

# Primary liver cancer spectrum: current knowledge and the next steps

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Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) constitute the main subtypes of primary liver cancers (PLCs) as a major cause of cancerrelated mortality and incidence. They emerge from varying quantities and levels of differentiation among major liver cells, comprising hepatocytes, mucin- or non-mucinproducing cholangiocytes, and hepatic progenitor cells (HPCs) with the capability to differentiate into either hepatocytes or cholangiocytes. Accordingly, PLCs have been considered as a continuum in which well or poorlydifferentiated HCC and small- and large-duct type iCCA are at the two ends of it, and other different tumors like combined HCC-CCA tumors and cholangiocellular carcinoma sharing some of the characteristics of HCC and CCA, are in the middle of this broad PLC spectrum (1-3).

Further classifications for intermediate tumors have also been suggested based on the distinct molecular patterns, cell originality, histology, prognosis, and tumor microenvironment. These include proliferative (*BRAF* and *KRAS* mutations, RAS and MET activation) and inflammatory (cytokines overexpression, STAT3 activation) subtypes of CCA (4). The immune-high subtype has a higher expression of genes related to immunity and inflammation, which may improve survival (5). Small-duct (originated from non-mucin-producing cuboidal cells) and large - duct (originated from mucin-producing columnar cells) iCCA have been shown to be etiologically similar to HCC (1).

The PLCs spectrum is reflected in the molecular, pathological, and radiological features. For instance, pseudoglandular and macrotrabecular/compact patterns were associated with BMP4 and oncogene YAP activation respectively (6). TP53-mutated HCC associated with unfavorable prognosis can be predicted by decreased relative enhancement ratio during the hepatobiliary phase of gadoxetic acid magnetic resonance imaging (MRI) and dilated vasculature during the arterial phase of dynamic computed tomography (CT) (7). Moreover, patients' age and HCC etiologies may also reflect some HCC molecular features. For example, telomerase reverse transcriptase (*TRET*) promoter mutation is more common in older patients or those with hepatitis C virus (HCV) (8).

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A better understanding of this spectrum at the different levels can translate into improved diagnosis, prognostication, treatment, and management of PLCs (9,10). For example, well-differentiated PLCs, such as HCCs with fewer HPC-like features, have better prognoses than PLCs with more HPC features. They have a higher likelihood of carrying mutations of cadherin-associated protein beta 1 (CTNNB1), which is associated with improved clinical outcomes among nonviral HCC. On the other hand, those with TP53 mutations had the poorest prognosis among nonviral HCC (11). However, prognostic associations remain exploratory.

Jeon et al. recently published a study in Hepatology (12) that integrated the transcriptome profiles of PLC patients with their radio-pathological features. They analyzed 78 HCC and 59 iCCA cases and combined them with an external dataset (62 HCC and 90 iCCA cases). Combined HCC - iCCA and intermediate carcinoma cases were excluded to evaluate the extent of a PLC spectrum in patients with HCC and iCCA. They identified four liver cancer (LC) subtypes including LC1 (from mature hepatocytes), LC2 (from HPCs), LC3 (from intermediate and differentiated hepatocytes or cholangiocytes), and LC4 (from mature cholangiocytes) using RNA sequencing of tumor tissues. Going from LC1 to LC4, there were less hepatocyte and more cholangiocyte features. However, this was not an exact and complete transition as LC3 has more hepatocyte and cholangiocyte cells compared to LC2. LC2 and LC4 had stem cell-like features with more aggressive clinical features including larger tumor size, more microvascular invasion, and more frequent mutations.

LC1, a typical HCC, has been associated with mutations of TERT promoters, with forkhead box M1 (FOXM1) as the main transcription factor binding to the solute carrier organic ion transporter family member B1 (SLCO1B1) promoter and activating bile acid (BA) metabolism. In MRIs of LC1 patients, the authors observed a high uptake of gadoxetic acid. LC2, an atypical HCC that resembles iCCA, has been characterized by TP53 mutations, HPC-like trait expression, and rim arterial - phase hyperenhancement in MRI. Mature hepatocytes can dedifferentiate into nestinpositive progenitor - like cells. LC2 has higher nestin expression than LC1, which suggests that LC2 originates from dedifferentiated hepatocytes. Moreover, LC2 has DNA copy number aberrations (CNA) gains of anterior gradient 2 (AGR2) and reduced expression of Hepatocyte nuclear factor 4A (HNF4A), one of the most important transcription factors in liver cells. These changes can lead

to increased AGR2 expression and more aggressive LC2. In fact, HNF4A is predicted to bind to the promoter of SLCO1B1 and activate its transcription. Therefore, lower HNF4A levels can decrease the expression of SLCO1B1 and the uptake of BA and gadoxetic acid. This can result in increased endoplasmic reticulum stress and AGR2 expression, and possibly a more aggressive HCC.

iCCA were classified into LC3-SD, LC4-SD, and LC4-LD. LC3-SD has more HCC-like etiologies including hepatitis B virus (HBV) infection and metabolic syndrome and is characterized by mature stroma and active immunotype. Conversely, both LC4-SD and LC4-LD have immature stroma and are majorly exhausted immunotypes. This highlights a possible association between histopathology and stroma types with active or exhausted immunotypes. Isocitrate dehydrogenase (*IDH*) 1/2 mutation can be characterized in LC3-SD and LC4-SD but *FGF* receptor 2 fusion and *KRAS* mutations are specifically linked to LC4-SD and LC4-LD.

These aforementioned relationships between mutations and PLC types are in line with prior studies. CTNNB1 mutation has been associated specifically with HCC but not with combined HCC-CCA or iCCA. In contrast, KRAS mutation is found in iCCA but not in combined HCC-CCA or HCC. Finally, both combined HCC-CCA or iCCA can have a mutation in IDH1/2 which is not seen in HCC cases. Other mutations, such as TP53, RB1, and CDKN2A, are not specific to each PLC type and occur at different frequencies in different PLCs. This integrated molecular histological analyses suggest that HCC and iCCA, at opposite ends of the PLC spectrum, have generally distinct mutation profiles, but what comes in the middle of this spectrum may share mutations with either end of the spectrum (13). In the clinical setting, these intermediate tumors may distinctly display features from one side of the PLC spectrum, presenting a challenge that impacts the precise diagnosis of PLC types and their management.

Major limitation of this project is the small sample size with homogeneous patient population which may affect the generalizability of the results. In the main dataset (YS-LC cohort), about 90% of HCC and 36% of iCCA cases were attributed to HBV and less than 6% of all cases were due to HCV. In the HCC validation cohort, 67.9% were related to HBV. There has been only 1 case of well differentiated HCC case in both main dataset and HCC validation cohort. It should be noted that cancer etiology can affect the molecular landscape of PLCs (14).

To strengthen the work, future research with a larger

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number of PLC patients from diverse ethnicities, different etiologies, BCLC stages, and age groups may provide more robust data on the molecular landscape of iCCA and HCC with clinical correlates. Analyzing cases with combined HCC-iCCA may also reveal more insights into the intermediate subtypes of PLCs. These may help identify key features related to PLC heterogeneity and clinical outcomes.

Validating the concept of a PLCs-wide spectrum with more comprehensive data sets, examining its effects on treatment and survival outcomes in more depth in prospective trials or cohort studies, will allow to establish practical methods for applying this concept in routine clinical care. Understanding of PLCs spectrum based on molecular clinical classifications will ultimately lead to better management of patients with PLCs. Simplified PLCwide spectrum concept will facilitate easier recognizing PLC subtypes in the clinical decision-making process. Finally, as artificial intelligence showed its ability in establishing practical biomarkers for targeted therapy in HCC (15), we believe that its use in different methods like genomic profiling, radiomics, multi-omics, etc. can be very helpful to simplify the combination of different genetic, molecular, and radiopathological data and bring the concept of PLCs into routine clinical practice, which should be examined in future research projects.

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#### Rezaee-Zavareh et al. PLC spectrum

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### 160