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ISSN

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Publication Date

DOI

Peer reviewed

Endoscopic Drainage of >50% of Liver in Malignant Hilar Biliary Obstruction Using Metallic or Fenestrated Plastic Stents

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OBJECTIVES: Endoscopic drainage of complex hilar tumors has generally resulted in poor outcomes. Drainage of >50% of liver volume has been proposed as optimal, but not evaluated using long multifenestrated plastic stents (MFPS) or self-expanding metal stents (SEMS). We evaluated outcomes of endoscopic drainage of malignant hilar strictures using optimal strategy and stents, and determined factors associated with stent patency, survival, and complications.

METHODS: Cross-sectional study was conducted at an academic center over 5 years. MFPS (10 French or 8.5 French) or open-cell SEMS were used for palliation of unresectable malignant hilar strictures, with imaging-targeted drainage of as many sectors as needed to drain >50% of viable liver volume. Risk factors were evaluated using regression analysis. The cumulative risk was assessed using Kaplan–Meier analysis.

RESULTS: 77 patients with malignant hilar biliary strictures (median Bismuth IV) underwent targeted stenting (41 MFPS and 36 SEMS). Comparing MFPS vs. SEMS, technical success (95.1 vs. 97.2%, $P = 0.64$), clinical success (75.6 vs. 83.3%, $P = 0.40$), frequency of multiple stents (23/41 vs. 25/36, $P = 0.19$), survival and adverse events were similar, but stent patency was significantly shorter ($P < 0.0001$). Factors associated with survival were Karnofsky score and serum bilirubin level at presentation. Outcomes were independent of Bismuth class with acceptable results in Bismuth III and IV.

CONCLUSIONS: Endoscopic biliary drainage with MFPS or open-cell SEMS targeting >50% of viable liver resulted in effective palliation in patients with complex malignant hilar biliary strictures. Patency was shorter in the MFPS group, but similar survival and complications were found when comparing MFPS and SEMS group.

INTRODUCTION

Most patients with malignant hilar strictures are unresectable at initial presentation due to advanced stage and patient comorbidity.[1] Endoscopic stenting of malignant hilar strictures is widely performed for palliation, but can be technically challenging, resulting in substantial failure, complications, and perhaps survival, particularly in complex Bismuth IV tumors, for whom some authors recommend percutaneous rather than endoscopic drainage.[2–6]

Extent of required drainage is controversial in palliation of malignant hilar strictures, with a prior focus on whether stents should be unilateral or bilateral.[7–10] Because the three liver sectors (right anterior, right posterior, and left) have substantial variation in congenital junction and degree of atrophy or tumor replacement, focus has shifted away from "unilateral or bilateral" stenting towards number of sectors drained based on the amount of viable liver drained. Selectively targeted drainage aimed at decompressing at least 50% of viable hepatic volume was associated with improved outcomes and survival. Such a strategy has only been evaluated in a single study utilizing plastic stents.[11]

Choice of stents for hilar malignant strictures remains controversial. A few prior studies have suggested that self-expanding metal stents (SEMS) resulted in longer patency, less re-interventions, and possibly improved survival compared with conventional plastic stents.[2,3,5,9] However, the most commonly used plastic stents are short and rigid polyethylene,[6] which are not ideal for complex hilar anatomy, and especially for left lobe segments which are sharply angulated and very long. Stent material may be a factor—a study using 10 French (Fr) pliable polyurethane stents demonstrated less stent migration compared to polyethylene stents.[12] A multifenestrated polyurethane plastic stent (MFPS) designed for pancreatic drainage may have similar potential advantages over conventional plastic biliary stents, with added benefit of large sideholes, conformable flexibility and greater length. We designed this study to describe the comparative performance of MFPS vs. open-cell SEMS, and factors associated with patient survival, stent patency and adverse events.

METHODS

Study design. We performed a retrospective cross-sectional study using a prospectively collected database of those with unresectable malignant hilar stricture treated with endoscopic stenting.

Patients. All patients treated with MFPS or SEMS for malignant hilar biliary obstruction at the University of Minnesota Medical Center between June 1, 2008 and December 31, 2013 were included ($n = 77$). The diagnosis of malignant hilar stricture was ascertained by tissue diagnosis, clinical and radiographic findings suggestive of cholangiocarcinoma, or metastatic lesions to the hepatic hilum from established primary tumors. The study was approved by the University of Minnesota Institutional Review Board (Minneapolis, MN).

Exclusion criteria were as follows; (1) age less than 18 years, (2) multiple areas of biliary stricture other than malignant hilar stricture, (3) loss of follow-up of less than 90 days after the procedure, (4) two or more active concurrent malignancy processes except non-melanoma skin cancer.

Stent types. Patients were categorized into two groups, including those treated with (1) MFPS at the time of the diagnosis of malignant hilar stricture, and (2) 10-millimeter open-cell SEMS. MFPS (Figure 1a–f) were Johlin pancreatic wedge stents (Cook Medical, Winston-Salem, NC, USA) which are composed of soft Pellethane, and multifenestrated with large, multi-sideholes, 8.5 Fr or 10 Fr, and length up to 22 cm, trimmed to desired length as necessary, with stents generally placed as deeply as possible into the targeted liver sectoral or segmental ducts. SEMS (Figure 2a–d) included Zilver Biliary (Cook Medical), or Flexxus (ConMed, Utica, NY, USA). Planned drainage was based on MRCP/CT findings with goal of adequate numbers of sectors (left, right anterior, and right posterior sectoral biliary ducts) to decompress more than 50% of the viable (non-atrophic, and majority not replaced by tumor) liver volume.

Selective access to right anterior, right posterior, and left sectoral ducts was achieved using a SwingTip steerable cannula (Olympus Endoscopy, Tokyo, Japan) and 0.025" guidewire (VisiGlide, Olympus Endoscopy, Hamburg, Germany) or 0.035" Terumo Glidewire (Boston Scientific, Natick, MA, USA). MRCP and/or CT were used to target the largest viable sector drainage, using selective guidewire cannulation without contrast injection above the stricture until the wire had been advanced deeply into that sector.[10] For two or more sector drainage using metallic stents, protocol was to place stents in a Y configuration;[6] guidewires were passed into all sectors planned for drainage, followed by balloon dilation of all strictures up to 4 or 6 mm, with subsequent placement of the left hepatic duct stent (if planned) first, followed by any right sector stent. Metallic stents were always positioned above the papilla, and after biliary sphincterotomy.

The decision to place plastic vs. SEMS at initial endoscopic retrograde cholangiopancreatography was at the discretion of the endoscopists. In general, patients without an established diagnosis or with consideration of surgical resection received plastic stents. Repeat endoscopic retrograde cholangiopancreatography with stent exchange was typically scheduled electively at 3 months for patients with MFPS if their condition warranted, while no planned repeat intervention scheduled for patients with SEMS unless radiofrequency ablation planned or evidence of stent malfunction occurred.

Clinical information. Demographics, clinical information,[13,14] and laboratory results at the time of malignant hilar stricture diagnosis were manually reviewed from electronic medical records. All patients were prospectively followed until 31 December 2016. The last follow-up visit, vital status, complications using consensus criteria[15] (pancreatitis, bleeding, perforation) and cause of death were recorded.

Technical success was defined intraprocedurally as (1) successful insertion of biliary stent(s) to the planned sectoral ducts, confirmed fluoroscopically, and (2) adequate flow visualized through the targeted sectoral ducts, confirmed endoscopically. Clinical success was defined as a decrease in bilirubin level to less than 50% of pretreatment value within 2 weeks. Cholangitis was defined as fever > 38 Celcius degrees post-ERCP with worsening bilirubin, and/or intraprocedural findings of pus. Cholangitis was recorded within 30 days and at any time after biliary stent placement. Reintervention was defined as any type of unplanned endoscopic, percutaneous, or surgical procedure to improve biliary drainage after the initial successful drainage. Stent patency was defined as either 1) time from initial stent placement to reintervention, whether due to scheduled biliary stent exchange or due to worsening liver enzymes, and/or clinical concerns of cholangitis. Survival time was defined as the time from first biliary stent, either MFPS or SEMS until time of death from any cause.

Statistical analysis. Baseline characteristics of patients who were treated with MFPS vs. SEMS after diagnosis of malignant hilar stricture were compared using the student's *t* test for continuous variables and the chi-square (Fisher and Pearson exact tests) for categorical variables. SPSS statistical software version 22.0 (SPSS Inc., Armonk, NY, USA) and JMP Pro 11 (SAS, Cary, NC, USA) were used for statistical calculations. Survival was estimated using Kaplan–Meier's method and compared using the log-rank test. Associations between predictor variables and survival were determined by hazards ratio (HR) and 95% confidence interval (CI) calculated using Cox proportional hazards regression. Associations between variables and complications were calculated using logistic regression analysis. For inter-related risk factors, only the factor with the strongest association was included to satisfy the linear independence assumption of regression. Variables with $P < 0.1$ in the univariate model were included in the multivariate models.

RESULTS

Baseline patient characteristics. Of the 77 patients with malignant hilar strictures, 41 (53.2%) were male and mean age was 63.3 ± 12.6 years (s.d.) (Table 1 and Supplementary Information S1 online). Forty-five (58.4%) had cholangiocarcinoma and 32 (41.6%) had local invasion or metastasis causing extrinsic compression of the hepatic hilum. Of 32
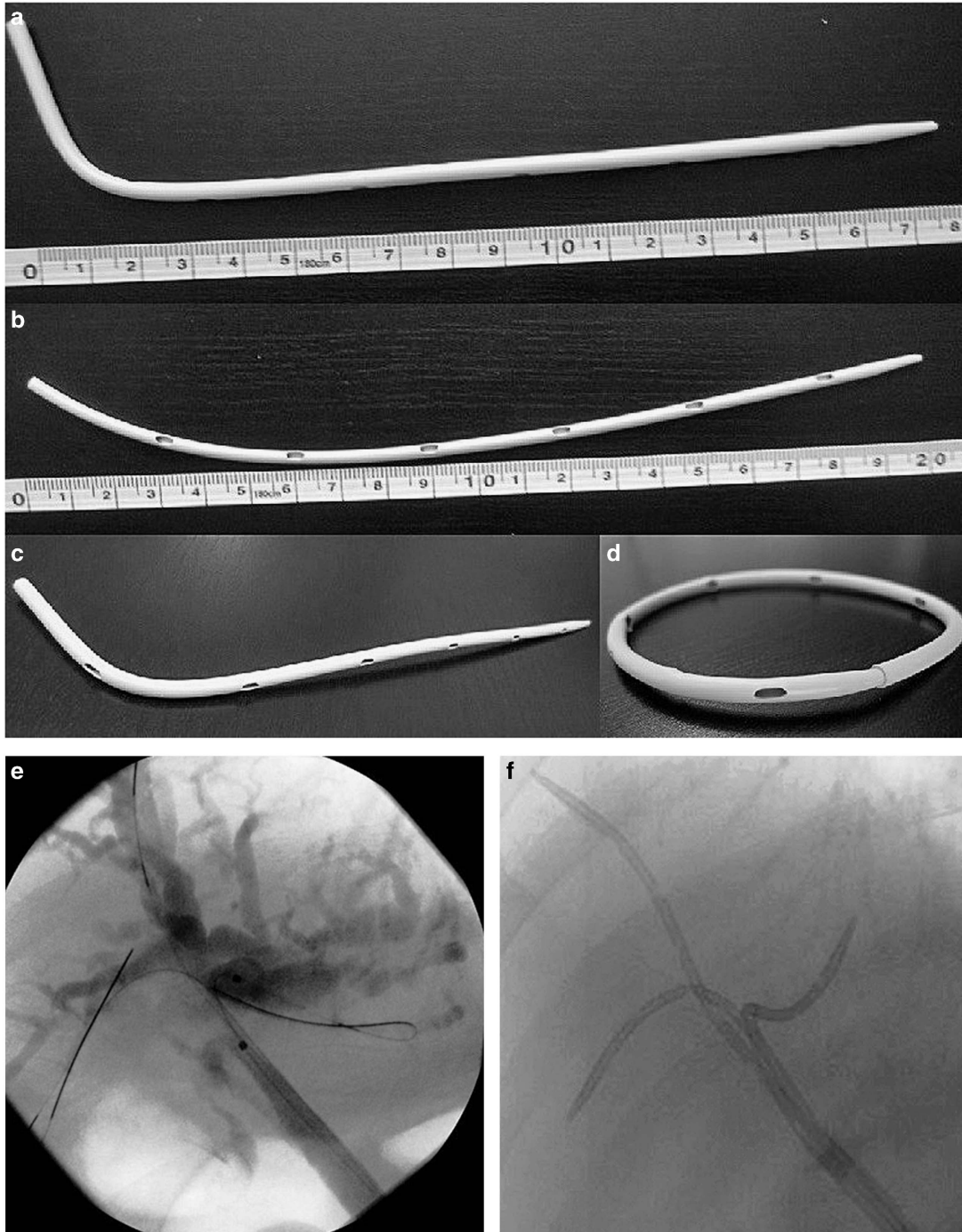
Figure 1 (**a–d**) MFPS 10 French 20 cm (upper, **a**), MFPS 8.5 French 20 cm (middle, **b**). MFPS is pliable (lower, left, and right, **c**, **d**) and is suitable for stenting of sectoral biliary ducts. (**e**, **f**) A tight hilar stenosis and severe upstream dilatation from metastatic rectal carcinoma to the hepatic hilum (**e**). This was treated with three 8.5 French 16 cm MFPS to all sectoral ducts (left, right anterior and right posterior) (**f**).

patients with local extension or metastasis to the hepatic hilum, the primary malignancies were colon cancer ($n=7$), pancreatic cancer ($n=4$), hepatocellular carcinoma ($n=4$), neuroendocrine tumor ($n=3$), gallbladder ($n=3$), and others ($n=11$). There was no statistically significant difference in any of the patient or procedural background variables listed in Table 1, except higher levels of pre-procedure aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in MFPS group. The median durations of follow-up were 435 (range 5–1,708) days and 416 (range 4–1,493) days in the MFPS and SEMS groups, respectively.

Survival of patients who were treated with MFPS versus SEMS. By Kaplan–Meier analysis, there was no statistical difference in median survival of all patients with malignant
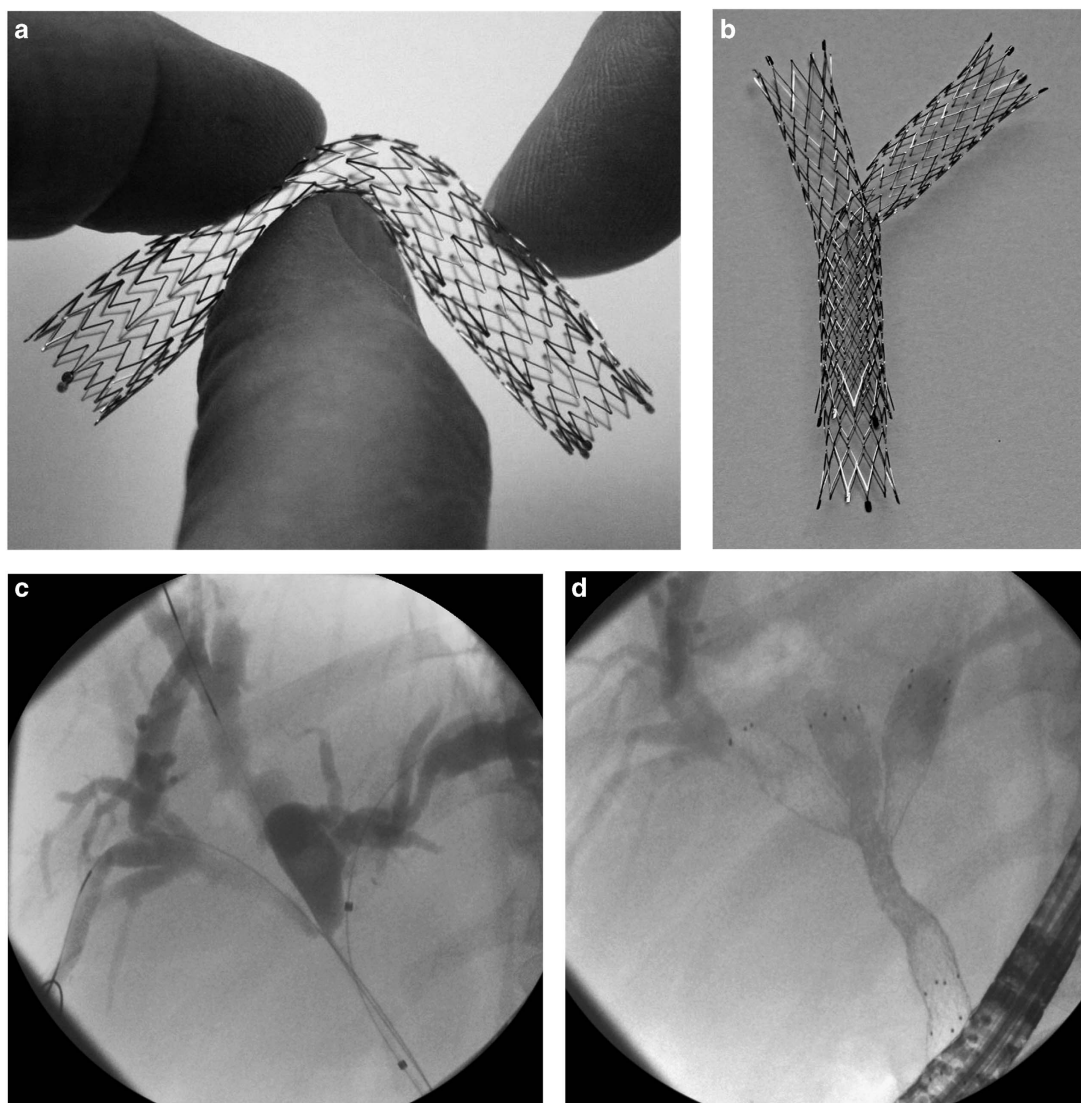
Figure 2 (**a**) Open-cell laser cut metallic stents used for hilar tumor drainage showing large interstices allowing Y stent placement. (**b**) Y configuration of standard open-cell laser cut metallic stent. (**c**, **d**) Complex Bismuth IV tumor (**c**) treated with three 10 mm laser cut stents in "Y" configuration to drain all three sectoral (left, right anterior, and right posterior) ducts (**d**).

hilar strictures who were treated with MFPS vs. SEMS (195 ± 131.9 days vs. 259 ± 145.5 days, $P = 0.88$, Figure 3a), or in the subgroups with cholangiocarcinoma compared to those with strictures secondary to hilar metastasis (Figure 3b,c). Cox regression with time dependent method showed no significant difference in survival between MFPS vs. SEMS at any time point up to 2 years. Seventy-one patients died during a median follow-up time of 259 days (range 4–1,708 days). Of these patients, 42 (59.2%) patients had information on causes of death available in the medical records; none died of direct stent-related complications.

At univariate analysis, cholangiocarcinoma (vs. distant metastasis), higher Karnofsky score, lower T stage, lower bilirubin, higher alanine aminotransferase, normal hemoglobin, and additional therapy with radiofrequency ablation (RFA) during endoscopic retrograde cholangiopancreatography and

chemotherapy were associated with better survival (Table 2 and Supplementary Information S2 online). At multivariate analysis, only higher Karnofsky score and lower serum bilirubin were associated with better survival. At multivariate analysis of a subgroup of patients who did not receive debulking surgery, higher Karnofsky score and radiofrequency ablation were associated with better survival.

Stent patency in patients who were treated with MFPS versus SEMS. The median stent patency of MFPS was significantly shorter than that of SEMS (27 ± 3.7 days vs. 87 ± 50.1 days, $P < 0.0001$, Figure 3d, for first stent of each group; and 29 ± 1.9 days vs. 87 ± 49.6 days, $P = 0.001$ for subsequent stents, respectively). Numbers of re-interventions were 1.8 ± 1.8 per patient in MFPS group compared to 1.1 ± 0.4 procedures per patient in SEMS group ($P = 0.03$). In subgroup analysis, MFPS compared to SEMS also had

Table 1 Characteristics of patients with malignant hilar biliary obstruction treated with multifenestrated plastic stents (MFPS) vs. open-cell self-expanding metal stents (SEMS)

Variables	MFPS ($n = 41$ patients)	SEMS ($n = 36$ patients)	P-value
Male (n, %)	21 (51.2%)	20 (55.6%)	0.70
Age (years, mean ± s.d.)	61.9 ± 12.2	64.9 ± 13.0	0.29
Year of procedure	6/2008–12/2013	6/2008–12/2013	0.90
Comorbidities (n)[a]	26(63.4%)	21(58.3%)	0.65
Nature of malignant strictures			0.76
Cholangiocarcinoma	24 (58.5%)	21 (58.3%)	
Local invasion	4 (9.8%)	2 (5.6%)	
Distant metastasis	13 (31.7%)	13 (36.1%)	
Cholestatic symptoms (n)[b]	35 (85.4%)	32 (88.9%)	0.55
Presence of fever before ERCP (n)	6 (14.6%)	8 (22.2%)	0.39
Presence of abdominal pain (n)	8 (19.5%)	4 (11.1%)	0.31
Presence of bacteremia before ERCP (n)	5 (12.2%)	3 (8.3%)	0.58
Karnofsky score (mean ± s.d.)	58.3 ± 18.8	58.1 ± 18.2	0.96
Tumor staging based on AJCC TNM system[c]			
T			0.83
T1 (n, %)	5 (12.2%)	4 (11.1%)	
T2 (n, %)	16 (39%)	18 (50%)	
T3 (n, %)	12 (29.3%)	10 (27.8%)	
T4 (n, %)	8 (19.5%)	4 (11.1%)	
N (n, %)	13 (31.7%)	17 (47.2%)	0.16
M (n, %)	18 (43.9%)	18 (50%)	0.59
Bismuth-Corlette classification type			0.49
Type I (n, %)	1 (2.4%)	1 (2.8%)	
Type II (n, %)	1 (2.4%)	0	
Type III (n, %)	14 (34.2%)	8 (22.2%)	
Type IV (n, %)	25 (61%)	27 (75%)	
Laboratory results			
Total bilirubin (mg/dl, mean ± s.d.)	8.0 ± 7.4	6.4 ± 5.8	0.30
Alkaline phosphatase (IU/l, mean ± s.d.)	623 ± 442	399 ± 207	0.007
AST (IU/l, mean ± s.d.)	159 ± 114	97 ± 58	0.004
ALT (IU/l, mean ± s.d.)	135 ± 105	73 ± 48	0.002
Hemoglobin (g/dl, mean ± s.d.)	11.7 ± 2	11.4 ± 2.7	0.60
INR (mean ± s.d.)	1.1 ± 0.2	1.1 ± 0.2	0.41
Creatinine (mg/dl, mean ± s.d.)	0.9 ± 0.4	0.8 ± 0.3	0.45
Endoscopic therapies			
Numbers of sectors drained (mean numbers of sectors ± s.d.)[d]	1.8 ± 0.5	2.0 ± 0.6	0.21
More than one sectoral stent placed (numbers of patients;numbers of procedures for stent placement)			0.19
1 sectoral stent	18;26	11;18	
2 sectoral stents	22;49	22;22	
3 sectoral stents	1;1	3;3	
Biliary sphincterotomy (n, %)[e]	29 (70.7%)	22 (61.1%)	0.37
Balloon dilation (n, %)	25 (61%)	29 (80.6%)	0.06
Radiofrequency ablation (n, %)	4 (9.8%)	6 (16.7%)	0.37
Additional therapies			
Chemotherapy (n, %)	25 (61%)	20 (55.6%)	0.63
Radiation (n, %)	1 (2.4%)	0	0.35
Surgery (n, %)	5 (12.2%)	5 (13.9%)	0.83

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography; INR, international normalized ratio.
[a]No statistical difference in types of comorbidities (coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency, and cirrhosis) and Charlson comorbidity index.
[b]No statistical difference in types of cholestatic symptoms (jaundice, acholic stool, dark urine, and pruritus).
[c]American Joint Committee on Cancer (AJCC) TNM system based on type of tumor.
[d]Number of sectoral drains (left sectoral, right anterior sectoral, right posterior sectoral biliary ducts) based on MRCP/CT with goal of draining > 50% viable liver volume.
[e]Biliary sphincterotomy performed at the index biliary stenting at the University of Minnesota.

shorter stent patency both in patients with cholangiocarcinoma (27 ± 4.1 days in MFPS group vs. 149 ± 65.9 days in SEMS group, $P = 0.002$) and in patients with local invasion or distant metastasis to the hepatic hilum (27 ± 7.2 days for MFPS vs. 56 ± 27.1 days for SEMS, $P = 0.01$).

In addition to type of stent, higher Karnofsky score, alkaline phosphatase level, more numbers of drained liver sectors, those received balloon dilation, and those who did not require a palliative debulking surgery were associated with better stent patency. At multivariate analysis, only MFPS and surgery
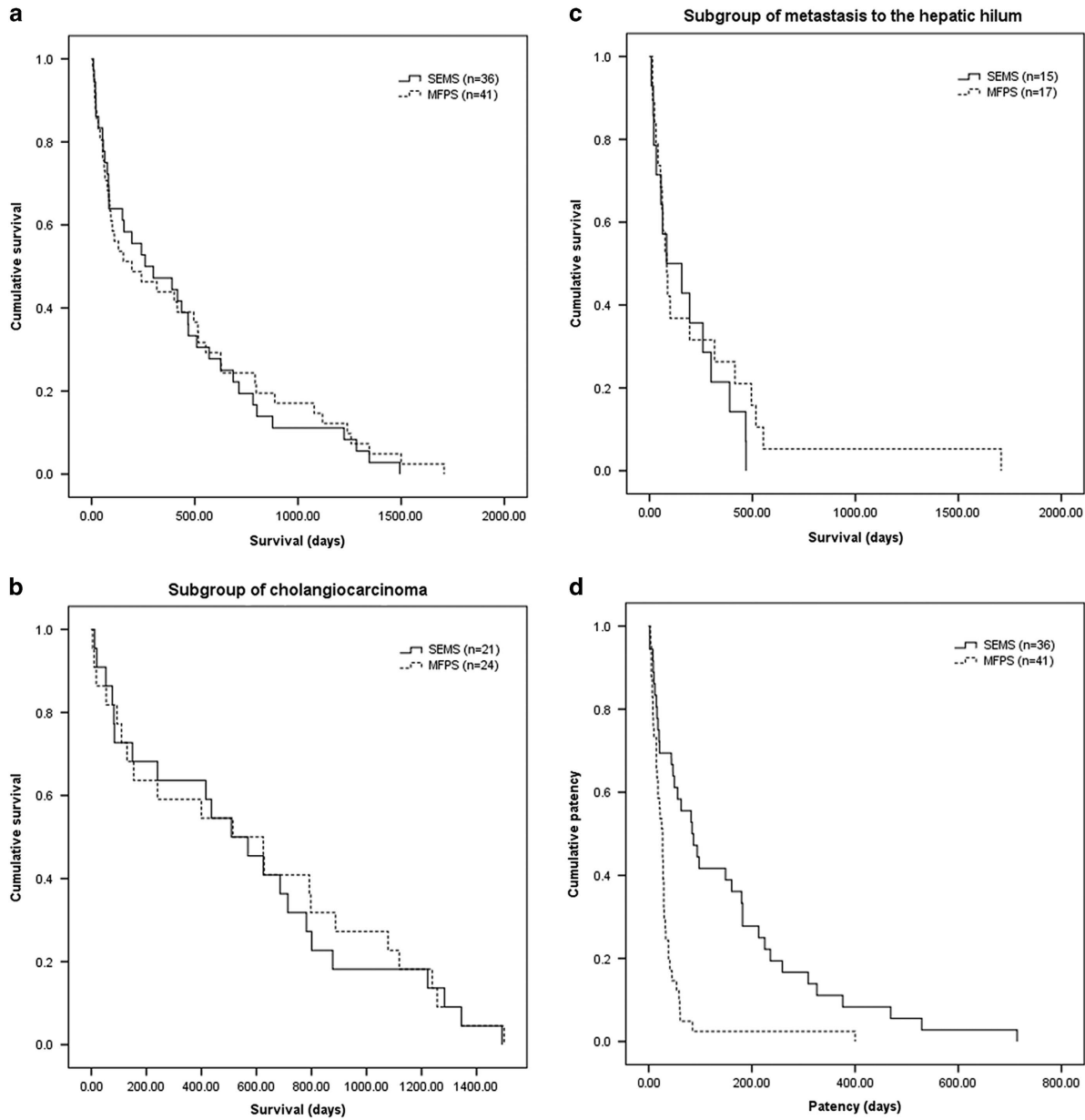
Figure 3 (**a**) Survival of patients with malignant hilar obstruction treated with multifenestrated plastic stents (MFPS) (*n* = 41) and self-expanding metal stents (SEMS) (*n* = 36), *P* = 0.88 by Kaplan–Meier analysis. (**b**, **c**) Survival of patients with malignant hilar obstruction treated with MFPS (*n* = 41) and SEMS (*n* = 36), stratified by nature of malignant hilar obstruction (*P* = 0.95 for cholangiocarcinoma subgroup, and *P* = 0.26 for distant metastasis subgroup). (**d**) Stent patency in patients with malignant hilar obstruction treated with MFPS (*n* = 41) and SEMS (*n* = 36), *P* < 0.0001 by Kaplan–Meier analysis.

requirement were associated with worse stent patency (Table 2). This factor remained statistically significant in a subgroup analysis of patients who did not receive debulking surgery (Supplementary Information S2).

Technical success, clinical success and adverse events related to MFPS versus SEMS stent placement. Technical success was found in 39/41 patients (95.1%) treated with MFPS vs. 35/36 patients (97.2%) treated with SEMS (*P* = 0.64). Clinical success was found in 31/41 (75.6%) in MFPS group vs. 30/36 (83.3%) in SEMS group (*P* = 0.40).

Adverse events (Table 3) were not significantly different between MFPS and SEMS, including unsuccessful stent placement, cholangitis (17.1% MFPS vs. 11.1% SEMS, *P* = 0.46), including cholangitis within 30 days of stent placement (*P* = 0.12), endoscopically documented stent occlusion (14.6% MFPS vs. 27.8% SEMS, *P* = 0.16) including stent occlusion within 30 days (*P* = 0.64), pancreatitis in one patient with SEMS (2.8%, *P* = 0.28), bleeding in a patient treated with MFPS (*P* = 0.35), stent migration (all distally towards the duodenal lumen) in three (7.3%) patients in MFPS group (*P* = 0.10), mortality within 30 days (14.6%

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Table 2 Cox proportional hazards analysis of variables associated with survival and stent patency in patients with malignant hilar obstruction treated with multifenestrated plastic stents (MFPS) and open-cell self-expanding metal stents (SEMS)

Variables	Survival				Stent patency			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
MFPS (compared to SEMS)	1.09 (0.69–1.71)	0.71			0.33 (0.20–0.55)	<0.0001	0.23 (0.12–0.45)	<0.0001
Male	0.83 (0.76–1.92)	0.43			0.84 (0.52–1.32)	0.45		
Age (years)		0.38				0.37		
50 or less	1.00 (reference)				1.00 (reference)			
51–70	0.62 (0.29–1.22)	0.17			1.58 (0.80–2.92)	0.18		
71 or more	0.74 (0.33–1.52)	0.43			1.58 (0.79–3.03)	0.19		
Year of procedure		0.79				0.36		
2008	1.00 (reference)				1.00 (reference)			
2009	0.68 (0.15–2.26)	0.55			1.09 (0.24–3.74)	0.90		
2010	0.53 (0.13–1.54)	0.27			0.56 (0.13–1.63)	0.32		
2011	0.63 (0.15–1.84)	0.43			0.56 (0.13–1.66)	0.32		
2012	0.51 (0.12–1.60)	0.27			0.97 (0.22–2.99)	0.96		
2013	0.38 (0.07–1.75)	0.21			0.70 (0.14–3.25)	0.65		
Comorbidities	0.91 (0.54–1.51)	0.71			1.21 (0.73–2.02)	0.46		
Nature of malignant stricture								
Local invasion or metastasis	1.00 (reference)	0.0002	1.00 (reference)	0.35	1.00 (reference)	0.13		
Cholangiocarcinoma	2.54 (1.55–4.12)		1.39 (0.69–2.79)		1.43 (0.90–2.26)			
Cholestatic symptoms	1.26 (0.75–2.24)	0.40			0.93 (0.57–1.49)	0.78		
Presence of fever before ERCP	0.69 (0.39–1.30)	0.24			1.13 (0.65–2.12)	0.67		
Presence of abdominal pain	0.55 (0.30–1.08)	0.10			1.00 (0.56–1.96)	0.99		
Presence of bacteremia before ERCP	0.50 (0.25–1.14)	0.10			0.75 (0.38–1.70)	0.46		
Karnofsky score								
<50	1.00 (reference)	<0.0001	1.00 (reference)	0.0002	1.00 (reference)	0.05	1.00 (reference)	0.06
50–70	3.13 (1.61–5.77)	0.001	2.64 (1.12–6.10)	0.03	1.01 (0.52–1.82)	0.99	0.99 (0.50–1.86)	0.97
≥71	7.22 (3.38–15.19)	<0.0001	8.30 (2.83–24.63)	0.0001	1.89 (0.93–3.73)	0.08	1.98 (0.92–4.20)	0.08
Tumor staging based on AJCC TNM system[b]								
T		0.03		0.97		0.40		
T4	1.00 (reference)		1.00 (reference)		1.00 (reference)			
T3	2.57 (1.21–5.25)	0.02	1.20 (0.45–3.05)	0.71	1.26 (0.60–2.49)	0.53		
T2	3.04 (1.45–6.00)	0.004	1.14 (0.45–2.77)	0.78	1.25 (0.61–2.37)	0.53		
T1	3.61 (1.35–10.46)	0.01	0.95 (0.23–3.92)	0.94	0.60 (0.24–1.62)	0.30		
No lymph node metastasis	1.07 (0.67–1.70)	0.76			1.19 (0.75–1.91)	0.47		
Bismuth–Corlette classification type		*0.39*				*0.37*		
Type I	1.00 (reference)				1.00 (reference)			
Type II	0.99 (0.09–21.33)	0.99			0.12 (0.01–2.67)	0.15		
Type III	2.85 (0.45–10.21)	0.22			0.93 (0.15–3.20)	0.93		
Type IV	2.19 (0.35–7.33)	0.34			1.14 (0.19–3.72)	0.86		
Laboratory results								
Total bilirubin (mg/dl)								
≥15	1.00 (reference)	0.09	1.00 (reference)	0.12	1.00 (reference)	0.22		
10–14.9	3.43 (1.34–8.59)	0.01	2.49 (0.88–7.66)	0.11	1.96 (0.77–4.98)	0.16		

Table 2 *(Continued)*

Variables	Survival				Stent patency			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
5–9.9	2.62 (1.11–5.74)	0.03	3.30 (1.15–9.21)	0.03	0.94 (0.40–1.99)	0.87		
2–4.9	2.73 (1.15–6.11)	0.02	3.96 (1.41–10.94)	0.01	1.36 (0.58–2.94)	0.46		
<2	2.51 (1.05–5.68)	0.04	4.29 (1.35–13.55)	0.01	1.76 (0.74–3.99)	0.20		
Alkaline phosphatase		0.17				0.06		0.09
<3 times upper normal limits	1.00 (reference)				1.00 (reference)		1.00 (reference)	
3–5 times upper normal limits	0.83 (0.51–1.41)	0.50			0.79 (0.48–1.33)	0.37	1.10 (0.63–1.95)	0.74
5–10 times upper normal limits	1.56 (0.78–3.45)	0.22			1.87 (0.91–4.36)	0.09	2.97 (1.25–7.89)	0.01
>10 times upper normal limits	0.26 (0.07–1.61)	0.12			0.22 (0.06–1.42)	0.10	0.59 (0.16–3.84)	0.52
AST		0.66				0.82		
<3 times upper normal limits	1.00 (reference)				1.00 (reference)			
3–5 times upper normal limits	1.01 (0.59–1.75)	0.98			0.77 (0.45–1.34)	0.35		
5–10 times upper normal limits	0.85 (0.47–1.61)	0.61			0.89 (0.49–1.71)	0.73		
>10 times upper normal limits	1.03 (0.45–2.78)	0.95			0.81 (0.36–2.18)	0.66		
ALT		0.09		0.67		0.34		
<3 times upper normal limits	1.00 (reference)		1.00 (reference)		1.00 (reference)			
3–5 times upper normal limits	1.50 (0.84–2.82)	0.18	1.35 (0.60–3.15)	0.47	1.19 (0.67–2.23)	0.57		
5–10 times upper normal limits	1.92 (1.09–3.53)	0.02	1.65 (0.75–3.76)	0.21	0.63 (0.36–1.16)	0.14		
>10 times upper normal limits	2.45 (0.86–10.34)	0.10	2.11 (0.34–15.71)	0.43	1.20 (0.43–5.01)	0.76		
Hemoglobin ≥12 g/dl	2.15 (1.34–3.46)	0.002	1.55 (0.74–3.26)	0.24	1.05 (0.66–1.66)	0.83		
Creatinine <1.0 mg/dl	1.69 (0.88–2.99)	0.11			0.68 (0.39–1.31)	0.24		
Endoscopic therapies								
Numbers of sectoral drained[c]		0.37				0.09		0.37
1 sector	1 (reference)				1.00 (reference)		1.00 (reference)	
2 sectors	0.71 (0.44–1.16)	0.17			1.66 (1.02–2.69)	0.04	1.47 (0.76–2.83)	0.25
3 sectors	0.71 (0.28–2.41)	0.55			1.82 (0.72–6.13)	0.22	0.82 (0.28–3.00)	0.74
Biliary sphincterotomy[d]	1.51 (0.92–2.45)	0.10			0.83 (0.50–1.34)	0.45		
Balloon dilation	0.94 (0.54–1.57)	0.82			2.41 (1.38–4.13)	0.002	1.38 (0.71–2.68)	0.34
Radiofrequency ablation	2.29 (1.22–4.80)	0.009	1.59 (0.69–4.01)	0.29	1.28 (0.69–2.66)	0.46		
Additional therapies								
Chemotherapy	1.97 (1.20–3.22)	0.007	0.96 (0.50–1.79)	0.89	1.07 (0.67–1.69)	0.76		
Radiation	14.72 (0.77–91.34)	0.10			0.08 (0.01–1.54)	0.10		
Surgery/palliative tumor debulking	1.88 (0.90–4.63)	0.10			0.42 (0.22–0.88)	0.02	0.43 (0.22–0.91)	0.03

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; HR, hazards ratio.
[a]Variables from univariate analysis with $P<0.1$.
[b]American Joint Committee on Cancer (AJCC) TNM system based on type of tumor.
[c]Number of sectoral drains (left sectoral, right anterior sectoral, right posterior sectoral biliary ducts) based on MRCP/CT with goal of draining >50% viable liver volume.
[d]Biliary sphincterotomy performed at the index biliary stenting at the University of Minnesota.

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Table 3 Complications, 30-day mortality and their associated predictors in patients with malignant hilar obstruction treated with multifenestrated plastic stents (MFPS) and self-expanding metal stents (SEMS)

Type of complications	MFPS[a]	SEMS[a]	P-value	Univariate of factors associated with each complication (odds ratio, 95% confidential interval, P-value)	Multivariate of factors associated with each complication (odds ratio, 95% confidential interval, P-value)
Unsuccessful stent placement	2 (4.9%)	1 (2.8%)	0.64	NS[b]	
Cholangitis in 30 days	5 (12.2%)	1 (2.8%)	0.12	NS[b]	
Cholangitis at any time	7 (17.1%)	4 (11.1%)	0.46	-Female (OR 6.50, CI 1.53–44.88, $P=0.01$) -Balloon dilation (OR 5.00, CI 0.87–94.69, $P=0.07$)	-Female (OR 6.17, CI 1.42–43.11, $P=0.01$)
Endoscopically documented stent occlusion in 30 days	2 (4.9%)	1 (2.8%)	0.64	NS[b]	
Endoscopically documented stent occlusion at any time	6 (14.6%)	10 (27.8%)	0.16	NS[b]	
Pancreatitis	0	1 (2.8%)	0.28	NS[b]	
Bleeding	1 (2.4%)	0	0.35	NS[b]	
Migration	3 (7.3%)	0	0.10	NS[b]	
30-day mortality	6 (14.6%)	5 (13.9%)	0.93	-Pruritus at presentation (OR 5.36, CI 0.92–101.75, $P=0.06$) -Bacteremia prior to stent placement (OR 5.31, CI 0.94–27.05, $P=0.06$) -Karnofsky score <50 (OR 12.54, CI 2.17–237.87, $P=0.003$) -Distant metastasis (OR 5.57, CI 1.28–38.81, $P=0.02$) -Hemoglobin <12 g/dl at presentation (OR 4.80, CI 1.10–33.43, $P=0.04$) -INR ≥ 1.2 at presentation (OR 4.77, CI 1.20–23.83, $P=0.03$) -Cr ≥ 1.1 mg/dl at presentation (OR 4.30, CI 0.95–18.32, $P=0.06$)	-Pruritus at presentation (OR 25.40, CI 1.78–2392.85, $P=0.01$) -Bacteremia prior to stent placement (OR 26.51, CI 1.65–2090.72, $P=0.02$) -Karnofsky score <50 (OR 51.14, CI 2.65–25966.63, $P=0.004$)
Perforation	0	0	—	—	
Stent breakage	0	0	—	—	
Overall complications	12 (29.3%)	14 (38.9%)	0.37	-Bacteremia prior to stent placement (OR 13.12, CI 2.16–252.84, $P=0.003$) -INR ≥ 1.2 at presentation (OR 4.41, CI 1.68–12.16, $P=0.002$) -Biliary sphincterotomy performed (OR 0.43, CI 0.16–1.12, $P=0.08$)	-Bacteremia prior to stent placement (OR 12.21, CI 1.61–263, $P=0.01$) -INR ≥ 1.2 at presentation (OR 4.50, CI 1.61–13.28, $P=0.004$)

CI, confidence interval; Cr, creatinine; INR, international normalized ratio; OR, odds ratio.
[a]MFPS placed in 41 patients (77 procedures), and SEMS placed in 36 patients (43 procedures).
[b]No association between variables (type of stent, gender, age, year of procedure, comorbidities, nature of malignant strictures, presence of cholestatic symptoms, fever, abdominal pain, or bacteremia, Karnofsky score, tumor staging based on TNM system, Bismuth-Corlette classification type, laboratory results, numbers of sectoral ducts drained, presence of biliary sphincterotomy at the index biliary stenting at the University of Minnesota, balloon dilation, or radiofrequency ablation, presence of additional therapies including chemotherapy, radiation or surgery), and each of complication.

MFPS vs. 13.9% SEMS, $P = 0.93$). There was no perforation or stent breakage related to MFPS or SEMS placement. The overall rates of combined short-term and long-term complications were 29.3% in MFPS group vs. 38.9% in SEMS group ($P = 0.37$).

At univariate analyses, factors associated with higher prevalence of cholangitis were female sex and those received balloon dilation. On multivariate analysis, only female sex was associated with higher rate of cholangitis ($P = 0.01$). Those with pruritus, bacteremia, worse Karnofsky score, presence of distant metastasis, anemia, coagulopathy and elevated serum creatinine at presentation were associated with higher 30-day mortality rate. At multivariate analysis, presence of pruritus ($P = 0.01$), bacteremia ($P = 0.02$) and worse Karnofsky score ($P = 0.004$) at presentation were associated with higher 30-day mortality. At univariate analysis, those with bacteremia and coagulopathy at presentation, and those without biliary sphincterotomy were associated with higher overall complications. At multivariate analysis, bacteremia ($P = 0.01$) and coagulopathy ($P = 0.004$) at presentation were associated with higher adverse events.

DISCUSSION

Outcomes of endoscopic stenting for complex hilar tumors have been mixed, with technically failed drainage, clinical failure to relieve jaundice, and complications, particularly cholangitis.[6,16] To date there have been four studies comparing SEMS and plastic stents, of which three were randomized trials and one was a cohort study.[2,3,5,17] All four studies showed improved stent patency and numbers of re-interventions for patients treated with SEMS, but mixed results for complication rates. Recent meta-analyses concluded that performance of SEMS was superior to that of plastic stents in terms of higher success, longer stent patency, and perhaps longer survival.[9,18,19] However, there were differences in the definitions of outcomes and complications in prior studies and these yielded statistically significant heterogeneity.[9] In addition, all published studies used conventional plastic stents that were relatively short, rigid, and straight, ranging from 7 to 10 Fr, and from 10 to 15 cm length. These stent characteristics might explain in part why plastic stents have demonstrated worse performance compared to SEMS, and to the type of MFPS used in the current study.

Several studies have aimed to identify whether unilateral or bilateral—or more appropriately, single sector vs. dual sector biliary stenting, yielded better outcomes.[7–9,20–22] A recent study demonstrated improved drainage with less risk of cholangitis using MRCP and/or CT to target drainage of more than 50% of the liver volume.[11] This concept is fundamentally different than "unilateral" or "bilateral" stent placement, as there are highly variable patterns of junction of the right anterior, right posterior, and left sectoral ducts, and of segmental atrophy or tumor replacement, such that a single stent may sometimes relieve obstruction of more than 50% of the viable liver, while "bilateral" stents may not, especially when the left lobe is atrophic, as commonly seen in cholangiocarcinoma arising in the left lobe. Achieving $> 50\%$ viable liver volume drainage usually requires a single stent in

patients with Bismuth type I–II, and dual stent placement in patients with Bismuth type III-IV. The pilot study by Vienne *et al.* involved only use of conventional plastic stents, and no study has previously evaluated this hypothesis using SEMS or soft pliable plastic stents.[11]

A recent randomized trial using Pellethane (radiopague polyurethane material) straight, non-side hole conventional design stents in both benign and malignant hilar strictures demonstrated a significant difference in migration rate compared to conventional polyethylene stents. The observed advantage likely resulted from the increased pliability of the stent conforming to biliary anatomy, especially in the left hepatic duct. However, the study was not powered to evaluate stent patency.[12] Our current findings support the concept that stents made of pellethane, combined with extreme length, large caliber, and multiple sideholes, might be more effective than conventional plastic stents for palliation of malignant hilar strictures.

The current study shows that using an image-targeted strategy to place one or more open-cell SEMS or a novel approach of MFPS achieves very successful technical ($> 95\%$) and clinical ($> 75\%$) drainage. Outcomes were equally good for Bismuth III and IV tumors. As such, this is the first paper to validate the hypothesis that targeted sector drainage of complex hilar tumors aimed at decompressing $> 50\%$ of viable liver volume achieves satisfactory outcomes in such patients.

As there are no validated factors associated with survival, stent patency, or complications in patients undergoing endoscopic stenting for malignant hilar strictures, we collected comprehensive data to find associations with outcomes. Our analyses found no statistical difference in survival for patients treated with MFPS vs. SEMS group. Cox proportional regression analysis showed that patients with lower Karnofsky score and higher serum total bilirubin level, particularly ≥ 10 mg/dl at presentation had significantly worse survival. To our knowledge, neither of these variables has been previously reported to be associated with survival in patients with malignant hilar strictures. Although only 10 patients were treated with RFA, the trend of improved survival was appreciated at univariate analysis level, consistent with other recent reports.[23–25]

For stent patency, MFPS were associated with shorter stent patency by multivariate analysis, correlating with results from prior studies.[2,3,5,17] Stent patency might appear to be artificially shortened for plastic stents because of scheduled stent replacement every 2–3 months, done to reduce risk of cholangitis.[4,6] However, there are several hypotheses to explain shorter patency for plastic stents, including sludge, bacterial colonization forming biofilm, calcium bilirubinate, and calcium palmitate crystals.[26–28] In addition, reflux of duodenal content into the biliary tract may be a contributing factor, as prior studies have shown that positioning above the papilla/sphincter of Oddi may improve patency for both plastic and metallic prostheses.[29–32] In addition, those required surgical tumor debulking had shorter stent patency at multivariate analysis, perhaps due to inflammatory chemokines produced by the tumor.[33]

Prior studies have generally suggested that compared with SEMS, plastic stents were associated with higher rates of

adverse events and unplanned biliary drainage procedures.[3,5,9] Our study, using a novel approach of fenestrated flexible plastic stent with scheduled changes, suggested similar overall outcomes to SEMS, as long as >50% of viable liver drained. Based on this cohort, clinical data, rather than stent types, were strongly associated with 30-day mortality (presence of pruritus, bacteremia and worse Karnofsky score at presentation) and overall procedure-related complications (bacteremia and coagulopathy at presentation).

Our study has several limitations. The study is a retrospective study and includes heterogeneity of primary and secondary malignancies. Some associations should be interpreted cautiously, such as the effect of adjuvant therapies and relationships to AJCC TNM staging.[34,35] Finally, these data were based on a single center, limiting generalizability.

In conclusion, this study shows that in a relatively large cohort of patients treated at a tertiary center, endoscopic biliary drainage with MFPS and SEMS using a predefined targeting and selective sectoral access strategy resulted in highly effective (technical success >95% and clinical success >75%) and relatively safe palliation in patients with complex malignant hilar biliary strictures. These outcomes are in distinction to other studies of hilar tumor drainage. These results validate the concept of draining at least 50% of viable liver volume with multiple sector stents as needed and suggest that MFPS are a viable alternative to SEMS. Further studies including prospective and randomized fashion of various strategies and stents for drainage, and including therapies such as RFA would be valuable. We also encourage researchers to apply additional techniques that might be more accurate than measurements obtained by clinicians, advanced endoscopists and radiologists,[10,11] such as those obtained from analytic morphomics to aim at draining >50% of liver volume.[36]

CONFLICT OF INTEREST

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Malignant hilar strictures treated with open-cell self-expanding metal stents may have improved survival, stent patency and less adverse events compared to polyethylene plastic stents.

✓ Endoscopic stenting aiming at >50% of viable liver volume was associated with improved outcomes in those treated with polyethylene plastic stents.

WHAT IS NEW HERE

✓ A novel approach of long multifenestrated pliable polyurethane plastic stents have comparable survival and adverse events but worse stent patency compared to open-cell self-expanding metal stents.

✓ Karnofsky score and serum bilirubin level were associated with survival.

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Supplementary Information accompanies this paper on the Clinical and Translational Gastroenterology website (http://www.nature.com/ctg)