

ARTICLE

Natural history of hepatocellular carcinoma

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Abstract

The natural history of hepatocellular carcinoma is variable. In many patients the tumor has a long-lasting subclinical incubation period and often grows as a solitary mass to a size at which it can be detected by ultrasound. In other patients, however, the onset of the tumor is multinodal with great variations in the growth rates. Prognostication of patients with hepatocellular carcinoma takes into account the size and number of tumor nodes and their relation to the portal veins, and the degree of liver impairment.

Keywords: *Hepatocellular carcinoma (HCC); cirrhosis; abdominal ultrasound; computed tomography; magnetic resonance; alpha-fetoprotein.*

Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, due to its high incidence (approximately 600 000 new cases in 2000), and high rates of mortality^[1]. The identification that chronic liver disease is the relevant risk factor for this tumour, has made surveillance campaigns aimed at early detection of HCC possible and surveillance is now universally recognised to be the practical approach for improving treatment of HCC patients^[2]. The few cases (less than 5%) of HCC that do not develop on the background of chronic liver disease present late and usually have poor chances of cure^[3]. The understanding of the natural history of HCC is hampered by the variability of the tumour, which is influenced by the co-occurrence of multiple co-morbidity factors in the same patient as well as by the presence of multiple distinct cell lines in the liver that may develop into liver cell cancer^[4].

Early cancer

The concept of early cancer has been evolving during the last two decades. Surveillance of patients with

cirrhosis has led to an increasing number of cancers detected early in the form of small nodules that first appear as well-differentiated tumours and proliferate along with gradual dedifferentiation^[5]. A sizable number of tumours arising in cirrhotic livers seem to occur in a multicentric distribution and a certain proportion of them may arise from dysplastic nodules^[6]. HCCs ranging from 1 to 2 cm in size may present with a fibrous capsule and/or fibrous septa in contrast with other indistinct nodular small cancers that have indistinct margins despite the fact that such tumours are clearly detected as hypoechoic or hyperechoic focal lesions on ultrasound (US) examination. The latter have been considered as 'carcinoma *in situ*' of the liver due to the absence of invasion into the portal vein branches and intrahepatic metastases^[7]. Minute HCCs of the indistinct nodular type are difficult to differentiate from high grade dysplastic nodules. The majority of small (less than 1.5 cm) HCCs of the indistinct nodular type are not detected as hypervascular tumours by contrast imaging, whereas distinct nodular type tumours almost invariably show hypervascular features during the arterial phase of contrast imaging. A combination of the lack of fibrosis capsule and reduced number of unpaired arteries per

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square millimetre in tumours measuring less than 1.5 cm accounts for many false negative diagnoses of HCC with contrast imaging.

Tumour prognostication

The outcome of curative treatments is greatly influenced by accurate staging of HCC. Tumour dedifferentiation and vascular invasion by tumour cells have constantly emerged as independent predictors of shortened survival in patients undergoing hepatic resection or transplantation for HCC. As the size and number of HCC nodes are the best clinical surrogates predicting tumour dedifferentiation and vascular invasion, survival of HCC patients is predicted by criteria combining tumour characteristics, functional status and liver function. In the Barcelona Clinic Liver Cancer (BCLC) staging classification, the functional status of the patient and the liver status are measured by the Performance Status and Child-Pugh score system, respectively^[8]. The Barcelona classification comprises four stages that select the best candidates for the best therapies available, i.e. from early tumour stage (Stage A), which includes asymptomatic patients with small tumours suitable for radical therapies, to late tumour stage (Stage D), which includes patients with untreatable disease (Table 1).

Table 1 *The Barcelona Clinic Liver Cancer Staging Classification of patients with hepatocellular carcinoma*^[8]

Staging	Performance status	Tumour stage	Child-Pugh
(A) Early	0	Single <5 cm, 3 nodes <3 cm	A & B
(B) Intermediate	0	Large/multinodular	A & B
(C) Advanced	1–2	Vascular invasion extrahepatic spread	A & B
(D) End-stage	3–4	Any of the above	C

The Cancer of the Liver Italian Program (CLIP) system allocates points for four variables that affect prognosis including Child-Pugh stage, tumour morphologic features (single, multiple or massive tumour), serum alpha-fetoprotein (AFP) level and portal vein thrombosis (Table 2)^[9]. Although this scoring system has been partially validated and is easy to use, the CLIP score has suboptimal sensitivity for tumour invasiveness, since patients with a score of 0 may have from 0% to 50% of their liver replaced by HCC. Since the score is definitively skewed towards more severely affected patients whose disease is not amenable to curative treatment, too many patients with a CLIP score of 0 will not meet currently accepted criteria for surgery or locoregional ablation of the tumour which have been proven to be efficacious in patients in whom there is one tumour node of less than 5 cm in size^[2]. In recent years, other staging systems have been proposed including the Chinese University

Prognostic Index^[10], the modified TNM^[11], a French scoring system^[12] and a German score system^[13]. Since staging scores developed thus far reflect differences in demographic features of the patients seen locally, expertise and treatment algorithms adopted in different centres, one wonders whether it is worth attempting to reach consensus on a single model for staging HCC. From a clinical point of view, it appears mandatory that prognostication of liver cancer should always incorporate treatment-dependent variables^[14].

Table 2 *Cancer of the Liver Italian Program (CLIP) staging classification of hepatocellular carcinoma (CLIP 1998)*

Score	Tumour morphology	Child-Pugh	AFP ($\mu\text{g}/\text{dl}$)	Vascular invasion
0	Uninodular <50% of the liver	A	<400	No
1	Multinodular >50% of the liver	B	>400	Yes
2	Massive	C	—	—

Natural history of the tumour

The tumour size when HCC is first detected does not predict the course of the disease in all cases. In fact, the median time of doubling volume for a small HCC may range from 1 to 20 months^[15]. The tumour is a clinically indolent disease during the early phases of growth, whereas in advanced stages it often presents with painful hepatomegaly and/or jaundice. In the majority of patients with compensated cirrhosis under surveillance, HCC is first detected as a single node (Table 3). The multinodular pattern of the tumour appears to be more common in patients with multiple aetiological factors than in those with a single aetiological factor^[20]. Primary and secondary HCCs may be differentiated by matching radiological and histopathological findings on explanted or resected livers, only. Distinction between these two conditions bears important clinical implications, since second primary tumours appear to be less aggressive than metastatic tumours and recur less frequently after ablation than the former tumours^[21]. The growth pattern of HCC varies greatly from one tumour to another and may have clinical implications, since it influences the choice and outcome of treatments. Slowly expanding tumours^[22] are more commonly seen in Caucasian and Asian patients than in South African patients who have more fast growing, replacing type tumours^[23]. Further complicating the assessment of tumour course is that some HCC nodes have constant rates of growth during follow-up, while others either have a declining growth rate in the late phases of follow-up or, after an initial phase of resting, increase in volume exponentially^[15]. This great diversity of the tumour growth patterns makes the predictive power of the size of the tumour at diagnosis not absolute and explains why prognostication in HCC

Table 3 Prevalence of single, small nodes of hepatocellular carcinoma (HCC) detected during surveillance programs with abdominal ultrasound (US) of patients with compensated cirrhosis

Study	Patients with cirrhosis	US periodicity (months)	HCC × year (%)	Single HCC <5 cm (%)
Oka <i>et al.</i> 1990 ^[16]	140	3	6.5	82
Colombo <i>et al.</i> 1991 ^[17]	447	12	3.2	54
Cottone <i>et al.</i> 1994 ^[18]	147	6	4.4	83
Bolondi <i>et al.</i> 2001 ^[19]	313	6	4.1	80

patients can more reliably be obtained by combining tumour size with liver function.

One controversial issue that has important clinical implications is the presence of microscopic vessel invasion by the tumour that is considered direct evidence of intrahepatic metastasis. Although macroscopic venous invasion seen with CT or MR scans is a well-established prognostic indicator and is one of the variables in the pathologic staging of HCC, the clinical significance of microscopic venous invasion in patients with operable HCC, remains unclear. Patients with microscopic venous invasion have higher serum levels of AFP, a larger tumour size and more nodules lacking a fibrous capsule^[24]. Interestingly, up to 40% of explanted tumours less than 2 cm show microscopic venous invasion, a feature that overestimates the actual risk of tumour recurrence in patients with tumours less than 5 cm undergoing liver transplantation^[24,25].

Treatment of early cancer as part of the natural history of HCC

With better understanding of the natural history of HCC, management of patients with this tumour has greatly improved worldwide. To this end, surveillance with abdominal ultrasound has been of strategic importance, since advances in HCC management can only come from treatment of early diagnosed small tumours. The re-analysis of a cohort of 417 HCC-free patients with compensated cirrhosis who had been under prospective surveillance for 148 months, showed a fall in liver-related mortality rates in HCC patients identified between 1997 and 2001. Mortality rates fell from 45% in the first quinquennium (1986–1991) to 37% in the second (1991–1996) and 10% in the third (1997–2001) (first vs. second, ns; first vs. third, $p = 0.0009$; second vs. third, $p = 0.018$) in parallel with a reduction in yearly mortality of treated patients (34%, 28% and 5%; first vs. second, ns; second vs. third, $p = 0.036$; first vs. third, $p = 0.0024$)^[26]. During the last quinquennium of surveillance, there was a shift of more patients from surgery towards the less aggressive locoregional ablative techniques, favoured by the application of stringent criteria for patient selection for hepatic resection and the limited availability of donated organs for treating HCC with liver transplantation. In addition, fewer patients with

a single small tumour were left untreated or missed radical treatments compared to previous periods (46% vs. 38% vs. 26%), and fewer patients treated with hepatic resection or locoregional ablative therapies died of causes unrelated to cancer (35%, 25%, 0%). The gain in survival of cirrhotic patients developing a HCC during the last 5 years was likely to be the consequence of improved management of the tumour and complications of cirrhosis.

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