



Vessels encapsulating tumor clusters in hepatocellular carcinoma: a unique and valuable pathological imaging

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We read with great interest a paper recently published in *Hepatology* entitled “VETC (vessels encapsulating tumor clusters) is a powerful predictor of aggressive hepatocellular carcinoma (HCC)” written by Renne *et al.*, a multi-center study from Italy, Korea, and Japan (1). VETC is characterized by the presence of CD34+ vessels completely encapsulating tumor clusters in pathological imaging. The paper reports that VETC is independently associated with early recurrence within 2 years (HR: 1.52, P=0.023), disease-free survival (DFS) [HR: 1.66, P=0.002], and overall survivals (OS) [HR: 2.26, P=0.001] in a large cohort of 541 resected HCCs. The term “VETC” first appeared in 2015, in a paper by Fang *et al.* in *Hepatology* (2). This earlier study also showed that VETC could predict higher metastasis and recurrence rates of HCC, and that VETC + HCC clusters were released into the bloodstream in an epithelial-mesenchymal transition (EMT)-independent manner using a PDX mouse model. The basic characteristics of VETC in HCC were already described in the preceding paper; however, the novelty of this paper is its detailed comparisons of the relationship between VETC and many clinicopathological variables using a large international multi-institutional cohort of resected HCCs with tissue microarray analyses.

The concept of VETC-mediated cancer metastasis is unique. In the classical metastasis model, cancer cells need to invade through the vascular wall and escape anoikis and immune attack. The EMT endows cancer cells with

these abilities. In VETC-mediated metastasis, the tissue organization and the encapsulating endothelium protect cancer cells from anoikis and immune assaults. Although the term “VETC” only appeared in 2015, the concept of VETC-mediated metastasis has long attracted attention under a different name. This unique metastasis pattern was first reported in the murine mammary carcinoma model as early as 1993 by Sugino *et al.* (3,4), who described it as “an invasion-independent pathway of blood-borne metastasis”; they also focused on “tumor nests” surrounded by sinusoidal blood vessels. This pathway is initiated by intravasation of tumor nests enveloped by endothelial cells of sinusoidal vasculature within the tumor. In clinical samples of 10 common human cancers, Sugino *et al.* also noted the presence of sinusoidal vasculature enveloping tumor nests and of subsequently generated endothelial-covered tumor emboli in efferent veins, especially in HCC, renal cell carcinoma, and follicular thyroid carcinoma (5). We usually consider these three cancers to have similar clinical and molecular characteristics, so their results matched our clinical impressions. In a further study of 80 HCC autopsy specimens, Sugino *et al.* documented the presence of tumor emboli in liver, lung, and lymphatic routes, consisting of CD31+/laminin+ sinusoidal tumor vasculature with basement membrane surrounding HCC nests (6). They named this process “sinusoidal tumor angiogenesis”. They did not use the term “VETC”; however, the basic concept of the non-EMT metastasis of VETC + HCC was

thoroughly described in their variable reports. Therefore, we wish to highlight the contributions of Sugino and his colleagues in this field.

The first report concerning the survival impact of VETC in HCC was published by Ding *et al.* in 2011 (7) from the same cancer center, (Sun Yat-sen University, China) as Fang *et al.* (2). They named HCC nests encapsulated by CD34+ endothelium “endothelium-coated tumor clusters (ECTCs)”, and ECTCs were an independent poor prognostic factor both in OS (HR: 1.949, P=0.001) and DFS (HR: 2.085, P=0.00002). In addition, ECTCs were associated with micrometastatic endothelium-coated emboli (P<0.001). Ding *et al.* showed high proliferation of ECTC-associated emboli using Ki-67 immunohistochemistry, and low apoptosis using TUNEL staining, compared with uncoated emboli. The authors also reported positive correlations between ECTCs and alpha-fetoprotein (AFP) >25 ng/mL (P=0.033), tumor size >5 cm (P=0.007), and grade of tumor differentiation III/IV (P=0.024). The clinical results of these three papers (1,2,7) concerning VETC in HCC were almost the same; however, the new paper by Renne *et al.* (1) is variable for several reasons. First, the preceding two papers (2,7) were from a single ethnic population, and patients’ characteristics were limited (HBV-related and tumor size >5 cm). This paper includes a more global HCC population with multiple etiologies and relatively small HCC ≤5 cm (82.4%). In addition, Renne *et al.* clearly defined the cut-off value of VETC+ as 55% or more fields using a K-adaptive partitioning algorithm. This cut-off value is very important to widely evaluate the clinical significance of VETC in HCC; therefore, we propose that a validation study using this cut-off value of 55% should be undertaken using another large cohort. Detailed clinicopathological comparisons between VETC + HCC and VETC – HCC were also performed in this study, and Renne *et al.* concluded that VETC was significantly associated with several features such as frequent macrotrabecular pattern (Macro-T), less compact pattern (C), less inflammatory infiltrates, and frequent vascular invasion. Finally, they added variable tissue microarray data.

The most important matter is understanding the molecular and pathological meanings of VETC in HCC, and utilizing this unique character in daily medical care of HCC patients. We also reported that histological architecture classification determines the recurrence pattern and prognosis after hepatectomy for HCC (8). Based on pathological architectural classification (9), patients with HCC were classified into four subtypes;

microtrabecular (Micro-T), pseudoglandular (PG), Macro-T, and C subtypes; we concluded that Macro-T/C subtypes had higher AFP levels and early recurrence within 1 year in multiple intrahepatic metastasis (≥4) or distant metastasis.

Until we read this paper by Renne *et al.*, we presumed that VETC + HCC and Macro-T HCC have almost the same biological behaviors because of their similar pathological figures and clinical features such as high AFP levels, poorly differentiation, and high rate of microvascular invasion. We also anticipated that Macro-T subtype would demonstrate the higher proliferative capacity of HCC cells more reliably than Micro-T and PG subtypes, and that most Macro-T HCC would display encapsulation by sinusoidal endothelial cells. This paper actually demonstrated a high rate of macro-trabecular massive HCC subtypes (MTM) in VETC + HCC; however, we were very surprised that MTM showed no survival impact for either OS or DFS. According to Renne *et al.*’s tissue microarray analyses, VETC + HCC impacted specific molecular subtypes (β-catenin/GS+); however, MTM was significantly higher in p53+ and lower in β-catenin/GS+. Fang *et al.* (2) reported that angiopoietin-2 (Ang-2) is essential to VETC formation and metastasis in HCC using orthotopic or subcutaneous Hepa 1–6 xenografts to silence mouse Ang-2. From these important data, we presumed that the difference between VETC + HCC and MTM is caused by the presence or absence of Ang-2 production. The deficiency of Ang-2 in MTM leads to less invasiveness, and has no survival impact. However, we cannot understand the difference in altered gene expression between VETC + HCC (β-catenin/GS+) and MTM (p53+). Further studies concerning the molecular difference between VETC+HCC and MTM are needed, and this analysis will require the establishment of a VETC + HCC carcinogenesis model.

Genomic studies in the past decade have elucidated numerous therapeutic targets that can be mapped onto the framework of HCC molecular classification defined by Hoshida *et al.* (named S1, S2, and S3) (10,11). S1 reflects an aberrant WNT signal pathway, TGF-β activation, steatohepatic HCC, and immune cell infiltrates. S2 is characterized by MYC/AKT activation, Macro-T/C subtypes, high expression of EpCAM, and high AFP levels. S3 is associated with hepatocyte differentiation (GS+), Micro-T subtype, and good prognosis. In this report by Renne *et al.*, the authors declared that VETC+HCC was classified into S1; however, according to most clinicopathological characteristics of VETC+HCC in this

paper, VETC+HCC seems to be classified into S2 as well as Macro-T subtype. The association between VETC+HCC and molecular subclasses remains as a further study issue.

Sorafenib (12) and lenvatinib (13) can be applied to patients with advanced HCC as first-line molecular targeting therapy. Fang *et al.* also stated that VETC pattern is a predictor of sorafenib benefit in patients with HCC (14). In this report by Renne *et al.* (1), the authors mentioned that VETC pattern would be easily diagnosed by the biopsy sample; however, we suspect that the discrimination of VETC from MTM patterns in a small sample, even with CD34 immunostaining, would be difficult. Therefore, the efficacy of pretreatment diagnosis of VETC pattern for the choice of drugs for advanced HCC should be prospectively confirmed.

VETC, both an old and a new concept of pathological subclass of HCC, is a unique approach to considering HCC behavior and metastasis. The key to further clarifying molecular mechanisms of VETC in HCC will be the ability to distinguish it from Macro-T pathological subtype, which does not have encapsulating vessels. Nevertheless, we anticipated that utilizing the unique characteristics of VETC in daily medical practices will contribute to improve survival of patients with HCC in the near future.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/hbsn.2019.11.16>). The authors have no conflicts of interest to declare.

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