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Efficacy of a Multiplex Paclitaxel Emission Stent Using a Pluronic® Mixture Membrane versus a Covered Metal Stent in Malignant Biliary Obstruction: A Prospective Randomized Comparative Study

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Background/Aims: A drug-eluting stent for unresectable malignant biliary obstruction was developed to increase stent patency by preventing tumor ingrowth. The safety and efficacy of a new generation of metallic stents covered with a paclitaxel-incorporated membrane using a Pluronic® mixture (MSCPM-II) were compared prospectively with those of covered metal stents (CMSs) in patients with malignant biliary obstructions. **Methods:** This study was initially designed as a prospective randomized trial but was closed early because of a high incidence of early occlusion. Therefore, the data were analyzed using the intent-to-treat method. A total of 72 patients with unresectable distal malignant biliary obstructions were prospectively enrolled. **Results:** The two groups did not differ significantly in basic characteristics and mean follow-up period (MSCPM-II 194 days vs CMS 277 days, p=0.063). Stent occlusion occurred in 14 patients (35%) who received MSCPM-II and in seven patients (21.9%) who received CMSs. Stent patency and survival time did not significantly differ between the two groups (p=0.355 and p=0.570). The complications were mild and resolved by conservative management in both groups. **Conclusions:** There were no significant differences in stent patency or patient survival in MSCPM-II and CMS patients with malignant biliary obstructions. **(Gut Liver 2017;11:567-573)**

Key Words: Drug-eluting stents; Biliary tract neoplasms; Pancreatic neoplasms; Self expandable metallic stents

INTRODUCTION

Biliary drainage through self-expandable metallic stent (SEMS) insertion is an important method of nonoperative management for unresectable malignant biliary obstructions.[1-3] The SEMS has been proven to have superior patency and efficacy in comparison with plastic stents.[4-6] Although the covered SEMS was developed to prevent the tumor ingrowth often seen with uncovered SEMS, it is still controversial whether there are differences in stent patency between uncovered and covered SEMS.[7] In addition, both types of SEMS can become occluded over time due to tumor ingrowth or overgrowth, mucosal hyperplasia into the stent, chronic inflammatory reactions to the stent mesh, and biliary sludge or food impaction.[8-10]

Since patency of SEMS is a significant factor in the prognosis of patients with malignant biliary obstruction,[6] studies have investigated the use of stents that elute antitumoral agents to improve their patency through preventing occlusion by tumor growth.[11-18] Previously, we demonstrated that endoscopic insertion of a metallic stent covered with a paclitaxel-incorporated membrane (MSCPM-I) was safe and effective both in animals[11] and in a preliminary human study.[12] However, a comparative prospective clinical study found no statistical differences in the duration of stent patency or survival time between MSCPM-I and non-drug-eluting covered metal stents (CMS).[17] These results seem to be caused by biodegradation of the membrane and short-term release of paclitaxel from MSCPM-I.

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To overcome these problems, we developed and modified a new-generation stent, a metallic stent covered with a paclitaxel-incorporated membrane using a Pluronic® mixture (MSCPM-II). Safety with enhanced local drug delivery of MSCPM-II was demonstrated in a previous animal study.[18] The patency durations of MSCPM-II and conventional CMS in unresectable malignant biliary obstruction in humans were evaluated in this clinical study. The secondary goal was to compare the safety and patient survival time of this new-generation stent with those of CMS.

MATERIALS AND METHODS

1. Patients

In this double-blind prospective randomized study, a total of 150 patients (75 patients in each group) were found to be required, according to the following calculation using the parameters for a noninferiority trial: 2.5% type I error, 80% statistical power, permeable effective range 20% and drop-out rate 10%. However, this study was closed early due to the high drop-out rate. A total of 72 patients with unresectable distal malignant biliary obstruction were enrolled from three university hospitals from November 2011 to December 2013. Malignant biliary obstruction was diagnosed by clinical and radiologic findings and confirmed by pathologic results.

The inclusion criteria were as follows: (1) adults between 19 years and 90 years of age who voluntarily agreed to take part in this clinical trial and completed a signed consent form; (2) patients with unresectable pancreatic cancer or bile duct cancer; (3) patients who had not been previously treated with metallic stent insertion; (4) patients whose expected survival time was more than 3 months (Karnofsky scores ≥60); and (5) patients who were not pregnant. Subjects who corresponded to any of the following criteria were excluded from the trial: (1) patients who had previous surgical biliary drainage; (2) patients with severe bleeding diathesis; (3) patients with malignant hilar and/or intrahepatic duct stricture; and (4) patients whose endoscopic intervention was judged to be impossible by the researcher.

Chemotherapy was performed at each institution according to the patient's disease, general condition, and tumor progression. The chemotherapy regimens used were gemcitabine-based chemotherapy (gemcitabine alone, gemcitabine plus erlotinib, gemcitabine plus capecitabine) and 5-fluorouracil (5-FU) plus oxaliplatin. Gemcitabine was administered intravenously at 1,000 mg/m^2 in 30-minute infusions three times weekly, every 4 weeks. Erlotinib was administered orally at 100 or 150 mg/day and capecitabine was administered orally at 1,660 mg/m^2/day (830 mg/m^2 twice daily) for 3 weeks, followed by 1 week without chemotherapy.

The protocol was approved by the institutional review boards of the participating institutions (Gangnam Severance Hospital, Inha University College of Medicine, and Asan Medical Center) and all participants gave written informed consent (ClinicalTrials.gov, NCT number: 01413386).

2. Stents

The MSCPM-II membrane (Niti-S stent, ComVi type with paclitaxel-eluting membrane; TaeWoong Medical, Kimpo, Korea) was composed of a double layer, in which the inner layer was made of polytetrafluoroethylene (PTFE) and the outer layer of paclitaxel-incorporated Pluronic® F-127–polyurethane (PTX–Plu–PU). The coating solution was made from 400 mg PTX–Plu–PU polymer and 10 mL tetrahydrofuran (THF). The PTX–Plu–PU polymer was formed using polyurethane, 10% (wt/vol) paclitaxel (Taxol; SamYang, Daejeon, Korea), 10% Pluronic® F-127, and THF solution, which is used as a solvent for polyurethane. The safety of the MSCPM-II membrane was demonstrated in previous animal study.[18] The membrane of the CMS (Niti-S stent, ComVi type; TaeWoong Medical) was covered with PTFE without paclitaxel. The MSCPM-II and CMS used in this study were 10 mm in diameter and 5 to 8 cm in length when fully expanded.

Antibiotics for both gram-positive and gram-negative bacteria were prophylactically administered to patients to prevent infection and sepsis before the procedure. Biliary sphincterotomy was performed in all patients after biliary cannulation to facilitate stent insertion. Stents were inserted using endoscopic retrograde cholangiopancreatography (ERCP), in which stents were deployed along a guide wire under endoscopic and fluoroscopic guidance. Stents were inserted with an extra 1 to 1.5 cm of coverage in the proximal and distal directions from both ends of the stricture.

3. Follow-up

Follow-up was performed for all enrolled patients in outpatient departments, following an established protocol. Clinical symptoms and laboratory tests including liver function tests (total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase) were performed before, immediately after, and on the third and the seventh days post stent insertion, and every month thereafter. Computed tomography (CT) was performed before and 6 months after stent insertion. When stent occlusion was clinically suspected during follow-up, CT and abdominal ultrasonography (US) were performed.

4. Definition

Technical success was defined as successful deployment of a SEMS in the intended location with sufficient coverage of the stricture.[19] Functional success was defined as a 50% decrease in or normalization of the bilirubin level within 14 days of stent placement. Recurrent biliary obstruction was defined as a composite endpoint of either occlusion or migration, and time to recurrent biliary obstruction refers to the time from SEMS

placement to the recurrence of biliary obstruction. Stent occlusion was confirmed based on ERCP findings, and endobiliary biopsy and brush cytology were performed to differentiate the causes of occlusion.

Tumor ingrowth was defined as direct growth of tumors through the stent mesh, whereas tumor overgrowth was defined as growth of tumors at the proximal and/or distal ends of the stent. Stent migration referred to proximal or distal displacement of the stent from the initial insertion site. Patients were regularly checked for procedure-related complications such as cholangitis, pancreatitis, cholecystitis, bleeding, and perforation; and the severity of complications was evaluated according to the consensus recommendations.[19] The duration of stent patency and patient survival time were evaluated until obstruction of stent or until death of the patient.

5. Statistical analysis

Quantitative data were compared using the Student t-test, and results were expressed as means±standard deviations. The chi-square test and Fisher exact test were used to calculate differences in categorical parameters. Stent patency and patient survival time in the two groups were compared using the cumulative curve of the Kaplan-Meier lifetime table and Cox proportional hazard ratio with a 95% confidence interval. All data were analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). The p-values less than 0.05 were considered statistically significant.

RESULTS

The insertions of MSCPM-II and CMS were performed endoscopically in 40 and 32 patients, respectively. Basic patient characteristics including mean age, male to female ratio, mean follow-up period, underlying disease status, and chemotherapy administration were not statistically different between the two groups (Table 1). Chemotherapy regimens used in this study were gemcitabine-based for pancreatic cancer and 5-FU-based for common bile duct cancer.

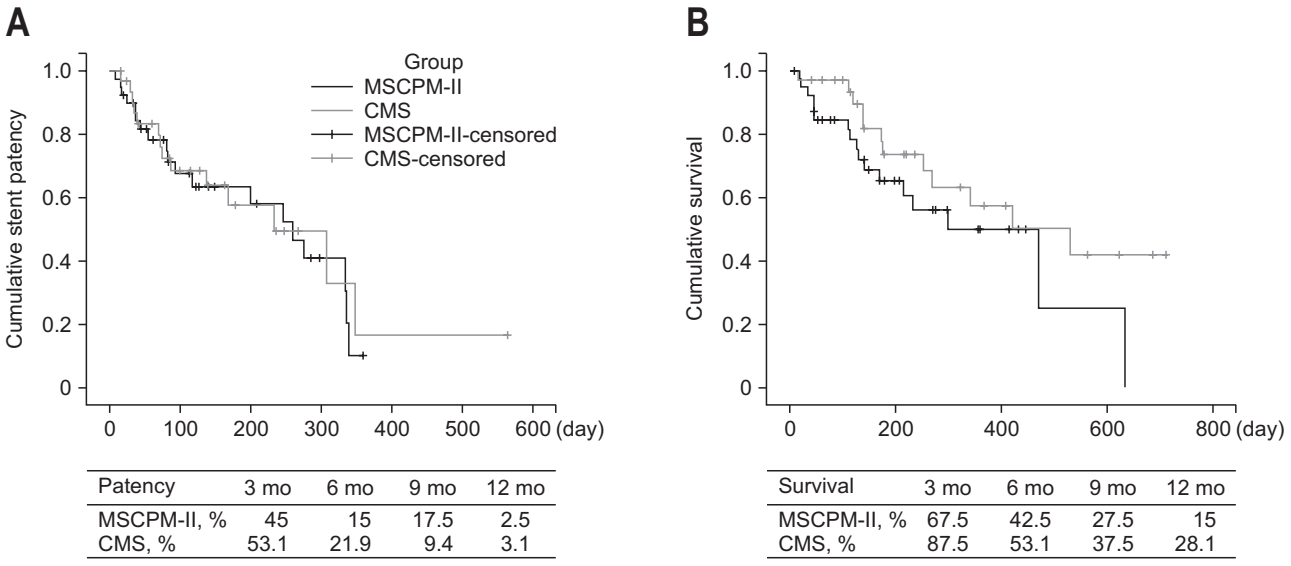
Mean stent patency (MSCPM-II vs CMS; 130 days vs 139 days; p=0.783) and mean survival time (MSCPM-II vs CMS; 194 days vs 277 days; p=0.202) were not significantly different between the two groups (Fig. 1). Stent occlusion occurred in 14 (35%) of the 40 MSCPM-II patients and seven (21.9%) of the 32 CMS patients, and the rate of stent occlusion was not statistically different between the two groups (p=0.271) (Table 2). The main cause of stent occlusion was sludge impaction (MSCPM-II, 11/14; CMS, 6/7). The other causes of stent occlusion were tumor ingrowth (MSCPM-II, n=1; CMS, n=1) and tumor overgrowth (MSCPM-II, n=2; CMS, n=0).

There was no procedure-related mortality, and the incidence of complications and stent migration did not differ significantly between the two groups. Cholangitis occurred in 12 patients in the MSCPM-II group and in eight patients in the CMS group on the day after stent insertion. Abdominal pain, fever, and worsening jaundice were observed in these patients, but follow-up ERCP found no stent occlusion. Cholangitis was resolved within 2 to 3 days with conservative management with antibiotics.

Table 1. Basic Patient Characteristics

Characteristic	MSCPM-II group (n=40)	CMS group (n=32)	p-value
Age, yr	69.9±12.4	67.8±14.9	0.647
Male:female	23:17	15:17	0.617
Follow-up period, day	194.2±152.1	277.0±198.4	0.063
Serum bilirubin level, mg/dL			
Baseline	5.9±6.5	7.1±6.7	0.703
1 Day after stent insertion	4.3±5.5	4.8±4.5	0.856
4 Weeks after stent insertion	1.8±3.8	1.2±0.9	0.098
Diagnosis			0.751
Pancreatic cancer	25 (62.5)	17 (53.1)	
CBD cancer	10 (25.0)	8 (25.0)	
Ampulla of Vater cancer	3 (7.5)	3 (9.4)	
GB cancer	2 (5.0)	4 (12.5)	
Chemotherapy			0.881
Gemcitabine-based	16 (40.0)	14 (43.7)	
Fluorouracil-based	3 (7.5)	1 (3.1)	

Data are presented as mean±SD or number (%).
MSCPM-II, metallic stent covered with a paclitaxel-incorporated membrane; CMS, covered metal stent; CBD, common bile duct; GB, gallbladder.



Patency	3 mo	6 mo	9 mo	12 mo
MSCPM-II, %	45	15	17.5	2.5
CMS, %	53.1	21.9	9.4	3.1

Survival	3 mo	6 mo	9 mo	12 mo
MSCPM-II, %	67.5	42.5	27.5	15
CMS, %	87.5	53.1	37.5	28.1

Fig. 1. (A) Kaplan-Meier graph showing the cumulative stent patency of a metallic stent covered with a paclitaxel-incorporated membrane using a Pluronic® mixture (MSCPM-II) and a covered metal stent (CMS). (B) Kaplan-Meier graph showing the cumulative patient survival of MSCPM-II and CMS.

Table 2. Outcomes of MSCPM-II and CMS

	MSCPM-II group (n=40)	CMS group (n=32)	p-value
Stent patency period, day	130.1±112.3	139.1±117.7	0.742
Survival period, day	194.2±152.1	277.0±198.4	0.079
Causes of stent occlusion	14 (35)	7 (21.9)	0.271
Tumor ingrowth	1 (2.5)	1 (3.1)	0.875
Tumor overgrowth	2 (5.1)	0	0.205
Sludge impaction	11 (28.3)	6 (18.8)	0.385
Complication	19 (47.5)	14 (43.7)	0.892
Cholangitis	12 (30.0)	8 (25.0)	0.642
Cholecystitis	2 (5.0)	1 (3.1)	0.690
Pancreatitis	2 (5.0)	2 (6.3)	0.823
Stent migration	3 (7.5)	3 (9.3)	0.781

Data are presented as mean±SD or number (%).
MSCPM-II, metallic stent covered with a paclitaxel incorporated membrane; CMS, covered metal stent.

Two patients in the MSCPM-II group and two patients in the CMS group experienced mild pancreatitis, which improved with conservative management. Distal stent migration occurred in three patients in both the MSCPM-II and the CMS groups. The migrated stents were removed and replaced successfully with another conventional CMS. Multivariate analysis revealed that cancer type or chemotherapy regime did not influence stent patency or survival time between the MSCPM-II and CMS groups.

DISCUSSION

Our previous single-arm pilot study demonstrated the safety and efficacy of MSCPM-I in 21 patients with malignant biliary obstruction.[12] However, a two-arm prospective comparative study found no significant differences in stent patency or patient survival time between MSCPM-I and conventional CMS.[17] These results were speculated to be affected by patient characteristics and stent membranes. The survival time of the patients enrolled in the study was short, and patient mortality before stent occlusion with MSCPM-I was approximately 50%. Therefore, since it was difficult to accurately measure stent patency over a long period, it is possible that stent patency was underestimated.[17] In addition, the membrane used for MSCPM-I was a single layer of polyurethane that could be biodegraded by hydrolysis, oxidation, and continuous contact with bile flow *in vivo*,[13,20,21] which could lead to microcrack or hole formation

and induce stent occlusion by tumor ingrowth.[13,22] Since stent occlusion might have occurred before the release of paclitaxel in MSCPM-I, the full evaluation of the inhibitory effects of MSCPM-I on tumor ingrowth was limited. To overcome the limitations of single-layer polyurethane, the double-layer drug-eluting stent MSCPM-II was developed. The inner layer of MSCPM-II was composed of PTFE, which is resistant to degradation by bile, and the outer layer was comprised of paclitaxel-containing polyurethane.[18] In addition, Pluronic® F-127 was added to MSCPM-II to achieve a constant release of paclitaxel.[18,23] While the stent patency of MSCPM-II was expected to be longer due to these modifications, there was no statistical difference in stent patency between the MSCPM-II group (130.1±112.3 days) and the CMS group (139.1±117.7 days) (p=0.742).

Although this prospective study was performed using double-blinded randomization, it was terminated early without enrolling the target number of patients. The reason for this early termination was due to a high dropout rate in the first six months caused by early stent occlusion by food scraps. The ComVi stent (Niti-S stent, ComVi type; Taewoong Medical) was the base stent of both the MSCPM-II and CMS. Since the membrane of this stent was sandwiched between two wire layers, wires were exposed to both the inner and outer layer surfaces of the stent.[24] These naked wires were exposed to the inner lumen where food scraps could get caught and refluxed to the stent lumen and cause occlusions.[24] In addition, the surface of the inner lumen was not smooth, which we also speculate played a major role in food impaction (Fig. 2). Moreover, protrusion of the uncovered portion into the duodenum may also cause occlusion.[24,25] Food is caught more frequently by the wire mesh of the ComVi stent than by other metallic stents.

In other studies using non-drug-eluting ComVi stents, stent occlusion by sludge and food debris impaction occurred in 16% of cases,[26] for which food scraps accounted for 15.9%.[24] These rates are comparatively higher than those of other conventional CMS, at less than 4%.[25] Stent occlusion by sludge and food debris impaction was as high as 28.3% in the MSCPM-II group and 18.8% in the CMS group in the present study, which is speculated to be caused by the ComVi stent characteristics.

The time points of stent occlusion by sludge were 50.3±35.5 days in the MSCPM-II group, and 64.1±47.2 days in the CMS group. Since the number of patients with early stent occlusion by sludge were high in both groups, this limited the evaluation of the efficacy of tumor ingrowth prevention of MSCPM-II. However, a subgroup analysis excluding patients who underwent early stent occlusion by sludge found no statistical differences in stent patency between the MSCPM-II group (160.5±116.8 days) and the CMS group (203.6±158.6 days). The

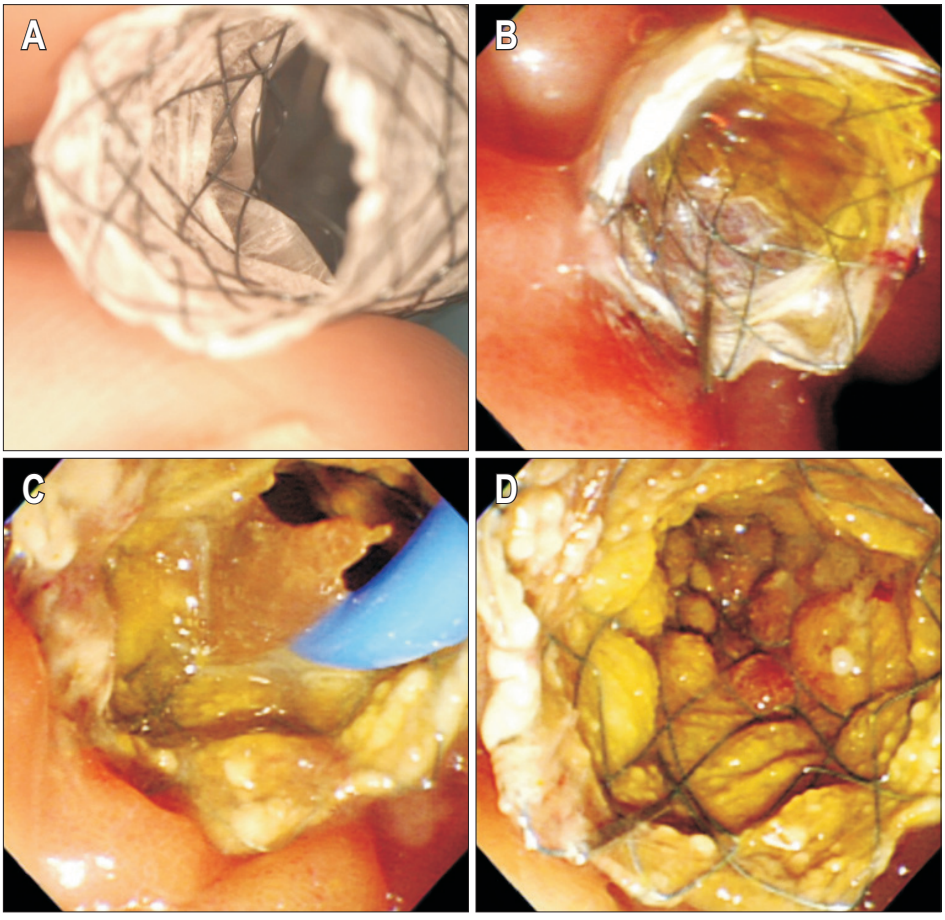


Fig. 2. Structure and inner surface of a metallic stent covered with a paclitaxel-incorporated membrane using a Pluronic® mixture (MSCPM-II). (A) The MSCPM-II stent had the same structure as the ComVi stent. It had three layers (outer wire-membrane-inner wire) and the inner surface was rough (due to the wire mesh). (B) After deployment, the uncovered portion of the stent protruded from the papilla to the duodenum. (C) A stent occluded due to food and sludge 1 month after stent insertion. (D) Although tumor ingrowth was not present, the inner surface of the stent was rough, resulting in a high risk of re-occlusion due to food and sludge.

patency of the ComVi stents (208.1±173.3 days) in other studies showed a similar result to the present study.[24] Thus, the present study failed to prove efficacy of stent patency of MSCPM-II compared with conventional CMS. On the other hand, it is noteworthy that stent occlusion by tumor ingrowth was as low as 2.5% (1/40) and 3.1% (1/32) in the MSCPM-II and CMS groups, respectively. In a previous MSCPM-I study, stent occlusion by tumor ingrowth occurred in 22.4% (13/58) of the MSCMP-I group. Reduction of stent occlusion by tumor ingrowth in the MSCPM-II group compared with the MSCPM-I group might be due to suppression of membrane biodegradation by PTFE, which is more resistant to bile flow than is polyurethane.

There was no significant difference in patient survival between the MSCPM-II and CMS groups regardless of the systemic chemotherapy regimen. In the previous MSCPM-I study, patient survival increased in pancreatic cancer patients treated with gemcitabine.[17] In direct contrast, systemic gemcitabine had no effects on stent patency or patient survival in the present study. Nakai *et al*.[27] reported that gemcitabine-based systemic chemotherapy had no effects on stent-related complications or stent patency. It is speculated that the discrepancies between previous results on MSCPM-I and the present results on MSCPM-II resulted from differences in enrolled patients. Although patients in the MSCPM-II group experienced cholangitis, cholecystitis, and mild pancreatitis, which were resolved by conservative management, there were no significant differences in incidence compared with the CMS group. Although this study failed to prove the efficacy of MSCPM-II through stent modification, its safety was proven in terms of inflammatory cell infiltration and fibrosis in an animal study,[18] and no severe complications occurred in this human trial. Therefore, we consider the safety of MSCPM-II in unresectable biliary malignancy to be clinically proven.

Although the two groups demonstrated no differences in stent patency, both the MSCPM-II and CMS groups had very low rates of tumor ingrowth in the present study. This could result from the effect of the bile acid-resistant PTFE membrane or the local antitumoral effects of the drug. However, since the administration of systemic chemotherapy, causative disease of malignant biliary obstruction, and time of the follow-up CT were heterogeneous in the present study, it was difficult to evaluate the changes of the cancer size. Because not all patients received systemic chemotherapy, it was hard to exclude its effects. In addition, since bile duct cancer, unlike pancreatic cancer which forms an original mass, has no measurable mass for comparative evaluation, there was a limitation in evaluating the changes of the mass size. Additionally, disease progression by metastasis caused more deaths than did disease progression by the primary lesion. Moreover, follow-up CT was performed 6 months after the diagnosis, which was too late to measure the effect of MSCPM-II on primary sites due to disease progression, hampering accurate evaluation. In the future, a well-designed study on local drug therapy by drug-eluting stents is necessary.

In addition to the passive effects of suppressing tumor ingrowth, it would be expected that local therapy of the cancer adjacent to the stent would increase the patency of drug-eluting stents. However, local therapy is possible only when the antitumor agent effectively penetrates the tumor mass. For a therapeutic agent to function on the target site in a biologically active state for a sufficient time, it is necessary to enhance the effects of the therapeutic agent within the tumor.[28] Therefore, a new stent has been developed with the addition of sodium caprate to aid in antitumoral agent penetration of the tumor.[29] In addition, to prevent stent occlusion by food sludge, the new stent has been modified to increase inner lumen smoothness, in that the membrane is not sandwiched between two wire layers, but instead, the stent wire is sandwiched between two membranes. A clinical trial is currently under way to assess this newly modified stent (ClinicalTrials.gov, NCT number: 02460432).

Limitations of the present study include early termination due to occlusion of the stent by food scraps, thus preventing the protocol of the study from being followed. Instead, the results were assessed using intention-to-treat analysis, limiting the extent to which we can prove the efficacy of nonvascular drug-eluting stents. In addition, type II error may have occurred, since per-protocol analysis was not followed, and the number of enrolled patients was small. Another limitation is that the number of commercialized biliary stents with a PTFE-covered membrane was too low for a comparison of efficacy with other covered SEMS. Nevertheless, drug-eluting stent insertion appears to be a promising, albeit challenging, procedure. It is necessary to challenge drug-eluting stent development through stent modifications and developments to overcome the problems associated with MSCPM-I and the limitations of MSCPM-II.

In conclusion, MSCPM-II showed no improved efficacy in terms of stent patency or survival duration in patients with malignant biliary obstructions compared with conventional CMS.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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