Editorial Commentary

Primary liver cancer spectrum: current knowledge and the next steps

Mohammad Saeid Rezaee-Zavareh[1]^, Ekaterina K. Koltsova[2], Yujin Hoshida[3], Ju Dong Yang[4,5,6]^

[1]Middle East Liver Diseases Center, Tehran, Iran; [2]Cedars-Sinai Cancer, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [5]Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Correspondence to: Ju Dong Yang, MD. Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Los Angeles 90048, CA, USA. Email: judong.yang@cshs.org.

Comment on: Jeon Y, Kwon SM, Rhee H, *et al*. Molecular and radiopathologic spectrum between HCC and intrahepatic cholangiocarcinoma. Hepatology 2023;77:92-108.

Keywords: Liver cancer spectrum; hepatocellular carcinoma (HCC); cholangiocarcinoma (CCA); integrated analysis

Submitted Nov 22, 2023. Accepted for publication Dec 06, 2023. Published online Jan 15, 2024.
doi: 10.21037/hbsn-23-607
View this article at: https://dx.doi.org/10.21037/hbsn-23-607

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) constitute the main subtypes of primary liver cancers (PLCs) as a major cause of cancer-related mortality and incidence. They emerge from varying quantities and levels of differentiation among major liver cells, comprising hepatocytes, mucin- or non-mucin-producing 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 poorly-differentiated 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).

^ ORCID: Mohammad Saeid Rezaee-Zavareh, 0000-0003-0447-6607; Ju Dong Yang, 0000-0001-7834-9825.

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 nestin-positive 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

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 PLC-wide 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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-607/coif). E.K.K. received research funding from Surface Oncology to investigate IL-27 antibody blockade in HCC and is inventor on filed patents not associated with the topic presented in this article. Y.H. serves as an advisor for Helio Genomics, Espervita Therapeutics, Alentis Therapeutics, Roche Diagnostics, and Elevar Therapeutics and he holds shares in Espervita Therapeutics and Alentis Therapeutics. J.D.Y. provides a consulting service for AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences, and Gilead Sciences. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Chung T, Park YN. Up-to-Date Pathologic Classification and Molecular Characteristics of Intrahepatic Cholangiocarcinoma. Front Med (Lausanne) 2022;9:857140.
2. Quaglia A. Hepatocellular carcinoma: a review of diagnostic challenges for the pathologist. J Hepatocell Carcinoma 2018;5:99-108.
3. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
4. Sia D, Hoshida Y, Villanueva A, et al. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. Gastroenterology 2013;144:829-40.
5. Nguyen CT, Caruso S, Maille P, et al. Immune Profiling of Combined Hepatocellular- Cholangiocarcinoma Reveals Distinct Subtypes and Activation of Gene Signatures Predictive of Response to Immunotherapy. Clin Cancer Res 2022;28:540-51.
6. Tan PS, Nakagawa S, Goossens N, et al. Clinicopathological indices to predict hepatocellular carcinoma molecular classification. Liver Int 2016;36:108-18.
7. Kitao A, Matsui O, Zhang Y, et al. Dynamic CT and Gadoxetic Acid-enhanced MRI Characteristics of P53-mutated Hepatocellular Carcinoma. Radiology 2023;306:e220531.

8. Kotiyal S, Evason KJ. Exploring the Interplay of Telomerase Reverse Transcriptase and β-Catenin in Hepatocellular Carcinoma. Cancers (Basel) 2021;13:4202.
9. Dhanasekaran R, Suzuki H, Lemaitre L, et al. Molecular and immune landscape of hepatocellular carcinoma to guide therapeutic decision making. Hepatology 2023. [Epub ahead of print]. doi: 10.1097/HEP.0000000000000513.
10. Shimada S, Tanaka S. The chronicles of hepatocellular carcinoma classification: Subtyping, modeling and treatment. Hepatology 2023. [Epub ahead of print]. doi: 10.1097/HEP.0000000000000588.
11. Murai H, Kodama T, Maesaka K, et al. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. Hepatology 2023;77:77-91.
12. Jeon Y, Kwon SM, Rhee H, et al. Molecular and radiopathologic spectrum between HCC and intrahepatic cholangiocarcinoma. Hepatology 2023;77:92-108.
13. Imamura T, Okamura Y, Ohshima K, et al. Molecular characterization-based multi-omics analyses in primary liver cancer using the Japanese version of the genome atlas. J Hepatobiliary Pancreat Sci 2023;30:269-82.
14. D'Artista L, Moschopoulou AA, Barozzi I, et al. MYC determines lineage commitment in KRAS-driven primary liver cancer development. J Hepatol 2023;79:141-9.
15. Zeng Q, Klein C, Caruso S, et al. Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab-bevacizumab in patients with hepatocellular carcinoma: a multicentre retrospective study. Lancet Oncol 2023;24:1411-22.

Cite this article as: Rezaee-Zavareh MS, Koltsova EK, Hoshida Y, Yang JD. Primary liver cancer spectrum: current knowledge and the next steps. HepatoBiliary Surg Nutr 2024;13(1):157-160. doi: 10.21037/hbsn-23-607