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Hepatocellular Carcinoma: Liver Biopsy in the Balance

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Abstract

The use of liver biopsy to diagnose hepatocellular carcinoma is governed by the balance of the risks of the procedure (morbidity, mortality, inadequate sampling), the relative utility of non-invasive techniques and the benefits of precise diagnosis, prognostic and theragnostic information and access to tissue for molecular analysis. In this issue of Hepatology, identification of the macrotrabecular subtype of hepatocellular carcinoma on liver biopsy is shown to add clinically useful prognostic information as well as molecular correlations.

Keywords

hepatocellular carcinoma; liver biopsy; prognosis; recurrence

The balance of risk and benefit defines many of the decisions that we make as providers and recipients of medical care. Our regulatory agencies evaluate the risk (safety) and benefit (efficacy) of new therapeutics and tests prior to approval. Physicians and patients weigh the potential risks and benefits of alternative therapies when managing disease, guided by analyses and recommendations of experts who cull the literature and their own experience for the evidence of risk and benefit. With respect to the use of liver biopsy in diagnosing hepatocellular carcinoma (HCC), the risks are well-defined and can be quantified. There are the risks of the procedure itself: predominantly the morbidity of pain and bleeding as well as a slight risk of death (1) and needle track seeding of tumor. There is also the risk that the procedure may fail to yield a diagnosis, either because the tissue is inadequate or does not sample the suspect lesion. Balancing these risks are the benefits provided by a biopsy. The main benefit has been the certainty of diagnosis since an adequate biopsy can distinguish between benign and malignant hepatocellular lesions as well as distinguishing between HCC, cholangiocarcinoma, mixed tumors and the plethora of rarer entities. This benefit is diminished by the ability of imaging techniques to classify mass lesions in patients with known cirrhosis (2), but is increased in proportion to the amount of prognostic and theragnostic information available from microscopic subclassification and molecular analysis of tumor biopsies. In this issue of Hepatology, Ziol and coworkers report on the prognostic significance of the macrotrabecular-massive subtype of hepatocellular carcinoma (MTM-HCC) and suggest that the knowledge provided by subtyping HCC adds to the potential benefits of liver biopsy (3).

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The World Health Organization divides HCC into three main architectural subtypes: trabecular, in which tumor cells are organized in cords of variable thickness; pseudo-glandular/acinar, in which tumor cells are arranged around dilated canalicular spaces; and compact, in which there are sheets of tumor cells with inconspicuous vessels (4). It is not unusual to see heterogeneity in the architecture, even within a single tumor mass and in the study of MTM-HCC, the authors required that at least 50% of the tumor had to show a macrotrabecular architectural pattern. As a specific subtype of HCC, macrotrabecular HCC has been rarely studied. A search of PubMed for studies containing the words “macrotrabecular”, “hepatocellular” and “carcinoma” identifies only 16 papers, only seven of which are focused on the analysis of HCC. The specific definition of macrotrabecular architecture varies between studies from a minimum of 6 to 9 tumor cells across the width of the trabeculae (5, 6) (Figure 1). Lauwers et al, in their international study of 425 cases of resected HCC, noted that tumors with macrotrabecular-predominant architecture made up 26.6% of cases and had worse overall survival than HCC with compact architecture (7). They also noted that the significance of this association disappeared when nuclear grade and microvascular invasion were considered.

The connection between histological subtypes and the molecular genetics of HCC has been recently explored in two papers, both of which highlight associations with the macrotrabecular phenotype. Tan et al. correlated the histopathological features of HCC with a subclassification based on transcriptomic analysis (8). Previous international studies of the HCC transcriptome characterized three subtypes, S1, S2 and S3 (9), and pathway analysis had suggested potential therapeutic targets for at least the S1 and S2 subtypes. Tumors with macrotrabecular architecture along with high alpha-feto protein (>400 ng/ml) correlated with the S2 subtype. The S2 subtype itself is associated with activation of the oncogene *YAP* and with expression of EPCAM and keratin 19. The second study, by Calderaro et al., evaluated HCC across multiple clinical, histopathological, immunohistochemical, transcriptomic and genomic dimensions, and produced a genotype-phenotype classification that breaks HCC into six subtypes, G1 through G6 (10). This paper defined the MTM-HCC subtype as those tumors that were composed mainly of macrotrabecular HCC. Tumors with MTM morphology were more likely to show vascular invasion (macro and micro), TP53 mutations, FGF19 amplification and activation of angiogenesis pathways. By immunohistochemical staining, these tumors more often expressed keratin 19, a marker of “stemness” also noted by Tan et al. (8). Genetically MTM-HCC tumors mapped to the G3 molecular phenotype. Survival data demonstrated that patients with MTM-HCC were at greater risk for early relapse and shortened survival.

This molecular study was a direct intellectual predecessor to that of Ziol et al., (3) who present data in this issue of Hepatology that consolidates MTM-HCC as a specific, important subtype of HCC and extends the prognostic analysis to cohorts undergoing either resection or radio frequency ablation (RFA). They examined a total of 521 cases (237 with surgical resection and 284 undergoing RFA) and evaluated MTM-HCC histology for significance considering demographic, clinical and histological factors known to have prognostic significance. 16% of the surgical resection specimens demonstrated MTM-HCC histology, with a smaller fraction in the RFA cohort sampled with needle biopsy. Nevertheless, the findings were similar in both cohorts. Patients with MTM-HCC had an

increased risk of tumor recurrence independent of other predictors with odds ratios of between 2 and 3, depending on the analysis. These findings corroborate the prognostic significance attributed to MTM-HCC and demonstrate that the finding carries weight even when identified on needle biopsy. As the authors note, it will be important to evaluate a cohort of patients undergoing liver transplantation to see if patients with the MTM-HCC subtype are also at greater risk of recurrence. It will also be important to verify these findings in patient cohorts from other countries.

Although there are not many studies that directly address macrotrabecular HCC, it is now clear that this is a distinct subtype with a characteristic molecular signature. It is easily recognized by pathologists and is present in a significant minority of HCC cases. As the promise of precision medicine comes to the management of HCC, it will be important to have rapid ways to divide cases into groups that can receive targeted therapy and routine histology is usually the first point of stratification. In addition, many targets can be identified with immunohistochemistry, a technique available to essentially all pathology laboratories, reducing the need for more expensive molecular testing. As the information content of the biopsy increases, the advantages of obtaining tissue on patient will shift the balance of risk and benefit. We must continually reassess this balance as new therapies are developed to match the information pathologists are able to provide from a needle core biopsy.

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Abbreviations

HCC	Hepatocellular carcinoma
MTM-HCC	Macrotrabecular-massive hepatocellular carcinoma
EPCAM	Epithelial cell adhesion molecule
YAP	Yes-associated protein
FGF	fibroblast growth factor

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Figure 1. Macrotrabecular hepatocellular carcinoma. The tumor is organized into wide plates of tumor cells separated by pseudo-sinusoidal spaces. The nuclei show moderate pleomorphism and hyperchromasia, consistent with high nuclear grade. This tumor also demonstrated microvascular invasion. (H&E, 200x)