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The endoscopist and malignant and non-malignant biliary obstruction☆

S.P. Pereira[a,b,*], G. Goodchild[b], G.J.M. Webster[b]

[a] UCL Institute for Liver and Digestive Health, University College London, UK
[b] Department of Gastroenterology, University College London NHS Foundation Trust, London, UK

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ABSTRACT

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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* Corresponding author at: UCL Institute for Liver and Digestive Health, Royal Free Campus, Pond Street, London, NW3 2PF, UK.
E-mail address: stephen.pereira@ucl.ac.uk (S.P. Pereira).

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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

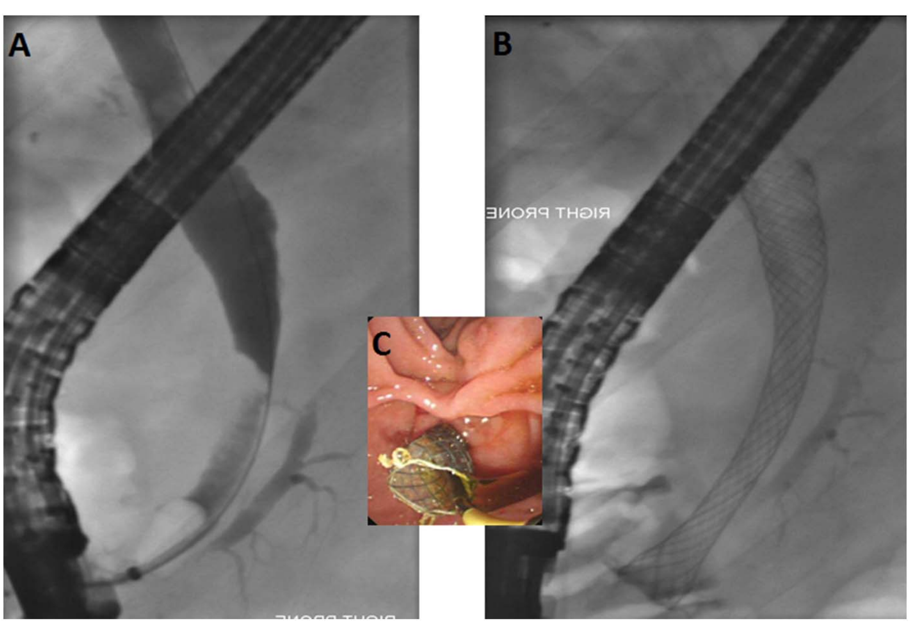

Fig. 1. Endoscopic evaluation and treatment of an extrahepatic biliary stricture due to a pancreatic mass lesion: A. fluoroscopic view of distal common bile duct stricture with double-duct sign; B. fluoroscopic view of fully-covered self-expanding metal biliary stent. C. endoscopic view of biliary stent.

specificity of the visual impression of malignancy at cholangioscopy was 90% and 96%, respectively. The sensitivity and specificity of cholangioscopy-guided biopsies for the diagnosis of malignancy was 85% and 100%, respectively [18]. A subsequent SRMA (10 studies, n = 456) reported a pooled sensitivity and specificity of 66% and 98% for the diagnosis of cholangiocarcinoma by cholangioscopic biopsy [19]. In the four studies where patients had negative or inconclusive brush cytology or intraductal biopsy prior to cholangioscopy, the pooled sensitivity and specificity for the diagnosis of malignant biliary strictures was 75% and 93%, respectively. Cholangioscopy therefore has a particular role when ERCP alone fails to obtain confirmatory cytology and the diagnosis remains unclear.

Several ultra-slim endoscopes have also been developed for cholangioscopy but have not been fully validated in prospective trials. 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 and larger biopsy samples of the biliary mucosa [20].

3. Novel optical techniques

3.1. Chromoendoscopy, autofluorescence and narrow-band imaging

Several techniques have been employed to augment the visualised mucosa during cholangioscopy. Biliary narrow-band imaging may assist in delineating tumours and distinguishing benign from malignant surface vascular patterns [8]. A prospective study of 21 patients concluded that narrow-band imaging was significantly better than white light at detecting the surface vascular pattern of strictures ($p < 0.05$) [21]. Initial cholangioscopic studies with autofluorescence have been less promising; poor specificity and high rates of false positivity were observed [7].

3.2. Light scattering spectroscopy

Light scattering spectroscopy (LSS) is a real time in vivo optical technique which detects changes in cells, via a probe which is passed through the working channel of an endoscope. It enables a field assessment for malignancy via an “optical biopsy”, a potential alternative to standard histology. Perelman et al. developed a spatial gating fibreoptic probe that is able to rapidly take optical biopsies within pancreatic cysts during EUS. In a recently reported double blind prospective study of 25 patients, this technique was able to accurately distinguish neoplastic, mucinous and serous lesions, thereby identifying the malignant potential in 21 out of 22 cystic lesions, achieving 95% accuracy in the detection of malignancy, compared to 58% accuracy for cytology [22].

3.3. Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) provides real-time images at the cellular level during ERCP and EUS. 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 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 images which correlate with standard histology and differentiate between malignancy, inflammation and normal mucosa. A recent SRMA found CLE combined with ERCP demonstrated 90% sensitivity in the assessment of biliary strictures (vs 58% for ERCP with biliary brushings plus intraductal biopsies) [23], supporting the American Society for Gastrointestinal Endoscopy guidelines that CLE is a useful tool for differentiating benign from malignant biliary strictures in patients with biliary neoplasia. Small studies have combined CLE with cholangioscopy and shown the diagnostic accuracy of the technique can be improved from 78% to 82% [23,24].

4. Therapy

4.1. Endoscopic biliary decompression in malignant obstruction

4.1.1. Pre-operative stenting

The aims of pre-operative biliary decompression are to improve symptoms and hepatic function prior to definitive surgical resection or neoadjuvant chemotherapy. The benefits of pre-operative biliary decompression in patients with resectable disease has been debated. In a multicentre trial of 202 patients with pancreatic cancer and obstructive jaundice randomised to either early surgery (< 1 week from randomisation) or pre-operative biliary stenting, serious complications were reported in 39% of the early surgery group and 74% in the biliary drainage group ($p < 0.0001$). Overall mortality rates were similar in both groups. The authors concluded that pre-operative biliary drainage is not indicated in patients with a bilirubin < 250 μmol/l [25]. Other studies have tried to address the issue of whether deeply jaundiced patients should undergo pre-operative biliary drainage. In this setting biliary drainage has been shown to reduce perioperative and post-operative complications [26]. The optimal type of stent remains controversial; one recent RCT found no significant difference between fully-covered self-expanding metal stents (FCSEMS) vs plastic stents (14.2% vs 16.3% re-intervention rate) although the mean interval from randomisation to surgery was only 13 days [27]. In those patients with a longer interval to surgery, such as those receiving neoadjuvant chemotherapy, FCSEMS provide longer patency than plastic stents therefore reducing the need for re-intervention and minimising interruptions to chemotherapy [28].

4.1.2. Palliative stenting

In general, self-expanding metal stents (SEMS) are superior to plastic stents in the palliative setting. Using SEMS for distal extrahepatic or hilar malignant biliary strictures results in significantly longer median patency and lower re-intervention rates when compared to plastic stents [29,30]. In a recent meta-analysis of 19 studies involving 1989 patients, SEMS were associated with significantly lower occlusion rates, less therapeutic failure (7% vs 13%), less need for re-intervention and lower rates of cholangitis (8% vs 21%) than plastic stents [31]. Whilst the unit cost of one SEMS exceeds that of a plastic stent, several studies looking into the overall cost-effectiveness of SEMS vs plastic stents have concluded that SEMS are more cost effective than plastic stents for patients with a life expectancy over four months [32]. In distal malignant biliary obstruction there is a choice between FCSEMS and uncovered SEMS, each with their own advantages and disadvantages. A recent meta-analysis comparing the two groups found the FCSEMS cohort to have a lower incidence of adverse events (OR: 0.74, 95% CI: 0.57 to 0.97, $p = 0.03$) with no difference in stent dysfunction, stent patency or patient survival [33].

4.1.3. Stenting of malignant hilar strictures

Intrinsic or extrinsic compression of the biliary tree at the liver hilum can lead to disconnection of the right and left systems. Hilar strictures are classified according to the Bismuth-Corlette classification. To relieve clinical jaundice, it is estimated that at least one third of the liver should be drained. Initial options for drainage include endoscopic, percutaneous or surgical approaches. Several studies have attempted to define optimal stenting practice based on cross sectional imaging in this setting. The majority of patients with malignant hilar strictures have non-resectable disease. In those with a predicted survival of greater than four months, uncovered SEMS are superior to plastic stents for palliation with respect to outcome and cost-effectiveness [34]. Adequate biliary drainage can generally be achieved with unilateral, bilateral side-by-side or bilateral stent-in-stent approaches, with evidence

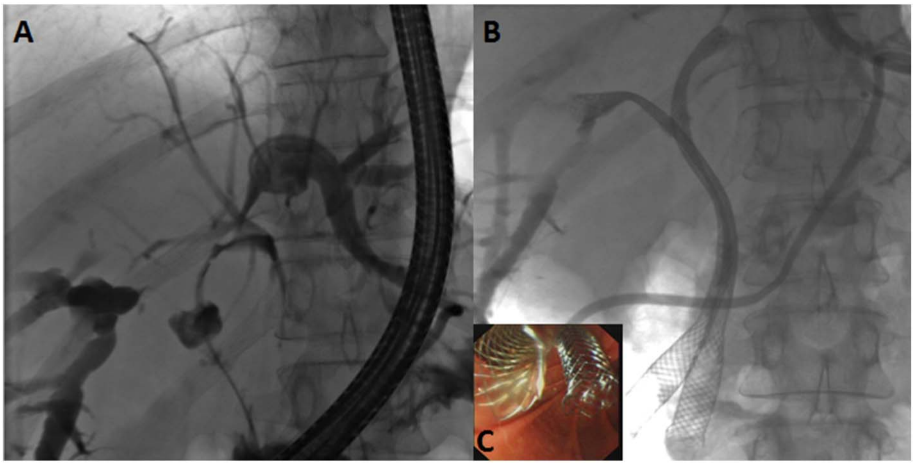

Fig. 2. Endoscopic assessment and treatment of a malignant hilar stricture: A. fluoroscopic view of malignant hilar stricture; B. fluoroscopic image after insertion of bilateral uncovered metal biliary stents; C. endoscopic view of the biliary stents.

currently lacking as to which of these approaches is optimal (Fig. 2) [34]. In jaundiced patients with potentially resectable hilar cholangiocarcinoma, a systematic review of one prospective and 9 retrospective studies did not show a clinical benefit of pre-operative biliary drainage [35]. Asia-Pacific consensus recommendations are to not routinely perform preoperative biliary drainage in patients with hilar cholangiocarcinoma, although portal vein embolisation and major hepatectomy remain absolute indications [34].

4.2. Endoscopic biliary decompression in benign obstruction

Important aetiologies of benign biliary strictures include post-surgical bile duct injury, chronic pancreatitis, primary sclerosing cholangitis (PSC) and IgG4-related disease. Of these, post-cholecystectomy bile duct injury (0.5% incidence) and post-liver transplant anastomotic strictures (10–40% incidence) are the most common aetiologies [36,37]. The treatment goals in managing benign biliary strictures are to relieve obstruction, maintain ductal patency and restore liver function. Data suggests that endoscopic therapy for benign biliary strictures is safe, effective and less invasive than surgical approaches [38], so that it is the first line therapeutic option in most patients with an accessible papilla [39].

Standard therapeutic approaches to benign strictures includes balloon dilation, insertion of multiple plastic stents with stent change each 3–4 months (up to 12 months) or remodelling the stricture through FCSEMS placement for 3–6 months. The last of these options has been shown to be safe, effective, technically straightforward and associated with fewer procedures [39]. In a recent international prospective study of 177 patients with benign biliary strictures who underwent temporary FCSEMS placement, all stents were successfully removed without complication and stricture resolution was achieved in 76.3% of patients [40].

Biliary stricture dilatation can be performed with either a balloon or bougie, although early dilatation of post-surgical strictures (< 4 weeks) may be associated with bile leak [41]. Balloon dilatation alone without subsequent stenting is associated with a high rate of stricture recurrence in anastomotic strictures and chronic pancreatitis [41]. The exception is dominant strictures in PSC where repeated balloon dilatations without stent placement is associated with improved long-term outcomes [42]. Gotthardt et al. prospectively studied 101 PSC patients with dominant strictures treated with either balloon dilatation or stenting. Long term follow-up showed excellent rates of bile duct patency with 5-year transplant-free and 10-year transplant-free survival rates of 81% and 52%, respectively [42]. For patients with IgG4-related biliary strictures stenting is not recommended unless there is severe jaundice or cholangitis, in which case a stent may bridge the patient until steroid response [43].

Placement of uncovered SEMS in benign biliary strictures or indeterminate strictures is usually contraindicated due to the likelihood of tissue ingrowth and subsequent stent embedment [39].

5. Alternative biliary drainage options if ERCP fails

5.1. 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. PTD is used for both hilar cholangiocarcinoma where it allows for selective duct drainage and in cases of failed endoscopic access due to gastric outlet obstruction, duodenal indwelling stents, or surgically altered anatomy such as Roux-en-Y hepaticojejunostomy [44].

5.2. Endoscopic ultrasound-guided biliary drainage

When ERCP fails, endoscopic ultrasound-guided biliary puncture from the duodenum or stomach is an alternative approach with outcomes similar to percutaneous drainage. 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. EUS-guided biliary drainage (EUS-BD) is a novel technique for patients who have failed endoscopic biliary stenting and may be considered as an alternative to PTD. In expert hands, success rates have been shown to be above 90% with rates of adverse events 17% [45]. A recent SRMA (9 studies, 483 patients) compared EUS-BD with PTD. They concluded that whilst there was no difference in technical success, EUS-BD was associated with higher rates of clinical success, less adverse events and lower rates of re-intervention. EUS-BD was also more cost effective [46].

5.3. Surgical bypass

Historically biliary decompression has been achieved through surgical biliary bypass procedures. A recent meta-analysis reported less recurrent biliary obstruction after surgical bypass when compared with endoscopic biliary stenting in the management of malignant biliary obstruction. Technical success rates and complication rates were also similar [47]. Surgical bypass is only suitable for surgically fit candidates, limiting its use in advanced cancer.

6. Novel endoscopic approaches to therapy

Patients with inoperable cholangiocarcinoma and pancreatic cancer have an extremely poor prognosis. Meta-analyses have not shown significant improvement with standard chemoradiation regimens [48], likely due to an advanced tumour stage at presentation coupled with aggressive tumour biology. However, two novel endoscopic interventions have shown promise in early studies: Photodynamic therapy (PDT) and radiofrequency ablation (RFA).

6.1. Photodynamic therapy

Photodynamic therapy (PDT) is an ablative technique involving intravenous administration of a photosensitising agent followed by endoscopic intraluminal laser irradiation. The agent concentrates within the tumour cells and once activated by the light of the laser generates reactive oxygen species. These cause photodamage of intracellular structures and cell membranes leading to tumour cell apoptosis and necrosis. A previous randomised controlled trial of PDT when compared to biliary stenting alone showed a significant increase in survival time from 98 d to 493 d [49], with another RCT showing median survival increasing from 210 to 630 d [50]. Retrospective data also contributes to the body of information supporting increased survival and quality of life when PDT is used in addition to biliary stents as well as chemotherapy [51,52]. The high cost of PDT may be a factor preventing its widespread use for local control of unresectable cholangiocarcinoma.

6.2. Radiofrequency ablation

Endoscopic Radiofrequency Ablation (RFA) is a palliative locoregional treatment that can be used in malignant biliary obstruction either as a first line treatment to improve the bile duct diameter or to treat tumour ingrowth of uncovered stents [53]. A catheter inserted into the biliary tree delivers a therapeutic heating zone leading to coagulation necrosis of the tumour. After treatment, a stent is usually placed. Evidence for the use of endoscopic RFA is restricted to retrospective analyses and small prospective cohort studies [54]. A recent retrospective comparison of PDT vs RFA in the palliation of malignant biliary strictures compared results in 48 patients (16 RFA, 32 PDT) demonstrating similar median survival (9.6 mo in RFA, 7.5 mo in PDT) [55].

7. Conclusion

The re-emergence of peroral cholangioscopy alongside several other novel diagnostic techniques has led to improvements in the diagnostic accuracy of endoscopic assessment of indeterminate biliary strictures. Further evaluation of these new techniques will define their place in diagnostic and management algorithms for patients with biliary strictures. Improvements in the range of biliary access techniques, endobiliary stents and novel ablative treatments along with local therapies have led to significant improvements in the palliation of pancreaticobiliary malignancy.

Abbreviations

CC	Cholangiocarcinoma
CLE	Confocal Laser Endomicroscopy
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS-FNA	Endoscopic Ultrasound-Fine Needle Aspiration
FCSEMS	Fully-covered Self-expanding Metal Stent
FISH	Fluorescence in situ Hybridisation
IDUS	Intraductal Ultrasound
PDT	Photodynamic Therapy
PTD	Percutaneous Transhepatic Drainage
RFA	Radiofrequency Ablation
SEMS	Self-expanding Metal Stent
SRMA	Systematic Review and Meta-Analysis

Disclosures

The authors declare that they have no disclosures.

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