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REVIEW

From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world

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Abstract

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy and the third cause of cancer-related death in the Western Countries. The well-established causes of HCC are chronic liver

infections such as hepatitis B virus or chronic hepatitis C virus, nonalcoholic fatty liver disease, consumption of aflatoxins and tobacco smocking. Clinical presentation varies widely; patients can be asymptomatic while symptomatology extends from right upper abdominal quadrant paint and weight loss to obstructive jaundice and lethargy. Imaging is the first key and one of the most important aspects at all stages of diagnosis, therapy and follow-up of patients with HCC. The Barcelona Clinic Liver Cancer Staging System remains the most widely classification system used for HCC management guidelines. Up until now, HCC remains a challenge to early diagnose, and treat effectively; treating management is focused on hepatic resection, orthotopic liver transplantation, ablative therapies, chemoembolization and systemic therapies with cytotocix drugs, and targeted agents. This review article describes the current evidence on epidemiology, symptomatology, diagnosis and treatment of hepatocellular carcinoma.

Key words: Hepatocellular; Cancer; Epidemiology; Treatment; Diagnosis; Staging; Transplantation

Core tip: Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy. It consists an epidemic problem for both developed and developing world. HCC remains a challenge to early diagnose, and treat effectively. This review article focuses on the current evidence on epidemiology, symptomatology, diagnosis and treatment of hepatocellular carcinoma. This review will be highly educational as it describes all the current data for HCC.

Dimitroulis D, Damaskos C, Valsami S, Davakis S, Garmpis N, Spartalis E, Athanasiou A, Moris D, Sakellariou S, Kykalos S, Tsourouflis G, Garmpi A, Delladetsima I, Kontzoglou K, Kouraklis G. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. *World J Gastroenterol* 2017; 23(29): 5282-5294 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i29/5282.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i29.5282

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy and the third cause of cancer-related death in the Western Countries. The causes of HCC are chronic liver infections, nonalcoholic fatty liver disease, consumption of aflatoxins and tobacco smocking. Clinical presentation varies; patients can be asymptomatic while symptomatology extends from abdominal paint and weight loss to jaundice and lethargy. Imaging is the first key and one of the most important aspects at all stages of diagnosis, therapy and follow-up of patients with HCC. HCC remains a challenge to early diagnose, and treat effectively; treating management is focused on hepatic resection, orthotopic liver transplantation, ablative therapies, chemoembolization and systemic therapies with cytotocix drugs, and targeted agents. This review article focuses on the current evidence on epidemiology, symptomatology, diagnosis and treatment of hepatocellular carcinoma.

LITERATURE SEARCH

An extensive literature search was conducted using the MEDLINE database. The key word used was "Hepatocellular carcinoma". A total of 82 papers were included for review.

EPIDEMIOLOGY

HCC is the most frequent primary liver malignancy and one of the most common malignancies worldwide. HCC is considered as the sixth most common cancer type and as the third cause of cancer-related death in the developed countries[1]; more than a million people are dying yearly due to HCC in the Western countries. It has been found that in countries with higher rates of chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV)[2], well established causes of HCC, the incidence of the disease varies from 15 per 100000 comparing to 3 per 100000 in the Western countries. Over the past 30 years a higher incidence of HCC has been noticed in the United States[3]. That must be attributed to the increased incidence of HCV infection as well as to the new immigration patterns across the world.

HCC seems to have strong sex preponderance; it is two to eight times more common in males comparing to females in low-and high-incidence areas. The higher incidence of HCC in males is related to higher rates of associated risk factors. In general, the incidence of HCC increases with age, but a tendency to develop HCC earlier in high-incidence areas has been noted. In addition, it has been reported the familial aggregation of HCC.

RISK FACTORS

Most of the HCC cases develop in the presence of advanced chronic liver disease related to viral hepatitis. In particular HBV and HCV infections are considered as major HCC risk factors worldwide. Moreover, heavy alcohol consumption and liver cirrhosis are a well-known pattern of increased risk for chronic liver disease and HCC development (higher hepatic DNA synthesis in cirrhosis). However, current studies provide strong evidence for increasing numbers of HCC in nonalcoholic fatty liver disease (NAFLD). NAFLD represents the hepatic manifestation of metabolic

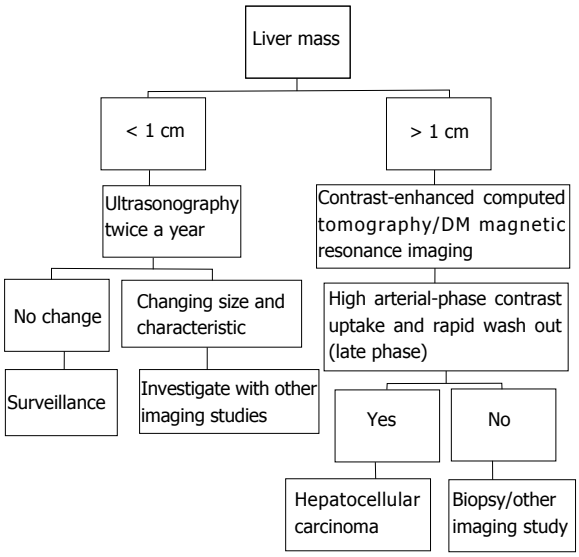

Figure 1 Imaging studies used in diagnosis, treatment planning, management and follow-up of hepatocellular carcinoma.

syndrome which is based on obesity and insulin resistance[4]. Consumption of aflatoxins; frequent contaminants of a number of staple foods, pose serious public health hazards including the causation of hepatocellular carcinoma by aflatoxin B[5]. Tobacco smokers' had been found to have a higher risk to non-smokers' population, as an independent factor, of developing HCC[6].

CLINICAL PRESENTATION - PHYSICAL EXAMINATION

The patients presenting with HCC are usually males with an average age of 50 years. In countries with high HBV prevalence, HCC often appears about 2 decades earlier and is attributed to HBV transmission perinatally or in early childhood.

HCC may progress silently in patients with sufficient liver function and escape early diagnosis due to vague complaints and non-specific–symptoms. This is why in developing countries with limited surveillance resources HCC diagnosis is usually delayed. On the other hand, clinical symptoms are accentuated in cases with impaired liver function. In advanced stages, symptoms and clinical findings include vague right upper quadrant abdominal pain, hepatomegaly, obstructive jaundice, hemobilia, and fever of unknown origin. Non-specific symptoms of advanced malignant disease such as anorexia, nausea, lethargy and weight loss often co-exist. Patients with unrecognized cirrhosis or known compensated cirrhosis may also present with liver decompensation. Complications include hepatic vein occlusion evolving to Budd-Chiari syndrome[7] and more often portal vein invasion and thrombosis while a severe complication is HCC rupture causing acute abdomen and intraperitoneal bleeding. HCC patients may initially appear with a paraneoplastic syndrome; the most common paraneoplastic syndromes associated with HCC are hypercholesterolemia, hypercalcemia, hypoglycemia and erythrocytosis[8].

DIAGNOSIS

The diagnosis of HCC is mostly based on imaging studies and laboratory tests as well. The imaging studies used in diagnosis, treatment planning, management and follow-up of HCC are ultrasonography (US), computed tomography (CT) scanning and magnetic resonance imaging (MRI)[9] (Figure 1).

In refer to laboratory tests, alpha-fetoprotein (AFP) is the most frequent used serological marker. However, sensitivity ranges from 25% for tumors smaller than 3 cm to 50% for lesions larger than 3 cm in diameter[10]. Other serum biomarkers and a new generation of IgM immunocomplexes did not succeed in providing diagnostic accuracy. However, simultaneous detection of these markers in various combinations could improve sensitivity.

Although current management guidelines for HCC do not require biopsy to prove the diagnosis[11], lesions greater than 2 cm on MRI or computed tomograph angiography (CTA) scans, with AFP either elevated more than 400 ng/mL or rising within sequential measurements do not require histologic confirmation according to the guidelines of the European Association for the Study of the Liver (EASL). In patients without chronic liver disease, liver biopsy is strongly recommended for the final diagnosis and proper treatment plan.

American Association for the Study of Liver Disease (AASLD) proposed guidelines on the management of HCC in 2005[12]. According to AASLD guidelines, liver nodules detected on abdominal US surveillance which measure less than 1 cm should be re-examined every twice a year. The AASLD as well as the EASL suggest abdominal ultrasonography as the preferred study for surveillance of patients at high risk of HCC twice a year[13]. If no radiological change of the lesion has occurred over a period of up to 2 years, routine surveillance can be continued.

Every suspicious lesion in high risk patients that has suggestive US findings for HCC should be further investigated with additional imaging studies. That includes 4-phase multidetector CT scan or dynamic contrast enhanced MRI. If the lesion has the typical characteristics of HCC, it should be treated as HCC. If a nodule is greater 2 cm at the initial diagnosis and it is compatible with HCC after one dynamic imaging study, biopsy is not necessary for the diagnosis of HCC. On the other hand, if the vascular profile of the liver tumor on imaging studies of a non-cirrhotic patient is not consistent with HCC, a second imaging study or biopsy of the lesion should be performed to rule out HCC. If the biopsy of a liver nodule is

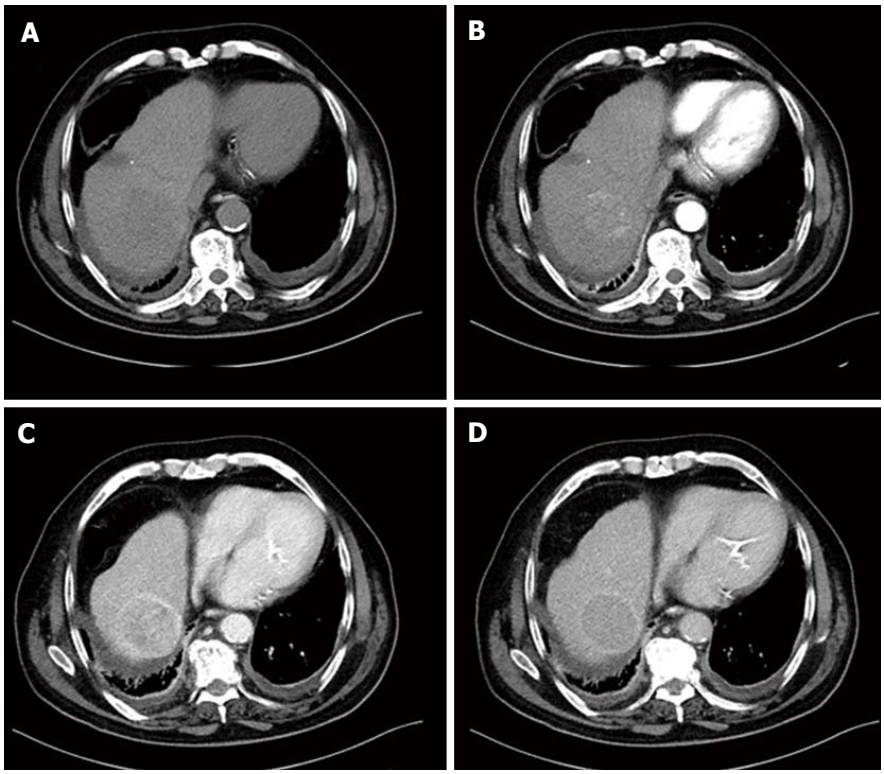

Figure 2 Multiphasic computed tomography in a large hepatocellular carcinoma located in the right liver lobe. A: Unenhanced image; B: Lesion's enhancement in the late hepatic arterial phase; C: Lesion's "washout" in the portal venous phase; D: Delayed phase image. The lesion has capsule appearance most shown in the portal venous and delayed phase.

negative for HCC, patients should be further surveilled *via* abdominal US every 3-6 mo until the nodule presents enlarged in size or with altered imaging characteristics. According to the guidelines of the Asia-Pacific Association for the Study of the Liver 2010[14], every nodular lesion with atypical vascular features should undergo further imaging investigation such as endoscopic ultrasonography (EUS)[14].

Most commonly, contrast enhanced CT scans and MRI scans are performed to expose, differentiate and examine a liver mass. HCC has often a unique imaging pattern[15]. On contrast-enhanced CT and MRI studies, high arterial-phase contrast uptake and rapid wash-out during in late phase are displayed, although these characteristics are not present in early stages or in not well-differentiated HCC (Figure 2). Furthermore, Triphasic CTA can identify more nodules, but in patients with nodular cirrhosis, contrast enhanced MRI should be preferred. Lesions between 1 and 2 cm in cirrhotic patients should be further examined with triphasic CTA and MRI in order to rule out HCC[16].

Angiography and contrast-enhanced ultrasound (CEUS) have complementary role in the investigation of a possible HCC lesion. The diagnosis of HCC is made using the same imaging criteria of arterial phase hypervascularity, but portal or delayed phase washout is observed in only 50% of cases[17]. Moreover, the depiction interval is short and comprehensive scanning of the entire liver is not possible. The CEUS sensitivity is further restricted to less than 50% in the investigation of small tumors[18]. Angiography for the diagnosis of HCC has been replaced mostly by cross-sectional imaging. Normal vasculature is typically displaced by a characteristic hypervascular large mass, with bizarre neovascularity and arteriovenous shunting. An enlarged hepatic artery may also be present[19].

Pozitron Emiting Tomography scan is not accurate for early diagnosis, but ^{18}F-fluorodeoxyglucose (FDG) uptake can significantly help investigating liver lesions. PET using FDG can detect extrahepatic metastases not revealed in CT or MRI scans[20].

Diffusion-weighted imaging (DWI) contributes to the molecular water composition and to the degree of tumor viability at the cellular level. DWI is particularly useful as an initial screening tool for liver study as nearly 70%-95% of HCCs can appear hyperintense[21]. Although DWI is high sensitive in detecting liver nodules, it cannot accurately distinguish between HCC and dysplastic nodules or other malignant and benign liver lesions. Contrast-enhanced MRI outperforms DWI in that field, consisting currently the method of choice for the characterization of malignant liver lesions in cirrhotic liver[22].

STAGING

The prognosis of HCC is related to tumor stage; staging in HCC should define outcome prediction and the optimum treatment management, liver function, portal pressure and clinical performance status of the

Table 1 Barcelona Clinic Liver Cancer staging classification

Tumor status				
Stage	PST	Tumor stage	Okuda Stage	Liver function studies
Stage A: early HCC				
A1	0	Single	I	No portal hypertension
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors < 3 cm	I - II	Child-Pugh A-B
Stage B: idermediate HCC	0	Large multinodular	I - II	Child-Pugh A-B
Stage C: advanced HCC	1-2[1]	Vascular invasion or extrahepatic spread	I - II	Child-Pugh A-B
Stage D: end-stage HCC	3-4[2]	Any	III	Child-Pugh C

[1]Stage C, at least one criteria: PST1-2 or vascular invasion/extrahepatic spread; [2]Stage D, at least one criteria: PST3-4 or Okuda Stage III/Child-Pugh C. PST: Performance status; Stage A and B, all criteria should be fulfilled.

Table 2 Child-Turcotte-Pugh score

Measurements	Score		
	1	2	3
Encephalopathy	None	Mild	Moderate
Ascites	None	Slight	Moderate
Serum Bilirubin (mg/dL)	1-2	2-3	> 3
Serum Albumin (mg/dL)	> 3.5	2.8-3.5	< 2.8
PT (seconds prolonged)	< 4	4-6	> 6

Stage A: 5-6 points; Stage B: 7-9 points; Stage C: 10-15 points.

Table 3 Model for end-stage liver disease, United Network for Organ Sharing modification

MELD Score = 9.57 × ln (Serum Creatinine in mg/dL)
+ 3.78 × ln (Serum Bilirubin in mg/dL)
+ 11.2 × ln (INR) + 6.43

MELD: Model for end-stage liver disease.

patient. However, prognosis for the patients with HCC is not only associated with the stage of the disease, but also depends on the underlying liver function as well as the performance status of each patient[23]. The current staging system for HCC, it is proposed by the Barcelona Clinic Liver Cancer (BCLC), and is recommended both for prognostic prediction and treatment allocation[24,25]. It is a staging system that also assigns treatment based on tumor stage, liver function, performance status, and treatment intent (Table 1).

The Child-Turcotte-Pugh (CTP) score is a simple and widely used grading system for liver function[26] (Table 2). On the other hand, there are many drawbacks using CTP system in liver function appraisal, including inter-laboratory variations, day-to-day fluctuations in the key parameters and the subjective nature of the clinical grading of chronic liver disease[27]. The most important disadvantage of CTP score is the presence of subjective parameters. Therefore, in the recent years the CTP score is gradually substituted by other scoring systems accessing the underlying liver function more accurately.

The Okuda classification was first applied in HCC patients more than two decades ago. It indicates parameters about the tumor stage (more or less than 50% of the liver parenchyma involved), as well as liver functional status, such as albumin, ascites and bilirubin. Okuda classification has been useful to identify the end-stage patients (Okuda stage III)[28].

The model for end-stage liver disease (MELD) score assess the severity of chronic liver disease and was initially developed to predict three month mortality following transjugular intrahepatic portosystemic shunt placement[29]. It is a logarithmic score that is comprised of serum creatinine, total serum bilirubin and International Normalized Ratio. It also included a variable based on the underlying etiology of the hepatic disease. However, the etiology of the underlying liver disease turned out to be relatively unimportant; therefore it was removed from the score calculation[30] (Table 3). MELD was adopted by the United Network for Organ Sharing in 2002 for prioritization of patients awaiting liver transplantation. However, the MELD score has been strongly criticized as it fails to classify the patients with advanced liver disease correctly[31]. Several groups have offered refinements to the MELD score calculation, including other parameters[32].

TNM system is based on histopathology of a tumor, while it examines the local expansion of the disease on local nodules as well as the adjacent organs. TNM is applicable in predicting survival for these patients who have undergone surgical excision of an HCC. The criteria of TNM system are developed jointly by the American Joint Committee on Cancer and the International Union for Cancer Control. Current edition of TNM for HCC is the seventh, which took effect in 2010[33] (Table 4).

PATHOLOGY

Macroscopic appearance of HCC depends on tumor size and the presence or absence of cirrhosis in the

Table 4 American Joint Committee on Cancer TNM Staging for Liver Tumors (7th edition, 2010)

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors, none more than 5 cm		
T3a	Multiple tumors more than 5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or the hepatic vein		
T4	Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional node metastasis		
N1	Regional lymph node metastasis		
Distal Metastases (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage Ⅰ	T1	N0	M0
Stage Ⅱ	T2	N0	M0
Stage ⅢA	T3a	N0	M0
Stage ⅢB	T3b	N0	M0
Stage ⅢC	T4	N0	M0
Stage IçA	Any T	N1	M0
Stage IçB	Any T	Any N	M1
Histologic grade (G)			
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Fibrosis core (F)			
The fibrosis score as defined by Ishak recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale			
F0	Fibrosis score 0-4 (none to moderate fibrosis)		
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)		

background liver[34]. Small HCC (less than 2 cm) can be vaguely nodular (early HCC) or distinctly nodular (progressed HCC)[35]. The majority of larger HCC show a nodular pattern, either unifocal or multifocal. In livers with cirrhosis a fibrous pseudocapsule is often formed while in noncirrhotic livers HCC tend to be unencapsulated[34]. Occasionally, HCC protrude outside the liver resulting in a pedunculated tumor. The "massive" HCC type represents a sizable tumor with relatively unclear boundaries that may occupy the entire liver lobe. The "diffuse type" is a rare growth pattern comprising of multiple scattered tiny nodules distributed throughout the liver mimicking cirrhosis[36].

On histological grounds, HCC mimics the hepatic parenchyma in structural and cytological features. Well and moderately differentiated HCCs show a trabecular (plate-like) growth pattern with sinusoidal capillarization expressed by CD34 positive endothelial cells. Rarefaction of reticular fibers is another microscopic characteristic while bile canaliculi are also formed and can be depicted by polyclonal carcinoembryonic antigen and CD10 expression. Poorly differentiated HCC shows a compact architecture and sinusoids are lost[34,37].

GRADING

The most widespread grading system is the WHO 4 tier system, classifying tumors into well differentiated (Figure 3A and B), moderate differentiated, poorly differentiated and undifferentiated. The Edmonson - Steiner system (1954) also divides HCC in 4 grades based on an assessment of cellular atypia and nuclear - cytoplasm ratio.

Tumor grade has proven to be of weak prognostic significance regarding clinical course and survival[38] in contrast to tumor size which constitutes a major prognostic factor, with a very good prognosis for small sized HCC[39]. Along these lines, the International Consensus Group for Hepatocellular Carcinoma adopted in 2009 the division of small HCC into two clinico-pathological groups, termed early HCC and progressed HCC[35]. They represent tumors at different stages of development, which differ in morphology, prognosis and treatment. Early HCC is a small tumor (less than 2 cm), with poorly defined margins and well differentiated histology that has been characterized by some investigators as carcinoma in situ or microinvasive carcinoma[39,40]. Angiographic findings are often not diagnostic because the main blood supply is through the portal vein. Major histologic features constitute preserved portal tracts, pseudoglandular pattern, diffuse fatty change and varying numbers of unpaired arteries (Figures 3A and 2B). The most helpful feature in differentiating early HCC from high-grade dysplastic nodule is portal tract or fibrous septa infiltration.

DIFFERENTIAL DIAGNOSIS

The histological diagnosis of HCC may be difficult due to morphological similarities between (1) well-differentiated HCC and benign hepatocellular lesions such as regenerative nodules, dysplastic nodules, hepatocellular adenoma and focal nodular hyperplasia; and (2) between poorly differentiated HCC and other primary liver (*e.g.,* cholangiocarcinoma) or metastatic cancers.

Immunohistochemical markers that can facilitate diagnosis include HepPar1, albumin, fibrinogen, a1-antitrypsin, alfa-fetoprotein and glypican-3 (GPC3). Among them, GPC3 appears to be the more suitable marker in poorly differentiated tumors[41,42]. Overexpression of desgamma-carboxyprothrombin, GPC3, heat-shock protein (HSP70) and glutamine synthetase favor malignancy in the differential diagnosis of hepatocellular nodules. The detection of at least two of the above markers enhances the diagnostic reliability.

A group of expert liver pathologists recently proposed the term well-differentiated hepatocellular neoplasm of uncertain malignant potential for a small subset of well-differentiated hepatocellular adenoma-

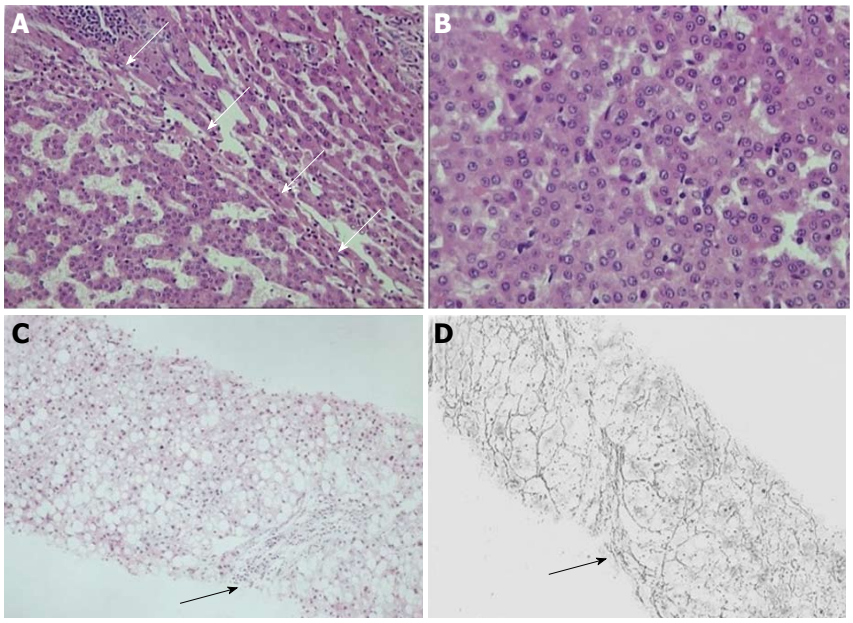

Figure 3 Well differentiated, (grade 1) hepatocellular carcinoma and early hepatocellular carcinoma with diffuse fatty change. A: White arrows indicate the interface between HCC (left) and background liver (right); B: HCC cells show high nuclear/cytoplasmic ratio and minimal nuclear atypia. A: H/E × 100, B: H/E × 200; C and D: Early HCC with diffuse fatty change. Black arrowhead depicts a preserved portal tract. Gomori stain shows rarefaction of reticulin network. C: H/E × 100, D: Gomori stain × 100. HCC: Hepatocellular carcinoma.

Table 5 Current treatment options for hepatocellular carcinoma

Surgical
Resection
Resection + ablation
Orthotopic liver transplantation
Ablative
Thermal ablation (radiofrequency ablation, microwave ablation)
Percutaneous alcohol (ethanol) injection
Transarterial
Embolization
Chemoembolization
Radiotherapy
Transarterial and ablative (combined)
Systemic chemotherapy + radioembolization

like lesions with atypical clinical, histologic or genetic features which raise the necessity for close follow-up[43].

HCC HISTOLOGICAL SUBTYPES

Besides conventional HCC there are rare histological types, which, except fibrolamellar HCC and HCC with stem cell features, are not associated with specific clinical characteristics or pathogenetic peculiarities.

Fibrolamellar carcinoma constitutes a special type of HCC occurring in children and young adults that has a better prognosis than HCC when arising in cirrhotic liver but similar to HCC in non-cirrhotic liver. FLC grow with pushing borders and tumor cells are arranged in sheets and trabeculae, separated by collagen fibers which are often hyalinized and provide a unique lamellar appearance. FLC cells are sizeable with eosinophilic granular cytoplasm and often contain pale bodies, hyaline bodies and copper[34].

HCC with stem cell features has been established on the ground of accumulating evidence indicating that a subset of adult HCC with worse survival rates exhibits, at least focally, a progenitor cell phenotype. These tumors retain stem cell markers and may also express a hepatobiliary immunophenotype (Figure 4). Acknowledging this fact, WHO has included in the Classification of Tumors of the Digestive System (2010) the "Combined Hepatocellular-Cholangiocarcinoma" category, encompassing primary liver carcinoma subtypes with stem cell features. In a recent review, Brunt *et al*[44] pointed out the need for the establishment of a more complete terminology including the different subtypes based on their differentiation status.

TREATMENT

Treating HCC has always been a challenge, regarding efficiency of interventional medicine, coherence of the practitioner physicians about the treating options and first and foremost the survival of the treated patients.

When feasible, complete HCC resection is the treatment of choice[45]. Otherwise, there is a variety of treatment options based on HCC stage, the patients' performance status and physical abilities, the available resources, and the level of practitioner expertise (Table 5). Most recommendations for staging-guided treatment are based on the findings of retrospective studies[46].

Resection of the HCC lesion should be the primary

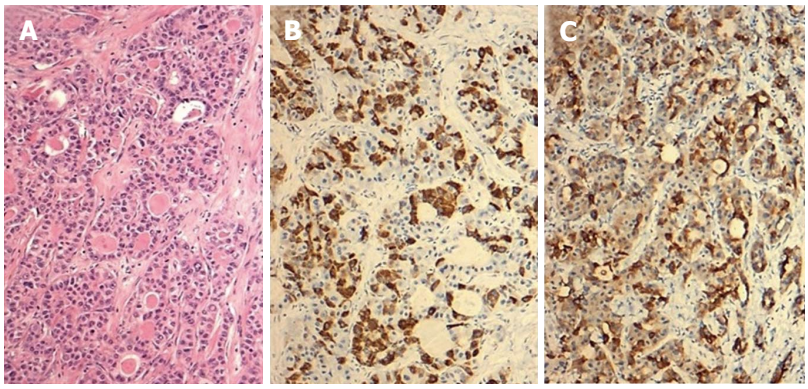

Figure 4 Combined hepatocellular-cholangiocarcinoma with stem cell features, intermediate cell subtype. Tumor expresses both hepatocellular (HepPar1) and biliary (CK19) immunohistochemical markers. A: H/E × 100; B: HepPar1 × 100; C: CK19 × 100.

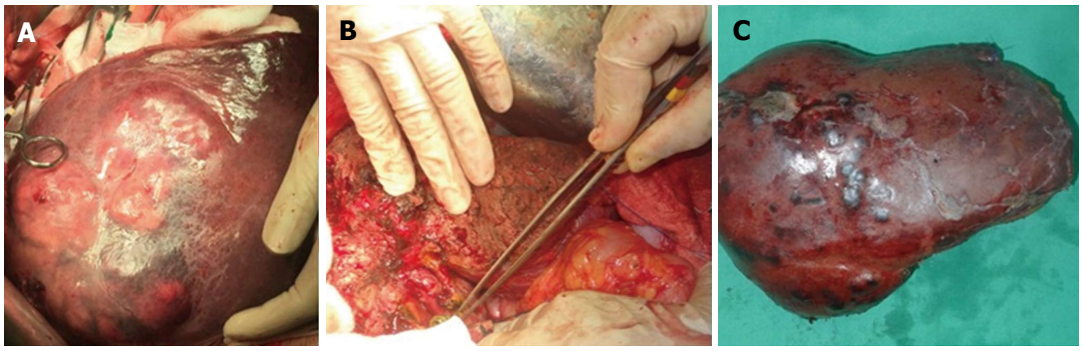

Figure 5 Intra-operative situs [prior (A) and post (B) right hepatectomy] and surgical specimen (C) of a large hepatocellular carcinoma located in the right liver lobe.

treatment option in patients with single HCC with well-compensated Child A cirrhosis[12]. It has been proven that 5-year survival excides 50% and 5-year recurrence rate is about 70% in the group of patients that had undergone previously a surgical HCC resection[47].

Major hepatectomy can be safely performed nowadays due to better understanding of the liver anatomy[48], advances in surgical instruments and implication of newer surgical approaches (Figure 5). The most commonly used techniques for liver resection are the anterior approach to avoid liver mobilization and rupture of large liver tumors[49], the Pringle maneuver[50], the hanging maneuver[51] as well as the careful adjustment of central venus pressure for reduction of blood loss peri-operatively[52]. Site and size of the lesion, vascular invasion as well as multifocal disease should be estimated pre-operatively. Anatomic resection should be intended in every case if not contraindicated.

It is well known that future liver remnant (FLR)/total liver volume (TLV) ratio should be more than 20%-25% in patients with normal liver functions (no cirrhosis) and more than 50% in patients with a Child-Pugh score A cirrhosis, who's PLTs are more than 100000/mm^3. The FLR/TLV ratio is being calculated *via* imaging studies pre-operatively. If FLR/TLV ratio is below recommended values, pre-operative portal vein embolization (PVE) should be considered in order to have a feasible liver remnant post-operatively, capable to actualize the metabolic needs of the patient[53]. It has been proven that PVE can increase the FLR size. In PVE, the ipsilateral portal vein which supplies the liver lobe harboring the tumor, thus inducing hypertrophy of the hepatic liver remnant[54]. PVE can be offered to cirrhotic patients, although liver regeneration and hypertrophy of the FLR is questionable in the presence of cirrhosis. In this group of patients the combination of PVE and trans-arterial chemoembolisation (TACE) represents a feasible treatment option[55].

The resectability of HCC often depends on the volume of the FLR. Stage hepatectomy is proposed for HCC with bilobar liver involvement. According to this procedure, two or more hepatectomies are performed at different time points in order to allow increase of FLR. This technique ensures adequate liver function as well as R0 resection. As prerequisites, the preserved portion of the liver should be sufficient and cancer free and adequate vascular inflow and outflow should be retained[56].

A newer technique, combines two stage hepatectomy with portal vein occlusion. Associating Liver Partition and Portal Vein Ligation in Staged Hepatectomy (ALPPS) is one of the main surgical innovations in hepatic surgery nowadays[57]. ALPPS aims to speed up hypertrophy of the liver remnant by right portal vein ligation and

Table 6 Treatment schedule proposed for hepatocellular carcinoma cirrhotic patients according to the Barcelona Clinic Liver Cancer classification system

Stage	Treatment intention	First/second choice
Stage A: early HCC		
A1	Radical	Surgical resection
A2		Surgical resection ð OLT/ percutaneous treatment
A3		OLT/percutaneous treatment (Ablation)
A4		OLT/percutaneous treatment (Ablation)
Stage B: intermediate HCC	Palliative[1]	Trasanterial embolization (associated or not to percutaneous treatment) Chemoembolization (TACE)
Stage C: advanced HCC	Palliative[1]	New agents (Sorafenib)
Stage D: end-stage HCC	Symptomatic	Supporting treatment

[1]In the setting of phase II investigations or randomized control trials. HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer.

in-situ splitting of the intended transection surface down to the inferior vena cava. The second stage of the procedure is executed several days later with an adequate volume of FLR for a safe and feasible hepatectomy.

Patients with solitary tumor who have adequate liver function, no major vascular invasion or intrahepatic metastases and adequate FLR should be considered eligible for surgery as a potentially curative option. In patients with advanced liver disease (multi-focal disease, inadequate liver function, major vascular invasion, a solitary tumor with multiple intrahepatic metastases, metastases on adjacent organs or missing enough healthy hepatic parenchyma to survive) the benefit of resection is vague and it should be weighed against the risk of liver failure and post-operative systemic complications[58]. It has to be taken into consideration that in these patients other treatment options might result in better long-term outcomes and similar rates of survival.

Liver transplantation (LT) is the ideal treatment for HCC, especially in the presence of underlying liver disease, because it eliminates the tumor and cure underlying cirrhotic liver that serves as a risk of HCC development. However, the major limitation of LT is organ shortage resulting in high dropout rate (12%-25% per year)[59]. There are studies that have proven that Milan Criteria is the most significant prognostic factor of patients with HCC undergoing LT[60]. In patients with tumor burden beyond the Milan Criteria, other treatments can be applied to downstage the tumor to meet acceptable criteria for LT. TACE or radiofrequency ablation (RFA) are the common modalities used for downstaging[61].

Few patients (less than 20%) are amenable to resection and transplantation due to difficulties related to size, location and number of tumors, vascular and extrahepatic involvement and functional hepatic reserve due to cirrhosis. The ultimate treatment choice for the remaining 80% is interventional therapies[62].

BCLC staging system should be used in patients with HCC and underlying cirrhosis. The system identifies those patients with early HCC who may benefit from resection or RFA (stage 0 and A), those at intermediate or advanced stage who may benefit from palliative treatments and those with a very poor life expectancy (Table 6).

Patients with early HCC who are not eligible for surgical resection or liver transplantation should undergo Local Ablative Therapy[63]. The procedure can be performed using or thermal ablation: RFA, microwave ablation (MWA), Laser-induced interstitial thermotherapy or either chemical: percutaneous alcohol injection (PEI). Under imaging guidance (US or CT) PEI is injected directly to the lesion. PEI is consisted of 95% ethanol, which causes local tumor necrosis. PEI is recommended for small lesions (10%-15% of liver lesions)[64], in cases where RFA is not feasible to apply due to technical reasons. Similar therapeutic results and rates of residual foci of untreated disease as well as equivalent complication rates have been showed for MWA and RFA use in liver lesions[65]. However, RFA offers the same results as WMA in fewer sessions[66], while MWA outweighs PEI on the local control of moderately or poorly differentiated small lesions. Furthermore, patients with a single tumor smaller than 4.0 cm and Child-Pugh class A cirrhosis have a higher probability of long-term survival after WMA rather than after RFA or PEI[67].

Transarterial chemoembolization (TACE), is a palliative treatment for inoperable HCC patients with large or multinodular lesions limited to the liver and with an adequate liver function[68]. Various treatment protocols have been applied using different chemotherapeutic agents[69]. The perfect TACE scheme should be that who would allow the maximum and also sustained concentration of the agent within the tumor, while keeping the systemic exposure as low as possible. Furthermore, a major issue is the lowest possible vessel obstruction, in order to reduce hepatic ischemia.

Radioembolization with yttrium-90 microspheres, is a palliative treatment for patients with Child-Pugh class A cirrhosis and intermediate-stage HCC. It has also been used for the bridging to liver transplantation and as a downstage method for non-operable tumors. Arterial radioembolisation have shown improve in 2-year survival rate after administration, comparing with conservative treatment[70].

Three-dimensional conformal radiotherapy (RT) has shown good results at doses between 40Gy and 60Gy for patients with advance HCC. Median response rate is 45% and median survival 10 to 15 mo. Furthermore 1-year survival excides 70%; 5-year survival rate is between 9%and 25%. RT combined with TACE in various dose schemes have given advantages

as salvage therapy. RT is an option in patients with advance liver disease that cannot be respected, in patients which are not suitable for liver transplantation, and those inoperable due to performance status or comorbidities[71].

SYSTEMIC THERAPY

HCC is more often diagnosed in late stages and on the background of chronic liver disease. This fact minimizes the possibilities for curative strategies, while palliative procedures prevail as therapeutic options, aiming to downstage or to alleviate a locally advanced disease.

The therapeutic options in advanced HCC are limited due to resistance of the carcinoma to chemotherapy. Systemic therapy with doxorubicin or cisplatin yields low objective response rates while drug-combinations may offer a better disease control without succeeding in improving survival rate. In addition, due to chronic liver disease and to underline liver dysfunction, HCC patients have limited tolerance to full doses of poly-chemotherapy. It has been proven that low response and no survival benefits ensure from cytotoxic chemotherapy[72].

Doxorubicin has been considered as one of the most active cytotoxic agents. Its use in HCC has reached 10% to 20% response rates as single agent chemotherapy. Clinical trials have demonstrated that Doxorubicin prolongs survival in advanced HCC compared to Nolatrexed (a thymidylate synthase inhibitor)[73]. Other cytotoxic agents, such as Gemcitabine, have shown fairly limited clinical benefit, despite their highly promising effect in *in vitro* studies[74].

Sorafenib is an oral multikinase inhibitor, which acts against platelet-derived growth factor receptor beta, vascular endothelial growth factor receptor as well as c-Raf and b-Raf. It was the first agent to achieve a statistically significant improvement of overall survival in Child-Pugh class A patients with advanced HCC[75]. In addition, administration of Sorafenib in patients with Child-Pugh class B has also given promising results[76]. Overall survival in patients with Child-Pugh A was encouraging after receiving combination therapy with Sorafenib plus Doxorubicin versus Doxorubicin alone[77].

RESPONSE ASSESSMENT AND FOLLOW-UP

Monitoring a patient treated for hepatocellular carcinoma is an important part of the clinical management; accurate assessment of tumor response is essential for favorable outcomes. Follow-up of patients who had been treated with surgical resection or RFA ablation should consist of the clinical evaluation of liver function and the tumor response to the particular therapy, by CT or MRI studies every 3 mo the first 2 years and lance every 6 mo later on by US, enhanced CT and MRI scans[78]. Patients with recurrence on follow-up imaging studies may still be candidates for curative therapies. Patients with HCC and end-stage cirrhosis being treated with TACE or systemic chemotherapy should be examined for possible liver dysfunction as well as for tumor progression by CT or MRI every 2 mo[12].

The evaluation of HCC response to administered therapy is based on Response Evaluation Criteria in Solid Tumors (RECIST)[79]. However, with the increasing clinical use of antineoplastic cytostatic agents and locoregional interventional therapies in hepatocellular carcinoma (HCC), conventional morphologic methods have strong limitations in response assessment. Current RECIST criteria were designed for the evaluation of cytotoxic agents[80].

Modified RECIST (mRECIST) criteria are mainly based on the measurement of the viable tumor component[81]. Additional criteria include evaluation of vascular invasion, lymph node involvement, effusions and new lesions[82]. Response assessment should be based on CT or MRI scans. Serum tumor markers may be helpful, but should not be used as the only determinant for treatment decision.

CONCLUSION

Summarizing and in order to emphasize to new data regarding the treatment of HCC following topics should be highlighted. Only a small proportion of patients with HCC (less than 20%) is amenable to resection or transplantation. ALPPS is nowadays one of the main innovations in hepatic surgery[57]. Regarding LT, treatments such as TACE or RFA can be applied to downstage tumors that initially do not meet the Milan Criteria[61]. Furthermore, a conventional treatment option that gains field in treatment of inoperable HCC is the RT[71].

In terms of chemotherapy, the administration of Sorafenib has given promising results in patients with Child-Pugh class B[76], while combination therapy with Sorafenib plus Doxorubicin seems to improve overall survival in patients with Child-Pugh A.

Despite the advances in diagnostic and invasive medicine, hepatocellular carcinoma remains the most fatal malignant liver cancer worldwide. At the present time, treatment has focused to early diagnosis and hepatic resection or transplantation. Combination therapies have been used to downstage the tumor and make it operable, to improve underlying liver status and prolong the survival period. Therefore, future studies on HCC management are tremendously important in order to offer better treatment outcome and prolong survival for HCC patients.

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