Staging of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is different from other malignancies because the prognosis in HCC is not only dependent upon the tumor stage but also on the liver function impairment due to accompanying cirrhosis liver. Various other staging systems used in HCC include the European systems [French staging system, Barcelona Clinic Liver Cancer (BCLC) staging system and the cancer of the liver Italian program (CLIP)] and Asian systems [Okuda staging system, Japan integrated Staging (JIS), Tokyo score and Chinese University Prognostic Index (CUPI)]. Out of all the staging systems used in HCC, Barcelona Clinic Liver Cancer (BCLC) staging system is probably the best because it takes in to account the tumor status (defined by tumor size and number, presence of vascular invasion and extrahepatic spread), liver function (defined either by the Child-Pugh's class) and general health status of the patient (defined by the ECOG classification and the presence of symptoms). Since most of the extrahepatic spread in HCC occurs to lymph nodes, lungs and bones, the assessment can be done with either PET/CT or a combination of CT (Chest and abdomen) and a bone scan. This article describes the various staging systems used in HCC, guides choosing a staging system particularly in the Indian context and the assessment of extra-hepatic spread in HCC. (J Clin Exp Hepatol 2014;4:S74–S79)

Staging

Staging of patients with hepatocellular carcinoma (HCC) is important both for the prognostication and deciding about the treatment. Staging in HCC also helps to know the impact of conventional or investigational treatment and to design the prospective trials.[1]

HCC is different from other malignancies because in this tumor the prognosis not only depends upon the tumor stage (like in other malignancies) but also on the liver function impairment due to underlying cirrhosis liver, which accompanies most of the patients.[1] General condition of the patient and the treatment given to the patient also determines the prognosis in a particular patient.

Various parameters have been studied to be of prognostic usefulness in patients with HCC. These include parameters related to the patient demographics like age, gender and general health of the patient. Liver function tests like estimation of bilirubin and albumin are important prognostic variables in HCC as are the presence of ascites or encephalopathy. Tumor characteristics are also important determinants of prognosis which include tumor stage, number (single, multicentric), growth rate and aggressiveness of the tumor, vascular invasion and extrahepatic spread of tumor, presence of tumor markers and receptors and finally the treatment given to the patient.[1] Recently various molecular markers (biomarkers) have also been shown to be of prognostic importance in patients with HCC.[2] Out of the various biomarkers, alpha feto protein (AFP) has been studied in detail and has a role both in diagnosis and prognosis of HCC.[3]

Other biomarkers include cellular malignancy phenotype related markers like DNA ploidy, cellular proliferation markers (PCNA, Ki 67 etc), p53 gene, tumor promoter genes (ras, c-myc), apoptosis related markers like Fas and Fas ligand, cell adhesion and extracellular matrix related markers like adhesive molecules (E-adherin, catenins, SICAM etc), angiogenesis related markers like vascular endothelial growth factor (VEGF), platelet derived–ECGF, intra tumor vascular density (ITVD) and genomics and proteomics related markers.[2]

All above-mentioned prognostic markers can be used either singly or as combination of various markers. Used singly these markers have less prognostic value in comparison to multiple prognostic criteria. The parameter which look at only one aspect of prognosis e.g. Child-Pugh classification for liver function, TNM staging system[4] for tumor stage and performance status for general well being of patient[5] have limited usefulness because the prognosis in HCC would depend on combination of these factors rather than on one parameter. Treatment given to the patient is an important determinant of prognosis, which in turn depends whether patient presents in early or advanced stage.[1]

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Abbreviations: AJCC: American Joint committee on cancer; BCLC: Barcelona clinic liver cancer; CLIP: cancer of the liver Italian program; CUPI: Chinese University prognostic index; ES: extra-hepatic spread; HCC: hepatocellular carcinoma; ITDV: intra tumor vascular density; LCSGJ: liver cancer study group of Japan; OLT: orthotopic liver transplant; TNM: tumor-node-metastasis; VEGF: vascular endothelial growth factor
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STAGING SYSTEMS IN HEPATOCELLULAR CARCINOMA

Many staging systems have been used to provide a clinical classification in patients with HCC and as mentioned earlier the best system would be that take in to account the tumor status (defined by tumor size and number, presence of vascular invasion and extrahepatic spread), liver function (defined either by the Child-Pugh's class or individually by the levels of serum bilirubin and albumin, presence of ascites and portal hypertension) and general health status of the patient (defined by the ECOG classification and the presence of symptoms). Various staging systems used in HCC include the European systems [French staging system,[6] Barcelona Clinic Liver Cancer (BCLC) staging system[7] and the cancer of the liver Italian program (CLIP)[8]], Asian systems [Okuda staging system,[9] Japan integrated Staging (JIS),[10] Tokyo score[10] and Chinese University Prognostic Index (CUPI)[11]].

Okuda for the first time used the combination of tumor variables (Tumor size < or > 50%) and liver functions (ascites, albumin, bilirubin) and divided the patients into three stages (Table 1).[9] Stage I patients have better prognosis in comparison to stage II & III with a median survival of 8.3 months, 2 months and 0.7 month respectively in untreated HCC patients.[9] The drawback of Okuda staging is that, it is useful mainly for patients with advanced stage and fails to adequately differentiate early from advanced stage. It does not take into account other tumor variables like the multicentricity of the tumor, vascular invasion, and the extrahepatic spread.[12] Japan integrated Staging (JIS),[10] which utilizes the assessment of liver damage by the liver cancer study group of Japan (LCSGJ) or Child-Pugh stages and combines it with TNM stage and is considered a useful staging of HCC in Japan. LCSGJ which was originally designed for patients undergoing hepatectomy, takes in to account the same parameters as used in Child-Pugh class except that the hepatic encephalopathy is replaced by the ICG retention at 15 min. JIS has been recently refined as bm-JIS by including biomarkers (AFP, DCP, AFP-L3).[13]

French staging[6] divides the patients into three stages (A, B, C) on the basis of performance status, serum bilirubin, serum alkaline phosphatase, serum alpha feto protein and portal vein obstruction on ultrasound (Table 2).

Table 2 French Staging of HCC.

Parameter	0	1	2	3
Karnofsky index	≥80			<80
Serum bilirubin (μmol/l)	<50			≥50
Serum alkaline phosphatase (ULN^2)	<2		≥2	
Serum alfa fetoprotein (μg/l)	<35		≥35	
Portal obstruction (ultrasonography)	No	Yes		

Patients in Stage A (score 0) have higher survival in comparison to stage B (Score 1–5) who have intermediate risks of death, and stage C (Score ≥ 6) who have the worst survival.[6] BCLC staging system[7] is the treatment based staging system where the patient in early stage (Stage A) are offered the curative treatment of either hepatic resection or orthotopic liver transplant (OLT) (Figure 1). The tumors in this stage are either single <5 cm or 3 nodules of <3 cm with good performance status and have 50–75% 5-year survival. Patients exceeding these limits are in intermediate stage (Stage B) and have 50% 3-year survival. Patients with advanced stage (Stage C) have vascular invasion or extrahepatic spread with poor performance status and their 3-year survival drops down to 10%. Patients in Stage D have a grim prognosis unless they are fit for liver transplantation.[7] CLIP staging is the most recent staging system[8] that takes into account the Child-Pugh status of the patient with tumor characteristics including the portal vein thrombosis and levels of AFP (Table 3). Patient have scores ranging from 0 to 6, CLIP—0 patient having a better prognosis than those patients with CLIP—6 score.

Recommendation

Staging system for HCC should take into account tumor stage, liver function and physical status and the impact of treatment (Level of evidence—2a).

CHOOSING THE STAGING SYSTEM

There have been many studies comparing various staging systems in HCC and have found variable results. The difference in results are predominantly dependent on the difference in the tumor characteristics, whether the disease

Table 1 Okuda Staging of HCC.

	Tumor size		Ascites		Albumin		Bilirubin	
	>50%	<50%			<3 mg/dl	>3 mg/dl	>3 mg/dl	3 mg/dl
Stage	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
I	(−)		(−)		(−)		(−)	
II	1 or 2 (1)							
III	3 or 4 (+)							

Staging