Cholangiocarcinoma (CCA) is a cancer of the biliary tract. Although it is an uncommon disease, it frequently presents at an advanced stage, which precludes surgical resection and carries a poor prognosis. This emphasizes the need for accurate diagnostic techniques and beneficial palliative therapy. This article reviews several endoscopic diagnostic techniques relevant to CCA including brush cytology, transpapillary forceps biopsy, endoscopic ultrasound, cholangioscopy, probe-based confocal laser endomicroscopy and optical coherence tomography. Additionally, this article discusses biliary stenting, endoscopic biliary radiofrequency ablation and photodynamic therapy.

INTRODUCTION

Cholangiocarcinoma (CCA) is a rare cancer that arises from biliary epithelium. The incidence is increasing and is more common in underdeveloped countries, and the prognosis is often poor. The clinical manifestations of CCA depend on the stage and tumor characteristics, but include jaundice, pale stools, abdominal pain, and constitutional symptoms. CCA is classified as intrahepatic or extrahepatic; extrahepatic is subdivided into perihilar and distal CCA. Extrahepatic CCA is more common than intrahepatic. The diagnostic workup of CCA includes radiographic imaging, which may demonstrate characteristic findings and delineate the relationship of the mass to the biliary tree and nearby vasculature. When imaging reveals a highly suspicious lesion that appears amenable to resection, timely surgical intervention is indicated. However, for patients that are not surgical candidates, or when imaging is non-diagnostic, confirmation with tissue diagnosis is essential prior to pursuing aggressive treatments (e.g., chemoradiation).

In general, a tissue diagnosis is obtained prior to any treatment. Several endoscopic techniques have been developed to maximize diagnosis of CCA, provide symptomatic relief, acquire valuable information about tumor characteristics, and potentially offer non-surgical interventions. This article reviews endoscopic diagnosis and management of cholangiocarcinoma.

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Biliary Brush Cytology
Acquisition of cellular material for cytologic analysis is typically obtained during routine endoscopic retrograde cholangiopancreatography (ERCP) via routine brush cytology. (Figure 1) After fluoroscopic visualization of a biliary stricture, a brush is introduced and moved across the lesion several times, with surface cells being captured in the brush and then sent for analysis. Brush cytology is still widely performed as it is very safe and has a low cost. However, this technique yields positive results in less than 50% of CCA cases.\(^4\) This may, in part, be due to the desmoplastic nature of these cancers resulting in hypocellular specimens. Several studies have noted low diagnostic sensitivity (5.5% to 60%) and high sensitivity (94.7% to 99%).\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) These values indicate that negative results do not reliably rule out CCA. A variation of this procedure involves biliary fluid aspiration rather than brushings. One study noted that aspiration of biliary fluids, alone or in combination with brushings, yielded sensitivities of 72.8% to 89%.\(^8\)\(^11\)

Fluorescence in Situ Hybridization
Fluorescence in situ hybridization (FISH) is an ancillary test that applies fluorescence-labeled DNA probes to nuclear material generally obtained via brush cytology. Demonstration of aneuploidy of chromosome 3, 7, or 17 or 9p21 deletion are the best characterized abnormalities in biliary cancers that can be exploited for improved diagnosis. It is estimated that 39-80% of biliary tract cancers demonstrate aneuploidy or aneusomy.\(^12\) Several studies have demonstrated that the addition of FISH to brush cytology can greatly improve diagnostic sensitivity, while maintaining high specificity.\(^10\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) FISH also enhances detection of CCA in patients with primary sclerosing cholangitis (PSC), a notoriously difficult population to accurately diagnose with malignancy given their baseline abnormal biliary ductal epithelium and high potential risk of developing CCA.\(^14\) Additionally, emerging data related to identification of epidermal growth factor receptors (EGFR or HER) via FISH may guide potential treatment options.\(^18\)\(^19\) A recent publication found that polysomy 7 was independently predictive of poor outcomes in CCA. Taken together, these data indicate a routine role for FISH in the diagnosis and management of CCA.

Transpapillary Forceps Biopsy
Transpapillary forceps biopsy (TPB) can be performed during ERCP in conjunction with biliary brushing. Closed forceps are introduced into the papilla and guided to the stricture under fluoroscopy. The forceps are then opened and pushed into the stricture to maximize tissue acquisition. These samples are then sent for histologic analysis. Forceps are not wire guided and often have difficulties in reaching and sampling lesions that are not readily accessible in the common bile duct or the common hepatic duct. In one study, use of TPB to diagnose CCA revealed sensitivity 73%, specificity 100%, positive predictive value 100%, and negative predictive value 31.2%.\(^20\) Several other studies demonstrate similar characteristics, and additionally provide evidence that TPB in combination with other diagnostic modalities (e.g., brush or aspiration cytology, FISH), greatly improves the diagnostic sensitivity without compromising specificity.\(^6\)\(^7\)\(^8\)\(^21\) Importantly, Kawashima et al.\(^22\) noted a 40% false negative rate when a single biopsy was taken. This group recommended that at least three biopsies should be acquired and analyzed if TPB was utilized.\(^22\) Proximal lesions can represent a difficult or impossible target to reach via TPB.

Endoscopic Ultrasound
Endoscopic ultrasound (EUS), with or without fine needle aspiration (FNA) and/or fine needle biopsy (FNB), is an advanced procedure that can be performed as a primary diagnostic method or when pathology results of biliary brushings or biopsy are inconclusive and clinical suspicion for malignancy remains high. In addition to diagnostic utility, EUS can assist in gathering essential tumor characteristics, and provides unique approaches to biliary drainage.

Diagnostic Use of EUS
The diagnostic use of endosonography in suspected CCA entails visualization of a biliary stricture of mass or abnormal perilesional lymph nodes, as well as FNA or FNB for histologic analysis. The exam is performed after introducing the echoendoscope,
equipped with either a radial or linear array probe, and tracing the biliary tree from the duodenal bulb as well as the ampullary region. The linear array probe allows the endoscopist to perform FNA/FNB.

Features suggestive of malignant strictures include visualization of duct wall thickness >3mm and irregularity of the outer bile duct wall. A meta-analysis of EUS in evaluation of biliary obstruction noted 78% sensitivity and 84% specificity in identifying malignant causes, although the data are not specific to CCA. EUS is generally a safe procedure, without apparent risks beyond that of routine EGD, and with diagnostic characteristics similar to that of magnetic resonance cholangiopancreatography (MCRP) but with the potential for tissue sampling.

A meta-analysis of 284 patients reviewed the performance of EUS-FNA in detecting malignant biliary strictures, and determined 84% and 100% sensitivity and specificity, respectively. A prospective study of 51 patients with suspected biliary malignancy compared EUS-FNA to ERCP techniques (brush cytology and TPB) and found 94% vs 50% sensitivity. However, only 14 of these patients were determined to have bile duct cancer; EUS-FNA and ERCP characteristics in this small subgroup were very similar.

One consideration relevant to EUS is the location of the lesion of interest, as EUS tends to perform better with distal as compared to proximal lesions. Accordingly, Mohamadnejad et al. found 81% and 59% sensitivity in proximal versus distal CCA. Another potential limitation is the concern for peritoneal tumor seeding during EUS-FNA. Despite a small sample size, Heimbach et al. concluded that EUS-FNA should be viewed as a contraindication to a potentially curative liver transplant. In general, most endosonographers will not perform EUS FNA/FNB of a primary suspected CCA if the patient is felt to be a candidate for surgery or transplantation given concerns about tumor seeding along the needle track, and in most patients the primary role of EUS with regards to tissue acquisition is to sample adenopathy.

A similar endoscopic procedure is intraductal ultrasound (IDUS). In this procedure, the biliary tract is cannulated via ERCP and an ultrathin radial ultrasound probe is introduced over a guidewire to generate EUS images from within the biliary tree itself. Similar to EUS, there are sonographic findings that can suggest malignancy (e.g., increased wall thickness, longer stricture length).

One group compared EUS to IDUS in evaluation of biliary strictures and found IDUS to be more accurate (89.1 versus 75.6%) and more sensitive (91.1% versus 75.7%). Despite these findings, IDUS is rarely used in clinical practice given the need for the specialized IDUS probe and a second ultrasound processor. This may also be because poor imaging depth is achieved, limiting evaluation to the biliary wall and its immediate surroundings.

**EUS Assessment Of Surgical Resectability**

Although various imaging modalities can assist in identifying factors that determine surgical resectability, some cases are not deemed unresectable until the time of surgery. Some endoscopic techniques, with the majority of data related to EUS, are emerging as options to determine tumor characteristics and aid in surgical planning. A few reports evaluated patients with suspected CCA and found that EUS not only accurately diagnoses malignancy, but also reliably identifies unresectable disease.

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that can pass directly into the biliary tree (direct peroral cholangioscopy). Cholangioscopy data relevant to CCA are limited but promising. In a study of 30 patients where both ERCP and EUS-FNA were non-diagnostic, cholangioscopy with intraductal biopsy diagnosed 23 cases of CCA. Similarly sized studies indicate 76.5% to 86% sensitivity.

Probe-Based Confocal Laser Endomicroscopy
Probe-based confocal laser endomicroscopy (pCLE) is an ERCP-based technique designed to allow the clinician to potentially make diagnoses in vivo. The probe emits laser light of a defined wavelength to illuminate the tissue of interest, and then detects reflected fluorescent light allowing for real time examination of cellular and subcellular structures. This procedure requires systemic or topical administration of fluorescein to enhance image quality, though there are limited data to suggest that nonmalignant hepatic cells demonstrate adequate autofluorescence in cases of intrahepatic CCA.

As with many diagnostic procedures, pCLE is subject to significant interobserver variability that improves substantially with standardized training. For this reason, a standard classification system has been proposed. The Miami classification describes 5 features to distinguish benign from malignant cells: thick white bands >20µm, thick dark bands >40µm, epithelial structures, dark clumps, and fluorescein leakage. Combining two or more of these criteria provided a sensitivity and specificity of 97% and 33%, respectively. Work by Caillol et al. noted this low specificity, due largely to false positive results in benign inflammatory conditions, and identified additional characteristics of malignancy such as vascular congestion, dark granular patterns, increased inter-glandular space, and thickened reticular structures.

Several studies have evaluated the diagnostic characteristics of pCLE in cases of pancreaticobiliary strictures and found sensitivity of 74.6% to 98%, specificity of 33% to 97%, positive predictive value (PPV) of 71% to 80%, and negative predictive value (NPV) of 97% to 100%. The uniformly high NPV of pCLE have led some to suggest that this method may be a useful tool in patients with benign inflammatory conditions such as PSC. pCLE is not widely used at this time and should still be considered experimental.

Optical Coherence Tomography
Optical coherence tomography (OCT) was first used to evaluate CCA in 2002. Miniature probes have been developed that can be passed through the ERCP working channel. Analogous to ultrasonography, OCT detects back-scattered infrared light to produce high-resolution, cross-sectional images in vivo that are similar in appearance to histologic sections. OCT remains experimental and the available literature relevant to CCA primarily describes image features (e.g., unrecognizable tissue layer architecture, papillary structures) that are suggestive of malignancy.

ERCP-Guided Biliary Stent Placement
Endoscopic biliary drainage is performed to manage cholangitis, provide palliative relief of cholestasis, and is routinely performed prior to neoadjuvant chemotherapy and hepatic resection in patients with obstructive jaundice. Most oncologists will not administer chemotherapy in the setting of jaundice. There are several methods available to achieve endoscopic biliary drainage, but most frequently involves ERCP-guided stent placement.
There are a variety of stents available, broadly categorized into plastic and metal stents. Plastic stents are smaller in diameter compared to self-expandable metal stents (SEMS). For this reason, a major disadvantage to plastic stents is early occlusion (1-3 months) due to accumulation of biliary sludge and thus plastic stents require periodic replacement. SEMS are available uncovered (an open frame meshwork) or covered by a thin membrane. Either variety remains patent significantly longer than plastic stents. The open meshwork of uncovered SEMS allows tissue ingrowth, which prevents migration of the stent, but this also leads to earlier stent occlusion (compared to covered SEMS) and precludes future removal. The thin membrane over covered SEMS mitigates stent occlusion but results in more frequent migration and are more expensive.

In general, preoperative patients are treated with plastic stents and nonoperative patients are treated with metal stents. Also, given that most patients with cholangiocarcinoma have proximal biliary obstruction, uncovered stents are typically warranted in these patients.

**Palliative Biliary Drainage**

For patients with unresectable CCA, palliative drainage with stent placement can relieve jaundice and pruritis and extend life. A number of recent meta-analyses have compared plastic versus uncovered SEMS for palliative drainage. The overall findings advocate the use of uncovered SEMS due to lower overall stent dysfunction, longer stent patency, fewer required re-interventions, and increased survival time. An interesting area of research which could further prolong palliation involves the development of radiation-emitting and drug-eluting biliary stents. Despite interest in these devices for years, they remain experimental.

There has been controversy regarding whether standard practice for endoscopic palliative biliary drainage in patients with hilar obstruction should be unilateral or bilateral. Three recent meta-analyses analyzed several retrospective cohorts patients with hilar obstruction (of any Bismuth type) and generally found that although unilateral stent placement was technically more successful, bilateral drainage resulted in better drainage and longer stent patency. Mortality and complication rates were no different. In the only prospective, randomized trial relevant to this topic, 133 patients (with Bismuth type 2-4 obstruction) were randomized to unilateral or bilateral metal stenting. Technical success rates were not different, but bilateral drainage relieved jaundice more effectively and the biliary tree remained patent significantly longer. Nonetheless, the question remains controversial and highly debated, and in practice many patients only receive...
unilateral stents and achieve adequate biliary drainage given the technical difficulties inherent in bilateral stent placement. Most endoscopists who do not perform high volumes of ERCP are uncomfortable placing bilateral stents. Studies into this question are ongoing.

**Preoperative Biliary Drainage in Perihilar CCA**

In operative candidates with perihilar CCA that present with obstructive jaundice, preoperative biliary drainage is routinely performed to restore hepatic function to an optimal state prior to major resection. Notably, two meta-analyses, by Liu et al.\(^1\) and Celotti et al.\(^2\), identified an increased risk of postoperative infection in patients that received preoperative endoscopic biliary drainage. However, hepatic resection of a jaundiced patient is associated with higher rates of significant adverse events and perioperative mortality.\(^3,4\) A major cause of death is hepatic failure.\(^5\) For this and other reasons, the current accepted practice is to preoperatively drain segments of the future remnant liver and is especially important when the predicted volume of the future liver remnant is <50\%.\(^6\) Antibiotic administration during and after ERCP in these patients is usually performed to reduce the risk of infectious complications.

In preoperative patients with perihilar disease, plastic stents are preferred due to easy endoscopic or intraoperative retrieval to avoid interference with resection. Tissue ingrowth through uncovered SEMS can often render resection impossible, and use of SEMS in preoperative patients with perihilar CCA is, in general, not advised (SEMS are routinely used in nonoperative patients).\(^7\) It should be recognized the plastic stents need maintenance and periodic removal and replacement to avoid recurrent biliary obstruction.\(^8\)

**Endoscopic Interventions**

There are a few endoscopic interventions, most commonly radiofrequency ablation (RFA) and photodynamic therapy (PDT), that are clinically useful in CCA, most commonly used in patients who are not felt to be surgical candidates. The utility of non-surgical treatment is highlighted by a report that over two-thirds of patients (in a cohort with greater than 6000 patients) with intrahepatic CCA were not considered surgical candidates, and that local treatment (such as RFA) significantly prolonged life.\(^9,10\)

**Endoscopic Biliary Radiofrequency Ablation (RFA)**

Biliary RFA is an endoscopic technique used to provide local therapy to a malignant stricture. Performed as part of a standard ERCP, a radiofrequency catheter is introduced to the biliary tree to the level of a target lesion and, using an electrosurgical generator as a power source, emits heat to induce coagulative necrosis directly at the site of the malignant stricture. RFA is primarily used in CCA as a palliative technique and is generally performed prior to placement of a SEMS to prolong patency. RFA is considered a safe procedure and has been shown not only to prolong stent patency and improve drainage but can also significantly prolong life.\(^11,12,13\) In patients with stage I intrahepatic CCA, RFA increased median survival time from 0.7 to 2.1 years. A retrospective study by Sharaiha et al.\(^14\) included 37 patients with extrahepatic CCA and compared RFA plus SEMS to SEMS alone. Increased survival time (17.7 months versus 6.2 months) was noted in the RFA plus SEMS group, with no difference in adverse events.\(^15\) Stent patency time was unchanged.\(^16\)

In one of the only prospective studies relevant to this topic, 65 patients with perihilar (Bismuth type I or II) or distal CCA were randomized to endoscopic RFA and placement of a plastic stent, or placement of a plastic stent only.\(^17\) RFA with stent placement increased median survival to 13.2 months (versus 8.3 months), and increased stent patency to 6.8 months (versus 3.4 months), and there was no difference in adverse event rates.\(^18\) Interestingly, the longer survival time was attributed to slowed tumor growth and later occurrence of metastasis.\(^19\) This may be explained by findings that local tumor ablation therapies increase tumor immunogenicity, inducing a temporary anti-tumor immune response, although this is largely conjecture.\(^20\)

In cases of occluded SEMS, management has historically included insertion of additional stents or percutaneous biliary drainage. RFA of tumorous ingrowth in an uncovered SEMS has been shown to restore biliary drainage, and performance of RFA for this indication is now commonly performed. The effect of RFA is attenuated by the presence

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of a SEMS, limiting its effect to cancerous tissue within the stent. A small, retrospective study included 50 patients with an occluded SEMS: 25 underwent RFA and the remaining 25 underwent placement of a plastic stent. Biliary drainage was immediately apparent in all patients, but patency was significantly longer in the RFA group (119 days versus 65 days). Altogether, the use of endoscopic RFA in CCA is emerging as a valuable therapy.

**Endoscopic Photodynamic Therapy (PDT)**

ERCP-directed PDT is an ablative therapy similar in concept to RFA. This procedure requires intravenous administration of a photosensitizing agent (hematoporphyrin or chlorine derivatives) that preferentially accumulates in neoplastic cells and is typically injected 48-hours prior to PDT. The procedure involves direction of the laser light-emitting PDT catheter to the lesion of interest and emission of light to the sensitized tissue. Activation of the sensitizer, via exposure to specific wavelengths of light, is thought to produce reactive oxygen species, which interacts with cell membranes and activates inflammatory pathways, resulting in cellular death. To maximize the therapeutic effect of PDT, supplemental oxygen is frequently administered during the procedure.

Endoscopic PDT is considered a palliative treatment and has been shown to extend survival time, prolong stent patency, and improve quality of life. Kahelah et al. reported prospective data on 48 patients with unresectable hilar CCA: 29 patients received biliary stents, and 19 underwent PDT and stent placement. Median survival time was 16.2 months in the PDT plus stent group, compared to 7.4 months in the stented group. Significant and similar serum bilirubin reduction was noted in both groups.

In a similar study, 184 patients with unresectable hilar CCA received either PDT with stent placement or stents only. In the PDT group, statistically significant findings included longer life, (12 versus 6.4 months), lower serum bilirubin values, and significantly improved quality of life. A randomized, controlled trial studied patients with unresectable perihilar CCA in which 39 patients were randomized to PDT with bilateral stent placement or bilateral stenting alone. In the PDT group, survival time was extended (median of 493 days versus 98 days), a greater percentage of patients demonstrated resolution of hyperbilirubinemia, and improved quality of life was reported. Non-fatal adverse events were relatively uncommon, but did include mild-to-moderate cases of skin photosensitivity. Studies that compared endoscopic RFA to PDT did not find significantly different survival times, though RFA was superior in terms of bilirubin reduction and unplanned stent replacement. RFA is also technically easier and faster to perform and carries no risk of photosensitization.

**CONCLUSION**

Cholangiocarcinoma is a rare malignancy with a historically dismal prognosis due to diagnosis at advanced stages. There are several endoscopic diagnostic techniques that are continually improving, and a number of newer techniques are emerging to assist in an early and accurate diagnosis. Endoscopic interventions such as bile duct stenting, RFA, and PDT are useful palliative techniques that improve quality of life and extend survival time.

**References**

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