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REVIEW

Endoscopic palliation of malignant biliary strictures

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Abstract

Malignant biliary strictures often present late after the window for curative resection has elapsed. In such patients, the goal of therapy is typically focused on palliation. While historically, palliative measures were performed surgically, the advent of endoscopic intervention offers minimally invasive options to provide relief of symptoms, improve quality of life, and in some cases, increase survival of these patients. Some of these therapies, such as endoscopic biliary decompression, have become mainstays of treatment for decades, whereas newer modalities, including radiofrequency ablation, and photodynamic therapy offer additional options for patients with incurable biliary malignancies.

Key words: Biliary strictures; Malignant; Endoscopic retrograde cholangiopancreatography; Photodynamic therapy; Endoscopy; Palliation; Endoscopic ultrasound; Radiofrequency ablation

Core tip: Palliative therapies for malignant biliary strictures are crucial for a disease that so often presents with surgical ineligibility. In this paper, we highlight both the established and more novel endoscopic palliative approaches for these types of strictures. Perhaps the most established of these therapies is endoscopic biliary deprecompression *via* endoscopic retrograde cholangiopancreatography (ERCP), which is notably approached differently in extrahepatic and intrahepatic strictures. In cases where traditional ERCP fails or is not feasible, endoscopic ultrasound-guided biliary drainage has quickly become the second-line intervention. Finally, we end by discussing the literature behind more novel therapies, namely intraductal radiofrequency ablation and photodynamic therapy.

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INTRODUCTION

Biliary strictures should be considered in any patient presenting with clinical signs such as jaundice, pale stool, dark urine and pruritus. Once confirmed, a crucial step in the work-up includes differentiating between malignant and benign etiologies. Historically, this has been a challenge since as many of 15%-30% of such cases are eventually determined to be benign inflammatory processes after histologic assessment[1,2]. Generally, the most common etiologies of malignant strictures include pancreatic adenocarcinoma (especially if located in the distal common bile duct) or cholangiocarcinoma (if in the mid- or proximal extrahepatic bile duct), although metastatic disease, ampullary neoplasia, gall bladder malignancy, hepatocellular carcinoma, and malignant periportal lymph nodes are all possibilities[3].

Pancreatic adenocarcinoma and cholangiocarcinoma typically present late in the course of the disease, with the vast majority of patients ineligible for curative resection[4], resulting in 5-year survival rates of under 5%[5,6]. The role of endoscopy in these patients has expanded from a diagnostic tool to a therapeutic one, providing palliation that allows for improved quality of life at faster rates and lower cost than surgical methods[6,7]. Endoscopic interventions for patients with malignant biliary strictures, includes endoscopic biliary drainage, intraductal radiofrequency ablation (RFA), and photodynamic therapy for cholangiocarcinoma.

A-ENDOSCOPIC BILIARY DECOMPRESSION

Extrahepatic biliary obstruction

While preoperative biliary drainage for malignant biliary strictures *via* endoscopic retrograde cholangiopancreatography (ERCP) remains controversial for surgically-eligible patients[8], endoscopic stenting has become the gold standard for palliative biliary obstruction in non-surgical candidates. In this method, stents are placed at the site of obstruction *via* endoscope, allowing for minimally invasive relief of obstructive symptoms. Other, non-endoscopic options for palliative therapy include percutaneous transhepatic stenting of the biliary tree and surgical bypass. Early studies comparing endoscopic palliation to surgical bypass in patients with malignant strictures found that endoscopic intervention was superior to surgical bypass in terms of survival procedure-related mortality and complications[9], survival (19 mo *vs* 16.5 mo[10]), and total lifetime cost. Similarly, a randomized trial of 75 patients with malignant obstructive jaundice endoscopic palliation demonstrated that endoscopic stenting had significantly higher success in relieving jaundice while also boasting a lower 30-d mortality due to fewer liver-associated complications[11].

A meta-analysis, which included 24 studies and over 2400 patients, found that, compared to surgical bypass, endoscopic intervention with plastic stents had similar rates of technical and therapeutic success, as well as improvement in quality of life[7].

Additionally, while endoscopic stenting with plastic stents had a lower risk of complications than surgical bypass, endoscopic intervention was, notably, also associated with a higher risk of recurrent biliary obstruction at 4 mo. Interestingly, given the recent increase in the use of metal (as opposed to plastic) stents in endoscopic palliation, assessing the comparative effectiveness of surgical *vs* endoscopic methods for palliative biliary obstruction becomes notably more difficult due to a paucity of available data. One small RCT (n = 30) that examined this comparison found no difference in complication rates, readmissions, or survival. However, those patients who received endoscopic therapy demonstrated better quality of life scores at roughly half the cost of surgical intervention[12] suggesting a cost-effectiveness benefit to the utilization of endoscopic, as opposed to surgical, interventions. Nevertheless, ERCP has, over the past two decades, become the first line therapy for those ineligible for curative resection.

ERCP maintains biliary patency through stenting, options for which are continually evolving[13]. Compared with plastic stents, self-expanding metal stents (SEMSs) have demonstrated significantly lower rates of migration and reocclusion[7,14-17], an advantage mechanistically attributed to a wider stent diameter. However, the cost of SEMSs exceed that of plastic stents by order of magnitude[18]. Therefore, the general consensus is that metal stents should be considered for patients with an estimated survival greater than 4-6 mo to maintain cost-effectiveness[16,19,20].

SEMSs can be made of steel, nitinol or platinol and can be uncovered, partially covered, or fully covered. Covered stents have been manufactured with a coating designed to improve removability and prevent occlusion from tumor ingrowth or tissue hyperplasia[21], however this theoretical advantage has not always been apparent from a clinical standpoint[22,23] and until now the data of whether to use covered or uncovered metal stents in malignant disease is mixed among randomized controlled trials[24-28] and even among metanalyses[29-31]. Underlying the inability powers those studies adequately. A recent study demonstrated longer patency of covered stent *vs* uncovered with the initial cost of the covered stent compensated by the benefit provide in patency.

Intrahepatic biliary obstruction

While biliary strictures commonly affect the extrahepatic biliary system, intrahepatic and hilar strictures tend to be less common, and can be asymptomatic in up to 30% of patients[32,33]. Malignant obstruction of the biliary hilum have an exceptionally poor prognosis, with less than 10% of patients living longer than 5 years[34]. The predominantly cause of malignant intrahepatic structures is cholangiocarcinoma[35], although squamous cell carcinoma, hepatocellular carcinoma, and metastatic disease are also potential etiologies[36].

Hilar biliary strictures can be difficult diagnose. Typi-

cally presenting with ductal dilation with the absence of stones, the best available diagnostic tool is probably magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP), which not only can locate intrahepatic biliary strictures with 97% accuracy[37], but also allows for the creation of a "road map" of the biliary tree to be used for planning endoscopic intervention (although notably, the specificity of MRCP may be more limited in the case of malignant strictures[38]).

Therapeutic management of hilar strictures is predicated on surgical resectability. Tumors are deemed surgically unresectable in cases with (1) bilateral intrahepatic bile duct spread to secondary or segmental biliary radicals; (2) involvement of the main trunk of the portal vein; (3) bilobar involvement of hepatic arterial and/or portal venous branches; and (4) a combination of unilateral hepatic arterial involvement with cholangiographic evidence of extensive contralateral duct spread[39].

A primary consideration in the management of hilar strictures is whether to unilaterally stent the obstructed duct or to, alternatively, place bilateral stents in both the left and right intrahepatic ducts. While unilateral stenting less expensive than bilateral stenting[40], a number of studies have suggested that bilateral stenting provides increased patency compared to unilateral stenting[41,42] (although it is still debated[43]). However, bilateral stenting is more challenging from a technical standpoint, requiring stent-within-stents or side-by-side deployment techniques[44].

Although the use of plastic *vs* metal stents for intrahepatic strictures is still debated, there is growing evidence to suggest metal stents are preferable to plastic, with recent trials suggesting that SEMSs placement provides higher long-term patency, higher success rates, increased survival, and decreased costs[14,41,45-47]. The use of metal stents is more crucial if the tumor is surgically resectable. Multiple studies examining the use of plastic stents in surgically resectable patients have noted high complication rates with no demonstrative mortality benefit[48-50], whereas upon meta-analysis, metal stents have been found to reduce mortality up to 6%[50], and are less likely to hinder future surgical intervention[51].

Furthermore, the choice of using covered *vs* uncovered metal stents has important implications. Covered SEMS have the theoretic potential to obstruct the intrahepatic bile ducts in proximal biliary strictures, and although this limitation has been challenged in recent years[52], most recommend placing uncovered metal stent in intrahepatic biliary obstruction. However, it warrants mention that compared to covered metal stents, uncovered stents have low migration rates, but are associated with a higher rate of stent dysfunction from tumor ingrowth and epithelial hyperplasia[53]. For these reasons, uncovered SEMSs may be beneficial in cases of known malignant disease without eligibility for resection, but should be avoided if the diagnosis is uncertainly, or if there is any possibility of surgical resection, since covered SEMS better allows for future removal.

ENDOSCOPIC ULTRASOUND-GUIDED BILIARY DRAINAGE

In advanced disease, such as when tumor involves the second part of the duodenum, or in patients with alternated anatomy from bariatric surgeries or intestinal diversions[54-56], endoscopic access to the biliary tree may be impaired, and ERCP not possible. Historically, upon failed ERCP, alternative therapies have included percutaneous transhepatic biliary drainage or surgical bypass. While in the past, arguments have been made in favor of these treatments[57,58], surgical bypass is now limited to good surgical candidates, while external drainage *via* percutaneous intervention has been showed to have, negative impact on a patient's quality of life and long term failure[59]. Furthermore, after a failed ERCP, attempting either of these interventions requires a separate intervention at a later date. Endoscopic ultrasound (EUS)-guided biliary drainage, has been offered for more than a decade in cases with (1) failed conventional ERCP; (2) altered anatomy; (3) tumor preventing access into the biliary tree; or (4) contraindication to percutaneous access (*i.e.,* ascites)[56].

EUS-guided biliary drainage, a method first described in 1996[60], is performed either through a transpapillary or transmural approach. The transpapillary approach consists of gaining access to bile ducts under EUS guidance, followed by placement of a guidewire across the obstruction. A conventional ERCP during a rendezvous can then be performed using the guidewire for access[61]. Reported success rates of this procedure can vary greatly (70%-100%)[62-65]. One of the largest study examining this procedure (n = 58) have reported favorable results, including success rates of over 98% with a complication rate of 6.9%[66]. Furthermore, a recent meta-analysis demonstrated a success around 95% with adverse event of 15%[67] related mainly to pneumoperitoneum, complication that has dramatically decreased since the use of CO_2.

In such cases where transpapillary drainage cannot be performed, transmural drainage may be taken, either through a transgastric-transhepatic (hepatico-gastrostomy) approach for intrahepatic obstruction or a transenteric-transcholedochal (choledocoduodenostomy) for extrahepatic obstruction. The transgastric-transhepatic approach is typically performed through the lesser curvature of the stomach to allow for visualization and drainage of the left intrahepatic bile ducts, whereas the transenteric-transcholedochal[68], is performed through the wall of the duodenum into the common bile duct[56]. Similarly to traditional ERCP, plastic stents were originally placed for drainage, but SEMSs are being increasingly used[69-71], due to their increased patency[71,72].

The complications of EUS-guided biliary drainage include perforation, infection, and bleeding. Theoretically, EUS-guided draining may have a decreased rate of bleeding, as there is less manipulation of the papilla with this method[73]. Furthermore, the manipulation of the wall integrity of the gastrointestinal tract could result in leakage

of bile, pneumoperitoneum, biloma, or bile peritonitis. However, the use of SEMSs should hypothetically minimize the risk of these complications by sealing the fistula created in these procedures[74].

One single center randomized controlled trial of EUS-guided biliary drainage compared with percutaneous biliary drainage demonstrated similar levels of technical success and no difference in adverse effects or cost[75]. Overall, EUS-guided biliary drainage in expert centers has become as a second-line therapy due to its minimal invasiveness and ability to be performed immediately after a failed ERCP.

C-INTRADUCTAL RFA

RFA is a technique in which monopolar or bipolar electrodes are inserted into tissue prior to applying an alternating electric current. The high resistance of the current in biological tissue results in the production of heat, which at sufficient levels, causes instant coagulative necrosis[76]. RFA is used in a wide variety of palliative therapies for malignancies, including lung cancer[77], renal cell carcinoma[78], prostate cancer[79], breast cancer[80], osteoid osteomas[81], and certain brain tumors[82]. Among gastrointestinal tumors, RFA is an established treatment for inoperable liver neoplasm, and is increasingly being used as palliative treatment for malignancy-related biliary obstruction and advanced pancreatic tumors.

The biologic rationale of using RFA in the treatment of malignancies extends beyond its a priori destructive properties. Evidence suggests that malignant tumor cells necrosis at lower temperatures than normal cells[83,84], indicating that cancerous cells will be disproportionally affected by thermal ablation. This effect is accentuated in areas of poor blood flow[85], indicating that hypovascular tumors, in particular, would be ideal targets of hyperthermic treatment.

There are numerous advantages to RFA tumor therapy. Notably, it is less expensive and less invasive than surgery, carrying an eight-fold lower complication rate and a two-fold shorter hospital stay[86,87]. For biliary obstruction, RFA is typically paired with SEMSs placement, with small trials demonstrating 100% patency at 30 d, and 85% patency at 90 d[88], with significant improvement in stricture diameter of 3.7 mm[89]. More impressively, in patients with malignancy-related biliary obstruction, a growing body of literature is suggesting that endoscopic RFA followed by stenting provides a significant survival benefit when compared to patients treated with stenting alone[90-93], advocating for the use of combination endoscopic therapy. Interestingly, a 62 patients study assessing the treatment of biliary strictures related to various neoplastic etiologies found that pancreatic cancer, in particular, was a significant predictor of stricture improvement with RFA[94], although the mechanism for this remains unknown.

D-PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) involves utilizing a specific wavelength of light to activate a intravenously given photosensitizing agent and cause ablation by directly damaging tumor cells, interfering with microvasculature of the tumor bed, and potentiating an immune response[95-99]. The photosensitizer-dependent wavelength light is typically delivered *via* optical fibers placed in the target tissue, with the penetrance dependent on the wavelength of light and the specific light source used[100]. PDT causes tissue necrosis by a non-thermal cytotoxic effect, mediated by the light-induced transfer of oxygen from a photosensitizer to molecular oxygen, generating a reactive oxygen species. Unlike other ablative methods, PDT has the unique ability to trigger apoptosis in neoplastic tissue[101] and is collagen-sparing, allowing for the maintenance of tissue architecture[102].

There have been numerous studies examining PDT for cholangiocarcinoma, which have demonstrated that PDT provides a survival benefit[103-106]. Further studies suggested that PDT in combination with endoscopic stenting was produced a mild survival benefit that was not matched by stenting alone[107,108]. A randomized control trials comparing survival rates in patients treated with biliary stenting alone with those treated with combination biliary decompression and PDT was terminated early, due to the survival and quality of life benefit in the patient who received PDT[109]. A meta-analysis of six studies found that, compared with biliary stenting, PDT was associated with improved biliary drainage, better quality of life, and longer survival with similar rates of biliary sepsis[110]. Overall however, PDT for malignant biliary obstruction remain a strong therapy, although a large-scale randomized trial is in progress to further validate its benefits.

CONCLUSION

Palliative endoscopic therapies for malignant biliary strictures are crucial for a disease that so often presents with surgical ineligibility. Endoscopic options range from biliary decompression to more advanced therapies, such as RFA or photodynamic therapy. The potential advantages of full utilization these methods, especially in the setting of minimally invasive EUS-guided therapy, has redefined the management of patients with inoperable biliary malignancies.

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