

Chapter 21: Diagnosis, Prognosis & Therapy

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Classification of HCC

Tumours are classified in order to stratify patients with respect to their prognosis for survival, to select and offer optimised therapeutic options at any tumour stage. In HCC the Barcelona Clinic Liver Cancer (BCLC) Classification has been adopted as the international standard, which is recommended by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) (Table 1). The BCLC classification takes into account several aspects of the disease: the patient's general state of health, the severity of the liver disease as well as the extent of tumour spread (Llovet 1999). Patients in stages BCLC 0 and A have a considerably better prognosis than patients in advanced stages of liver cancer (Mazzaferro 1996). Nevertheless approximately only 25% of patients with liver cancer are diagnosed at an early stage. Both EASL and AASLD guidelines also provide recommendations regarding which therapy is best-suited to treat patients at each stage of the BCLC classification. Unlike classification schemes in other types of malignancy the BCLC classification is particularly helpful because it is entirely based on clinical parameters - molecular characteristics are not yet able to reliably assess the individual prognosis of patients with HCC.

Tumor stage	General state of health	Tumour characteristics	Child stage
0 Very early	good	single nodule <2 cm	A & B
A Early	good	single nodule <5 cm, 3 nodules <3 cm	A & B
B Intermediate	good	large, multiple nodules	A & B
C Advanced	reduced	vascular invasion, extrahepatic secondaries	A & B
D Terminal	severely reduced	any form	C

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Table 1. Barcelona Clinic Liver Cancer (BCLC) Classification.

Epidemiology

HCC has an annual incidence of more than 600,000 newly diagnosed patients. Thus, HCC constitutes the sixth most frequent form of cancer worldwide, and it holds third place concerning malignancy-related mortality (Parkin 2005). Incidence rates of HCC are steadily rising both in Europe and the US.

Chronic hepatitis B is the major risk factor for developing HCC in Africa and Asia, while in the US, Europe and Japan chronic hepatitis C is the leading cause of HCC. Eighty

percent of liver cancers are found in cirrhotic livers, which in themselves carry a high risk for HCC. Chronic carriers of hepatitis B virus (HBV) have a 100-fold increased risk as compared to a non-infected healthy reference population. Reports from Taiwan indicate a direct link between HBV viral loads and the risk of developing liver cancer within 10 years (Chen 2006; Iloeje 2006). The risk of HCC is significantly increased once HBV viral loads exceed 10,000 copies/ml irrespective of the degree of hepatic inflammation. In developing world countries exposure to aflatoxins further increases this risk of HCC.

Approximately 170 million people are infected with the hepatitis C virus worldwide, 20 to 30% of whom will develop liver cirrhosis, which carries a 3-5% annual risk of ultimately progressing to liver cancer. In practical terms this means that approximately one third of cirrhotic patients with hepatitis C will go on to develop HCC. Unlike hepatitis B a close relationship between HCV viral loads and the risk of developing HCC apparently does not exist (Bralet 2000). As a general rule patients will not develop liver cancer in chronic hepatitis C before their disease has progressed to the stage of cirrhosis. Consumption of alcohol or tobacco enhances the risk of HCC (Donato 2002; Gelatti 2005). Beyond that, obesity (Calle 2003) and diabetes mellitus (Davila 2005) must be considered neglected but nevertheless pivotal factors that can multiply the risk of liver cancer in western countries resulting in 4 to 40-fold increased HCC rates among patients with chronic viral hepatitis.

Surveillance of patients at high risk and early HCC diagnosis

Surveillance using ultrasound at 6-month intervals is generally recommended for all patients with liver cirrhosis or other risk factors of HCC. Significantly more patients with early hepatocellular carcinoma were detected in a single large randomised study in China, when patients were in a regular HCC screening programme, irrespective of the presence of cirrhosis (Zhang 2004). When 3- versus 6-month surveillance intervals were compared in a randomized study involving 1200 patients, there was no evidence that the shorter interval improved rates of early diagnosis and therapeutic outcomes (Trinchet 2007). If patients with cirrhosis harbour nodular lesions, however, the 3-month control interval is preferred due to the high potential of malignancy and growth characteristics of such lesions (Yao 2006). Alfa-fetoprotein (AFP) is no longer recommended as a tool for HCC surveillance, because repeated AFP measurements have proven only marginally beneficial for HCC outcomes. Novel biomarkers such Des-Gamma-Carboxyprothrombin (DCP) or the Lectin 3-Fraction of AFP (AFP-L3) have also not been established as reliable tools to detect early HCC. Nevertheless the consistent use of ultrasound for patients with early carcinoma enable us to make an early diagnosis in 30% of patients who then have a reasonable chance of curative therapy via the improved treatment options available.

Diagnosis

The diagnosis of HCC can either be made by detecting malignantly transformed hepatocytes in a liver biopsy or by demonstrating characteristic radiological features in a hepatic lesion after application of contrast media, which confirm arterial hyperperfusion of the tumour. Thus, these novel guidelines enable the diagnosis of HCC in

a cirrhotic liver without histopathology or reference to elevated tumour markers.

The distinction between a dysplastic nodule and early HCC poses a particularly challenging and as yet unsolved task for the pathologist, because markers showing the unequivocal differentiation between these two entities in difficult-to-assess histological specimens have yet to be identified. Glypican-A or a combination of three markers (glypican-A, LYVE-1 and survivin) may become tools for the pathologist enabling a correct histological diagnosis in up to 85-95% of patients. Other markers like serin/threonin kinase 15, phospholipase A2 or telomerase reverse transcriptase (TERT) are currently under evaluation. At the present time, clearly dysplastic nodules should be submitted to radiological surveillance quickly, since such lesions retain a high potential for malignant transformation resulting in transition to HCC in approximately one-third of cases.

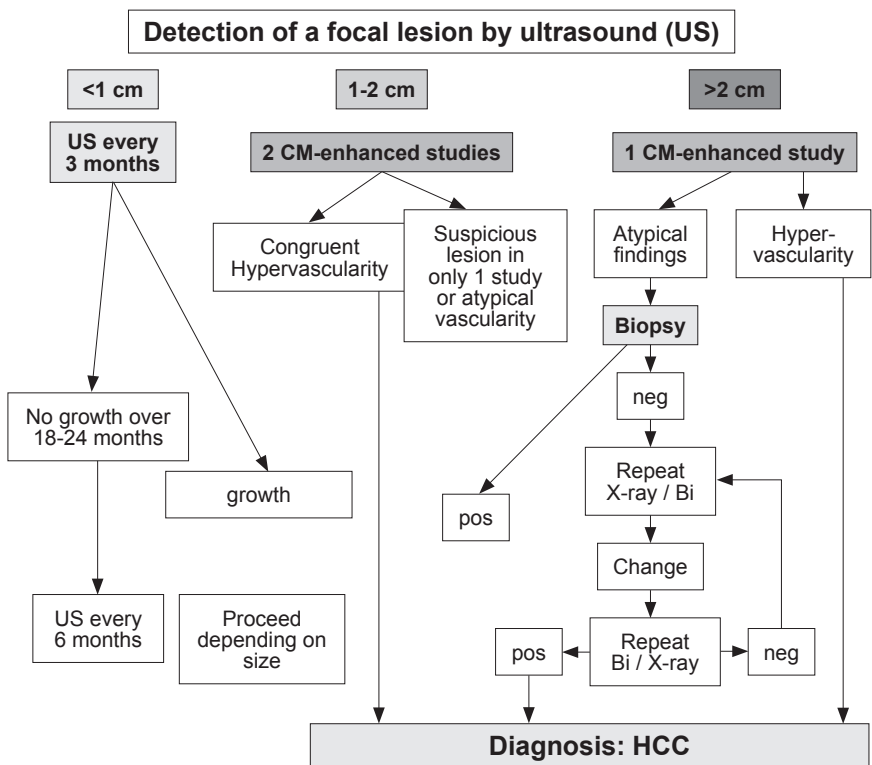


Figure 1. Diagnostic algorithm for the diagnosis of hepatocellular carcinoma depending on tumour size.

Radiological diagnosis of HCC uses detection of hyper-vascularized nodular lesions. Contrast-enhanced ultrasound, computed tomography (CT) or nuclear magnetic spin resonance tomography (MRT) are all considered to be equivalent diagnostic tools, and novel international consensus guidelines accept a diagnosis of HCC without

histopathology, if the patient has a nodular lesion in the cirrhotic liver that exhibits obvious hyper-vascularisation after application of contrast medium. Hyper-vascularisation is characterised by contrast enhancement in the early arterial phase, which rapidly disappears in the late venous phase (the so-called wash-out phenomenon) of the contrast study. Contrast-enhanced ultrasound, spiral CT and MRT in combination with gadolinium-enhancement exhibit similarly excellent diagnostic sensitivity and specificity in lesions larger than 2 cm. For this very reason detection of signs of hyper-vascularisation with any one of these three radiological techniques is sufficient to make a confident diagnosis of HCC in tumours >2 cm. Diagnostic precision is considerably less in lesions of 1-2 cm diameter. To account for that loss of precision, a diagnosis of HCC in these smaller tumours must be based on the congruent detection of a hyper-vascularised lesion in at least two independent radiological procedures. In equivocal situations the diagnosis must be clarified by biopsy in small nodules, which may have to be repeated within a short period of time. A diagnostic algorithm recommended by EASL and AASLD is shown in Figure 1. Small tumours should be either monitored in short-term intervals (every 3 months) or directly investigated by a liver biopsy to clarify their significance.

Stage-adapted therapy for liver cancer

A. Potentially curative therapy in stages BCLC 0-A

Patients with early HCC have excellent chances for curative cancer treatment. They can achieve 5-year survival rates of 50-70% by surgical resection, liver transplant or percutaneous, ablative procedures.

Surgical resection constitutes the backbone of curative treatment in patients with early HCC. It is the treatment of choice in patients with localised tumour spread and small-size cancers and tumours in a non-cirrhotic liver (evidence grade IIIA). Prognosis after surgical resection is excellent, if the tumour is not larger than 2 cm in diameter (5-year survival rates 70-90% with rates of tumour recurrence below 10%). Excluding patients with poor liver function keeps peri-operative mortality below 5%. Favourable criteria for surgical resection comprise single nodules less than 5 cm in size or a maximum of 3 nodules in a single liver lobe in patients with only moderately impaired liver function (cirrhosis stage Child A) without portal hypertension (hepato-portal-venous pressure gradient >10 mm Hg or presence of oesophageal varices or splenomegaly together with reduced platelet counts <100,000/ μ l) and serum bilirubin in the normal range. However, it is noteworthy that even the most modern CT and MRT scanner still underestimate the extent of vascular invasion in 30% of patients with early HCC.

Liver transplantation is an alternative therapeutic option, if the liver cancer cannot be cured by local resection due to anatomical reasons, if residual liver function after resection is anticipated to be poor or there is multi-nodular tumour spread into both liver lobes (evidence grade IIIA). Commonly patients with HCC are selected for liver transplant according to the so-called Milan criteria, i.e., the patient has a single nodule

of less than 5 cm in diameter or at most has 3 nodules, none of which exceeds 3 cm in diameter (Mazzaferro 1996). Milan criteria patients usually achieve survival rates of 80% and 70% one and five years after liver transplantation. However, it has been demonstrated that patients with more extensive stages of liver cancer can be transplanted with reasonable long-term outcomes (Yao 2001). Selection of patients according to the so-called San Francisco criteria comprises solitary large nodules up to 6.5 cm as well as multi-nodular HCC with a maximum of 3 nodules, each of which must be smaller than 4.5 cm with a total sum of all nodule diameters below 8 cm. Patients who remain within these extended selection criteria can still reach 70-80% five-year survival rates after liver transplantation.

A central issue in liver transplantation is the process of fair organ allocation. Shortage of donor organs is particularly critical in patients with liver cancer, because the tumour will continue to expand while the patient is on the waiting list, and can ultimately reach a stage that makes liver transplantation a futile option. It has been estimated that after one year on the waiting list approximately 40% of patients can no longer be cured by liver transplant (Poon 2007). In the Eurotransplant registry donor livers are allocated to patients according to their MELD scores, which take into account kidney function, serum bilirubin and the degree of coagulopathy. As a rule, patients with early HCC, who are eligible for liver transplantation, still have rather low MELD scores, which would give them only low priority for organ allocation. To circumvent this shortcoming of the MELD-based allocation system and to ensure a fairer organ allocation, Eurotransplant accepts the diagnosis of HCC within the Milan criteria as a so-called standard exemption, and the patient receives additional points on top of his so-called lab-MELD score. More points are added after each 3-month waiting period to adjust the patient's total MELD score to the steadily increasing risk of tumour spread and to accelerate organ allocation.

Most transplant centres have adopted the supplementary strategy of treating liver cancers locally while the patient is on the waiting list. It is recommended to immediately treat patients by transarterial chemoembolisation once the patient has been accepted onto the waiting list. This strategy probably also improves selection of patients for liver transplantation, because those with stable disease after chemoembolisation achieve a greater than 90% five-year survival rate after liver transplant, while only 35% of patients in the group with progressive tumour expansion survive five years after liver transplantation (Otto 2006).

Patients with HCC that is limited to a distinct region of the liver but who are older or have significant co-morbidity for other reasons are candidates for local-ablative procedures. Percutaneous ethanol injection or radiofrequency ablation, at least mid-term, achieves equal outcomes to resection and liver transplantation. Five-year survival rates are estimated at 70-80% for nodules less than 3 cm in diameter and at 50% for tumours between 3 and 5 cm in size (Lopez 2006). Radio frequency ablation seems to do a little better than ethanol injection owing to the more favourable rates of local tumour recurrence of 2-18% after 2 years (evidence grade ID). Best outcomes are achieved in patients with Child A liver cirrhosis and tumours <2 cm in size (Sala 2004). A direct head-to-head comparison of the different local-ablative procedures within the same study is still pending.

Adjuvant therapy, in the context of resection, liver transplantation or local-ablative procedures, does seem to offer additional benefits. Thus far, antiviral treatment of hepatitis B with nucleos(t)ide analogues remains the single approved treatment after removal or local destruction of HCC that has been proven an effective therapeutic adjuvant to reduce the risk of tumour recurrence.

B. Palliative therapy in stages BCLC B and C

Palliative treatment remains the only therapeutic option for patients with advanced stages of liver cancer that cannot be controlled by local therapy.

Arterial chemoembolisation is the most frequent intervention offered to patients whose HCC cannot be resected. Usually lipiodol combined with an embolising agent such as gelatine or microspheres is mixed with cytostatic drug and applied to the liver via an intra-arterial catheter. Suitable cytotoxic agents are doxorubicin, mitomycin and cis-platinum, but the optimal combination of drugs and treatment schedules has not been established. In randomised studies demonstrating a benefit of chemoembolisation doxorubicin or cis-platinum were given in 3-4 angiographic sessions per year. Chemoembolisation carries the risk of ischemic damage to the liver, potentially leading to fulminant liver failure. To minimize this risk chemoembolisation should be offered only to patients with good residual hepatic function, who have asymptomatic multi-nodular liver cancer without vascular invasion or extrahepatic tumour spread. Vice-versa patients with decompensated liver disease (liver cirrhosis, Child B or C) or imminent hepatic failure should not undergo chemoembolisation.

Taken together, chemoembolisation is currently the only palliative treatment demonstrated to significantly improve patient survival in controlled studies (Llovet 2002). It has been shown to achieve partial responses in 15-55% of patients in tumour progression as well as vascular invasion (evidence grade 1D).

Radiotherapy applying ^{90m}Yttrium-loaded microspheres has recently been developed as a novel alternative palliative treatment of liver cancer with unexpectedly impressive anti-tumoural activity in selected individual cases (Sangro 2006; Jacobs 2007; Salem 2006; Liu 2004). Of note, unlike chemoembolisation, some types of microspheres do not occlude the blood vessels and can be applied irrespective of the presence of portal vein thrombosis. However, the therapeutic potential of ^{90m}Yttrium-loaded microspheres cannot currently be assessed with certainty because these novel procedures have not yet been evaluated in randomized, prospective controlled studies.

Systemic chemotherapy on the other hand has been proven repeatedly not to offer survival benefits, irrespective of whether it is given as a single agent or as part of combination chemotherapy (Llovet 2003). Likewise, anti-hormonal therapy with tamoxifen or octreotide has not provided any improved patient survival when studied under controlled conditions (Gallo 2006; Yuen 2002).

Molecular-targeted therapeutic strategies, based on improved knowledge of intracellular signal transmission and regulation of apoptosis, offer new hope for effective pallia-

tive therapy in liver cancer. Such strategies are targeted at inhibition of growth factors or interruption of signalling pathways that are essential for tumour growth and expansion such as angiogenesis or activation of telomerases. Sorafenib (Nexavar®) is a novel orally available multi-kinase-inhibitor acting on several distinct tyrosine kinases (VEGF-R2, PDGF-R, c-Kit receptor) as well on serine/threonine kinases (b-Raf. P38). Thus, by inhibiting angiogenesis and cellular proliferation, sorafenib can block two of the major signalling pathways pivotally involved in the pathogenesis of HCC development. In a phase III study involving 602 patients, sorafenib (400 mg BID) was well tolerated and associated with improved survival in 44% of patients resulting in 3 months extended survival in treated patients (10.7 months in the sorafenib arm versus 7.9 months in the control arm). Diarrhea, weight loss, hand-foot-syndrome and hypophosphatemia were the most important side effects that occurred significantly more frequently in patients on sorafenib. Thus, sorafenib has become the first systemically acting substance demonstrated to prolong life at the expense of moderate side effects in patients on palliative treatment of liver cancer. Further antagonists which probably block VEGF-R, EGF-R, ErbB2, Akt/mTor or Wnt/b-catenin signal transmission pathways are still awaited and are currently under evaluation in phase II studies. Figure 2 gives a summary and succinct overview of stage-adapted therapy for hepatocellular carcinoma.

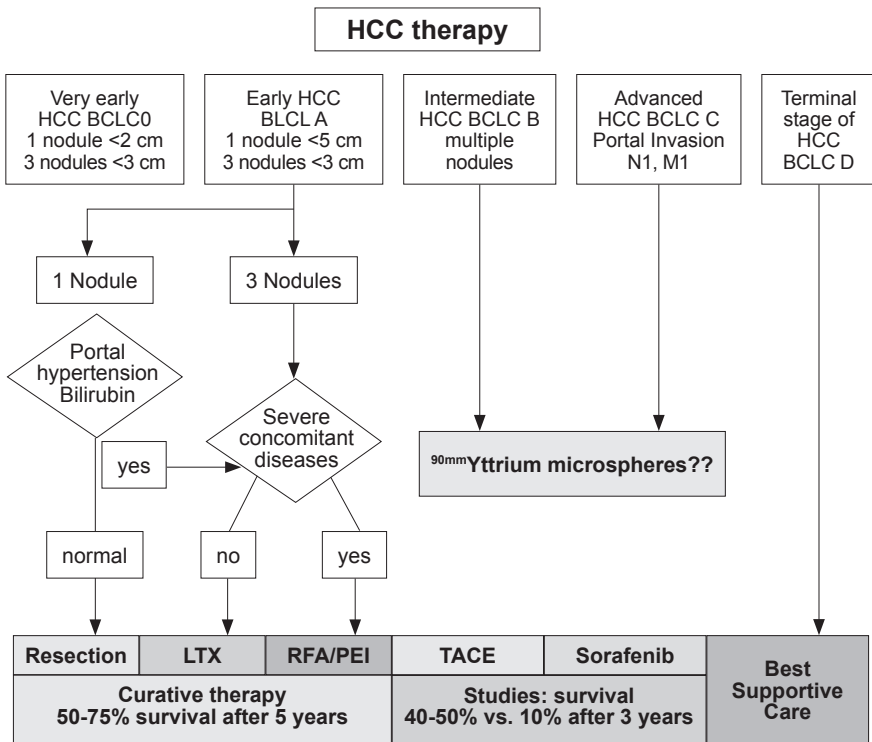


Figure 2. Overview of stage-adapted liver cancer therapy in relationship to BLCL criteria.

Prophylaxis of liver cancer

Despite conspicuous progress concerning liver cancer diagnosis and therapy, prognosis of HCC has not improved very much over time. Thus, prophylactic measures are of pivotal importance. Vaccination against HBV, as is now recommended by many national vaccination councils, has been proven in Taiwan to markedly reduce HBV infection rates along with the incidence of HCC as a complication of chronic hepatitis B in later life (Lok 2004).

Patients with chronic HBV and patients with chronic hepatitis C should be offered antiviral therapy as effective secondary prophylaxis of HCC. Both HBe-antigen positive (van Zonneveld 2004) and HBe-antigen negative patients with chronic hepatitis B show reduced incidence rates of HCC (Papatheoridis 2001; Brunetto 2002; Lampertico 2003) when successfully treated with interferon. Likewise, antiviral therapy with nucleo(t)side analogues has been demonstrated to reduce the risk of HCC in patients with chronic hepatitis B (Liaw 2005) and several meta-analyses confirm that successful interferon therapy leads to a reduced risk of HCC in chronic hepatitis (Camma 2001; Papatheoridis 2001a; Veldt 2004). Nevertheless, patients who have reached the stage of cirrhosis prior to starting antiviral therapy should be maintained on close HCC surveillance programmes, since the risk of developing liver cancer remains high in this subgroup of patients even after sustained virologic elimination is achieved (Yu 2006). Therapeutic management of additional risk factors such as obesity and poorly controlled diabetes mellitus provide additional chances for prophylactic measures to reduce the risk of HCC development. Finally, consumption of two or more cups of coffee per day seems to reduce the risk of liver cancer by 40-50% in patients with chronic viral hepatitis (Gelatti 2005; Bravi 2007; Larsson 2007; Wakai 2007).

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