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Review

Diagnosis and management of intrahepatic cholangiocarcinoma: A comprehensive update for the radiologist

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There is increasing focus on intrahepatic cholangiocarcinoma (IHCC) due to its rising incidence worldwide and relatively poor prognosis, with the revised TNM classification (2009) introducing a separate staging system for IHCC for the first time. In this article, we comprehensively review the current role of the radiologist in the diagnosis and management of patients with IHCC.

Introduction

Cholangiocarcinoma is the most common neoplasm of the biliary tree. It is further classified based on its location as intrahepatic or extrahepatic. Extrahepatic cholangiocarcinoma is subdivided as perihilar (Klatskin's tumour) and distal extrahepatic cholangiocarcinoma. The anatomical site of origin distinguishing intrahepatic cholangiocarcinoma (IHCC) from extrahepatic cholangiocarcinoma is the second-order (segmental) bile duct, with extrahepatic cholangiocarcinoma originating from the first-order bile duct (right and left hepatic ducts) to the common bile duct (CBD).[1,2] The exact distinction between perihilar and distal cholangiocarcinoma is not well-defined, with some using the junction of the cystic duct and the CBD as the landmark (although this can be variable) and others using the point where the CBD passes under the first part of the duodenum.[3,4] IHCC is the least common of the three, accounting for approximately 8–10% of cholangiocarcinoma.[3,5,6] The incidence of IHCC is significantly different worldwide with a much higher incidence in Asia than in Europe and America (0.95 per 100,000 in USA as compared to 96 per 100,000 in Thailand).[7] However, its incidence is increasing across the world, attributable to a true increase rather than to improved diagnosis. This has lead to an increasing focus on IHCC in recent times.[8] Mortality, however, has shown a progressive decrease in USA between 1996 to 2010 as per a recent study of 8805 patients from the Surveillance, Epidemiology and End Results (SEER) database.[9]

The imaging features of IHCC have been well described. However, in addition to diagnosis, radiology also plays an important role in patient prognostication and management, which will be an important focus of this article. In this

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review, we will discuss the aetiopathogenesis of IHCC, explain the revised 2009 TNM classification, which introduced a separate staging for IHCC for the first time, discuss in detail the role of imaging in the diagnosis, prognostication, and follow-up of IHCC, and provide an update on the management of IHCC with emphasis on the role of the radiologist.

Aetiopathogenesis

The most common age group affected by IHCC is between 55–75 years, with a slight male preponderance in both incidence and mortality.[10–13] Risk factors include various disorders, which cause chronic biliary inflammation, including primary sclerosing cholangitis, parasitic infestation (endemic in Southeast Asia), hepatolithiasis, hepatitis B and C, and cirrhosis, as also congenital abnormalities of the biliary tract such as choledochal cyst and fibrocystic liver disease.[10,12,14]

The Liver Cancer Group classified cholangiocarcinoma into three types based on their morphological appearance and pattern of spread: mass-forming, periductal-infiltrating, and intraductal growing.[1] The mass-forming type forms a definite intrahepatic mass and is the predominant subtype of IHCC, responsible for up to 79–86% of all cases.[1,15] A mixed mass-forming and periductal-infiltrating subtype has also been described and is reported to be associated with a worse prognosis.[16–18]

Pathologically, IHCC has a tendency to develop abundant desmoplastic response, particularly at its centre, due to which it is a grey–white hard mass on gross pathology. On histopathology, IHCC is an adenocarcinoma arising from the bile ducts with the presence of central fibrous stroma and foci of coagulative necrosis. Mucinous degeneration may occasionally be present in the centre, and the tumour may rarely show calcification.[13,19–22] Definite histopathological identification of IHCC remains difficult, and IHCC ultimately remains a diagnosis of exclusion. Certain immunohistochemistry features are considered suggestive including expression of cytokeratin 7 (CK7), CK19, and anion exchanger (AE)1/3 and absence of CK20, caudal type homeobox 2 (CDX2), trefoil factor 1 (TFF1), and mucin 2 (MUC2). Colorectal metastases are a close differential but are CK7 negative and CK20, CDX2, and MUC2 positive.[7,23]

Revised TNM classification

Until the sixth edition (2002) of the American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) TNM staging system, no distinction was made between the classification of hepatocellular carcinoma (HCC) and IHCC. However, a study of 598 patients obtained from the SEER database concluded that tumour size was not an important prognostic factor, whereas the presence of vascular invasion and multiple nodules predicted worse prognosis in IHCC. In light of these findings, the seventh edition of AJCC TNM staging system (2009) introduced a separate staging system for IHCC, with tumour size no longer included in the staging and the latter two factors (vascular invasion and multiple nodules) making the tumour T2a and T2b, respectively (Table 1).[24,25]

Other important factors associated with better survival include lack of lymph node metastases and negative resection margins.[5,26–29] Right regional lymph nodes include hilar, periduodenal, and peripancreatic nodes, whereas left IHCC regional lymph nodes include hilar and gastrohepatic nodes. Coeliac, periaortic, and pericaval adenopathy is considered as M1 stage.[25] Various surgical series reveal lymph node metastases to be present in 30–40% of patients with IHCC.[7,27,30]

Imaging features

Imaging can be discussed with regards to three aspects: imaging features of primary IHCC, role of imaging in patient prognostication, and imaging of recurrent/metastatic disease.

Imaging features of primary IHCC with pathological correlation

On ultrasound, IHCC does not have any characteristic features and may be hypoechoic, hyperechoic, or demonstrate heterogeneous echotexture, and may show associated biliary dilatation.[31] Contrast-enhanced ultrasound is more accurate, with late-phase washout being a specific feature.[32,33] However, ultrasound is less accurate for assessing disease burden and tumour resectability, and as per the National Comprehensive Cancer Network (NCCN) guidelines, contrast-enhanced CT or MRI with delayed-phase imaging is ideal for the evaluation of IHCC.[31,34]

The cross-sectional imaging features of IHCC are directly related to its pathological features (Table 2). At CT/MRI, IHCC presents as an ill-defined, hypodense/heterogeneously T2 hyperintense and T1 hypointense mass. The active peripheral part of the tumour is T2 hyperintense, whereas the central fibrous stroma may appear T2 hypointense.[21,35] Associated capsular retraction is present in up to 21–36% of patients due to the fibrotic nature of the

Table 1
Revised 7th edition of the AJCC/UICC TNM classification of intrahepatic cholangiocarcinoma.

Primary tumour (T)	
T0	No evidence of primary tumour
T1	Solitary tumour without vascular invasion
T2a	Solitary tumour with vascular invasion
T2b	Multiple tumours, with or without vascular invasion
T3	Tumour perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
T4	Tumour with periductal invasion
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastasis present