Hilar Biliary Obstruction

Subjects: Oncology

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Malignant hilar biliary obstruction (HBO) represents a complex clinical condition in terms of diagnosis, surgical and medical treatment, endoscopic approach, and palliation. The main etiology of malignant HBO is hilar cholangiocarcinoma that is considered an aggressive biliary tract's cancer and has still today a poor prognosis.

personalized endoscopy malignant hilar strictures self-expandable metal stents plastic biliary stents endoscopic retrograde cholangiopancreatography

1. Introduction

The management of malignant hilar biliary obstruction (HBO) is still today a medical challenge in terms of diagnosis, treatment alternatives, and palliation options. The etiology of malignant HBO includes mainly the cholangiocarcinoma originating between the cystic duct and the segmental branch of the intrahepatic bile ducts (Klatskin tumor or hilar cholangiocarcinoma) [1]. More rarely, hilar obstruction can be determined by the local extension of adjacent tumors, such as gallbladder, liver, and pancreatic cancer, or by metastasis from distant malignancies [2]. The Bismuth-Corlette classification system is used to classify hilar cholangiocarcinoma taking into account the involvement of the biliary confluence and the intrahepatic ducts. Patients may be classified into four categories—Bismuth type I when the stricture is localized in the main biliary duct and does not involve the confluence; type II when the stricture involves the main confluence; type IIIa when the stricture involves the confluence and the right sectorial confluence sparing the left one; type IIIb when the stricture involves the confluence and the left sectorial confluence sparing the right one; and type IV when confluence, right, and left sectorial confluence are all involved [3].

The prognosis of hilar cholangiocarcinoma is poor for the locally aggressive behavior with a tendency to infiltrate adjacent tissues and neural, perineural, and lymphatic involvement [4]. The only curative approach is surgery; however, it is feasible only in 30–40% of patients [5]. The clinical presentation generally consists of obstructive jaundice and cholangitis, however, cholangiocarcinoma can be asymptomatic for a long time [4].

Endoscopy plays a crucial role in terms of diagnosis, management of obstructive jaundice, and palliation. The complexity of malignant HBO makes each patient a singular case requiring a personalized approach from the diagnosis to the final treatment. In this setting, a multidisciplinary is mandatory with the involvement of surgeons, endoscopists, interventional radiologists, and oncologists in order to find the best approach that properly fits with the patients' characteristics.

2. Diagnostic Approach in HBO

The diagnostic approach to HBO has the aim to distinguish whether a stricture is malignant or benign and, in case of malignancy, to evaluate the resectability. The patient with HBO generally presents cholestasis and obstructive jaundice, in this setting the first-line imaging technique is classically an abdominal ultrasound (US). Although it is a useful tool in the initial management, US is an operator-dependent technique and is burdened by low sensitivity and specificity [6]. Multidetector computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP) are generally required to perform an accurate diagnosis. CT and MRCP are complementary—on one hand, CT can provide information on the primary tumor, locoregional infiltration, vascular infiltration, and distant metastasis, and on the other hand, MRCP has the best sensitivity and specificity in defining the intraductal extension [7][8]. The role of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is controversial; it can be appropriate in case of indeterminate lesions and in the detection of distant metastasis, however, it is not routinely performed and its application should be evaluated in the singular patient [4].

Endoscopy plays a crucial role in the diagnostic algorithm in patients with malignant HBO mainly for the collection of cytological or histological samples.

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is nowadays considered a therapeutic procedure, however, during ERCP several diagnostic tools can be used—brush cytology, endobiliary biopsy, and cholangioscopy. Brush cytology is an easy procedure, routinely performed in suspicious biliary strictures, characterized by low sensitivity (ranges 20–40%) and high specificity (ranges 92–100%) [6]. The sensibility can be improved by performing multiple brushings during the same ERCP and performing fluorescence in situ hybridization (FISH) analysis on the sample [9][10]. Endobiliary forceps biopsy allows the collection of a more complete tissue sample, including the subepithelial stroma, however, it is less commonly performed and technically more complex than brush cytology. This procedure has a sensitivity ranging between 43% and 81% [11]. The combination of brush cytology and forceps biopsy increases the sensitivity to 59.4% [12]. Both brush cytology and forceps biopsy are burdened by a low negative predictive value, thus when the report is negative for cancer but the radiological and clinical suspicious is high, other techniques should be applied to obtain a proper pathological analysis. Peroral cholangioscopy is a technique allowing direct visualization of the biliary mucosa and consequently a visual interpretation of the biliary stricture (Figure 1A). There are three types of cholangioscopy systems—mother and baby, single operator, and direct peroral cholangioscopy. In a meta-analysis, de Oliveira et al. reported that cholangioscopy has a sensitivity of 94% and a specificity of 95% [13]. Recently, the Monaco classification, in order to increase the diagnostic accuracy, identified eight visual parameters for biliary evaluation during cholangioscopy—the presence of stricture, lesion type, mucosal features, papillary projections, ulceration, abnormal vessels, scarring, and pronounced pit pattern [14]. Moreover, the direct visualization of a suspect area allows the execution of a targeted forceps biopsy increasing the accuracy of malignancy detection (Figure 1B) [15]. However, cholangioscopy devices are burdened by high costs and their widespread is consequently limited.

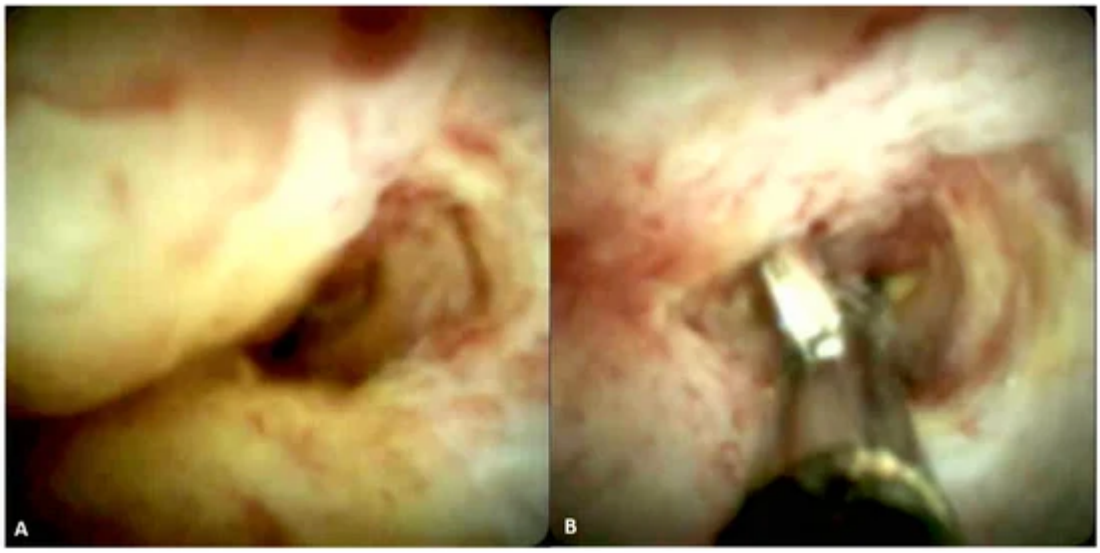

Figure 1. Peroral cholangioscopy of (**A**) a malignant hilar stricture and (**B**) target biopsy under direct visualization.

Echoendoscopy (EUS) is another endoscopic technique that can be used to evaluate a biliary stricture. EUS allows the visualization of the primary lesion and the locoregional staging evaluating the infiltration of adjacent tissues, lymph nodes, and vessel involvement [16]. The diagnostic accuracy of EUS has been shown to be higher in distal biliary tract strictures than in hilar strictures [17]. EUS fine-needle aspiration (EUS-FNA) is a well-established procedure for cytological sample collection, however, its application in hilar cholangiocarcinoma is not widely performed because of technical complexity [17]. In a meta-analysis involving 957 patients, the sensitivity and specificity of EUS-FNA in biliary stricture were respectively 80% and 97%. The sensitivity of EUS-FNA in proximal stricture was significantly lower than in distal strictures (respectively 76% and 83%) [18]. EUS-FNA can be a useful tool in case of ERCP sample collection failure [19].

Ultrasound imaging can be used also inside the biliary tree performing an intraductal endoscopic ultrasound (IDUS). It consists of a tiny probe inserted into the biliary ducts in order to evaluate the presence of malignant stigmata on the biliary ducts' walls. In a retrospective study, IDUS showed a sensitivity and specificity in malignancy detection of 93.2% and 89.5% [20]. Other authors documented a higher sensitivity of IDUS when compared with EUS [21].

Recently, two other techniques became available for a direct evaluation of the biliary walls—confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT). CLE uses a low-power laser to create a magnification of the mucosal layers (Figure 2) [22].

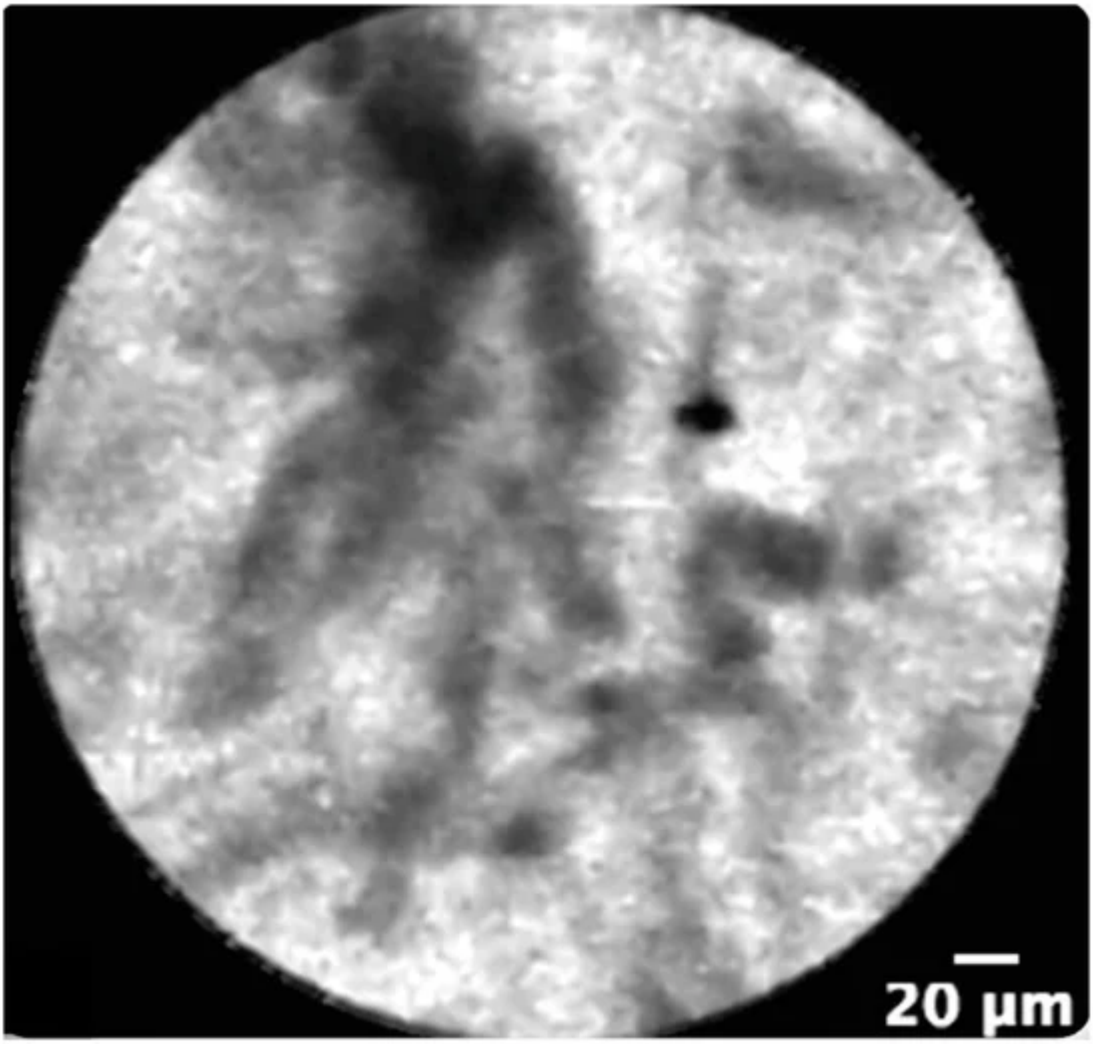

Figure 2. Confocal laser endomicroscopy showing a thickened reticular structure representing a criterion for malignancy.

During ERCP, a CLE probe can be advanced through the duodenoscope channel and inserted into the biliary tree. The classification of Miami and the Paris inflammatory criteria have been developed in order to distinguish a malignant from an inflammatory biliary stricture [23][24]. The sensitivity and specificity of CLE have been reported to be 90% and 72%, respectively [25]. Conversely, OCT uses an infrared-light providing cross-sectional images of tissue reflectance in order to obtain information on microscopical tissue architecture [26]. Volumetric laser endomicroscopy (VLE) is a newer OCT that allows us to obtain higher definition in vivo cross-sectional images of the biliary wall layers [27]. OCT increases the sensitivity and accuracy of malignancy detection when compared to brush cytology alone [28]. M. Arvanitakis et al. described the role of OCT during ERCP to assess the diagnosis of a biliary stricture using two OCT criteria for malignancy—the unstructured walls layers and the presence of neovascularization. They reported an increased diagnostic accuracy when standard techniques (e.g., brush cytology and forceps biopsy) are combined with OCT [28]. However, the role of OCT as a single diagnostic tool in biliary malignancy is not well defined yet, and its use and widespread are limited due to high costs.

Endoscopy can play also a role in the biomarkers' evaluation allowing bile samples collection. Classically in cholangiocarcinoma carbohydrate antigen 19-9 (CA 19-9) is considered the most accurate serum biomarker. However, CA 19-9 level >100 UI/mL has a sensitivity of 53% and a specificity of 75–90% in detecting cholangiocarcinoma [29]. Moreover, CA 19-9 can be raised in other malignancies (e.g., pancreatic cancer) and in benign conditions (e.g., cholangitis and primitive sclerosing cholangitis) [30]. Some authors used bile samples collected during ERCP to perform a multi-omic analysis (both metabolomic and proteomic), obtaining a panel of lipids and proteins that can discriminate patients with bilio-pancreatic malignancy [31]. Moreover, the role of extracellular vesicles (EVs) is raising for cancer detection. EVs concentration in bile collected during ERCP showed the capability to distinguish patients with malignancy from patients with benign biliary strictures with a higher level of accuracy when compared with EVs concentration in serum [32].

3. Indication for Biliary Drainage in Malignant HBO

The choice for biliary drainage is a complex assessment that should be taken by a multidisciplinary team. The first rule to keep in mind is that it is essential to complete the radiological abdominal staging, as the placement of a device into the biliary tree can interfere with the abdominal cross-sectional imaging (e.g., CT and MRI) [33]. Hence, the patients can be divided into two main groups—those who are eligible for a resection surgery and those requiring palliation therapy.

In resectable malignant HBO, the preoperative biliary drainage (PBD) is not routinely performed. Several retrospective studies showed that PBD increases the risk for post-surgical infections without any effect on survival [34][35][36]. In a systematic review and meta-analysis including 501 patients who underwent PBD and 391 patients who had not PBD, Celotti A. et al. showed that the two groups did not differ in terms of mortality rate but in terms of morbidity with increased risk for infective complications in patients undergoing PBD [37]. Scheufele et al. demonstrated that PBD induces a shift of the biliary microbiome with an increase of aggressive and resistant bacteria [38]. Given this background, the indication for PBD should be done balancing risks and benefits for each patient. In those undergoing left hepatectomy, PBD is not indicated as it increases the mortality rate mainly for the occurrence of post-operative sepsis [34]. Differently, one of the main causes of death after right hepatectomy is liver failure, and it has been shown that it is significantly more frequent in patients who did not undergo PBD [34]. This difference can be attributed to the higher volume of parenchyma loss in the right hepatectomy when compared to the left one, therefore, the quantification of future liver remnant (FLR) volume is essential to indicate whether PBD should be performed [39]. When the FLR volume is less than 30%, portal vein embolization (PVE) is required to obtain hypertrophy of the remnant liver; in this setting, PBD appears to reduce the risk for hepatic insufficiency and should be definitely performed [40]. Moreover, there is consensus that PBD is indicated in patients with cholangitis, hyperbilirubinemia-induced malnutrition, hepatic insufficiency or renal insufficiency, patients needing neo-adjuvant therapy, severely symptomatic patients, and those with delays in surgery [33].

The prognosis of cholangiocarcinoma is still today poor. Surgery is the only curative approach but it is feasible in just 30–40% of patients [5]. Criteria for non-resectability are distant metastases, lymph node metastases beyond the hepatoduodenal ligament, the bilateral ductal extension to the secondary (or sectorial) biliary branches,

encasement or occlusion of the main portal vein (or common hepatic artery) proximal to its bifurcation, unilateral involvement of secondary (or segmental) biliary radicles with contralateral vascular involvement, lobar atrophy with the involvement of contralateral secondary (or sectorial) biliary radicles, and lobar atrophy with the involvement of contralateral portal vein or hepatic artery [41]. Biliary drainage in unresectable HBO represents the cornerstone for palliation. The aims of palliative biliary drainage are to enable chemotherapy and radiotherapy administration and improve the quality of life, relieving jaundice, pruritus, pain, and cholangitis [4].

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