Editorial

Improve the precise pathological diagnosis of intrahepatic cholangiocarcinoma: introduction to 2022 expert consensus on pathological diagnosis of intrahepatic cholangiocarcinoma in China

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Intrahepatic cholangiocarcinoma (ICC) is a highly aggressive intrahepatic epithelial neoplasm with biliary differentiation. The clinicopathological characteristics of ICC and extrahepatic cholangiocarcinoma are significantly different[1]. In the last 10 years, notable progress has been made in the pathological research of ICC, and some of them have been compiled by the 5th edition of the World Health Organization (WHO) Classification of Tumors of the Digestive System. However, the diagnostic strategy of ICC in the current WHO classification still has something to be further refined for routine practice. In order to standardize the pathological diagnosis of ICC and provide an elaborate pathological basis for personalized treatment in the clinic, 46 experts in the field of liver tumors, representing seven professional societies/academic groups of China, including pathology, surgery, oncology, and basic disciplines, developed the expert consensus on ICC pathological diagnosis[2].

The nationwide screening of primary liver cancer shows that hepatocellular carcinoma (HCC), ICC, and combined hepatocellular-cholangiocarcinoma account for 93.0%, 4.3%, and 1.6% of primary liver cancer, respectively, in China[3]. The incidence of ICC is on the rise, especially in people over 65 years old[4]. HBV infection is probably one of the most important factors in China among the risk factors for ICC development[5,6]. The application of multiple therapies, including antiviral treatment and targeted therapies, can prolong long-term survival in ICC[7,8].

There are three main macroscope patterns of ICC, including mass forming pattern, periductal infiltrating pattern, and mixed pattern (mass forming pattern + periductal infiltrating pattern). Different sampling methods are recommended according to the macroscope patterns. For mass forming and mixed pattern ICCs, the seven-point baseline sampling method is recommended. For the periductal infiltrating pattern ICC, the specimen is mainly collected from the junction between the invaded bile duct wall and liver parenchyma as well as the surgical margin, so as to check the extent of ICC invasion and the presence of precancerous lesions.

Intrahepatic biliary ducts can be divided into three bile duct groups, the large bile duct group (area bile ducts-segmental bile ducts, 300-800 μm), the small bile duct group (interlobular bile ducts-septal bile ducts, 15-300 μm), and the terminal bile duct group (canals of Hering, < 15 μm). Based on the histological and anatomical characteristics of bile duct groups, ICC is histologically classified into four subtypes, namely large bile duct, small bile duct, cholangiolocarcinoma, and ICC with ductal plate malformation pattern[5,9]. ICC with different histological subtypes is highly heterogeneous in cell origin, tissue structure, immunophenotype, and molecular alteration.

The morphological characteristic of large bile duct subtype, which originates from the intrahepatic large bile ducts group, shows columnar tumor cells and mucus-secreting cells arranged in irregular ductal patterns, with a desmoplastic response. This subtype usually shows an aggressive growth pattern with portal triads, vascular, lymphatic, and perineural invasion, as well as lymph node metastasis. Immunohistochemical (IHC) markers, such as S100 calcium-binding protein P (S100P), mucin 5AC, and trefoil factor 1 are positive. The representative molecular alteration is KRAS mutation. Large bile duct subtype has the worst postoperative prognosis among the ICC subtypes.

Small bile duct subtype arises from the interlobular bile duct or septal bile ducts, showing cuboidal or low-columnar cells arranged in a regular ductal pattern. Small bile duct subtype is less aggressive than large bile duct subtype, rarely invading the portal areas, blood vessels, lymphatic vessels, and nerves, and rarely involving lymph node metastasis. C-reactive protein (CRP), N-cadherin, and CD56 are useful biomarkers for confirming small bile duct subtype. It is noteworthy that S100P may also be positive in small bile duct subtype, depending on the selected clones of antibodies. Isocitrate dehydrogenase1/2 mutations and FGFR2 fusion/rearrangement are presentative targeted therapeutic markers, which are recommended to be detected in small bile duct subtype. The postoperative prognosis of small bile duct subtype is much better than that of the large bile duct subtype. The 5-year recurrence-free survival rate of small bile duct and large bile duct subtypes is 10% and 38%, respectively, and the 5-year overall survival rate is 20% and 60%, respectively[10].

Cholangiolocarcinoma originates from the smallest branches of the intrahepatic biliary tree (canals of Hering and bile ductules) and is considered a unique small bile duct subtype. Cholangiolocarcinoma is morphologically characterized by well-differentiated angular small ductular loosely arranged in hyalinized collagen fiber stroma. This subtype is less invasive. The IHC markers and molecular variations are similar to those of small bile duct subtype. It is important to note that HCC-like ICC often appears in

cholangiolocarcinoma[11-13]. HCC-like ICC is composed of polygonal eosinophilic tumoral cells arranged in a trabecular pattern, morphologically resembling HCC, and prone to be misdiagnosed. It is recommended to use IHC staining to distinguish HCC-like ICC from HCC. The former expresses cholangiocyte-lineage markers, such as CK7 and CK19, but not hepatocyte-lineage markers, such as Arginase-1 (ARG1) and Hepatocyte Paraffin 1 (Hepar-1). The surgical prognosis of cholangiolocarcinoma is better than that of small bile duct and large bile duct subtypes[14,15].

Ductal plate malformation subtype is another special and rare small bile duct subtype, characterized by irregular dilated cystic lumens with polypoid protrusions in the lumen[5,12,16]. This subtype is less aggressive and its postoperative prognosis is generally well. The IHC markers and molecular alterations of ductal plate malformation subtype are similar to those of small bile duct subtype.

The mixed type (hybrid pattern) of ICC, which contains multiple ICC components, may reflect different biological behaviors and clinical prognoses. It is recommended to describe the proportion of each histological component in the pathological report. The combination of large bile duct subtype markers (S100p + mucin 5AC) with small bile duct subtype markers (CRP + N-cadherin) is suggested as the first-line IHC panel for ICC subclassification. The recommended second-line panel includes MUC6, trefoil factor 1, and CD56.

At present, the diagnostic terminology of "ICC" is not fully consistent. WHO classification recommends using the term "intrahepatic cholangiocarcinoma" rather than "cholangiocellularcarcinoma" and "cholangiolocellularcarcinoma"[5], whereas the 8th UICC-TNM staging system prefers to use "cholangiocellular carcinoma" to refer to cholangiolocarcinoma and ICC[17,18]. The consensus supports the opinion of WHO and recommends using "intrahepatic cholangiocarcinoma" as the standard term for pathological diagnosis.

In the era of targeted therapy and the recent shift towards immunotherapy for ICC, specific biomarkers have been proposed by both the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) guidelines for biliary tract cancers, which put forward higher requirements for the detection of biomarkers. The consensus classified and summarized all the molecular targets of ICC based on the molecular characteristics of different ICC subtypes, and listed the corresponding targeted drugs and detection methods[2], establishing a molecular-pathological foundation for the precise and individualized treatment of ICC.

Accurate pathological classification is the basis for personalized treatment and prognosis prediction of ICC. The present consensus emphasized the establishment of a diagnostic model for the ICC pathological classification[2]. In this model, clinical characteristics, macroscopic patterns, cell morphology, histological structure, immunophenotype, and biomarkers for targeted therapy and immunotherapy should be comprehensively considered for subtype diagnosis. This consensus, together with the previously established guidelines for the pathological diagnosis of HCC[19,20], may improve the overall homogeneity of pathological diagnosis of primary liver cancer in China.

DECLARATIONS

Authors' contributions
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Manuscript writing: Zhang X, Wang H, Chen J, Sheng X, Zhang H, Zhang L

Conflicts of interest
All authors declared that there are no conflicts of interest.

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Not applicable.

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