Endoscopic considerations for the management of cholangiocarcinoma

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Abstract
Cholangiocarcinoma (CCA) is a rare malignancy of the biliary tract. The goals of endoscopy in CCA are to (a) provide an accurate diagnosis (tissue acquisition) and staging of disease and (b) relieve biliary obstruction and associated symptoms such as pruritus (stent placement). This then facilitates optimal treatment to occur; be this surgical resection, uninterrupted chemotherapy or improvement in symptoms. Endoscopy can involve endoscopic retrograde cholangiopancreatography with or without cholangioscopy, or endoscopic ultrasound with fine-needle aspiration to support these goals of making surgery safer and chemotherapy possible while avoiding endoscopy complications such as pancreatitis and sepsis.

KEYWORDS
cholangiocarcinoma, cholangioscopy, ERCP, EUS (Endoscopic ultrasound)

1 | INTRODUCTION

Cholangiocarcinoma (CCA) is a heterogeneous set of malignant tumours that arise from any part of the biliary tree. It is a rare cancer, with an incidence of 0.3-6 per 100 000 inhabitants per year. Unfortunately, there has been only modest improvement in prognosis in the last 20 years, survival at 5 years remains low (7%-20%) and recurrence after resection still common.

CCA can be divided into three groups, based on location: intrahepatic CCA (iCCA, 10%-20%), perihilar CCA (pCCA, 50%-60%) and distal CCA (dCCA, 20%-30%). Perihilar tumours, also known as Klatskin tumours, involve the hepatic duct bifurcation and are the most common. The patterns of CCA growth can be described as either; mass forming within the liver, periductal-infiltrating (growing inside the duct wall and spreading along) or intraductal-growing (forming a polypoid tumour in the lumen). These anatomical locations and tumour growth patterns have implications for endoscopic acquisition of tissue for diagnosis and treatment approaches for endoscopic biliary drainage.

Accurate knowledge of tumour extent and anatomy as well as obtaining a tissue diagnosis is important in determining therapeutic options. Diagnosis is hard because desmoplastic reaction means there are frequently scanty tumour cells and the position of the cancers make access for percutaneous, endoscopic or even surgical approaches frequently challenging.

In this article, we will review the endoscopic modalities available in the diagnosis and management of CCA. Most patients will need some form of endoscopic intervention either for tissue diagnosis or to improve biliary drainage. The only patients where this will not be required are those with local disease having up front surgery and...
patients at the other end of the spectrum, where advanced disease and or underlying frailty mean they should be for best supportive care from the outset. In this group of patients, the prognosis is poor, with a median survival time of just 10 weeks.³

This article will breakdown the two elements of endoscopic care in CCA, although they increasingly occur at the same time. It will not discuss the surgical, radiological or oncological management except in passing or where these are alternative treatments.

Management of CCA is complex and one fundamental point is that the endoscopic management of CCA is only part of the picture and all decisions should be made through an MDT setting also acknowledging the patient’s wishes. Endoscopic approaches can diagnose and treat CCA effectively but used injudiciously they can prevent other better treatments (compromise surgery), cause sepsis (if duct drainage is incomplete, especially if contrast is left undrained in segments) or be an unpleasant, unhelpful step for a patient who will derive no benefit. An example of the latter being a patient having a stent placed in the context of advanced disease with no symptoms to relieve, and no possibility of going on the chemotherapy.

2 | ENDOSCOPIC APPROACH TO DIAGNOSIS

Most patients considered to potentially have CCA, will present either with jaundice or constitutional symptoms such as abdominal pain, malaise, nausea, anorexia and weight loss. At this stage cross-sectional imaging is usually performed and often identifies biliary strictures and/or mass lesions along the biliary tract.

In upfront resectable cases, a biopsy is not needed if; imaging is characteristic, there are elevated serum levels of CA19-9 and normal IgG4 levels.⁴ Otherwise, before embarking on endoscopic diagnostic assessment, a CT is considered in all three types of CCA. CT provides a broad evaluation of the primary tumour, the relationship with adjacent structures, and distant spread. MRI is useful in differentiating iCCA from other liver cancers especially hepatocellular carcinoma in the context of cirrhosis, while MRCP is a vital part of staging for pCCA drainage including which modality, endoscopic or surgical. There are no easy answers, and each case deserves time in the appropriately skilled MDT to discuss the options.

2.1 | ERCP

ERCP with brush cytology remains the most commonly used method for achieving tissue confirmation of CCA. The cholangiogram acquired at ERCP typically shows a stricture or a filling defect with upstream dilation. The strictures are most commonly long (≥10 mm), asymmetric and irregular. Brush cytology using up to 10 passes is well established, technically usually straightforward and safe, while Endobiliary biopsy usually with three bites offers greater tissue acquisition but can be challenging technically and has modestly greater risks. Overall a meta-analysis of nine studies, found the pooled sensitivity of brush cytology, intraductal biopsy and both to be 45%, 48% and 59%, respectively, with the corresponding specificity of 99%, 99% and 100%.⁶

Efforts on improving sensitivity have focused on enhancing the cytological assessment of the collected sample. One method of using FISH technology to analyse specific DNA sequences on a chromosome to look for known genetic aberrations can increase sensitivity from 20% to 43% as compared to routine cytology.⁷ This has led some commentators to suggest triple assessment with brush, biopsy and FISH with a sensitivity of up to 82%.⁸

Even if this is reproducible clinically then there remains a significant proportion of patients with strictures suspicious for malignancy but with negative endobiliary cytology. These lesions are termed ‘indeterminate’ and options include further attempts at the same modalities (but assessment of samples is harder once stents are placed), the use of other tools, such as EUS (particularly in cases where there is a mass to target) or proceeding to surgery (but here series show 5%-30% may be benign lesions⁹). There are no easy answers, and each case deserves time in the appropriately skilled MDT to discuss the options.

2.2 | Cholangioscopy

One appealing endoscopic advance is direct visualisation and biopsy of a stricture by passing a ‘baby’ endoscopy from the working channel of the ‘mother’ duodenoscope. The only commercially available being the SpyGlass DS from Boston Scientific. While certain visual features appear typical of malignancy (a nodular or papillary lesion or an irregular/fragile surface) a biopsy is still usually required. Here the specific Spybite biopsies have a sensitivity of 64%,¹⁰ It has to be borne in mind that ERCP itself comes with significant risks and complications even in expert centres, with overall, severe and lethal complication rates of 4%, 0.7% and 0.06% respectively.¹¹ Cholangioscopy itself probably has higher complication rates and although becoming more commonly used throughout the world, it remains expensive, complex and probably still in need of further technical refinement and thus should be reserved for cases of indeterminate strictures where the initial ERCP biopsy was inadequate for diagnosis.
2.3 | Endoscopic ultrasound

Endoscopic ultrasound offers an extraluminal perspective of the stricture/mass that can only really be inferred from ERCP and, therefore offers several additional and complementary features. The most important feature being able to see, assess and guide biopsy to any mass associated with the known stricture. There are caveats, however, and while EUS affords excellent resolution to the mid-distal extrahepatic biliary tree, as well as regional lymph nodes, and vessels. It does, however, have limitations problematic to many cases of CCA in that visualising the hilum and especially the right-sided intrahepatic ducts are difficult and the presence of stents degrades the important assessment of the surrounding area.12

Endoscopic ultrasound utility is clearly demonstrated by a meta-analysis which reported a sensitivity of 81% for proximal stricture (but 59% for proximal lesions) and crucially 45% when no mass lesion was evident at cross-sectional imaging and 59% when brush cytology was negative. Equally reassuringly the procedure is safe, bleeding (1%), perforation (0.4%) and infection (0.3%) and the risk of tumour seeding is extremely low.6

Finding the correct place and timing for EUS in CCA diagnosis is still debated, it does seem to improve the yield when included in the same session as ERCP as compared to EUS alone. However, despite this, the negative predictive value of EUS in indeterminate strictures is low (from 29% to 67%) and so cannot exclude malignancy confidently.13

Overall endoscopy provides a key source of local and regional staging information as well as tissue acquisition for CCA, however, it should always follow cross-sectional imaging, often in the form of MRI/MRCP. The complementary use of ERCP supplemented with enhanced tissue processing (FISH) and cholangioscopy and EUS has been firmly established, however, the main issue remains the low-negative predictive value and those future work should look to integrate other diagnostic techniques such as tumour markers and circulating tumour cells.

3 | ENDOSCOPIC APPROACH TO MANAGEMENT

3.1 | ERCP

This topic has been debated for decades and is still not settled; however, we should look to the principles goals of treatment and be guided by high-quality studies and international guidelines. This starts with the overall goal of treatment, is it curative resection or long-term palliation of symptoms. Of course, this is not always known at the outset and once again makes the point for considered MDT discussing. As a principle, therefore routine biliary drainage should be avoided before staging and assessment of resectability is complete and in cases awaiting an operation.14 There are, however, well-accepted indications for pre-operative drainage, these include cholangitis, cases where severe malnutrition makes surgery prohibitively risky, hepatic or renal insufficiency, patients undergoing portal vein embolisation or neoadjuvant chemotherapy and those with significant jaundice.15

In palliative cases, endoscopic approaches are superior to surgical drainage in terms of improved survival (19 vs 16 months) and reduced morbidity and overall costs.1

Many of the technically considerations are beyond the scope of this article but briefly put, biliary stents can inserted in now three ways; the traditional approaches of a percutaneous transhepatic cholangiography (PTC) approach, ERCP or more recently EUS-guided stent delivery (more of which at the end of this article). Irrespective of delivery mode, the stents may be plastic or metal (which may be covered or uncovered). Plastic and covered stents are removable which is important if inserted before CCA confirmation while metal stents seem to offer higher patency duration because of their wider calibre.16

Endoscopic management of dCCA is usually relatively straightforward and usually a covered metal stent is employed. In terms of pCCA, the decisions are more complex and should always be done after careful assessment of a prior MRCP and with a definite plan already established.

For Bismuth types I and II, an ERCP first approach is usually correct. Percutaneous trans-hepatic cholangiography and drainage (PTCD) is usually the next step if primary endoscopic drainage fails, and some evidence has shown that PTCD is superior in unresectable Bismuth types IV. While management of type III depends on individual stricture anatomy, including the angulation of the duct in the sector needed draining relative to the common hepatic duct, as well as local expertise.17 While a recent RCT in potentially resectable pCCA, strongly came down in favour of ERCP and was actually prematurely stopped because of the higher rate of pre-surgical mortality among PTC patients (PTC vs ERCP: 41% vs 11%), this may not reflect clinical reality.18 Overall, for most cases, an ERCP first approach seems appropriate.

In deciding the plan, thought should be given to the volume of liver that can be drained. This can formally be done by assessing volumetry of the three main sectors (left, right anterior and right posterior) and a study with a mixed group of Bismuth II, III and IV, found drainage of >50% was associated with significantly longer survival (119 vs 59 days, P = .05) and furthermore that drainage of an atrophic sector (defined as <30%) was not only pointless but actually increased cholangitis risk (P = .01).19 Depending on the stricture type (Bismuth classification, Figure 1) then stents can be deployed bilaterally or within a single obstructed lobar segment. While this has been endlessly debated, a more pragmatic approach was shown in a study of Bismith II patients, comparing unilateral opacification and drainage with bilateral. Although there was a faster fall in bilirubin with bilateral drainage there was actually a higher risk of long-term problems (stent migration and clogging) with bilateral and overall, there were no differences in 12-month survival. This can probably most simply be inferred that the endoscopist should drain what they opacify with contrast, be it unilateral or bilateral, sparing atrophic segments and achieving effective drainage of all other opacified
segments.\textsuperscript{20} Finally, if there is doubt about how to proceed placing a plastic stent is best as it allows future revision.

Stent selection also favours metal in pCCA but plastic should be used if there is still a question of resectability of malignancy. Uncovered (and, therefore unremovable stents) are preferred because of the risk of both contralateral duct and ipsilateral radicle occlusion in using covered stents.

### 3.2 | Endoscopic ablative techniques

Various endoscopically delivered ablative techniques, including photodynamic therapy, radiofrequency ablation and brachytherapy have been developed to try and improve active control of tumour growth and long-term patency of stents. This is especially the case for Bismuth type III and IV hilar lesions, where the success of endoscopic stenting is worse compared to in dCCA. Radiofrequency ablation is currently the most studied and available technique, relieving heat energy to cause local tissue necrosis and is applied through an ERCP scope or sometimes percutaneously. A recent RCT in Bismuth type III and IV cancers has shown improved survival (13 vs 8 months) in RFA and stented patients compared to those with stenting alone, without increasing adverse events.\textsuperscript{21}

### 3.3 | EUS-guided biliary drainage

Endoscopic ultrasound-guided biliary stenting has emerged as a useful tool to drain obstructed biliary systems, using either the stomach (hepaticogastrostomy [HG]) or duodenum (choledochoduodenostomy [CD]).\textsuperscript{22} CD is only appropriate for dCCA while HG could feasibly drain pCCA in the 10% of cases where ERCP fails. These are now appropriate alternatives to PTC. The technique involves viewing the biliary tree with EUS, accessing it often with a fine-needle aspiration needle and guidewire, creating a fistulous tract with cautery and/or dilation, and ultimately deploying a decompressing stent under endosonography and fluoroscopy. There is a newer method called the ‘freehand technique’ where the fine-needle aspiration needle, guidewire and dilatation steps are avoided. HG can be used in cases of pCCA and even when the right intrahepatic system is occluded.\textsuperscript{23}

Studies now show these approaches probably have higher rates of clinical success, with reduced morbidity compared to PTC, however, they are complex procedures with a risk of serious complications (including perforation) and should only be performed by experts in large volume centres.\textsuperscript{21}

### 4 | FUTURE PERSPECTIVES

To think about how endoscopic management of CCA will develop, we must first consider how we would want the management of the disease to evolve irrespective of endoscopic involvement. Ultimately, we would wish to retire completely the diagnostic element of the job, by gaining sufficient information non-invasively, via high-quality imaging linked to liquid biopsies. Together imaging and liquid biopsy could not only accurately diagnose and stage the disease, but also inform management. Specifically in defining operability and guiding a personalised approach to chemotherapy, based on genetic mutations.\textsuperscript{1} Prior to that, steps must continue to improve the accuracy of diagnosis, especially where CCA is early, and the possibility of benefit is greatest. This may initially involve a greater reliance on multimodality approaches, with Cholangioscopy/FISH and EUS biopsy occurring more often simultaneously rather than sequentially.

In terms of endoscopic treatment, we are close to an inflection point, where the tried and tested approach of ERCP and PTC lose primacy and we look from the outset to an EUS-guided approach. The aim of therapeutic endoscopy is the same as it has always been; reliable long-term, safe biliary drainage. EUS may be useful as it can effectively reduce the most common complication (post ERCP pancreatitis from 4% to 10% to effectively 0%).\textsuperscript{25} However, currently
the best evidence comparing EUS vs ERCP shows comparable efficacy and improved safety.²⁶

As devices and training improve, one may expect EUS-guided techniques to gain greater acceptance. Ultimately, there must be a change in the thinking of endoscopy pioneers, to consider how optimal drainage may be achieved, not only short term for 6-12 months but for a much longer duration, that is 10-20 years to match improvements in oncological therapy.

5 | SUMMARY

Endoscopy has a key role in tissue acquisition and using standard ERCP brushing with newer techniques including cholangioscopy will remain the workhorse in establishing the diagnosis. The type of biliary drainage should reflect the overall objectives of care for the patient and follow detailed cross-sectional imaging. In operative cases drainage should be avoided if safe to do and if not then an ERCP first approach is best. In palliative pCCA then Bismuth I and II are usually best approached by ERCP first, while PTCD may be more appropriate in some types III and most type IV. In these cases, drainage strategies should aim to use uncovered metal stents draining >50% of the liver volume. EUS-guided drainage is gaining momentum and an effective alternative currently to PTC and probably (once refinements in techniques and equipment have occurred) to ERCP. Ablative techniques require further study in large trials to define their optimal use but may have a role in gaining better local control of disease. The future of endoscopic management of CCA lies in improving diagnostic sensitivity with a platform of diagnostics, which also allow better characterisations of the tumour and likely response to systemic treatments (personalised medicine), with therapeutic inputs, that allow long term and safe biliary drainage to improve patient quality of life (Figure 2).

CONFLICT OF INTEREST
The authors do not have any disclosures to report.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analysed in this study.

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