Chapter 15
Diagnosis and Staging of Cholangiocarcinoma

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Key Learning Points

1. Cholangiocarcinoma (CCA), the most common biliary tract malignancy, is unfortunately often diagnosed late with resultant poor survival outcomes.
2. Accurate staging is of paramount importance both for identifying patients with potentially curable disease amenable to resection and for guiding treatment in patients with locally advanced or metastatic disease.
3. Radiological evaluation usually involves CT staging, with the option of MRI, PET, EUS, US and cholangiography for further clarification of disease status.
4. To guide treatment, CCA can be classified into early, locally advanced or metastatic stages. More detailed staging can also be achieved using the AJCC/UICC TNM system or other staging methods. Laparoscopic evaluation is capable of detecting sub-radiological disease.
5. Future considerations include the development of biomarkers to enhance early and specific diagnosis as well as to guide systemic treatment. Furthermore, improved imaging techniques to allow accurate identification of patients who may benefit from potentially curative surgical intervention.

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Areas of Controversy and Uncertainty

1. Due to the scirrhous nature of lesions as well as the histological and molecular features shared with other malignancies, the pathological diagnosis of Cholangiocarcinoma (CCA) can be challenging.
2. Currently there is no universal staging system in use for CCA; the AJCC/UICC system incorporates information on survival and is the most commonly used. Accurate staging is vital to guide treatment.
3. Radiological evaluation of CCA can be a challenge even with the most modern CT imaging techniques. Radiological distinction between CCA, HCC and metastases to the liver from non-hepatobiliary sites can be difficult; this often requires complex evaluation of arterial uptake of index lesions and the assessment of surrounding tissue as well as further imaging techniques such as MRI or possibly PET.
4. Meaningful improvement in outcomes for patients with CCA necessitates systematic evaluation, often requiring a multimodal approach to patient workup.

Introduction

Cholangiocarcinoma (CCA) is the broad term for malignancies originating from biliary epithelial cells. CCA is the most common malignancy of the biliary tract. CCA can be classified based on anatomical location into intrahepatic (iCCA), perihilar (pCCA, Klatskin tumours), distal (dCCA, extrahepatic tumours) and gall bladder cancer. iCCA is located proximal to the second-degree bile ducts, pCCA is defined as tumour in the area between the second-degree bile ducts and the insertion of the cystic duct into the common bile duct, while dCCA is defined as tumour in the area between the insertion of the cystic duct to the bile duct and the ampulla of Vater [1].

The majority of CCAs occur in the perihilar region (60–70%) with the remainder occurring in the distal common bile duct (20–30%) or within the liver (5–15%) [2]. pCCA which accounts for the majority of tumours can be classified using the Bismuth-Corlette classification (Table 15.1; [3]).

Table 15.1 Bismuth–Corlette classification of Perihilar (Klatskin) tumours (adapted from Bismuth and Corlette [3])

Type	Description
Type I	Limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts
Type II	Tumour extends into the bifurcation but not into intraphepatic bile ducts
Type IIIa	Tumour occlusion of the common hepatic duct and the right hepatic duct
Type IIIb	Tumour occlusion of the common hepatic duct and left hepatic duct
Type IV	Tumour involving the confluence and both right and left hepatic ducts

Diagnosis

Clinical Presentation

The clinical presentation of CCA can be fairly unspecific. Extrahepatic tumours usually present with painless jaundice, steatorrhoea, dark urine and pruritus related to biliary obstruction. Conversely, iCCA can present with pain, most commonly localised to the right upper quadrant of the abdomen. Other clinical features include fatigue, weight loss and fever. Differential diagnosis is wide, including hepatocellular carcinoma (HCC), pancreatic carcinoma, cholangitis, cholelithiasis, parasitic infestations or metastases to the liver from non-hepatobiliary (non-HB) malignancies. While the definitive diagnosis of cholangiocarcinoma is histological, various less invasive tests are useful for the exclusion of differential diagnosis and staging of the disease.

Radiological Imaging Investigations

Ultrasonography (US)

Abdominal ultrasonography, although cheap, non-invasive and often the first line of investigation, is of limited value in the diagnosis of CCA. Large intrahepatic mass lesions may be identified on US. However, smaller intrahepatic, perihilar and gall bladder lesions can be more difficult to visualise. The sensitivity of US in detecting pCCA ductal masses or thickening is operator-dependent and reported to range from 87 to 96% [4]. Irregular thickening of the duct wall and polypoid intraluminal masses can also be seen in some cases of iCCA [5]. Despite its limitations, contrast-enhanced US can be utilised in the radiological exclusion of HCC for patients unable to tolerate contrast-enhanced CT or MRI [6].

Endoscopic Ultrasound (EUS)

EUS allows clear visualisation of the distal biliary tree, gall bladder, local blood supply and regional lymph nodes. This modality can be utilised to facilitate fine needle aspiration of suspicious areas, allowing differentiation between malignant and benign lesions. However, the sensitivity and specificity of EUS are variable- and user-dependent. Meta-analysis has found a sensitivity of between 59 and 80% for EUS-FNA in the diagnosis of CCA [7].

Computerised Axial Tomography (CT)

Triple-phase contrast-enhanced hepatobiliary CT is the routine initial test for assessment of HB tumours in many centres. Furthermore, thoraco-abdominal CT is a particularly useful tool in the perioperative evaluation and staging of early HB

tumours (including CCA). Besides visualising masses and showing biliary duct stricturing or dilatation, CT allows clear delineation of macrovascular invasion which is imperative for estimating operative feasibility. In these respects, meta-analysis has suggested that CT has a sensitivity of over 80% and specificity of over 90% for staging CCA [8]. However, its sensitivity is lower for smaller lesions (<3 cm), excluding distant metastases (63%) and identifying regional lymph node metastases (54%) [9, 10].

As regards diagnosis, even with triple-phase (arterial, portal venous and delayed/washout phase) imaging on the most modern CT scanners, the radiological distinction between CCA, HCC and metastases to the liver from non-HB sites can be challenging. The best validated criteria are for distinguishing HCC where in a cirrhotic liver, HCC appears hypervascular compared with liver parenchyma on the hepatic arterial phase of scans. This hypervascularity diminishes during the washout phase. According to the American Association for the Study of Liver Diseases (AASLD) [11] and the European Association for the Study of the Liver (EASL) [12], in a cirrhotic liver, demonstration of intense arterial uptake followed by washout is diagnostic of HCC. However, these criteria are not diagnostic of HCC in non-cirrhotic livers. In comparison, CCA (more common in non-cirrhotic livers) appears as a hypo-dense lesion with rim enhancement, often accompanied by biliary duct dilatation and contrast enhancement on delayed images, similar to non-HB metastases. A previous study reported that iCCA in patients with cirrhosis had varied enhancement patterns on triple-phase contrast CT [13]. Additionally, the study suggested that even though most iCCA did not display the same radiological characteristics as HCC, the rate of misdiagnosis of iCCA for HCC was significant [13]. Consequently, histological confirmation of CT findings would be recommended when feasible. Nevertheless, typical radiological features of CCA and its common differential diagnoses are outlined in Table 15.2.

Table 15.2 Summary of histological and molecular markers of the most common primary and secondary hepatobiliary malignancies

Malignancy	Cholangiocarcinoma (CCA)	Hepatocellular carcinoma (HCC)	Metastatic adenocarcinoma
Expressed	*Common*: CK7, CK19, MOC31, Claudin 4, Ber-Ep4, mCEA, pCEA (non-canalicular), Mucin (Extra-hepatic): CK20 *Rare*: GPC3	*Common*: Hep Par1, albumin (by in-situ hybridization), AFP, pCEA (canalicular), GPC3 *Rare*: CK7, CK19, MOC31, claudin 4, Ber-Ep4, mucin	*Common*: *Gastro-oesophaeal and pancreatic*: similar to CCA *Lower GI*: CK19, CK20, Ber-Ep4, pCEA (non-canalicular)
Radiology	Hypo-dense hepatic lesion with rim enhancement on portal venous or washout phase	In a cirrhotic liver, lesion with arterial phase enhancement and washout in portal venous or washout phase	Hypo-dense hepatic lesion with rim enhancement on portal venous or washout phase (primary tumour may be evident)
Serological marker	Ca19-9, CEA	AFP	Multiple markers including AFP, Ca19-9 and CEA
Not expressed	Hep Par1, AFP	mCEA	Hep Par1, AFP

Magnetic Resonance Imaging (MRI)

Triple-phase gadolinium-enhanced images of the liver can also be obtained during MRI evaluation. Better separation of the MRI phases can be achieved compared with CT, allowing hypervascular lesions and washout to be identified more clearly for radiological exclusion of HCC. During the arterial phase of gadolinium-enhanced MRI, iCCAs tend to appear hypointense compared with liver tissue on T1-weighted images. However, iCCAs tend to look hyperintense on T2-weighted images, due to fibrosis and the presence of mucin within tumours [14]. Given that the distinction between smaller iCCA and HCC on CT scans of cirrhotic livers remains a challenge [15], lesion intensity on T1-and T2-weighted MRI may help to further clarify the nature of such liver masses. In a study of the accuracy of MRI distinction between HCC and CCA (for lesions > 2 cm), MRI had a sensitivity of 85% and specificity of 89.7% [16]. However, MRI is less accurate for the differential diagnoses of smaller lesions or metastases from non-hepatobiliary primary sites. Furthermore, in livers with chronic biliary stricturing conditions such as primary sclerosing cholangitis, the specificity of typical MRI appearances for CCA can be as low as 37% [17]. As regards CCA staging, trials comparing the accuracy of contrast-enhanced CT with MRI (including MRCP) are yet to be conducted. However, from small studies, their overall accuracy is considered broadly equivalent [18]. Nevertheless, MRI may provide more detail on hepatic architecture and smaller iCCA particularly when radical surgery is feasible.

Positron Emission Tomography (PET)

For lesions which remain indeterminate for malignancy after CT and MRI evaluation, PET may be useful, providing metabolic rather than anatomical information on tumours. The main limitations of PET imaging include poor resolution and anatomical localisation. The development of PET-CT fusion images has been of help in overcoming this issue to some degree. Studies evaluating the accuracy of PET-CT in staging CCA are fairly limited. However, they seem to suggest its utility for exclusion of distant metastatic disease. One small study found that only 25% of distant metastases detected on PET were evident on contrast-enhanced CT scan [19]. Another study has reported a sensitivity of 95% for detection of distant metastases by PET compared with 63% for CT [9]. Nevertheless, PET is less reliable for the detection of lymph node and peritoneal metastases. While PET may be a potential tool for preventing unnecessary radical surgery for cholangiocarcinoma, adequately powered studies are required to validate its role.

Cholangiography

Magnetic resonance cholangiopancreatography (MRCP) is the most accurate non-invasive means of imaging of the entire biliary tree and is as sensitive as ERCP for detecting extrahepatic CCA [20]. This could be of value when selective bile duct dilatation is crucial to the differential diagnosis of periampullary lesions. Invasive

cholangiography permits direct visualisation of the biliary tree utilising various techniques such as endoscopic retrograde cholangiopancreatography (ERCP), single-operator peroral cholangiopancreatography (SpyGlass endoscopy) or percutaneous transhepatic cholangiography (PTC). ERCP is useful in the diagnosis of pCCA and dCCA as well as obtaining brush samples of epithelium for cytological analysis. Specificity of cytology is high (60–100%); however, sensitivity is low (9–24%) [21]. In addition, ERCP and PTC both facilitate therapeutic stent deployment to relieve biliary obstruction. SpyGlass endoscopy is utilised as an option to overcome some of the limitations of standard ERCP. It provides a useful alternative technique of stent deployment and obtains a tissue diagnosis when ERCP is unsuccessful [22]. However, diagnostic radiological imaging is recommended to be obtained prior to any intervention, to prevent anatomical distortion precluding interpretation of imaging.

Laboratory Investigations

Serology

Liver Function Tests

Common biochemical abnormalities associated with CCA typically reflect biliary obstruction which include raised levels of bilirubin, alkaline phosphatase and gamma-glutamyltransferase. In more advanced cases, aspartate aminotransferase and alanine aminotransferase can also become deranged, along with impaired clotting and falling albumin levels indicative of failing synthetic liver function. However, these are non-specific for a cholangiocarcinoma diagnosis.

Tumour Markers

The value of tumour markers in the diagnosis of CCA is limited. Carbohydrate antigen (CA) 19-9 remains one of the best studied markers. Carcinoembryonic antigen (CEA) is another well-studied marker. Both markers are, however, rather non-specific and can be raised in a multitude of inflammatory conditions such as cholangitis and with other malignancies. On the other hand, patients who are Lewis antigen negative will not be able to produce CA 19-9. Thus the sensitivity and specificity of currently studied tumour markers are low for a cholangiocarcinoma diagnosis.

Histopathology

CCA is thought to develop through a series of stages from early biliary glandular hyperplasia, through metaplasia, to dysplasia and finally carcinoma. CCAs are adenocarcinomas comprising tubules, acini, solid nests or trabeculae,

embedded in desmoplastic stroma [23]. As they can be surrounded by extensive fibrosis, it is often difficult to distinguish cholangiocarcinoma from chronically inflamed tissue morphologically. iCCA is usually found in non-cirrhotic livers. However, in the setting of an intrahepatic lesion on a background of cirrhosis, differentiation of CCA from HCC morphologically is sometimes problematic. Morphologically, iCCA can be classified into mass-forming, periductal-infiltrating, intraductal, superficial spreading and undefined subtypes [24]. Furthermore, pCCAs can be classified into exophytic mass-forming and intraductal subtypes. Periductal and mass-forming types harbour the poorest prognosis.

CCAs can range from being undifferentiated to well-differentiated. Papillary adenocarcinoma is by far the commonest variant. Subtypes of CCA other than papillary adenocarcinoma account for <10% of tumours and include mucinous, adenosquamous, squamous cell, signet-ring cell, mucoepidermoid, glycogen-rich clear-cell and spindle cell or undifferentiated carcinomas. Adenosquamous and spindle cell carcinomas are thought to have a worse prognosis than adenocarcinoma [23]. The difference between poorly differentiated CCA, HCC with a pseudoglandular pattern of differentiation and metastases to the liver from non-HB sites can be challenging. Immunohistochemical and molecular markers which could be of assistance in this respect are shown in Table 15.2.

Staging

The staging of CCA guides management and helps with prognostication. The complexities of staging this tumour group are well documented due to the variation in anatomical location of the tumour as well as the limited sensitivity of even the most modern imaging modalities. To guide treatment, CCA can be simply classified into early, locally advanced (LA) or metastatic stages. Early CCA is potentially resectable, dependent upon patient suitability. LA CCA is deemed surgically unresectable due to macrovascular or lymph node involvement. However, there is ongoing interest in the role of locoregional ablative treatment approaches and the potential for conversion to resectable disease (particularly when LA by virtue of macrovascular invasion). Finally, metastatic CCA occurs with spread to adjacent or more distant organs, only amenable to palliative systemic treatment.

While no staging system has been universally adopted, at least three well-known comprehensive staging systems are currently available which incorporate prognostic factors to expand on the basic classification. Variations exist in each of these staging systems according to the anatomical location of tumour. These include the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), the Liver Cancer Study Group of Japan (LCSGJ) and the National Comprehensive Cancer Network (NCCN) staging systems. The AJCC/UICC is the only system which has shown correlation between stage and survival, is the most often used and will be discussed in more detail. This staging system underwent

recent revision with an 8th edition projected to come into effect globally in January 2018 [25].

Radiological Staging

Intrahepatic CCA

For iCCA, T classification (AJCC/UICC staging) is dependent upon the number of lesions present, the presence of macrovascular invasion and invasion of adjacent structures. Tumour size has been controversial as a prognostic factor; however, size has been shown to correlate with tumour grade which could confound such analysis [26]. The AJCC/UICC system for intrahepatic CCA (8th edition; [27]):

T Stage

T1a: solitary tumour, <5 cm without macrovascular involvement
T1b: solitary tumour >5 cm, also without macrovascular involvement
T2: solitary tumour with intrahepatic macrovascular invasion or multiple tumours, with or without macrovascular invasion
T3: tumours perforating visceral peritoneum
T4: tumours directly invading local extrahepatic structures

N Stage

N0: refers to no regional lymph node involvement
N1: refers to regional lymph node involvement

M Stage

M0: refers to no distant metastases or nodal involvement
M1: refers to distant metastatic spread or distant nodal involvement

The 8th edition (AJCC system) has been shown to be better able to stratify the risk of death for stage III and T3 patients [28]. A further study claimed the 8th edition provided more discrete stratification of patient prognostic groups in general [29].

Perihilar CCA

For pCCA, the presence of lymph node metastases, differentiation, macrovascular invasion, perineural invasion and surgical resection margins has been shown to be of prognostic relevance [30, 31]. The Bismuth-Corlette system (Table 15.1) is not a staging system but can help guide surgical management. The two main staging systems in common use include AJCC/UICC and the Memorial Sloan Kettering Cancer Centre (MSKCC) staging system. The AJCC/UICC system for pCCA (8th Edition):

T Stage

T1: tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2: tumours which invade beyond the wall of the bile duct to surrounding adipose tissue or adjacent hepatic parenchyma
T3: tumours which invade unilateral branches of the portal vein or hepatic artery
T4: tumours which invade the main portal vein or its branches bilaterally, the common hepatic artery, the unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

N Stage

N0: refers to no lymph node involvement
N1: refers to involvement of one to three lymph nodes within the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal and/or portal vein lymph node groups
N2: refers to involvement of four or more lymph nodes from the sites mentioned for N1 (above)

M Stage

M0: refers to no distant metastases or nodal involvement
M1: refers to distant metastases or distant nodal involvement

Distal CCA

For distal CCA, factors such as depth of invasion, the presence of lymph node metastases, microscopic vascular invasion, direct invasion into the pancreas/adjacent structures, resection margins and perineural invasion have been suggested to be independent prognostic factors [31, 32]. The AJCC/UICC 8th edition is currently the only accepted staging system for distal CCA [33].

T Stage

T1: tumours invading the bile duct wall with a depth less than 5 mm
T2: tumours invadeing the bile duct wall with a depth of 5–12 mm
T3: tumours invadeing the bile duct wall with a depth greater than 12 mm
T4: tumours are classed as involving the celiac axis, superior mesenteric artery and/or common hepatic artery

N Stage

N1: disease encompasses metastasis in one to three regional lymph nodes
N2: disease is classed as four or more regional lymph nodes involved

M Stage

M0: refers to no distant metastases or nodal involvement
M1: distant metastasis or distant nodal involvement

Laparoscopy and Surgical Staging

Laparoscopy has been shown to be able to detect sub-radiological intra-abdominal metastases by facilitating closer evaluation of the liver surface, which may allow detection of occult hepatic metastases. Staging laparoscopy can also detect occult peritoneal metastases. A previous study [34] found that in patients with CCA that initially appeared resectable after combined imaging modalities, staging laparoscopy detected peritoneal and liver metastasis in one third of patients (accuracy was found to be 92% and 71%, respectively). It could not however detect lymph node or vascular involvement which was only observed during laparotomy [34]. Consequently preoperative laparoscopy has been said to prevent unnecessary laparotomy in up to 30% of patients. Expert consensus recommends preoperative laparoscopy in patient with high-risk localised CCA, such as defined by T stage and Ca 19-9 levels in secretors [35]. Nevertheless, a previous study suggested that the presence of metastases on laparoscopy was not contingent with radiological staging [36].

Furthermore, laparoscopy allows biopsy of lesions which appear indeterminate on imaging, providing histological confirmation in case of uncertainty. The addition of laparoscopic ultrasound also aids the diagnosis of hepatic metastases and should be combined with staging laparoscopy to determine local stage and rule out metastatic disease [37]. Nevertheless, surgical resectability cannot be guaranteed without complete abdominal exploration at the time of surgery.

Future Considerations

With respect to the diagnosis of cholangiocarcinoma, further research into potential biomarkers to enhance early diagnosis with a high degree of sensitivity and specificity is ongoing [38]. Furthermore, improved resolution of imaging is crucial for accurate selection of cases which are potentially curable by surgery. Techniques such as PET-CT and PET-MR and the use of cholangiocyte-specific contrast media are currently undergoing evaluation [39]. Finally, in this era of genomic and precision medicine, molecular biomarkers to distinguish liver metastatic upper gastrointestinal malignancies from CCA and to identify clinically relevant subsets of cholangiocarcinoma may be crucial to optimising the benefit from systemic therapy for cancer [40].

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