Overview of Malignant Biliary Obstruction: Clinical Features and Management

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Abstract: Malignant biliary obstruction (MBO) is a challenging condition, requiring a multimodal approach for both diagnosis and treatment. Malignant bile duct strictures are usually due to pancreatic adenocarcinoma and cholangiocarcinoma. The diagnosis of malignant biliary obstruction involves a combination of clinical assessment, diagnostic imaging, tissue sampling, and minimally invasive options, with the primary aim of identifying candidates for curative resection. The most common causes of obstruction are pancreatic adenocarcinoma and cholangiocarcinoma, and most cases are too advanced for surgical options. Palliative options for biliary drainage, such as covered stents, bare metal stents, and plastic stents, are provided by interventional radiologists and gastroenterologists. This article offers an updated review of the clinical features and options for the management of MBO.

Keywords: Malignant Biliary Obstruction; Clinical Features; Management

Tob Regul Sci. ™ 2022 ;8(2): 617-624
DOI : doi.org/10.18001/TRS.8.2.40

Introduction

The two most common malignant neoplasms known to occlude the bile ducts are pancreatic ductal adenocarcinoma and primary bile duct cancer (cholangiocarcinoma). Other causes of malignant biliary obstruction can include ampullary carcinoma, primary duodenal adenocarcinoma, pancreatic neuroendocrine tumors, or occlusion of the hepatic hilum due to lymphadenopathy at the porta hepatis (1).

Biliary obstructions are typically classified by their location (proximal, distal or mid). Primary tumour infiltration (e.g. cholagiocarcinoma), compression by local extension of other tumours as hepatic, gallbladder, pancreatic cancers, ampullary carcinoma, primary duodenal adenocarcinoma, or extrinsic compression by lymph node metastases are common causes for malignant biliary obstruction (2).

An external drain involves the insertion of a catheter extending from outside the body to the bile ducts, while an internal-external drain involves a catheter from outside the body to the bile duct and extending to the small intestine. Efficacy and appropriateness of treatment type depend on the patient and their expected prognosis, the site of obstruction and local expertise (3).

Clinical Features and Initial Management

The most common clinical presentations of pancreatobiliary cancers include jaundice, weight loss, and anorexia with significant impact on quality of life, morbidity, and mortality **(4)**. MBO leads to jaundice (conjunctiva and skin), discolored stools, dark urine, pruritus, nausea and vomiting **(5)**.

A complete physical examination is necessary to identify jaundice, the presence of organomegaly or lymphadenopathy. Laboratory tests should include total bilirubin, conjugated bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST). Bilirubin levels have been consistently identified as a strong predictor of malignant disease, the higher the bilirubin level at presentation, the greater the likelihood of malignant disease **(6)**.

A retrospective study of 830 patients showed that patients with a biliary stricture and completely normal liver function tests are unlikely to have a primary hepatopancreaticobiliary malignancy. Those presenting with normal bilirubin but an alteration of ALP and/or ALT are more likely to have a malignant disease, requiring a higher degree of clinical suspicion **(7)**.

The most common tumor markers used in the diagnosis or prognosis of pancreaticobiliary cancers are carbohydrate antigen 19–9 (CA 19–9) and carcinoembryonic antigen (CEA). A CA 19-9> 37U/mL showed a sensitivity of approximately 74% in patients with MBO but a very low specificity **(8)**.

Indeed CA 19–9 can also be increased in case of non-malignant pathologies including cholestasis, cholangitis, cirrhosis, acute pancreatitis and other cancers such as gastric and colon cancer **(9)**. CEA showed 33-68% of sensitivity and 75-95% of specificity for cholangiocarcinoma.20 Although they may be useful as prognostic markers, their diagnostic usefulness is limited.22 New biomarkers such as Glypican-1 and micro-RNA's for early detection of pancreatic cancer are currently being studied **(10)**.

Once pancreaticobiliary malignancy is suspected based on the history, physical examination, and initial laboratory test results, imaging studies such as transabdominal ultrasonography (TUS), computed tomography (CT) scan, or magnetic resonance imaging (MRI) and cholangiopancreatography (MRCP) are the next step to establish the diagnosis **(11)**.

A Proposed Diagnostic Algorithm

The first step in the management of MBO is to establish the diagnosis and identify the stage of the disease. According to the availability of imaging modalities, CT-scan and/or MRI are the two main imaging techniques to assess tumor extension, establish vascular involvement and the presence or the absence of metastases. The second step will focus on obtaining tissue samples to confirm the diagnosis:.

i. EUS-FNA if a mass is identified as well as surrounding lymph nodes or identified metastases (ex in the left liver or the peritoneum).
ii. ERCP with biliary brushings and forceps biopsies, if no mass is identified

These two steps aim to identify patients with a resectable disease that can benefit from surgery from the outset of those who will need a neoadjuvant treatment for a downstaging or a palliative treatment in patients with advanced disease **(12)**.

There are several blood biomarkers used in diagnosis and differentiation of cholangiocarcinoma from other similar types of tumorsincluding carbohydrate antigen (CA), carcinoembryonic antigen

(CEA), exostosin1 (EXT1), micro-RNA (miRNA), cathepsin B to cystatin C ratio, heat shock protein (HSP70) related, and angiopoietin-2 (Angpt-2) **(13)**.

Treatment

Factors affecting treatment include resectability, location of the obstruction, patient status, and clinical expertise. The goals of therapy are to improve quality of life (control or delay the onset of tumour-related symptoms) and if possible, prolong life. A multidisciplinary team should be consulted in the treatment of those suspected to have malignant biliary obstruction. The team should include medical oncologists, gastroenterologists, interventional radiologists and hepatobiliary surgeons **(14)**.

I. Resectable

1. Proximal resectable obstructions

Early referral to a hepatobiliary surgeon is recommended to assess resectability prior to any instrumentation. If resection is entertained, a contrast enhanced MRI liver and magnetic resonance cholangiopancreatography (MRCP) are indicated, preferable before a drain is inserted because it is difficult to define the extent of biliary involvement once a stent has been placed. A percutaneous transhepatic cholangiogram (PTC) may assist in staging where noninvasive imaging is unable to clarify the proximal extent of disease. In the context of primary biliary sclerosing cholangitis and concurrent suspected malignant obstruction, PTC is recommended for initial drainage and may be used to obtain brushings **(15)**.

The role of preoperative biliary drainage is controversial for hilar tumors. If a resection is planned, preoperative drainage may be considered to normalize coagulation status and to optimize liver function if an extensive liver resection is planned. The potential benefit of preoperative drainage when remnant liver volume is <30% was shown in patients with hilar cholangiocarcinoma who underwent hepatic resection **(16)**.

Ultimately, until more definitive data are available, the decision for preoperative drainage rests with the operating surgeon. Importantly, if pre-operative biliary drainage is considered, the drainage procedure should provide optimal preservation of the surgical field **(15)**.

If there is a delay to surgery (>1 week) or if drainage would improve the patient's condition, consider insertion of a percutaneous drain (e.g. external or internal/external drain). Endoscopic procedures for proximal obstructions are often technically difficult therefore percutaneous biliary drainage is strongly preferred **(17)**.

A retrospective study comparing percutaneous and endoscopic preoperative drainage in patients with hilar cholangiocarcinoma found higher technical success rate (81% endoscopic group vs. 100% percutaneous group, p=0.20), significantly fewer infectious complications (48% endoscopic group vs. 9% percutaneous group, p<0.05) and significantly fewer additional drainage procedures (2.8 endoscopic group vs. 1.4 percutaneous group, P<0.01) with percutaneous preoperative drainage **(18)**.

2. Distal resectable obstructions

Immediate surgery is preferred. Patients with resectable pancreatic cancer (n=202) compared preoperative endoscopic biliary drainage with plastic stents followed by surgery to surgery alone. This

study found more serious complications in the preoperative drainage group (74% vs. 39%, respectively) and no difference in mortality rates. However, study limitations included a high failure rate and complication rate **(19)**.

This observation is confirmed by a meta-analysis focusing on preoperative drainage for distal obstructions which reported significantly increased infection rates with preoperative drainage compared with no drainage ($p<0.0005$) and no significant difference in mortality and morbidity. They identified 26 studies (including six randomized controlled trials) in their review and the majority of patients (67%) had endoscopic biliary drainage with plastic stents. If there is a delay to surgery (>1 week), consider insertion of an endoscopic plastic stent as a preoperative stent may help to normalize coagulation profile and improve nutritional status. Endoscopic procedures are less invasive than percutaneous procedures and plastic stents are easily removed, however, they may require reintervention due to stent occlusion **(20).**

3. Mid resectable obstructions

Early referral to a hepatobiliary surgeon is recommended to assess resectability. If resection is entertained, a contrast enhanced MRI liver and MRCP are indicated, preferable before biliary drainage is achieved, because it is difficult to define the extent of biliary involvement once a stent has been placed. A contrast enhanced CT of the chest; abdomen and pelvis should be considered, in addition to the MRI and MRCP, to identify metastatic disease **(14)**

If there is a delay to surgery and decompression is needed an endoscopic approach or percutaneous transhepatic cholangiography (PTC) and drainage are viable options. Obstructions at this level require clinician expertise to determine the most appropriate approach to drainage **(15).**

II. Unresectable:

In patients with unresectable or metastatic disease, biliary drainage can be used for palliation. The appropriate approach depends on the expected prognosis of the patient and the multidisciplinary team should be consulted **(21).**

If imaging suggests intrahepatic duct dilatation and no extrahepatic duct involvement, then refer to interventional radiology. If extrahepatic duct dilatation, then consider referral to gastroenterologist for endoscopic procedure. Additional imaging (e.g. MRI liver and MRCP) may be necessary to define the full extent of biliary involvement prior to stenting **(14)**.

There is a lack of evidence to recommend the use of prophylactic antibiotics. A Cochrane review from 2010 suggested that further research was required and there is not enough evidence to support prophylactic antibiotics with an ERCP. If biliary drainage fails to relieve the biliary obstruction then antibiotic administration could be considered **(22).**

4. Proximal unresectable obstructions

Proximal obstructions are best managed with percutaneous biliary drainage. Treatment of these obstructions is dependent on life expectancy.

- If life expectancy < 3 months, consider insertion of a percutaneous internal/external drain.
- If life expectancy > 3 months, consider initial access via insertion of a percutaneous internal/external drain. Thereafter, consider insertion of a metal stent (via percutaneous or endoscopic approach) for patients with excellent performance status and whose condition markedly improved with the insertion

of the internal/external drain. Metal stents have a life span of 6-12 months which could mean repeat consult and insertion of another stent **(23).**

- A systematic review of the management of malignant hilar obstructions identified four studies (one randomized controlled trial and three retrospective studies) that compared endoscopic and percutaneous drainage with or without metal stent. Their results suggest initial percutaneous access is preferred because of higher therapeutic success, shorter time to reach desired drainage and negligible conversion rate **(24).**

In particular, the review included a randomized controlled trial that compared endoscopic biliary drainage with a plastic stent to percutaneous biliary drainage. This study reported a significant difference in therapeutic success for initial percutaneous biliary drainage (89% percutaneous biliary drainage vs. 41% endoscopic biliary drainage, $p<0.001$) **(25).**

The European Society of Gastrointestinal Endoscopy 2012 guideline suggests percutaneous drainage may be associated with fewer complications than the endoscopic approach and that the decision to perform endoscopic drainage be based on local expertise **(26).**

5. Distal unresectable obstructions

Endoscopic drainage with insertion of a metal stent is the treatment of choice. Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred treatment approach for distal unresectable obstructions as it is less invasive and has lower reported complication rates **(27).**

A Cochrane systematic review compared surgery, metal endoscopic stents and plastic endoscopic stents for treatment of distal biliary obstruction in patients with inoperable pancreatic carcinoma. The review included 29 studies and found endoscopic metal stents were associated with a lower risk of recurrent biliary obstruction (RR 0.48, 95% CI 0.38-0.62), but no differences in technical success, therapeutic success, or complications. They also noted that metal stents were reported to have significantly longer stent patency than plastic stents in several studies **(28).**

The stent patency of metal and plastic stents were examined in a retrospective study of patients (n=112) with distal malignant biliary obstructions. A significantly longer mean stent patency was reported for metal stents (278 days) compared to plastic stents (133 days) with no difference in total mean cost **(29).**

If ERCP is unavailable or fails, then percutaneous biliary drainage should be considered to obtain palliative drainage. Definitive placement of a metallic stent can be achieved once the patient's condition has improved percutaneously or by a rendezvous procedure if internal access cannot be achieved percutaneously. A rendezvous procedure involves accessing the biliary tree percutaneously with placement of a guidewire to facilitate the completion of a challenging or failed ERCP **(14).**

In select circumstances, such as failed ERCP, endoscopic ultrasound (EUS) guided biliary decompression can be considered. A randomized trial compared EUS-guided biliary drainage (n=13) after failed ERCP for distal malignant biliary obstructions with percutaneous drainage (n=12) and found similar outcomes for both procedures **(30).**

The advantage of EUS-guided biliary drainage is it can be performed in the same session as failed ERCP. A recent review of EUS-guided biliary drainage suggested that EUS-guided biliary drainage is a safe procedure that requires technical expertise and that back-up procedures, such as surgery or percutaneous drainage, be available. For EUS-guided choledocoduodenostomy, potential complications include peritonitis (4.0%), pneumoperitonitis (3.1%) and bleeding (2.7%) **(31).**

If an ERCP has been attempted and cannulation of the biliary tree was not successful, then an urgent referral for percutaneous drainage is indicated. Inoculation of an obstructed system with bowel flora can lead to biliary sepsis. For this reason, it is important to achieve biliary drainage as soon as possible after failed ERCP **(14).**

6. Mid unresectable obstructions.

Endoscopic drainage or PTC is both viable options for biliary decompression. Obstructions at this level require clinician expertise to determine the most appropriate technique for drainage **(14).**

Role of surgical drainage

As previously mentioned if the obstruction is determined to be unresectable then non-surgical treatment is preferred. However, if unresectablity is determined when the patient is already in the operating room surgical drainage can be performed. Surgical drainage is most relevant to distal obstructions as surgical drainage of proximal tumours is technically challenging **(31).**

A meta-analysis compared immediate stent placement and surgical bypass for management of palliative malignant biliary obstruction. They concluded that patients who are good surgical candidates may benefit from surgical bypass as it was associated with lower risk of recurrence (RR 0.14, 95% CI 0.03-0.63; $p<0.01$) **(32).**

CONCLUSION:

Malignant biliary obstruction is still a diagnostic and a therapeutic challenge requiring a multidisciplinary approach.

Diagnosis at advanced stage leading to poor outcomes and negatively affecting the quality of life of patients. The development of cholangioscopy is promising, with the possibility of targeted biopsies in case of failure of standard techniques.

Endoscopic transpapillary biliary drainage is the standard of care for unresectable hilar MBO and bilateral metal stent placement.

Conversion surgery for initially unresectable biliary malignancies may be feasible and achieve survival for patients.

No Conflict of interest.

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