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Bilateral Versus Unilateral Metallic Stent Deployment in Patients with Malignant Hilar Biliary Strictures Due to Biliary Tract Carcinoma

Hirofumi Kawamoto[1*], Kousuke Minaga[2], Yukitaka Yamashita[2], Hironari Kato[3], Yoshinari Furukawa[4], Masayuki Kitano[5], Kazuhiro Kamada[6], Tsuneyoshi Ogawa[7], Koichi Fujita[8], Yoshinobu Okabe[9], Ryohei Kaji[10], Daisuke Masuda[11], Maiko Murata[12], Shinichi Hashimoto[13], Kiyohito Tanaka[14], Yoshifumi Arisaka[15], Kazuya Matsumoto[16], Hidekazu Mukai[17], Bilio-Pancreatic Stenting Study Group

[1]Department of General Internal Medicine, Kawasaki Medical School, Japan

[2]Department of Gastroenterology and Hepatology, Japanese Red Cross Wakayama Medical Center, Japan

[3]Departments of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Japan

[4]Department of Gastroenterology, Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Japan

[5]Department of Gastroenterology and Hepatology, Kinki University Faculty of Medicine, Japan

[6]Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Japan

[7]Department of Medicine, Hiroshima Citizen Hospital, Japan

[8]Department of Gastroenterology, Yodogawa Christian Hospital, Japan

[9]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Japan

[10]Department of Gastroenterology, Tagawa Hospital, Japan

[11]Department of Gastroenterology, Osaka Medical College, Japan

[12]Department of Gastroenterology, Osaka Police Hospital, Japan

[13]Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Japan

[14]Department of Gastroenterology, the Second Kyoto Red Cross Hospital, Japan

[15]Department of Gastroenterology, Kobe University Graduate School of Medicine, Japan

[16]Department of Gastroenterology, Tottori University Graduate School of Medicine, Japan

[17]Department of Gastroenterology, Yodogawa Christian Hospital, Japan

[*]**Corresponding author:** Hirofumi Kawamoto, Department of General Internal Medicine, Kawasaki Medical School, 2-6-1 Nakasange Kita-ku Okayama city, Japan. Tel: +81-862252111; Fax: +81-862328343; Email: hirofumi.kawamoto@gmail.com

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Abstract

Background/Aim: Several single arm studies demonstrated the feasibility of using a Metallic Stent (MS) to manage Malignant Hilar Biliary Strictures (MHBS). We conducted a multi-center, prospective, randomized study to investigate the clinical significance of bilateral MS deployment in patients with MHBS caused by unresectable Biliary Tract Carcinoma (BTC).

Methods: The patients with MHBS due to unresectable BTC were randomly allocated to endoscopic unilateral or bilateral stenting. The primary endpoint was the stent dysfunction rate at 6 months.

Results: Between April 2011 and March 2014, 40 patients were randomly allocated to the bilateral group and 39 patients to the unilateral group. The procedure success rate was 93% (37/40) in the bilateral group and 100% (39/39) in the unilateral group (NS). The median survival time was 237 days in the bilateral group and 236 days in the unilateral group (NS). However, the median stent-functioning time was 295 days in the bilateral group and 187 days in the unilateral group (p=0.049, generalized Wilcoxon test).

Conclusion: Despite including a smaller number of patients than planned, our findings suggest that bilateral MS deployment should be the first treatment for patients with MHBS due to unresectable BTC.

Keywords: Bilateral metallic stent deployment; Biliary tract carcinoma; Malignant hilar biliary strictures; Stent dysfunction

Introduction

Endoscopic biliary decompression is a treatment option for unresectable Biliary Tract Carcinoma (BTC) involving the hilar portion, and its efficacy and safety have been reported [1-3]. Generally, the bilateral procedure is technically demanding. If intractable cholangitis develops after deployment failure, the prognosis of the patients is poor [4]. A Metallic Stent (MS) can be used to treat Malignant Hilar Biliary Strictures (MHBS) but the material, deployment style, re-intervention, etc. must be considered [5-10]. It was previously suggested that unilateral MS deployment was sufficient, because the procedure is easier and safer than bilateral deployment [11,12]. However, some patients with more complex strictures need bilateral MS deployment to ameliorate jaundice and prevent liver failure [13]. Although newer MSs have an improved design and diameter [14,15], bilateral MS deployment is still challenging. Several single arm studies demonstrated the feasibility of the endoscopic bilateral MS deployment for MHBS [16-19]. However, despite these promising results, only one study compared the efficacy of the bilateral MS deployment with that of unilateral MS deployment in patients with MHBS [20]. We conducted a multi-center, prospective, randomized study to investigate the clinical significance of bilateral MS deployment in patients with MHBS caused by unresectable BTC (UMIN000005182).

Patients and Methods

Study Design

Between April 2011 and March 2014, patients with MHBS, caused by pathologically confirmed unresectable BTC, who were admitted to a hospital affiliated with the Bilio-Pancreatic Stent Study Group (BPSS) were considered for inclusion in this study and followed until September 2014. The type of MHBS was more complex than Bismuth type 2, and the cause of inoperability included the patient's age and performance status in addition to the stage of the disease, which was at least Stage 2B by UICC criteria. This study was designed to evaluate the efficacy and safety of bilateral vs. unilateral MS deployment. To optimize this comparison, we excluded patients who required bilateral MS deployment to ameliorate jaundice. Patients with MHBS first underwent unilateral biliary decompression, which was usually performed on the branch that drained the maximum volume of the liver with a nasobiliary catheter or an internal plastic stent. Cases were only included if there was improvement in a liver test value within a maximum of 4 weeks. Patients whose left or right portal vein was involved and obliterated by the tumor or whose unilateral lobe was diffusely occupied by a massive tumor were excluded. Eligible patients were then allocated to unilateral or bilateral MS deployment and were stratification by age, sex, and the type of stricture pattern according to Bismuth criteria.

The primary endpoint of this study was the stent dysfunction rate at 6 months, and the secondary outcomes were overall survival and the time to stent dysfunction. Stent dysfunction was defined as stent-associated complications that required interventional treatment using ERCP or PTBD. The time to stent dysfunction was calculated based on the period from the MS deployment to the second biliary decompression. The trial was designed to have 80% power to detect an 18% decrease in the stent dysfunction rate (37% to 19% in our preliminary retrospective data) at 6 months in patients undergoing bilateral vs. unilateral MS deployment. Allowing for dropouts, a total of 200 patients would be required, when using a chi-square test with a two-sided significance level of 5%. All analyses were performed on an intention-to-treat basis. This study was approved by the research and ethics committees of all hospitals affiliated with the BPSS group and this protocol was registered in the UMIN Clinical Trials Registry (UMIN000005182). All study procedures were performed in accordance with the Declaration of Helsinki. Therefore, all patients provided written informed consent. When patients registered on-line, they were randomly allocated to the unilateral or bilateral MS deployment group by the computer.

MS Deployment

The MS employed in this study was the Zeo-stent (Zeon Medical, Tokyo, Japan). This is a laser-etched MS with 12 waves and three joint struts in the circumference and it is mounted in a thin 7Fr introducer. Since the laser-etched MS does not shorten, it can be deployed in the planned position precisely. In the bilateral group, success was defined as endoscopic deployment of two MSs, in the previous target branch and the branch that drained the maximum volume of the contralateral lobe, over the stricture using the partial stent-in-stent procedure (Figure 1), which was described previously [21].

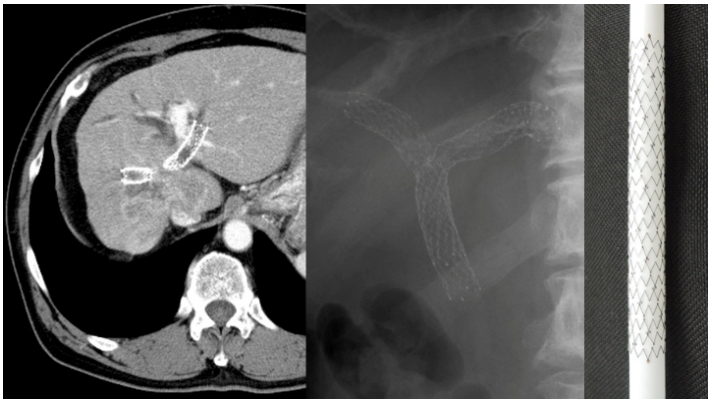

Figure 1: The CT and X-ray images of the Zeo-stent deployed in a patient with hilar bile duct carcinoma using a partial stent-in-stent procedure. The original structure of the stent is shown on the left.

Anti-Tumor Therapy

Anti-tumor therapy was performed at the physician's discretion. In this study, only S-1, or gemcitabine, or the combination of gemcitabine and cis-platinum was administrated based on the patients' conditions [22-24].

Statistical Analysis

Statistically significant differences in baseline characteristics, clinical outcomes, and adverse events between the two groups were determined using the chi-square test or Mann-Whitney U test, as appropriate. The mean survival time and time to stent dysfunction between the two groups were evaluated using the generalized Wilcoxon test. The Cox proportional hazard model was employed to analyze the factors that might affect the time to dysfunction of the MS. P <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 12.0 for Windows (SPSS; Chicago, Illinois, USA).

Results

Flow Diagram of the Study

Eighty-six patients were initially enrolled in this study using our strict inclusion criteria (Figure 2). More patients were not included because most of those with jaundice that improved with unilateral drainage were amenable to surgery. For the analysis, there were 39 patients in the unilateral group and 40 patients in the bilateral group.

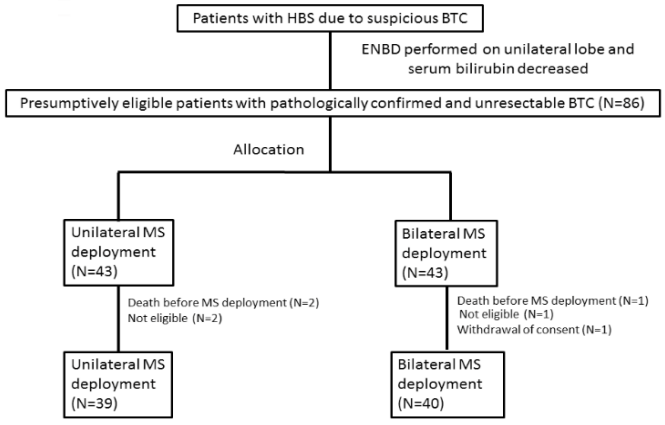

Figure 2: The flow diagram for this study.

Patients' Characteristics

The patients' characteristics are summarized in Table 1. There was no significant difference between the two groups for any parameter.

	Unilateral (n=39)	Bilateral (n=40)	P-value
Age (mean)	76.3-1-2.8	75.3±8.1	0.70
Gender(M:F)	19:20	21:19	0.82
T.Bil(mg/dI)(IOR)	6.1(2.4-10.5)	4.3(1.4-11.0)	0.82
Primary disease			
Bile duct	26	25	0.70
Gallbladder	13	15	
PS			
0	22	19	0.50
1	13	13	
2	4	8	
ASA			
0	2	1	0.66
1	19	18	
2	15	17	
3	3	4	
UICC stage			
I	2	1	0.82
II	9	7	
III	7	9	
IV	21	23	
Blthmuth			
II	15	11	0.34
III	10	14	
IV	14	15	
Metastasis			
(+)	21	28	0.17
(-)	18	12	
Chemotherapy			
(+)	22	24	0.82
(-)	17	16	

Short-Term Outcomes of the Patients

The success rate of MS deployment was 100% (39/39) in the unilateral group, and 92.5% (37/40) in the bilateral group (P=0.25).

Three cases in the bilateral group were incomplete and did not undergo another intervention. The short term complications noted were: cholangitis, cholecystitis, pancreatitis, and pain at the MS dilatation site. There was no difference in the complication rates of the groups (P=0.95).

Long-Term Outcomes of the Patients

The median survival time was 185 days in the unilateral group and 216 days in the bilateral group (P=0.88). Stent dysfunction within 180 days, which required re-intervention, was observed in 64.1% (25/39) of the unilateral group patients and in 42.5% (17/40) of the bilateral group patients (P=0.054). The cumulative stent-functioning rate curves during the study period are shown in Figure 3.

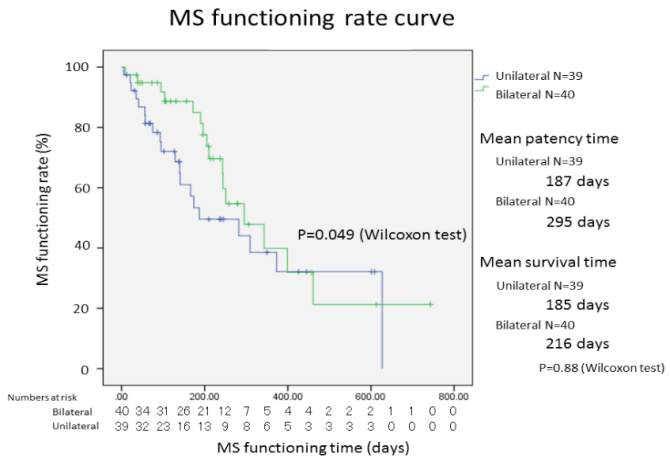

Figure 3: The cumulative stent-functioning rate curves for the two groups. There was a significant difference in the functioning time between the groups (generalized Wilcoxon test).

The median time to stent dysfunction were 187 days for the unilateral group and 295 days for the bilateral group, and there was a significant difference between the two groups (P=0.049). Stent occlusion was a major cause of stent dysfunction, and occurred in 18 patients from the unilateral group and in 13 patients from the bilateral group. For these patients, plastic or metallic stents were deployed in 15 patients (83.3%) in the unilateral group and in 12 patients (92.3%) in the bilateral group. These procedures were always conducted using an endoscopic technique. Univariate analysis using the Cox model was performed to detect factors that might have affected the stent function. Unfortunately, there was no significant factor, probably due to the small number of the patients.

Discussion

Unlike a braided MS, there are limited data regarding the use of a laser-etched MS for MHBS. This is the first randomized control study that compared the efficacy between unilateral and bilateral deployment of a laser-etched MS in patients with unresectable MHBS due to BTC. The results of this prospective study suggest bilateral metallic stent deployment is superior to unilateral deployment, based on the stent-functioning time. Several papers reported that unilateral MS deployment could be used in patients with MHBS if patients had at least one-third healthy liver volume [1-3]. However, the results from this study do not support that the outcomes from unilateral MS deployment are comparable to bilateral MS deployment. As the time to stent dysfunction of patients in the bilateral group was significantly longer than that of the unilateral group patients, the bilateral MS deployment should be employed first for patients with MHBS. Although there was no significant difference in the survival time between the two groups, the longer time to stent dysfunction may benefit patients, e.g. by increasing the patients' initial outpatient time.

Vienne et al. reported that better survival was attained with more than 50% drainage, which requires bilateral stenting [12]. Furthermore, Uchida et al. reported that, when using chemotherapy, greater drainage of the liver segment contributed to the stent patency and patient survival [25]. These data strongly support that the functional liver volume should be better maintained using multiple biliary stents for longer survival and stent patency. In this study, we made sure to exclude patients who required bilateral MS. Despite this, the outcome of the bilateral group was favorable regarding the time to stent dysfunction.

In this study, we employed a laser-etched MS; although, in many preliminary studies the braided MS was used for MHBS. Furthermore, we used a partial stent-in-stent procedure, which was a more complex technique than the side-by-side procedure. However, we demonstrated its potential for treating MHBS, including the high rate of recovery from stent dysfunction after the procedure. Although the data regarding the efficacy of using a laser-etched MS for MHBS have been scarce, our findings demonstrate that it is an option for treating MHBS. This study has several weaknesses. The desired number of patients was not reached and the primary endpoint did not quite reach significance at 6 months. However, we could significantly demonstrate the superiority of the bilateral MS deployment when evaluating time to stent dysfunction, despite our strict inclusion criteria. The strength of this study lies here.

Conclusion

Our findings suggest that endoscopic bilateral MS deployment should be used for initial biliary decompression in patients with MHBS due to BTC.

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