The management of hepatocellular carcinoma. Current expert opinion and recommendations derived from the 10th World Congress on Gastrointestinal Cancer, Barcelona, 2008


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This article summarizes the expert discussion on the management of hepatocellular carcinoma (HCC), which took place during the 10th World Gastrointestinal Cancer Congress (WGICC) in Barcelona, June 2008. A multidisciplinary approach to a patient with HCC is essential, to guarantee optimal diagnosis and staging, planning of surgical options and selection of embolisation strategies or systemic therapies. In many patients, the underlying cirrhosis represents a challenge and determines therapeutic options. There is now robust evidence in favour of systemic therapy with sorafenib in patients with advanced HCC with preserved liver function. Those involved in the care for patients with HCC should be encouraged to participate in well-designed clinical trials, to increase evidence-based knowledge and to make further progress.

Key words: hepatocellular carcinoma, liver transplantation, chemoembolisation, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is an epithelial liver tumour of which the cells share some characteristics with normal hepatocytes [1]. HCC is the fifth most frequent cancer in the world and the third most common cause of cancer-related mortality in the world [2]. Interestingly, the world map of the prevalence of HCC is identical to the distribution of hepatitis B (HBV) and hepatitis C viral (HCV) infection, underscoring etiological factors and making HCC unique in the field of oncology. A liver with advanced fibrosis—irrespective of the cause of the liver disease—represents the ideal soil for the development of an HCC. It is now accepted that a dysplastic lesion can evolve into a malignant tumour, which paralels the genetic progression model that has been demonstrated in other tumours [3]. In addition, HCC may evolve from recently defined subclasses of adenomas [4, 5]. In less than 10% of cases, HCC occurs in a normal liver. There remains uncertainty about the cell of origin, which can either be a liver stem cell or a mature hepatocyte. HCC may be regarded as a heterogeneous disease and a molecular classification system has yet to be described [6]. Some hepatocellular carcinomas contain biliary type cytokeratins (CK7 and/or CK19) positive cells, which may point to a progenitor cell origin; these cases have a poor prognosis [7]. Fibrolamellar HCC—occurring in young patients without risk factors—are rare variants that are usually excluded from HCC therapeutic trials, because of their slow growing nature and significantly better prognosis. The incidence of hepatocellular carcinoma is rising worldwide due to the HBV and HCV epidemics and the successful treatment of other complications of cirrhosis. The individual risk may differ and relates to the accumulation of...
risk factors, which forms the basis for surveillance programs of HCC. Some risk factors are related to the cause(s) of liver disease (HBV, HCV, alcohol, iron overload, fatty liver), the severity of the liver disease (advanced fibrosis), epidemiological factors (male gender, age, obesity, diabetes) or pathological findings on liver biopsies (dysplastic lesions). Unlike many other cancers, HCC is a preventable disease and there remains an unmet need for implementing programs in the prevention, vaccination, early diagnosis and treatment of liver disease [8]. Surgical therapy, including resection and liver transplantation, remains the primary curative treatment option in early hepatocellular carcinoma. Unfortunately, no more than 30% of patients are candidates for curative therapeutic strategies, and the majority face a rather poor outlook.

Several clinical guidelines are available, which are endorsed by societies involved in clinical care and research in HCC [9, 10]. In order to master this rapidly evolving field, clinicians need more than minimal guidelines and this is the stage where the expert comes in. This article summarizes the expert discussion on the management of HCC, which was organized during the 10th World Gastrointestinal Cancer Congress in June 2008 in Barcelona, Spain. Opinion leaders and experts from different nationalities, selected on scientific merit, participated in the discussion. In preparation of this discussion, a questionnaire was sent to all participants and the questions, answers and conclusions were rediscussed at the meeting. Expert committee reports reflect clinical experience in addition to evidence-based medicine. By this strategy the authors hope to help clinicians in the difficult task of making treatment choices in daily clinical practice.

Multidisciplinary groups should decide on the optimal diagnosis, staging and treatment of the individual patient. These teams should involve expert physicians in hepatology, gastrointestinal oncology, hepatobiary surgery, liver transplantation, liver pathology, abdominal and interventional radiology. The experts considered the input of a psychologist or social worker equally important.

**diagnosis**

The diagnosis of hepatocellular carcinoma is based on the combination of clinical, laboratory, imaging and pathology examinations. Diagnostic confirmation and assessment of tumour extent are essential for the management of patients. HCC shows a variety of imaging features that reflect the variable pathological characteristics of this tumour. The cirrhotic liver harbours large regenerative nodules and dysplastic nodules (DNs), which may be indistinguishable from small HCCs on ultrasound. The vascular supply to the lesion represents the key pathologic factor for differential diagnosis that is also reflected in imaging characteristics. Through the progression from low-grade DN to high-grade DN and finally early HCC, there is a development of arteries which become the dominant blood supply [11]. This neo-angiogenesis allows the imaging diagnosis of HCC. Although ultrasonography (US) by an experienced physician is widely accepted for tumour surveillance in patients at risk for HCC, spiral computed tomography (CT) or magnetic resonance (MR) imaging are required for diagnostic confirmation and intrahepatic tumour staging. A standard CT-protocol for HCC should include unenhanced and contrast-enhanced images obtained in the arterial, portal-venous and delayed phase [12]. In experienced hands, contrast-enhanced ultrasound may be used to confirm the diagnosis of HCC [13, 14]. The typical characteristics and performance of the different imaging techniques for the diagnosis of HCC are summarized in Table 1.

Unlike many other cancers, it is possible and accepted to make the diagnosis of HCC in a cirrhotic liver by non-invasive clinical criteria (imaging and alpha-foetoprotein [AFP]), but identifying a small (<2 cm) HCC in a cirrhotic liver represents a true challenge [15, 16]. This is an increasing problem due to the implementation of surveillance programs of patients at risk for HCC. In the case of very small lesions (<1 cm) the experts suggest the measurement of AFP and imaging follow-up at 3-month intervals. For lesions between 1 and 2 cm or atypical imaging characteristics, clinicians should consider to obtain pathological proof [9, 10]. New MRI-techniques are under investigation (e.g. diffusion weighted imaging), which may improve the specificity of current imaging [17].

Alfa-foetoprotein is the only serological marker commonly used in diagnosis, but has a poor sensitivity ranging from 39% to 65% and a specificity ranging from 76% to 97% [18]. This high variability relates to the different cut-offs used in various (retrospective) studies. At values over 200 IU/ml AFP is reliable as tumour marker, but the percentage of patients with such high levels is very small. The experts considered AFP of limited value in surveillance of cirrhotic patients, but a consistent rise in AFP may warrant a shortened interval of follow-up examinations.

**comments on tumour biopsy of a suspicious lesion**

The expert panel felt that every decision on biopsy of a focal liver lesion should be discussed by the multidisciplinary team, including a hepatobiliary and transplant surgeon. There is a risk of tumour seeding that varies between 0% and 11% [19]. A major risk factor for seeding is a percutaneous biopsy of a subcapsular lesion. There is no indication for biopsy of a focal lesion in a cirrhotic liver when the patient is: (i) not a candidate for any form of therapy because of serious co-morbidity; (ii) in case of decompensated cirrhosis and the patient is on the waiting list for liver transplantation and (iii) when the patient is a candidate for resection that can be performed with an acceptable morbidity and mortality risk. In the future, it is anticipated that obtaining tissue for molecular studies and targeted therapy will be increasingly important in HCC.

**staging**

Staging of HCC is considered crucial for planning of optimal therapy and includes assessment of tumour extent, liver function, portal pressure and clinical performance status [10]. Relevant techniques to evaluate tumour extent include contrast-enhanced MRI or helical CT; chest CT and a bone scan should be considered in advanced disease. Liver function is assessed by the Child-Pugh scoring system. The finding of oesophageal varices signifies clinical significant portal hypertension, which can also be measured by the transjugular
Table 1. Characteristics and performance of imaging modalities for the diagnosis of hepatocellular carcinoma [12, 13, 14, 15, 36]

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<th>Imaging modality</th>
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| Ultrasound                    | ● Hypoechoic, isoechoic, or hyperechoic mass in comparison with the surrounding liver parenchyma  
   ● Margins: sharp or irregular  
   ● Hyperechoic pattern of small HCC may reflect fatty change or dilated (‘peliotic’) changes of tumour vascular spaces  
   ● Doppler US techniques may show arterial hypervascularity and/or pulsatile flow with arterial waveform, especially in larger lesions | ● Lesion sensitivity: 20–72% (in seven series that reported the correlation between pretransplantation US and pathologic examination of explanted liver) [12] |
| Ultrasound contrast agents    | ● HCC shows a strong intratumoural enhancement in the arterial phase (within 25 to 35 s after the microbubble contrast injection) followed by rapid washout with an iso- or hypoechoic appearance in the portal venous and delayed phases  
   ● Large regenerative nodules and DNs usually do not show any early contrast uptake and resemble the enhancement pattern of liver parenchyma | ● In comparison with spiral-CT the sensitivity of contrast-US in the detection of arterial hypervascularity was 97% in lesions >3 cm, 92% in lesions ranging from 2 to 3 cm, 87% in lesions from 1 to 2 cm, and 67% in lesions <1 cm [13] |
| Contrast enhanced CT          | ● Typical HCC-lesion: hypervascular pattern, with enhancement in the arterial phase and rapid washout in the portal venous and delayed phases  
   ● Larger tumours: the presence of a tumour capsule, an internal mosaic architecture or invasion of portal vein branches may support the diagnosis of HCC | ● CT remains relatively insensitive for the detection of tiny HCC lesions. In six series that reported careful lesion-by-lesion imaging-pathologic correlations in explanted livers, the sensitivity of spiral-CT in detection of HCC lesions ranged from 52% to 79% (reviewed by Lencioni et al. 2005 [12]). Only 10–43% of lesions smaller than 1 cm and 44–65% of lesions of 1–2 cm were identified. |
| Dynamic MRI                   | ● The variable characteristics in tumour architecture, grading, and stromal component as well as intracellular content of fat, glycogen or metal ions, greatly affect the appearance of the lesion on baseline T1-weighted and T2-weighted MR images  
   ● Well-differentiated HCC: T1-hyperintense, T2-isointensity  
   ● Moderately-poorly differentiated HCC: T1-hypointense, T2-hyperintense  
   ● Dynamic MR imaging demonstrates the typical vascular features of overt HCC (arterial phase enhancement with portal venous phase washout) | ● MR imaging remains relatively insensitive for the detection of tiny HCC nodules. In series in which MR imaging findings were correlated with histopathologic results after thin-section slicing of the explanted liver, lesion-by-lesion analysis revealed a sensitivity of 33–78%, with positive predictive values ranging from 54 to 90%. Only 4–71% of lesions <1 cm and 52–92% of lesions of 1–2 cm were identified (reviewed by Lencioni et al. 2005 [12]) |

route (hepatic-venous pressure gradient >12 mmHg). Several staging systems—incorporating some or all of the above mentioned items—have been developed, but there is no worldwide consensus on a particular system. No staging system was considered as ‘the best’, as every system has advantages and drawbacks. The Cancer of the Liver Italian Program (CLIP)-score has shown to be of particular value in advanced cases in a French population [20, 21]. The pTNM system is based on the pathology report and may be extremely relevant to stratify patients for studies on adjuvant treatments. The Barcelona-Clinic-Liver-Cancer (BCLC) staging system links staging of HCC in cirrhosis with treatment modalities [22]. The BCLC-system is widely used and encompasses all HCC patients. The system identifies those patients with early HCC who may benefit form curative therapies (stage 0 and A), those at intermediate (stage B or C) or advanced stage who may benefit from palliative treatments, and those with a very poor life expectancy (stage D). A staging algorithm, largely based upon the BCLC-system is given in Figure 1, with two important modifications. Portal hypertension is taken out of the algorithm and gives more freedom regarding the clinical decision concerning resection. In addition, patients with poor liver synthetic function (Child-Pugh C) and a limited tumour should in our opinion not be denied the possibility of liver transplantation (and are therefore not classified as terminal stage as is the case in the original BCLC-system).

**criteria for radical (curative) therapies**

Radical treatments include surgery, local destruction techniques (radiofrequency ablation [RFA] or percutaneous ethanol injection [PEI]) and liver transplantation. There are no randomized trials comparing the efficacy of these three approaches and all evidence is based on cure rates in patient series. Resection is the preferred treatment in cases without advanced fibrosis, as long as an R0-resection can be performed.
that support one of these options. In addition, there are no randomized controlled trials available of tumour progression and to offer a ‘bridge’ to transplant. transarterial chemoembolization in order to minimize the risk of tumour and the underlying liver disease. Criteria have been put forward that guarantee a 5-year disease-free and overall survival of more than 70%. The Milan-criteria include patients with less than three nodules less than 3 cm in size or a solitary lesion less than 5 cm [27]. Criteria should not be followed as a dogma, but are subject to local (multidisciplinary) decisions within a (supra)national framework that defines priority rules (e.g. Eurotransplant, United Network for Organ Sharing [UNOS]) and are in evolution [28]. Due to organ shortage, liver transplant candidates are confronted with long waiting times, which may be associated with tumour progression beyond the Milan-criteria. In the case of a long anticipated waiting time (>6 months) patients may be offered resection, local ablation or transarterial chemoembolization in order to minimize the risk of tumour progression and to offer a ‘bridge’ to transplant. Unfortunately, no randomized controlled trials are available that support one of these options. In addition, there are no adjuvant therapies of proven benefit that reduce the chance of tumour recurrence following a radical strategy. However, the STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) international trial opened to accrual August 2008. The target enrollment for this randomized placebo controlled international multicenter study is 1100 patients and will include patients who have received surgical resection or local ablation. The primary endpoint of the study is recurrence-free survival in patients who receive sorafenib 400 mg BID for up to 4 years.

**palliative treatments**

Palliative treatments include transarterial chemoembolization (TACE), systemic therapy and radiotherapy. These therapies are offered with the intention to improve survival or to maintain quality of life without the prospect of cure. Although primarily intended for patients with advanced stage HCC, these techniques may be used with success in patients with early stage HCC who have contraindications for radical therapies.

**transarterial chemoembolization (TACE)**

TACE includes the selective injection through the hepatic artery of antineoplastic agents (e.g. cisplatin, doxorubicin, mitomycin), together with selective obstruction of tumoral feeding vessels (e.g. with coils, gelatine sponge particles). TACE yields response rates of 35–42% and prolongs life in comparison with best supportive care in selected patients with intermediate advanced HCC (Child-Pugh A, no portal invasion or extrahepatic metastases) [29, 30]. The most common side-effect is a post-embolization syndrome, characterized by fever, abdominal pain and risk of liver failure. The latter risk is minimized by the exclusion of patients with poor liver function or thrombosis of the portal vein.

There is no agreement on a standard technique or protocol. More recently, results have been presented of a multi-center trial in a heterogenous population of early and advanced HCC, comparing TACE with doxorubicin eluting beads versus classical TACE, which represents the first major effort of standardizing the technique [31]. The interim results showed a similar response rate (50%) at 6 months, but the group with the drug eluting beads had less systemic side effects due to a reduced systemic exposure to doxorubicin.
systemic therapy
Systemic therapy with classical cytotoxic drugs (doxorubicin or cisplatin chemotherapy) yields low objective response rates (<10%) without proven survival benefit. In addition, chemotherapy is poorly tolerated, due to underlying cirrhosis, coexisting cytopenias and unpredictable pharmacokinetics (altered activity of drug metabolizing enzymes, fluid retention).

Recently, the results of a randomized, placebo-controlled, double-blind phase III study with the multitargeting inhibitor sorafenib were reported, representing a breakthrough in the field [32]. Sorafenib is an oral drug which blocks PDGF-, VEGF-, c-Kit- and rat signalling, both on the tumor cell and the surrounding endothelial cells. Six-hundred and two patients with advanced HCC, no prior systemic treatment and good liver synthetic capacity (Child-Pugh A) were randomized between sorafenib 400 mg bid or placebo. Sorafenib was well tolerated and yielded a statistically significant relative improvement (44%) in overall survival. Median survival increased from 7.9 to 10.7 months (hazard ratio 0.69, 95% CI 0.55–0.87). Side-effects include hand–foot skin reaction, diarrhea and fatigue, but sorafenib was not found to be toxic to the liver. A similar benefit of sorafenib was demonstrated in a subsequent Asian randomized controlled trial. Sorafenib should be restricted to patients with an inoperable HCC, good liver synthetic function (Child–Pugh A) and who are not good candidates for TACE. Patients should be evaluated by imaging every 3 months. There was no consensus among the experts regarding treatment beyond progression. For patients with end-stage disease with heavily impaired liver function or a poor performance status (due to the tumour involvement of the liver) only symptomatic treatment is advocated, as they will die within 6 months [9, 10].

In case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials. Outside clinical trials, chemotherapy is a possible option in young and fit patients with rapid disease progression (GEMOX, FOLFOX, doxorubicin, 5-FU/ capecitabine...), even though no clear data on activity/efficacy are available. There is no support for the therapeutic use of tamoxifen in advanced HCC [33].

radiation therapy
The intrahepatic application of radioactive (e.g. Yttrium-90) microspheres via the hepatic artery allows locoregional therapy of multifocal HCC, even in the presence of portal vein thrombosis [34]. The technique was found to be safe in selected patients with preserved liver function, but randomized phase II studies are lacking to judge efficacy.

Three-dimensional conformal radiotherapy makes it possible to direct high dose radiation to HCC with sparing of the surrounding non-tumoral liver parenchyma and represents a promising powerful technique which needs further validation [35].

research agenda
The future is brighter for patients and clinical researchers in HCC, fueled by many challenges in the diagnostic and therapeutic field. The use of new imaging techniques (such as diffusion-weighted magnetic resonance imaging) should be investigated for the characterisation of lesions in cirrhotic livers. More work needs to be done on the molecular profiling of HCC, to define prognostic subgroups and therapeutic targets.

There is an unmet need for trials on the use of sorafenib and other new targeted agents in the adjuvant and palliative setting (including ‘less fit’ patient groups). Predictive markers need to be identified to limit this costly therapy to those patients that are most likely to benefit. We need better criteria by new imaging techniques to evaluate tumour efficacy for drugs that may induce no tumour shrinkage by standard criteria. Physicians all over the world that are caring for patients with HCC, should be encouraged to enter their patients in clinical trials.

conflict of interest
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