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# Management of Hilar Biliary Strictures

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**Biliary strictures at the liver hilum are caused by a heterogeneous group of benign and malignant conditions. In the absence of a clear-cut benign etiology, *i.e.* bile duct damage during surgery, hilar biliary strictures remain a diagnostic and therapeutic challenge for which a multidisciplinary approach is often necessary. A definitive diagnosis can be achieved in only 40–60% of the patients, while in all the other cases strictures are treated as though they are malignant until surgical pathology determines otherwise. Surgical resection is the only treatment that prolongs survival in patients with malignant strictures. Because these tumors frequently extend longitudinally via the hepatic ducts into the liver parenchyma, partial hepatic resection has been gradually added to biliary resection to ensure tumor-free surgical margins. For unresectable cases, endoscopic stenting of biliary obstruction is considered the preferred palliation modality to relieve pruritus, cholangitis, pain and jaundice, while the percutaneous approach has been reserved for cases of failure. Other modalities of treatment such as radiotherapy, chemotherapy, and photodynamic therapy currently remain investigational. For benign post surgical hilar strictures, surgical repair can be difficult and requires specific skills and experience. As an alternative, a multi-stent technique with endoscopic placement of an increasing number of stents over time until complete resolution of the stricture has been proposed.**

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## INTRODUCTION

The diagnosis and treatment of hilar strictures remains a clinical challenge, requiring a multidisciplinary approach that includes radiologists, endoscopists, surgeons, oncologists, and pathologists. The hepatic hilum is a complex anatomical region consisting of biliary, arterial, and venous structures. At the hepatic hilum, the hepatic artery and the portal vein divide into two main branches, while bile ducts merge to form the common hepatic duct, what has been termed the main hepatic confluence. A thorough understanding of hilar anatomy is required to conceptualize the many anatomical variations that can occur (absence of the right hepatic duct, aberrant confluence of a sectorial hepatic duct, aberrant confluence of a right segmental duct, etc.) (Fig. 1). The term "aberrant" is used rather than "accessory" or "anomalous," as each single duct provides the sole biliary drainage for its respective portion of liver parenchyma and is not an additional drainage duct (1).

Hilar strictures may be benign or malignant (Table 1). Both are amenable to surgical, endoscopic, and percutaneous treatment. Curative surgical resection is appropriated for selected primary tumors (cholangiocarcinoma) and often requires partial liver resection. Palliative treatment of jaundice is usually achieved by less invasive techniques such as endoscopic stenting and percutaneous transhepatic drainage (PTD). Chemotherapy and radiotherapy (external or intraluminal) may have a role both after surgical resection and in the palliative management after jaundice relief is achieved.

## CLASSIFICATION SYSTEMS

Malignant strictures involving the hilum are classified using the Bismuth-Corlette classification system based on the extension of the stricture into the intrahepatic ducts (Fig. 2) (2, 3). Bismuth type I strictures involve the proximal common hepatic duct and spare the confluence between the left and right ductal systems; type II strictures involve the confluence and spare the segmental hepatic ducts; types IIIa and IIIb involve either the right or left segmental hepatic ducts, respectively; and type IV strictures involve the confluence and both the right and left segmental hepatic ducts. This classification is limited to the description of bile duct involvement and does not characterize other structures such as the common hepatic artery and the portal vein, or liver atrophy, and may not therefore predict surgical resectability (4). This system does, however, account for the frequent anatomical variations in biliary anatomy, which may be helpful in planning operative or endoscopic therapy

A different classification that takes into account the length of the healthy biliary mucosa available for anastomosis with the jejunum has been proposed by Bismuth and Lazorthes for postsurgical biliary hilar strictures (5, 6) (Fig. 3). The details of this classification are described below.

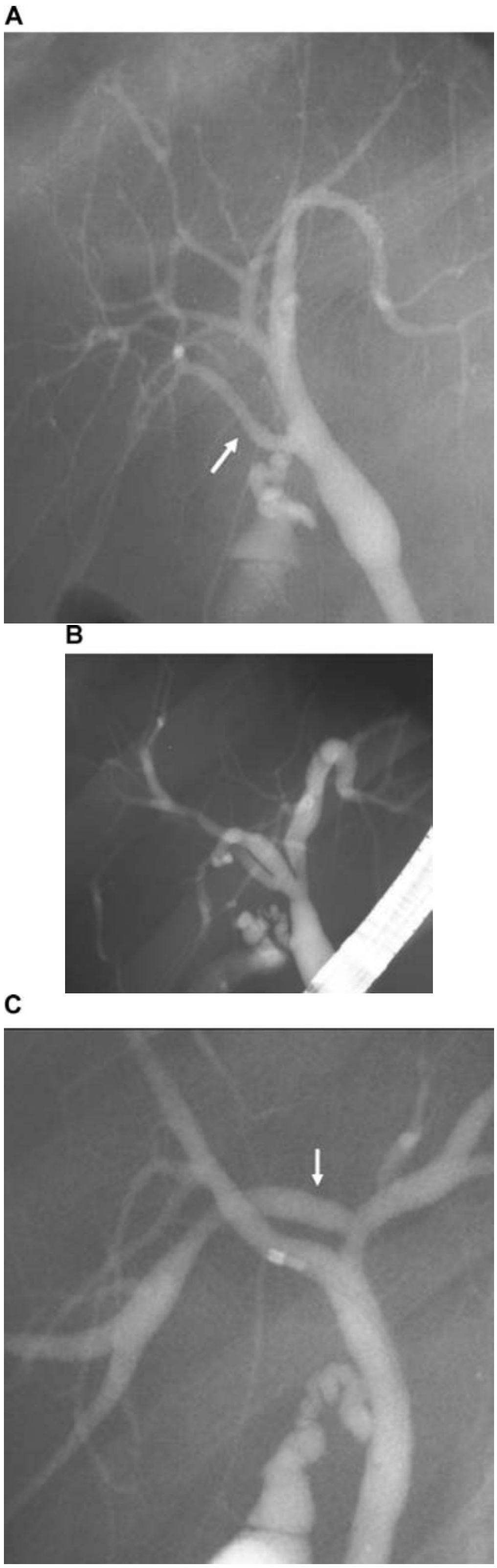



**Figure 1.** Examples of anatomical variations of the biliary tree as detected at ERC. (*A*) A sectorial intrahepatic duct (arrow) is implanted on the common bile duct a few centimeters below the main hepatic confluence. (*B*) Trifurcation of the main biliary hepatic confluence. (*C*) The sectorial posterolateral duct (arrow) (hepatic segment VI and VII) drains into the left hepatic duct.

**Table 1.** Etiology of Benign and Malignant Hilar Strictures

| |
|---|
| Malignant Hilar Strictures |
| • Primary tumors (cholangiocarcinoma) |
| • Local extension (gallbladder cancer, hepatocarcinoma, and pancreatic cancer) |
| • Lymph node metastases (Breast, colon, stomach, ovaries, lymphoma, and melanoma) |
| Benign Hilar Strictures |
| • Postoperative injuries (cholecystectomy, liver transplantation, liver resection, and biliodigestive 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) |

## STRICTURE ETIOLOGY

### *Malignant Hilar Strictures*

Cholangiocarcinoma is the most frequent cause of malignant hilar strictures. Other malignant strictures may be due to adjacent gallbladder, liver, and pancreatic tumors, or to metastatic hilar lymphadenopathy (Table 1).

Cholangiocarcinoma is a primary bile duct tumor that accounts for 3% of all gastrointestinal cancers worldwide and is the second most common primary hepatic tumor (7, 8). More than 90% of these tumors are adenocarcinomas, and 60–70% arise at the main confluence of the hepatic ducts or hilum, 20–30% in the distal common bile duct, and 5–10% arise peripherally within the intrahepatic ducts of the liver parenchyma (9). Cholangiocarcinomas may be classified anatomically as intrahepatic, hilar, and extrahepatic (10), or altenatively by growth characteristics as mass-forming, periductal-infiltrating, and intraductal-growing type (11).

Hilar cholangiocarcinoma (HCCA) was first described by Altemeier *et al*. in 1957 (12). However, it was only after Klatskin's series of 13 patients in 1965 that this tumor became recognized as a distinct clinical entity (13), now known as Klatskin tumor. These are uncommon tumors with a reported annual incidence of 1.2 per 100,000 individuals in the United States (14). Patients with HCCA are usually in their 6th or 7th decade, over 90% present with "painless" jaundice, and few survive for more than 6 months without treatment. At the opposite side of the spectrum are the younger patients in their 3rd to 5th decade of life who are affected by primary sclerosing cholangitis (PSC) and develop HCCA. PSC is the most common known risk factor in the west, and 8–40% of patients will go on to develop cholangiocarcinoma (15). Differentiating cholangiocarcinoma, especially HCCA, from chronic inflammatory benign hilar strictures in PSC patients is extremely difficult, as mass lesions are infrequently identified on imaging studies and significant intrahepatic biliary tree dilation is often absent (16).

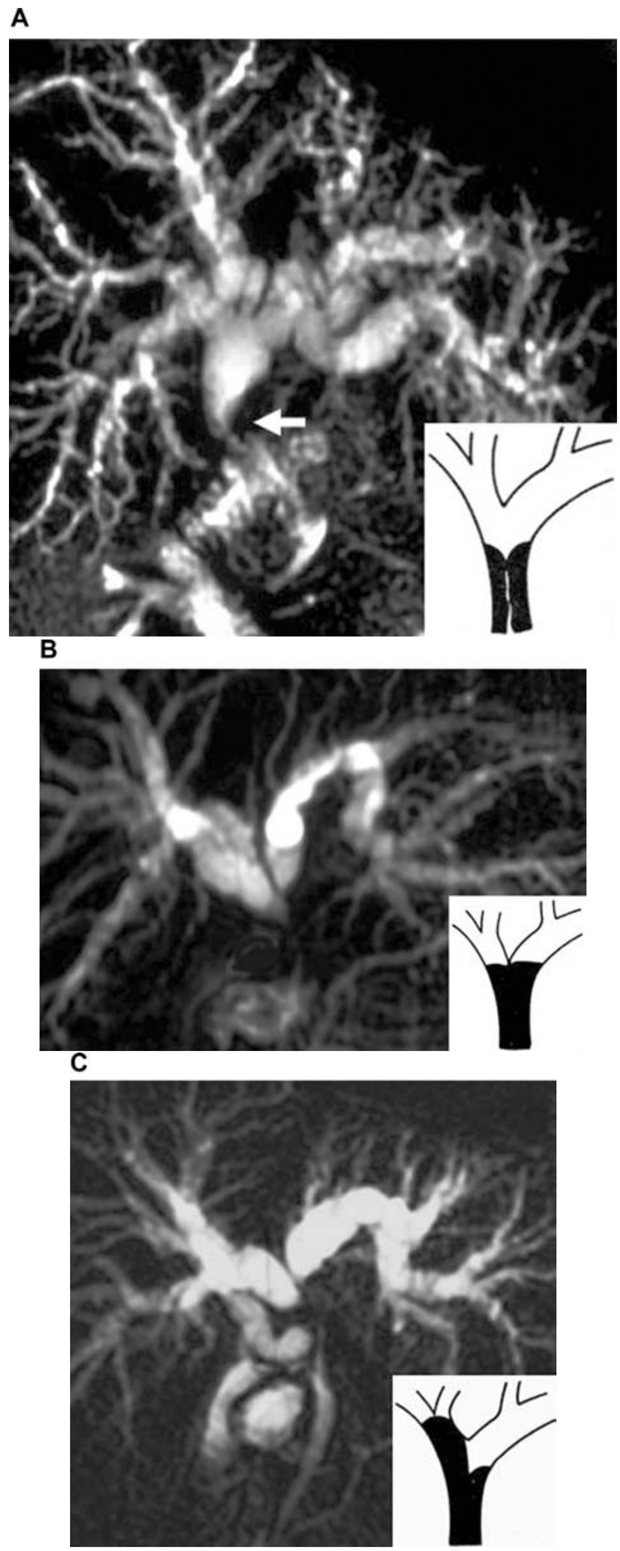



**Figure 2.** Modified Bismuth-Corlette classification of hilar tumors (2, 3). (*A*) Type I: stricture does not interrupt the main hepatic confluence (arrow). (*B*) Type II: stricture interrupts the main hepatic confluence. (*C)* Type IIIa: stricture interrupts the main and the right secondary hepatic confluence. (*D*) Type IIIb: stricture interrupts the main and left secondary hepatic confluences. (*E*) Type IV: Primary and both right and left secondary hepatic confluences are interrupted.

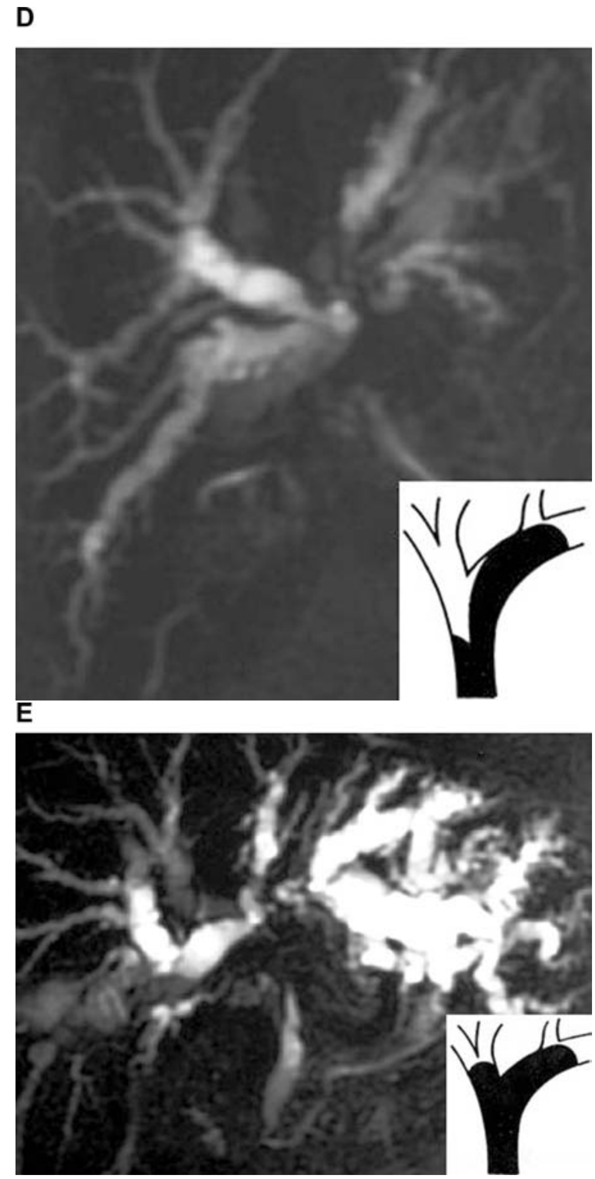



**Figure 2.** continued.

Other risk factors for HCCA are choledochal cysts, familial polyposis, congenital hepatic fibrosis, history of thorium dioxide exposure (Thorotrast), hepatolithiasis, and biliary infection from *Clonorchis sinensis* (southern China, Hong Kong, and Korea) and *Opistorchis viverrini* (northeastern Thailand, Laos, and western Malaysia) (9). Chronic inflammation, which can lead to cell death, epithelial proliferation, and the production of endogenous mutagens, is a common finding in these conditions (9). The association between PSC and HCCA is likely similarly explained on the basis of necroinflammation leading to malignant transformation.

Hepatolithiasis is a rare cause of HCCA in western countries, but is reported in 53–69% of patients who undergo liver resection for HCCA in the Far East, where it is endemic (17, 18). In general, hepatolithiasis is more commonly associated with peripheral cholangiocarcinoma than with HCCA (18).

### *Benign Strictures*

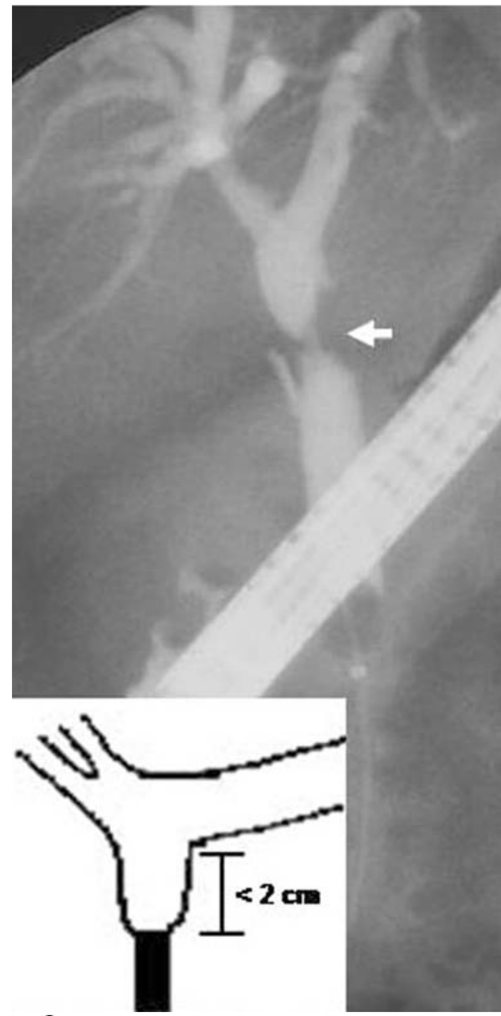
Benign hilar strictures are usually iatrogenic, most frequently as a result of cholecystectomy. The incidence of this complication has increased with the widespread use of the laparoscopic technique (5, 19, 20).

After liver transplant, nonanastomotic hilar strictures tend to occur within 6 months and are more common in patients with PSC (21), in whom the biliary anastomosis has conventionally been performed using a Roux loop rather than a choledochocholedochostomy to reduce the risk for recurrent disease affecting the distal bile duct. Possible causes are hepatic artery occlusion, ductopenic arteriopathic rejection, and cytomegalovirus infection. In about one-third of the patients, however, no identifiable cause of strictures can be found (22). These strictures may be endoscopically or percutaneously dilated, but long-term resolution is achieved in only 25% of cases, and 50% of patients need retransplantation or they die (22).

A


**Figure 3.** Bismuth-Lazorthes classification of postsurgical benign biliary strictures (5, 6). (*A*) Type I: common hepatic or main bile duct stump ≥2 cm. (*B*) Type II: common hepatic duct stump <2 cm. (*C*) Type III: ceiling of the biliary confluence is intact, right and left ductal system communicate. (*D*) Type IV: ceiling of the confluence is destroyed, bile ducts are separated. (*E*) Type V: type I, II, or III plus stricture of an isolated right duct.

B




C

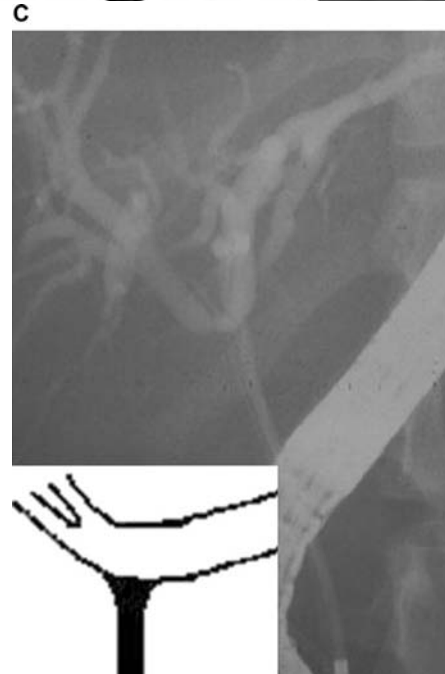


**Figure 3.** continued.

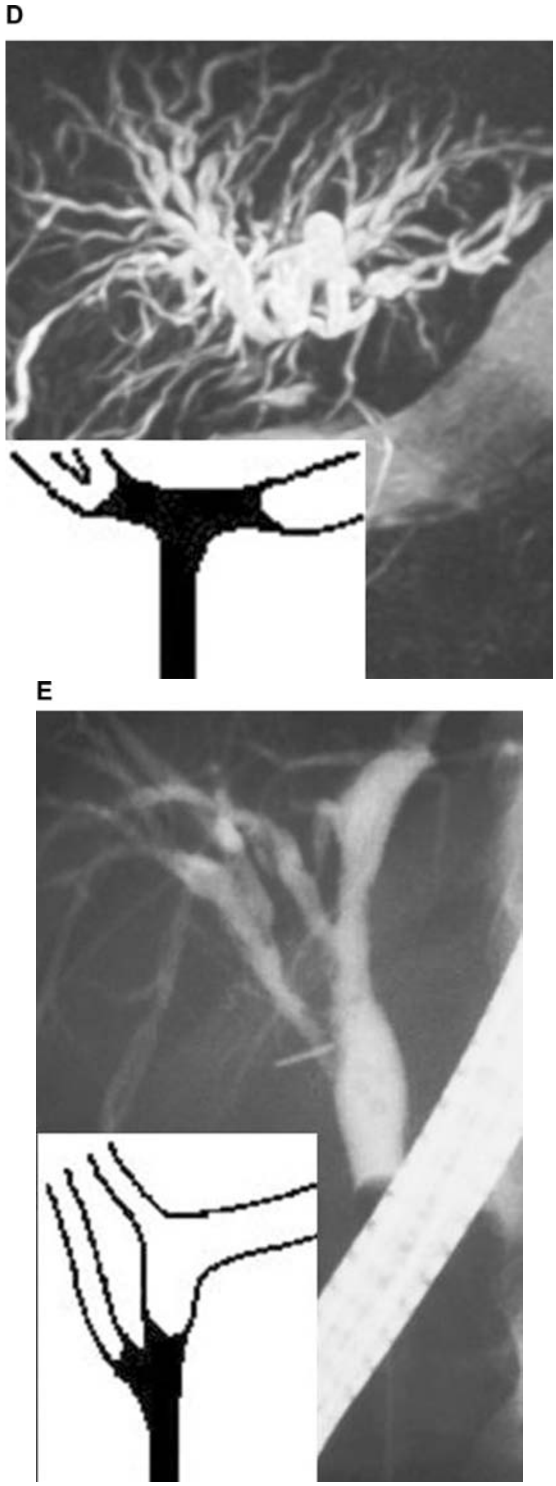


**Figure 3.** continued.

Hepatolithiasis can be associated with inflammatory hilar strictures, which carry a high risk for stone recurrence after percutaneous or endoscopic extraction. When practical, hepatic resection is the treatment of choice, especially given the carcinogenic potential.

Localized PSC, eosinophilic cholangitis, granulomas, glandularis proliferans (characterized by florid intramural proliferation of glandular elements in addition to an intense inflammatory component), leiomyoma, periductal fibrosis, and lymphoplasmacytic sclerosing are benign fibroinflammatory processes that can cause hilar strictures clinically indistinguishable from HCCA (23–30). They were termed *malignant masquerade* by Hadjis and colleagues in 1985 (31).

## DIAGNOSIS AND STAGING

Once a hilar stricture is suspected from the clinical presentation and from findings of the first-line imaging study performed, two important questions need to be addressed: (a) is the stricture malignant or benign? (b) is the stricture amenable for surgical resection?

To answer these fundamental questions many imaging studies such as transcutaneous abdominal ultrasound (TUS), computed tomography (CT), endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and magnetic resonance (MR) cholangiography (MRC) with their ancillary sampling techniques can be used.

Differentiation of benign and malignant hilar strictures is a major diagnostic dilemma, especially in those cases with intrahepatic bile duct dilatation without a definite mass on TUS or CT. Integration of liver function tests (LFT) with imaging findings may be useful in identifying a malignant etiology. Increased levels of alkaline phosphatase and CA 19-9 in association with bile duct wall thickening of $\geq$5 mm and regional lymph node enlargement ($>$1 cm) on CT scan, or the observation of an abrupt cutoff and separation of bile ducts on direct cholangiography, are significantly more frequent in malignant than in benign hilar strictures (32). These are imperfect predictors, however, as highlighted by Koea *et al*. (33), who described 49 patients with hilar mass lesions on TUS or CT scan, increased carcinoembryonic antigen (CEA) and CA 19-9 serum levels, and cholangiographic features of malignancy (irregular and eccentric stricture with an abrupt cutoff) who were found to have had benign diseases in 24% of cases after surgical resection. This result, obtained after having excluded patients with suspected iatrogenic biliary injury, is similar to other series reporting incorrect preoperative diagnoses of malignancy in about 15–18% of patients with hilar strictures (34–36). Intraductal ultrasonography (IDUS) using high-frequency probes can help in distinguishing malignant from benign strictures. Disruption of the normal sonographic structure of the bile duct wall and presence of a hypoechoic mass with irregular margins or with infiltration of the surrounding tissues are highly suggestive of malignancy (37). IDUS has been shown to enhance the diagnostic accuracy of ERC (88%) in differentiating malignant from benign biliary strictures when compared with MRC (58%) or ERC alone (76%) (38). Even higher rates of accuracy have been reported by others with the use of intraductal wire-guided probes (39, 40). However, its use is limited by the inability to obtain tissue samples. Accurate delineation of the etiology of hilar lesions may, therefore, remain impossible outside the operating room, and patients without preoperative histologic confirmation of malignancy should know that they might undergo surgery for a benign disease. As surgical resection remains the mainstream of treatment even for benign conditions, this controversy rarely changes the management (41). On the other hand, diagnosing a malignant etiology of hilar strictures other than HCCA, in particular, a metastatic lymphadenopathy, drastically changes the therapeutic plan from surgical resection to palliative treatment.

Various methods used to obtain a preoperative cyto/histologic diagnosis of hilar strictures are used and will be briefly described below.

### *Bile Aspirate Cytology*

Bile aspirate cytology can be easily performed on the bile collected from a percutaneous drain or during ERC (42, 43). Although it is simple and inexpensive, bile aspiration cytology adds little or nothing to the other methods with higher sensitivity.

### *Brush Cytology*

Brush cytology is technically easy, safe, and quick, and is the most commonly used tissue sampling technique during ERC (44). Performing multiple brushings during the same procedure may improve sensitivity (44). The yield of cytologic diagnosis may be improved by newer techniques such as digital imaging analysis (DIA) and fluorescence in situ hybridization (FISH) (45, 46).

### *Exfoliative Retrieved Stent Cytology*

Exfoliative retrieved stent cytology is impractical as a first-line sampling technique as diagnosis is delayed until the stent is removed. Cells from the removed stent are retrieved by rinsing it with saline followed by centrifugation of the rinse to obtain a sediment that is finally smeared and Papanicolaou stained. This technique can be useful when other methods have failed to provide a definitive diagnosis (47).

### *Endobiliary Forceps Biopsy*

Endobiliary forceps biopsy provides a sample of the bile duct epithelium, eliminating the problem of inadequate sampling that is encountered with cytologic methods (44). This technique is the most sensitive of all the tissue sampling techniques for biliary strictures during ERC and PTC, even though it is time-consuming and can be technically difficult. The development of more flexible biopsy forceps might increase its use.

It is important to emphasize that the best yield of ERC-related techniques is when at least one cytological method (*e.g.*, brushing) and endobiliary forceps biopsy are combined (sensitivity of 55–73%) (44).

### *Endoscopic Ultrasound-Guided Fine-Needle Aspiration*

The possibility of using endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in the evaluation of hilar lesions was first described by Fritscher-Ravens and colleagues (48). This procedure is not widely performed because it is technically demanding, especially when the echoendoscope needs to be held in the desired position while the needle is guided into the hilar lesion through the wall of either the prepyloric or the postpyloric region. Despite this difficulty, the same authors have described a cohort of 44 patients with suspected hilar cholangiocarcinoma and a previous negative brush cytology in which the accuracy, sensitivity, and specificity of EUS-FNA were reported to be 91%, 89%, and 100%, respectively (49). EUS-FNA was able to correctly diagnose HCCA and metastatic tumors in 26 and 5 patients, respectively, with only four false-negative cases in the 12 patients with benign cytologic findings. EUS and EUS-FNA results also changed the surgical approach in 61% of the patients. In a more recent publication from Indiana University (50), EUS was shown to be able to visualize a mass lesion in 23 of 24 (96%) patients with proximal biliary strictures and a negative ERC brush cytology study. Unfortunately, the good sensitivity and accuracy (77% and 79%, respectively) of EUS-FNA found by these investigators was paralleled with an extremely low negative predictive value (29%), indicating that a negative result cannot reliably exclude malignancy, thus limiting the value of this procedure for patients with HCCA. More data are necessary before conclusions on the value of EUS-FNA in the differential diagnosis of hilar strictures can be drawn.

BIOPSY AT CHOLANGIOSCOPY. Biopsy samples can also be obtained during nonsurgical cholangioscopy, which can be performed by the peroral or the percutaneous route. PTC achieves excellent visualization of bile duct lesions even in difficult anatomical situations (51), allowing the obtainment of targeted biopsies useful in the differentiation between benign and malignant strictures (52, 53). On the other hand, tissue sampling during peroral cholangioscopy has not been rigorously studied and appears as a major challenge because of the limited maneuverability of the available scopes and the difficulty in obtaining meaningful tissue samples due to the small size of the biopsy forceps that can be utilized (54).

When a malignant hilar stricture is suspected, the goal of the subsequent workup is to identify candidates for surgical resection. The extent of ductal and vascular infiltration are the most crucial pieces of information in patient selection. With the increasing use of aggressive hepatic resection, preoperative evaluation of hepatic reserve has become another important parameter as well.

Spiral CT has 100% positive predictive value and 50% negative predictive value in the detection of vascular invasion and tumor resectability, but has some limitations in assessing biliary and tumor anatomy (55). The advent of rapid scanning multidetector CT with 1-mm sections and 3-dimensional imaging reconstruction may overcome these limitations (56, 57).

MRC is an increasingly important imaging technique in the evaluation of hilar strictures. MRC provides a detailed cholangiographic map noninvasively, including the extent of the stricture, without the risks of invasive direct cholangiography. These procedures, especially ERC, carry a significant risk for infection when injection of contrast medium into the obstructed ducts is not followed by an immediate drainage procedure. The accuracy of MRC in the evaluation of intraductal tumor extension ranged between 78 and 84% in two recent studies (58, 59), and was comparable to ERC. Also like ERC, MRC may be capable of differentiating extrahepatic bile duct cholangiocarcinoma from benign causes of hilar stricture (60). Advantages of MRC over ERC include better visualization of tumor spread in cases of tight proximal bile duct strictures, which may be difficult to assess with ERC because of the insufficient contrast filling. In addition, MRC has the potential to detect liver parenchyma invasion and calculate hepatic volumes, which are important for planning the therapeutic strategy to be chosen (61). Dynamic contrast-enhanced MR imaging may also assess vasculature involvement. Results are comparable to angiography in assessing portal vein invasion in patients with HCCA (62), which has been correctly detected in 67% of cases with this technique (63). A recent study comparing MR angiography (MRA) to digital subtraction angiography (DSA) to predict vasculature involvement has found comparable accuracy of the two imaging modalities in recognizing portal vein involvement, while DSA had significantly higher specificity as compared to MRA to depict involvement of the hepatic artery (99% *vs* 93%, $P = 0.01$) (64). In view of all the available evidence, MR with MRC and MRA is emerging as the investigation of choice for the evaluation of patients with malignant-appearing hilar strictures (65). In Asian countries, the more invasive PTC technique has a major role in the staging of hilar strictures (66). It is still considered the most accurate preoperative examination to evaluate both the extent of cancer and the pattern at the proximal border of HCCA to design the most appropriate resective procedure as well as the reconstructive method to be used in each patient (67, 68). Longitudinal tumor extension can also be evaluated with IDUS, which has the advantage of being able to investigate the hepatic artery and the portal vein for possible tumor infiltration/invasion (38–40).

## MANAGEMENT OF MALIGNANT HILAR STRICTURES

### *Surgical Treatment*

Complete resection is the only cure for hilar tumors. Curative resection with histologically negative margins (R0) is difficult to achieve and is technically demanding due to the proximity of the bile duct confluence and the vascular inflow of the liver, as well as the tendency of these tumors to grow into the surrounding perineural and hepatic tissue. About 70–75% of patients with HCCA evaluated for surgery are candidates for resection, and over half of the procedures are aborted, mainly due to metastatic disease (4). Thus, staging laparoscopy with exploration of the peritoneal surfaces for carcinomatosis and laparoscopic ultrasonography to detect occult liver metastases are increasingly being used before laparotomy for HCCA (69).

**Table 2.** Criteria for Unresectability (4)

1. Hepatic duct involvement up to secondary biliary radicals bilaterally.
2. Encasement or occlusion of the main portal vein proximal to its bifurcation.*
3. Atrophy of one hepatic lobe with encasement of the contralateral portal vein branch.
4. Atrophy of one hepatic lobe with encasement of the contralateral secondary biliary radicals.
5. Distant metastases.

*Relative criteria due to the possibility of performing portal vein resection and reconstruction.

Surgical management of hilar tumors was originally based mainly on the resection of the biliary system and on the creation of a bilioenteric anastomosis to the intrahepatic ducts (2, 70). Early proponents (71, 72) of the addition of liver resection to bile duct resection were vigorously criticized until Nimura and colleagues in 1990 clearly demonstrated that the biliary ducts of the caudate lobe are almost always involved (44 of the 45 patients, 97.7%) and that the addition of caudate lobe resection was associated with increased survival in these patients (73). As a result, partial liver resection has been routinely used to manage those tumors with direct hepatic invasion (74). With this shift towards liver resection, the Bismuth-Corlette (2, 3) classification system, which relies on tumor extension into the bile ducts, and not on portal vein involvement and liver atrophy, has turned out to be less effective in predicting resectability. In an attempt to overcome these limitations, a new system has been proposed with extended criteria of unresectability (Table 2) and a different preoperative staging system (Table 3) that stratifies patients into three groups with predictable resectability rates and survival (4, 74). This system incorporates patient-related factors, the degree of biliary and portal venous involvement, and hepatic lobar atrophy, and has been reported to have a stronger correlation with resectability than the Bismuth-Corlette system (75).

The increased risk for liver failure reported in patients with biliary obstruction undergoing extended liver resections (76, 77) has raised the question of preoperative biliary decompression by ERC or PTC. This decompression, however, may increase the rate of perioperative infections. A recent comprehensive review of all the published studies found no benefit of preoperative biliary drainage (78). However, the five randomized trials available in the literature (79–83) differed in the method of drainage utilized and included obstructing tumors located anywhere throughout the biliary tree, highlighting

**Table 3.** Proposed T-Stage Criteria for Hilar Cholangiocarcinoma (4)

| |
|---|
| T1: Tumor involving biliary confluence ± unilateral extension to secondary biliary radicals. |
| T2: Tumor involving biliary confluence ± unilateral extension to secondary biliary radicals and ipsilateral portal vein involvement ± ipsilateral hepatic lobe atrophy. |
| T3: Tumor involving biliary confluence + bilateral extension to secondary biliary radicals; unilateral extension to secondary biliary radicals with contralateral portal vein involvement; unilateral extension to secondary biliary radicals with contralateral hepatic lobe atrophy; or main or bilateral portal vein involvement. |

the need for properly designed trials before a definitive answer to this controversial issue can be drawn. Despite the lack of evidence supporting preoperative drainage, Japanese surgeons (84–86) routinely performed preoperative placement of percutaneous drainages in patients with Klatskin tumors followed by cholangioscopy to provide tissue diagnosis, to help in assessing disease extension prior to major liver resections, and to detect submucosal spreading of the tumor as this is one of the most important predictors of poor outcome (85, 87, 88).

The feasibility of extensive liver resection depends on the volume of residual parenchyma. In some cases, the liver lobe with tumor involvement is atrophic with corresponding hypertrophy of the other hepatic segments, thus making a major liver resection possible. Improved remnant liver function may also be achieved with portal vein embolization (PVE) of the hepatic lobe to be resected, with the aim of inducing contralateral compensatory hypertrophy (Fig. 4) (89, 90). It has been speculated that this intervention not only prevents primary liver failure, but also provides a degree of hepatic function reserve that will allow the patients to better tolerate any complications (75). The largest experience with PVE before extended hepatectomy (right or left trisectionectomy or right hepatectomy) for hilar tumors is the one from Nagoya University in Japan (91). These researchers recently reported on 240 consecutive patients with hilar tumors over 13 yr, 193 of whom underwent resection (91). The authors found that for HCCA, extended and complex hepatectomy following PVE was associated with a mortality rate comparable to that in other patients who underwent a less than 50% resection of the liver without PVE during the same period. These potential benefits of PVE, however, have not been validated in any randomized controlled trial, and well-planned prospective studies to define which patients could benefit the most from this procedure have been advocated (92).

These advances in surgical and preoperative management of hilar tumors have increased the rates of negative resection margins, with a 5-yr survival rate after R0 resection of up to 45% in a recently published series (75). The use of portal vein and hepatic artery reconstruction, as well as extended liver resections (93, 94), may further improve these outcomes.


**Figure 4.** (*A*) Computed tomography image of a patient with hilar tumor before portal vein embolization. (*B*) Compensatory hypertrophy of the left liver lobe after right portal vein embolization.

While resection is the treatment of choice, several groups have evaluated the role of orthotopic liver transplantation (OLT) for patients with locally advanced, unresectable HCCA (85–99). Given the disappointing 12–36% 5-yr survival rates and the liver graft shortage, HCCA has become a contraindication to OLT (100). However, a recently published experience from the Mayo Clinic (101), where OLT combined with neoadjuvant chemoradiation therapy in patients with unresectable localized HCCA and without regional lymph node metastases had an 82% 5-yr survival rate, suggests that liver transplantation may play a role in selected patients.

***Palliative Treatment***

The primary aim of palliative treatment of malignant hilar strictures is to improve quality of life by providing biliary drainage with long-term relief of jaundice, pruritus, pain,

**Table 4.** Palliative Treatment Modalities for Malignant Hilar Strictures

| | |
|---|---|
| Biliary drainage procedures (mandatory) | Endoscopic stenting<br>Percutaneous biliary drainage/ stenting surgical bypass |
| Additional therapies (investigational, based on center preference, protocols) | Radiotherapy<br>Chemotherapy<br>Photodynamic therapy (PDT) |

and cholangitis (Table 4). When possible, percutaneous or endoscopic drainage are preferred over technically demanding surgical palliative resection (102). Despite lasting biliary drainage, no survival benefits have been demonstrated in surgically treated patients, making the less invasive stenting techniques preferable to surgical biliary enteric bypass. When expertise is available, endoscopic drainage of hilar strictures is now the preferred drainage modality, to be used with back up PTC in the event of failure (102).

PERCUTANEOUS TRANSHEPATIC DRAINAGE. PTD may be done as an external or internal drainage. The former, which was the first nonsurgical method used to relieve jaundice in patients with malignant biliary strictures (103), entails placement of external catheters into the obstructed biliary system under ultrasound guidance. In cases of complex hilar strictures, placement of multiple external biliary catheters may be necessary to achieve complete drainage. Disadvantages of external drains are the need for frequent catheter exchanges due to their tendency to clog or displace, patient discomfort, and the constant reminder to them of their disease (104). Other reported disadvantages are the risk or hemorrhage during the puncture, spontaneous dislodgement of the catheter, inflammation and pain at the puncture site, leaks of ascites and bile, and loss of fluid and electrolytes. For these reasons, external drains are more often used to guide endoscopic drainage ("rendezvous procedures") in difficult Bismuth type III and IV strictures or as a temporizing measure for patients after a failed endoscopic procedure. In such patients, internal drainage with percutaneous insertion of plastic or self-expandable metal stents (SEMS) may be attempted. It is well established that SEMS have a longer patency than plastic stents for malignant common bile duct strictures and they become cost-effective in patients who survive for at least 3–6 months (105), while limited but promising data favor the use of SEMS also in proximal lesions (106).

When hilar strictures involve the main hepatic confluence, there is controversy as to whether partial or complete biliary drainage should be done. Inal *et al*. (107) performed percutaneous drainage with SEMS in 138 patients with hilar malignant strictures by placement of one (N = 74) or two (N = 64) stents. The overall complication rate, as well as stent patency in Bismuth type II and III strictures did not differ between the two groups, while in type IV strictures placement of two parallel stents (Y configuration) through dual transhepatic accesses was associated with a significantly longer patency than with single stent insertion (107).

ENDOSCOPIC DRAINAGE. Endoscopic drainage of patients with malignant hilar strictures is technically difficult and should only be performed in referral centers with adequate case volume and expertise. Infectious complications after ERC and stent insertion occur in 5–38% of patients (Table 5) and are the result of contrast injection above the stricture without adequate drainage of all opacified ducts. As with PTD, whether unilateral or complete liver drainage should be attempted in complex hilar strictures is still a matter of debate. It is known that only 25–30% of the liver needs to be drained to achieve relief of jaundice (117). Therefore, a single stent into one lobe of the liver free of disease should theoretically provide adequate palliation of jaundice. All the published series investigating this issue (108, 111, 113) have compared unilateral with bilateral stenting. The only study with a prospective randomized design is the one conducted by De Palma *et al*. (113), in which 157 consecutive patients with malignant hilar obstruction were randomized to either unilateral or bilateral hepatic duct drainage. In the intention-to-treat analysis, unilateral drainage was associated with a significantly higher rate of successful stent insertion (88.6% *vs* 76.9%, $P = 0.041$) and drainage (81% *vs* 73%, $P = 0.049$), and a significantly lower incidence of early complications (18.9% *vs* 26.9%, $P = 0.026$), primarily because of a lower rate of cholangitis (8.8% *vs* 16.6%, $P = 0.013$). These

**Table 5.** Results of Endoscopic Palliative Drainage of Malignant Hilar Strictures

| | | | | Complete Drainage | | Incomplete Drainage | |
|---|---|---|---|---|---|---|---|
| Author (ref) | Year | Study Design | No. of Patients | Cholangitis (%) | 30-Day Mortality (%) | Cholangitis (%) | 30-Day Mortality (%) |
| Deviere *et al*. (108) | 1988 | Retrospective | 48 | 17 | 8 | 38 | 29 |
| Polydorou *et al*. (109) | 1989 | Retrospective | 151 | – | – | 11 | 16 |
| Polydorou *et al*. (110) | 1991 | Prospective | 132 | – | – | 10 | 25 |
| Chang *et al*. (111) | 1998 | Retrospective | 98 | 0 | 3 | 20 | 14 |
| Hintze *et al*. (112) | 2001 | Prospective (MRC) | 35 | – | – | 6 | 6 |
| De Palma *et al*. (113) | 2001 | Prospective | 157 | 18 | 11 | 18 | 7 |
| De Palma *et al*. (114) | 2003 | Prospective (MRC + SEMS) | 59 | – | – | 5 | 0 |
| Freeman *et al*. (115) | 2003 | Prospective (MRC/CT + SEMS) | 25 | – | – | 0 | 0 |
| Singh *et al*. (116) | 2004 | Prospective (MRC + SEMS) | 18 | – | – | 0 | 0 |

MRC = magnetic resonance cholangiography; CT = computed tomography; SEMS = self-expandable metal stent.

results, however, need to be interpreted with caution because of some study biases. One-third of the patients in each group had a Bismuth type I stricture, for which one stent is sufficient. Subgroup analysis of these cases was not performed; thus, it is impossible to determine how their inclusion might have affected the results. Furthermore, the authors placed only one or two stents, which, in cases of complex hilar strictures (Bismuth type III and IV), would not be sufficient for complete drainage. In fact, the number of stents needed to achieve complete drainage should be equal to the number of obstructed ducts at the primary and secondary (right or left) hepatic confluence (*i.e.*, three stents for Bismuth type III and IV strictures). Thus, bilateral stent placement might have resulted in a higher rate of cholangitis because some of the ducts filled with the injected contrast were left undrained.

CT or MRC may also help to select the optimal hepatic lobe and biliary segment(s) to be drained (112, 114, 115). Once the biliary anatomy is delineated by MRC, selective guidewire cannulation and stenting of the targeted hepatic lobe can be accomplished, without contrast injection. Hintze *et al*. (112) used this technique in 35 patients with nonresectable Klatskin tumors (13 type III and 22 type IV), in whom a single plastic 10-Fr stent was inserted in the targeted duct. Only two patients (6%) developed cholangitis within the first 30 days. In another study by Freeman and Overby (115), MRC- or CT-guided SEMS placement was evaluated in 35 patients (31 unilateral, 4 bilateral). No early complications were observed, resolution of jaundice was achieved in 76% of the cases, and no further intervention was required in 71%. Median survival was significantly longer in patients with successful drainage than in those with failure (7.5 months *vs* 1.4 months, $P < 0.05$) (115).

The results of this study also support the use of SEMS over plastic stents for the endoscopic palliation of hilar tumors, as previously suggested by a few nonrandomized studies (111, 118). This conclusion is also sustained by a small prospective randomized trial reporting a substantially lower rate of cholangitis and resultant hospitalization when SEMS were placed (9 patients) as compared with plastic stents (11 patients) (119). Uncovered SEMS are usually recommended for hilar tumors, in order to avoid blockage of smaller biliary branches joining the main ducts at the hilum. Multiple SEMS placement can also be facilitated by using a temporary plastic stent, as recently suggested by a feasibility study by the Brussels group (120).

Which is the best endoscopic approach (unilateral *vs* complete drainage and SEMS *vs* plastic stents) for palliation of hilar strictures still remains to be determined. Prospective, randomized controlled, multicenter studies to answer these important clinical questions are needed.

RADIOTHERAPY AND CHEMOTHERAPY. HCCA is a slow-growing tumor that tends more frequently to have a locoregional recurrent pattern after a potentially curative resection (121). Local control of the tumor with radiotherapy or photodynamic therapy (PDT) may thus translate into sustained palliation and prolonged survival, while for metastatic disease chemotherapy is preferred option.

The most common form of radiotherapy used in HCCA is external beam radiotherapy (EBRT), which is usually prescribed in a dose of 42–50 Gy. EBRT can be administered alone as neoadjuvant or adjuvant therapy or as a means of local tumor control after biliary palliation. However, the effects of EBRT alone as adjuvant therapy or after stenting in this clinical setting remain controversial (122–126), and most of the studies are retrospective and conducted on a small number of patients.

In view of the presence of radiosensitive organs that limit the dose of EBRT that can be delivered, different methods of intensification of radiotherapy, such as brachytherapy, intraoperative radiotherapy, and combined chemotherapy and radiotherapy, have been developed.

Intraluminal brachytherapy (ILBT), which allows local delivery of a high dose of radiation (30–50 Gy) at 1–1.5 cm from the source axis with minimal exposure to adjacent organs, seems promising. The use of ILBT for cholangiocarcinoma was first described in 1979 (127). Iridium-192 seeds are usually placed inside percutaneous drains, but an endoscopic approach is also possible (128–130). Malignant strictures may be temporarily reopened by ILBT. A recent paper (131) reported 25 patients with nonresectable cholangiocarcinoma who underwent percutaneous drainage of biliary strictures, EBRT plus ILBT, and cholangiography 2–6 wk after the completion of radiotherapy. Disappearance of the biliary strictures allowing for removal of the drainage was observed in 19 cases (76%). However, recurrence of stricture after a mean of 76 days led the authors to conclude that biliary drainage by plastic stent or SEMS is mandatory after ILBT to obtain long-term relief from jaundice (131). Endoscopic placement of two or more biliary SEMS in addition to ILBT (Fig. 5) appears to not only prolong the stent's patency, but also improves the survival (27% after 2 yr) in inoperable patients with Klatskin tumors (129, 132). A combination of EBRT and high-dose ILBT (group A) was superior to EBRT alone (group B) to treat patients with nonresectable HCCA. The overall 2-yr survival rate was significantly greater in group A than in group B (21% *vs* 0%, $P = 0.015$) (133).

There is no standard chemotherapy protocol for HCCA, but 5-fluorouracil, gemcitabine, and cisplatin have been used in uncontrolled trials (69). The combination of 5-fluorouracil with cisplatin is considered as one of the standard treatments, and the response rates are reported to vary from 20 to 40% (134, 135).

The combination of radiotherapy and chemotherapy is theoretically the most attractive treatment for patients with unresectable HCCA with a lesion less than 2 cm in size and no evidence of distant metastases. The initial experience with this combination therapy is encouraging, with several studies reporting a beneficial effect (130, 136). In a recent study, a combination of EBRT and transarterial infusion of chemotherapeutic agents (epirubicin, mitomycin C, and 5-fluorouracil)

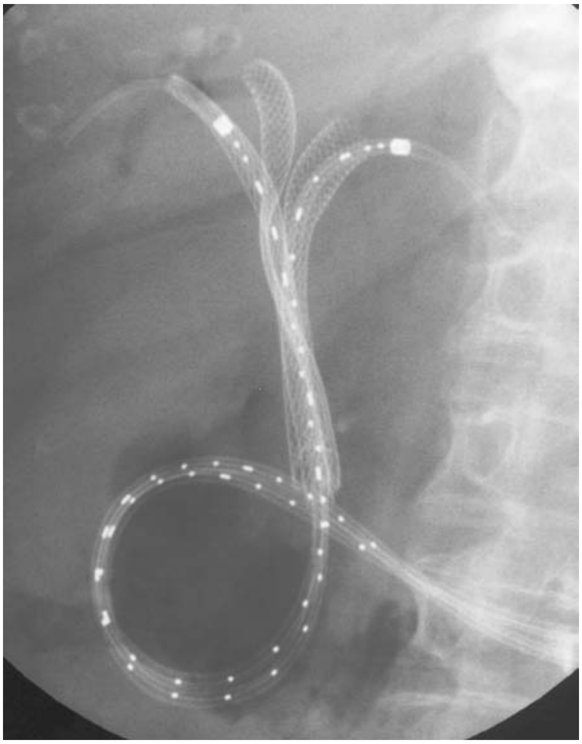


**Figure 5.** Fluoroscopic view of three metal stents endoscopically placed in a patient with type III hilar stricture due to cholangiocarcinoma. The Ir-192 wires are inserted through two nasobiliary drains.

after infusion of a vasoconstricting agent (epinephrine) was used in 23 patients with nonresectable HCCA (137). Stricture relief was obtained in 41% of the patients.

An interesting approach for the management of locally unresectable HCCA is neoadjuvant biliary brachytherapy with chemotherapy followed by OLT. Excellent results were recently presented by the Mayo Clinic group (101), as previously discussed in the surgical treatment section.

PHOTODYNAMIC THERAPY. PDT is a promising new technique, which involves intravenous administration of a photosensitizing agent (sodium porfimer or $\delta$-aminolaevulinic acid, ALA) that selectively accumulates in malignant cells. An ERC is performed 1–2 days later, and a catheter with a laser quartz fiber is inserted into the bile ducts at the level of the stricture. A 630 nm wavelength of red light that destroys the sodium porfimer-sensitized malignant cells is then delivered over about 10 minutes.

In the recent nonrandomized studies on a small number of patients with unresectable cholangiocarcinoma, PDT decreased serum bilirubin concentration, and improved quality of life and survival (138). Only one prospective randomized trial has been published to date, in which PDT with stenting ($N = 20$, group A) was compared with stenting alone ($N = 19$, group B) in patients with Bismuth type II, III, and IV nonresectable cholangiocarcinoma (139). An impressive improvement in survival was observed in the PDT group (median 493 days *vs* 98 days, $P < 0.0001$).

PDT has also been used as a neoadjuvant treatment in a series of seven patients before surgical resection for HCCA (140). PDT achieved selective destruction of the superficial 4-mm layer of the bile duct tumor. One year after treatment, the recurrence-free survival rate was 83%.

The major downsides of PDT are the limited availability, the high costs, and the photosensitivity reaction that occurs with the administration of sodium porfimer that may last from 4 to 6 weeks after use of the compound.

## MANAGEMENT OF POSTOPERATIVE HILAR STRICTURES

### *Surgical Treatment*

Postsurgical biliary strictures (POBS) were originally classified by Bismuth and Lazorthes according to the lowest level at which healthy biliary mucosa is available for anastomosis (5, 6) (Fig. 3). Surgical repair of biliary injuries is difficult and requires specific skills and experience. Apposition of healthy biliary mucosa to the jejunal mucosa of a Roux-en-Y loop is essential for the long-term success of a biliary repair.

Strictures involving the hepatic hilum (types III, IV, and V of Fig. 3) are intuitively the most difficult to treat. In type III strictures, in which the ceiling of the biliary confluence is intact and the right and left ductal systems communicate, the dissection is continued until the hilar plate is lowered and is followed by an anterior opening of the left duct to provide a satisfactory length of healthy mucosa for anastomosis. In type IV strictures, the ducts are separated or communicate only by a narrow opening with indurated lining; thus, reconstruction of the ceiling of the biliary confluence or alternatively separate anastomoses of the right and left ducts have to be performed. Finally, in type V lesions, in which a separate right duct is present in addition to stenosis of the main bile duct, reconstruction of a new biliary confluence or creation of a separate anastomosis is mandatory.

Surgical repair of hilar strictures is associated with worse outcomes as compared to the repair of lesions below the hepatic confluence. In a recent series, for example, stricture recurrence and cholangitis occurred in 14% of patients with hilar lesions, whereas no patient with lesions below the biliary junction had such complications (141).

When POBS are subclassified into type IIIA (the confluence, roof, and floor are healthy) and type IIIB (floor of the confluence involved and roof is healthy), a significant reduction in mean operative blood loss, units of blood transfused, and duration of surgery was found in type IIIA. Recurrence of biliary symptoms occurred in 13% and 9% of patients with types IIIA and B, respectively, after a mean follow-up of 5.4 yr (142). Overall, data coming from large series have demonstrated the surgical repair of POBS to be safe, with a complication rate of 17–26% and no mortality (143–145). However, long-term follow-up studies have shown that 12–45% of patients will experience recurrent symptoms due to newly formed strictures at the anastomotic site(s) (145, 146).

***Endoscopic Treatment***

Endoscopic treatment of POBS is safe and effective. The “classical” approach (147, 148) involves temporary placement of two 10-Fr plastic stents for 1 yr with elective exchange every 3 months, to avoid cholangitis due to stent clogging. Endoscopic stenting is possible in about 80% of cases. Long-term (mean 9.1 yr) follow-up data in one cohort of 47 patients treated in this way revealed a stricture recurrence rate of 20%, with symptom onset at a mean of 2.6 months (range 1 wk–2 yr) after stent removal (149). Eight patients had benign hilar strictures (Bismuth types III, IV, and V) and stricture recurrence was higher in this group. Proximal strictures are more difficult to treat endoscopically, and are more frequently associated with recurrence. In the above series, the hilar strictures recurred in all cases within 2 years of stent removal, likely due to incomplete dilation of the stricture.

Our group has proposed a more aggressive strategy with placement of the maximum possible number of stents. These stents are then exchanged every 3–5 months, with an increase in the number of stents in each procedure, until the complete morphological resolution of the stricture (150). In our series of 40 patients (18 with hilar strictures), only one recurred during a mean follow-up of 4 yr (range 2–11 yr), with an overall success rate of 89%. This multistent technique is now the preferred approach for hilar POBS in many centers. The use of SEMS in this clinical setting must be discouraged due to the unacceptable rate of late occlusion caused by tissue ingrowth through the mesh of the stent (151).

## SUMMARY AND FUTURE PERSPECTIVES

Although surgery remains the mainstay of treatment for hilar strictures, improvements in preoperative diagnosis and staging may prevent unnecessary complex and risky surgery. As interventional cardiologists now use drug-eluting stents for coronary strictures, chemotherapy-impregnated biliary stents may be valuable in the management of malignant hilar strictures (152). In addition, more data are needed concerning the palliative and therapeutic value of adjuvant therapies, including ILBT, PDT, and the experimental high-frequency ultrasonography (153). Lastly, the development of chemotherapeutic agents, specifically targeting receptors expressed by cholangiocarcinoma cells (EGF, cyclooxygenase-2), will improve tumor response rates with decreased systemic side effects.

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## CONFLICT OF INTEREST

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