Benefit of endoscopic stenting for dominant strictures in patients with primary sclerosing cholangitis



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ABSTRACT

Background and study aims Dominant strictures (DS) occur in up to 60% of patients with primary sclerosing cholangitis (PSC). Data regarding the long-term effects of stenting vs. dilation remain limited. The aim of this study was to compare the two treatment modalities in terms of transplantation-free survival.

Patients and methods This single-center, retrospective study examined patients with PSC and DS treated endo-scopically with a minimum of 1 year follow-up. Patients were divided into two cohorts: 1) those who received dilation alone; and 2) those who received both dilation and stenting. The primary outcome was transplantation-free survival, defined as time after index ERCP to liver transplantation.

Results In all, 169 patients (54 in dilation cohort, 115 in stenting cohort) were included. The stenting cohort had a significantly higher Mayo PSC Risk Score $(1.8 \pm 1.1 \text{ vs}. 0.9 \pm 1.2)$ and presented with cholangitis more frequently (22.6% vs. 1.9%). During a follow-up period of 1198 person-years, 69 (40.8%) patients received transplantation at a mean of 3.4 (± 2.9) years. There was no difference in transplantation rate in the stenting cohort [68 (95% CI 5.2–8.8) per 100 person-years] compared to the dilation cohort [3.7 (95% CI 2.1–6.0) per 100 person-years] and no difference in risk for transplantation (dilation cohort adjusted hazards ratio 0.67, 95% CI 0.33–1.32).

Conclusions Despite a higher Mayo Risk Score in the stenting group, there was no difference in transplantation-free survival between patients managed with stenting vs. dilation alone. Stenting, therefore, may offer benefit in patients with advanced PSC and DS.

Introduction

Primary sclerosing cholangitis (PSC) represents a cholestatic disease process that results in inflammation and fibrosis within the biliary system [1]. This disease, if symptomatic, most commonly presents with hepatosplenomegaly, abdominal pain, pruritus, jaundice, or fatigue. Cholangitis and cirrhosis are life-

threatening complications of this disease and given the lack of adequate medical therapy for PSC, liver transplantation is often needed as definitive therapy for this disease [2]. The development of a dominant stricture (DS), a narrowing of an extrahepatic duct to <1.5 mm, or an intrahepatic duct <1 mm, is of particular concern in that not only does it occur in up to 60% of patients with PSC, but it is also associated with higher rates of cholangitis as well as cancer [1, 3–5].

The management of DS is primarily endoscopic via either balloon dilation or balloon dilation in addition to stenting [6]. Both methods have been demonstrated to result in clinical improvement as well as biochemical improvement [5, 7–11]. Balloon dilation has the advantage over stenting in terms of not requiring a second procedure for removal of a stent, but carries the disadvantage of potential early restenosis. Stenting carries a theoretical risk of cholangitis due to premature stent occlusion or possibly restricting drainage from smaller and strictured intrahepatic segments adjacent to the stent. The recent DILS-TENT trial directly compared balloon dilation and stenting with balloon dilation alone in PSC patients with DS, finding no difference between the two treatments in terms of DS recurrence within 2 years, although patients with cholangitis or severe PSC were excluded [12]. Despite this, stenting remains a common treatment option for symptomatic DS and this study aimed to compare balloon dilation alone with balloon dilation and stenting in symptomatic dominant PSC strictures in regard to transplant-free survival.

Patients and methods

Study design and population

This was a retrospective review of all patients with PSC who received an ERCP at our institution during the time period of January, 2006 to June, 2015.

Inclusion criteria included patients with PSC who had undergone ERCP at our institution and were found to have a DS. A DS was defined as a narrowing of an extrahepatic duct to <1.5 mm, and an intrahepatic duct to <1 mm. A minimum of one-year follow-up was required for inclusion in the study. All included patients were followed in the hepatology clinic, where clinical symptoms and improvement or worsening could be determined from electronic medical records. Exclusion criteria included patients who received percutaneous interventions prior to endoscopic therapy and those who developed recurrent PSC after liver transplantation. Furthermore, patients found during index ERCP to have a malignant stricture were excluded. The stenting cohort included patients treated with both dilation and stent placement. The dilation cohort consisted of patients who were treated with dilation alone. Patients were referred for liver transplantation once their Model for End-Stage Liver Disease (MELD) score was ≥ 15, they developed recurrent or refractory cholangitis, and/or developed intractable pruritus.

Study variables

Demographic information collected included age, gender, and disease duration. Laboratory information included liver function tests just prior to and one month after the intervention. Laboratory data prior to the index ERCP was used to calculate the Mayo PSC Risk Score, a risk stratification system that predicts the risk of death in PSC patients, and a MELD score if cirrhosis was present [13, 14]. The Mayo PSC Risk Score incorporates the patient's age, total bilirubin level, serum albumin level, serum aspartate aminotransferase (AST) level, and variceal bleed-

ing history with each unit increase on the score translating to a 2.5-fold increase in the risk of death. Transplantation data was also collected to ascertain the time to transplantation after index ERCP. Adverse events from the endoscopic interventions were also documented.

Endoscopic dilation and stenting

Once a DS was identified on cholangiography, a sphincterotomy was typically performed prior to dilation or stenting. While the decision to dilate alone or place a stent in addition to dilating was made per the discretion of the endoscopist, dilation alone was typically performed when the fluoroscopically-visible "waist" at the stricture resolved with dilation and contrast upstream of the stenosis easily drained. Stenting was typically performed for patients presenting with jaundice and when a persistent waist was seen during balloon dilation and balloon sweeping was met with resistance even after dilation. For dilation, strictures were dilated up to the diameter of the upstream duct or smaller (4-10 mm) utilizing fixed-size polyethylene balloons (Hurricane RX, Boston Scientific, Malborough, Massachusetts, United States). Balloon sweeping was performed to remove any debris, sludge, or stones in each case. For stenting, after balloon dilation was performed, a 7, 8.5, or 10Fr plastic stent was placed. Stents were exchanged or removed at 8week intervals at the discretion of the endoscopist or if ensuing cholangitis symptoms necessitated earlier intervention.

Statistical analysis

The primary outcome was liver transplantation-free survival, defined as time from ERCP to receipt of transplantation. Secondary outcomes included clinical success (defined as improvement in symptoms and liver function tests), development of cholangitis, and adverse events (AE)s. A Cox proportional hazards model was used to assess the risk of transplantation. Variables significant at P<0.05 on univariate analysis were included in a multivariate model. Continuous variables were compared between the two treatment groups utilizing a two-tailed t test. A chi square test was used for comparison of categorical variables. All statistical analysis was performed using STATA 15.1 (StataCorp, College Station, Texas, United States). P<0.05 was considered to be statistically significant.

Results

A total of 188 patients with PSC were initially screened for inclusion in this study (**> Fig. 1**). Of these, 17 patients did not have the minimum follow-up period of at least 1 year and two patients received percutaneous biliary drainage as initial therapy, leading to their exclusion from the study. A total of 169 patients were included in the final analysis, of which 115 received both balloon dilation and stenting and 54 received balloon dilation alone.

Baseline characteristics

There were no significant baseline differences between the two cohorts in terms of demographic variables including age, gender, stricture location, follow-up period, and disease duration



(**> Table 1**). There was however a significant difference between the two cohorts in terms of their Mayo PSC Risk Score with the dilation and stenting cohort exhibiting a significantly higher PSC Risk Score, both in terms of raw value (stenting and dilation: 1.8 ± 1.1 vs. dilation alone: 0.93 ± 1.2 , P < 0.001) and risk stratification. The proportion of patients with cirrhosis was similar in both cohorts, and there was no difference in MELD scores. A significantly higher proportion of patients in the dilation and stenting cohort presented with cholangitis (22.6% vs. 1.9%).

Liver transplantation-free survival

During a follow-up period of 1198 person-years (mean of 6.4 years, SD 3.7) after index ERCP, a total of 69 patients (40.8%) received liver transplantation at a mean of 3.4 (SD 2.9) years. In the stenting and dilation cohort, 54 (46.9%) underwent transplantation and in the dilation alone cohort, 15 (27.8%) un-

Table 1 Baseline comparison of dilation alone cohort with stenting and dilation cohort.

Variable	Dilation (n=54)	Stenting and Dilation (n=115)	P value	
Age (years)	44.8±15.7	48.1±15.3	0.21	
Sex	66.1 % male (n = 76)	74.1% male (n = 40)	0.29	
Indication			< 0.001	
LFT elevation	42.5% (n=23)	38.2% (n=44)		
 Jaundice 	11.1% (n=6)	24.4% (n=27)		
Recurrent cholangitis	1.9% (n=1)	22.6% (n=26)		
 Abnormal imaging 	38.9% (n=21)	14.8 % (n = 17)		
Abdominal pain	3.7% (n=2)	3.5% (n=4)		
Pruritus	1.9% (n = 1)	3.5% (n=4)		
Dominant stricture location				
Common bile duct	27.8% (n=15)	38.3% (n=44)		
Common hepatic duct	22.2% (n=12)	31.3% (n=36)		
Right hepatic duct	14.8% (n=8)	6.1% (n=7)		
Left hepatic duct	18.5% (n=10)	14.8% (n=17)		
Multifocal	16.7% (n=9)	9.6% (n = 11)		
Follow-up period from index ERCP (years)	6.3±3.6	6.4±3.7	0.91	
Mayo PSC Risk Score	0.93±1.2	1.80±1.1	< 0.001	
Mayo PSC Risk Score risk group			< 0.004	
- Low	24.0% (n = 13)	14.8 % (n = 17)		
Intermediate	59.3% (n=32)	42.6% (n=49)		
High	16.7% (n=9)	42.6% (n=49)		
Cirrhosis	51.9% (n = 28)	62.6% (n = 72)	0.19	
MELD score	13.9±7.3	15.8±7.5	0.25	
Disease duration (at time of index ERCP)	5.1±5.1	4.8 ± 6.0	0.71	

LFT, liver function test; ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis; MELD, Model for End-Stage Liver Disease.

Variable	Univariate hazard ratio (95% CI)	P value	Multivariate hazard ratio (95% CI)	P value
Age	0.97 (0.95-0.99)	0.002	0.97 (0.95–0.99)	0.004
Male sex	1.52 (0.85–2.69)	0.16		
Disease duration	1.02 (0.98–1.06)	0.3		
MELD score	1.07 (1.03–1.11)	< 0.001	1.06 (1.0–1.11)	0.04
Mayo PSC Risk Score	1.47 (1.15–1.87)	0.002	1.17 (0.81–1.68)	0.40
Dilation alone	0.48 (0.26-0.87)	0.02	0.67 (0.33–1.32)	0.25

Table 2 Cox proportional hazards ratios for risk of liver transplantation

MELD, Model for End-Stage Liver Disease; PSC, primary sclerosing cholangitis.

derwent transplantation. The overall transplantation rate was 5.8 (95% CI: 4.5–7.2) per 100 person-years with a transplantation rate of 68 (95% CI: 5.2–8.8) per 100 person-years in the stenting and dilation cohort and 3.7 (95% CI: 2.1–6.0) per 100 person-years in the dilation alone cohort. There was also no significant difference in time to transplantation between the two cohorts (3.4 years in stenting and dilation cohort vs. 3.3 years in dilation alone cohort) in those who received transplantation.

Multivariate analysis (► Table 2) revealed that there was no difference in the risk of liver transplantation between the stenting and dilation cohort compared to the dilation alone cohort (dilation arm adjusted hazard ratio [aHR]: 0.67 [95% CI: 0.33–1.32]) (► Fig. 2). Increasing MELD score in patients with cirrhosis had a slightly higher risk of transplantation (aHR: 1.06, 95% CI: 1.0–1.11) and increasing age was associated with a slightly lower risk of transplantation (aHR: 0.97, 95% CI: 0.95–0.99).

Secondary outcomes

The stenting and dilation cohort had a significantly greater improvement $(2.5 \pm 3.9 \text{ mg/dL})$ in bilirubin levels one month after the procedure (**► Table 3**) compared to the dilation alone cohort (0.8 ± 2.5) . At 1 month post-procedure, clinical success was equivalent between the two cohorts (92.2%) in the stenting and dilation cohort vs. 96.3% in the dilation alone cohort). Stricture recurrence occurred in 7.3% (n=9) of patients in the stenting and dilation cohort compared to 3.1% of patients in the dilation alone cohort. (14.8\%) patients in the stenting and dilation cohort alone cohort.

In the stenting and dilation cohort, the most commonly used stent size was 10 Fr and patients received an average of 1.3 stents during their index ERCP (**Supplementary Table 1**). Stents stayed in for 52.5 days on average before removal and each patient had a mean of 6.5 ERCP procedures, which was significantly more than the mean number of ERCP procedures (3.1) in the dilation group. The rate of cholangitis or number of ERCPs were not associated with the number of stents or stent diameter.



Fig. 2 Transplantation-free survival curves.

Adverse events

The stenting and dilation arm had a significantly higher rate of AEs (33.1%) compared to the dilation alone cohort with stent occlusion resulting in cholangitis (21.8%) representing the vast majority of AEs in the stenting cohort (**> Table 3**). There was no difference in post-ERCP pancreatitis between the two cohorts (8.1% in stenting and dilation cohort vs. 9.4% in dilation alone cohort).

Discussion

Endoscopic dilation and stenting remain the most common treatment options for DS in patients with PSC and while a recent randomized trial between the two modalities did not reveal any differences in stricture recurrence rates, ambiguity remains in the optimal management of patients with severe PSC and acute episodes of cholangitis [12]. In our large retrospective study with long-term follow-up, there was no difference in transplantation-free survival between patients treated with PSC stenting and dilation vs. dilation alone despite the stenting cohort having patients with more severe PSC as characterized by higher Mayo PSC Risk Scores. Clinical improvement was equivalent between the two therapies suggesting that stenting can **Table 3** Comparison of procedural outcomes between dilation alone group and dilation with stenting group.

Variable	Dilation (n=54)	Stenting and dilation (n=115)	P value
Initial bilirubin (mg/dL)	3.5±5.7	4.9±5.7	0.13
Bilirubin 1 month after endoscopic treatment (mg/dL)	2.6±4.6	2.4±2.9	0.75
Change in bilirubin (mg/dL)	0.8±2.5	2.5±3.9	< 0.005
Initial alkaline phosphatase (IU/L)	260.8±198.1	405.6±293.9	< 0.001
Alkaline phosphatase 1 month after endoscopic treatment (IU/L)	222.1 ±161.9	339.6±216.7	< 0.0005
Change in alkaline phosphatase (IU/L)	38.8±125.5	66.0±212.2	0.38
Clinical improvement	96.3% (n=52)	92.2% (n = 106)	0.24
Number of ERCPs during follow-up period	3.1 ± 2.7 (n = 167)	6.5±5.9 (n=748)	< 0.001
Adverse events	17.5% (n = 11)	33.1% (n=41)	0.02
Cholangitis	5.6% (n=3)	23.5% (n=27)	
Pancreatitis	11.1% (n=6)	8.7 % (n = 10)	
Guidewire perforation	3.7% (n=2)	1.7% (n=2)	
Bleeding	0 % (n = 0)	0.9% (n = 1)	

ERCP, endoscopic retrograde cholangiopancreatography.

still play a role in the management of patients with DS, particularly in those with more severe disease.

Endoscopic stenting represents a standard approach in the management of biliary strictures and in benign strictures, stents are often exchanged every 3 months until stricture resolution [15]. Current European guidelines, however, recommend removal of stents 1–2 weeks after insertion in the treatment of DS due to the concern for rapid stent occlusion in PSC patients, although few studies have compared stenting durations [6]. In accordance with these recommendations, in the DILSTENT trial, after placement of a single 10Fr plastic stent, the stent was removed 7 to14 days after the procedure with a median recurrence-free rate of 34 weeks [12]. In our study, stents were removed after a mean of 52.5 days, which represents a substantially longer time period than the aforementioned study. Similarly, van Milligen de Wit et al examined stent removal after 2 to 3 months, finding a significant improvement in liver function tests [11]. Premature stent occlusion remains the primary concern with longer stent duration, and in our study, stent occlusion leading to cholangitis occurred in 23.5% of patients at a mean of 50.7 days. This is consistent with the 30% stent occlusion rate see in the aforementioned study by van Milligen de Wit et al, suggesting that further studies are needed to determine the optimal stent duration that leads to effective stricture resolution, but also avoids premature stent occlusion [11]. In our study, stenting was preferentially chosen over dilation alone in patients where balloon dilation alone was believed to be inadequate for biliary drainage, which mirrors the stenting practices described in prior studies reporting endotherapy success in PSC patients [5, 7]. This scenario is often seen in patients presenting with cholangitis, which were seen more frequently in our stenting cohort, but were excluded from the DILSTENT study. Thus, our study may offer applicability to real-world

practice where endoscopists often choose to stent when adequate biliary drainage is required.

Despite the potential AE of premature stent occlusion, endoscopic stenting was associated with similar transplantation-free survival to performing dilation alone in our study population despite the greater proportion of patients with more advanced disease in the stenting cohort. The DILSTENT trial did not include patients with advanced disease (Mayo PSC Risk Score>2) and in a retrospective study with long-term follow-up, Rupp et al compared transplantation-free survival in patients with PSC and DS who received scheduled yearly endoscopic evaluations with those who received endoscopic therapy based on clinical need (i.e. cholangitis, jaundice) [12, 16]. Endoscopic therapy consisted of balloon dilation alone, and they found that scheduled ERCPs were associated with a higher rate of transplantation-free survival with liver transplantation performed in nearly 30% of their cohort. In comparison to this study, our overall cohort had significantly higher Mayo PSC Risk Scores, suggesting a study population with more advanced PSC, particularly in the stenting cohort (Mayo PSC Risk Score mean of 1.8, compared to mean of -0.3 in the Rupp et al cohort), which may help explain the higher liver transplantation rates in our study in addition to the growing utilization of living donor liver transplantation at our center. Thus, in patients with advanced PSC and DS, endoscopic stenting may offer an effective treatment method and our study is one of few studies to provide long-term transplantation-free survival data after endoscopic stenting for treatment of DS.

The drawbacks of endoscopic stenting must be weighed against its potential benefits in this population. As mentioned previously, stent placement carries the risk of premature stent occlusion, which accounted for the vast majority of AEs in the stenting cohort. While it was our preference to keep stents in

for 2 months, patients should be cautioned regarding the risk of premature occlusion, emphasizing the need for patients to be mindful of the development of new symptoms. Furthermore, endoscopic stenting necessitates more procedures as ERCPs are required even for stent removal. This is reflected in the doubling of mean procedures seen in the stenting cohort compared to the dilation cohort. The need for more procedures certainly increases costs and healthcare burden and cost-effectiveness analyses are needed to ascertain the financial impact of endoscopic stenting. One consideration to combat early stent occlusion and reduce the number of procedures would be placement of a fully covered metal stent for patients with an extrahepatic DS. A recent study examined treatment with a metal stent for 3 months in these patients, finding this to be safe and effective with only one case (5%) of premature occlusion [17]. Caution is warranted, however, with the use of fully covered stents given that patients with PSC often have narrow ducts that may not accommodate the commonly available 8- and 10-mm diameter metal stents and are prone to developing stent-associated strictures due to their reactive nature.

Several limitations of this study merit further discussion. The single-center retrospective design inherently limits the generalizability of the results of our study. With its retrospective nature, treatments were not inherently equal as stenting would necessitate repeat procedures, during which further treatment could be offered. Additionally, as subjects were not randomized to the two treatments, selection bias remains a distinct possibility as seen in the sicker patient cohort who received stenting. Furthermore, the type of stent and duration of stenting was left to the discretion of the endoscopist with no standardized protocol, making it difficult to ascertain the optimal mode of stenting. Lastly, tertiary referral bias remains a possibility given our active liver transplant program and incorporation of living donor liver transplantation, which can further decrease the generalizability of these results.

Conclusions

In summary, we found that while endoscopic stenting did not offer an advantage over dilation alone in terms of transplantation-free survival, the cohort of patients who received endoscopic stenting had significantly more advanced disease than the cohort of patients treated with dilation alone. The primary limitations of endoscopic stenting appear to include the need for repeat procedures and premature stent occlusion which may be related to long indwelling stent durations. Thus, despite evidence from a recent randomized trial suggesting that stenting offers no benefit over dilation in the management of DS in patients with PSC, our study suggests that endoscopic stenting may aid in the management of patients with advanced PSC, equalizing transplant-free survival time in these patients to those with less severe disease.

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Competing interests

The authors declare that they have no conflict of interest.