
Histopathology of Hepatocellular Carcinoma

Valérie Paradis

Abstract

Hepatocellular Carcinoma (HCC) is the most frequent primary liver malignancy, mostly occurring in the context of chronic liver diseases leading to cirrhosis. Epidemiological data demonstrate the increasing incidence of HCC worldwide, mainly related to viral hepatitis and metabolic syndrome. Pathological analysis recognizes several types of HCC according to macroscopic and microscopic features. A subset of HCC can develop on normal liver and usually corresponds to specific variants, including fibrolamellar carcinoma mostly encountered in young population. Prognosis of HCC remains poor, depending on delayed tumor diagnosis, the clinical status of the patient but also tumor behavior with a great propensity for angioinvasion.

Contents

1	Introduction.....	22
2	Hepatocellular Carcinoma Associated with Chronic Liver Diseases.....	22
2.1	Pathological Diagnosis of Hepatocellular Carcinoma	22
2.2	Grading and Pathological Prognostic Factors	25
2.3	Preneoplastic Lesions and Early HCC	26
3	Hepatocellular Carcinoma Without Cirrhosis	27
3.1	Hepatocellular Carcinoma Associated with Chronic Liver Diseases.....	27
3.2	Hepatocellular Carcinoma on Normal Liver.....	27
3.3	Conclusions.....	29
	References.....	29

V. Paradis (✉)
Departement of Pathology, Beaujon Hospital—Assistance Publique—Hôpitaux
de Paris, 100 bd Général Leclerc, 92110 Clichy, France
e-mail: vparadis@teaser.fr

1 Introduction

Hepatocellular Carcinoma (HCC), ranking as the 6th position of human cancers, is the most common type of primary liver cancer, followed by cholangiocarcinoma. Importantly, HCC represents the main complication of cirrhosis, and shows a growing incidence worldwide related to the increased prevalence of the various risk factors of chronic liver diseases, such as hepatitis infection with hepatitis C and B viruses, and more recently Fatty Liver Diseases which are mostly associated with metabolic syndrome [1, 2, 3].

Although most HCC develop in the background of chronic liver disease, some may occur on normal liver and usually correspond to specific types, including fibrolamellar HCC mostly encountered in young population, or malignant transformation of hepatocellular adenomas. Overall, HCC is still associated with a poor prognosis depending on delayed diagnosis, the clinical status of the patient but also tumor behavior showing a great propensity for angioinvasion. Liver tumor classification has recently been reviewed according to the 2010 WHO classification [4].

Pathological analysis of HCC is an overall procedure able to provide its accurate diagnosis and prognosis by evaluating both tumor macroscopic (including tumor size, growth pattern of development, ...) and microscopic features (including grade of differentiation, vascular invasion, ...), and aspect of non-tumoral liver, especially the identification of preneoplastic changes. At last, pathogenesis of HCC is complex, involving different molecular pathways that may reflect both underlying etiologies and biological tumor behavior.

2 Hepatocellular Carcinoma Associated with Chronic Liver Diseases

HCC represents one of the main complications of chronic liver diseases. As a result, most HCCs develop in the background of advanced liver fibrosis and cirrhosis, highlighting the multistep process of liver carcinogenesis through the progressive malignant transformation of cirrhotic nodules and premalignant lesions [5].

2.1 Pathological Diagnosis of Hepatocellular Carcinoma

Pathological analysis of HCC is based on macroscopic and microscopic aspects that are highly diversified and associated with prognosis for some of them.

2.1.1 Gross Macroscopy of Hepatocellular Carcinoma

HCC typically form soft masses with a heterogeneous macroscopic appearance, polychrome with foci of hemorrhage or necrosis. They could be single or multiple with a size ranging from less than 1 cm to over 30 cm. Usually on cirrhosis, size of HCC is smaller compared to those developed in non-fibrotic liver [6]. Grossly, three main patterns are described [7]. The nodular or expanding pattern is the most

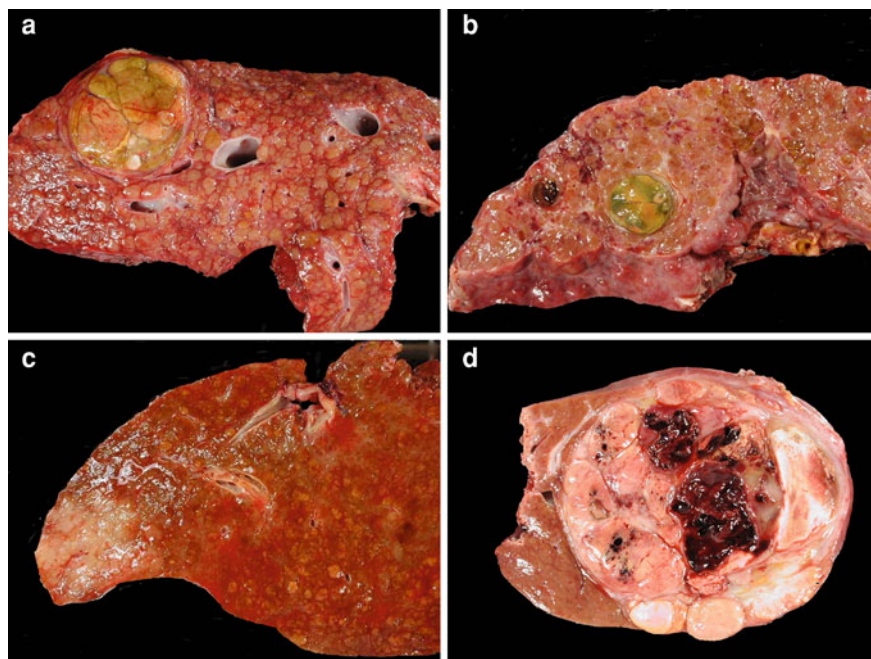


Fig. 1 Macroscopic aspects of Hepatocellular carcinoma: **a** Nodular pattern of HCC developed in a cirrhotic liver. **b** Infiltrative pattern of HCC developed in a cirrhotic liver. **c** Early HCC (progressed type) on a cirrhotic tissue. **d** Nodular HCC developed in a normal liver in the context of metabolic syndrome

common and defined by multiple nodules with one dominant, frequently partly or totally limited by a fibrous capsule, throughout the cirrhotic tissue. Small tumoral nodules described at the vicinity of the main tumor, known as satellite nodules, are considered as metastatic nodules. The infiltrative or massive pattern, composed of a large poorly circumscribed single mass, with invasive borders, is usually encountered in a non-cirrhotic liver and associated with a poor prognosis (Fig. 1). The less frequent diffuse pattern represents a widespread infiltration by numerous small nodules that virtually replace the entire liver. Vascular invasion of HCC may be seen at macroscopy (macroscopic vascular invasion) with involvement of portal veins and less frequently hepatic veins and represents a poor prognostic factor.

Recently, small HCC, with a maximum diameter of <2 cm, has been subdivided into vaguely and distinctly nodular HCC, two patterns with differences in prognosis with the vaguely nodular form (early HCC) having a better prognosis than the distinctly nodular one (progressed HCC) (the [8, 9]).

2.1.2 Histology of Hepatocellular Carcinoma

On histology, the main hallmark of HCC is its resemblance to the normal liver both in its plate-like growth and its cytology [10]. HCC is usually a hypervascularized tumor showing different degrees of hepatocellular differentiation,

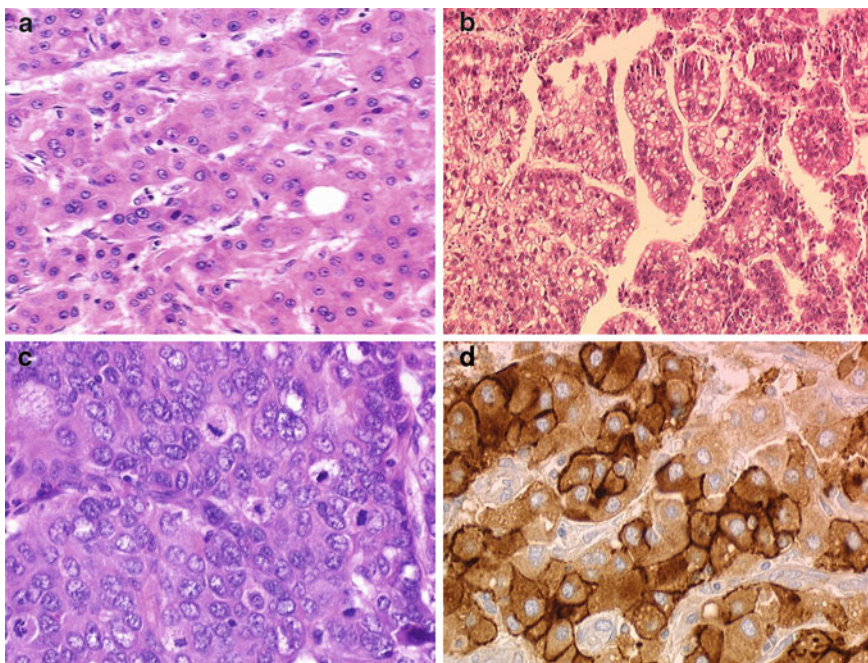


Fig. 2 Fibrolamellar hepatocellular carcinoma: **a** Macroscopic view showing a large well-limited tumor, polychrome with fibrous stroma. **b** Histologically, tumoral cells are surrounded by hyaline fibrous bands. **c** Tumor cells are large, eosinophilic with prominent nucleoli. **d** Pale bodies may be observed in the tumor cells

ranging from well to poorly differentiated, that are based upon the architectural and cytologic features. Different histological patterns may be seen: (1) the trabecular pattern of growth where tumoral hepatocytes are arranged in plates of various thickness, separated by sinusoid vascular spaces, (2) the acinar or pseudoglandular pattern showing gland-like dilatation of the canaliculi between tumor cells (lumens can contain bile) or central degeneration of trabeculae (lumen containing mainly fibrin), and (3) the compact or solid pattern composed of thick trabeculae compressed into a compact mass (Fig. 2).

Cytologically, tumoral hepatocytes are polygonal, displaying an eosinophilic granular cytoplasm, rounded nuclei and prominent nucleoli. The importance of cell pleomorphism varies according to the degree of differentiation. Several variants of HCC are described according to the cytological aspect of the hepatocellular proliferation. The clear cell variant is made of clear cells which may contain fat or glycogen. In the scirrhous HCC, tumor cells are generally smaller in size, showing a granular eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli [11]. Sarcomatoid HCC is characterized by a sarcomatous-appearing component of spindle-shaped or giant tumor cells [12]. Sclerosing HCC is a rare variant characterized by abundant, diffusely distributed fibrous stroma and compressed malignant

hepatocytes. Such tumor tends to occur in an older age group, affect men and women equally, and might be associated with hypercalcemia [11].

2.1.3 Molecular Tissue Markers of Hepatocellular Carcinoma

Additional study, such as immunohistochemistry, may be used in routine practice for the diagnosis of HCC. A large variety of immunophenotypical markers of HCC has been described, including highly specific markers (HepPar1, albumin, fibrinogen, α 1-anti-trypsin and Alfa-Fetoprotein). In cases of poorly differentiated tumors, such markers display insufficient performance and additional markers are useful. Among them, Glypican-3 (GPC-3), an oncofetal protein, seems to be the more efficient with more than 80 % of HCC immunopositive [13, 14]. Interestingly, immunophenotyping, based on a panel of antibodies, has shown its performance in the differential diagnosis of early HCC and dysplastic nodules [15, 16].

Furthermore, genomic studies provided molecular classifications of HCC based on gene expression [17, 18]. Such analysis allowed the identification of subgroups of patients according to etiological factors, stage of the disease, recurrence and survival [19, 20, 21]. Major classes of tumors emerging from these comprehensive analyses are also related to important carcinogenesis pathways such as activation of β -catenin, AKT/mTOR, or inactivation of TP53 and RB1 [22, 21].

2.2 Grading and Pathological Prognostic Factors

Grading of HCC has relied for many years on Edmondson and Steiner system, which divided HCC into four grades from I to IV on the basis of histological differentiation [23]. Grade I is the best differentiated consisting of small tumor cells arranged in thin trabeculae. Cells in grade II are larger with abnormal nuclei and glandular structures may be present. In grade III nuclei are larger and more hyperchromatic than grade II cells and cytoplasm is granular and acidophilic, but less than grade II. In grade IV, tumor cells are much less differentiated with hyperchromatic nuclei and loss of trabecular pattern. In fact, most of HCC present as grade II or III. Importantly, grading heterogeneity inside a tumor is frequently observed and may significantly limit performance of biopsy for grading, especially when using a four-tier grade scaling [24]. Therefore, and compared to other carcinomas, there is a tendency to simplify the grading and use a three-scale system including well-, moderately and poorly differentiated HCC. Finally, tumor grade appears as a weak independent predictor of the clinical course, providing little prognostic information [25, 26]. The main prognostic factors of HCC are related to tumor stage (number and size of nodules, presence of vascular invasion and extrahepatic spread), liver function (defined by Child-Pugh's class, bilirubin, albumin, portal hypertension) and general health status. Among them, size is a major prognostic factor, with a very good prognosis for small or minute carcinomas. The presence of vascular invasion and satellite nodules around the main tumor has also been recognized as predictor of recurrence and survival in several studies [27, 28].

Using microarray technology, recent studies have shown that a subset of adult HCC displays phenotypical traits of progenitor cells. These tumors retain stem cell markers and express Cytokeratin (CK) 7 and CK19. Interestingly, worse survival was demonstrated for this subgroup ([29], Gut).

2.3 Preneoplastic Lesions and Early HCC

2.3.1 Dysplastic Nodules

It is commonly accepted that in the context of cirrhosis, there is a stepwise progression from cirrhotic nodule to HCC. A unified nomenclature of such liver nodules has been recently reviewed [8]. According to such classification, one distinguished benign macroregenerative nodules that are histologically indistinguishable from the adjacent parenchymal cirrhotic nodules and dysplastic nodules (DN) that differ from the surrounding liver parenchyma with regard to size, color, texture and degree of bulging of the cut surface. DN are further subdivided into low (LGDN) and high grade (HGDN), the latter being closer to HCC in the spectrum of hepatocarcinogenesis. The premalignant nature of DN is supported by different clues including the common association with HCC in cirrhotic livers, the presence of cyto-architectural abnormalities and morphologic evidence of neo-angiogenesis, the detection of both genetic and epigenetic changes close to overt HCC [30, 31, 32, 33]. LGDN display features suggestive of a clonal cell population without significant architectural atypia while HGDN show cytological and architectural atypias (including enlarged, crowded, or irregular nuclei, irregular thickening of hepatic plates with focal loss of reticulin framework) but insufficient for a diagnosis of malignancy.

2.3.2 Small Hepatocellular Carcinoma

According to the international consensus on small nodular lesions in cirrhotic liver, small HCC are subdivided into two different entities: early (vaguely nodular type) and progressed HCC (distinctively nodular type) [8]. Although less than 2 cm, both types may display significant morphological changes with different vascular dynamic profiles on imaging. The progressed form is usually a moderately differentiated HCC able to invade the vessels and to metastasize. Early HCC are rather considered as “in situ carcinoma” showing well-differentiated proliferation [34, 35]. Differential diagnosis of early HCC and HGDN relies on a set of morphological features. Among them, stromal invasion, defined as the presence of tumor cells invading into the portal tracts or fibrous septa, has been proposed as the most relevant feature discerning HGDN from early HCC [8]. Such feature, initially reported in the Japanese series, may be difficult to identify, especially on biopsy specimens. In that context, surrogate immunomarkers, including a three antibodies panel (GPC-3, Glutamine synthetase, and HSP70), have been shown to be helpful in the differential diagnosis of HGDN and early HCC as well as in the recognition of stromal invasion in early HCC using CK 7 immunostaining [15, 36].

2.3.3 Dysplastic Foci

Dysplastic foci are defined as microscopic changes incidentally recognized in cirrhotic tissue. They are recognized, based on cytologic criteria, into large or small liver cell changes previously reported as large/small liver cell dysplasia. While large liver cell change consists of abnormal but non-neoplastic hepatocytes that is predictor of HCC development, small liver cell change is composed of neoplastic cells that are direct precursor of HCC [37, 38].

3 Hepatocellular Carcinoma Without Cirrhosis

Although the large majority of HCC arise in patients with advanced chronic liver diseases, HCC may be observed without advanced liver fibrosis or even in underlying normal liver. Altogether, such HCC appear to have a better prognosis, mainly related to the absence of advanced damages in the background liver.

3.1 Hepatocellular Carcinoma Associated with Chronic Liver Diseases

HCC may occur early in the process of chronic liver diseases before the stage of advanced fibrosis and cirrhosis. Although this situation may be observed whatever the etiological cause, it is especially encountered in the context of hepatitis B viral infection and metabolic syndrome (MS) [39, 40, 41]. Due to the increase in the prevalence of MS worldwide, HCC associated with MS will become a major concern. Fatty liver diseases, which represent the liver manifestation of MS, encompass a large spectrum of liver changes, from simple steatosis to steatohepatitis that may progress to fibrosis [42, 43, 44]. Although, and as in other chronic liver diseases, the presence of cirrhosis may promote *per se* development of HCC in such patients, diabetes and obesity, as factors of MS, also appear to be independent risk factors in liver carcinogenesis [45, 46]. Interestingly, several studies reported significant number of cases of HCC in patients with non-advanced liver fibrosis [47–49, 41]. These data support the hypothesis that liver carcinogenesis related to MS may follow distinct molecular pathways of tumorigenesis, independently from the usual multistep process-fibrosis-cirrhosis-HCC at least in some cases. A small subset of these HCC, mainly occurring in male patients, develops from the malignant transformation of preexisting hepatocellular adenoma [50]. Morphologically, these HCC present as larger and better differentiated tumors compared to those diagnosed in a background of cirrhosis.

3.2 Hepatocellular Carcinoma on Normal Liver

In fact, very few HCC are observed in patients with strictly normal liver. They correspond to distinct variants of tumors, occurring either in specific population or

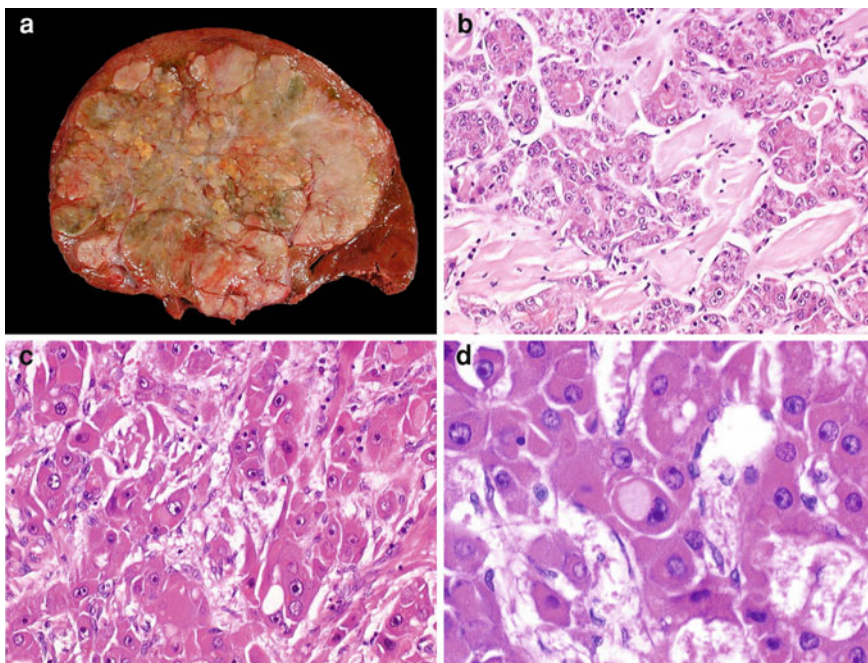


Fig. 3 Histologic features of Hepatocellular carcinoma: **a** Well-differentiated HCC with trabecular architecture, few pseudoglandular structures are present. **b** HCC showing steatotic tumor cells. **c** Poorly differentiated HCC with increased mitotic figures. **d** Glypican-3 immunostaining showing cytoplasmic positivity in most of tumor cells

specific context. Such situation may partly explain their better prognosis compared to HCC arising in patients with advanced chronic liver diseases.

3.2.1 Fibrolamellar Type of Hepatocellular Carcinoma

Fibrolamellar HCC, first described by Edmondson in 1980, is a rare entity, accounting for less than 1 % of all cases of primary liver cancer [51]. Fibrolamellar HCC is mostly encountered in young population without chronic liver disease, or other known predisposing risk factors [52]. On gross examination, fibrolamellar HCC is firm, mostly well-defined single nodule ranging from 5 cm to over 20 cm. On cut section, prominent fibrous septa subdivide the mass and may connect with a central zone of scarring and calcifications may be observed. Histologically, the key-features include the presence of lamellar stromal bands surrounding nests of large polygonal eosinophilic tumor cells with prominent nucleoli. Cytoplasmic inclusions of various types are common, including ground-glass pale bodies, eosinophilic cytoplasmic globules of variable PAS-positivity, and rarely, Mallory bodies. In contrast to most HCC, fibrolamellar HCC seems to express abundantly type CK 7 and, in some cells, biliary-type CK 19 [53]. Despite its large size at time of diagnosis, prognosis of fibrolamellar HCC is usually

considered better than conventional HCC, especially due to the good shape clinical condition of the patient without chronic liver disease. Fibrolamellar HCC tends to be slow-growing and frequently surgically resectable with a better prognosis than other types. However, when adjustment is made for tumor stage, all series do not demonstrate this better prognosis. Successfully resected patients have good chance of long-term survival despite occurrence of extrahepatic recurrences (Fig. 3).

3.2.2 Malignant Transformation of Hepatocellular Adenomas

Hepatocellular adenomas (HCA) are rare benign neoplasms of the liver, mainly observed in young women, strongly associated with oral contraceptive use [54]. This tumor can also occur in men receiving anabolic steroids [55] or be associated with underlying metabolic diseases, such as glycogenosis and more recently MS [56, 57]. Malignant transformation into HCC is one of the most important complications of HCA, reported between 4 and 10 % in the literature [58, 59, 56]. Several risk factors for malignant transformation are now recognized, including the gender (increased in male patients), the size (>5 cm), and the subtype of HCA (especially those displaying β -catenin activation) [58, 50]. Importantly, the number of HCA does not impact their malignant potential. Malignancy commonly displays well-differentiated HCC inside the HCA, with exceptional vascular invasion or satellite nodules [50].

3.3 Conclusions

Pathology of HCC is still evolving, mainly due to the significant advances in the molecular pathways of liver carcinogenesis and the relative changes in epidemiologic factors, with a noteworthy increase in MS. Molecular pathology, allowing more accurate tumor phenotyping, will play a key role for diagnostic and prognostic purposes.

References

1. El-Serag HB (2007) Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 37:S88–S94
2. Nordenstedt H, White DL, El-Serag HB (2010) The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 42:S206–S214
3. Sherman M (2005) Hepatocellular carcinoma: epidemiology, risk factors, and screening. *Semin Liver Dis* 25:143–154
4. Bosman FT, Carneiro F, Hruban RH et al (2010) WHO classification of tumours of the Digestive System 4th edn. IARC Press, Lyon, pp 322–326
5. Colombo M, de Franchis R, Del Ninno E et al (1991) Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 325:675–680
6. International Working Party (1995) Terminology of nodular hepatocellular lesions. *Hepatology* 22:983–993
7. Okuda K, Peters RL, Simson IW (1984) Gross anatomic features of hepatocellular carcinoma from three disparate geographic areas: proposal of new classification. *Cancer* 54:2165–2173

8. International Consensus Group for Hepatocellular Carcinoma (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 49:658–664
9. Htyiroglou P, Park YN, Krinsky G et al (2007) Hepatic precancerous lesions and small hepatocellular carcinoma. *Gastroenterol Clin North Am* 36:867–887
10. Anthony PP (1973) Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. *J Pathol* 110:37–48
11. Omata M, Peters RL, Tatter D (1981) Sclerosing hepatic carcinoma: relationship to hypercalcemia. *Liver* 1:33–49
12. Kojiro M, Sugihara S, Kakizoe S et al (1989) Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. *Cancer Chemother Pharmacol* 23:4–8
13. Shafizadeh N et al (2008) Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum. *Modern Pathol* 21:1011–1018
14. Wang XY, Degos F, Dubois S et al (2006) Glypican-3 expression in hepatocellular tumors: diagnostic value for preneoplastic lesions and hepatocellular carcinomas. *Human Pathol* 37:1435–1441
15. Di Tommaso L, Franchi G, Park YN et al (2007) Diagnostic value of HSP70, Glypican 3 and Glutamine synthetase i hepatocellular nodules in cirrhosis. *Hepatology* 45:725–737
16. Libbrecht L, Severi T, Cassiman D et al (2006) Glypican-3 expression distinguishes small hepatocellular carcinomas from cirrhosis, dysplastic nodules, and focal nodular hyperplasia-like nodules. *Am J Surg Pathol* 30:1405–1411
17. Chuma M, Sakamoto M, Yamazaki K et al (2003) Expression profiling in multistage hepatocarcinogenesis: identification of HSP70 as a molecular marker of early hepatocellular carcinoma. *Hepatology* 37:198–207
18. Villanueva A, Newell P, Chiang DY et al (2007) Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 27:55–76
19. Boyault S, Rickman DS, de Reynies A et al (2007) Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. *Hepatology* 45:42–52
20. Ladeiro Y, Couchy G, Balabaud C et al (2008) MicroRNA profiling in hepatocellular tumors is associated with clinical features and oncogene/tumor suppressor gene mutations. *Hepatology* 47:1955–1963
21. Villanueva A, Chiang DY, Newell P et al (2008) Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 135:1972–1983
22. de La Coste A, Romagnolo B, Billuart P et al (1998) Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. *Proc Natl Acad Sci U S A* 95:8847–8851
23. Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 7:462–503
24. Pawlik TM, Gleisner AL, Anders RA et al (2007) Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. *Ann Surg* 245:435–442
25. Chuong JJ, Livstone EM, Barwick KW (1982) The histopathologic and clinical indicators of prognosis in hepatoma. *J Clin Gastroenterol* 4:547–552
26. Lai CL, Wu PC, Lam KC et al (1979) Histologic prognostic indicators in hepatocellular carcinoma. *Cancer* 44:1677–1683
27. Nathan H, Schulick RD, Choti MA et al (2009) Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg* 249:799–805
28. Pawlik TM, Delman KA, Vauthey JN et al (2005) Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl* 11:1086–1092

29. Lee J-S, Chu I-S, Heo J et al (2004) Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. *Hepatology* 40:667–676
30. Ferrell L, Wright T, Lake J et al (1992) Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. *Hepatology* 16:1372–1381
31. Mion F, Grozel L, Boillot O et al (1996) Adult cirrhotic liver explants: precancerous lesions and undetected small hepatocellular carcinomas. *Gastroenterology* 111:1587–1592
32. Takayama T, Makuuchi M, Hirohashi S et al (1990) Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. *Lancet* 336:1150–1153
33. Theise ND, Schwartz M, Miller C et al (1992) Macroregenerative nodules and hepatocellular carcinoma in forty-four sequential adult liver explants with cirrhosis. *Hepatology* 16:949–955
34. Kojiro M, Roskams T (2005) Early hepatocellular carcinoma and dysplastic nodules. *Semin Liver Dis* 25:133–142
35. Theise ND, Park YN, Kojiro M (2002) Dysplastic nodules and hepatocarcinogenesis. *Clin Liver Dis* 6:497–512
36. Park YN, Kojiro M, Di Tommaso L et al (2007) Ductular reaction is helpful in defining early stromal invasion, small hepatocellular carcinoma, and dysplastic nodules. *Cancer* 109:915–923
37. Borzio M, Bruno S, Roncalli M et al (1995) Liver cell dysplasia is a major risk factor for hepatocellular carcinoma in cirrhosis: a prospective study. *Gastroenterology* 108:812–817
38. Lee RG, Tsamandas AC, Demetris AJ (1997) Large cell change (liver cell dysplasia) and hepatocellular carcinoma in cirrhosis: matched case-control study, pathological analysis, and pathogenetic hypothesis. *Hepatology* 26:1415–1422
39. Lam CM, Chan AO, Ho P et al (2004) Different presentation of hepatitis B-related hepatocellular carcinoma in a cohort of 1863 young and old patients: implications for screening. *Aliment Pharmacol Ther* 19:771–777
40. Marrero JA, Fontana RJ, Su GL et al (2002) NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 36:1349–1354
41. Paradis V, Zalinski S, Chelbi E et al (2009) Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology* 49:851–859
42. Adams LA, Lymp JF, Sauver JS et al (2005) The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 129:113–121
43. Angulo P (2002) Non alcoholic fatty liver diseases. *New Engl J Med* 346:1221–1231
44. Farrell GC, Larter CZ (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 43:S99–S112
45. El-Serag HB, Tran T, Everhart JE (2004) Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 126:460–468
46. Nair S, Mason A, Eason J et al (2002) Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology* 36:150–155
47. Cuadrado A, Orive A, García-Suárez C et al (2005) Non-alcoholic steatohepatitis (Nash) and hepatocellular carcinoma. *Obes Surg* 15:442–446
48. Guzman G, Brunt EM, Petrovic LM et al (2008) Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? *Ach Pathol Lab Med* 132:1761–1766
49. Kawada N, Imanaka K, Kawaguchi T et al (2009) Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. *J Gastroenterol* 44:1190–1194
50. Farges O, Ferreira N, Dokmak S et al (2011) Changing trends in malignant transformation of hepatocellular adenoma. *Gut* 60:85–89
51. Craig JR, Peters RL, Edmondson HA et al (1980) Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinico-pathologic features. *Cancer* 46:372–379
52. El-Serag HB, Davila JA (2004) Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. *Hepatology* 39:798–803

53. Van Eyken P, Sciot R, Brock P et al (1990) Abundant expression of cytokeratin 7 in fibrolamellar carcinoma of the liver. *Histopathology* 17:101–107
54. Rosenberg L (1991) The risk of liver neoplasia in relation to combined oral contraceptive use. *Contraception* 43:643–652
55. Socas L, Zumbado M, Pérez-Luzardo O et al (2005) Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. *Br J Sports Med* 39:e27
56. Dokmak S, Paradis V, Vilgrain V et al (2009) A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 137:1698–1705
57. Paradis V, Champault A, Ronot M et al (2007) Telangiectatic adenomas: an entity associated with increased body mass index and inflammation. *Hepatology* 46:140–146
58. Bioulac-Sage P, Laumonier H, Couchy G et al (2009) Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 50:481–489
59. Deneve JL, Pawlik TM, Cunningham S et al (2009) Liver cell adenoma: a multicenter analysis of risk factors for rupture and malignancy. *Ann Surg Oncol* 16:640–648

Multidisciplinary Treatment of Hepatocellular Carcinoma

Vauthey, J.-N.; Brouquet, A. (Eds.)

2013, X, 262 p., Hardcover

ISBN: 978-3-642-16036-3