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Consensus

Expert Consensus on Pathological Diagnosis of Intrahepatic Cholangiocarcinoma (2022 version)

Han Wang[1#], Jun Chen[2#], Xin Zhang[3#], Xia Sheng[4#], Xiao-Yan Chang[5], Jie Chen[5], Min-Shan Chen[6], Hui Dong[1], Guang-Jie Duan[7], He-Ping Hu[8], Zhi-Yong Huang[9], Wei-Dong Jia[10], Xiao-Qing Jiang[11], Dong Kuang[12], Shan-Shan Li[13], Zeng-Shan Li[14], Chang-Li Lu[15], Shu-Kui Qin[16], Xue-Shan Qiu[17], Li-Juan Qu[18], Chun-Kui Shao[19], Feng Shen[20], Guo-Ming Shi[21], Su-Sheng Shi[22], Yu-Jun Shi[23], Hui-Chuan Sun[21], Xiao-Dong Teng[24], Bin Wang[25], Zhan-Bo Wang[26], Tian-Fu Wen[27], Jia-Mei Yang[28], Qiao-Qiao Yang[29], Sheng-Long Ye[30], Hong-Fang Yin[31], Zhen-Gang Yuan[32], Jing-Ping Yun[33], Feng-Lin Zang[34], Hong-Qi Zhang[35], Li-Hong Zhang[35], Jing-Min Zhao[36], Jian Zhou[21], Wei-Xun Zhou[5], Jia Fan[21], Xiao-Ping Chen[9], Wan Yee Lau[37], Yuan Ji[3*], Wen-Ming Cong[1*] and Chinese Society of Liver Cancer of Chinese Anti-Cancer Association; Digestive Disease Group of Chinese Society of Pathology, Chinese Medical Association; Chinese Society of Pathology of Chinese Anti-Cancer Association; Hepatic Surgery Group of Chinese Society of Surgery, Chinese Medical Association; Biliary Tract Tumor Committee of China Anti-Cancer Association; Chinese Society of Clinical Oncology

[1]Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [2]Department of Pathology, the Affiliated Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China; [3]Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai, China; [4]Department of Pathology, Minhang Hospital, Fudan University, Shanghai, China; [5]Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [6]Department of Liver Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China; [7]Department of Pathology, The First Affiliated Hospital, Army Medical University, Chongqing, China; [8]Department of Hepatobiliary Medicine, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [9]Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [10]Department of General Surgery, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, Hefei, Anhui, China; [11]Department of Biliary Surgery I, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [12]Department of Pathology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [13]Department of Pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, Henan, China; [14]Department of Pathology, Xijing Hospital, Air Force Medical University, Xi'an, Shaanxi, China; [15]Department of Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [16]Cancer Center of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China; [17]Department of Pathology, The First Affiliated Hospital, China Medical University, Shenyang, Liaoning, China; [18]Department of Pathology, The 900 Hospital of the Chinese People's Liberation Army Joint Logistics Team, Fuzhou, Fujian, China; [19]Department of Pathology, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China; [20]Department of Hepatic Surgery IV, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [21]Department of Liver Surgery and Transplantation, Zhongshan Hospital, Fudan University, Shanghai, China; [22]Department of Pathology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [23]Institute of Clinical Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [24]Department of Pathology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; [25]Department of Pathology, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China; [26]Department of Pathology, The First Medical Center, Chinese PLA General Hospital, Beijing, China; [27]Department of Liver Surgery & Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [28]Department of Special Medical Care, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [29]Department of Neurosurgery, Zhongshan Hospital, Fudan University, Shanghai, China; [30]Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [31]Department of Pathology, Beijing Tsinghua Changgung Hospital, Beijing, China; [32]Department of Oncology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China; [33]Department of Pathology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China; [34]Department of Pathology, Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China; [35]Department of Anatomy, Histology and Embryology, Shanghai Medical College, Fudan University, Shanghai, China; [36]Department of Pathology and Hepatology, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [37]Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China

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Abstract

Intrahepatic cholangiocarcinoma (iCCA) can originate from the large bile duct group (segment bile ducts and area bile ducts), small bile duct group (septal bile ducts and interlobular bile ducts), and terminal bile duct group (bile ductules and canals of Hering) of the intrahepatic biliary tree, which can be histopathological corresponding to large duct type iCCA, small duct type iCCA and iCCA with ductal plate malformation pattern, and cholangiolocarcinoma, respectively. The challenge in pathological diagnosis of above subtypes of iCCA falls in the distinction of cellular morphologies, tissue structures, growth patterns, invasive behaviors, immunophenotypes, molecular mutations, and surgical prognoses. For these reasons, this expert consensus provides nine recommendations as a reference for standardizing and refining the diagnosis of pathological subtypes of iCCA, mainly based on the 5th edition of the World Health Organization Classification of Tumours of the Digestive System.

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive tumor that arises from the lining epithelium and peribiliary glands from the second order intrahepatic bile ducts to the smallest intrahepatic bile branches, and it expresses cholangiocyte-specific markers.[1–5] iCCA accounts for 10–20% of primary liver cancers[6] and 20–30% of cholangiocarcinomas.[7,8] Based on a study in China, hepatocellular carcinoma (HCC) and iCCA account for 90.2% and 8.2% of 26,684 cases of surgically resected primary hepatic malignant tumors, respectively.[9] The age-standardized incidence rates of iCCA in China did not rise significantly from 2006 to 2015 (2.0/100,000–2.2/100,000), but there was a significant increase in patients age over 65 years (3.4/100,000–4.5/100,000) during the study period.[10] iCCA is a highly malignant tumor with a 5-year overall survival rate of less than 50% even after surgical resection with curative intent.[5,11]

The clinicopathological features of iCCA and extrahepatic cholangiocarcinoma are significantly different.[12] In the past, there was no refined diagnostic mode on iCCA owing mainly to its inconsistent histological types and unclear diagnostic criteria for its subtypes. However, notable progresses have been made in the pathological research of iCCA in the past decade, some of which have been adopted by the World Health Organization (WHO) Classification of Tumours of the Digestive System (fifth edition). However, the criteria for histological classification of iCCA, the differential diagnosis of histological variation, the selection of immunohistochemical (IHC) markers, and the detection of molecular targets need to be refined in order to be better applied in practice. To our knowledge, no guidelines for contouring the iCCA pathological subtype diagnosis have been previously reported. As a consensus on the diagnosis of histological subtypes can help to standardize the routine pathological diagnosis of iCCA, thus providing an elaborate pathological basis for individualized treatment in clinical practice, the present consensus on pathological diagnosis of iCCA was jointly formulated by the expert team in China.

Methodology

Forty-seven experts who represented six professional academic groups were selected to form an expert consensus group based on their expertise and contribution to research and scholarship in the field of liver pathology, surgery, oncology, and basic scientific disciplines in China. All participants disclosed potential conflicts of interest and they did not receive any financial compensation for participation. The expert consensus group decided to engage in small-consensus draft team brainstorming discussions aligned with the expertise and interests of the participants, which was then discussed as a large group and vetted by the rest of the participants. The literature search was conducted on multiple electronic data libraries that included the PubMed, China National Knowledge Infrastructure, Web of Science, Medline, and EMBASE databases up to May 2022. No limits were incorporated into the literature search to obtain all available evidence. A review of the incorporated articles was then undertaken to identify and synthesize evidence to support the creation of recommendations based on the available evidence.

Draft versions of the present consensus were repeatedly presented, discussed, and subsequently revised at several online-to-offline expert consensus meetings to come up with a consensus on the applicability and challenges of each recommendation in clinical practice. Then, the members of expert consensus group received literature specific to the revised consensus statements and indicated their agreement opinions. Consensus was defined as universal agreement of the participants and categorized based on the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) system. The quality of evidence scale ranged from high, moderate, to low and very low, and the recommendation levels for clinical practice were strong and conditional (Supplementary Table 1).[13,14]

Structure and heterogeneity of the intrahepatic biliary system

iCCA originates from the lining epithelium of the intrahepatic bile duct tree, the peribiliary glands and hepatic stem/progenitor cells.[15] In addition, mature hepatocytes can also give rise to iCCA caused by reprogramming mechanisms.[1,8] Based on the caliber of bile ducts, the intrahepatic biliary tree can be divided into a terminal bile duct group with canals of Hering (CoH) and bile ductules, < 15 μm, a small bile duct group with interlobular bile ducts and septal bile ducts, 15–300 μm, and a large bile duct group with areas of bile ducts and segmental bile ducts of 300–800 μm (Fig. 1). The histogenesis

Keywords: Intrahepatic cholangiocarcinoma; Pathology; Histological type; Immunohistochemistry; Molecular variation.

Abbreviations: AB-PAS, Alcian blue and Periodic acid Schiff; CD, cluster of differentiation; CK, cytokeratin; CLC, cholangiolocarcinoma; CoH, canals of Hering; CRP, C-reactive protein; dMMR, mismatch repair deficiency; DPM, ductal plate malformation; GRADE, Grading of Recommendations Assessment, Development, and Evaluations; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcioma; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; MUC, mucin; S100P, S100 calcium-binding protein P; TFF1, trefoil factor 1; TMB, tumor mutational burden; WHO, World Health Organization.

#Contributed equally to this work.

*__Correspondence to:__ Yuan Ji, Department of Pathology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. ORCID: https://orcid.org/0000-0002-2631-9082. Tel: +86-21-64041990, Fax: +86-21-64041990-695401, E-mail: ji.yuan@zs-hospital.sh.cn; Wen-Ming Cong, Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, 225 Changhai Road, Shanghai 200438, China. ORCID: https://orcid.org/0000-0002-8924-5551. Tel/Fax: +86-21-81875193, E-mail: wmcong@smmu.edu.cn

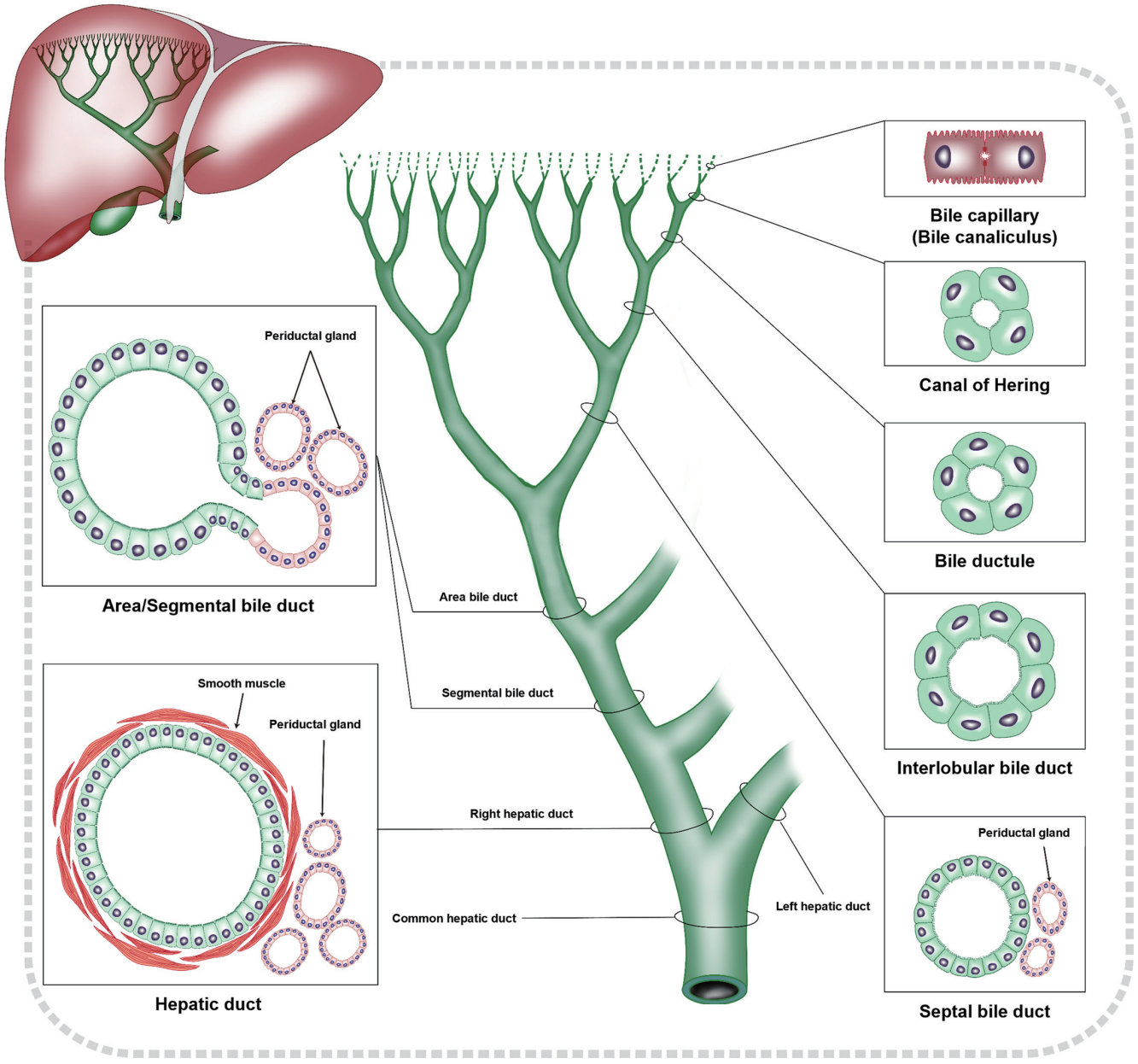

Fig. 1. Schematic diagram of structural characteristics of intrahepatic biliary system.

and the anatomic sites of each group is the basement of histopathologic classification of iCCA [corresponding to cholangiolocarcinoma (CLC), small duct type iCCA and iCCA with ductal plate malformation (DPM) pattern, as well as large duct type iCCA, respectively].[16–18] iCCA with different histological subtypes is highly heterogeneous in its cell origin, tissue structure, immunophenotype, and molecular mutations. For example, iCCA can express not only biliary lineage markers such as cytokeratin 19 (CK19) which indicates a cholangiocyte origin, but also stem cell lineage markers such as cluster of differentiation 56 (CD56) which indicates a hepatic stem/progenitor cell origin.[19]

Cholangiocytes are also diverse in their morphology and immunophenotyping. For example, IHC staining is positive for epithelial membrane antigen on the cell membrane at the edge of glandular lumen of the small interlobular bile ducts similar to the staining pattern in CoH, while medium-sized interlobular bile ducts have a cytoplasmic staining pattern similar to that of septal bile ducts and large bile ducts.[19–21] In addition, the septal bile ducts in the small bile duct group are invisible in the gross specimens of liver. However, from these bile ducts, columnar cells, mucus-secreting cells, and peribiliary glands which are gradually appear.[2,22] Thus, the heterogeneity of cholangiocytes should be considered in the diagnosis of histological subtypes of iCCA.

Recommendation 1: The histological and anatomical characteristics of terminal bile ducts (CoH and bile ductules), small bile ducts (interlobular bile ducts and septal bile ducts) and large bile ducts (area bile ducts and segmental bile ducts) in the intrahepatic biliary system serve as the histological

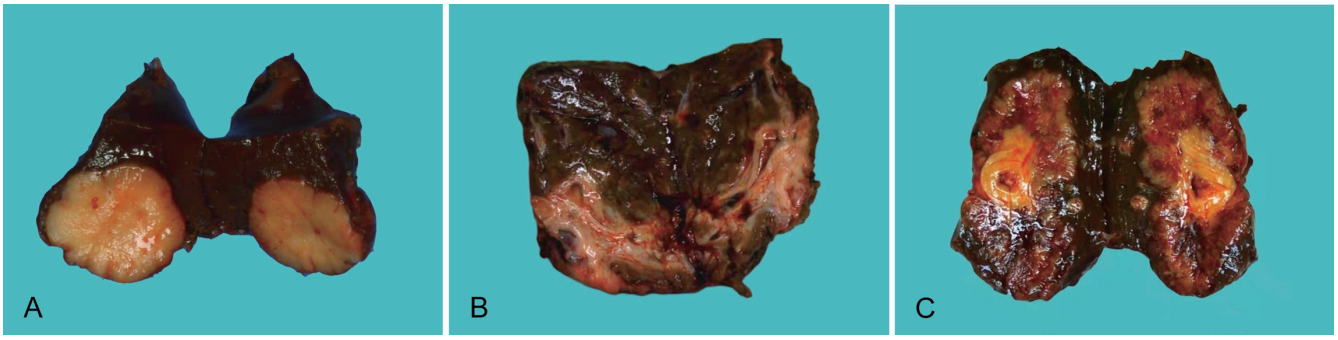

Fig. 2. Gross pattern of iCCA. (A) Mass forming pattern; (B) Periductal infiltrating pattern; (C) Mixed pattern. iCCA, intrahepatic cholangiocarcinoma.

and anatomical foundation for classification of the iCCA histological subtypes (i.e., CLC, small duct type iCCA and iCCA with DPM pattern, and large duct type iCCA), to form the basis for better understanding and refining the diagnosis of the histological subtypes of iCCA (moderate-quality evidence and strong recommendation).

Gross Patterns of iCCA

Mass forming pattern

This pattern is common in the peripheral area of the liver.[23,24] Grossly, the tumor is a gray-white, nodular solid mass formed in the liver parenchyma with a clear boundary (Fig. 2A). The surrounding liver tissues are normal or accompanied by chronic viral hepatitis or liver cirrhosis. Histopathologically, it is the most common pattern of small duct type iCCA.

Periductal infiltrating pattern

This pattern often involves large bile ducts near the hilar area.[23,24] The tumor grows longitudinally along the bile duct wall in an infiltrating manner (Fig. 2B) and may be accompanied by diseases such as intrahepatic biliary ductal stones, sclerosing cholangitis, and biliary parasites. It remains as a common pattern of large duct type iCCA.

Mixed pattern (mass forming pattern + periductal infiltrating pattern)

The tumor penetrates the bile duct wall and invades into the surrounding liver parenchyma while growing along the bile duct wall, thereby forming a nodular mass which is embedded within a residual bile duct cavity (Fig. 2C).[23,24] This is a common gross pattern of large duct type iCCA. Periductal infiltrating and mixed pattern iCCAs have a 45% higher risk of long-term mortality than the mass forming pattern iCCA.[25] The mixed pattern iCCA is more prone to portal vein invasion, biliary invasion, or lymph node metastasis.[26] Nevertheless, some scholars argue that the gross pattern of iCCA is not significantly correlated with the postoperative overall survival rate or metastasis-free survival rate.[27] iCCA with the intraductal growing pattern has similar morphological characteristics to those of intraductal papillary tumor.[28] Therefore, the previously reported intraductal growing pattern is no longer regarded as a growth pattern of iCCA by the Union for International Cancer Control, and the WHO categorizes it as a unique entity of intraductal papillary tumor with associated invasive carcinoma.[24,29,30]

Sampling of iCCA Gross Specimens

1. The surgeon should indicate the hepatic lobes or segments where the tumor was located on the pathological examination application form, because it is necessary for the pathological diagnosis of whether the tumor arose from intrahepatic or extrahepatic biliary ducts. The surgical margins (both liver and bile duct) can be stained with dye or marked with a surgical suture for accurate sampling. iCCA has a lymph node metastatic incidence rate of 30–60%.[31,32] Metastasis to lymph nodes tend to occur in the regions of the hepatoduodenal ligament, along the common hepatic artery, and posterior to the pancreas.[33] Any freely sampled lymph nodes including their locations and numbers sent for testing should be marked clearly and separately. The clinicians are recommended to perform a regional lymphadenectomy containing six or more lymph nodes for histological examination. If the regional lymph nodes are negative, but the number ordinarily examined is not met, classify as N0 staging.[34]
2. The seven-point baseline sampling method is recommended for mass forming and mixed pattern iCCA specimens.[13,35] The maximum diameter and number of tumors as well as the presence of macroscopic tumor invasion of vessels and adjacent organs are crucial in gross pathological examination, as they directly affect the pathological tumor–node–metastasis stage of iCCA.[34] Microvascular invasion is an important pathological predictor of postoperative prognosis of iCCA patients[36,37] and it should be pathologically graded as in HCC.[13,35,38] It is more encouraging to employ some IHC biomarkers (i.e. CD34 and D2-40) to distinguish the blood vessels and lymphatics as different types of microtumor thrombus may represent different recurrence patterns.[39,40]
3. The periductal infiltrating pattern iCCA specimens should basically be collected in the following manner: After the invaded bile duct wall has been dissected longitudinally, the length of the invaded bile duct, the thickness of the duct wall, and the shortest distances of the tumor from the surgical margins are measured. Samples are taken from the junction between the involved bile duct wall, the surrounding liver parenchyma and the surgical margins of the liver and bile duct to study the depth and extent of bile duct invasion.

Recommendation 2: The gross pattern of iCCA is related to the histological subtype. For mass forming and mixed pattern iCCAs, the seven-point baseline sampling method should be used. For periductal infiltrating pattern iCCA, specimens are taken from the junction between the invaded bile duct wall, the liver parenchyma, and the surgical margins to study the extent of iCCA invasion and presence of any precancerous lesions (moderate-quality evidence and strong recommendation).

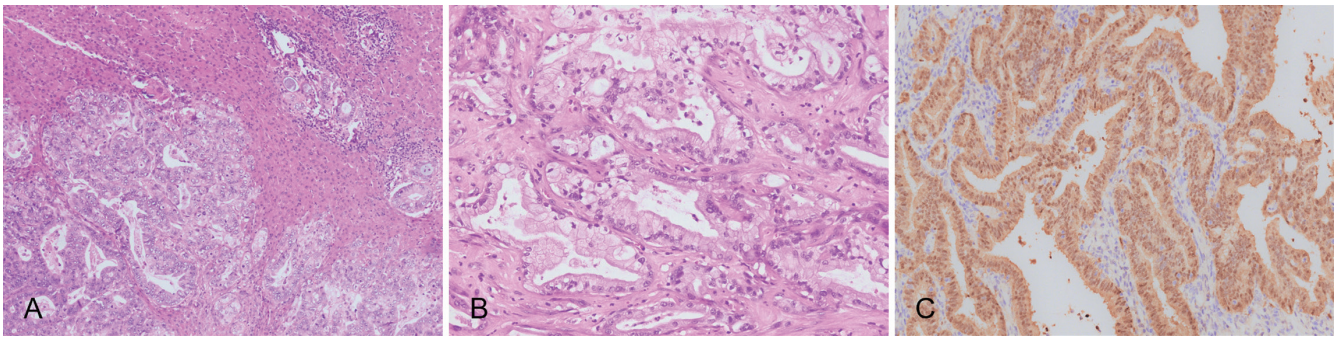

Fig. 3. Large duct type iCCA. (A) Columnar tumor cells arranged in irregular glandular structures, invading multiple portal areas adjacent to the carcinoma; (B) High columnar tumor cells secret mucus; (C) S100 calcium-binding protein P-positive in IHC staining. iCCA, intrahepatic cholangiocarcinoma; IHC, in immunohistochemical.

Histopathological characteristics of iCCA

Pathological concepts of iCCA

Almost all iCCAs are adenocarcinomas (> 95%).[24,41] Generally, the diagnosis of iCCA is pathologically represented as an adenocarcinoma which originates from lining epithelium and/or peribiliary gland cells of intrahepatic bile ducts. Other rare malignant tumors of intrahepatic large bile duct include adenosquamous carcinoma, squamous cell carcinoma, mucinous carcinoma, signet ring cell carcinoma, lymphoepithelioma-like carcinoma (with highly expressed programmed death ligand 1 and better prognosis in patients with Epstein–Barr virus infection[42]), and sarcomatoid carcinoma (including multiple molecular targets[43]), etc. All these tumors need to be separately diagnosed and classified because of specific differences in specific pathogenesis, morphology, biological behavior, and clinical prognosis.[44] The WHO classification does not recommend using the term cholangiocellular carcinoma.[24]

Histological types of iCCA

Large duct type iCCA

Cell origin: This type of iCCA arises from the lining epithelium or peribiliary gland of intrahepatic large bile ducts. It accounts for 41–59% of all iCCA cases.[18,45] In large duct type iCCA, the serum cancer antigen 19–9 and carcinoembryonic antigen levels can be increased to varying degrees.[46] There may be precancerous lesions such as intraepithelial neoplasia of bile duct or intrahepatic papillary tumor adjacent to the cancer boundary.

Histological characteristics: Large duct type iCCA has cuboidal or columnar cells, which are mainly moderately–poorly differentiated, arranged in irregular ductal or tubular patterns (Fig. 3A), with mucus-secreting cells or intraluminal mucus (Fig. 3B). These features are similar to those seen in hilar cholangiocarcinoma. A prominent desmoplastic response is commonly observed in large duct type iCCA, which correlates with the high invasiveness of the tumor and its resistance to chemotherapy and targeted drugs.[47,48] There are often portal area, blood vessel and lymphatic and perineural invasion and lymph node metastasis.

IHC markers and special staining: S100 calcium-binding protein P (S100P; Fig. 3C), mucin 5AC (MUC5AC), MUC6, and trefoil factor 1 (TFF1) are usually positive, among them, S100P is a highly sensitive (95%) and moderately specific (71%) marker for large duct type iCCA.[49] However, the expression results can be affected by antibodies from different clones. For instance, it has been reported that in large duct type iCCA, the positive rates of S100P varied from 29–95%[49] or from 13–56%.[50] Positive Alcian blue and Periodic acid Schiff (AB-PAS) staining is indicative of presence of mucus-secreting cells.

Representative molecular alterations: The rates of the *KRAS* mutations vary from 15% to 30%, which are frequently correlated with poor postoperative prognosis. The mutation of other target genes, such as *BRAF*, *EGFR*, and *HER2* might be harbored.[4,46]

Surgical prognosis: Comparing the large duct type and the small duct type iCCAs, the postoperative 5-year recurrence-free survival rates were 10% and 38%, respectively, and the 5-year overall survival rates were 20% and 60%, respectively.[46] Positive S100P staining indicates strong invasiveness and poor prognosis.[51,52]

Recommendation 3: Large duct type iCCA are mainly composed of cuboidal or columnar cells with mucinous cytoplasm, and they are arranged in irregular ductal or tubular pattern with abundant fibrous stroma. The tumor usually shows a more aggressive growth pattern which is commonly associated with portal area, blood vessel, lymphatic and perineural invasion and lymph node metastases. S100P, MUC5AC, MUC6, TFF1, and mucus staining should be positive on IHC. *KRAS* Mutation is frequent. Large duct type iCCA has worse long-term prognosis than the other subtypes of iCCA (moderate-quality evidence and strong recommendation).

Small duct type iCCA

Cell origin: It originates from interlobular bile ducts or septal bile ducts,[8] accounting for 41–58% of iCCA cases.[18,45] Biliary hamartoma and biliary adenoma are regarded as possible precancerous lesions.[22,53–56]

Histological characteristics: The tumor cells are cuboidal or low columnar with scant cytoplasm, mostly moderately–highly differentiated and lack of mucus-secreting. However, mucus-secreting cells may be present in small duct type iCCA arising from septal bile duct.[2] Most tumor tissues are arranged into dense and regular small ductal structures (Fig. 4A, B). Obvious fibrous stroma is frequently observed in the central area of the tumor of which the constitutive cells may be highly relevant to the immunotherapeutic response.[48] Usually, there is no capsule around the tumor, and there are few invasions into adjacent portal area, blood vessel, lymphatic vessel, or nerve. Small duct type iCCA can also show a lot of morphological variations, such as the branching duct shape, branching trabecular shape, microcystic shape, cribriform shape, papillary shape, and solid shape, which may increase the difficulty of subtype diagnosis.[46,49]

IHC markers and special staining: C-reactive protein (CRP), N-cadherin (Fig. 4C) and CD56 are usually positive. It is reported that the sensitivity and specificity are 97%

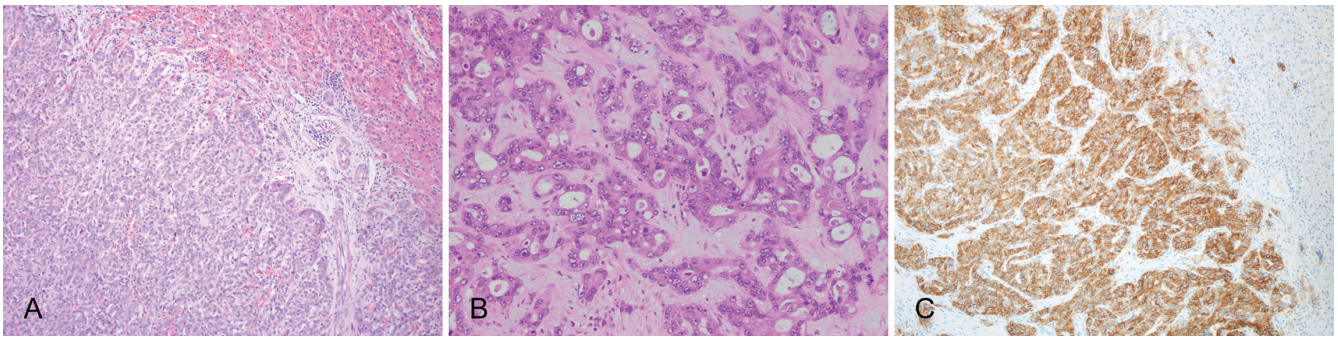

Fig. 4. Small duct type iCCA. (A) Cuboidal tumor cells arranged in dense small glandular structures, uncovered by a capsule; (B) Tumor arranged in a solid or trabecular like structure; (C) N-cadherin-positive in IHC staining. iCCA, intrahepatic cholangiocarcinoma; IHC, in immunohistochemical.

and 95% in CRP, and 87% and 84% in N-cadherin, respectively.[46,49] Mucus staining is usually negative. However, the positive rates of S100P, TFF1, and mucus staining in small duct type iCCA can reach up to 51.4%, 15%, and 54.1%, respectively.[19,57] As above indicators are partly overlapping, the differential diagnosis between small duct type iCCA and large duct type iCCA should be carefully combined with the features of morphology and immunohistochemistry (Table 1).

Representative molecular alterations: *IDH1/2* mutation and *FGFR2* fusion/rearrangement are the most representative of the druggable molecular alterations in small duct type iCCA.[4,24,45,46]

Surgical prognosis: Generally, the surgical prognosis of it is much better than that of the large duct type iCCA.[46,58] The prognosis of small duct type iCCA with mutant *IDH1/2* is better than that with wild-type *IDH1/2*.[59]

Recommendation 4: Small duct type iCCA, which is predominantly composed of cuboidal or low columnar cells, is often constituted with dense small ductal structures, and a deficiency of mucus-secreting cells, and it frequently presents with multiple histological variations. It rarely invades portal area, blood vessel, lymphatic vessel, nerve, with few lymph node metastases. IHC usually shows positive CRP, N-cadherin and CD56 staining, but mucus staining usually shows a negative result. *IDH1/2* mutation and *FGFR2* fusion/rearrangement are its representative targetable mutations. The surgical prognosis of small duct type iCCA is better than that of the large duct type iCCA (moderate-quality evidence and strong recommendation).

CLC

Cell origin: CLC had been considered as a specific subtype of combined hepatocellular-cholangiocarcinoma with stem cell features, while the following molecular analysis showed that CLC was an independent entity without the traits of HCC.[60] The available evidence suggests that CLC originates from the cells of the terminal branches of intrahepatic bile duct tree, as well as hepatic stem cells or progenitor cells,[8,19,30] making up 0.6–1% of primary liver cancers[61] and 13–40% of iCCAs. The discrepancy may come partly from different diagnostic criteria,[62,63] and it is often complicated with liver diseases such as chronic viral hepatitis B.[64] The WHO classification does not recommend using the term cholangiolocellular carcinoma.[24]

Histological characteristics: CLC is a unique morphological subtype simulating CoH, bile ductules,[8] or ductular reaction, and a lumen diameter < 15 μm can be used as one of the diagnostic criteria.[65] CLC cells have a small cuboidal shape, a high nuclear-to-cytoplasmic ratio, oval nuclei, pale cytoplasm, insufficient mucus, without or with minimal ductal atypia and high differentiation, characterized by a loose, angular small ductular, cord-like or branched arrangement in a hyalinized collagen fiber stroma (Fig. 5A). CLC seldom invades adjacent portal area, blood vessel, or lymphatic vessel. CLC and small duct type iCCA can be complicated with HCC-like iCCA components.[2,63,64,66] These components are formed by polygonal tumor cells which are rich in eosinophilic cytoplasm and arranged in a trabecular or nest-like pattern, thus resembling HCC (Fig. 5B). However, these cells express cholangiocyte-lineage markers such as CK7/CK19 (Fig. 5C) and stem cell markers such as epithelial cell adhesion molecule, but they do not express hepatocyte-lineage markers which is essentially different from combined hepatocellular-cholangiocarcinoma that is defined by unequivocal presence

Table 1. Histological subtypes and pathological characteristics of iCCA

Histological subtype	Large duct type iCCA	Small duct type iCCA
Gross pattern	Peritubular infiltrating pattern, mixed pattern	Mass forming pattern
Cell morphology	Columnar-cuboidal	Cuboidal-low columnar
Tissue structure	Irregular large ductal or tubular adenocarcinoma	Dense small ductal adenocarcinoma
Invasiveness	++ – +++	– –+
Mucus staining	++ – +++	– –+
Immunohistochemistry	S100P, MUC5AC, MUC6, TFF1	CRP, N-cadherin, CD56
Genetic variation	*KRAS* gene mutation	*IDH1/2* gene mutation, *FGFR2* gene fusion/rearrangement

iCCA, intrahepatic cholangiocarcinoma; S100P, S100 calcium-binding protein P; MUC, mucin; TFF, trefoil factor 1; CRP, C-reactive protein; CD56, cluster of differentiation 56.

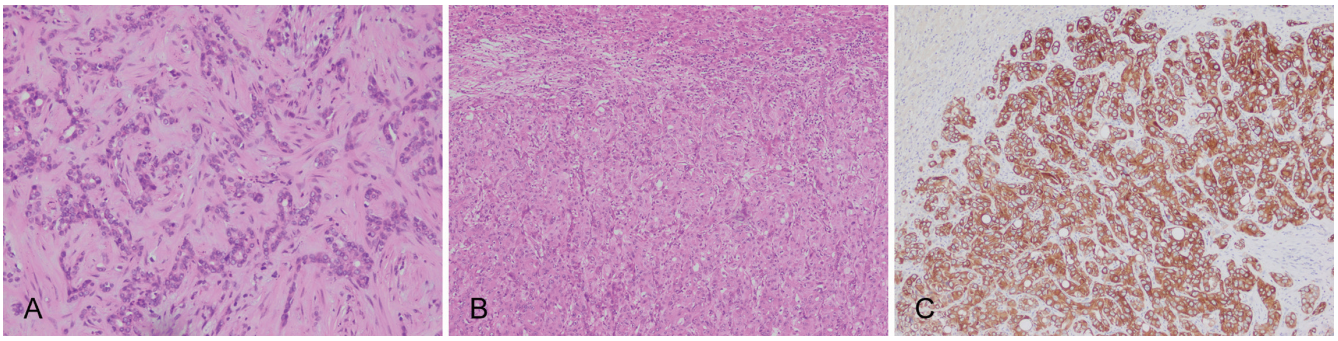

Fig. 5. CLC and HCC-like ICC. (A) CLC, Small cuboidal tumor cells in sparse branching glandular structures, with hyaline degeneration of fibrous stroma; (B) HCC-like iCCA, with polygonal tumor cells in trabecular patterns; (C) HCC-like iCCA, cytokeratin 19-positive IHC staining. CLC, cholangiolocarcinoma; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcioma; IHC, immunohistochemistry.

of both hepatocytic and cholangiocytic differentiation within the same tumor.[67] The HCC-like iCCA components are thought to be originating from hepatic precursor cells[45,63,68,69] or are the manifestation of poorly differentiated CLC.[63] HCC-like iCCA may be similar to HCC on imaging features or clinical features and needs to be distinguished from HCC.[70]

IHC markers and molecular alterations: They are similar to those of small duct type iCCA. Moreover, positive staining of CD56 is more frequent in CLC compared with classical iCCA.[66,70]

Surgical prognosis: It is better than that of small and large duct type iCCAs.[19,24,61,64]

Recommendation 5: CLC is composed of small cuboidal tumor cells with low atypia forming a sparsely branched small ductular configuration embedded in a hyalinized fibrous stroma. The IHC markers and molecular variations are similar to those of small duct type iCCA. CLC has lower invasiveness and better surgical prognosis than that of small and large duct type iCCAs (moderate-quality evidence and strong recommendation).

iCCA with DPM pattern

Cell origin: This type of tumor mimics DPM, which is found in Caroli's disease, congenital hepatic fibrosis or von Meyenburg complexes from each parts of intrahepatic biliary system, and is considered as a rare subtype of small duct type iCCA.[24,71,72] Whether its occurrence is associated with DPM remains controversial.[73,74] iCCA with DPM pattern is often complicated by liver diseases such as viral hepatitis B.[75]

Histological characteristics: It has saccate, adenoid, or fissure-like tumor ducts lined by a single layer of flat, small cuboidal or low columnar epithelium, with clear and sparse cytoplasm, small and pale nuclei, and a few mucus-secreting cells. The lumens are dilated as irregular cystic lumens of varying sizes and the lining epithelium has polypoid protrusions into the lumen (Fig. 6A, B). The lumens in the central region of the tumor are large, with dense fibrotic stroma, while those in the peripheral region are small, without a capsule, and grows invasively with rare blood vessel and lymphatic invasion as well as lymph node metastasis.[63]

IHC markers and molecular alterations: They are similar to those of small duct type iCCA (Fig. 6C). In addition, *ARID1A* mutation and absent expression may occur.[70,76–78]

Surgical prognosis: Postoperative recurrence and metastasis are rare.[75]

Recommendation 6: iCCA with DPM pattern is formed by small cuboidal or low columnar cells characterized by irregular cystic dilatation of lumen with polypoid protrusions in the lumen. IHC markers and molecular mutations of iCCA with DPM pattern are similar to those of small duct type iCCA. iCCA with DPM pattern is less aggressive and has a better prognosis after surgery (moderate-quality evidence and strong recommendation).

Indeterminate/Mixed Pattern iCCA

Multiple histological subtypes of iCCA sometimes co-exist, and they account for 56.5% of iCCA,[19,24,49,64,71,77,79] representing the high intratumoral heterogeneity of iCCA (Fig. 7). Among them, the tumor dominated by CLC components has the better prognosis.[65] To objectively assess the biological characteristics of this kind of iCCA, it is recommended to di-

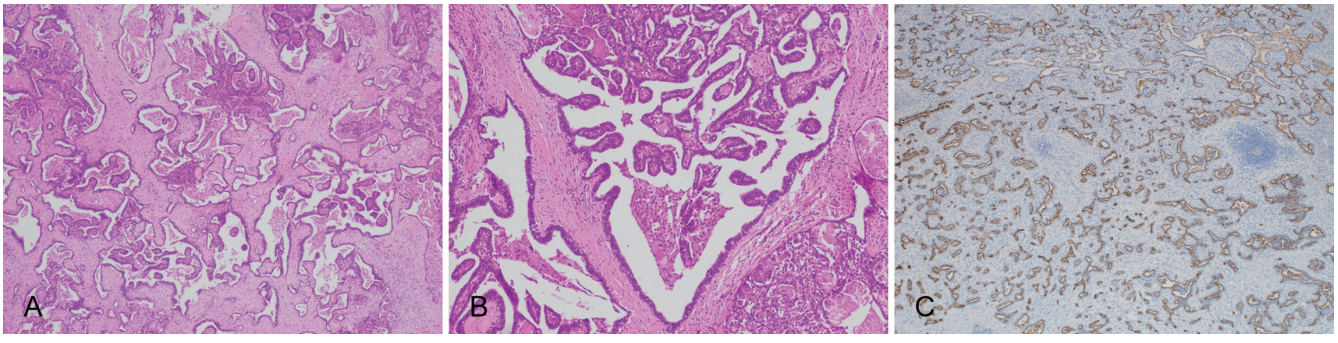

Fig. 6. iCCA with DPM pattern. (A) Irregular cystic dilated tumor glandular ducts with abundant fibrous stroma; (B) Polypoid protuberance in the tumor crypt; (C) IHC staining for mucin 1 shows positive results on the marginal surface of the lumen. DPM, ductal plate malformation; iCCA, intrahepatic cholangiocarcioma; IHC, immunohistochemistry.

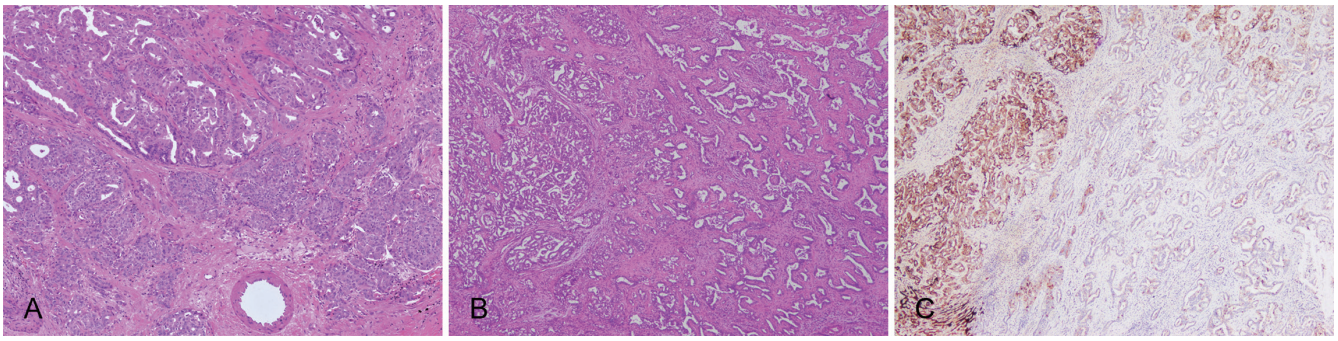

Fig. 7. iCCA with multiple histological subtypes. (A) Large duct type iCCA (upper left) and small duct type iCCA (bottom right) components in the same tumor; (B) Small duct type iCCA (left) and DPM pattern iCCA (right) components in the same tumor; (C) IHC staining for CRP shows strong positive results on small duct type iCCA (left) components and weak positive results on DPM pattern iCCA (right) components. CRP, C-reactive protein; DPM, ductal plate malformation; iCCA, intrahepatic cholangiocarcioma; IHC, immunohistochemistry.

agnose iCCA according to the dominant and other components of the tumor and to illustrate the proportions of all histological components in the pathological report. It is reported that according to conventional histologic assessment, 32.4% of iCCA initially fall into the mixed category including those with mixtures of typical large duct and small duct types and those with nontypical histology, such as columnar cell tumors without mucin, cuboidal cell tumors with abundant mucin production, or poorly differentiated tumors. However, by just choosing the appropriate IHC profiles can classify most iCCA cases (96%) into the definite histological subtypes.[46] Hence, it is recommended to pair large duct type iCCA markers with small duct type iCCA markers to help with the subtype diagnosis. Combining with published experimental data, S100P, MUC5AC, CRP, and N-cadherin are recommended as the first option IHC panel for iCCA subclassification, and MUC6, TFF1, CD56, MUC1, and AB-PAS mucus staining as beneficial supplements to the diagnosis if necessary.[21,24,50,57,69,78,79] This combination should continuously be optimized in pathological practice.

Recommendation 7: iCCA is a highly heterogeneous tumor, with histological subtypes which cannot always subtly match the IHC phenotypes and molecular alterations. Great efforts should be made to establish the model of diagnosis of pathological subtypes for iCCA. The comprehensive clinical characteristics, gross pattern, cell morphology, histological structure, immunophenotype, mucus secretion, and molecular mutations should be considered in its diagnosis and differential diagnosis. A four-antibody panel of IHC markers (S100P, MUC5AC, CRP, and N-cadherin) is recommended for distinguishing the histological subtypes of iCCA (low-quality evidence and conditional recommendation).

Targeted therapy and immunotherapy biomarkers of iCCA

Targeted therapy and immunotherapy biomarkers of iCCA should be detected based on the National Comprehensive Cancer Network as well as the Chinese Society of Clinical Oncology Clinical Practice Guidelines for biliary tract cancers to provide a reference for targeted inhibitor therapy for unresectable and metastatic disease.[80,81] Table 2 shows the authorized drugs and their relevance to managing patients with different subtypes of iCCA.[78,79,82,83] An increasing number of studies confirm that drugs designed for several targetable genetic aberrations, such as *IDH* and *FGFR2*, show the

Table 2. Targeted therapy and immunotherapy biomarkers of iCCA

Molecular variation	Mutation frequency*	Targeted drug	Pathological type	Test methods
FGFR2 fusion/ rearrangement	2–13%	Pemigatinib; Infigratinib	Common in small duct type iCCA	FISH, second generation sequencing
IDH1/2 mutation	7.5–16%	Ivosidenib	Common in small duct type iCCA	First/second generation sequencing
NTRK fusion	5%	Entrectinib; Larotrectinib	iCCA	FISH, RT-PCR, second generation sequencing
RET fusion	1.80%	Pralsetinib	iCCA	FISH, second generation sequencing
BRAF^{V600E} mutation	4.3–11.1%	Dabrafenib + trametinib	iCCA	RT-PCR, first/second generation sequencing
HER2 amplification	1.8–8%	Trastuzumab + pertuzumab	iCCA	Immunohistochemistry, FISH Second generation sequencing
MSI-H/dMMR	2–4.8%	Pembrolizumab	iCCA	PCR, immunohistochemistry
TMB-H	10.40%	Pembrolizumab	iCCA	Second generation sequencing

*iCCA data in China.[78,79] iCCA, intrahepatic cholangiocarcinoma; FISH, fluorescence *in situ* hybridization; RT-PCR, reverse transcription polymerase chain reaction; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficiency; TMB: tumor mutational burden.

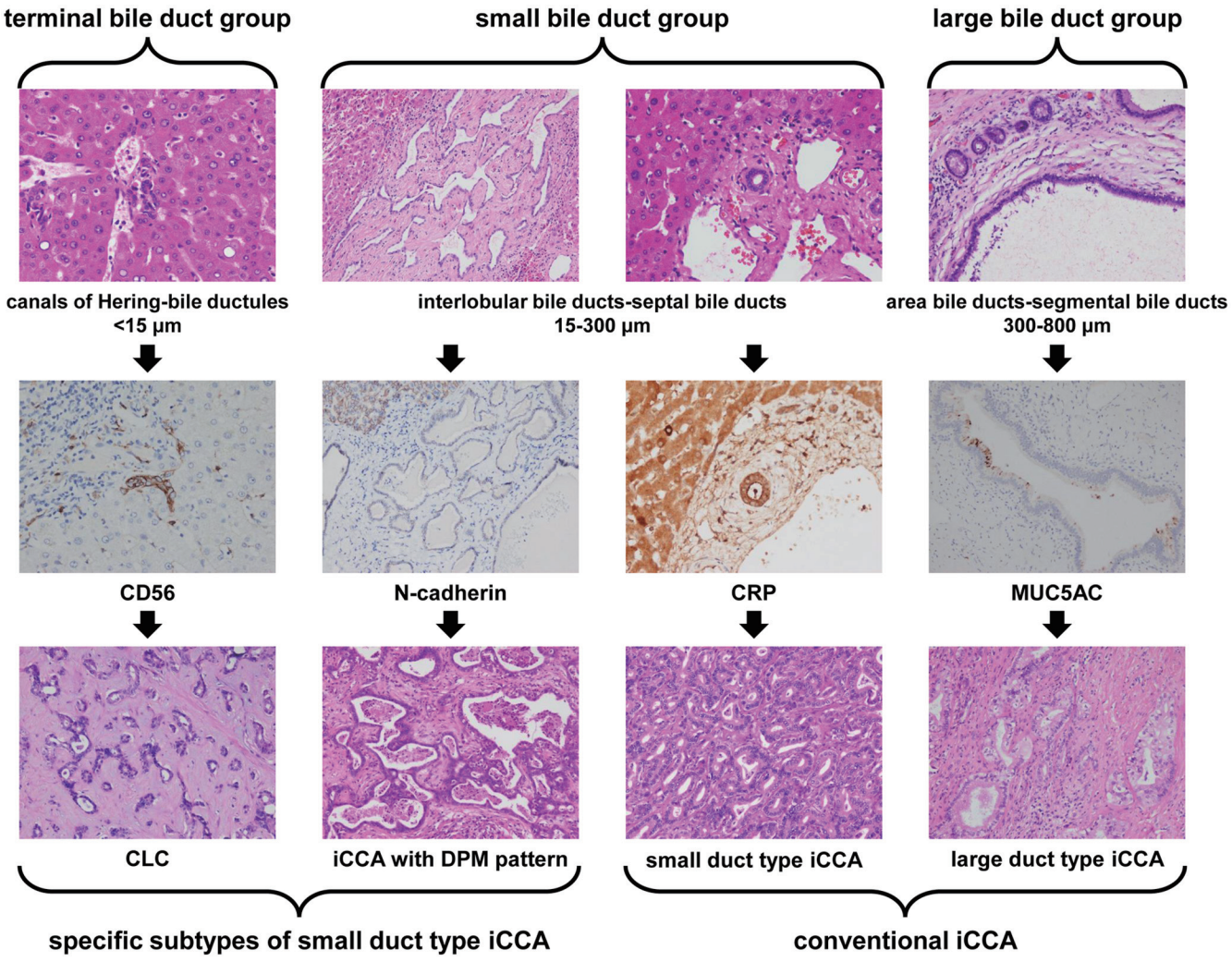

Fig. 8. Correspondence between the intrahepatic bile duct groups and iCCA subtypes. iCCA, intrahepatic cholangiocarcioma.

therapeutic potential and correlation with histological subtypes,[84–86] while only a small proportion of patients harboring these specific gene alterations could obtain survival benefit. On this account, agents targeting programmed death ligand 1 and programmed death receptor 1 immune checkpoint are currently under investigation and is emerged as a new paradigm of therapy.[87,88] Referring multiple valuable biomarkers, such as *KRAS* and tumor mutational burden (TMB), to predict whether the patients with iCCA could benefit from clinical trial provides a new idea for further expansion of the appropriate population for targeted therapy and immunotherapy.[89] Therefore, it is warranted to provide some associated pathologically detectable targets to meet clinical requirements.

Recommendation 8: Rapid progress in clinical research on targeted therapy and immunotherapy of iCCA has led to higher requirements for screening and detection of biomarkers of targeted inhibitors. More attention should be paid to detection of predictive biomarkers of therapeutic targets and immune checkpoints referring to histological subtype of iCCA to allow refined personalized treatment with improved treatment efficacy, and to help to establish the molecular-pathological basis for individualized iCCA treatment (high-quality evidence and strong recommendation).

Summary of key points of the pathological diagnosis of iCCA

Diagnosis of histological subtypes should be supposed as the core in iCCA routine pathological diagnosis. Differential diagnosis between large duct type and small duct type iCCAs is the key of iCCA routine pathology. Optimizing a combination of IHC marker panels should be used as a reference for histological subtyping. Molecular targets and immunotherapy biomarkers should be detected consulting the histological subtype of iCCA. The main pathobiological characteristics of iCCA should be illustrated in the pathological report form. The diagnostic term intrahepatic cholangiocellular carcinoma is not recommended to be used to refer to iCCA. The correspondence between intrahepatic bile duct groups and iCCA subtype is shown in Figure 8. The flowchart of pathological diagnosis of iCCA is shown in Figure 9.

Recommendation 9: In the pathological report of iCCA, it is important to illustrate the pathological characteristics associated with the risks of postoperative recurrence and metastasis to assist in the clinical treatment planning.[13,44,90] These should include the gross type, histological subtype, immunophenotype, differentiation grade, microvascular invasion, biological behavior, status of surgical margin, pathological tu-

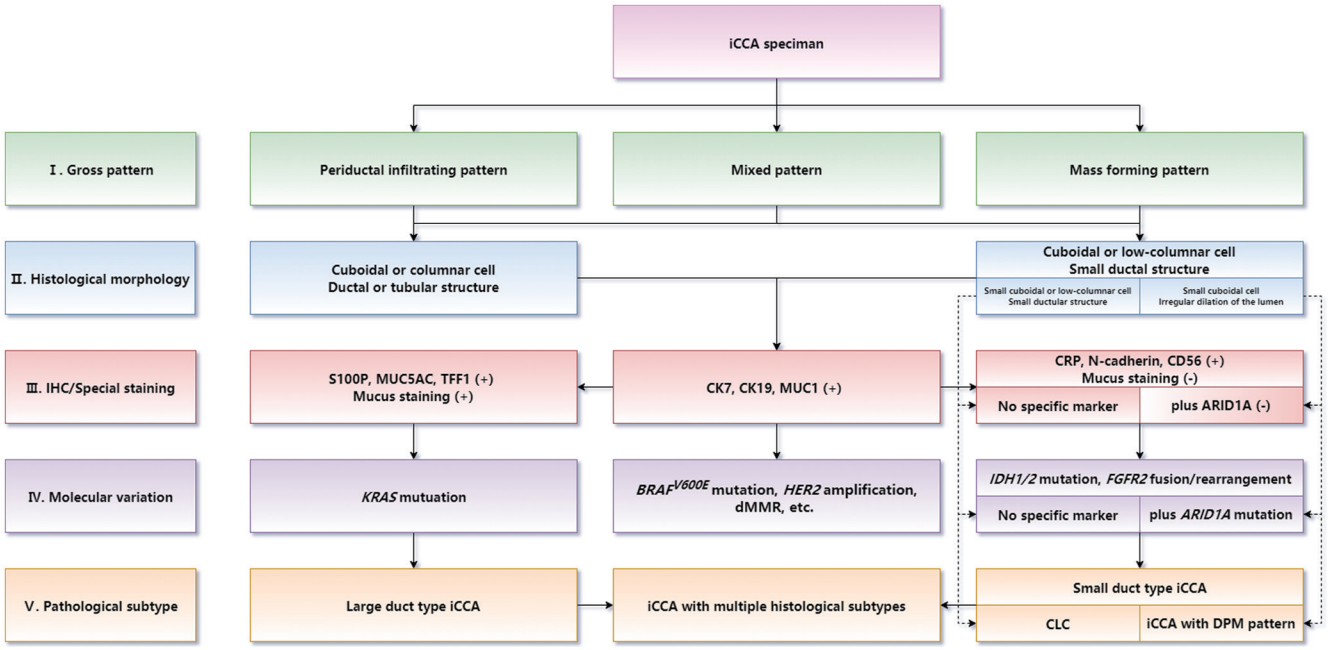

Fig. 9. Flowchart of the pathological diagnosis of iCCA. iCCA, intrahepatic cholangiocarcioma.

mor–node–metastasis stage, background of liver disease, and other important relevant information. To improve the homogeneity of pathological diagnosis of iCCA, the use of a template for pathological diagnostic reporting should be encouraged (moderate-quality evidence and strong recommendation).

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design (WMC, YJ), professional support (JF, XPC, WYL), provision of study materials (all authors), collection and assembly of data (HW, JC, XZ, HQZ, LHZ, XS, ZGY, YJ, WMC), pathology photography and figure drawing (HW, BW, XZ, QQY, manuscript writing (HW, JC, XZ, XS, YJ, WMC), and revisions and final approval of the manuscript (all authors).

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