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MINIREVIEWS

Still elusive: Developments in the accurate diagnosis of indeterminate biliary strictures

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Abstract

Indeterminate biliary strictures pose a significant diagnostic dilemma for gastroenterologists. Despite advances in endoscopic techniques and instruments, it is difficult to differentiate between benign and malignant pathology. A positive histological diagnosis is always preferred prior to high risk hepatobiliary surgery, or to inform other types of therapy. Endoscopic retrograde cholangiopancreatography with brushings has low sensitivity and despite significant improvements in instruments there is still an unacceptably high false negative rate. Other methods such as endoscopic ultrasound and cholangioscopy have improved diagnostic quality. In this review we explore the techniques available to aid accurate diagnosis of indeterminate biliary strictures and obtain accurate histology to facilitate clinical management.

Key Words: Indeterminate biliary stricture; Benign biliary stricture; Malignant biliary stricture; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Primary sclerosing cholangitis

Core Tip: Indeterminate biliary strictures remain a diagnostic challenge, despite significant advances in imaging and endoscopic techniques; there remains a risk of false reassurance of absence of cancer or over-treatment of benign disease. While various guidelines have been developed to help clinicians in their diagnostic approach, these strictures need to be assessed on an individual basis and often with the help of a multidisciplinary team. Enhanced optical modalities, possibly combined with rapid molecular analysis and the use of artificial intelligence, may lead to significant improvements in the next decade.

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INTRODUCTION

Indeterminate biliary strictures pose a diagnostic dilemma despite significant radiological and endoscopic advances. They can be either malignant or benign, and making a definitive and timely histological diagnosis is imperative, as the management is vastly different for both. The treatment of benign strictures is mainly medical or endoscopic, whereas malignant strictures may require surgical resection based on staging. This has a profound impact on mortality, morbidity and quality of life. Endoscopic retrograde cholangiopancreatography (ERCP) with biliary brushings and/or biopsy for cytology remains the primary diagnostic tool in the assessment of biliary strictures, particularly in patients presenting with obstructive jaundice. However, this technique has varying reports of sensitivity ranging from 6%-64% (*i.e.* high rate of false negatives), and so cannot be depended on exclusively for a definitive diagnosis. Availability and improved resolution of cholangioscopy has enabled direct visualisation and targeted biopsies within the biliary tract[1]. Despite this, 20% of suspected cholangiocarcinoma prove to be benign strictures at surgery[2]. Definitive guidelines about the role of cholangioscopy were lacking until a consensus guideline was published in 2022[3]. In 2023, the *American College of Gastroenterology*[4] and the *American Society for Gastrointestinal Endoscopy* published guidelines for management of indeterminate strictures[5]. Endoscopic ultrasound (EUS) with fine needle aspiration is an invaluable tool where strictures are associated with a mass.

In about 20% of biliary strictures[6], a clear-cut diagnosis is not made and they are thus labelled as 'indeterminate strictures'; these continue to pose a diagnostic challenge. A biliary stricture is classed as indeterminate when there is no associated mass on non-invasive imaging (CT/MRI) and subsequent ERCP with brush cytology and/or forceps biopsy is non-diagnostic[7]. The aetiology of these indeterminate strictures is variable and challenging with both intrinsic causes and extrinsic causes such as gall bladder, pancreatic and hepatological pathology. Aetiology of biliary strictures is shown in Table 1.

Significant endoscopic advances have helped improve the diagnostic accuracy of an indeterminate biliary stricture. However, there is no single gold-standard test and the diagnosis will ultimately be a product of a combination of investigations. The aim of this article is to review the current literature and novel advancements regarding the challenges and developments in the endoscopic diagnosis of indeterminate biliary strictures.

ERCP

With advances in imaging and availability of magnetic resonance imaging, ERCP is no longer indicated purely for the purposes of diagnostic cholangiography. However, this form of imaging (performed alongside tissue acquisition or stricture dilatation/stenting) does allow morphological differentiation of benign from malignant stricture and demonstrates location, anatomy and extent of a stricture[6]. The physical characteristics of a stricture can be suggestive of aetiology, although are by no means a reliable diagnostic tool on their own. Malignant strictures tend to be long and irregular, often with an abrupt cut-off which is associated with upstream biliary dilatation[6,8]. A double duct sign (dilatation of both the common bile and pancreatic ducts seen on cross sectional imaging) is also suggestive of a malignant aetiology[6]. In contrast, benign strictures tend to be smooth[6,9]. These criteria give cholangiography alone a diagnostic sensitivity and specificity of 74% and 70%[10].

ERCP remains the most widely used endoscopic tool for tissue acquisition and therapeutic interventions. Brush cytology and intraductal biopsies during ERCP are routinely performed for tissue acquisition, despite their low sensitivity[11]. Currently, there is no proven superiority of tissue acquisition of intraductal biopsy over brushings. Sensitivity rates for brushings can range from 15%-70% whereas specificity is close to 100%[12]. Difficulty accessing complex anatomical sites and considerable inter-observer variability contribute to this[13]. Intraductal biopsies have a sensitivity of 40%-60% and specificity up to 100%[11]. Brush cytology is used more as it is less demanding to perform and complications are rare; conversely, there is a lot of resistance to performing intraductal forceps biopsies as it is technically challenging and can be associated with perforation[14]. Over-the-wire forceps and paediatric forceps may reduce the risk of complications. Various endoscopic techniques have been suggested in order to improve diagnostic yield; these include stricture dilatation before brushings and biopsies, the use of novel brushes and performing repetitive brushings[6].

Technical developments to enhance the diagnostic yield of biliary brushings and intra-ductal biopsies

Novel brushes with variable orientation of bristles or increased angulation (Infinity® sampling device, Cytolong® brush) are more expensive and have demonstrated similar performance to traditional brushes[15]. Repeated brushing can increase yield. Biliary scraping devices have not proven to be useful[16]. FNA under fluoroscopic guidance with a biliary catheter has been trialled but is not commonly used[17]. Combining brushings with intraductal biopsies increases sensitivity from 47% to 86% and a combination of bile aspiration, brushing and biopsy results in sensitivity of 85%[18,19].

Table 1 Aetiology of biliary strictures

Benign		Malignant
1 Stone disease	Choledocholithiasis, Mirizzi syndrome	1 Pancreatic cancer; 2 Cholangiocarcinoma; 3 Gallbladder cancer; 4 Duodenal cancer; 5 Hepatocellular cancer; 6 Lymphoma; 7 Metastatic disease
2 Inflammation	Chronic pancreatitis, Histiocytosis, Mast cell cholangiopathy	
3 Autoimmune	IgG4 cholangiopathy, Primary sclerosing cholangitis, Sarcoidosis	
4 Iatrogenic	Liver transplantation, Post-cholecystectomy, Whipple's procedure, Radiation injury, Medication (*e.g.* Ketamine)	
5 Infection	AIDS cholangiopathy, Recurrent cholangitis, Trematodiasis/flukes (*e.g.* Clonorchis sinensis, Fasciola)	
6 Vascular	Vasculitis, Ischaemic cholangiopathy, Sickle cell disease hepatopathy, Choledochal varices	

A retrospective single-centre study[20] assessed the diagnostic yield of ERCP biliary brushings when supported with rapid on-site evaluation (ROSE) performed by a histopathologist. Of 206 included patients, 99% had an adequate sample at ROSE after a mean of 2.6 passages. The diagnostic yield had an accuracy of 83%, sensitivity of 74.6% and specificity of 98% with ROSE; a far higher sensitivity than the use of biliary brushings alone.

Other methods to further enhance the diagnostic reliability of a standard ERCP have been explored. A study measured the levels of vascular endothelial growth factor (VEG-F) in bile aspirated during an ERCP, for patients with biliary strictures[21]. Their results found that the median bile VEG-F levels were significantly elevated in patients with pancreatic compared with benign conditions, primary sclerosing cholangitis and cholangiocarcinoma.

Another study aimed to evaluate the role of serum and biliary insulin-like growth factor-1 (IGF-1), as well as VEG-F, in the diagnosis of biliary strictures[22]. Whilst there was no statistically significant difference in the levels of serum IGF-1 and VEGF in patients with benign and malignant strictures, there was a statistically significant difference in biliary levels of these markers. At a given cut-off, biliary IGF-1 and VEGF were found to be diagnostic of a malignant biliary stricture with 91.4% sensitivity and 89.5% specificity.

A further study assessed the diagnostic value of immunohistochemical and immunofluorescence (IF) staining for methionyl-tRNA synthetase 1 (MARS1) compared to conventional Pap staining[23]. They obtained endobiliary brush cytology specimens during ERCP in patients with extra-hepatic biliary strictures. They found that MARS1 IF staining showed strong signals in malignant biliary strictures, with a sensitivity and specificity of 98.1% and 96.1%, respectively. This was in contrast to conventional Pap staining which had a 70.4% sensitivity and 96.2% specificity. This was further assessed by the same group with a multi-centre prospective study, which produced similar results; sensitivity and specificity of 93.6% and 96.7% with MARS1 IF staining, in comparison to 73.2% and 100% with conventional Pap staining [24].

A prospective study looked to evaluate the combined accuracy of fluorescence in situ hybridization (FISH) and polymerase chain reaction-based DNA mutation profiling (MP) of specimens collected using standard brush techniques [25]. It compared routine cytology, FISH analysis, MP analysis and combined FISH and MP analysis, in the diagnosis of biliary malignancy. The results demonstrated that FISH was able to identify 9 out of 28 malignancies not detected by cytology alone and MP an additional 8 malignancies. FISH and MP together identified 17 out of 28 malignancies, not detected by cytology alone. Thus, concluding that the addition of FISH and MP significantly increased the sensitivity of diagnosing malignancy in biliary strictures.

EUS WITH FINE-NEEDLE ASPIRATION/BIOPSY

EUS can provide high-resolution imaging of the pancreato-biliary structures and allow for tissue sampling using fine-needle aspiration and biopsy at the same time[6]. It has been demonstrated that EUS has a diagnostic accuracy of 90% in malignant strictures and 92% in benign strictures[26]. EUS has been shown to be superior to CT and MRI in detecting subtle malignancy[27]. EUS also avoids complications that are associated with ERCP (pancreatitis, infection, bleeding).

Ultrasonographic appearances can be used to determine the aetiology of a biliary stricture. Findings such as a pancreatic head mass/an irregular bile duct and bile duct wall thickness measuring 3mm or more were found to be sensitive for malignancy (88% and 79% respectively) in a single-centre study[28].

A multi-centre study comparing the diagnostic performance of EUS-FNA and ERCP-based tissue sampling concluded that a combination of both modalities was superior for both pancreatic masses and biliary lesions, but that EUS-FNA was sufficient in cases where there is a large mass (defined as measuring >/-4 cm)[29]. A prospective study that compared the accuracy of EUS-FNA and ERCP for tissue sampling[30] showed that the EUS-FNA was superior to ERCP tissue sampling in sensitivity (93.8% *vs* 60.4% respectively). It also demonstrated that a combined procedure of both EUS-FNA and ERCP is both feasible and safe, as both procedures have similar complication rates.

Advanced techniques such as contrast enhanced EUS have been shown to be superior to contrast enhanced CT for detection of masses < 2 cm[31]. Combining this with EUS FNA increases sensitivity for solid lesions from 92% to 100% [31]. There is been a shift in preference of EUS-FNB over FNA to obtain tissue, especially with numerous novel FNB devices being available. A recent meta-analysis showed diagnostic accuracy, tissue core rate and adequate tissue with fewer passes was better with FNB[32].

Intraductal US during ERCP is also an option, but is not used widely. A large retrospective study demonstrated that intraductal US gave an accurate differentiation of benign and malignant strictures with a sensitivity of 93% and specificity of 90%[33]. However, use of this is limited by its tendency to under-stage tumours, with poor staging of lymph nodes and relative lack of tissue acquisition[34].

Despite its utility there are some concerns raised in recent case reports about tumour seeding *via* needle tract[35]. Careful consideration and multidisciplinary discussion are required before undertaking EUS-FNA and should only be performed if it will direct clinical management.

CHOLANGIOSCOPY

Cholangioscopy is an invaluable diagnostic tool to characterise indeterminate biliary strictures with direct visualisation of the biliary tree combined with the facility to obtain targeted biopsies.

Whilst cholangioscopy has been around for many years, it previously required two trained operators to use the system, rendering it too cumbersome for regular use. The development of the first-generation single-operator per-oral cholangioscope revolutionised this, particularly following the development of digital versions: SpyGlass Direct Visualisation System from Boston Scientific and the PolyScope from PolyDiagnost[36]. These provided better image quality, as well as an irrigation and an aspiration channel.

A consensus guideline was published on the role of cholangioscopy in the diagnosis of indeterminate biliary strictures [3]. A panel of international experts performed a systematic review of evidence and agreed on nine final statements, to serve as guidance on the roles and limitations of cholangioscopy in managing indeterminate biliary strictures. Of note, they agreed that the visual impression of a biliary stricture was more sensitive (though less specific) than biopsy and described a number of imaging characteristics which are suggestive of malignant disease. These included "tumour vessels, papillary projection, nodular or polypoid mass and infiltrative lesions". They also stated that there is a higher risk of adverse events with cholangioscopy than standard ERCP, namely cholangitis, and so stressed the importance of administering prophylactic antibiotics and ensuring adequate biliary drainage.

A systematic review found that cholangioscopy-guided biopsies had a pooled sensitivity and specificity of 60.1% and 98.0%, respectively, in the diagnosis of malignant biliary strictures[37]. Among studies that included patients with previous negative sampling, they found that the pooled sensitivity and specificity for the diagnosis of malignant biliary strictures was 74.7% and 93.3%, respectively.

Novel biopsy forceps have been developed (SpyBite Max forceps; Boston Scientific) with microteeth and larger cup volume to increase diagnostic accuracy. Data to show definitive benefit of these forceps is not available. ROSE was evaluated in a single centre study that showed that one biopsy with ROSE and a median of three biopsies without ROSE had similar diagnostic accuracy[38]. However, this is not standard practice in most centres.

Despite improved resolution, one of the major challenges with cholangioscopy is inter-observer variability in the interpretation of pathology, including experts in the field[39,40]. Numerous classifications like Monaco, Carlos Robles-Medranda and Mendoza have been developed to improve diagnostic accuracy[41,42]. Deep learning artificial intelligence models have been developed and evaluated and show improved diagnostic accuracy[43].

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is an endoscopic imaging technique whereby intravenous contrast is administered to the patient and a confocal laser probe, passed through the accessory channel of an endoscope, can assess the micro-architecture of abnormal mucosa in real-time.

A systematic review and meta-analysis found that CLE, in the diagnosis of an indeterminate biliary stricture, had a pooled sensitivity and specificity of 90% and 72%, respectively[44]. CLE can therefore significantly improve diagnostic yield, compared with standard ERCP biliary brushings and biopsy alone. This technique is, however, limited by high capital cost and the need for specialised operator training, and therefore is only available in very specialist centres at present.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is an imaging technique whereby a probe is passed through the accessory channel of a duodenoscope during an ERCP, and using low-intensity infrared light, produces cross-sectional imaging of the intra- and extra-hepatic bile duct[6,7]. Malignant strictures are characterised by the presence of disorganised bile duct wall layers and the presence of tumour vessels.

A pilot study assessed the potential use of OCT during ERCP to detect malignant biliary strictures[45]. They considered two OCT criteria for malignancy including "unrecognisable layer architecture and the presence of large, non-reflective areas compatible with tumour vessels". Their results showed that malignancy was confirmed by biliary brushings/biopsy alone in 63% of patients, whereas combining this with at least one OCT criterion improved this to 84%.

A newer OCT imaging system, NVision Volumetric Laser Endomicroscopy, allows for in vivo cross-sectional imaging of the ductal wall during ERCP. A study was conducted to identify and evaluate the characteristics of a malignant strictures on OCT[46]. They included 86 patients from 6 centres who underwent OCT over a year and identified nine recurrent characteristics of a malignant stricture, including hyper-glandular mucosa, hyper-reflective surface and scalloping; which were found to increase the odds of malignancy by 6-fold, 4.7-fold and 7.9-fold respectively.

INDETERMINATE BILIARY STRICTURES IN PATIENTS WITH PSC

In a review article about indeterminate biliary strictures, it is prudent to discuss patients with primary sclerosing cholangitis (PSC), who are at risk of developing dominant strictures and subsequently cholangiocarcinoma. PSC is a chronic cholestatic liver disease, characterised by inflammation and stricturing of the bile ducts, eventually leading to biliary cirrhosis and end-stage liver disease[47,48].

A dominant stricture (DS) is found in up to 45% of patients with PSC[47]; and although these strictures can be benign, representing the trajectory of chronic inflammation of bile ducts, they can also be the first presentation of a cholangiocarcinoma (CCA). A DS in PSC is defined as a stricture < 1.5 mm diameter in the CBD, or < 1 mm in the left or right main hepatic ducts[49]. Patients with dominant strictures have poor long-term outcomes as these strictures often harbour a CCA. A longitudinal study showed that mean survival in patients with DS was worse at 13.7 *vs* patients without DS in PSC[50]. CCA occurs in 7%-15% of patients with PSC, with an annual incidence of 0.5%–1.5%[51-54]. Establishing a diagnosis of CCA in PSC patients can be challenging, and there have been no effective surveillance strategies for early detection during the potentially treatable stages[48].

Similar to indeterminate biliary strictures in the general population, the diagnosis of a dominant stricture and/or CCA in PSC patients is challenging. Annual surveillance with interval MRCP/MRI liver imaging is widely adopted in CCA surveillance in PSC patients, despite the absence of high-quality evidence for its effectiveness[55,56]. ERCP with endobiliary brush cytology has also been suggested as a means of surveillance, namely in patients with advanced bile duct disease such as DS patients[48,55]. This of course comes with the same limitations discussed previously; endobiliary brushings and cytology in PSC patients have a similarly low sensitivity (17%–73%)[57-61]. There is also an increased risk of cholangitis in PSC patients undergoing multiple endoscopic procedures[48]. FISH analysis has also been advocated in this group of patients; chromosomal polysomy detected by FISH has been shown to identify patients with early CCA[48]. Direct cholangioscopy is often more difficult because the cholangiographic features of PSC make it difficult to detect new malignant strictures[47].

CONCLUSION

Despite significant advances in imaging and endoscopic techniques, the diagnosis of indeterminate biliary strictures remains a serious challenge, with an ongoing risk of false reassurance of cancer or over-treatment in benign cases. While various guidelines have been developed to help guide clinicians in their approach, ultimately these strictures will need to be assessed on an individual basis and often with the help of a multi-disciplinary team. Many of these advances are also limited by cost and skill, which also need to be kept in mind, particularly in the United Kingdom's National Health Service, where resources are finite. Enhanced optical modalities, possibly combined with rapid molecular analysis and the use of artificial intelligence, may lead to significant improvements in the next decade.

FOOTNOTES

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