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Combined Hepatocellular-Cholangiocarcinoma: Changes in the 2019 World Health Organization Histological Classification System and Potential Impact on Imaging-Based Diagnosis

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Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a primary liver cancer (PLC) with both hepatocytic and cholangiocytic phenotypes. Recently, the World Health Organization (WHO) updated its histological classification system for cHCC-CCA. Compared to the previous WHO histological classification system, the new version no longer recognizes subtypes of cHCC-CCA with stem cell features. Furthermore, some of these cHCC-CCA subtypes with stem cell features have been recategorized as either hepatocellular carcinomas (HCCs) or intrahepatic cholangiocarcinomas (ICCs). Additionally, distinctive diagnostic terms for intermediate cell carcinomas and cholangiolocarcinomas (previous cholangiolocellular carcinoma subtype) are now recommended. It is important for radiologists to understand these changes because of its potential impact on the imaging-based diagnosis of HCC, particularly because cHCC-CCAs frequently manifest as HCC mimickers, ICC mimickers, or as indeterminate on imaging studies. Therefore, in this review, we introduce the 2019 WHO classification system for cHCC-CCA, illustrate important imaging features characteristic of its subtypes, discuss the impact on imaging-based diagnosis of HCC, and address other important considerations.

Keywords: *Liver cancer; Hepatocellular carcinoma; Cholangiocarcinoma; World Health Organization; Classification*

INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a distinct primary liver cancer (PLC) that manifests as a biphenotypic tumor with unequivocal features of both hepatocytic and cholangiocytic differentiation, and accounts for 1.0% to 4.7% of all PLCs. Although it is known to be a rare form of cancer, the importance of considering cHCC-CCA in differential diagnoses among PLCs has recently been recognized (1). Specifically, this biphenotypic PLC predominantly appears in patients with chronic viral hepatitis or liver cirrhosis which are similar risk factors for the development of hepatocellular carcinomas (HCCs), and subsequently can lead to imaging-based misdiagnoses of HCCs (2, 3).

Although the pathophysiology of cHCC-CCA remains unclear with several theories suggested, there have been evidences that some types of cHCC-CCA manifested features of hepatic stem/progenitor cells (HPCs) (4, 5), which are capable of both hepatocellular and cholangiocytic differentiation, and furthermore, that HPCs may be the origin of cHCC-CCA (6). At the same time, however, there have also been controversies regarding the specific role of HPCs in this disorder, since "stem cell" phenotypes are recognized to be present in many other types of PLCs.

In 2018, an international group of hepatic pathologists,

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radiologists, surgeons, and clinicians proposed a consensus terminology for PLCs (1). Moreover, in the recently updated 2019 World Health Organization (WHO) classification of tumors of the digestive system (7), the subtype of cHCC-CCA with stem cell features, present in the 2010 WHO classification is no longer used. The "classical" form of cHCC-CCA persists in the updated classification.

Dynamic contrast-enhanced imaging plays a vital role in the noninvasive diagnosis of HCC in high-risk patients. It is imperative for radiologists and clinicians to understand the impact of the new classification system on the diagnoses of HCCs and other PLCs, particularly because HCCs, cHCC-CCAs, and ICCs all lie within a spectrum of disease (7).

In this review, we introduce the 2019 WHO classification of cHCC-CCA, illustrate imaging features according to its subtypes, and discuss the potential impact on diagnostic imaging in patients with HCC.

Pathogenesis of cHCC-CCA and the Concept of HPCs

The pathophysiology of cHCC-CCA is still debated, although there are a few potential theories (8). Conventionally, cHCC-CCA had been believed to arise from the collision of HCCs and ICCs, which arise from hepatocytes and cholangiocytes, respectively. Various classification systems have been proposed accordingly. For example, Allen and Lisa (9) classified cHCC-CCA as an HCC and an ICC in the same tumor (type C). Goodman et al. (10) reorganized cHCC-CCA into type I (collision), type II (transitional), and type III (fibrolamellar). However, the concept of collision tumor has been proven invalid; the exclusion of collision tumor, e.g., separate foci of HCC and ICC without intimate mixing, is obligatory in the diagnosis of cHCC-CCA (7, 11).

Recently, plasticity or transdifferentiation of HCC has been proposed for the occurrence of cHCC-CCA. Several mouse models have demonstrated that mature hepatocytes can undergo reversible transdifferentiation into biliary cells or even dedifferentiation into HPCs (12, 13). In this regard, mature HCC cells have the dynamic potential to shift into biliary cells, to increase tumor heterogeneity, and to initiate new tumorigenesis into cHCC-CCA, as determined by various intrinsic and extrinsic cues such as inflammation, injury, or oncogenic stress (14, 15).

The identification of HPCs has prompted another insight into the origin of cHCC-CCA. HPCs, which reside in bile ductules and the canals of Hering, are postulated to transform into cancer stem cells by various genetic and epigenetic alterations resulting from repeated inflammation and regeneration in patients with chronic liver disease (16). A growing body of evidence suggests that cHCC-CCA may arise from these transformed HPCs (17, 18). HPCs are characterized by their expression of multiple "stemness-related" markers, including keratin 19, neural cell adhesion molecule (CD56), epithelial cell adhesion molecule, epithelial membrane antigen (Muc-1), c-kit (CD117) and CD133 (7, 19). The expression of these stemness-related markers has been identified in many types of PLCs, including a subset of HCCs and cHCC-CCAs, and has been associated with a poor prognosis (18, 20-22).

cHCC-CCA in the 2010 WHO Classification System

cHCC-CCA is defined as PLC with unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor. As evidence for the connection between HPCs and the pathophysiology of cHCC-CCAs accumulated, the 2010 WHO classification system for cHCC-CCAs adopted the concept of HPCs in its own classification. This schema classified cHCC-CCAs into a "classical" type, or into three variants with stem cell features (11). These variants included a "typical" subtype, an "intermediate cell" subtype, and a "cholangiolocellular" subtype (Table 1).

The classical type of cHCC-CCA shows areas of typical HCC and areas of typical ICC, often with transitional zones in between. These transitional zones are often composed of tumor cells that are morphologically intermediate between HCCs and ICCs, express stemness-related markers such as keratin 19 and epithelial cell adhesion molecule, and show morphological features similar to HPCs (23). cHCC-CCAs with stem cell features are composed of tumor cells with HPC features. Although the cut-off proportion of tumor cells with HPC features for the diagnosis of cHCC-CCAs with stem cell features is not suggested according to the 2010 WHO classification, previous studies defined cHCC-CCAs with stem cell features if the proportion of tumor cells with HPC features was more than 5–10% (20, 24). The "typical" subtype is further characterized by mature-looking hepatocytes surrounded by smaller tumor cells with scant cytoplasm, high nuclear/cytoplasmic ratios, and hyperchromatic nuclei that resemble HPCs (25). The "intermediate cell" subtype is comprised of tumor cells that are histopathologically and

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Table 1. Comparison of WHO Histological Classification Systems for PLC

Descriptive Classification	4th WHO Classification System from 2010	5th WHO Classification System from 2019
HCC	HCC	HCC
Classical cHCC-CCA	cHCC-CCA, classical type	cHCC-CCA
cHCC-CCA with "typical" stem/progenitor cell features	cHCC-CCA with stem cell features, typical subtype	Omitted*
cHCC-CCA with "intermediate" stem/progenitor cell features	cHCC-CCA with stem cell features, intermediate cell subtype	Intermediate cell carcinoma† - No strong consensus as to whether or histological pattern of cHCC-CCA
Cholangiolo-predominant carcinomas with HCC and ICC	cHCC-CCA with stem cell features, cholangiolocellular subtype	cHCC-CCA-CLC - Categorized under cHCC-CCA when HCC components are present
Cholangiolo-predominant carcinomas with ICC component	Unclassified	cCCA-CLC - Categorized under ICC when CLC is admixed with conventional ICC
Classic CLC (> 80% of tumor consists of CLC)	CLC - Considered as cHCC-CCA with stem cell features, cholangiolocellular subtype	CLC - Categorized under ICC when CLC is present alone
ICC	ICC	ICC

*May be diagnosed as HCC harboring stem cell features, †Note that diagnosis of intermediate cell carcinoma should be reserved for PLCs in which intermediate features are present in entire tumor and focal presence of intermediate tumor cells in cHCC-CCA does not qualify for diagnosis. cHCC-CCA = combined hepatocellular-cholangiocarcinoma, CLC = cholangiolocarcinoma, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, PLC = primary liver cancer, WHO = World Health Organization

immunohistochemically intermediate between hepatocytes and cholangiocytes. These tumor cells are aligned in strands, trabeculae, or solid nests in a desmoplastic stroma, and show immunohistochemical positivity for hepatocytic, cholangiocytic, and HPC-related markers (23). The third "cholangiolocellular" subtype is characterized by small cells that are morphologically similar to HPCs and are arranged in distinct tubular or cord-like anastomosing architectural patterns recapitulating ductular reactions, with positivity for HPC markers, including keratin 7, keratin 19, and neural cell adhesion molecules (26).

Unsolved Issues Related to the 2010 WHO Classification System for cHCC-CCA

In the 2010 WHO classification system, PLCs included classic HCCs, classic ICCs, and cHCC-CCAs. The cHCC-CCAs were subdivided further into classical cHCC-CCA and cHCC-CCA with stem cell features, which was subdivided further into typical, intermediate cell, and cholangiolocellular subtypes. There were, however, a few critical unresolved issues related to the 2010 WHO classification system for cHCC-CCAs.

First, "stem cell" phenotypes, small uniform tumor cells with scant cytoplasm and inconspicuous nucleoli, have been demonstrated in many forms of PLCs, and the 2010 WHO subcategories under cHCC-CCA with stem cell features were not clearly distinguishable (24, 27). In other words, cHCC-CCA showed wide histologic diversity with immunophenotypic expression of HPC markers to various degrees, rendering it difficult to assign distinct diagnosis for each subtype of cHCC-CCA.

Second, the three subtypes of cHCC-CCA with stem cell features did not show a significant difference in terms of clinical outcome, therefore lessening the importance of this classification system (27).

Lastly, there was no mention of the percentage of stem cell area that was required to categorize a disease as cHCC-CCA with stem cell features, rendering it difficult to achieve consistent and robust diagnosis according to this classification.

Changes in the Updated 2019 WHO Classification System: PLC, not Classic HCC, or ICC

In 2019, the WHO classification of cHCC-CCA was updated, with significant changes from the previous version (Table 1). First, the category of cHCC-CCA with stem cell features is no longer used. Subsequently, routine stains (i.e., hematoxylin

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and eosin stain ± histochemical stains for matrix proteins or mucins) remain the primary method for the histopathological diagnoses of cHCC-CCA and immunohistochemical stains are secondary, providing supplemental evidence (1, 7). It is now recommended to simply note "HPC features present" in a pathologic comment.

Second, due to limited data on molecular characteristics and clinical outcomes, there is no strong consensus as to whether intermediate cell carcinoma is a distinct entity, or a histological pattern of cHCC-CCA. As a result, only intermediate cell carcinoma requires confirmatory immunohistochemistry for diagnosis, due to the mixture of both hepatocytic and cholangiocytic features on a cell-by-cell basis, demonstrating a mixture of differentiation markers (1). As of now, PLCs purely comprised of "intermediate cells" are referred to as intermediate cell carcinomas (1).

Third, cholangiolocarcinoma (CLC) (previously cholangiolocellular carcinoma subtype) can still be a component of a cHCC-CCA if an HCC component is also present; however, a CLC that is present alone, or admixed with a conventional ICC, is now considered to be a subtype of ICC.

Lastly, it is recommended that each component should be mentioned when combinations of PLCs are present (e.g., cHCC-CCA-CLC, cHCC-CCA-intermediate cell carcinoma, etc.) (1, 7).

Imaging-Based Diagnosis of cHCC-CCA Based on the 2010 WHO Classification System

Characteristic Imaging Findings and Differential Diagnosis

HCC is unique as it can be diagnosed and treated in high-risk patients based solely on noninvasive imaging criteria without histological confirmation. Therefore, it is crucial to distinguish non-HCC malignancies clinically (i.e., ICC, cHCC-CCA) from HCCs during diagnostic imaging in order to determine if a biopsy is necessary, or if patients should promptly proceed to treatments like liver transplantation or radiofrequency ablation for HCC. Furthermore, as established treatments for HCCs and ICCs do not formally apply to patients with cHCC-CCAs, the diagnosis of cHCC-CCA must be made carefully such that patients are not exempted from receiving beneficial treatments specifically targeted to HCCs or ICCs.

Most previous studies that investigated diagnostic imaging of cHCC-CCA were based on the 2010 WHO classification scheme (3, 28-32). As cHCC-CCAs usually demonstrate histological characteristics of both HCCs and ICCs, the imaging features of cHCC-CCAs intuitively include a mixture of those seen in HCCs and ICCs. Although it remains controversial whether enhancement patterns reflect the proportion of dominant tumor components (33, 34), cHCC-CCAs may show arterial hyperenhancement (APHE) with a corresponding washout appearance (3, 32, 35) similar to HCCs (i.e., HCC mimickers) (Fig. 1A, B), or may show gradual APHE in the periphery of the tumor (28, 35) similar to ICCs (i.e., ICC mimickers) (Fig. 1C-E). The proportion of HCC mimickers varies among studies and is reported to be up to 54.1% (2, 3, 30) and that of ICC mimickers has been reported to be more prevalent (reported in up to 61.4% of cases), and are associated with larger tumor size (> 20 mm), worse surgical outcomes, and earlier recurrences (3, 28). Regarding both HCC mimickers and ICC mimickers, a few distinguishing imaging features from HCC (2, 28, 29) and ICC (2, 28, 30, 32) have been reported, respectively. Furthermore, utilizing serum tumor markers such as carbohydrate antigen 19-9 (CA19-9) and α-fetoprotein (AFP) in conjunction with the imaging findings in cHCC-CCA diagnosis has been suggested (35); as CA19-9 and AFP are useful serum markers for suspecting patients with ICC and HCC respectively, cHCC-CCA may be suspected when both markers are simultaneously elevated or elevated in discordance with presumptive imaging findings (i.e., elevated AFP with imaging findings of ICC pattern). Recent studies have shown the prognostic value of imaging patterns in cHCC-CCA (33, 34). cHCC-CCA with hypervascular enhancement (i.e., HCC mimicker) showed better survival outcomes than in those with non-hypervascular enhancement (i.e., ICC mimicker) (34) and radiographic classification (either HCC mimicker vs. ICC mimicker) showed significant difference in overall survival between the two groups whereas histopathologic classification (either HCC dominant or ICC dominant, with cut-off value of 50% of dominant histopathology proportion) failed to show a significant difference (33).

Few studies have investigated the imaging features of the cholangiolocellular subtype of cHCC-CCA with stem cell features (36-38) and reported imaging features including peripheral location, dot- or band-shaped internal enhancement, absence of a fibrous capsule, or larger arterial ring enhancement ratio (defined as the measured thickness of the arterial ring enhancement divided by the maximum diameter of the tumor).

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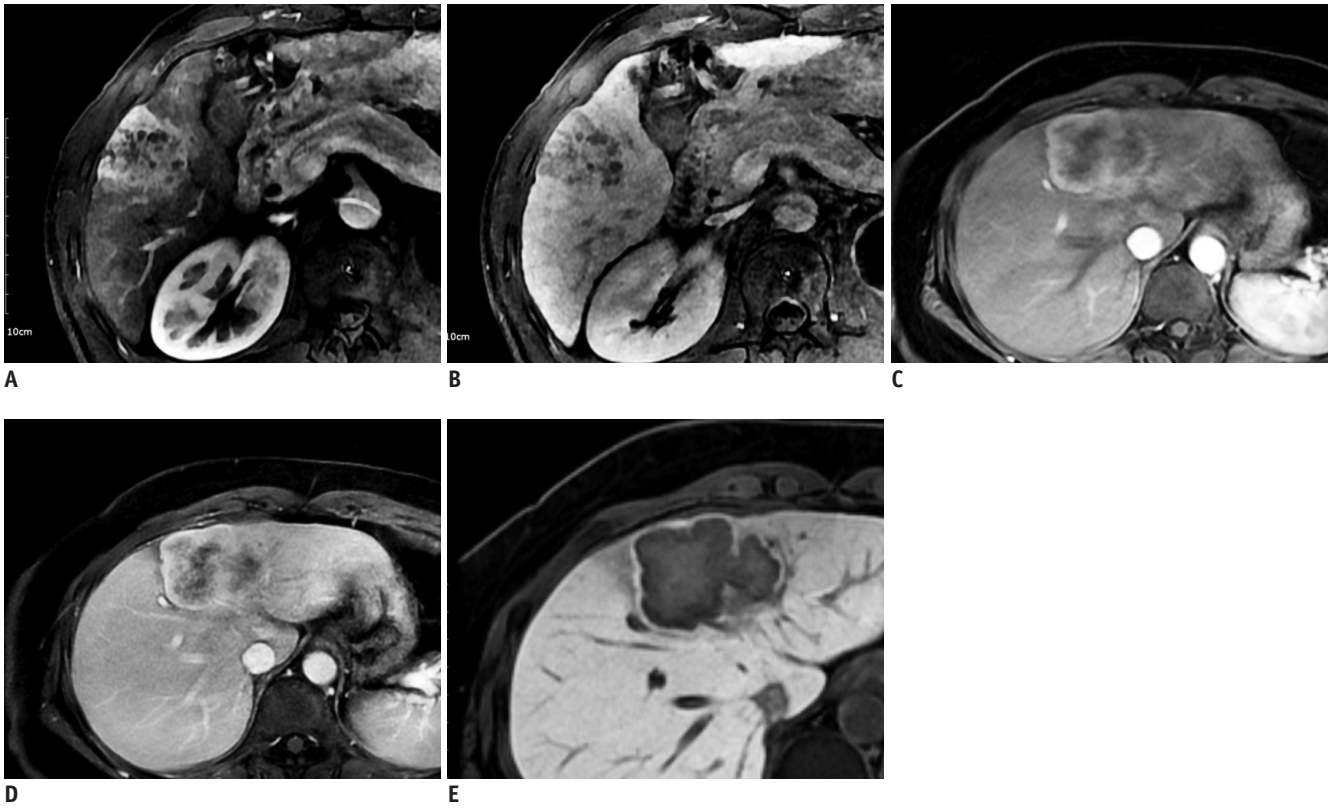

Fig. 1. Pathologically confirmed classical cHCC-CCA mimicking either HCC or ICC.
A, B. HCC mimicker in a 59-year-old male with chronic hepatitis B. **A.** On gadoxetic MRI, there is a lobulated hepatic mass with heterogeneous APHE in the right lobe of the liver. **B.** The corresponding lesion with APHE shows washout in transitional phase. **C-E.** ICC mimicker in a 48-year-old male with chronic hepatitis B. **C.** On gadoxetic MRI, there is a lobulated mass with peripheral APHE in S4 of the liver. **D.** The mass shows gradual centripetal enhancement on portal phase. **E.** The mass shows marked hypoenhancement with a hyperintense rim in HBP, indicating peritumoral retention. Note that there is no significant biliary dilatation. APHE = arterial phase hyperenhancement, cHCC-CCA = combined hepatocellular-cholangiocarcinoma, HBP = hepatobiliary phase, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, MRI = magnetic resonance imaging

There is limited information on characteristic imaging features of the typical subtype and the intermediate cell subtype of cHCC-CCA with stem cell features, with only an anecdotal report of the intermediate cell subtype showing heterogeneous arterial-enhancing masses with prolonged enhancement without portal phase washout on computed tomography (CT) in a review article (8).

Application of Liver Reporting and Data System

The Liver Imaging Reporting and Data System (LI-RADS) has been developed to standardize the diagnostic algorithm, interpretation, and reporting of CT and magnetic resonance imaging (MRI) findings of patients at high risk for HCC (3). In its latest version (v.2018), LI-RADS assessed the relative probability of diagnosis using a 5-point scale, with values ranging from definite benignity (LR-1) to definite HCC (LR-5). Category LR-M is reserved for observations that are definitely or probably malignant, not specific for HCC. Thus, PLCs other than HCC, including ICCs and cHCC-CCAs, are expected to fall into the category LR-M.

Masses that meet LR-M criteria are subdivided into those with either a targetoid or a non-targetoid appearance, with certain characteristic features. For example, masses that have a targetoid appearance may have rim APHE, peripheral washout, delayed central enhancement, and a targetoid appearance on diffusion-weighted, transitional-phase, or hepatobiliary phase (HBP) images (3). Masses with a non-targetoid appearance may have an infiltrative appearance, marked diffusion restriction, necrosis, severe ischemia, and other features that, in the radiologist's judgment, suggest non-HCC malignancy. These other features of non-HCC malignancies include capsular retraction, biliary dilatation, or multiplicity, and are mostly closely associated with the imaging features of ICCs, as it is the most common form of non-hepatocellular PLC (3, 39).

There are a few studies evaluating the relevance of category

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LR-M in distinguishing HCC from other non-HCC malignancies, including cHCC-CCAs (2, 3, 29, 39, 40). Potretzke et al. (2) reported that the application of the ancillary features of non-HCC malignancies leads to correct LR-M assignment in most cHCC-CCAs (87.8%, 29 out of 33). Another study reported similar results, showing that a substantial portion of cHCC-CCAs (93.9%, 31 out of 33) demonstrated at least one LR-M feature, and that the presence of a targetoid appearance yielded the highest sensitivity for the diagnosis of cHCC-CCA (75.8%, 25 out of 33) (39). On the other hand, some studies suggested that LR-4/5 could be falsely assigned to cHCC-CCAs. Jeon et al. (3) reported that more than one-third of cHCC-CCAs were incorrectly categorized as LR-4 or LR-5, and Ludwig et al. (40) noted that most false-positive LR-5 observations were due to cHCC-CCAs (63–86%). It is noteworthy that the proportion of HCC assigned as LR-M varies among studies (range, 10–87.8%), suggesting that differences in the reviewers' diagnostic sensitivity for LR-M features may have contributed to the diverse assignment proportion of LR-M for cHCC-CCA among studies (range, 61.4–93.9%) (2, 3, 29, 39, 40).

Making a preoperative diagnosis of cHCC-CCA based on imaging features alone is still challenging (28); however, the correct application of category LR-M during diagnostic evaluations would be a practical approach before proceeding to confirmatory biopsies for the diagnosis of cHCC-CCA. Furthermore, considering recent studies on the prognostic value of LI-RADS categorization in cHCC-CCA (3, 41), where cHCC-CCA categorized as LR-4 or LR-5 showed better postsurgical outcomes compared to those categorized as LR-M, LI-RADS may be beneficial for predicting prognosis in patients with cHCC-CCA. Prospective studies with larger scales are needed to elucidate the role of category LR-M in the diagnosis and prognosis prediction of cHCC-CCA.

Application of Korean Liver Cancer Association-National Cancer Center Guidelines

Among many noninvasive diagnostic guidelines for HCC, the Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) guidelines are unique in that they extend the washout to the portal, transitional, and HBP when using gadoxetic MRI (42). Furthermore, the guidelines consider the presence of a targetoid appearance and/or marked T2 hyperintensity, as exclusion criteria, before applying the extended washout. These unique characteristics allow the KLCA-NCC guidelines to preserve specificity for the HCC diagnosis and to rule out the most common confounders that show hypointensity on HBP images, including hemangiomas, ICCs, and cHCC-CCAs. Moreover, these characteristics allow the guidelines to achieve sensitivities between 92.5% and 95.2% and specificities between 82% and 87.4% for the diagnosis of HCC (43, 44). Notably, in a study by Joo et al. (44), even though these exclusion criteria were applied to rule out either ICCs or cHCC-CCAs from HCCs, more than half of the cHCC-CCAs did not show a typical targetoid appearance, and therefore, contributed to false-positive diagnoses of HCC, substantiating the considerable overlap in the imaging appearances of cHCC-CCAs and HCCs. This discrepancy may indicate the higher sensitivity of the diagnostic criteria in the KLCA-NCC guidelines in comparison to LI-RADS, which only includes washout confined to the portal venous phase for HCC diagnosis, and inevitably entails higher false-positive rates for diagnoses of HCC when encountering cHCC-CCAs.

Potential Impact of the Updated WHO Classification System on Imaging-Based Diagnosis of HCC

Though it is not known how the updated 2019 WHO classification of cHCC-CCA will influence imaging-based diagnoses of HCCs, as some subtypes of cHCC-CCA with stem cell features may now be misdiagnosed as HCC and CLCs may now be misdiagnosed, as either cHCC-CCA or ICC according to the histopathologic component; it is crucial to take into consideration the prevalence of cHCC-CCA in the 2019 WHO classification. Most of PLCs are HCC (75–85%), and ICC (10–15%) or cHCC-CCA (2–5%) make up the rest of the PLCs and previous studies dealing with cHCC-CCA were case-control study designs analyzing relatively higher prevalence of cHCC-CCA than that in real clinical setting. Therefore, considering the relatively low incidence of cHCC-CCA, false positive diagnosis of cHCC-CCA may contribute to an insignificant clinical impact, except for the clinical situations when 100% specificity is required.

There are a few other potential impacts according to the imaging diagnostic systems that may be predicted.

LI-RADS

First, while the typical subtype of cHCC-CCA with stem cell features was recognized in the 2010 system, it will now likely be considered a HCC harboring stem cell features in the new 2019 WHO classification system. If these cHCC-CCAs with typical stem cell features were previously classified as

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category LR-M, they may now lower the sensitivity of LR-5 (Fig. 2). On the other hand, if the disease manifested as a HCC mimicker and a false-positive LR-5, the specificity of LR-5 may now be increased with the new WHO classification system (Fig. 3). It is unclear, however, how frequently cHCC-CCA with stem cell features was categorized as either LR-5 or LR-M; therefore, the exact impact on the diagnostic accuracy of LR-5 still needs to be determined.

Second, the new classification system designates CLCs as a subtype of ICC if it is present alone or admixed with conventional ICC, except when there is an HCC component in the same tumor. As CLCs were previously categorized as a subtype of cHCC-CCAs, and showed heterogeneous imaging features resembling those of ICCs (36, 38), the incorporation of CLCs without HCC components into the category of ICCs may have little impact on the diagnostic performance of LR-4 or LR-5 (Fig. 4).

Furthermore, the diagnostic performance of LR-M in differentiating cHCC-CCAs from HCCs varies, and is even contradictory in the studies described above. As a result, the use of LR-M in differentiating cHCC-CCAs from HCCs in the new 2019 WHO classification system will also require further investigation.

KLCA-NCC Guidelines

As previously mentioned, the KLCA-NCC guidelines create the potential for false-positive diagnoses of HCCs when encountering cHCC-CCAs. Accordingly, the transition from using the category of a typical subtype of cHCC-CCAs with stem cell features to the new category of a HCC harboring stem cell features may increase the diagnostic specificity of the KLCA-NCC guidelines.

Similar to LI-RADS, the KLCA-NCC guidelines do not distinguish subtypes of cHCC-CCAs from ICCs; therefore, the incorporation of CLCs without HCC components into the category of ICCs may have little impact on the diagnostic performance of the KLCA-NCC guidelines.

Remaining Issues

There are still unresolved concerns regarding the diagnosis of PLCs, even after the release of the updated

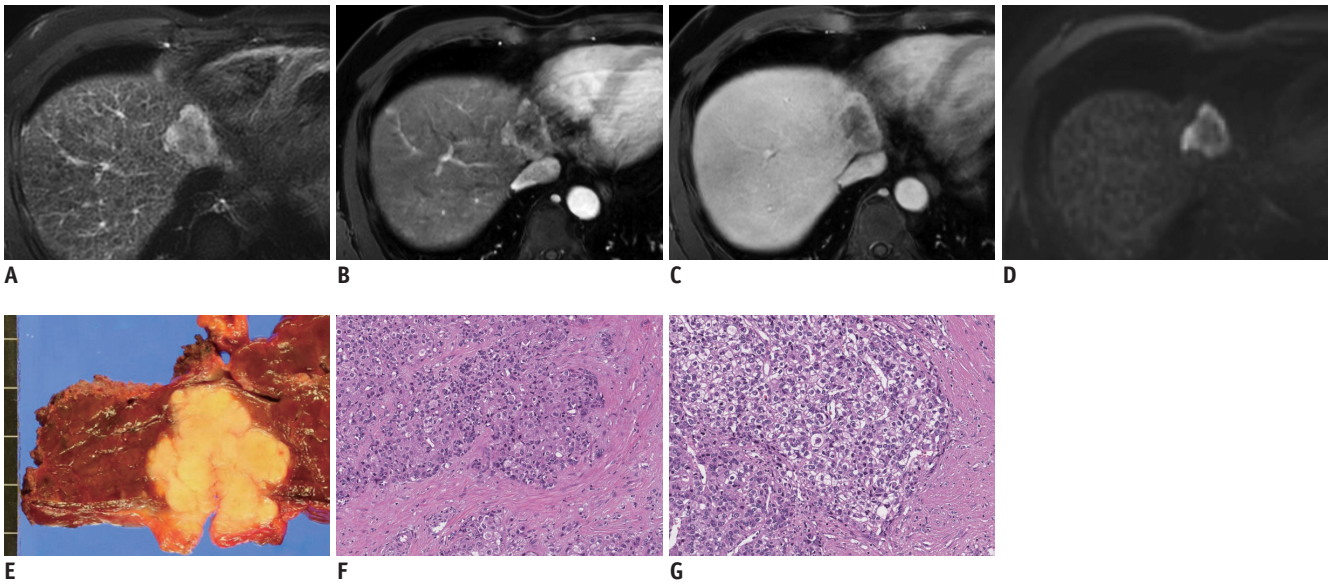

Fig. 2. HCC, which was previously classified as cHCC-CCA with stem cell features, typical stem cell subtype, in a 51-year-old male with chronic hepatitis B.

A-D. Gadoxetic acid-enhanced MRI showing a mass with lobulation in the left hepatic lobe dome. **A.** The mass shows heterogeneous hyperintensity on T2-weighted image. **B.** The mass shows rim APHE. **C, D.** The mass shows a targetoid appearance on both transitional-phase and diffusion-weighted images. **E-G.** Histopathologic findings of mass. **E.** Gross examination reveals a lobulated solid mass on a cirrhotic background. **F.** Representative area demonstrates nests of neoplastic cells resembling mature hepatocytes that are vaguely rimmed by smaller primitive-looking tumor cells, and embedded in thick fibrotic stroma (H&E stain, x 200). **G.** Other areas of tumor demonstrate more conventional HCC (H&E stain, x 200). The presence of components depicted in **(F)** led to diagnosis of cHCC-CCA with stem cell features, typical stem cell subtype in previous classification; however, in current classification, presence of such "stem cell-like" features no longer definitively leads to diagnosis of cHCC-CCA. Note that this lesion is assigned to category LR-M and therefore, accurately contributed to designation of cHCC-CCAs in category LR-M using previous 2010 WHO classification system. However, it may now contribute to lower sensitivity for category LR-5 using 2019 WHO classification system. WHO = World Health Organization

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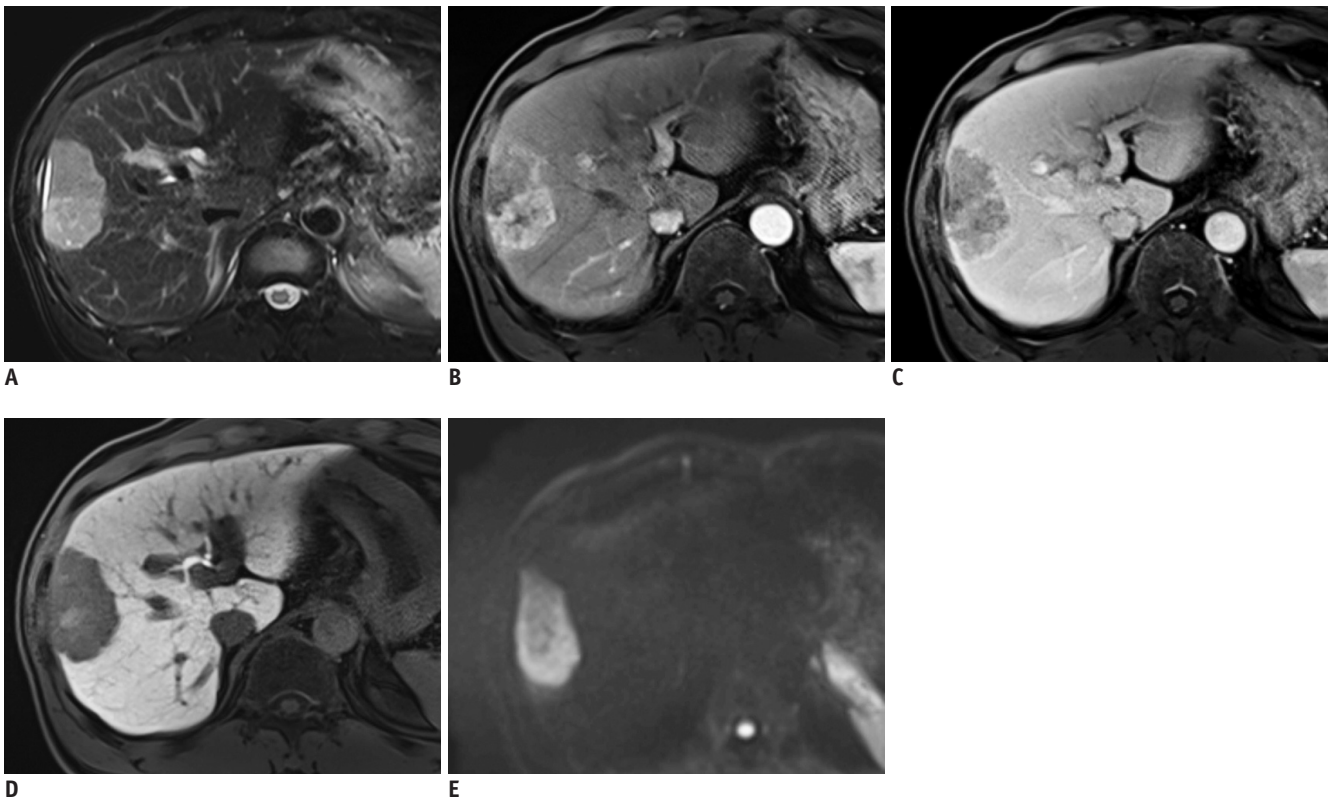

Fig. 3. HCC, which was previously classified as cHCC-CCA with stem cell features, typical stem cell subtype according to the WHO 2010 classification system in a 53-year-old male with no high-risk factors for HCC development.
A-E. Gadoxetic acid-enhanced MRI showing a mass with lobulation in the right lobe of the liver. **A.** The mass shows heterogeneous T2 hyperintensity. **B, C.** The mass shows non-rim APHE and non-peripheral washout in the portal phase. **D, E.** The mass shows hypoenhancement in HBP with diffusion restriction on diffusion-weighted image. Note that this lesion was previously determined to be a false-positive category LR-5; however, using 2019 WHO classification system, it is now likely to be a true-positive for category LR-5, potentially increasing specificity of LR-5.

2019 WHO histological classification system.

First, it is unclear which histologic component plays the most critical role in prognosis and disease outcome when multiple components are present in a single tumor.

Second, there is still no definite description or specific cut-off value for the amount of tumor that should be present for a pathological diagnosis. Without objective criteria, regarding the minimum (or satisfactory) amounts of specific components required for pathological diagnoses, the final diagnosis might depend on the preference of different pathologists. The resultant lack of uniformity will inevitably affect the accuracy of diagnostic imaging and impede systematic studies of PLCs other than HCC and ICC. Indeed, previous studies of PLCs other than HCC or ICC have utilized their own histological cut-off values for diagnoses. For instance, Akiba et al. (27) categorized each cHCC-CCA subtype according to the predominant histologic pattern, defined as the pattern occupying 50% or more. Ikeda et al. (20) defined cHCC-CCAs based on predominant histologic components without setting objective criteria. Considering the heterogeneous and complex nature of PLCs other than HCC and ICC, a standardized objective cut-off that facilitates a more accurate pathological diagnosis and minimizes inter-observer variability is necessary.

Third, it is still unclear whether conventional treatments for HCCs, including surgical resection, liver transplantation, locoregional therapy, or systematic agents, can also be used as treatments for cHCC-CCA. Furthermore, considering that cHCC-CCA classified as LR-4 or LR-5 showed better post-surgical prognosis than that classified as LR-M (41), not only the optimal treatment for cHCC-CCA, but also the specified treatment approach and biological behavior investigation according to the imaging features of cHCC-CCA need to be clarified in the future.

Lastly, the use of diagnostic systems initially designed for HCCs (including LI-RADS) may not be appropriate for other PLCs. Since these imaging-based diagnostic systems were specifically developed for populations with high-risk predisposing factors for HCC development, the pre-test probability of disease and the resultant positive predictive

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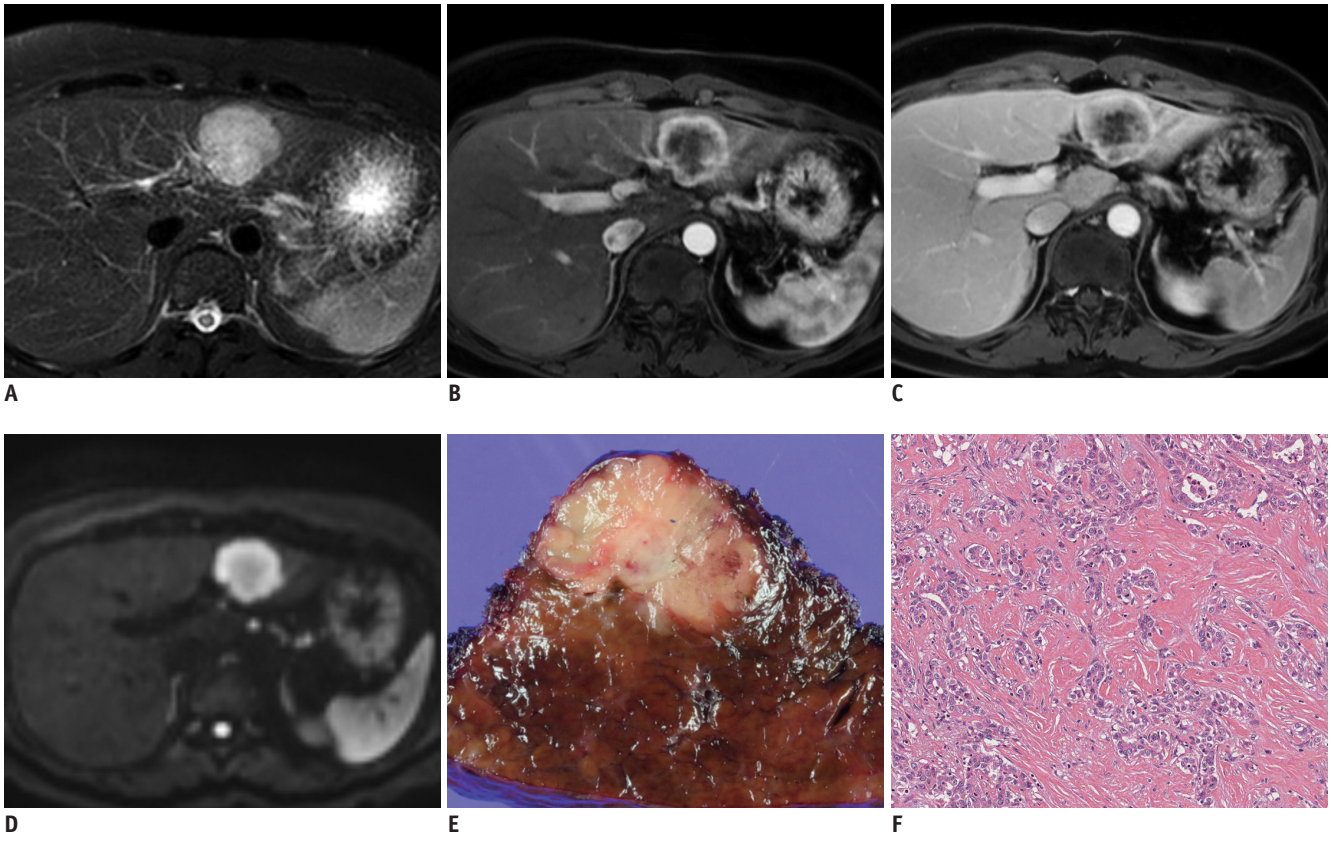

Fig. 4. Cholangiocellular carcinoma as subtype of ICC, which was previously classified as cHCC-CCA with stem cell features according to the WHO 2010 classification system, cholangiocellular subtype, in a 46-year-old female with chronic hepatitis B. **A-D.** Gadoxetic acid-enhanced MRI showing a mass with lobulation in the left hepatic lobe. **A.** The mass shows homogenous hyperintensity on T2-weighted image. **B, C.** The mass shows rim APHE with centripetal enhancement on portal phase. **D.** The mass shows targetoid restriction on diffusion-weighted image. **E, F.** Histopathologic findings of the mass. **E.** Gross examination reveals a lobulated solid pinkish-tan mass on a cirrhotic background. **F.** The entire tumor is composed of small vaguely tubular structures resembling ductular reactions. Neoplastic cells are small and cuboidal and there is no evidence of mucin production (H&E stain, x 200). Although the presence of these features were associated with "stemness" and, therefore, classified as cHCC-CCA with stem cell features, cholangiolocellular subtype in the previous WHO classification, this pattern is now regarded as a subtype of ICC unless there is HCC component in the same tumor.

value of the test may be influenced if used with these other PLCs. Although pathologic diagnosis for PLC is required in patients without any risk factors for HCC development, it is important to evaluate the applicability and performance of these diagnostic imaging guidelines in these patients as it may provide insight for different imaging features of cHCC-CCA according to the presence of risk factors. For example, cHCC-CCA arising in cirrhotic liver was more likely to resemble imaging features of HCC than that arising in non-cirrhotic liver (45). Furthermore, different priorities in treatment practices among guidelines should also be taken into account when adapting these imaging guidelines to PLCs other than HCCs (46). For instances, western guidelines such as LI-RADS try to achieve high specificity for the diagnosis of definite HCC, on order to avoid false-positive HCC diagnoses in liver transplantation, whereas eastern guidelines such as KLCA-NCC try to achieve high sensitivity for the detection of early HCCs to favor early treatment and access to locoregional ablative therapies.

CONCLUSIONS

In the updated WHO histological classification system for cHCC-CCAs, the presence of stem cell features within tumors no longer warrants categorization into formal diagnostic subtypes of cHCC-CCA; instead, these cells are considered mere features of the tumor. In addition, CLCs, which have been categorized under cHCC-CCAs, can now be diagnosed as a subtype of ICC if there is no HCC component within the tumor. Further studies are warranted in order to decide whether intermediate cell carcinoma is a distinct entity or a histological pattern of cHCC-CCA. The impact

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of this new classification system on the imaging-based diagnoses of PLCs should be carefully considered, as the new classification inevitably influences the noninvasive diagnostic accuracy of HCC, possibly due to the transition from using the category of a typical subtype of cHCC-CCA with stem cell features to the category of HCC harboring stem cell features. Future studies with particular attention paid to the mixture of imaging features seen in cHCC-CCAs are warranted to reveal the complex imaging features that correlate with histopathology and the percentage of each tumor component that is required during histopathological diagnosis, disease prognosis, and optimal treatment of these tumor types.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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