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The endoscopist and malignant and non-malignant biliary obstruction☆

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A B S T R A C T

Patients with biliary strictures often represent a diagnostic and therapeutic challenge, due to the site and complexity of biliary obstruction and wide differential diagnosis. Multidisciplinary decision making is required to reach an accurate and timely diagnosis and to plan optimal care. Developments in endoscopic ultrasound and peroral cholangioscopy have advanced the diagnostic yield of biliary endoscopy, and novel optical imaging techniques are emerging. Endoscopic approaches to biliary drainage are preferred in most scenarios, and recent advances in therapeutic endoscopic ultrasound allow drainage where the previous alternatives were only percutaneous or surgical. Here we review recent advances in endoscopic practice for the diagnosis and management of biliary strictures. This article is part of a Special Issue entitled: Cholangiocytes in Health and Diseaseedited by Jesus Banales, Marco Marzioni and Peter Jansen.

1. Introduction

The accurate diagnosis of biliary strictures based on imaging alone is frequently challenging, as there is a wide range of benign and malignant aetiologies (Table 1). Due to different management algorithms, these conditions need to be diagnosed swiftly and accurately to guide appropriate therapy and optimise outcomes for patients. Because of the diagnostic difficulties sometimes encountered, definitive treatment such as surgery or chemotherapy may be delayed or given incorrectly, with potential consequences for patients. In one study of 238 patients undergoing surgical resection of suspected cholangiocarcinoma, 13% were found to have benign disease [1]. Many of these patients have an autoimmune cholangiopathy (including IgG4-related disease) which can be effectively treated with steroids and other immunosuppressives. Pathologic confirmation of malignancy can also be challenging, and may require endoscopic techniques such as endoscopic ultrasound and single operator cholangioscopy. In those with unresectable malignant biliary obstruction, effective biliary decompression improves symptoms and enables patients to undergo palliative therapies, whilst in surgical candidates, routine preoperative biliary intervention may worsen outcomes. In this review, we outline latest innovations in endoscopic techniques for the diagnosis of indeterminate biliary strictures and the management of malignant and non-malignant biliary obstruction.

2. Diagnostics

2.1. ERCP with biliary brushings and endoluminal biopsy

Endoscopic retrograde cholangiopancreatography (ERCP) is a well-established technique, typically undertaken after cross-sectional imaging to provide therapy such as biliary stent insertion. It allows high-resolution fluoroscopic images to be obtained during therapeutic procedures, which provide information on stricture site, length and the presence of mucosal irregularity or shouldering (Fig. 1). Fluoroscopic stricture imaging is able to distinguish malignant from benign strictures with an accuracy of at best 80%, so that tissue sampling by biliary brushings or endoluminal biopsies is also required [2]. Standard ERCP and brush cytology has a variable sensitivity for malignancy of 26–73% (pooled sensitivity of 45% in a recent meta-analysis) [3], although this may be improved by techniques such as Fluorescence In Situ Hybridisation (FISH) and digital image analysis [4]. These techniques allow DNA analysis for chromosomal aneuploidy and nuclear DNA content - both of which are directly related to the risk of malignancy – and enhance tumour detection by up to 23% [5,6]. A recent systematic review and meta-analysis (SRMA) of eight studies involving 828 patients demonstrated that the pooled sensitivity and specificity of FISH polysomy to detect cholangiocarcinoma was 51% and 93%, respectively. They concluded that whilst FISH was highly specific, the limited sensitivity highlights the need for better markers in the early detection of cholangiocarcinoma [4].

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Table 1
Differential diagnosis of indeterminate biliary stricture.

Prognosis	Condition
Benign	Post-operative (following laparoscopic cholecystectomy or biliary anastomosis)
	Chronic pancreatitis
	Primary sclerosing cholangitis
	Autoimmune cholangiopathy, IgG4-related disease
	Post-radiotherapy
	Infections (TB, histoplasmosis, viral, parasitic, HIV cholangiopathy)
	Choledocholithiasis/Mirrizzi syndrome
	Vasculitis
	Trauma
	Ischaemia
	Post biliary sphincterotomy
	Extraluminal compression (lymph nodes, vascular)
Malignant	Cholangiocarcinoma
	Pancreatic cancer
	Metastatic disease

Novel imaging techniques, such as narrow-band imaging, autofluorescence, confocal laser endomicroscopy and elastic scattering spectroscopy allow augmented views of the visualised mucosa during ERCP [7,8]. In cases where IgG4-related disease is suspected, ampullary biopsies may be diagnostically useful. In one study, ampullary biopsies stained positive for IgG4 in 18/27 (67%) symptomatic patients with autoimmune pancreatitis, compared with none from patients without the disease [9].

Additional endoscopic approaches to standard ERCP include endoscopic ultrasonography with fine-needle aspiration, intraductal ultrasound or single operator cholangioscopy systems (Spyglass, Boston Scientific Corp, Natick, Massachusetts, USA), as described below.

2.2. Endoscopic ultrasonography

Endoscopic ultrasound and fine needle aspiration (EUS-FNA) allows visualisation and sampling of the pancreas and biliary tree. EUS-FNA is a standard approach for evaluating solid pancreatic masses and is increasingly used in the evaluation of biliary strictures. A recent SRMA involving 957 patients reported a pooled sensitivity and specificity of 80% and 97% for the diagnosis of cholangiocarcinoma by EUS-FNA [10]. Disadvantages of biliary EUS-FNA include a small risk of tumour seeding. In one retrospective study, patients undergoing EUS-FNA prior to liver transplantation for perihilar cholangiocarcinoma were more likely to have peritoneal metastases at the time of staging laparotomy (83% vs. 8%), although the number of patients who underwent EUS-FNA was small (n = 16) [11]. Peritoneal seeding has not been reported after transduodenal EUS-FNA for distal extrahepatic cholangiocarcinoma, where the EUS-FNA tract is resected during pancreatoduodenectomy. There have also been isolated case reports of peritoneal seeding after EUS-FNA of pancreatic cystic lesions. The PIPE study evaluated the frequency of postoperative peritoneal seeding in patients with malignant and non-malignant intraductal papillary mucinous neoplasm (IPMN) who had undergone preoperative EUS-FNA (n = 175) and compared it with that of patients with IPMN who had surgery without preoperative EUS-FNA (n = 68). The frequency of postoperative peritoneal seeding was similar in the two groups (2.3% vs. 4.4%; p = 0.403) [12].

EUS-FNA can be combined with other techniques such as transient elastography and contrast agents when assessing pancreatic lesions and lymph nodes, which improve the diagnostic accuracy of the technique [13,14].

2.3. Intraductal ultrasound

Intraductal ultrasonography (IDUS) provides real-time, cross-sectional imaging of the bile ducts and surrounding structures using a high-frequency ultrasound transducer advanced at the time of ERCP. In a retrospective study of 379 patients with indeterminate biliary strictures undergoing ERCP, IDUS was able to differentiate cholangiocarcinoma from benign strictures with a sensitivity and a specificity of 98% [15]. In a single centre study of 193 patients, IDUS more accurately diagnosed proximal than distal ductal strictures (98.1 vs 82.7%, p = 0.006) [16].

2.4. Peroral cholangioscopy

Peroral cholangioscopy with visually targeted biopsies has been reported to have a greater diagnostic accuracy than standard ERCP with non-targeted biopsies [17]. Recent improvements in cholangioscopes have led to a re-emergence of this technology. A single operator cholangioscopy system (Spyglass, Boston Scientific Corp, Natick, Massachusetts, USA) produces a 6000-pixel fibre optic image and enables visually directed intrabiliary biopsies via small disposable forceps. In a multicentre, prospective study of 105 patients, the sensitivity and

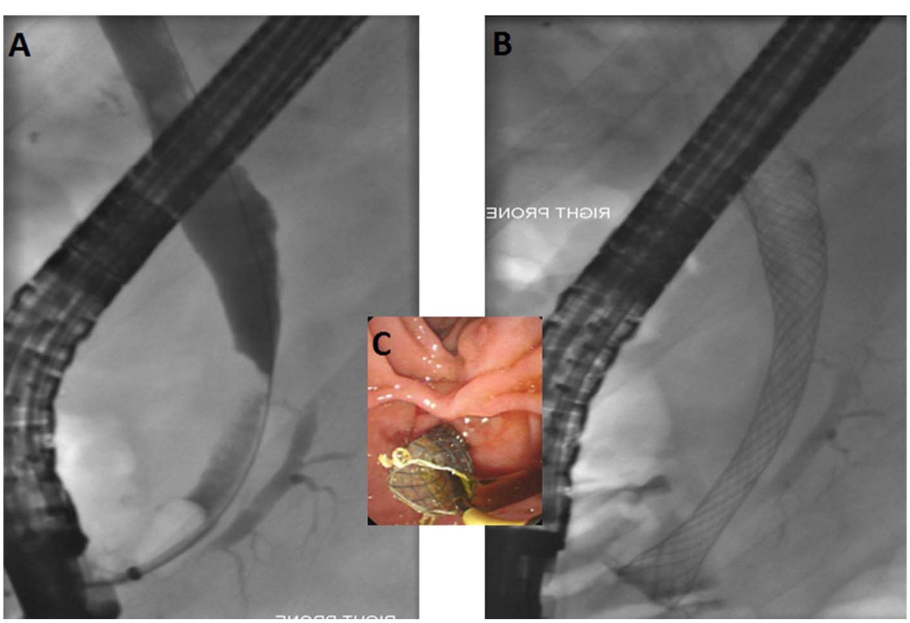

Fig. 1. Endoscopic evaluation and treatment of an extrahepatic biliary stricture due to a pancreatic mass lesion: A. fluoroscopic view of distal common bile duct stricture with double-duct sign; B. fluoroscopic view of fully-covered self-expanding metal biliary stent. C. endoscopic view of biliary stent.