

Endoscopic management of hilar biliary strictures

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Abstract

Hilar biliary strictures are caused by various benign and malignant conditions. It is difficult to differentiate benign and malignant strictures. Postcholecystectomy benign biliary strictures are frequently encountered. Endoscopic management of these strictures is challenging. An endoscopic method has been advocated that involves placement of increasing number of stents at regular intervals to resolve the stricture. Malignant hilar strictures

are mostly unresectable at the time of diagnosis and only palliation is possible. Endoscopic palliation is preferred over surgery or radiological intervention. Magnetic resonance cholangiopancreatography is quite important in the management of these strictures. Metal stents are superior to plastic stents. The opinion is divided over the issue of unilateral or bilateral stenting. Minimal contrast or no contrast technique has been advocated during endoscopic retrograde cholangiopancreatography of these patients. The role of intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy, and endoscopic ultrasound still remains to be defined.

Key words: Biliary strictures; Malignant; Benign; Endoscopy; Endoscopic retrograde cholangiopancreatography

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Core tip: Management of benign or malignant hilar biliary strictures is difficult. Surgery is technically demanding for benign hilar biliary strictures and results of endoscopic management are not very satisfactory. Endoscopic palliation is preferred modality of managing malignant hilar strictures. However, it is still controversial to drain unilaterally or bilaterally. Use of contrast during endoscopic retrograde cholangiopancreatography and leaving some ducts undrained is a major problem in these patients. We have reviewed the literature on all these aspects of hilar biliary strictures.

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INTRODUCTION

Biliary strictures at hepatic hilum are not uncommon and present a difficult diagnostic and therapeutic

Table 1 Etiology of benign and malignant hilar strictures^[1]

Malignant hilar strictures
Primary tumors (cholangiocarcinoma)
Local extension (gallbladder cancer, hepatocellular carcinoma, and pancreatic cancer)
Lymph node metastases (Breast, colon, stomach, ovaries, lymphoma, and melanoma)
Benign hilar strictures
Postoperative injuries (cholecystectomy, liver transplantation, liver resection, and biliary anastomosis)
Primary sclerosing cholangitis
Others (stone disease, follicular cholangitis, parasite infection, granular cell tumor, chronic fibroinflammatory process, compression from portal cavernomatosis, granulomatous process, and lymphoplasmacytic sclerosing pancreatitis/cholangitis)

problem. Hilar strictures can be benign or malignant which are often difficult to differentiate. Various modalities as surgery, endoscopy and radiology have been used in the management of these strictures with variable results. The role of some newer modalities, *e.g.*, intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy (PDT), still remain investigational.

Etiology

Etiologically, these strictures can be divided into benign or malignant causes^[1] (Table 1). The differentiation of benign from malignant hilar strictures is difficult.

Diagnosis

The alkaline phosphatase isoenzyme and CA19-9 have been used to discriminate benign from malignant strictures with variable sensitivity and specificity^[2-4]. Radiologic evaluation of patients with hilar strictures can be done with ultrasonography, contrast-enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP). These modalities can help to delineate the level of biliary obstruction along with the extent of biliary dilatation. Any mass lesion or distant metastasis can also be detected with these methods^[5-9]. Increased alkaline phosphatase and CA19-9 levels, increased thickness of bile duct wall to ≥ 5 mm and regional lymphadenopathy (> 1 cm) on CT scan, and cholangiographic appearance of abrupt cutoff and separation of biliary ductal system suggest a malignant etiology of hilar obstruction^[10]. Another study showed an association of raised bilirubin levels of > 8.4 mg% and CA19-9 level > 100 U/L with malignant etiologies of biliary obstruction^[11]. MRI/MRCP performed better than CT to differentiate benign and malignant causes of biliary obstruction^[11]. However, in a study of 49 patients with mass lesion at hilum on abdominal ultrasonography or CT scan, raised CEA and CA 19-9 levels, and presence of irregular, eccentric strictures with abrupt cutoff suggesting malignancy on cholangiography, benign diseases was documented in 24% of cases on surgical histopathology^[12]. Endoscopic

Table 2 Brush cytology in malignant biliary obstruction

No.	Ref.	No. of patients	Sensitivity (%)	Specificity (%)
1	Venu <i>et al</i> ^[13]	53	70	100
2	Foutch <i>et al</i> ^[16]	24	60	100
3	Ferrari Júnior <i>et al</i> ^[17]	70	56	100
5	Singh <i>et al</i> ^[18]	30	37	100

Table 3 Bismuth-lazorthes Classification of postsurgical benign biliary strictures

Type I: Common hepatic or main bile duct stump ≥ 2 cm
Type II: Common hepatic duct stump < 2 cm
Type III: Hilar stricture- ceiling of the biliary confluence is intact, right and left ductal system communicate
Type IV: Ceiling of the confluence is destroyed, bile ducts are separated
Type V: Type I, II or III plus stricture of an isolated right duct

retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) provide a better assessment of the biliary tree. It also enables brush biopsy and cytology studies providing a histological diagnosis in these patients. However, these procedures carry a significant risk of complications^[13,14]. Various studies have shown a variable sensitivity (37%-70%) and high specificity ($> 95\%$) for biopsies or brush cytology (Table 2)^[15-18].

Endoscopic ultrasound (EUS) has shown promising results for the diagnosis of hilar strictures. In a study of 24 patients with negative or unsuccessful brush cytology results in cases of proximal bile duct obstruction, EUS revealed a mass lesion in 23 patients (96%)^[19]. EUS-FNA in these patients provided a sensitivity of 77% and accuracy of 79%. However, the negative predictive value was quite low (29%). In another study of 44 patients with negative brush cytology in cases of suspected hilar cholangiocarcinoma, EUS-FNA had an accuracy of 91% with 89% sensitivity and 100% specificity^[20]. Intraductal ultrasonography enhances the diagnostic accuracy of ERC (88%) as compared to MRC (58%) or ERC alone (76%)^[21].

MANAGEMENT

Benign biliary strictures

Benign biliary strictures at the hepatic hilum most commonly result from surgical injuries, most often after cholecystectomy. Post-cholecystectomy strictures develop in 0.2%-0.5% of patients undergoing surgery and account for 80% of benign hilar strictures^[22]. Post-liver transplant strictures develop in 5.9% of patients^[23].

The management and outcome of postsurgical strictures depends on the type of stricture. Bismuth and Lazorthes classified postsurgical biliary strictures based on the level of healthy biliary mucosa suitable for anastomosis (Table 3)^[24,25].

Surgical management of postsurgical benign biliary strictures carries a morbidity of 18%-51%, mortality

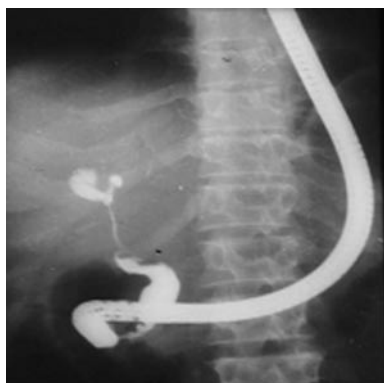


Figure 1 Postoperative type 3 hilar stricture with patent confluence.



Figure 2 Postoperative type 5 hilar stricture involving right hepatic duct.

Table 4 Bismuth classification of malignant hilar block^[31]

Type I: Obstruction within 1 cm of bifurcation but confluence patent
Type II: Obstruction limited to confluence
Type III: Obstruction at confluence with proximal extension to right or left side
Type IV: Obstruction involving bilateral secondary or tertiary branches or multifocal strictures

of 4%-13%, and recurrence rate of 10%-30%^[22]. It, therefore, requires specific skills and expertise. The management of hilar postsurgical strictures (types III, IV, and V) is more challenging and results in worse outcomes (Figures 1 and 2)^[1]. A retrospective study of 57 patients surgically treated for cicatricial biliary strictures showed a higher rate (14%) of stricture recurrence and cholangitis in patients with hilar obstruction compared to none in patient with lesions below the hilum^[26]. A recent study reported the safety and efficacy of right hemihepatectomy with choledochojejunostomy in patients with strictures involving secondary bile duct branches associated with vascular injuries. The study showed 100% survival without stricture recurrence after a mean follow up of 80 mo. No major postoperative complications were documented^[27].

Endoscopic management of postsurgical strictures is more safe and efficacious. Two 10F plastic stents are placed in for a maximum duration of 12 mo. Stent exchange is done at 3 mo interval to reduce the risk of stent blockage and cholangitis (classical approach)^[28,29]. Endoscopic management is feasible in 80% of cases. Stricture recurrence occurs in 20% of patients after stent removal over a period of 9.1 years. All the instances of restenosis were noted within 2 years of stent removal. Mean time from stent removal to symptom onset was 2.6 mo (range 1 wk–2 year)^[29].

An aggressive approach involves insertion of an increasing number of plastic stents until resolution of stricture, with stent exchange performed at 3–5 mo interval^[30]. In a study of 40 patients with 18 hilar strictures, overall success rate with this approach was 89%. Recurrence occurred in only one patient after a

mean follow up of 48.8 mo (range 2–11.3 years). Mean number of stents used was 3.2 ± 1.3 (range 1–6) over a period of 12.1 ± 5.3 mo (range 2–24 mo)^[30].

Malignant biliary strictures

Cholangiocarcinoma, carcinoma gall bladder (GB) and secondaries account for majority of malignant hilar biliary strictures. Malignant hilar biliary strictures are classified as per the Bismuth Classification (Table 4)^[31]. It carries a poor prognosis with 5 year survival of < 10%. Curative resection is feasible in < 10%. Palliation remains the mainstay of therapy. However, surgical palliation is associated with an unacceptable 33% mortality^[31,32].

Current options for palliation include surgical bypass, percutaneous drainage and endoscopic stenting. Endoscopic drainage is safer and more successful with a lower propensity to bile leak, infection and haemorrhage. However, a recent randomized controlled study of 54 patients with unresectable carcinoma GB with Bismuth type 2 (Figure 3) or 3 hilar block showed better drainage (89% vs 41%) and lower complication rate (cholangitis 48% vs 11%) with percutaneous approach^[33]. Both the groups had similar procedure-related mortality (4% vs 8%), 30-d mortality (4% vs 8%) and median survival (60 d in both; $P = 0.71$). Percutaneous drainage resulted in a significantly better quality of life, as assessed at 3 mo after the procedure^[33]. This study used plastic stents instead of metal stents in unresectable carcinoma GB with Bismuth type 2 or 3 hilar block and biliary ducts were left opacified and undrained after contrast injection which could be responsible for higher rates of complication with endoscopic approach. Hence, the results need to be interpreted with caution.

Endoscopic stenting in hilar obstructions can be done with plastic or metal stents (Figures 4–7). Plastic stents are less expensive, have technically easy insertion with relatively easy removal and exchange. But, they have limited stent patency. Metal stents have prolonged stent patency, do not occlude side branches and have easier passage across biliary strictures due to relatively smaller delivery system. But, greater cost and difficulty

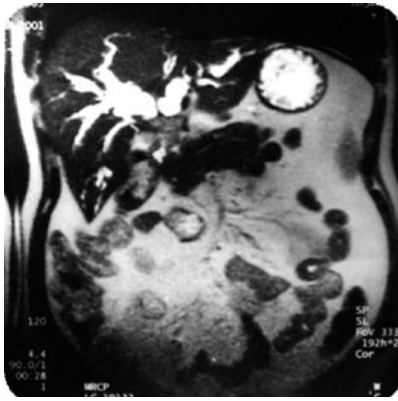


Figure 3 Magnetic resonance cholangiopancreatography showing type 2 malignant hilar stricture.



Figure 5 Type 2 malignant hilar stricture.



Figure 4 Type 1 malignant hilar stricture.



Figure 6 Type 2 malignant hilar stricture with bilateral guide wires.

in removal once blocked are the limitations^[34].

Metal stents have been shown to perform better than even large bore plastic endoprostheses. A prospective randomized trial of 20 patients with Bismuth type II-IV hilar obstruction compared 14 French plastic stents with 24 French metal endoprostheses in the management of malignant hilar obstructions with obstructive jaundice^[35]. Metal stents insertion was associated with greater success as well as patency rates compared to placement of plastic stent. It was also cost-effective due to lower number of re-interventions required in these patients. Another randomized controlled trial of 108 patients with Bismuth type II-IV unresectable hilar cholangiocarcinoma demonstrated better drainage and more prolonged survival with self-expandable metal stents compared to plastic stents^[36]. A meta-analysis of 10 trials showed a significantly higher successful drainage rate [odds ratio (OR) = 0.26; 95%CI: 0.16-0.42; I^2 = 40.3%], lower early complication rate (OR = 2.92; 95%CI: 1.65-5.17; I^2 = 0%), longer stent patency [hazard ratio (HR) 0.43; 95%CI: 0.30-0.61; I^2 = 57.6%], and longer patient survival (HR = 0.73; 95%CI: 0.56-0.96; I^2 = 56.9%) with metal stents in comparison with plastic stents^[37].

There is much controversy regarding the placement of unilateral or bilateral stents for hilar strictures. In a study of 190 patients with Bismuth type I-III hilar

strictures, successful drainage after single stent was achieved in 80% of patients^[38]. The placement of a second stent was considered only in patients with new onset cholangitis or incomplete resolution of cholestatic symptoms. Early complications were observed in 7%, 14% and 31% patients with type I, II and III strictures, respectively. De Palma *et al*^[39,40] showed that unilateral stenting is feasible, safe and effective. In a prospective study of 61 patients with hilar malignancy, the placement of a single metal stent across the stricture into duct easier to access achieved successful stent insertion in 96.7% and successful drainage in 96.7% patients. Median survival of these patients was 140 d with median stent patency of 169 d. Stent malfunction was seen in 4.9%^[40]. A recent meta-analysis also revealed that unilateral and bilateral biliary drainage may have equivalent efficacy in hilar biliary obstruction with a higher success rate for unilateral stent placement^[37]. A case series of 151 patients with unresectable Bismuth type II and III hilar biliary obstruction revealed similar successful drainage rate, complications, 30-d mortality, number of re-interventions and survival based on whether right or left biliary ductal system was drained^[41]. However, in patients with bilobar opacification of biliary ductal system, bilateral drainage should be obtained to reduce the risk of cholangitis^[42].

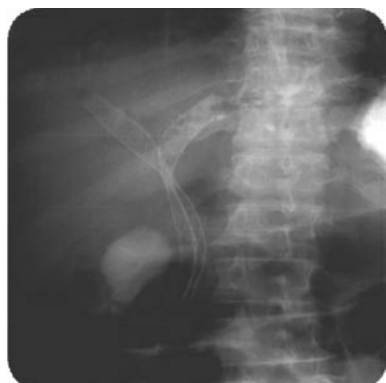


Figure 7 Bilateral metal stents in type 2 malignant hilar stricture.

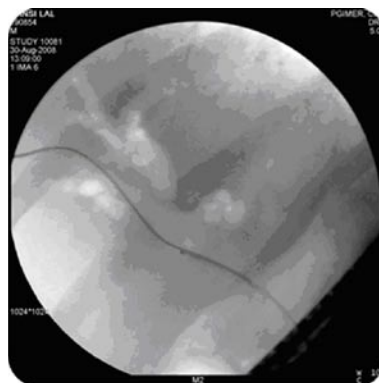


Figure 8 Air cholangiogram showing type 2 malignant hilar stricture.

It was widely held that draining 25% of liver volume provides adequate palliation of obstructive jaundice with biochemical improvement in these patients^[43]. However, a recent study of 107 patients with Bismuth type II-IV hilar strictures concluded that drainage of more than 50% of liver volume predicts efficacy of drainage and translates into longer survival (119 d vs 59 d, $P = 0.005$), especially in Bismuth type III hilar strictures^[44]. Bilateral stent insertion is often required to achieve more than 50% drainage. The study, however, has several drawbacks. The study had a retrospective design, most of the patients underwent plastic instead of metal stenting in hilar biliary obstruction and majority of the patients had cholangiocarcinoma which has relatively prolonged survival and can confound the results.

Failure to drain the hepatic lobes or segments after contrast injection is responsible for most of the cases of post procedure early cholangitis and mortality^[42]. It brought to the fore the concept of contrast free stenting^[45,46]. To avoid bilateral contrast injection and stent placement in Bismuth-type III and IV Klatskin tumors, Hintze *et al*^[47] used MRCP in 35 patients for ERC and unilateral stent insertion. The placement of stents under MRCP guidance reduced incidence of post-ERC bacterial cholangitis. A prospective study of 18 patients with Bismuth type II malignant hilar biliary obstruction demonstrated successful endoscopic drainage in all the patients and no cholangitis or 30-d mortality with MRCP guided contrast-free unilateral metal stenting^[45]. Another study of 15 patients with Bismuth type II malignant hilar strictures used contrast-free balloon-assisted unilateral plastic stenting with 100% successful drainage and no cholangitis or 30-d mortality^[48]. Comparison of air and iodine contrast cholangiography in hilar strictures in a retrospective study showed less cholangitis with air contrast in Bismuth type II-IV strictures^[49]. Subsequently, two studies showed 100% successful stent placement and drainage with no cholangitis and 30 d mortality with contrast-free air cholangiography-assisted (Figure 8) unilateral stent deployment^[50,51]. A recent randomized controlled study compared CO₂ cholangiography with iodine contrast

cholangiography in 36 patients with Bismuth type II-IV malignant hilar obstruction and revealed lower incidence of cholangitis in CO₂ group (5.6% vs 33.3%, $P = 0.04$)^[52].

NEWER APPROACHES

Novel approaches including drug eluting stents, EUS guided biliary drainage, intraluminal brachytherapy, intraductal ablation devices and PDT have recently been used with variable results.

External beam irradiation therapy in malignant biliary strictures is limited by radiation tolerance of liver, bowel and kidneys. Intraluminal brachytherapy allows greater radiation dose locally administered to predefined volume of tissue. It can be administered *via* endoscopic or percutaneous route. A few recent studies have documented the safety and efficacy of intraluminal brachytherapy in association with stent placement in unresectable, malignant hilar strictures. This new method resulted in prolonged survival in these patients^[53-56].

PDT is a promising mode of therapy for unresectable cholangiocarcinoma. It uses a combination of photosensitising chemical and light of appropriate wavelength to generate cytotoxic reactive oxygen species culminating in tumour cell death by necrosis or apoptosis. Continuous biliary drainage is achieved by stent implantation after the procedure. A randomized controlled study of 39 patients with histologically confirmed unresectable cholangiocarcinoma was terminated prematurely due to prolongation of survival (median 493 d vs 98 d; $P < 0.0001$), more effective biliary drainage and improved quality of life with stenting and PDT in comparison with stenting alone^[57]. In a recent retrospective study of 184 patients with hilar cholangiocarcinoma managed with either surgery (60), stenting (56) or stenting with PDT (68); PDT had a longer survival compared to stenting (12.0 mo vs 6.4 mo, $P < 0.01$) and comparable survival to R1/R2 resection (12.2 mo)^[58]. In conclusion, management of hilar biliary strictures is a difficult problem. Surgical, endoscopic and percutaneous approaches have been

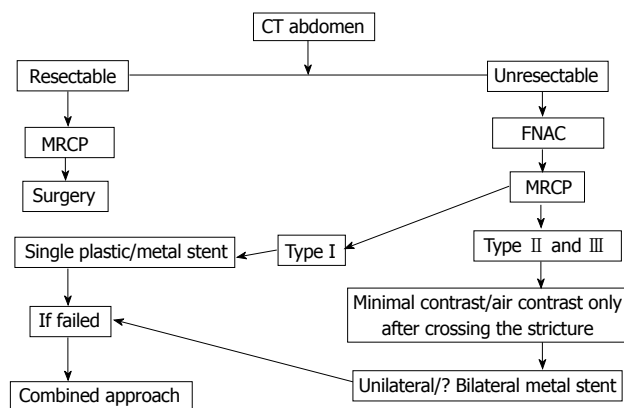


Figure 9 Approach to malignant hilar biliary strictures. CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography; FNAC: Fine needle aspiration cytology.

used in the management of these strictures with variable results. However, the appropriate management also depends on expertise available at that centre. Endoscopic management with increasing number of plastic stents and surgery for failed cases in benign biliary strictures is a reasonable approach. Appropriate management algorithm for malignant hilar strictures is given in Figure 9.

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