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Hepatocellular Carcinoma: Challenges in Indian Scenario

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ABSTRACT

Hepatocellular carcinoma (HCC), a leading solid organ malignancy is on the rise across the world, including India. Its incidence has almost tripled in the last 30 years and it is among the fastest growing malignancy in the USA. It is the third most frequent cause of death from cancer and the eighth most commonly occurring cancer in the world. A disease of multifactorial etiology, HCC poses many challenges. It demands multidisciplinary care involving diagnostic, medical and surgical inputs. A lot of research is ongoing in terms of attempts to improve its treatment and results thereof. Identification of some of the causative factors has resulted in efforts towards its primary prevention as well. Universal immunization against Hepatitis B virus is one such effort in this direction. Identification of role of various molecular pathways is leading to targeted drug developments offering personalized treatment to concerned patients. The authors have been involved in the diagnosis and management of this important liver cancer. This article summarizes the various challenges encountered in the diagnosis and management of HCC in India.

Keywords: Hepatocellular carcinoma (HCC), risk factors, staging of HCC, liver transplantation, transarterial chemoembolisation (TACE), transareterial radioembolisation (TARE), targetted therapy, sorafenib.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer related deaths worldwide (1). Significant advances have been made in our knowledge regarding the risk factors and pathogenic mechanisms of this tumor. However, the burden of this tumor continues to rise worldwide, and it is among the leading cause of death among patients with cirrhosis. The most common risk factors for HCC that have been identified in the Indian setting are viral Hepatitis B and C, alcoholic cirrhosis, non-alcoholic fatty liver disease (NAFLD) and aflatoxins (2). HCC develops in the setting of cirrhosis in 80-90%, which itself is a pre-neoplastic state. The treatment of HCC depends not only on the tumor characteristics itself, but also on the presence and stage of underlying cirrhosis. The development of preclinical models have shown the importance of molecular signaling pathways and angiogenesis in the pathogenesis of HCC (3). This has led to the use of molecular targeted therapy with agents such as sorafenib, a multikinase inhibitor, in the treatment of HCC (3, 4). Despite only a modest benefit in the overall survival with the use of sorafenib, its use in HCC has been an important milestone that has opened up the options of using newer molecular targeted therapies.

Epidemiology

HCC is the most frequent cause of all liver cancers and constitutes 90% of cancers of liver globally. The prevalence of HCC available in autopsy data of Dhir and Mohandas (Table 1) revealed that 0.2–1.9% of autopsy cases

Table 1 : Autopsy Date on HCC in India (5)

Place	Autopsies (No.)	HCC (%)
India		
Mumbai	**6000**	**0.2**
Mumbai	**4000**	**0.2**
Agra	**1234**	**0.7**
Guntur	**629**	**1.1**
Andhra Pradesh	**2789**	**1.6**
Chennai	**1218**	**1.9**

had HCC with a higher prevalence in southeastern states of India (5). The incidence of HCC in cirrhotics in India is 1.6% per year. The male:female ratio for HCC in India is 4:1. The age of presentation varies from 40 to 70 years. The age standardized mortality rate for HCC in India for men is 6.8/100,000 and for women is 5.1/100,000. The available data indicate that the age adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year, the highest being reported from Sikkim and Mizoram (6).

Patients with cirrhosis of liver of any cause are at a high risk for developing HCC, and almost 80% of HCC cases reported globally have underlying cirrhosis. Reports from tertiary care centres in India on HCC indicate that 70–97% of patients with HCC at the time of diagnosis had underlying cirrhosis of liver (7, 8). Long term cohort follow-up studies from Europe and USA indicate that annual frequency of HCC in HBV-cirrhosis, HCV-cirrhosis and alcohol-induced cirrhosis have been 2.2%, 3.8% and 1.7%, respectively (9, 10).

In a prospective observational study, patients with Child's A and Child's B cirrhosis without HCC at enrollment (n = 194) were followed up for a median duration of 44 months with ultrasonography and AFP at 6 month interval, and triphasic CT annually. During the follow-up, nine cases of HCC (all males) were detected with an annual incidence rate of 1.6% (95% CI—0.07–3) (11). The authors concluded that incidence rate of HCC among Indian patient with cirrhosis is intermediate between high rates in Japan for East and European countries (11). However, unpublished data from various tertiary care centres suggest that the incidence of HCC is increasing in India.

Risk Factors for Hepatocellular Carcinoma

In India HBV and HCV infection, overt cirrhosis of the liver and alcohol intake are the predominant risk factors for the development of HCC (12). The relative risk of developing HCC in Indian patients with chronic HBsAg infection was estimated to be 17.89 from various studies (13). Hepatitis B virus is known to cause genomic integration in the liver tissue resulting in chromosomal deletions and in turn metaplasia. The transactivating potential of HBx protein

can alter the p53 tumor suppressor gene (14-16). HCV-related carcinogenesis is possibly related to chronic inflammation and cirrhosis (17). Nalpas *et al* (18) reported a positive association between HCC and consumption of alcohol in which alcohol works as a cofactor for hepatotoxins and hepatitis viruses.

Alcohol acts as a cocarcinogen in the pathogenesis of HCC, by inducing cirrhosis, and by increasing the risk of viral infections (HBV and HCV). It also has as its effects on P450 mixed function oxidase system, thus causing enhanced activation of chemical carcinogens (15). Diabetic patients with NAFLD are at increased risk of advanced liver disease, cirrhosis and HCC. Diabetes and obesity can cause hepatic inflammation which leads to oxidative stress and lipid peroxidation of the phospholipid constituents of hepatocyte and intracellular membranes, resulting in hepatocyte injury and necrosis, and subsequently HCC (19). Diabetes mellitus was shown to increase the risk of primary liver cancers in the presence of other risk factors such as hepatitis C or B, or alcoholic cirrhosis (20).

Aflatoxins, a secondary metabolite produced by *Aspergillus flavusital* and *Aspergillus parasiticus*, are potent human carcinogens implicated in HCC (21) and also it is proved to have a significant association with HCC in India. Approximately about one quarter of HCC cases diagnosed in India do not have any known predisposing risk factors.

Tumor Staging

Tumor staging, the cornerstone in deciding the management approach in HCC, involves assessment of the extent of the disease, the presence and severity of underlying cirrhosis, its complications, and the performance status of the patient. Several prognostic factors have been identified that correlate with tumor burden and degree of liver dysfunction (22, 23). Several staging symptoms for HCC have been developed such as Barcelona Clinic Liver Cancer (BCLC) (24), Cancer of the Liver Italian Program (CLIP) (25), Groupe d'Etude et de traitement du Carcinome Hepatocellulaire (GRETCH) (26), Tumor-node-metastases system (TNM) (27), Chinese University Prognostic Index (CUPI) (28) and Japanese Integrated System (JIS) (29). Of these, the BCLC staging system is used

most commonly which allows stage-based treatment of HCC. A significant proportion of HCC patients in India are diagnosed at a late stage, which precludes curative treatment options.

Barcelona Clinic Liver Cancer (BCLC) Staging System

The BCLC staging incorporates tumor characteristics, severity of underlying liver disease, performance status, and a recommended treatment algorithm for each stage (Fig. 1). In addition, the BCLC system also provides an estimate of life expectancy based on treatment response (30). It categorizes the patients in to early HCC (stage 0 and A), intermediate stage HCC (stage B), advanced stage HCC (stage C) and end-stage HCC (stage D). Based on tumor stage, the treatment can be either curative or palliative. The curative treatment modalities include surgical resection, local ablative therapies such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), and liver transplantation, whereas the palliative treatment modalities include transarterial chemoembolization (TACE) or radioembolisation (TARE), and molecular targeted therapy with Sorafenib. Those with end-stage HCC

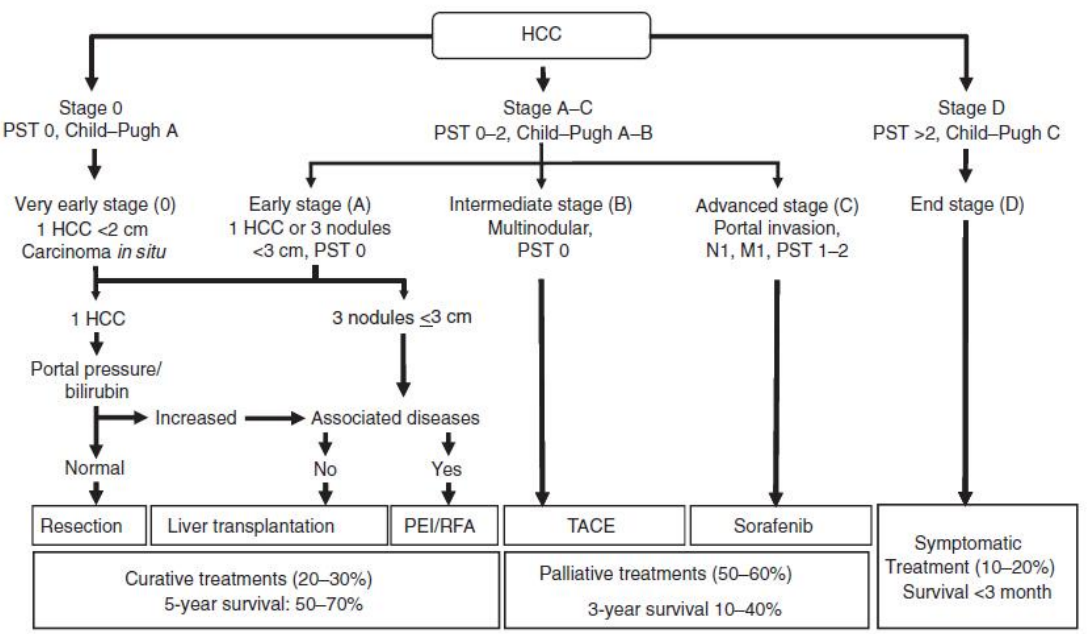

Fig. 1: The Barcelona Clinic Liver Cancer (BCLC) staging classification for the management of hepatocellular carcinoma (Adapted from Ref. 30).

are offered symptomatic treatment only. The therapeutic strategies based on HCC stage are discussed below in details.

Therapeutic Approaches based on HCC Stage

The management of HCC is largely guided by the tumor stage as defined by the BCLC criteria. Majority of HCC cases in India are diagnosed at a late stage that precludes curative treatment options.

Management of Early-Stage HCC (Stages 0 and A)

Early stage HCC can be treated by curative therapies such as surgical resection, local ablation, liver transplantation.

Resection: Patients with early stage HCC with Child's A cirrhosis can be treated with local resection as the risk of hepatic decompensation is low. However, the risk of tumor recurrence in the remnant cirrhotic liver can be as high as 70% at 5 years (31). It is important to evaluate the liver function carefully prior to liver resection so as to avoid post-resection liver decompensation.

Local Ablative Strategies: RFA and PEI are the two most common modes of local tumor ablation. Ablative therapies are useful for patients with small tumors who are poor surgical candidates, either because of impaired liver function or significant co-morbidities (32). RFA is the modality of choice; however, it is significantly more expensive as compared to PEI. RFA is not suitable for tumors in sub-capsular location. Also, it is less effective for tumors that are in close proximity to large blood vessels (due to the 'heat sink' effect that lowers the lethal heat needed for tumor coagulation). As PEI is less expensive, it continues to have its importance in India.

Liver Transplantation: Liver transplantation is often considered as the treatment of choice as it not only removes the tumor, but also removes the cirrhotic liver which itself is in a pre-neoplastic state. The 5-year tumor recurrence rate following transplantation is lower in early stage HCC as compared to resection (10-20% versus 70-80%, respectively). Liver transplantation is now a well established treatment modality in India. Its results in India are at par with the best in the world. Patient selection for liver transplantation is guided by several well described criteria of which "Milan criteria" is the most widely accepted (Table 2). Patients offered transplantation within Milan

Table 2: Criteria for selection of HCC patients for liver transplantation

Conventional Criteria	Country, year (Ref.)	Details	Results
Milan Criteria	Italy, 1996 (33)	Single tumor ⩽5 cm, or ⩽3 tumors none exceeding 3 cm and No vascular invasion and /or extrahepatic spread	5 year survival >70% 5 year tumor recurrence <15%
Extended Criteria			
UCSF Criteria	USA, 2001 (34)	Single tumor ⩽6.5 cm, or ⩽3 lesions none exceeding 4.5 cm with total tumor diameter ⩽8 cm No vascular invasion and /or extrahepatic spread	1 year survival 90% 5 year survival 75.2%
Asan Criteria	Korea, 2008 (35)	Diameter ⩽5 cm Number of lesions ⩽6 No gross vascular invasion	5 year OS 76.3% 5 year recurrence 15%
Hangzhou criteria	China, 2008 (36)	Lesion ⩽8 cm or Lesion ⩾8 cm if AFP ⩽400 and well-differentiated No gross vascular invasion	1 year DFS 83.7% 5 year DFS 62.4% 5 year OS 70.7%
Up to 7 criteria	Italy, 2009 (37)	Sum of the largest tumor diameter in cm and number of tumors ⩽7	1 year recurrence 4% 5 year recurrence 14% 5 year survival 71%

OS = Overall Survival; DFS = Disease Free Survival

criteria have an expected 4-year survival rate of 85% and a recurrence-free survival rate of 92% (33). With greater experience, many centres are extending the Milan criteria, and have adopted the UCSF criteria or beyond (34-37). Many centres in India performing living donor liver transplantation (LDLT) have adopted this strategy as it obviates the donor waiting time and does not interfere with deceased organ sharing, which itself is a scare resource. For patients with decompensated cirrhosis (Child Pugh Class B or C) with HCC who fall within the transplantation criteria, liver transplantation is clearly the treatment of choice. Patients with tumors beyond the accepted criteria are down-staged with bridging therapies such as TACE or RFA, either alone or in combination (38).

Management of Intermediate Stage HCC (Stage B)

Transarterial Chemoembolisation (TACE) : Intermediate stage HCC (stage B) patients typically have large or multifocal tumors, without macrovascular invasion or extrahepatic spread with adequate liver function. These tumors are not amenable to local ablation or curative resection, and are beyond the accepted criteria for liver transplantation. TACE or transarterial embolization (TAE) is the recommended treatment option for these patients. In TACE, various chemotherapeutic agents such as doxorubicin, cisplatin or epirubicin are delivered to the lesion selectively prior to arterial obstruction. Some randomized studies have shown survival benefit following TACE for intermediate stage HCC with an improvement from 10% to 40-50% at 3 years (39, 40). However, a recent meta-analysis which included six trials assessing TACE versus control and three trials assessing TAE versus control did not show a significant survival benefit in patients with unresectable HCC (41).

Besides conventional TACE, another novel strategy to use is drug eluting beads loaded with doxorubicin, also called DEB TACE or Precision TACE. The deformable beads absorb the chemotherapeutic agent, which is then released slowly at the tumor site, with minimal systemic toxicity. Recent trials of TACE with drug eluting beads have shown good response rates with minimal systemic side effects of chemotherapy (42, 43).

Transarterial Radioembolisation (TARE) : TARE is a form of intra-arterial therapy that delivers radiation selectively at the tumor site using yttrium-90 microspheres. These microspheres can be delivered selectively to one or more tumor sites, where they get trapped in the tumor capillary bed. These microspheres selectively induce tumor necrosis by delivering up to 150 Gy of beta radiation, and also by microscopic embolization by obstructing the tumor capillary bed (44). One of the advantages of TARE over TACE is that it can be used in patients with portal vein thrombosis (45).

Management of Advanced Stage HCC (Stage C)

Systemic Therapy for Advanced HCC : Majority of patients with HCC have advanced, unresectable disease at diagnosis. Some of these can be helped by ablative techniques and embolization procedures. However, those with very advanced widespread disease are offered

systemic therapy.

Chemotherapy : HCC is a relatively chemo-resistant tumor, due to expression of multidrug resistance gene protein on the surface of these cancer cells, resulting in active eflux of chemotherapeutic drugs. Some of the chemotherapeutic agents that have shown activity include doxorubicin, cisplatin, fluorouracil, gemcitabine and capecitabine (46-48). These have resulted in response rates of approximately 10% only with no impact on the overall survival. The combination chemotherapy results in improved response rates of about 20%, but has failed to provide any survival advantage.

Chemoimmunotherapy has also been used to treat advanced metastatic HCC. A combination of cisplatin, interferon-alpha, doxorubicin and infusional 5-fluorouracil (PIAF) resulted in response rates of 26%. The median survival was also longer with PIAF regimen than with single drug doxorubicin. However, treatment-related toxicity was also much greater. Chemoimmunotherapy could thus be used only for young patients without cirrhosis and with normal serum bilirubin levels (49).

Targeted Therapy : More recently, targeted therapies have been developed for treatment of various malignancies including HCC. Sorafenib is one such targeted drug approved for treatment of advanced HCC. It is an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis. In a randomized placebo controlled phase III trial (Sorafenib in advanced hepatocellular carcinoma – SHARP study (4), 602 patients with advanced HCC were randomized to receive Sorafenib or best supportive care. The median overall survival was significantly longer in the Sorafenib arm (10.7 months versus 7.9 months in the placebo arm; $p < 0.001$). Approximately 70% of patients in this study had macroscopic vascular invasion, extrahepatic disease or both; and majority had preserved liver function and good performance status.

The Asia Pacific study (50) was another phase III study of Sorafenib that enrolled only Asian patients. In contrast to SHARP study, the patients in Asia Pacific study were more likely to be younger, have HBV-related disease, symptomatic disease and a higher number of tumor sites. The reported median overall survival was 6.5 months in Sorafenib arm versus 4.2 months in the placebo arm. Sorafenib was well

tolerated in both these studies.

These studies suggested that Sorafenib is an effective treatment for patients with advanced HCC. It's efficacy in patient's with Child Pugh class B liver function, appears to be lower than in patients with Child Pugh class A liver functions. A phase II study by Abou-Alfa et al (51), reported lower median overall survival for patients in Child Pugh class B patients (3.2 months compared to 9.5 months in class A patients). Similar worse outcomes have been reported for class B and C patients in many other studies. Based on these reported studies, Sorafenib is considered as category 1

Table 3: Targeted Therapy for HCC: Newer targets

Class	Agents	Phase of development	Outcome/ result
1. Antiangiogenesis	Sunitinib	III (first-line)	failed to demonstrate superiority / non-inferiority to sorafenib
	Brivanib	III (second-line)	failed to demonstrate improved OS in second-line
	Linifanib	III (first-line)	ongoing
	Ramucirumab	III (second-line)	ongoing
	Bevacizumab	II	modest clinical activity as single agent & in combination with erlotinib/chemotherapy
2. Epidermal-Growth Factor Receptor inhibitors	Erlotinib	II	modest activity in single-arm studies
	Gefitinib	II	no convincing anti-tumor activity
	Lapatinib		
	Cetuximab		
3. mTOR inhibitors	Everolimus	I & II	tolerable, efficacious in single-arm studies
	Temsirolimus	III	ongoing
	Sirolimus		
4. c-Met inhibitors	Tivantinib	II	improved time to progression
	Cabazantinib	II	evidence of anti-tumor activity
5. MEK inhibitors	Selumetinib	Multicentre single-arm study	minimal single agent activity
6. Histone deacetylase inhibitor	Belinastat	I	ongoing trials
	Vorinostat		
7. HSP-90 inhibitor	STA-9090	I	ongoing trials

option for selected patients with Child Pugh class A liver function and as category 2A option for patients with class B liver functions.

The recommended target dose of Sorafenib is 400 mg twice daily. In clinical practice, many clinicians adopt a step-up approach, wherein they start patients on 400 mg daily and gradually increase the dose to 800 mg daily as per tolerance. Common adverse effects of Sorafenib include fatigue, anorexia, hand-foot syndrome and diarrhea. It could also be associated with hypertension, laboratory abnormalities (elevations in serum amylase and lipase, hypophosphatemia), etc.

New molecular targets have been identified in HCC and various targeted therapies have been developed. These are in various phases of development and are listed in Table 3 (52-55).

Conclusion

Thus management of this complex disease, HCC continues to be challenging for the treating healthcare professionals on many counts such as:

(a) HCC is a clinically, pathologically, and molecularly a heterogeneous disease.

(b) Its management involves multidisciplinary team approach including the hepatologist, interventional radiologist, surgeon, medical oncologist and pathologist. Hepatologists are crucial to integrated care, because they are the specialists most involved in screening and diagnosis, presurgical and postsurgical resection or liver transplantation, and care of the patients with liver cirrhosis and decompensated liver disease. But such an integrated team of experts is available at very few centres in India.

(c) Latent and asymptomatic presentations in some patients make early detection and treatment very difficult.

(d) Presently available tumor markers have limitations, and there is a need for newer biomarkers to better define the tumor biology and outcome, and choose the optimum treatment.

(e) Screening for HCC is still a matter of considerable controversy.

(f) Few patients are suitable for

surgery on presentation of disease because of advanced disease, age, or co-morbidities.

(g) There is scarcity of liver donors in deceased donor setting, and several centres in India have adopted the living donor liver transplant approach.

(h) Another unique aspect of HCC biology is its recurrence after resection. Even when HCC is successfully treated and cure is achieved, most patients have underlying liver cirrhosis and face a 70% 5-year recurrence risk.

(i) There are little data or RCTs supporting the use of adjuvant therapy.

(j) There is lack of awareness of the disease among the general public, healthcare providers, policy makers, and population at risk.

(k) There is generally poor accessibility to healthcare, and lack of screening programs in large parts of the country.

(l) The number of patients with HCC is rising.

(m) Sorafenib is the only FDA-approved systemic therapy for advanced HCC. However, the outcomes are not uniform for all patients and are far from satisfactory.

(n) The very high cost of treatment and care of patients with HCC, as well as high morbidity and mortality rate are other challenges in India.

The management plan of patients with HCC is affected by the presence of underlying liver disease, the etiology of HCC and its effect on the host liver. The outcome has definitely improved for Indian patients as well with resections, liver transplantation and regional therapies. Over the past decade, there have been active efforts towards drug development to treat such patients. Many molecular targets have been identified and drugs developed. Sorafenib has been approved for advanced HCC based on Phase III trials demonstrating survival benefit. Universal immunization against Hepatitis B virus is an important step towards primary prevention of HCC in India. Active research is ongoing towards refining surgical techniques and identifying molecules for sorafenib failures. As in many other malignancies, we have moved ahead towards personalized treatment in HCC as well.

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