

The role of endoscopic treatment in palliative care of hilar malignant strictures

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SUMMARY

Malignant hilar strictures (MHS) are caused by a heterogeneous group of tumours. They have an extremely poor prognosis, with the vast majority of patients dying in the first year after the diagnosis. Palliation of patients with MHS is a difficult clinical problem with little consensus regarding the optimal treatment approach. The choices for palliation of jaundice in these patients include surgical bypass and percutaneous or endoscopic drainage. Endoscopic endoprosthesis insertion has a high successful drainage rate, is associated with acceptable morbidity and low procedure related mortality. Endoscopic biliary stenting can offer effective palliation of jaundice, improve the global quality of life and a variety of symptoms. Those working with endoscopic biliary stenting need to be familiar with the indications, the endoscopic difficulties and be able to recognise and deal competently with the complications. In this article we review the experience with therapeutic ERCP in the management of MHS.

Type I: stenosis within the common hepatic duct.

Type II: stenosis limited to primary confluence.

Type III: stenosis involving either the right (type IIIa) or the left (type IIIb) secondary intrahepatic ducts.

Type IV: stenosis involving the secondary intrahepatic ducts bilaterally.

MHS are caused by a heterogeneous group of tumours that includes primary bile duct cancer (commonly referred to as Klatskin tumour),³ cancers that involve the hepatic confluence by direct extension (gallbladder and hepatocellular carcinoma) and metastatic cancer. MHS account for less than 20% of extrahepatic bile duct carcinomas.⁴ These tumours have an extremely poor prognosis, with less than 10% of patients surviving 5 years, while the vast majority die in the first year after diagnosis.^{3,5} In this article we review the experience with therapeutic ERCP in the management of MHS.

INTRODUCTION

Hilar malignancy was first reported in 1957.¹ Malignant hilar strictures (MHS) are classified according to the degree of involvement of the adjacent bile ducts, by the classification proposed by Bismuth and Corlette,² as follows:

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PRETREATMENT EVALUATION

The majority of MHS are due to gallbladder carcinoma and cholangiocarcinoma, while in few cases the responsible tumour is hepatoma or metastatic disease.^{6,7} The diagnosis and differential diagnosis is often difficult and US, CT and mainly MRI are used in the work-up of these patients. MRI cholangiography is able to identify the presence of biliary tract dilatation, give indication of the site of obstruction and the presence and extent of liver infiltration.⁸ This information is useful in planning subsequent therapeutic interventions, selecting patients who will benefit from a drainage procedure, and decreasing the time of the procedure and risk of complications.

Histologic confirmation of hilar malignancy is fre-

quently established by surgically obtained biopsy, by specimens obtained during ERCP with biopsy forceps or biliary brushing and by percutaneous tissue sampling. When no histological diagnosis is possible the diagnosis may be presumed, based on the clinical findings and the typical features on radiological imaging. Thus, diagnosis is often based on a high index of suspicion for malignant disease in patients who present with radiographic evidence of hepatic duct bifurcation obstruction, with no previous history of biliary tract disease or intervention and no associated features to suggest primary sclerosing cholangitis or infective agents.

In many cases, a double stricture of the common bile and pancreatic ducts (double-duct sign) in radiography is commonly accepted as indicative of carcinoma of the head of the pancreas. On the other hand, an eccentric stricture of the common bile duct and, at the same time a lacking in opacification of the gallbladder, is indicative of gallbladder carcinoma.

In spite of the typical radiographic features and the classical clinical presentation, the presumed diagnosis of malignancy may remain in question. In two large series,^{9,10} among 186 patients diagnosed with malignant hilar tumour preoperatively, 19 were found to have benign lesions on examination of surgical or postmortem specimens.

THERAPEUTIC APPROACH

General consideration

The therapeutic approach is usually determined on an individual basis and depends on the location of the stricture and the extent of intrahepatic ductal involvement. The choice of therapy should take the following into account.¹¹

1. The general condition of the patient, including assessment of life expectancy, quality of life and residual hepatic function.
2. The effectiveness of the various therapies.
3. The anatomy and, if possible, the histology of the obstruction.
4. The cost of therapy.
5. The risk of the procedure, including the potential introduction of new problems into the patient's life.
6. The expertise at a given institution.

These factors should be weighed in each case and the appropriate treatment should be individualised accordingly.

Surgical treatment of hilar malignancy

Surgical resection remains the main chance for cure, but the majority of these tumours are non-resectable, with a resection rate ranging from 5% to 20%.¹² For this reason, patients with metastatic disease affecting the porta hepatis and invasive gallbladder or hepatocellular carcinoma causing hilar biliary obstruction are not candidates for curative resection. Aggressive surgical therapy was performed in the past but the 5-years survival rate in 499 patients compiled from 40 series reported since 1980 was 13%, with 12% operative mortality.¹³

On the other hand, palliative surgery is usually difficult, often impossible. Surgical approaches to palliation have included a variety of internal or external drains and hepaticoenteric bypass. Although, surgical bilioenteric bypass has been the traditional palliative approach, this therapy cannot be applied in all patients. Operative mortality has been reported to be high, approximately 20%^{2,5,14} and when extensive resection is required it rises to 33%.¹⁵ Nowadays, gastroenterostomy is performed in selective patients with MHS only to prevent future duodenal obstruction. However, randomised controlled trials comparing endoscopic stenting and palliative surgery have failed to demonstrate a survival benefit for surgery,^{16,17} except the fact that surgically treated patients have fewer late complications.¹⁸

Percutaneous transhepatic treatment

In view of the risks and difficulties of surgery in patients with MHS, many authors advocate palliative bypass by percutaneous transhepatic cholangiographic drainage (PTCD). PTCD was the first developed non-operative biliary intervention for obstructive jaundice. Several options exist for percutaneous drainage. These include either draining only one ductal system (in IIIA and IIIB obstructions or when there is atrophy of the contralateral lobe), or draining both systems by using drains in a Y-shaped or T-shaped configuration.⁸

The percutaneous approach is associated with problems of multiple puncturing of the liver, bile leakage, haemorrhage and sepsis. Incomplete opacification of intrahepatic ducts is not an uncommon event, and in some cases 15-20 punctures of individual ducts may be required.^{19,20} The reported rate of serious complications after PTCD varies between 3.4% and 4.8%.²⁰ Moreover, the 30-day mortality after percutaneous stent insertion in one study was as high as 39%.²¹ However, PTCD is generally considered superior to the endoscopic retrograde route in cases of hilar strictures with complete obstruction of the biliary duct. In addition, combined per-

cutaneous and endoscopic procedures (rendezvous technique), in order to achieve complete drainage of both liver lobes, are used in more than 25% of patients in one study.²²

Endoscopic treatment

Although the percutaneous transhepatic technique is considered to have good results, prospective randomised trials have reported that the endoscopic approach is apparently superior for definitive biliary drainage, leading to better results in MHS.²³ With the advent of large channel therapeutic duodenoscopes in 1982, endoscopic insertion of large diameter plastic biliary endoprotheses became possible. Nowadays, endoscopic retrograde cholangio-pancreatography (ERCP) is particularly valuable in the management of MHS, where it may play a diagnostic as well as a therapeutic role. Thus, ERCP is frequently used in management focused on palliation of MHS. Endoscopic stenting is safe, less invasive, and comfortable for the patients, has low cost, high success rate for relief of jaundice, improves comfort and nutritional status of the patients and has a relatively low morbidity and mortality. In addition, during the same procedure, brush cytology and biopsy for diagnosis can be accomplished.

ENDOSCOPIC PROCEDURES FOR THE TREATMENT OF MALIGNANT HILAR STRICTURES

Patient preparation

A review of the medical history, medication, allergies and a physical examination must be performed before the therapeutic procedure. All patients must undergo routine pre-procedural testing including a complete blood count, serum electrolytes, liver function tests and coagulation studies. Ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI) performed before admission facilitate the intervention. Each patient must give informed consent after being informed of the risks and benefits and alternatives to therapeutic ERCP. All patients must receive antibiotics intravenously to cover gram-negative organisms immediately before and for a variable period after the procedure, depending on clinical circumstances. The antibiotic chosen should penetrate an obstructed biliary tree (Cefoxitin, Cefamandole, Piperacillin plus Tazobactam, etc).

Endoscopic examination and stenting are conducted under conscious intravenous sedation. Hysoscine-N-butylbromide (Buscopan) is given intravenously as needed to reduce duodenal peristalsis. Glucagon could be used

in selected cases. Vital signs including pulse and respiratory rate are monitored continuously. All patients must receive low-flow oxygen via nasal cannula throughout the procedure.

Strictures' approach

Experienced endoscopists must perform the procedure with the assistance of two hepatobiliary fellows, by the use of a large channel duodenoscope. An adequate sphincterotomy greatly facilitates the general manoeuvre of instruments such as guide-wires, balloons and stents.

After cholangiography, the endobiliary stents are inserted, over a guide-wire and coaxial catheter, across the stricture to secure optimal biliary drainage. A hydrophilic atraumatic guide-wire with a flexible tip and a more rigid body is useful for negotiating difficult and tight strictures.

It is preferable to begin by cannulating the left ductal system as this is usually the more difficult. In order to facilitate selective cannulation, the guide-wire is inserted into a catheter with pre-curved tip. Once the guide-wire is inserted into a biliary segment, the anatomy must be demonstrated by contrast injection. It is important (in stenosis type II or greater), that bilateral guide-wire access is obtained before dilatation, because dilatation makes subsequent passage of a guide-wire into the undilated system extremely difficult. Dilatation of the stricture is performed using a hydrostatic guide-wire, guided balloon or gradual bougie.

Stent placement

The success rate of endoscopic stent placement ranges from 84 to 94%¹¹. Stent diameter is chosen on the basis of the maximal size that could be inserted, taking into account the possible need for two or more stents in selected cases. Polyethylene stents 8.5, 10 and 11.5 F in width, 10, 12 and 15 cm in length or self-expanding metallic endoprosthesis are used. The dimensions of the stents are selected depending on the underlying anatomy. The angulation of the left biliary system makes stent deployment difficult and, accordingly, the left side stent is inserted first. In addition, the endoscopist must take into account that the mean length of the right hepatic duct is about 0.9 cm with early division into secondary branches, whereas the left hepatic duct has a longer course of 3 to 3.5 cm before dividing¹¹.

The major disadvantage of plastic stents is obstruction which occurs within 3 months in 30% of cases and in 6 months in up of 70%¹. More recently, metal expandable stents are used to treat patients with MHS with a high success and lower reintervention rate.^{1,24} The ex-

pandable diameter of metal stents is up to 30F and they have a median patency of 9.8 months.²⁵ These devices, however, are expensive, difficult to reposition and may be occluded due to tumour ingrowth. The choice of plastic or metal expandable stents for MHS palliative treatment needs to be looked at, with emphasis on their cost-effectiveness²⁶. Prospective randomised studies have suggested that metal stents are more cost effective in patients who have a relatively longer life expectancy.^{27,28}

Stenting difficulties

In about 4% of patients it is not possible to reach the papilla.⁶ The reasons for failure are usually duodenal stenosis or previous Billroth II gastrectomy. In our study,⁶ 7% of the patients were characterised unsuitable for endoscopic stenting after cholangiography, on the basis of diffuse involvement of the tumour, while in 5% of the patients the attempt to stent was unsuccessful. In these conditions, the patients were subjected to PTC and in many cases the percutaneous catheter was subsequently converted into an internal endoprosthesis with the combined percutaneous-endoscopic approach.

Unilateral or bilateral drainage?

A single stent is sufficient for lesions limited to the common hepatic duct (type I stenosis), when the obstruction is limited to one ductal system, or when there is atrophy of the contralateral lobe. For strictures type II or greater, endoscopic studies focusing on the outcome of unilateral versus bilateral liver lobe drainage have revealed conflicting results.^{1,4,6,11,12,22,29}

According to some authors, draining only 25% of the hepatic parenchyma will palliate the clinical and metabolic sequelae of biliary obstruction.^{4,30} They suggest that drainage of 25% of the liver volume is needed to achieve biochemical improvement and relief of symptoms. In addition, they suggest that, when given a choice of a duct in which to place a stent, the endoscopist should select the technically easiest duct for the procedure, provided that more than 25% of the liver parenchyma is drained. It does not seem to be of any advantage to choose one lobe of the liver over the other. An understanding of the biliary anatomy provides a framework to help make a decision. Approximately 55% to 60% of the liver volume is drained via the right hepatic duct, 30% to 35% by the left hepatic duct and the caudate lobe accounts for 10%.^{31,32}

However, concerns regarding unilateral drainage alone include the inability to relieve jaundice and the potential for bacterial contamination of an undrained segment, especially when contrast is introduced, increas-

ing the danger of biliary sepsis and death. For this reason, many authors believe that draining both sides is necessary to provide adequate palliation and to prevent early cholangitis.^{1,4,6,22} In general terms, bilateral drainage is technically demanding, but drainage of both obstructed ductal systems has been shown to significantly reduce the morbidity and mortality rate due to decreased incidence of cholangitis and septicemia.²²

In our study,⁶ we have tried to insert multiple stents to achieve complete biliary drainage, which was successful in 58.7% of patients with MHS. We observed that, the incidence of complications was significantly lowered in patients with complete, compared with those with incomplete, biliary drainage. In addition, Deviere et al²², comparing the outcome of patients with complete or incomplete drainage concluded that complete drainage was associated with significant increase in mean survival, lower 30-day mortality, less frequent early cholangitis and less death from sepsis.

However, the decision to drain one or more biliary ducts, should be made on an individual basis and depends on:

- a. the general condition of the patient
- b. the underlying diagnosis
- c. the residual hepatic function
- d. the presence of cholangitis
- e. the extent of biliary obstruction

Procedure related cholangitis

Prosthetic palliation of patients with MHS poses particular difficulties, especially in advanced lesions (type II or higher). The risk of cholangitis after contrast injection into the biliary tree in cases where incomplete drainage is achieved is well known. The post-procedure cholangitis rate varies in various series between 3% to 38%.^{1,4,6,11,12,21,22,27,28,31} Several factors, such as stricture type, drainage completion and use of antibiotics may explain these differences.

As was mentioned above, retention of the contrast and subsequent segmental cholangitis is a risk associated with endoscopic attempts to treat advanced hilar strictures. However, there is a theoretical concern that even in the absence of contrast contamination, there may be an increased risk of cholangitis in an obstructed segment, related to the rise in intrabiliary pressure affecting normal host defence mechanisms. Factors that may increase the sepsis in obstructed biliary tree have been reviewed.²³ These include disruption of the tight junctions between

hepatocytes, impaired Kupffer cell function, and lack of clearance of contaminants, which occurs with the normal bile flow. In addition, the protective action of secretory IgA and biliary mucus, which prevent bacterial adherence, is lost.

To prevent procedure related cholangitis, minimal contrast medium should be injected only into the duct to be drained. Once access is obtained to the obstructed segment, the pressure in the system should be reduced before more complete filling by aspirating bile. Manipulation of ducts that will not be drained should be avoided if possible. Nevertheless, if post-procedure cholangitis occurs, ERCP or PTCO to drain the obstructed lobe of the liver, should be performed promptly.

Post-procedure control and follow-up of the treated patients.

At the end of the procedure the endoscopist must assess the successful endoprosthesis placement. This is estimated from observation of bile flow through the stent after the successful passage across the stricture, together with clinical improvement, reduction in serum bilirubin and bilateral aerobilia on a plain abdominal radiograph at 48 hours after stenting.

All patients must be informed of the possible symptoms of stent blockage and regularly undergo clinical and biochemical examination. In the case of post-procedure sepsis or unrelieved jaundice, the patients must be referred for further drainage. Stents should be replaced when there is clinical evidence of occlusion.

Early complications

Early complications are defined as those occurring within 30 days of stent placement. These occurred in 18.9 - 26.9% of treated patients.^{1,6,12,26-29} Early complications in our study were recorded in 26% of the patients⁶, the main being: acute cholangitis (10%), haemobilia in (5%), early stent dysfunction (5%), bleeding (3%), intrahepatic abscess (3%), acute pancreatitis (1%), retroperitoneal perforation (1%) and acute cholecystitis (0.6%). Patients with type III and type IV strictures had a higher complication rate compared to patients with type I and type II strictures. In addition, patients with complete biliary drainage had a lower complication rate compared to patients with incomplete drainage.

Late complications - Stent occlusion

Late complications occur in 35 to 42%^{4,12,33} of the patients and are related to stent occlusion. This is a result

of biliary sludge formation as has recently been reviewed³³. The overall mean duration of stent patency is 3 to 4 months,^{6,26} and stent obstruction is revealed by recurrence of jaundice, fever, pruritus and pain or deterioration of liver function in the blood biochemistry tests. Blocked plastic stents can be removed endoscopically and usually replacement is easier than initial insertion as there is a pre-existing channel. Treatment with broad-spectrum antibiotics is advocated for a short period of time. In case of self-expanding metal stent dysfunction, a plastic stent may be inserted through the metal wire mesh.

Enhancing plastic stent patency could require multiple strategies as larger inner diameter of the stents, improved materials which avoid bacterial adherence, lacking of side holes and straight shape of the stents to promote bile flow and the use of antimicrobials either incorporated into the stent or exogenously administered.³⁴

Survival in endoscopically treated patients

In endoscopically treated patients with MHS, the 30-day mortality rate ranges from 0% to 43% in various studies.^{1,4,6,11,12,22,28,29,33} In many reports, procedure related cholangitis and sepsis is the main cause of 30-day mortality.^{4,11,12,22,28} In our study⁶ the 30-day mortality rate was 9.2% and the more frequent ascertained causes of early death were: tumour-related poor general conditions, septicæmia and gastrointestinal bleeding.

The mean survival of patients with MHS undergoing endoscopic drainage ranges from 46 to 225 days.^{4,6,11,12,22,29,33} The best survival is usually noted in patients with bilateral drainage,^{4,6,22} in type I strictures and in these with a diagnosis of cholangiocarcinoma.^{6,12} The mean survival in our study⁶ was 196.2 days (range 1 to 1500 days), from the first attempted drainage procedure. The mean survival in patients with complete drainage was significantly longer than in those with incomplete drainage, as it has been previously reported.²² There was a survival advantage in the patients without distal metastasis and in those with a proven diagnosis of cholangiocarcinoma who additionally underwent intraluminal irradiation with Ir¹⁹². A survival disadvantage was observed in patients who additionally underwent PTCO or surgical intervention.

Endoscopic stenting improves quality of life?

Stenting in patients with malignant biliary obstruction relieves jaundice and greatly reduces the length of hospital stay.^{23,35} It is also well established that, endoscopic treatment improves quality of life by relief of pruritus and nausea of cholestasis.³⁶ In addition, after biliary stenting there is a clear improvement in emotional and cog-

nitive functions, in appetite, sleeping and steatorrhoea, in parallel with objective improvement in liver function tests.³⁷

Additional advantages of endoscopic stenting

Although many studies have failed to show that biliary drainage for patients with MHS offers worthwhile advantages, emphasising the significant risk of cholangitis,^{38,39} ineffective endoscopic drainage and high procedure related mortality⁴⁰, the prompt improvement in hepatic function after endoscopic approach underscores its validity. Moreover, internal drainage reverses the negative metabolic effects, deranged T and B cell function and results in a more rapid recovery of cell mediated immunity.⁴¹

However, the desired outcomes of endoscopic stent placement include not only clinical and biochemical amelioration, but also the opportunity for further palliative treatment. In potentially responsive tumours, radiotherapy or chemotherapy should be considered after endoscopic stenting. Certain chemotherapeutic agents cannot be safely administered to patients with jaundice without considerable dose reduction. Endobiliary stenting can relieve jaundice and allow safer and potentially more aggressive cancer treatment.⁴² In addition, internal biliary drainage followed by intraluminal Ir¹⁹² radiotherapy, is well known as likely to improve the survival of patients with hilar cholangiocarcinoma.^{6,42}

Conclusions

In conclusion, endoscopic stenting is an acceptable therapeutic approach for patients with malignant hilar stricture. Therapeutic ERCP for palliation of malignant hilar obstruction can be safely and successfully performed. Endoscopic stent insertion considerably improves a range of symptoms and enhances quality of life. Improvement of stent materials to prevent early blockage remains an active area of research. Newer methods of non-operative endobiliary stenting certainly warrant consideration for the future.

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