Common controversies in management of biliary strictures

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Abstract

Biliary strictures are caused by a heterogeneous group of benign and malignant conditions, each requiring a specific treatment approach. Management of biliary strictures often involves endoscopy either for definite treatment, as a bridge to surgery or for palliative purposes. Endoscopic treatment of various types of biliary strictures is not standardized and there are multiple areas of controversy regarding the best treatment options. These controversies are mainly due to lack of well-designed comparative studies to support a specific therapy. This paper reviews three common areas of controversy in the endoscopic management of biliary strictures. The areas discussed in this editorial include the role of biliary drainage in resectable malignant strictures and whether such drainage should be performed routinely prior to surgery, the best endoscopic palliation for unresectable hilar strictures and whether unilateral or bilateral stenting should be attempted, and the optimal endoscopic management for dominant strictures in patients with primary sclerosing cholangitis. The goal of this editorial is twofold. The first is to review the current literature on management of the aforementioned strictures and offer recommendations based on available evidence. The second goal is to highlight the gaps in our knowledge which in turn can encourage future research on these topics.

Key words: Biliary stricture; Benign; Primary sclerosing cholangitis; Malignant; Controversy; Biliary drainage; Preoperative; Hilar stricture

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Core tip: Based on available evidence preoperative biliary drainage is not routinely indicated in resectable malignant strictures. However, it is appropriate in acute cholangitis, in severely symptomatic patients and in those with delayed surgery. In patients with unresectable hilar stricture, cross-sectional imaging is advised prior to attempt at palliative drainage. In such patients unilateral stenting during endoscopic retrograde cholangiopancreatography is adequate in most cases. Routine stenting of dominant strictures in primary sclerosing cholangitis patients is not recommended. Stenting of dominant strictures is appropriate...
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INTRODUCTION

Preoperative biliary drainage in resectable malignant strictures

The rationale behind preoperative biliary drainage is the belief that cholestasis is associated with higher postoperative morbidity and mortality and that preoperative biliary drainage may improve surgical outcomes by improving the liver synthetic function, increasing clearance of endotoxins and improving the gastrointestinal mucosal barrier function which in turn may reduce the risk of bacterial translocation[1]. Increased risk of surgery in jaundiced patients has been suggested for decades. In fact, the first report of preoperative biliary drainage has been attributed to Allen Whipple who in 1935 described performance of cholecystogastrostomy to relieve jaundice prior to pancreatoduodenectomy for treatment of peripancreatic cancers[2]. The issue of preoperative biliary drainage, however, has remained controversial.

Preoperative drainage in distal biliary strictures

In an attempt to shed some light on the role of preoperative drainage for distal biliary strictures, a clinical trial randomized patients with pancreatic head cancer and obstructive jaundice with bilirubin levels between 2.3-14.6 mg/dL to preoperative biliary drainage or early surgery. The preoperative biliary drainage group underwent endoscopic retrograde cholangiopancreatography (ERCP) with plastic stent placement followed by surgery 4-6 wk later. The early surgery group had surgery within a week of randomization. The investigators compared serious adverse events between the two groups within 120 d of randomization. In all, 102 patients were randomized to preoperative biliary drainage while 94 patients were randomized to early surgery. The early surgery group had a total of 520 patients, of whom 265 had received preoperative biliary drainage and 255 did not. The meta-analysis showed that although there were no differences in mortality rate or hospital length of stay, preoperative biliary drainage was associated with significantly higher morbidity[3].

Recommendations for preoperative drainage in distal biliary strictures: Based on available evidence preoperative biliary drainage is not routinely indicated in patients with resectable distal strictures[4]. However, preoperative biliary drainage is appropriate in patients with acute cholangitis, those who are severely symptomatic and also those who have delayed surgery either because of logistical issues or need for neo-adjuvant therapy. If preoperative biliary drainage is to be performed, metallic stents are preferable to plastic stents. Both covered and uncovered metallic stents can be used in this setting. If uncovered metallic stents are to be used, shortest possible stent length should be utilized in order to prevent interference with surgery.

Preoperative biliary drainage in hilar strictures

There are no randomized controlled trials assessing the role of preoperative biliary drainage in hilar strictures. There are, however, multiple retrospective studies available[11-15]. With the exception of one study which suggested a decreased incidence of intra-abdominal

higher than expected stent-related complications[4-6]. Some experts argued that if the study investigators had used metallic rather plastic stents, the stent-related complications would have been lower, possibly leading to different study results[7].

The investigators therefore conducted a follow up study in which patients with pancreatic cancer and obstructive jaundice who could not undergo early surgery were assigned to undergo ERCP with metallic stent placement[8]. The observed outcomes in these patients were compared to the patients in the original study[3,8]. Comparison of the patients who received plastic stent with those who received metallic stent showed that the drainage-related complications were significantly lower in the metallic stent group mostly because of a significant decrease in the stent-related complications[9]. However, when the study investigators compared the metallic stent group with early surgery group, the early surgery group still had significantly less serious complications. The authors concluded that early surgery is preferable to preoperative biliary drainage independent of the type of the stent used[9].
abscess formation\[14\], other studies have shown a deleterious effect associated with preoperative biliary drainage in the form of increased rates of postoperative infections or increased length of hospital stay\[11-13,15\]. None of the studies showed any survival benefit associated with preoperative biliary drainage\[11-15\]. A systematic review and meta-analysis of studies up to 2010 showed no clinical benefit associated with preoperative biliary drainage in patients with hilar stricture and suggested that preoperative biliary drainage in such strictures may increase postoperative adverse events and infectious complications\[16\].

**Recommendations for preoperative biliary drainage in hilar strictures:** Based on available evidence preoperative biliary drainage is not recommended routinely in patients with malignant hilar stricture. Preoperative biliary drainage, however, is appropriate in patients with acute cholangitis, those who require neo-adjuvant therapy and those who have hyperbilirubinemia induced malnutrition, hepatic insufficiency or renal insufficiency\[17\]. Severely symptomatic patients and those with delays in surgery should also be considered for preoperative biliary drainage.

**PALLIATION OF UNRESECTABLE HILAR STRICTURES**

Regardless of histology less than 30% of malignant hilar strictures are suitable for curative resection. Palliation is therefore needed in the majority of patients and biliary drainage is a major component of palliation in such patients. Whether biliary drainage for palliation of unresectable hilar strictures is best achieved by unilateral or bilateral stenting remains a controversial issue. Two randomized controlled trials have assessed unilateral versus bilateral drainage for palliation of hilar strictures\[18,19\].

In the first trial, 157 patients with hilar strictures were randomized to ERCP with unilateral plastic stent placement (79 patients) or ERCP with bilateral plastic stent placement (78 patients). Technical success was significantly higher in patients with unilateral stent placement\[18\]. Complications including infectious complications were significantly lower in patients with unilateral stent placement. Drainage success, defined as at least 75% reduction in pre-procedure bilirubin levels, were significantly higher in patients with unilateral stent placement compared to those who had bilateral stenting\[18\]. Survival did not differ between the two groups. The investigators of the study, therefore, concluded that routine bilateral stenting is not advised\[18\].

The second trial included 60 patients with hilar strictures who were randomized to ERCP with plastic stent placement (30 patients) or ERCP with metallic stent placement (30 patients)\[19\]. Within each group approximately half of the patient’s received unilateral while the other half received bilateral stenting. Although the main goal of the study was to compare metallic with plastic stents, subgroup analysis of unilateral versus bilateral stenting were performed. This study did not show any difference in patency time between unilateral versus bilateral stenting\[19\]. Re-intervention success, however, was significantly higher in patients with unilateral stent placement compared to those who had bilateral stenting\[19\]. The study also showed that metallic stents had longer patency time and less need for re-intervention compared to plastic stents\[19\].

One prospective and multiple retrospective studies have also looked at this topic\[20-24\]. Although none of the studies showed any survival benefit with unilateral or bilateral stenting, they showed mixed results in other areas. A study by Chang et al\[20\] utilizing plastic stents showed that survival is worse if the ducts in both liver lobes are injected during ERCP but only one lobe drained. A small prospective study by Freeman et al\[21\] utilizing metallic stents showed that unilateral stenting is adequate in most patients. A retrospective study by Naitoh et al\[22\] utilizing metallic stents suggested longer patency time with bilateral stenting although survival time and complication rates were the same as with unilateral stenting. A retrospective study by Iwano et al\[23\] utilizing metallic stents showed that unilateral stenting is associated with lower infection rates but the same survival and stent patency compared to bilateral stenting. A retrospective study using both metallic stents and plastic stents by Liberato et al\[24\] suggested that bilateral stenting is associated with longer stent patency time without affecting survival time. Metallic stents in that study had longer patency time than plastic stents\[24\].

A French retrospective study suggested that drainage of more than 50% of liver volume confers longer survival\[25\]. It also suggested that injection of contrast during ERCP and stenting of an atrophic lobe in the liver is associated with higher complication rates. That study suggested that preprocedural cross-sectional imaging would be of value to avoid stenting or injecting an atrophic lobe during ERCP\[25\].

A recent meta-analysis, including 7 studies with 634 patients, did not find any difference in mortality, stent occlusion rate or cholangitis rate between those who had unilateral versus bilateral stenting for palliation of malignant hilar strictures\[26\]. The meta-analysis concluded that there are no benefits to routine bilateral stenting for palliation of unresectable hilar strictures\[26\].

**Recommendations for endoscopic palliation of unresectable hilar strictures**

A cross-sectional imaging study such as CT or MRI is advised prior to attempt at palliative drainage of unresectable malignant hilar strictures as a roadmap to better define the biliary anatomy and avoid injecting
or stenting an atrophic liver lobe. Unilateral stenting during ERCP in such patients seems to be adequate in most cases. Bilateral injection of contrast, however, requires bilateral stenting to assure drainage. For palliation of hilar strictures, metallic stents seem to have longer patency and require less re-intervention that plastic stents.

**MANAGEMENT OF DOMINANT STRICTURES IN PRIMARY SCLerosING CHOLANGITIS**

Primary sclerosing cholangitis (PSC) is a chronic progressive disease that can affect both intrahepatic and extrahepatic bile ducts. According to epidemiologic studies, intrahepatic and extrahepatic bile duct involvement are seen in approximately 69% of the patients while involvement of only intrahepatic or only extrahepatic ducts are seen in 25% and 4% of the patients respectively. Endoscopic therapy in the form of ERCP is effective in patients with strictures localized to the extrahepatic and large intrahepatic bile ducts, described as dominant strictures. On cholangiography, dominant strictures are defined as stenoses measuring < 1.5 mm in the common bile duct or < 1.0 mm in the hepatic ducts. Between 45%-58% of patients with PSC develop dominant biliary strictures during their course of disease. In addition to cholangiocarcinoma, dominant strictures have been associated with increased risk of ascending cholangitis, stone formation and hepatic decompensation. Treatment of dominant strictures is therefore recommended.

Endoscopy for treatment of dominant strictures is the preferred mode of therapy and multiple observational studies have shown that endoscopic treatment of dominant strictures not only leads to clinical improvement but also can lead to biochemical and radiological improvements. Endoscopic approaches to treatment of dominant strictures include ERCP with stent placement, balloon dilatation or both. The optimal endoscopic approach to treatment of dominant strictures in patients with PSC, however, is not known. There are no randomized controlled studies assessing effectiveness of balloon dilatation vs stenting in patients with PSC and dominant stricture. There are, however, a few retrospective studies available. In a retrospective study 34 patients were treated with only balloon dilatation, while 37 patients had balloon dilatation and stenting of dominant strictures. During a median follow-up of 24 mo, there were 30 complications associated with balloon dilatation plus stenting compared to 6 complications in the group who had balloon dilatation only. Postprocedure cholangitis rates were significantly higher in patients who had stenting compared to those who had only balloon dilatation.

In another retrospective study 64 ERCP procedures were performed in 30 patients with PSC associated dominant stricture. Thirteen of those ERCP procedures were performed with only balloon dilatation and 51 with stenting. Although the difference in the rate of complications between the groups who had dilatation versus dose who had stenting did not reach statistical significance, percentagewise there were twice as many complications with stenting compared to dilatation. It is likely that statistical significance could not be reached due to low number of patients. Two other retrospective studies have compared balloon dilatation with stenting in patients with PSC related dominant strictures. In a retrospective study involving 75 patients, the investigators reported that stenting was not associated with an increased risk of adverse events. On the other hand, another retrospective study including 72 patients found that even short-term stenting was associated with higher likelihood of adverse events.

**Recommendations for endoscopic treatment of dominant strictures in PSC**

Based on the available evidence ERCP with balloon dilatation is effective in most patients with PSC and dominant stricture. Routine stenting of dominant strictures in PSC patients is not recommended. Stenting of dominant strictures is appropriate if there is poor drainage of contrast after dilatation and concern for collapse of the bile duct comprising biliary drainage. If stenting is performed, short-term stenting should be considered. These recommendations are in line with the American College of Gastroenterology clinical guidelines.

**CONCLUSION**

Preoperative biliary drainage in patients with resectable malignancies has been a controversial issue for many years. Based on current evidence preoperative biliary drainage is not routinely indicated. However, it is appropriate in patients who suffer from acute cholangitis, are severely symptomatic or in cases of delayed surgery. Another point of controversy has been whether unilateral or bilateral stenting would offer the best palliation for patients with unresectable hilar strictures. In such patients unilateral stenting during ERCP seems to provide adequate palliation in most cases while maintaining minimal risk.

Finally, the best management strategy for endoscopic treatment of dominant strictures in PSC patients remains unknown. Based on currently available evidence routine stenting of such strictures is not recommended. However; stenting of dominant strictures may become necessary if there is poor drainage of contrast after dilatation or concern for collapse of the bile duct compromising biliary drainage.
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