Morphologic Subtypes of Hepatocellular Carcinoma

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KEYWORDS

- Hepatocellular carcinoma subtypes • Carcinosarcoma
- Clear cell hepatocellular carcinoma • Cirrhotomimetic hepatocellular carcinoma
- Diffuse hepatocellular carcinoma • Fibrolamellar carcinoma
- Sarcomatoid hepatocellular carcinoma • Scirrhous hepatocellular carcinoma

KEY POINTS

- Hepatocellular carcinomas show substantial morphologic variability.
- This morphologic variability segregates into distinct entities.
- These entities are called subtypes and have unique clinical, biological, and molecular findings.

INTRODUCTION

Hepatocellular carcinomas are malignant epithelial neoplasms that originate in the liver and show exclusively or primarily hepatic differentiation. However, hepatocellular carcinomas are not homogenous and within this broad definition there are many distinctive subtypes. These subtypes are important for several reasons. First, they are important to recognize in surgical pathology as part of the acceptable spectrum of changes for a diagnosis of hepatocellular carcinoma. As part of this, some of the variants present specific diagnostic pitfalls. For example, the scirrhous variant can resemble a cholangiocarcinoma. Second, the variants provide prognostic information beyond that contained in tumor grade. Third, morphologic findings predict genetic findings, not exclusively, but with sufficient strength that including morphology improves the quality of molecular studies. As 1 example, a specific microdeletion is found in fibrolamellar carcinoma. Finally, it seems reasonable to believe that hepatocellular carcinoma subtypes, define by both morphology and genetics, will be increasingly relevant to prognosis and to therapy in the future.

GROWTH PATTERN VERSUS SUBTYPE

There are 4 major growth patterns in hepatocellular carcinomas: trabecular (70%), solid (20%), pseudoglandular/acinar (10%), and macrotrabecular (1%).[1] Of note,

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these growth patterns should not be equated with subtypes. In addition to these 4 main growth patterns, some hepatocellular carcinomas have nodules that show distinctly different tumor morphology within the same tumor mass, a finding often called “nodule within a nodule.” In these cases, one of the nodules often shows higher grade cytology, suggesting tumor evolution that led to the emergence of a more aggressive clone. In other cases, multiple morphologies of similar grades can be present, perhaps representing genetic instability without significant selection pressure.

DEFINITION OF A HEPATOCELLULAR CARCINOMA SUBTYPE

Hepatocellular carcinoma subtypes, when fully developed, have 4 primary elements.[2] Of course, each of the 4 elements will not be fully or equally developed when a subtype is first defined, but each of these 4 elements will develop over time.

1. Reproducible histologic findings on hematoxylin and eosin (H&E) staining. The subtype should have a histologic pattern that is strong enough to strongly suggest the diagnosis on H&E examination. The core set of histologic findings in most subtypes will not be absolutely specific, but should have high sensitivity to be useful.
2. Additional testing that helps to confirm the diagnosis of a specific subtype in cases with compatible H&E findings. These confirmatory testing can be immunohistochemistry, fluorescence in situ hybridization, or other molecular studies.
3. Clinical correlates. The type and strength of the clinical correlates varies considerably among subtypes. In some cases, clinical findings may be similar to conventional hepatocellular carcinomas.
4. Unique molecular findings. These findings are often incorporated into step 2, being used as the foundation for confirmatory testing.

Using this approach, 12 reasonably well-established subtypes and 6 proposed subtypes have been defined, together constituting approximately 35% of all hepatocellular carcinomas (**Table 1**). These subtypes and their definitions are discussed further herein. It is anticipated that better definitions will develop over time for some or all of these subtypes, and that is a good thing. What has not been a good thing is that many authors have written many papers on hepatocellular carcinoma subtypes using idiosyncratic definitions, which makes the literature challenging to interpret and can seriously muddle the field. Studies should as much as possible use a common reference definition as part of the study design. If the authors have a refinement on the definition, that is excellent and will hopefully advance the field, but it is best practice to include both the reference definition and the refined definition in the study design and data analysis, so that the published data can be reasonably synthesized.

MOLECULAR SUBTYPES

An alternative approach is to rely solely on molecular findings to define hepatocellular carcinoma subtypes, an approach fully embraced by most of the molecular papers on hepatocellular carcinoma. However, this approach has been disappointing to date. It is not the case that molecular subtypes do not contain, for example, prognostic information, but instead that they contain less information than the current approach of stage, grade, and morphologic subtype. In part this reflects the widespread genetic variability that can be seen within a single hepatocellular carcinoma, leading to many subclones, and, perhaps surprisingly, evidence that these clones are often not under strong Darwinian type selection pressure.[3]