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Novel endoscopic approaches in the diagnosis and management of biliary strictures

Margaret G. Keane[1], Neale J. Marlow[2] and Stephen P. Pereira[1]*

Addresses: [1]UCL Institute for Liver and Digestive Health and [2]UCL Medical School, University College London, London, UK

* Corresponding author: Stephen P. Pereira (stephen.pereira@ucl.ac.uk)

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Abstract

Indeterminate bilary strictures present the clinician with a wide differential diagnosis. Histological confirmation is usually required for treatment, but tissue acquisition remains challenging. Novel developments in endoscopic technology, such as single operator cholangioscopy and confocal endomicroscopy, have led to improvements in diagnostic accuracy in recent years. In patients with non-resectable malignant biliary obstruction, effective biliary decompression improves symptoms and enables patients to undergo palliative therapies. Improvements in endoscopic techniques, biliary stents and the development of local ablative techniques have led to further improvements in stent patency and survival in these patients. In this article, we review emerging diagnostic and therapeutic techniques for the endoscopic management of indeterminate biliary strictures.

Introduction

Despite improved diagnostic techniques, strictures of the biliary tree (abnormal narrowing of the biliary duct, which drains bile) remain a diagnostic challenge. Competing diagnoses, which share initial clinical and radiological findings, include cholangiocarcinoma, primary sclerosing cholangitis and autoimmune cholangiopathy. This presents the clinician with a wide differential (Table 1) for the underlying cause of a biliary stricture, which is usually difficult to differentiate on imaging alone [1-3]. Due to the different management algorithms and outlook, it is essential that these conditions be diagnosed swiftly and accurately in order to guide appropriate therapy and optimise outcomes for patients.

Because of the difficulties sometimes encountered in establishing a diagnosis, definitive treatment may be delayed (e.g. surgery or palliative chemotherapy) or occasionally incorrectly given: for example, 8-25% of patients who undergo surgical resection for suspected cholangiocarcinoma will ultimately be found to have benign disease [4,5]. Many of these patients have an autoimmune cholangiopathy that can be effectively treated with steroids and other medical therapies [6-8].

Carbohydrate antigen (CA) 19-9 is the most widely used tumour marker of pancreaticobiliary malignancy, but its sensitivity and specificity are low and its role in clinical practice remains uncertain. The discovery and validation of new biomarkers for pancreaticobiliary malignancy remains an active field of research. A summary table of some of the biomarkers currently being investigated for the diagnosis of cholangiocarcinoma has been included for reference (Table 2).

Pancreaticobiliary malignancy is often diagnosed late and at an advanced stage when very few patients are eligible for curative surgical resection. However, in non-surgical patients, effective biliary decompression improves symptoms. This review will provide an overview of the latest innovations in endoscopic techniques for the diagnosis and management of indeterminate biliary strictures.

Table 1. Differential diagnosis of indeterminate biliary stricture

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

Table 2. Summary table of biomarkers for cholangiocarcinoma currently being evaluated

Biomarkers (Serum)	Sensitivity (%)	Specificity (%)
CA 19-9 (>100 U/ml) [57-61]	60-89	80-97
TTR (transthyretin)+CA19-9 [62]	98	100
CEA (>22 micog/L) [63]	68	82
IL-6 (>25 pg/ml) [64]	73	92
MUCIN-5AC [65]	88	90
CYFRA 21-1 (>1.5 ng/mL) [66]	56	88
Matrix metalloproteinase-7 (MMP 7) (>5.5ng/ml) [60]	75	78
M2-PK [61]	84	90
Biomarkers (Bile)		
CA 19-9 [67]. CEA [67], Ca 125 [67], fibronectin [68], Pancreatic elastase/amylase ratio [69], Mcm5 [70], Mac-2BP [71], SSP411 [72], Insulin-like growth factor 1 [73], neutrophil gelatinase-associated lipocalin [74].		

Diagnostics

Standard endoscopic retrograde cholangiopancreatography with biliary brushings and intraluminal biopsy

Endoscopic retrograde cholangiopancreatography (ERCP) is typically undertaken following cross-sectional imaging, to enable tissue to be obtained for cytological or histological assessment. Standard ERCP and brush cytology have a variable sensitivity for malignancy of 9-57% [9-12] and new techniques with improved diagnostic accuracy would be welcome.

Cholangiocarcinoma has been associated with mutations in several oncogenes and up to 80% of tumour cells have been shown to exhibit chromosomal aneuploidy [13]. Fluorescence *in situ* hybridization (FISH) and digital image analysis can therefore be used to assess for the presence of these DNA abnormalities in brush cytology. They have been shown to improve the overall sensitivity for detecting cholangiocarcinoma and in primary sclerosing cholangitis, where confirmation of cholangiocarcinoma is particularly challenging, presence of polysomy is highly suggestive of cholangiocarcinoma [14,15]. To date, their routine use in clinical practice has only been adopted by a few centres.

Diagnostic endoscopic ultrasonography

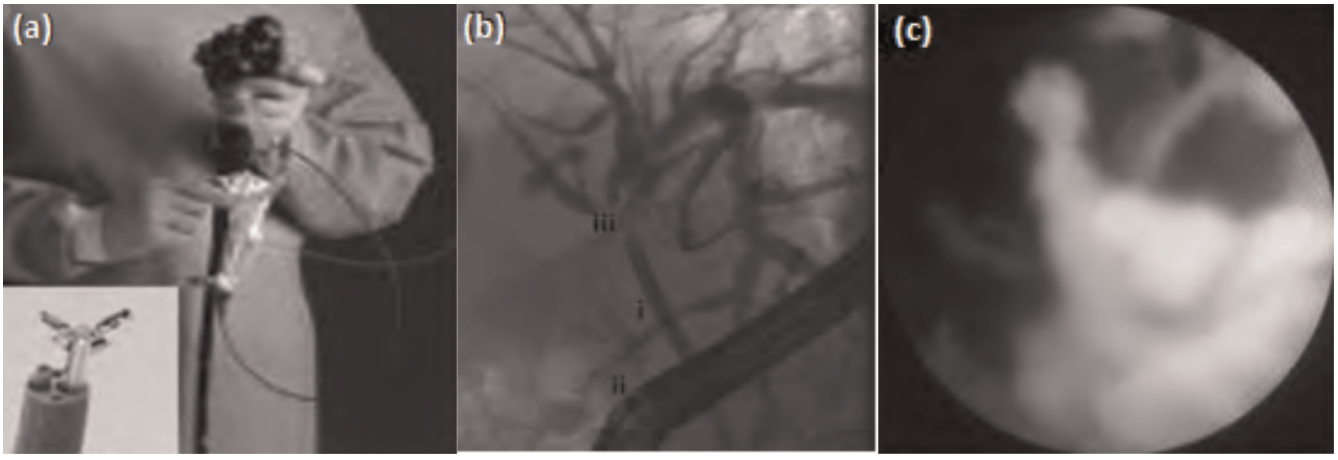
If ERCP findings are inconclusive, endoscopic ultrasonography with fine-needle aspiration (EUS-FNA) provides an alternative method for visualising and sampling the extrahepatic biliary tree, hilar masses, gallbladder and peri-hilar lymph nodes and vessels. A recent single-centre study found the technique to have a sensitivity for diagnosing cholangiocarcinoma of 73%; sensitivity was significantly better in distal compared to proximal tumours (81% vs. 59%, respectively) [16]. In preoperative staging, EUS-FNA has been shown to locally stage cholangiocarcinoma more accurately than standard cross-sectional imaging. Following EUS-FNA, an additional 15-20% of patients are found to have locally advanced disease that is not amenable to surgical resection. However, concerns remain around the possibility of tumour seeding [17,18]. Some studies have combined EUS with novel techniques such as transient elastography when assessing pancreatic lesions and lymph nodes to improve the diagnostic accuracy of the technique [19].

Small studies have explored the efficacy of intraductal ultrasound in the pre-operative staging of cholangiocarcinoma. Initial studies have shown it to have a diagnostic accuracy of up to 90% and to have a particular role for detecting periductal tumour extension and portal vein invasion [20].

Peroral cholangioscopy

Peroral cholangioscopy and visually targeted biopsies are known to have a greater diagnostic accuracy than standard ERCP [21]. 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) was introduced in 2006, which produces a 6000-pixel fibre optic image and enables visually directed intrabiliary biopsies via small disposable forceps (Figure 1). A multicentre study of single operator cholangioscopy, which included 140 patients with 'indeterminate' biliary strictures of unclear aetiology, found that sufficient material for histological examination was obtained in 88% and a definitive diagnosis was achieved in 85%. The specificity and sensitivity for visually directed biopsies was 98% and 49%, respectively. Higher sensitivities were observed for intrinsic biliary malignancy compared to extrinsic compressing tumours [22]. Several

Figure 1. Single operator cholangioscopy in a patient with an indeterminate hilar stricture



(a) Spyglass cholangioscope system (Boston Scientific Corp, Massachusetts, USA) with magnifed view of Spybite forceps. (b) Fluoroscopic view of hilar stricture at ERCP. (c) Cholangioscopic view of a hilar stricture with visualisation of the ulcerated, friable biliary mucosa.

ultra-slim endoscopes have also been developed. In comparison to single-operator cholangioscopy they are usually placed following standard ERCP, sphincterotomy and guidewire cannulation. Procedure times are therefore longer but compared with single-operator cholangioscopy they enable superior image quality, larger biopsy samples and chromendoscopy of the biliary mucosa [23].

Novel optical techniques

Chromendoscopy, autofluorescence and narrow-band imaging

Several techniques have been employed to augment the visualised mucosa during cholangioscopy. Methylene blue can successfully differentiate malignant lesions (staining them dark blue) [24] and ischemic strictures from normal mucosa [25]. Biliary narrow-band imaging enhances the vascular pattern of the mucosal surface and delineates tumour extent effectively [26,27]. Initial cholangioscopic studies with autofluorescence have been less promising; poor specificity and high rates of false positivity were observed [28].

Elastic scattering spectroscopy

Elastic scattering spectroscopy is a real time *in vivo* optical technique that detects changes in cells, via a probe that is passed through the working channel of an endoscope. It enables a field assessment for malignancy via an "optical biopsy", which has the potential to become an alternative to standard histology. A pilot study of elastic scattering spectroscopy from the distal duodenum, conducted by our group [29], gave a sensitivity of 86% and a specificity of 72% for the detection of pancreaticobiliary malignancy. These early results highlight its potential as a novel minimally invasive diagnostic test for pancreaticobiliary malignancy.

Confocal laser endomicroscopy

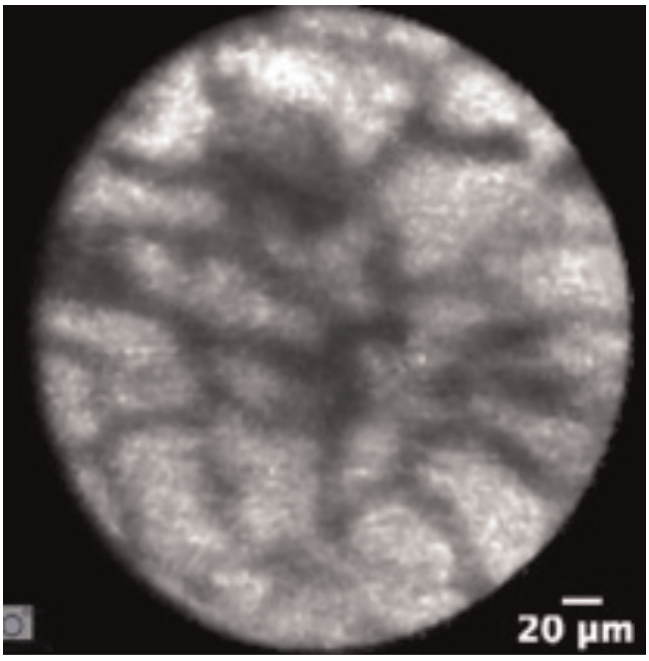
Confocal laser endomicroscopy (CLE) provides real-time histology during ERCP (Figure 2). A "cholangioflex" confocal probe (Mauna Kea Technologies, Paris, France) can be placed down a 1.2 mm working channel of a cholangioscope or the standard channel of a duodenoscope. Following an intravenous injection of fluorescein, a low-power laser directs light onto a single point on the biliary mucosa. Light emanating from this point is focused through a pinhole to a detector. This technique produces specific patterns that correlate with standard histology and differentiate between malignancy, inflammation and normal mucosa [30,31]. A recent multicentre study of 89 patients found CLE provided significantly higher diagnostic accuracy for malignant biliary strictures than standard ERCP (90% vs. 73%) [32]. Small studies have combined CLE with cholangioscopy and shown the diagnostic accuracy of the technique can be improved further (from 73% to 83%) [32].

Therapy

Endoscopic biliary decompression in malignant obstruction

The majority of patients diagnosed with pancreaticobiliary malignancy have unresectable disease. Receiving palliative chemotherapy is dependent on achieving adequate biliary drainage. Endoscopic biliary stenting to relieve obstruction has been associated with longer survival (19 vs. 16.5 months), fewer short-term complications and better cost-effectiveness than surgical decompression [33]. In most centres endoscopic management

Figure 2. Confocal endomicroscopic image of normal biliary mucosa; identified by light grey background and reticular network of thin dark branching bands (<20microns). Image obtained with Cellvizio CholangioFlex® miniprobe. [Image courtesy of Mauna Kea Technologies, France]



has therefore become the accepted initial approach in treating patients with malignant biliary obstruction.

Cholangiocarcinoma

Distal common bile duct obstruction

A meta-analysis of seven studies (1992-2006) compared plastic stents with self-expanding metal stents for malignant distal biliary obstruction [34] and found the relative risk (0.52) of recurrent biliary obstruction was significantly lower in the metal stent group. Since uncovered self-expanding metal stents are permanent, many patients are initially managed with a plastic stent while the confirmation of malignancy is awaited. However, the introduction of removable covered metal stents (WallFlex RX, Boston Scientific) has changed this practice.

Three randomised controlled trials have compared uncovered and covered self-expanding metal stent insertion in distal biliary obstruction. No significant differences in stent patency time, survival or complication rates were observed between covered and uncovered metal stents when used in the management of malignant distal biliary obstruction. However, covered stents did migrate significantly more often than uncovered stents, and tumor ingrowth occurred more frequently in uncovered stents [35-37].

Proximal biliary obstruction

Intrinsic or extrinsic compression of the biliary tree at the liver hilum can lead to disconnection of the right and left systems. In order for clinical jaundice to be relieved, it is estimated that at least one third of the liver has to be drained. Several studies have attempted to define the optimal stenting requirements in hilar obstruction and have found that 75-80% of patients will achieve decompression through a single stent but the remaining 20-25% will require two or more stents [38,39]. Bilateral stents can be placed side-by side or by a stent-in-stent technique. No discernible differences have been observed between the two methods [40]. Recently, a novel Y-shaped metal stent has been developed. In a preliminary study of 30 patients, 87% were successfully decompressed and stent occlusion occurred at a median of 176 days [41].

Pancreatic Cancer

Preoperative management of jaundiced patients with resectable pancreatic cancer remains controversial. A randomised controlled trial compared preoperative biliary drainage with surgery 4–6 weeks later to early surgery at 1 week. At 120 days after randomisation, 74% of patients in the preoperative drainage group had suffered a serious complication, compared with 39% of patients in the early surgery group ($P < 0.001$). Length of hospital stay and mortality did not vary between the groups [42]. However, in patients who are intensely symptomatic and those requiring neoadjuvant chemoradiotherapy, there may be a role for preoperative endoscopic biliary drainage, but a multidisciplinary team discussion is recommended in these complex cases [43]. In palliative lesions of the pancreas that are causing common bile duct obstruction and symptoms, a similar approach to the management of a distal cholangiocarcinoma is followed, typically with insertion of a self-expanding metal stent to enable longer-term palliation.

Alternative biliary drainage options if access at ERCP fails

Percutaneous transhepatic drainage (PTD)

Endoscopic drainage, particularly of hilar strictures, can be challenging and PTD with stent placement provides an alternative method of biliary decompression. A retrospective study comparing percutaneous with endoscopic self-expanding metal stent insertion found rates of successful bilary drainage to be significantly higher in the percutaneous vs. the endoscopic group (93% vs. 77%). Rates of complications and survival were similar in the two groups [44].

Surgical bypass

Historically, biliary decompression has been achieved through surgical biliary bypass procedures. Although an effective technique, when compared to endoscopic drainage, surgery is associated with more short-term complications, increased mortality (14% vs. 3%, P = 0.01) and longer recovery times (26 vs. 20 days in hospital, P < 0.01) [45].

Endoscopic ultrasound-guided biliary drainage

When endoscopic decompression is impossible due to failed cannulation, case series have shown that endoscopic ultrasound-guided biliary puncture from the duodenum or stomach is an effective alternative approach [46-49]. Passage of a guidewire through the tract enables standard cannulation and stent placement via a 'rendezvous' technique, or alternatively a stent can be placed across the tract to allow bile to drain directly into the duodenum or stomach.

Novel endoscopic approaches to therapy

A number of novel ablative and local therapies have been developed to treat cholangiocarcinoma. Ablative therapies such as photodynamic therapy or radiofrequency ablation can improve biliary drainage as individual treatments, in combination with biliary stenting, or unblock self-expanding metal stents *in situ*. Randomised studies comparing photodynamic therapy with biliary stenting to stenting alone have had conflicting results. Initial studies reported prolonged stent patency and improved survival after photodynamic therapy [50,51]. However, a subsequent UK phase III study closed early as overall survival was longer in those treated with stenting alone [52]. Radiofrequency ablation in combination with self-expanding metal stent placement has been reported in a small study of 22 patients, with a stent patency of 100% at 30 days [53]. Rarely, centres have used radiofrequency ablation alone to achieve biliary drainage but results of ongoing randomised controlled trials are awaited for validation of this technique [54]. Local therapies such as intraluminal brachytherapy can be applied to the tumour during ERCP. In two case series, median survival of patients with advanced hilar cholangiocarcinoma undergoing this technique was 11 and 14.5 months respectively [55,56].

Conclusion

The re-emergence of peroral cholangioscopy, along with the development of several novel diagnostic techniques has led to improvements in the diagnostic accuracy of endoscopic assessment of indeterminate biliary strictures. Further evaluation of these new techniques through on-going trials will define their place in the algorithm of the diagnosis and management of pancreaticobiliary malignancy. Improvements in the range of biliary access techniques, endobilary stents and novel ablative treatments along with local therapies have led to significant improvements in the palliation of cholangiocarcinoma.

Abbreviations

CA, carbohydrate antigen; CLE, confocal laser endomicroscopy; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, endoscopic ultrasound – fine-needle aspiration; FISH, fluorescence in situ hybridisation; PTD, percutaneous transhepatic drainage.

Disclosures

The authors declare that they have no disclosures.

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