Treatment Algorithms for Managing Hepatocellular Carcinoma

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Treatment

Early diagnosis and aggressive therapy improves outcome in hepatocellular carcinoma (HCC). Several potentially curative as well as palliative treatment options are available for patients. The choice of therapy is influenced by factors such as extent of tumor and severity of underlying liver dysfunction as well as availability of resources and of expertise. A systematic, algorithmic approach would ensure optimal therapy for each patient and is likely to improve outcomes. Even after receiving therapy for HCC, patients remain at risk for recurrent HCC as well as progression of underlying cirrhosis. Proper assessment and monitoring is needed for the underlying liver disease, which may progress to liver failure and have a major impact on long-term survival. Comprehensive care for patients with cirrhosis includes interventions such as antiviral therapy for HBV and HCV, abstention from alcohol, management of fatty liver disease, endoscopic surveillance and treatment for complications of portal hypertension and, if indicated, immunization against HAV and HBV. An algorithmic approach is useful for choosing the most appropriate treatment option for the individual patient from among the various options that are available. The general consensus is that the BCLC system should be preferred for staging HCC as it is useful in predicting outcomes and planning treatment. The BCLC system classifies patients with HCC into five categories: very early, early, intermediate, advanced, and terminal. It incorporates data on tumor status (number and size of nodules, vascular invasion, extra-hepatic spread), liver function (CTP status, presence of portal hypertension) and overall health status (constitutional symptoms, cancer symptoms, performance status). Treatment allocation according to sub-class of patients is a merit of the BCLC system; a few limitations have been noted, particularly with respect to patients with BCLC stage B and C disease. The treatment algorithm as per BCLC system is summarized in this review. (J CLIN EXP HEPATOL 2014;4:S80–S89)

Abbreviations: AJCC–UICC: American Joint Committee on Cancer and Union for International Cancer Control; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; bm-JIS: biomarker JIS; CEUS: contrast-enhanced ultrasound; CLIP: Cancer of the Liver Italian Program; CTP: Child–Turcotte–Pugh criteria; CUPI: Chinese University Prognostic Index; EASL: European expert panel; EBRT: external beam radiotherapy; HCC: hepatocellular carcinoma; JIS: Japanese integrated system; LT: liver transplantation; MAA: macro-aggregate albumin; MCT: microwave coagulation therapy; MWA: microwave ablation; NCCN: National Comprehensive Cancer Network; PAI: percutaneous acetic acid injection; PEI: percutaneous ethanol injection; PLT: primary LT; RBV: ribavirin; RECIST: response evaluation criteria in solid tumors; RFA: radiofrequency ablation; SIRT: Selective Internal Radiation Treatment; SLT: salvage liver transplant; TACE: trans-catheter arterial chemo-embolization; TACE-DEB: TACE with drug eluting beads; TAE: transarterial embolization; TAI: trans-catheter hepatic arterial infusion; TARE: transarterial radio-embolization; TNM: Tumor-Node-Metastasis; WHO: World Health Organization

Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Typically, diagnosis is late and median survival following diagnosis is approximately 6–20 months.[1] This highlights need for early diagnosis and aggressive therapy in order to improve outcome in this.

Several potentially curative as well as palliative treatment options are available for patients with HCC (Table 1). Although surgical resection is the mainstay of therapy, this is possible in fewer than 5% of patients. The choice of therapy is influenced by factors such as extent of tumor and severity of underlying liver dysfunction as well as availability of resources and of expertise. A systematic, algorithmic approach would ensure optimal therapy for each patient and is likely to improve outcomes.

Even after receiving therapy for HCC, patients remain at risk for recurrent HCC as well as progression of underlying cirrhosis. Proper assessment and monitoring is needed for the underlying liver disease, which may progress to liver failure and have a major impact on long-term survival. Comprehensive care for patients with cirrhosis includes interventions such as antiviral therapy for HBV and HCV, abstention from alcohol, management of fatty liver disease, endoscopic surveillance and treatment for complications

Table 1 Treatments for HCC.

Surgical therapy	Local ablative therapy	Loco-regional therapy	Systemic therapy
Resection	Radiofrequency ablation (RFA)	***Trans-catheter therapy***	Systemic chemotherapy
Liver transplantation	Percutaneous ethanol injection (PEI)	Chemo-lipiodolization	Hormone therapy
	Percutaneous acetic acid injection (PAI)	Bland transarterial embolization (TAE)	Immune therapy
	Microwave ablation (MWA)	Transarterial chemo-embolization (TACE)	Molecular targeted therapy
	Cryoablation	TACE with drug eluting beads (TACE-DEB)	
	Irreversible electroporation	***Radiotherapy***	
	HIFU	Transarterial radio-embolization (TARE)	
	Photodynamic therapy	External beam radiotherapy (EBRT)	
		Stereotactic radiotherapy	

of portal hypertension and, if indicated, immunization against HAV and HBV.

The questions posed by the INASL taskforce were

- What should be the treatment algorithm based on the preferred staging system?
- How should the response to treatment be assessed?
- What should be the treatment algorithm for recurrence of HCC?

PREFERRED STAGING SYSTEM AND TREATMENT ALLOCATION FOR HEPATOCELLULAR CARCINOMA

To answer the first question, a word about the various staging systems that have been used for HCC is in order. Staging systems in cancer are generally used for prognostication but may also be useful for choosing appropriate therapy. HCC presents a unique situation among solid tumors where the staging system is required to assess risk from two life-threatening conditions present at the same time ie. cancer

and cirrhosis of the liver. Hence, it is understandable that any staging system used for HCC must incorporate prognostic indicators not only for tumor status but also for liver function and overall health status.[2] When choice of 'curative' therapies is being debated (eg. local ablation vs. resection vs. transplantation), more detailed anatomical information, as provided in the TNM staging system, as well as more accurate prediction of the risk of HCC recurrence, which is likely to be provided in the near future by biomarkers and molecular classification systems, is needed.

Over the years, several systems have been proposed for staging HCC including Okuda staging,[3] Pugh's modification of Child–Turcotte criteria (CTP),[4] TNM staging,[5] the French staging system,[6] the Cancer of the Liver Italian Program (CLIP),[1] the Chinese University Prognostic Index (CUPI),[7] the Japanese integrated staging system (JIS)[8] and biomarker JIS (bm-JIS),[9] Barcelona Clinic Liver Cancer (BCLC) staging,[10,11] etc. Different staging systems used for HCC are compared in Table 2. However, these staging systems have not been compared in randomized trials and recommendations rely on observational studies.

Table 2 Comparison of Staging Systems for HCC.

System	Tumor status	Liver function status	General health status	External validation	Remark
Okuda	**Yes**	No	No	No	May be useful in advanced HCC
Child–Turcotte–Pugh (CTP) criteria	No	**Yes**	No	No	Useful only for medically treated patients
Tumor-Node-Metastasis (TNM, AJCC)	**Yes**	No	No	**Yes**, for liver resection and LT	Pathology and operative details needed
Cancer of liver Italian Program (CLIP)	**Yes**	**Yes**	No	**Yes**	Includes PVT, AFP Useful at advanced stages, few effectively treated
Chinese University Prognostic Index (CUPI)	**Yes**	**Yes**	**Yes**	**Yes**	Useful at advanced stages, few effectively treated
Japanese Integrated System (JIS)	**Yes**	**Yes**	No	No	
Biomarker JIS (bm-JIS)	**Yes**	**Yes**	No	**Yes**	Includes AFP, DCP, AFP-L3
Barcelona Clinic Liver Cancer system (BCLC)	**Yes**	**Yes**	**Yes**	**Yes**	Treatment allocation as per sub-stage

Treatment