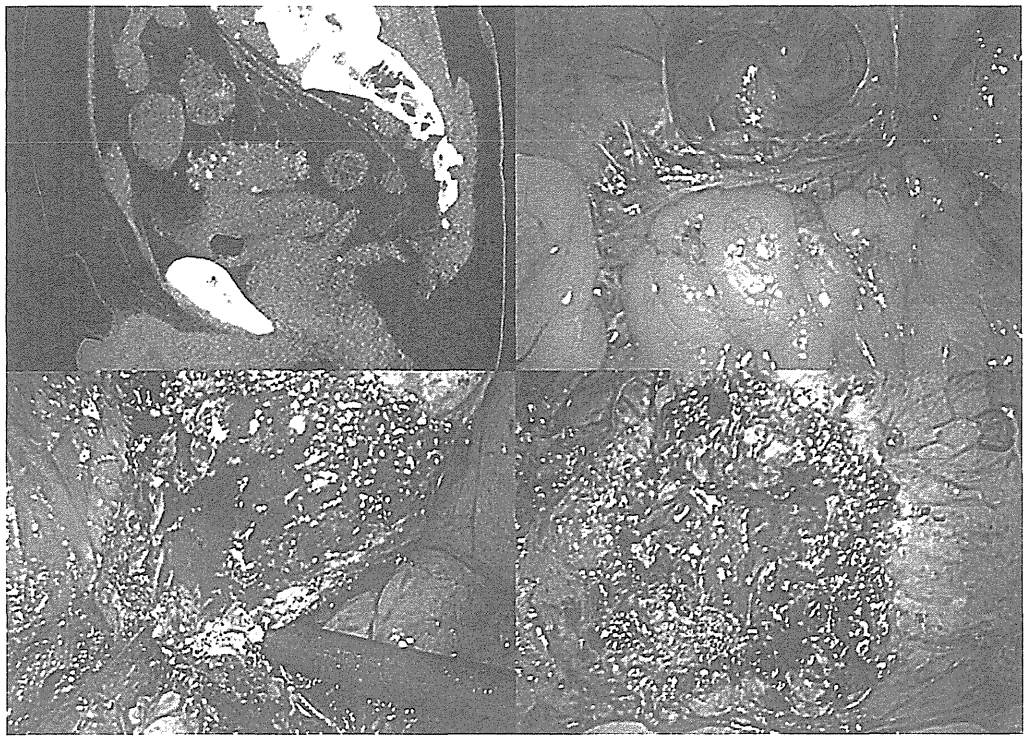

Fig. 1. Case 1. The patient was an 80-year-old man with EVF caused by diverticulitis of the sigmoid colon. Bladder fistula was identified at the base. Severe inflammatory adhesion due to previous diverticulitis existed around the sigmoid colon. We dissected around the sigmoid colon and dissected the fistula sharply along the diseased intestine. The water leak test was negative, and hence no additional treatment for the bladder was needed.

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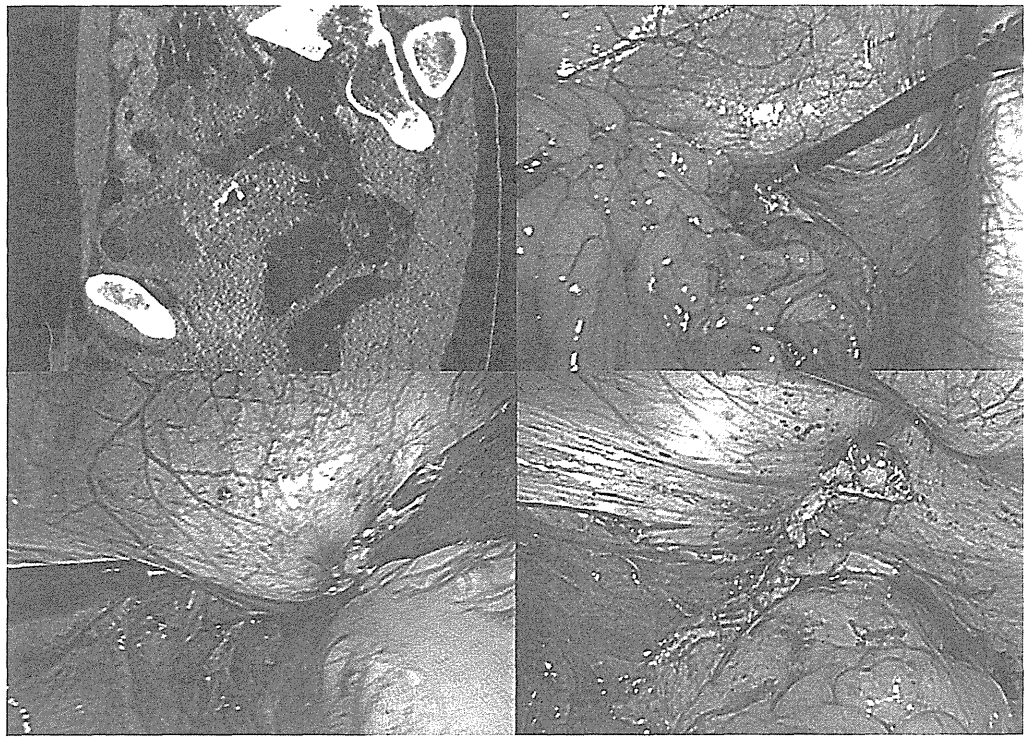

Fig. 2. Case 2. The patient was a 40-year-old man with EVF caused by diverticulitis of the sigmoid colon. Bladder fistula was identified at the trigone. The inflammatory adhesion around the fistula was very mild, and we could perform taping around the fistula. Thus, we identified the ureter and performed a stapling dissection of the EVF.

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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

MicroRNA-10b is a Prognostic Indicator in Colorectal Cancer and Confers Resistance to the Chemotherapeutic Agent 5-Fluorouracil in Colorectal Cancer Cells

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ABSTRACT

Purpose. Recent evidence has shown that altered patterns of microRNA (miRNA) expression correlate with various human cancers. We investigated the clinical significance of *miR-10b* and its involvement in chemotherapeutic resistance to 5-fluorouracil (5-FU), which is a key component of common chemotherapy regimens in colorectal cancer.

Methods. Quantitative RT-PCR was used to evaluate the clinicopathologic significance of *miR-10b* expression in 88 colorectal cancer cases. We also investigated the chemotherapeutic sensitivity to 5-FU in *miR-10b*-overexpressing colorectal cancer cells. To explore the mechanism of chemoresistance in *miR-10b* transfected cells, we examined whether *miR-10b* inhibits the pro-apoptotic BH3-only Bcl-2 family member *BIM(BCL2L11)*, a key mediator of chemotherapy-induced cell death.

Results. High level *miR-10b* expression was found to be significantly associated with high incidence of lymphatic invasion ($P = 0.0257$) and poor prognosis ($P = 0.0057$). Multivariate analysis indicated that high *miR-10b* expression is an independent prognostic factor for survival. In vitro studies revealed that *miR-10b* directly inhibits pro-apoptotic *BIM*, and the overexpression of *miR-10b* confers chemoresistance in colorectal cancer cells to 5-FU.

Conclusions. *MiR-10b* is a novel prognostic marker in colorectal cancer. Moreover, the expression of *miR-10b* is a potential indicator of chemosensitivity to the common 5-FU-based chemotherapy regimen.

Naohiro Nishida, Shinya Yamashita contributed equally to this work.

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Colorectal cancer is the third most common malignancy and the fourth largest cause of cancer mortality. More than 1 million new cases are diagnosed worldwide each year, and the incidence rises with the progressive "westernization" of lifestyles in Asian and African countries.[1] Multimodal treatment, including chemotherapies, such as FOLFOX (5-FU + folinic acid (leucovorin) + oxaliplatin (Eloxatin)) and FOLFILI (5-FU + folinic acid (leucovorin) + Irinotecan (Camptosar; Campto)) have significantly improved prognosis; however, once metastasis or recurrence has occurred, prognosis is very poor.[2,3] For accurate diagnosis and adequate treatment of colorectal cancer, identification and understanding of the molecules responsible for cancer progression are critical.

MicroRNAs (miRNAs) constitute a class of small (19–25 nucleotide) noncoding RNAs that function as posttranscriptional gene regulators. Alterations in miRNA expression are involved in the initiation, progression, and metastasis of human cancer.[4–7] MiRNAs can function as either oncogenes or tumor suppressors and, therefore, have been increasingly recognized as useful biomarkers, as well as therapeutic tools.[6,8] Moreover, recent evidence suggests that miRNA expression is significantly associated with chemosensitivity in human cancer cells.[9–12]

MiR-10b has been shown to be involved in cancer progression in several kinds of cancers, including those of the breast, pancreas, and central nervous system.[13–16] Ma et al.[13] reported for the first time that *miR-10b* is induced by the transcription factor Twist and positively regulates cell migration and invasion through activation of *RHOC*. Subsequent reports also have suggested that *miR-10b* is highly expressed in highly metastatic cancer cells and plays a central role in cancer metastasis.[17–20]

In the current study, we investigated the clinical significance of *miR-10b* in human colorectal cancer. *MiR-10b* has been recognized as an invasion- and metastasis- related molecule; we also focused on the antiapoptotic effect of *miR-10b* and explored the chemoresistance of *miR-10b* to 5-fluorouracil (5-FU) in colorectal cancer cells in vitro. In this study, we show how *miR-10b* is involved in cancer progression in human colorectal cancer.

MATERIALS AND METHODS

Patients and Sample Collection

Tissues from 88 cases of colorectal cancer were obtained during surgery. Cancer tissues and normal tissues were obtained from different patients. All patients underwent resection of primary tumors at Kyushu University Hospital at Beppu and affiliated hospitals between 1993 and 2006. Written, informed consent was obtained from all patients, and the study protocol was approved by the local ethics committee. All patients were clearly identified as having colorectal cancer based on the clinicopathologic criteria described by the Japanese Society for Cancer of the Colon and Rectum. Resected cancer tissues were immediately cut and embedded in Tissue-Tek OCT medium (Sakura), frozen in liquid nitrogen, and kept at −80°C until the time of RNA and DNA extraction. Detailed information is described in Supplementary Data.

Evaluation of miR-10b Expression in Clinical Samples

For *miR-10b* quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) cDNA was synthesized from 10 ng of total RNA using TaqMan™ MicroRNA hsa-*miR-10b*-specific primers (Applied Biosystems) and a TaqMan™ MicroRNA Reverse Transcription Kit (Applied Biosystems). The following temperature profile was used: initial denaturation at 95°C for 10 min, followed by 45 cycles of denaturation at 95°C for 10 s, annealing at 60°C for 10 s, and extension at 65°C for 10 s. PCR was performed in a LightCycler™ 480 System (Roche Applied Science) using the LightCycler™ 480 Probes Master kit (Roche Applied Science). Expression levels of *miR-10b* were normalized to that of the small nuclear RNA RNU6B (Applied Biosystems) transcript. Each assay was performed three times to verify the results, and the mean normalized value of mRNA expression was used for subsequent analyses.

EXPERIMENTAL STUDIES

Cell Lines and Cell Culture

The human colorectal cancer cell line HCT-116 was purchased from American Type Culture Collection (ATCC) and maintained in MEM (GIBCO) containing 10% fetal bovine serum with 100 units/mL of penicillin and 100 units/mL of streptomycin sulfate and cultured in a humidified 5% CO_2 incubator at 37°C.

Transfection of a microRNA-10b Precursor (Pre-miR™-10b)

Using HCT-116, a colorectal cancer cell line, either pre-miR-10b or a pre-miR negative control (Ambion® Pre-miR™ miRNA Precursors Applied Biosystems Japan Ltd.) was transfected at 50 nM (final concentration) using Lipofectamine™ RNAiMAX (Invitrogen Life Technologies) according to the manufacturer's instructions.

RNA Extraction from Cell Lines after Transfection

For RNA analysis, the HCT-116 cell line was seeded at 2×10^5 cells per well in a volume of 2 mL in six-well flat-bottomed microtiter plates. Total RNA was isolated using the mirVana™ miRNA Isolation Kit (Ambion) 48 h after transfection. Transfection efficiency was determined by measuring *miR-10b* expression in transfected cells by qRT-PCR.

Assessing Chemosensitivity to 5-FU

5-FU was purchased from Kyowa Hakkou (Tokyo). To assess the sensitivity to 5-FU in vitro, cell viability assays were performed. Logarithmically growing HCT-116 cells were transfected with Pre-*miR-10b* or Pre-miR-negative control with or without addition of 5-FU (at concentrations of 0.5, 1.0, 5, and 10 μg/mL, and no treatment as control) and were seeded at 8.0×10^3 cells/well in 96-well flat-bottomed microtiter plates in a final volume of 100 μL of culture medium per well. Cells were incubated in a humidified atmosphere (37°C and 5% CO_2) for 96 h after initiation of transfection.

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Roche Diagnostics Corp.) was used to measure cell viability. After incubation, 10 μL of MTT labeling reagent (at a final concentration of

0.5 mg/mL) was added to each well, and the plate was incubated for 4 h in a humidified atmosphere. Solubilization solution (100 μL) was added to each well, and the plate was incubated overnight in a humidified atmosphere. After confirming that the purple formazan crystals were completely solubilized, the absorbance of each well was measured by a Model 550 series microplate reader (Bio-Rad Laboratories) at a wavelength of 570 nm corrected to 655 nm. The assay was performed using six replicates.

Plasmid Construction

The 3' untranslated region (3'UTR), including *miR-10b* binding site of *BIM*, was amplified by RT-PCR. The sequence of primers are as follows: Forward-TAATTCTAGTTGTT-TAAAGCAGGTGGTTCTGCCATCCC; Reverse-GCAG GTCGACTCTAGATCTGCAGTTATTTACAGCAG. The amplified product (254 bp) was sub-cloned and ligated into the pmirGLO Dual-Luciferase miRNA Target Expression Vector (Promega) using the In-Fusion® HD Cloning Kit (Clontech) at DraI and XbaI sites. The entire resulting sequence of the insert and vector was confirmed by sequencing.

Luciferase Assay

Luciferase assays were conducted using 5×10^3 HCT-116 cells per well plated in 96-well plates. Transfections were performed using Lipofectamine™ 2000 (Invitrogen) in OptiMEM reduced serum media (GIBCO). Cells were transfected with 30 ng of pmiRGLO constructs containing the *BIM* 3'UTR sequences and 100 nM of pre-miR negative control or pre-*miR-10b*. Twenty-four hours after transfection, cells were assayed for both firefly and *renilla* luciferase using the Dual-Glo™ Luciferase Assay System (Promega) according to the manufacturer's instructions. All transfection experiments were conducted in triplicate.

Protein Expression Analysis

Western blotting was used to confirm the expression of BIM and β-actin in pre-miR-negative control or Pre-*miR-10b* transfected cells. Total protein was extracted from samples using Tris-NaCl-EDTA (TNE) buffer containing protease inhibitors 72 h after transfection. Aliquots of total protein were applied to 10% polyacrylamide gradient gels. After electrophoresis, the samples were electroblotted (0.2 A, 120 min, 4°C) onto a polyvinylidene membrane (Immobilon; Millipore, Inc.). BIM protein was detected with an anti-BIM rabbit monoclonal antibody (Epitomics, Inc.) at a 1:500 dilution. The levels of each protein were normalized to the level of β-actin protein, which was detected by a 1:1,000 dilution of mouse polyclonal anti-β-actin antibody (Cytoskeleton Inc.). The blots were developed using horseradish peroxidase-conjugated anti-rabbit or anti-mouse immunoglobulin (Promega, Inc.) at a dilution of 1:1,000.

Statistical Analysis

Data from RT-PCR analysis and in vitro transfected cell assays were analyzed with JMP 5. Overall survival rates were calculated actuarially according to the Kaplan–Meier method and were measured from the day of surgery. Differences between groups were estimated using the χ^2 test, Student's t test, repeated-measures ANOVA test, and the log-rank test. Variables with a value of $P < 0.05$ in univariate analysis were used in a subsequent multivariate analysis based on the Cox proportional hazards model. A probability level of 0.05 was chosen for statistical significance.

RESULTS

Clinicopathologic Significance of miR-10b mRNA Expression in Colorectal Cancer

We classified 88 colorectal cancer cases into two groups according to the median *miR-10b* expression level (median = 22.0, normalized to RNU6B), as determined by quantitative RT-PCR. Patients in the high *miR-10b* expression group (above median) had a significantly poorer prognosis than those in the low *miR-10b* expression group (below median; $P = 0.0057$; Fig. 1). In clinicopathologic analysis, the high *miR-10b* expression group showed a higher incidence of lymphatic invasion ($P = 0.026$) and a stronger tendency to be associated with tumor depth ($P = 0.06$) than the low *miR-10b* expression group. However, no significant differences were observed with respect to age, gender, histology, venous invasion, liver metastasis, or clinical stage (Table 1). When we used the mean value as the *miR-10b* cutoff instead of the median, patients with *miR-10b* expression above mean value (mean value = 39.7, normalized to RNU6B; $n = 28$) showed a significantly more frequent occurrence of lymph node metastasis than those with *miR-10b* expression below mean value ($n = 60$; $P = 0.034$; Supplementary Table S2). The results of univariate and multivariate Cox proportional hazards regression analyses for overall survival are shown in Table 2. Multivariate analysis indicated that the high expression level of *miR-10b* was an independent and significant prognostic factor for survival (odds ratio (OR), 1.56; 95% confidence interval (CI), 1.06–2.38; $P = 0.025$; Table 2). When only the Dukes C and D patients ($n = 42$) were analyzed, the patients in the *miR-10b* high expression

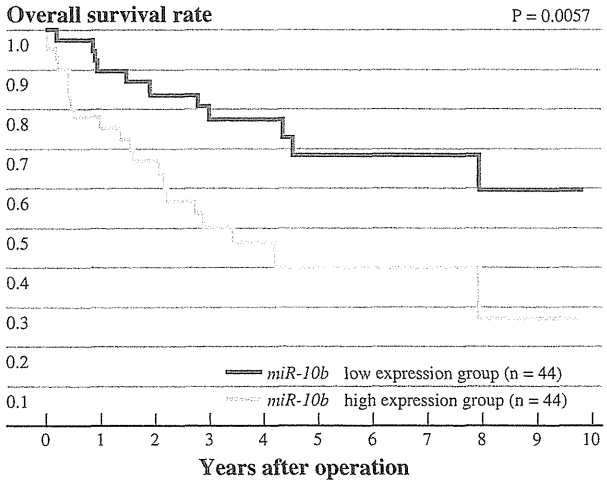

FIG. 1 Kaplan–Meier overall survival curves of colorectal cancer patients according to the level of *miR-10b* expression. Patients in the high *miR-10b* expression group had a significantly poorer prognosis than those in the low *miR-10b* expression group. The high *miR-10b* expression group ($n = 44$) was composed of patients with higher than median expression levels (median = 22.0, normalized to RNU6B); the low *miR-10b* expression group ($n = 44$) had lower than median expression levels as determined by quantitative RT-PCR ($P = 0.0057$)

group ($n = 21$, above median; median = 26.8, normalized to RNU6B) showed a significantly poorer prognosis than those in the low expression group ($n = 21$, below median; $P = 0.019$; Supplementary Fig. 1). These data suggest that *miR-10b* also is involved in cancer progression in advanced metastatic positive colorectal cancer patients. To clarify the association between *miR-10b* expression and the efficiency of chemotherapy, we analyzed the survival data only in patients who received 5-FU-based adjuvant chemotherapy ($n = 49$). The chemotherapy regimens used are listed in Supplementary Table S1. Again, in this analysis, the *miR-10b* high expression group ($n = 21$, above mean value; mean value = 34.8) had a significantly poorer prognosis than the low expression group ($n = 28$, below mean value; $P = 0.046$; Supplementary Fig. S2).

MiR-10b Confers Resistance to the Chemotherapeutic Agent 5-Fluorouracil in Colorectal Cancer Cells

Cell viability assays were performed to evaluate the contribution to chemoresistance of *miR-10b* in colorectal cancer cells. 5-FU-treated HCT-116 cells transfected to overexpress *miR-10b* showed a significantly increased viability compared with negative control-transfected cells. At the maximum concentration of 10 μg/mL, the cell viability of negative controls was reduced by 29.8 ± 2.09%, whereas the viability of *miR-10b* transfected cells was 69.2 ± 4.5% (Fig. 2).

MiR-10b Regulates BIM in Colorectal Cancer Cells

We focused on the pro-apoptotic BH3-only Bcl-2 family member *BIM* (*BCL2L11*) as a potential mediator of the chemoresistance of *miR-10b* overexpressing cells. Using *in silico* microRNA target prediction tools, including miRanda, PicTar, and TargetScan, we identified *miR-10b* binding sites in the 3′UTRs of transcripts encoding *BIM* (Fig. 3a).[21–23] To investigate binding and repression of BIM by miR-10b, a luciferase reporter assay was performed with a vector that included the 3′UTR of *BIM* downstream from the luciferase reporter gene. Transient cotransfection of HCT-116 cells with the reporter plasmid and Pre-miR-10b significantly reduced luciferase activity compared with the negative control ($P = 0.0024$; Fig. 3b), suggesting that *BIM* mRNA is a direct target of *miR-10b*.

To determine whether *miR-10b* suppresses *BIM* in the colorectal cancer cell line HCT-116 at the protein level, cell lysates of transfected cells were analyzed by Western blotting. Using RT-PCR, we confirmed that *miR-10b* expression in Pre-miR-10b-treated cells was significantly higher than that in Pre-miR-negative control-treated cells ($P = 0.002$; Fig. 3c, upper). Suppression of BIM was observed in Pre-miR-10b–treated cells compared with negative controls (Fig. 3c, lower).

DISCUSSION

In the current study, we show that altered *miR-10b* expression significantly affects cancer progression and prognosis in human colorectal cancer. Clinicopathological analysis revealed that high *miR-10b* expression contributes to more advanced lymphatic invasion ($P = 0.026$) and poor prognosis ($P = 0.0057$; Table 1; Fig. 1). This finding is consistent with previous reports showing that *miR-10b* enhances the mobility of cancer cells and promotes invasive ability. Multivariate analysis revealed that *miR-10b* is an independent prognostic factor for survival ($P = 0.025$; Table 2). To our knowledge, this is the first report describing the clinical significance of *miR-10b* in colorectal cancer.

MiR-10b is known to function as an oncogene in various kinds of cancers, including those of the breast, pancreas, esophagus, and central nervous system.[13–16,19,24] One of the representative targets of *miR-10b* is *HOXD10*, whose inhibition leads to the activation of the pro-metastatic gene *RHOC*.[13] This pro-metastatic effect was confirmed in an in vivo study that showed that an antisense nucleotide against *miR-10b* (*miR-10b* antagomirs) suppresses metastasis in a mouse mammary tumor model.[25] Recently, in addition to its metastasis-promoting role, an antiapoptotic effect of *miR-10b* has been reported. Gabriely et al.[16] demonstrated that *miR-10b* suppresses proapoptotic *BIM* in glioblastomas

TABLE 1 *miR-10b* expression and clinicopathological factors

Factors	Tumor low expression ($n = 44$)		Tumor high expression ($n = 44$)		*P* value
	Number	%	Number	%	
Age (mean ± SD)	66.36 ± 1.78		64.61 ± 1.78		0.490
Sex					
Male	26	59.1	29	65.9	0.501
Female	18	40.9	15	34.1	
Histological grade					
Well	26	59.1	29	65.9	0.509
Moderately, Poorly	18	40.9	15	34.1	
Depth of tumor invasion[a]					
m, sm, mp	17	38.6	9	20.5	0.06
ss, se, si	27	61.4	35	79.5	
Lymph node metastasis					
Absent	29	65.9	23	52.3	0.193
Present	15	34.1	21	47.7	
Lymphatic invasion					
Absent	33	75.0	23	52.3	0.0257*
Present	11	25.0	21	47.7	
Venous invasion					
Absent	35	79.5	38	86.4	0.384
Present	9	20.5	6	13.6	
Liver metastasis					
Absent	37	84.1	34	77.3	0.417
Present	7	15.9	10	22.7	
Dukes stage					
A/B	25	56.8	21	47.7	0.393
C/D	19	43.2	23	52.3	

[a] Tumor invasion of mucosa (m), submucosa (sm), muscularis propria (mp), subserosa (ss), penetration of serosa (se), and invasion of adjacent structures (si)

* $P < 0.05$

TABLE 2 Univariate and multivariate analysis of overall survival (Cox regression model)

Factors	RR	Univariate analysis			Multivariate analysis	
		95% CI	*P* value	RR	95% CI	*P* value
Age (<65/66<)	1.00	0.970–1.03	0.959	–	–	–
Sex (male/female)	1.00	0.690–1.43	0.990	–	–	–
Histology grade (well/others)	1.26	0.877–1.87	0.216	–	–	–
Depth of tumor invasion (m, sm, mp/ss, se, si)[a]	2.22	1.32–4.54	0.0012*	1.35	0.761–2.83	0.328
Lymph node metastasis (negative/positive)	2.34	1.16–3.61	0.0001*	1.97	1.30–3.11	0.0011*
Lymphatic invasion (negative/positive)	2.17	1.52–3.17	0.0001*	1.81	1.22–2.74	0.0029*
Venous invasion (negative/positive)	1.71	1.15–2.46	0.0096	1.24	0.809–1.85	0.314
Liver metastasis (negative/positive)	1.77	1.20–2.54	0.0048*	1.44	0.936–2.19	0.0953
miR-10b expression (low/high)	1.65	1.15–2.44	0.0060*	1.56	1.06–2.38	0.0253*

RR Relative risk, *CI* Confidence interval

[a] Tumor invasion of mucosa (m), submucosa (sm), muscularis propria (mp), subserosa (ss), penetration of serosa (se), and invasion of adjacent structures (si)

* $P < 0.05$

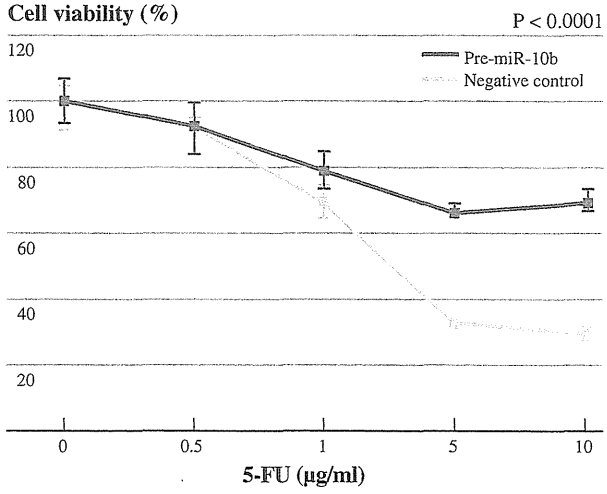

FIG. 2 *miR-10b* overexpressing cells are resistant to 5-FU. HCT-116 colorectal cancer cells transfected with Pre-miR-10b or Pre-miR-negative control were treated with the indicated concentrations of 5-FU for 96 h. Cell viability was analyzed by MTT assay, as described in "Materials and Methods" section. Ratios of mean absorbance of wells containing drug over mean absorbance of drug-free wells were plotted against different concentrations of 5-FU. The results are the mean ± standard deviation (SD) of three replicates

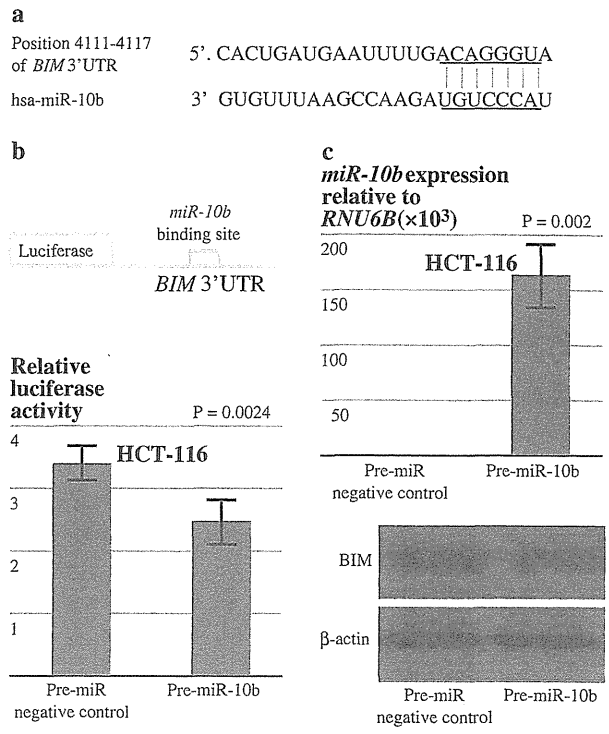

FIG. 3 *MiR-10b* targets *BIM*. **a** Sequence of the *miR-10b* binding sites in the 3'UTRs of transcripts encoding *BIM*. **b** (*Upper*) schematic diagram of the luciferase reporters in target validation. Seed sequence on microRNA and its complementary sequence on target mRNA are underlined. (*Lower*) *MiR-10b* represses its target in the luciferase assay in HCT-116. Relative luciferase activity (*firefly/renilla*) was significantly decreased in Pre-miR-10b transfected HCT-116 cells. Luc, raw firefly luciferase activity; *Renilla*, internal transfection control *renilla* activity; *Pre-miR* n.c., *Pre-miR*™ negative control. The *error bar* represents the SD from six replicates. **c** (Upper) *miR-10b* expression after treatment with negative control or *Pre-miR-10b* in HCT-116 (RT-PCR). *MiR-10b* expression in Pre-miR-10b-treated cells is significantly higher than in Pre-miR-negative control-treated cells. The results are the mean ± SD of triplicates. (*Lower*) Western blotting analysis of BIM in HCT-116 cells transfected with Pre-miR-10b or negative control. The levels of these proteins were normalized to the level of β-actin

and that alterations of *miR-10b* expression significantly influence the expression of apoptosis-related genes.

BIM is a member of the *BCL-2* homology 3(BH3)-only subgroup of the *BCL-2* family, which also includes *BID*, *BAD*, *BIK*, *NOXA*, and *PUMA*. *BIM* potently induces apoptosis by interacting with and inhibiting the antiapoptotic members of the BCL-2 family.[26] Previous reports demonstrated that *BIM* plays a critical role in chemosensitivity to 5-FU and cisplatin.[27,28] Moreover, Sinicrope et al.[29] reported that in colorectal cancer patients who received 5-FU-based chemotherapy, low expression of *BIM* is associated with poor prognosis. In this study, we found that *miR-10b* regulates *BIM* in colorectal cancer cells. This could partly explain the chemoresistance to 5-FU in *miR-10b*-overexpressing cells. Recent reports suggest that miRNAs seem to be critical regulators of drug resistance.[9–12] Regarding the association between miR-10b expression and chemoresistance in colorectal cancer patients, Kaplan–Meier analysis of patients who received 5-FU-based chemotherapy revealed that the miR-10b high expression group had a significantly poorer prognosis than the low expression group (Supplementary Fig. S2). The data show that miR-10b could be a prognostic indicator in colorectal cancer patients who received 5-FU-based chemotherapy. However, further studies are required to confirm accurately the chemoresistant effect of *miR-10b* in clinical samples.

Other oncogenic miRNAs, such as those in the *miR-17-92a* and *miR-106b-25 clusters*, *miR-32*, and *miR-181a*, also are known to be direct regulators of *BIM*, and of these, the *miR-17-92a* cluster has been shown to be upregulated in colorectal cancer.[2–7] Therefore, the *miR-10b-BIM* pathway is not the only miRNA pathway regulating *BIM* in colorectal cancer, and some of these miRNAs are believed to be coordinately involved in suppression of *BIM*.

In conclusion, we have demonstrated that high expression levels of *miR-10b* are associated with enhanced malignant potential and poor prognosis. Furthermore, in vitro studies have revealed that *miR-10b* expression is associated with chemoresistance to 5-FU. *MiR-10b* is a meaningful prognostic marker and a potential indicator of chemoresistance in human colorectal cancer.

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LETTER TO THE EDITOR

Transumbilical laparoscopic-assisted appendectomy for children and adults

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Dear Editor:

In 1983, Semm reported the first laparoscopic appendectomy. Since then, several randomized controlled trials and meta-analyses have demonstrated that laparoscopic appendectomy is associated with fewer wound infections, less pain, faster recovery, earlier return to work, and cosmesis compared with open appendectomy. However, the longer operation time and increased hospital costs relative to open appendectomy continue to fuel the debate over these techniques.

The use of single-port laparoscopic surgery is steadily increasing and several authors have reported the feasibility of single-port laparoscopic appendectomy. However, this technique is technically demanding and requires special devices that increase costs.

Transumbilical laparoscopic-assisted appendectomy (TULAA) was first reported by Pelosi and colleagues in 1992 as "Laparoscopic appendectomy using a single umbilical puncture (minilaparoscopy)". The authors claimed that, in some cases of appendicitis, the appendix could be pulled out through a small umbilical incision and be resected, and the special laparoscope enabled easy exteriorization of the appendix. However, TULAA is still not routinely performed. One reason is the need for a special laparoscope, in which 5-mm laparoscopic forceps can be inserted through its mounted operative channel. Another reason is the notion that it is difficult to extract the appendix from the umbilicus in adult patients, which has led many surgeons to limit TULAA to children.

We modified the TULAA technique by using a usual laparoscope. Additionally, we extended the indication of TULAA to adults and analyzed the relationship between feasibility and body habits.

With the patient under general anesthesia, we made a 15–20-mm longitudinal incision in the umbilicus and attached a wound protector. The right lower quadrant abdominal wall was then lifted with a thin surgical retractor to provide a working space in the peritoneal cavity. Pneumoperitoneum was not used, eliminating the need for any ports. We inserted a 5-mm laparoscope and 5-mm laparoscopic forceps through the incision. When the appendix was identified under laparoscopy, it or the mesoappendix was grasped and exteriorized through the incision. The mesoappendix and appendix were then dissected and ligated as in open appendectomy. Finally, we washed the peritoneal cavity with saline and closed the wound cosmetically. We converted to a laparoscopic approach if a complicated inflammatory mass was found or when the appendix and mesoappendix could not be exteriorized because of immobility of the appendix. When a massive abscess and/or severe adhesion were found, the operation was converted to an open appendectomy. All of the surgeons were 3–5-year postgraduates while the first assistants were surgeons with at least 7 years of experience.

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Ninety-five children and 63 adults diagnosed with acute appendicitis between 2005 and 2008 underwent this procedure. The indications included being a child or an adult with a desire for minimal scarring. All patients were diagnosed with acute appendicitis based on clinical history, laboratory tests, and computed tomography (CT) scans. Exclusion criteria included an abscess >50 mm in diameter on CT scans, severe complications (e.g., sepsis, paralytic ileus, or contraindications to general anesthesia), or a lower abdominal operative scar. The study was conducted in accordance with the principles of the Helsinki Declaration. All patients or their guardians gave written informed consent.

The severity of appendicitis at the time of laparoscopic identification was classified as either simple (no perforation or abscess) or ruptured (with perforation and/or abscess). Patients with an incision >20 mm were defined as conversion to open appendectomy. Those that required laparoscopic dissection of the appendix in the peritoneal cavity were defined as conversion to laparoscopic appendectomy. The conversion rate, operation time, intra- and postoperative mobility, and length of stay (LOS) were evaluated for children and adults.

A total of 158 patients underwent the procedure (66 males and 92 females), including 95 children and 63 adults. The overall conversion rate was 20.9%; 26 patients were converted to laparoscopic appendectomy and seven to an open appendectomy. Reasons for conversion included appendix volvulus (n=1, 3.0%), an inflammatory mass (n=20, 60.4%), and appendix immobility (n=12, 36.6%).

The severity of the appendicitis influenced the operative results. Among 136 simple cases, the conversion rate was 10.9% vs. 86.7% among 22 ruptured cases (p<0.001). The mean ± SD operation time was 53.7±35.3 min and was significantly shorter in simple cases than in ruptured cases (46.2 vs. 86.7 min, p<0.001).

No intraoperative morbidity occurred. A wound infection developed at the right lower quadrant incision in one converted case. An abdominal abscess occurred in four cases and a prolonged ileus occurred in three cases. Two patients required reoperation for abdominal abscess. All morbidities occurred in ruptured cases and none of the patients died. The mean LOS was 3.3 days and was significantly shorter for simple cases than for ruptured cases (2.5±1.3 vs. 8.0±4.1, p<0.001).

Among the 158 cases in our series, 63 (40%) were adults. The rates of conversion and operation times in children and adults were 17.9% vs. 25.3% and 50.4 vs. 58.8 min, respectively. Although the rate of conversion and operative time tended to be higher in adults, the differences between the two groups did not reach statistical significance.

Children had a mean height of 142.8±18 cm, body weight of 37.6±13.3 kg, and BMI of 18.5±9.3 kg/m^2, while those for adults were 158.1±6.9 cm, 51.2±10.5 kg, and 20.5±3.2 kg/m^2, respectively. We observed no relationship between height and conversion rate. However, the conversion rate was significantly associated with both body weight and BMI. The mean body weight (47.2 vs. 42.0 kg, respectively, p=0.039) and BMI (20.2 vs. 18.4 kg/m^2, respectively, p=0.003) were significantly greater in converted cases than in non-conversion cases. We also observed a significant association between the conversion rate and the distance from the umbilicus to the appendix. In 128 available CT scans, this distance was significantly longer in conversion cases than in non-conversion cases (97.1±21.0 vs. 80.4±21.67 mm, p=0.001).

Since Pelosi's report, several surgeons have demonstrated the feasibility of this technique. D'Alessio reported the benefits of TULAA include cosmesis, and Stanfill and Visnjic separately reported shorter operation times and reduced costs compared with laparoscopic appendectomy.

Although laparoscopic appendectomy has become a standard technique, its cosmetic outcomes are only slightly better than those of conventional open appendectomy. The combined length of the three incisions for the laparoscopic procedure is equivalent to the length of the single incision made for open appendectomy. Single-port laparoscopic appendectomy improves cosmesis leaving no scar outside the umbilicus. Similarly, TULAA leaves no scar outside the umbilicus.

TULAA might also require a shorter operative time than the standard approach. In a comparison of TULAA and standard laparoscopic operation times reported by Visnjic, TULAA was significantly quicker to perform (33 vs. 39 min, p<0.05). The main reason for this was quicker extracorporeal dissection. Because TULAA does not require expensive disposable laparoscopic devices, Visnjic also reported that the cost of TULAA is 7.8-fold less than that of laparoscopic appendectomy.

To date, TULAA was mainly indicated for appendicitis in children. The studies by Pelosi and Rispoli are the only two that have been carried out in adults; however, those reports did not analyze the effects of height, body weight, or BMI on conversion and outcomes. To our knowledge, ours is the first study to analyze possible associations between such parameters and the feasibility of performing TULAA without conversion to open or laparoscopic appendectomy. In fact, we found that body weight, BMI, and the distance from the umbilicus to the appendix influenced feasibility.

Some limitations of our study exist. These include a relatively small sample size, selection bias, and no follow-up

after hospital discharge. Larger prospective studies are needed to explore options for standardized TULAA equipment, techniques, and long-term outcomes.

Our modification enables surgeons to perform TULAA in community hospitals. Furthermore, we showed that TULAA was feasible and safe in children and normal-sized adults. Accordingly, this method may provide an attractive alternative to the conventional operative methods for patients suffering from appendicitis.

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Original article

Performance comparison of peripherally inserted central venous catheters in gastrointestinal surgery: A randomized controlled trial

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SUMMARY

Background & aims: Peripherally inserted central venous catheters (PICC) are long-term vascular access devices inserted through a peripheral vein of the arm and serve as an alternative to traditional central venous catheters. Currently different types of PICCs are available. No data, however, are available in regard to materials and tip designs. We designed a prospective, randomized trial comparing two major PICCs with different material and tip design: a silicone catheter with distal side slits (Groshong Catheter) and a polyurethane catheter with open-end tip (PI Catheter).

Methods: Twenty-six patients who underwent PICCs placement between August 2010 and December 2010 were enrolled in the study. The primary endpoint was the completion rate of PICC indication. Secondary endpoints were complications rate.

Result: The completion rate of PICC indication was not different significantly (81.8% and 92.9%, $p = 0.5648$) and the total complication rate were also not different significantly (9.1% and 14.3%, $P = 1.0000$) between two catheters. In detail, PI Catheter were associated with a significantly higher incidence of catheter occlusion, and Groshong Catheter were associated with a significantly hemorrhages after removal.

Conclusion: There was no difference in the durability and the complication between Groshong Catheter and PI Catheter. (UMIN Clinical Trial Registry UMIN000005451).

1. Introduction

The complications e.g. pneumothorax and hemorrhage, have been serious consequences following central venous catheter (CVC) placement with subclavian vein puctures.[1–4] Peripherally inserted central venous catheters (PICCs) are long-term vascular access devices inserted through a peripheral vein of the arm, and has gained wider clinical acceptance as less-invasive alternative to traditional CVCs. The known advantages of PICCs are its introduction at the bedside, minimal pain at insertion, low rate of complications from its placement to removal,[5] and lower infection rates compared to traditional CVCs.[6–11] However, there remain a number of complications both at insertion and maintenance phases, [12]including catheter malposition,[13] thrombosis,[13–15] phlebitis,[13,16] inadequate dripping, and line fracture.[17,18]

Currently, various types of PICC with different biomaterials and different specifications are commercially available. Despite widespread use in daily practice, however, there has been a lack in reliable data regarding the impacts of materials/specifications of PICC catheters on their performances: handleability, safety, and durability. We designed a prospective, randomized trial comparing two major PICCs with different material and tip design: a silicone catheter with distal side slits (Groshong, Bard Access Systems, Salt Lake City, UT, USA) and a polyurethane catheter with open-end tip (PI Catheter, Covidien, North Heaven, CT, USA), to compare their performances.

2. Materials and methods

This study was approved by the Institutional Review Board of Osaka University Hospital. After the protocol was approved, a written informed consent was obtained from all patients prior to the entry into the study. All data obtained in this study were kept confidential. The study was registered at UMIN (http://www.umin.ac.jp; clinical trial no. UMIN000005451).

Abbreviations: PICC, Peripherally inserted central venous catheter; CR-BSI, catheter related blood stream infection; CVC, central venous catheter.

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2.1. Patients

Twenty-six consecutive patients, who underwent PICC placement for chemotherapy and/or perioperative intravenous nutritional support between August 2010 and November 2010, were enrolled in the study. The inclusion/exclusion criteria were shown in Table 1. A coordinating center in our institution was responsible for creating the treatment allocation code using a computer-generated randomization table. Treatment allocation was arranged prior to catheter placement. The patients were randomly assigned to either Groshong group or PI Catheter group, and following data were registered in the database: Age, Gender, Disease and Indication of PICC.

The primary endpoint was the completion rate of PICC indication. Secondary endpoints were complications rate, e.g. blood stream infection, hemorrhage at the insertion site, phlebitis, vein thrombosis, and catheter malfunction such as partial/complete occlusion and fracture. The patients continued to be followed up until their discharge from the hospital.

2.2. Data collection

Patients were reviewed daily during their hospitalization. Data were recorded prospectively in a case report file (CRF). The following items in the CRF were recorded by an attending doctor: PICC insertion time, arm used, site of insertion, hemorrhage, tip location at confirmation fluoroscopy, and difficulty in catheter insertion/advancement. Additional information e.g. vital signs, duration of PICC placement, symptom of brachium, dripping condition during infusion, skin finding at a dressing site, any patient's complaint about catheter placement, were obtained by an attending nurse. Any hemorrhage at the insertion site, i.e. bleeding within 24 h after insertion or after removal of PICC catheter, was also registered with a three-grade scale: "fair", "little", and "none". The grade "fair" means the hemorrhage requiring pressure hemostasis for control, "little" as limited bleeding noted as coagulation formation in a dressing, and "none" as no observable bleeding. The catheter was removed prematurely when any catheter related blood stream infection (CR-BSI) was suspected according to Centers for Disease Control and Prevention guidelines.[11] A catheter removal was also considered in case of complete occlusion or partial occlusion with drip disturbance. The tip of the removed catheter was carefully inspected and served for subsequent culture. Phlebitis-related complications were defined and scored as described by Maki et al.[19]

Table 1
Criteria of this study.

Inclusion criteria
1. PICC[a] is needed clinically in chemotherapy or the intravenous-nutrition purpose newly
2. Age between 20 and 80 years.
Exclusion criteria
1. Taking warfarin or an antiplatelet medicine within two weeks of an insertion day
2. Past history of pulmonary embolism, deep vein thrombosis, and an endocarditis.
3. Patients judged to be inappropriate as a subject

[a] PICC: Peripherally inserted central venous catheter.

2.3. PICC catheters

Although both Groshong and PI Catheter have similar outer diameter (4 French size) and length (60 cm), a different material is used: silicone for Groshong and polyurethane for PI Catheter (Fig. 1). Both materials are less-thrombogenic therefore biocompatible, and have been validated as suitable for intravenous use. One characteristic of the polyurethane catheter is a larger internal diameter compared to the silicone catheter with same French size, which may lead to more stable and faster drip during infusion. On the other hand, the polyurethane catheter is harder than the silicon catheter. Although it softens with body temperature after insertion, this characteristic of PI Catheter might increase risk of phlebitis and thrombosis.

One more critical difference between these two products is a tip configuration. Groshong has their patented three way "Groshong valves" distal to the closed semi-round tip. These valves remain closed when subjected to normal central venous pressure. When positive pressure is applied inside the catheter, the valves open to allow infusion. With negative pressure, the valves open in another way, allowing "aspiration" into the catheter. Whereas, PI Catheter has a simple, open end at its tip, no valves are equipped in the system. Table 2 depicts the differences of these two catheters including cost.

2.4. Procedure

All PICCs were inserted by doctors under radiologic guidance without ultrasound. The patient was positioned in supine with his/her arm extended and abducted at 90° or as tolerated. The arm was cleaned and draped with a tourniquet applied over the upper arm. A suitable vein in the mid arm was identified and entered using a 22-gauge venous cannula. A 0.018-inch guide wire was then passed through the cannula into the vein. After subcutaneous administration of 1% lidocaine for local anesthesia, the cannula was exchanged for a 4.5 French peelaway sheath, whichever catheter was selected. The catheter was then advanced through the peel-away sheath until the tip was located at the superior vena cava, under radiologic guidance. The sheath was peeled away, and the catheter was sutured through the suture wing onto the skin, close to the entry site. The puncture site was cleaned and covered with a clear sterile dressing. In a patient whose existing PICC failed, a new catheter was inserted through a different vein of the same arm or through a vein in the opposite arm.

2.5. Statistical analysis

The differences between the two catheter groups for patient demographics, indication, underlying morbidity, procedural data, and outcome were investigated with Fisher's exact test for categorical variables and student t test for continuous variables. These analyses were carried out using JMP version 8.0.1 (SAS Institute, Cary, NC, USA) for Windows. A P value of less than 0.05 denoted the presence of statistical significance.

3. Results

The study was initially designed with 1:1 randomization and was scheduled to enroll 20 patients in each arm respectively. As Groshong arm became unable to be continued because of a recall due to insufficient product registration document, we were obliged to terminate this study at the time that 26 patients were enrolled in total.

Twenty-five PICC placements were successful in 26 enrolled patients (success rate = 96%). One failed patient had bilateral