CHAPTER

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Hepatocellular Cancer (HCC): Screening and Management

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INTRODUCTION

The World Cancer report published in 2014 by the International Agency for Research on Cancer (IARC), WHO, documented that hepatocellular cancers (HCC) are the second most frequent cause of cancer related deaths in the world. As per this report, collated by 250 leading scientists from 40 countries, the most common causes of cancer death in 2012 were cancers of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%).[1] During the last three decades, information on various aspects in HCC has exploded leading to improved prevention, diagnosis, staging and management. Liver transplant (LT) in HCC today is feasible and successful, with a 5 year survival reaching up to 70%. On the other hand, incidence of HCC globally has doubled and HCC related deaths have increased during the last two decades. Possible reasons for this rise include inadequate control strategies to ameliorate hepatitis B virus (HBV) and hepatitis C virus (HCV) infection which are the leading causes of HCC globally. Moreover, there is also a steady rise in the prevalence of lifestyle related diseases like non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease, which are also important causes of HCC. Between 1999 and 2009, at least 32 well evaluated guidelines on prevention, diagnosis, staging and management of HCC have been published. Most of these consensus recommendations have emanated from the developed world. Such recommendations, even though evidenced based, are often inadequate in resource constrained countries like India where the infrastructure for holistic approach to control and treat HCC is still inadequate and may be considered sub-optimal.[2] Moreover, due to substantial hepatic reserve, often liver diseases do not have specific phenotypic clinical manifestations. Usual clinical experience in India suggests that HCC most often presents clinically in very advanced stages when curative or even effective palliation cannot be offered to these sick patients. It is ironical to have such a dichotomy between rapid and substantial advancement in this area and transferring these benefits to those with HCC in India due to inadequate awareness and infrastructure. In this review, we provide a concise approach to HCC in relevance to our population.

EPIDEMIOLOGY RELEVANT TO INDIA

Globally, approximately 6 lakh new cases of HCC occur every year, which makes HCC the 5th most common cause of cancers affecting humans. The mortality is also very high; approximately 2.5 lakh deaths due to HCC occur annually.[3] In India, information on HCC is inadequate. From 1988 till December 2015, i.e over two and a half decades, only 74 publications have been listed in the PUBMED- all from tertiary care centers, on select areas and most studies include small samples. The cancer registries in India probably do not provide accurate estimates of HCC prevalence due to their predominant urban locations. The sources of information about cancers are from cytology, oncology sites, and municipal registers of death. HCC are diagnosed and treated by Gastroenterologists/ Hepatologists/ Transplant Surgeons as well as G.I. Surgeons. Most of the patients treated by these specialists are presumably are not listed in the registries. Furthermore, these days the diagnosis of HCC is made by non-invasive imaging techniques rather than by histology/ cytological techniques as used in almost all other cancers. Therefore, the collated information from oncology/cytology/pathology departments may not be having the records of considerable proportions of HCC cases. Lastly, cancers are not a reportable disease in India. National cancer registry program of the Indian Council of Medical Research (ICMR) has recently expanded to include 21 population based and 6 hospital based cancer registries. The last published registry data by ICMR available in the cancer registry website (www.ncrpindia.org) provides information on various cancers from 2012 to 2014. The other source of information is the report published by World Health Organization (WHO). According to the available data, the age adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 per 100,000 population and, for women 0.2 to 2.2 per 100,000 population. The male: female ratio for HCC in India is 4:1.[2] The age of presentation varies from 40 to 70 years. According to a recent study conducted by verbal autopsy in 1.1 million homes representing the whole country, the age standardized mortality rate for HCC in India for men is 6.8/100,000 and for women is 5.1/100,000.[2] According to another study, the incidence of HCC in cirrhotics in India is 1.6% per year.[4] The unpublished data from various tertiary care centers suggests that the incidence of HCC is increasing in India.[2]

Worldwide, the single largest risk factor in the development of HCC is cirrhosis of any etiology. Cirrhosis is present in about 70–97% of those who have HCC.[5,6] Among the etiologies, chronic HBV infection, chronic HCV infection, alcohol consumption, and aflatoxin exposure are important risk factors for HCC development.[3] Less common causes include NAFLD, hereditary hemochromatosis, alpha-antitrypsin

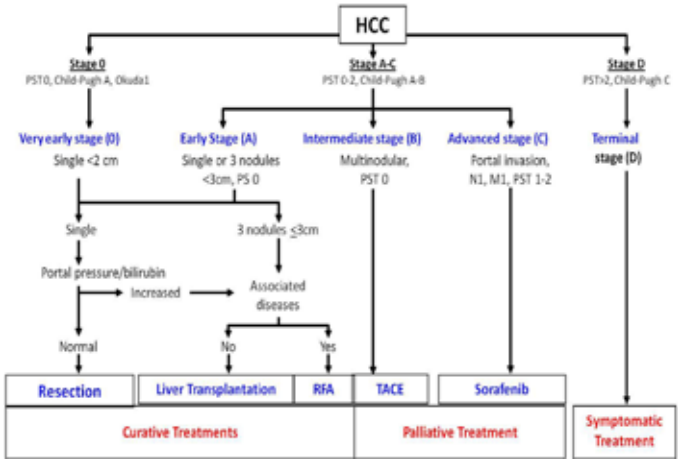

Fig. 1: The Barcelona Clinic Liver Cancer Staging System for HCC[7]

deficiency, autoimmune hepatitis, porphyrias, Wilson's disease, smoking and tobacco use. The distribution of these risk factors among patients with HCC is highly variable, depending on geographic region and race or ethnic group. Diabetes mellitus is also known to be associated with elevated risks of both HCC incidence and mortality. Indian studies have also corroborated these findings and cirrhosis of liver due to HBV, HCV, alcohol consumption, and aflatoxin exposure have been found to be the most important risk factors for HCC development. In addition to these, NAFLD is now increasingly being recognized in India as a cause of HCC. Diabetes, in addition to being a risk factor of HCC in India, has also been found to be associated with more advanced HCC and poor outcome.[3]

STAGING OF HCC AND ITS RELEVANCE

Five important factors influence the prognosis, type of therapy needed and the response to therapy, a) the underlying liver disease status, b) tumor burden at diagnosis, c) tumor infiltration into the vessels present in the liver, d) constitutional symptoms and e) spread of the tumor outside the confinements of the liver. In addition, the underlying etiology of the primary liver disease needs to be treated effectively to prevent subsequent recurrence of tumor and progress of the underlying liver disease. Any staging of HCC ideally should account for each of them. However, such an ideal staging system is yet to be devised. There is no worldwide consensus about the use of any HCC staging system, and the choice of system varies significantly by country. These staging systems include TNM, French staging, Okuda staging, Cancer of the Liver Italian Program (CLIP), Japan Integrated staging systems (JIS), Tokyo scores, Chinese University Prognostic Index (CUPI) and Barcelona Clinic Liver Cancer (BCLC) staging systems.

The BCLC and CLIP staging systems are used most frequently in Europe, whereas the JIS system has been accepted as a standard in Japan. However, BCLC staging has been widely used as the standard means of assessing the prognosis as well as for allocation of treatment for patients with HCC.[3] In this review, we will discuss only the BCLC staging system which is most commonly followed in India (Figure 1).

SCREENING FOR HCC

Why screening?

HCC usually clinically presents in advanced stages when therapeutic options are limited, treatment with a curative intent is not feasible and prognosis is dismal.[2,3] Those patients who are diagnosed at an early stage can be offered curative options.[2] The high risk conditions for development of HCC are well known. Surveillance of at-risk patients with simple, widely available and less expensive screening strategies- like ultrasonography at 6 monthly intervals- have been reported to detect small/early HCCs. Such advancement in early cancer detection associated with cure is yet unusual in other solid cancers in human.

Whom To Screen

Throughout the globe, cirrhotic patients and those with advanced hepatic fibrosis irrespective of its etiology have been reported to have the highest incidence of HCC. If the annual risk of HCC development exceeds >1.5%, screening has been suggested by WHO as well as most of the guidelines due to its cost benefit aspect. In India, cohort follow up studies in cirrhotics have revealed an annual incidence of HCC of around 1.6%. Therefore, cirrhosis patients should be undergo regular surveillance for early HCC detection.[5]

High incidence rates of HCC are also observed in patients with chronic HBV infection, even without cirrhosis. Consequently, screening of this sub-group of patients depends on the regional incidence of HBV infection. INASL guidelines recommend screening for chronic HBV infected patients in males older than 40 years and in women older than 50 years.[3] In addition, screening should be performed for all CHB patients with a family history of HCC. In India, fibroscan is now available in most tertiary care centers. There are now reports indicating identification of high risk candidates for HCC as per the liver stiffness value detected by fibroscan. However, more information is necessary to provide region specific guidelines to use fibroscan to identify high risk patients for HCC.

How to Screen

The effectiveness of HCC surveillance depends on adherence to screening and sensitivity of the surveillance method. Generally, surveillance utilization and sensitivity has been suggested to be at least 34% and 42%, respectively, for a meaning full screening strategy.[8] Cost-effectiveness of screening by using abdominal USG has been reported in several studies and constitutes the backbone of all recommendations. In India, ultrasound is widely available, non-invasive and less inexpensive than any other imaging modalities. It's accuracy in detecting early HCC can be improved by an ultrasonologist experienced at HCC detection. It is preferable to conduct such screening of high risk population at tertiary care referral centers.

The ideal screening interval for cirrhotic patients of six months has been suggested by most practice guidelines

Table 1: Survival of HCC with and without treatment as per BCLC staging[7]

BCLC Stage	Median survival without treatment	Survival with stage specific therapy	Type of therapy offered
Stage 0	>36 months	5 year survival in 80-90% patients	Resection, Ablation, LT
Stage A	36 months	5 year survival in 50-75% patients	Resection, Ablation, LT
Stage B	16 months	2 year median survival in 60% patients	TACE
Stage C	4- 6 months	8-12 months	TARE, Sorafenib
Stage D	< 4 months	Survival improvement is uncertain in patients with distant metastasis and poor liver function	Supportive If small tumor and fulfills Milan's criteria or UCSF transplant criteria without distant spread, despite poor liver function results are good with LT

because it significantly improves sensitivity of early HCC detection compared to 12 months (70% vs 50%). A shorter screening interval of three months did not yield either earlier stage lesions or patients eligible for curative treatment and additionally increased cost.

Additional biomarkers such as alfa-fetoprotein (AFP) and PIVKA II with abdominal ultrasonography have been reported to increase the sensitivity for early HCC detection, in patients at risk. However, elevated serum AFP has been documented in cirrhotic patients without HCC particularly in those with active ongoing inflammation and regeneration. A cut-off value of 20 ng/ml was shown to have a satisfactory level of specificity of AFP; however, sensitivity remained only 60%. Reducing the cut off level to below 20 ng/ml has been reported to cause high rate of false positivity. In an Indian study, estimation of AFP levels was not found to be sensitive enough and its addition did not enhance the detection frequency of HCC in cirrhotics.[5] Therefore, INASL, AASLD and EASL do not recommend the inclusion of AFP levels in the screening tools in the surveillance programs for HCC detection.

Management

In the earlier section (staging of HCC), we briefly discussed about specific management of HCC depending upon the stage of HCC as per BCLC staging system. With treatment, irrespective of the stage of HCC, survival has been reported to improve substantially (Table 1).

Treatment of Very Early and Early HCC

In recent years, by surveillance of cirrhotic population, increased numbers of patients are detected with very early HCC. They can be subjected to curative options such as liver resection (LR), LT, and RFA. The early HCC which includes BCLC-A (Child A status, three tumors with largest ≤ 3cm, Okuda 1, PST 0, without vascular invasion or extrahepatic spread) for Indian context can also follow same strategies as in very early HCC, except for the fact that in such patients LT (if available) may be a better option than LR or RFA. However, studies comparing all the three forms of therapy in very early HCC in homogeneous population with similar liver reserve are unavailable. There are prospective as well retrospective studies comparing RFA and liver LR. LT is considered to be the best option for any HCC in a cirrhotic liver provided the patient satisfies the defined criteria for such therapy. LT removes the diseased cirrhotic liver as well as the tumor and corrects the sequelae of cirrhosis as well. However, at present, according to most expert opinions, LT in very early HCC is considered to be a second line therapy to RFA or LR because of its cost, accessibility, expertise, unavailability of organs, post transplant management strategies with follow-ups and regional prioritization as well as the type of LT (Diseased donor or Live-related LT). Moreover, LR or RFA provides almost similar overall and disease free survival. Table 2 summarizes the indications, long term results, recurrence rates and advantages of various therapies available for management of very early and early HCC.

Treatment of Intermediately advanced HCC

These patients can be subjected to liver transplant with good outcome, but the other curative options such as RFA and LR lacks adequate evidence as curative options in such patients. In absence of LT these patients are subjected to palliative therapy such as TACE or TARE.[3]

Transarterial chemoembolization (TACE)

TACE is a radiological interventional procedure in which sequential, intra-arterial injection of chemotherapeutic agents (usually doxorubicin, or epirubicin or a combination of mitomycin C, doxorubicin, and cisplatin) mixed with Lipiodol is injected through the artery feeding the tumor in the liver using image guided transarterial microcatheters followed by an embolising particles such as Gelfoam or preferably, calibrated particles to block the feeding artery after delivery of the chemotherapeutic agents to the tumor. These chemotherapeutic agents also cause damage to the surrounding hepatocytes and can leak into systemic circulation and therefore are associated

Table 2: Summary of available therapies in Early and very early HCC in presence of Cirrhosis of liver

	Liver Resection (LR)	Radio Frequency Ablation (RFA)	Liver Transplant (LT)
Tumor size, number and location Liver reserve and Portal hypertension (PHT)	Usually small, ≤ 3 cm up to 3 tumors preferably located in one segment/ lobe. Single tumor up to 5 cm preferably in peripheral location and not in central locations. Liver reserve should be good (as assessed by Child status - preferably Child A/ MELD-10/ Indocyanine green clearance test may be used to assess hepatic reserve to prevent post hepatectomy liver failure. Absence of PHT (HVPG < 10 mm Hg or absence of portosystemic collaterals in imaging and endoscopy)	Same as in LR but can be present in both lobes and can be offered even to those who do not satisfy criteria for surgery. Preferable for centrally located tumors. To be avoided if tumor is on surface, near major vessels or gall bladder. Good liver function is associated with better long term results.	LT should be offered if with similar tumor characteristics as mentioned in LR and RFA, but the liver function is bad (Child B or C) and both RFA or LR are not possible
Availability of Skill & Expertise	LR should be done in preferably in high volume hepatobiliary surgical unit with expertise to recognize and treat the post operative liver failure as its complication	RFA should be preferably performed by a team of interventional trained Radiologist in combination with hepatologists	LT needs a team of well trained experts in transplant surgery, hepatology, radiology, pathology, transfusion services and infection control.
Over all 4 to 5 year survival	52-82%	30-81%	75-85%
Disease Free 3 to 5 year survival	50-76%	40-60%	70-80%
Recurrence rates in 1-2 years	30-50%	50-70%	5-10%
Complications	20-50%	4-10%	3-10%
Advantages	With good liver function and limited tumor burden it can have similar survival as LT. In presence of organ shortage can be used as bridge to LT. Salvage transplant can be offered if liver function deteriorates or recurrence occurs. Also, resected specimen provides the tumor biology such as microvascular invasion, degree of differentiation and small satellite nodules all of which indicate high recurrence rate and therefore can be transplanted at a suitable time	Can be offered if surgery cannot be done due to lack of sufficient liver reserve, presence of PHT or hyperbilirubinemia. It can be used as a first line therapy due to its less invasive nature with much less complications than in surgery. It can be also used as a bridge to liver transplant	Removes diseased liver and the tumor and corrects the sequels of cirrhosis in long term. Can be used for salvage if LR and RFA fails or tumor recurs

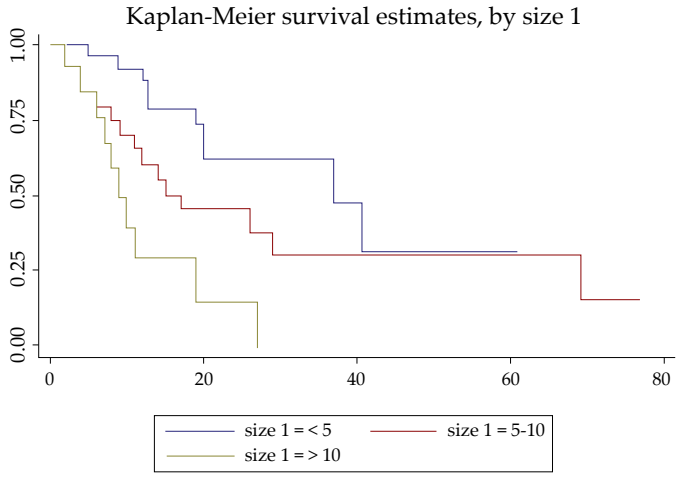

Fig. 1: Kaplan-Meier survival curve shows the survival of patients of TACE with different sizes of the mass at the time of treatment. Patients with a tumor size of less than 5 cm (blue curve) have a longer survival period than those with a mass size of 5-10 cm (red curve) or more than 10 cm (green curve)

with hepatotoxicity as well as systemic side effects of the chemotherapeutic agents. To overcome these hepatic and systemic side effects, recently drug eluding beads (DEBs) have been developed.

DEBs are produced from a biocompatible polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups for the controlled loading and delivery of chemotherapeutic drugs. DEBs occlude the blood flow to the target tissue and deliver a local and sustained dose of drug direct to the tumor and have been reported to cause less hepatic and systemic side effects with controlled delivery of the drug to the tumor over a longer period of time. Therefore, DEB based TACE is also known as DEB-TACE. Both TACE and DEB-TACE are used in repeated sessions with a follow up Triphasic CT or MR to evaluate the residual tumor tissue after 4 to 8 weeks of TACE or DEB-TACE. Usual recommendation is to do at best 4 sessions of such therapy over 6 month to 1 year in patients with HCC having BCLC-B status.[3]

Meta analysis and many randomized controlled trial have distinctly documented the survival benefit of the treatment in intermediately advanced unresectable HCC in whom RFA or LT is not possible. All these trials included patients with good liver function without distant spread and vascular invasion. Even these treatments have been used in early HCC in whom RFA or LR is not feasible with good results in terms of tumor control and survival. However, the survival rates subsequent to TACE as reported in various series have been variable. Reported 1, 2 and 5 year survival rates with TACE, as available in published literature, are 53-90%, 11-67%, and 8-26% respectively which seems to be better than untreated patients under similar conditions, as shown in Table 1. In one Indian study, patients with cirrhosis (Childs A and B) with HCC who were subjected to TACE- 1 to 4 sessions over 12 month of median follow up- had 1, 2 and, 3 year survival of 66 %, 47%, and 36.4% respectively.[9] In this study the initial tumor size was main predictor of survival

Table 3: Absolute and relative contraindications to TACE and DEB-TACE

Absolute contraindications
Decompensated cirrhosis (jaundice, ascites, encephalopathy, recent variceal hemorrhage)
Technical contraindications to intra-arterial treatment
Renal failure (serum creatinine> 2 mg/dl, glomerular filtration rate < 30 ml/min)
Massive tumour involving both lobes
Severely impaired portal vein blood flow (main or branch portal vein thrombosis, hepatofugal blood flow)
Relative contraindications
1. Large tumour size (> 10 cms)
2. Bile duct occlusion or incompetent papilla due to stent or surgery
3. Untreated varices at high risk of bleeding
4. Segmental or branch portal vein thrombosis
5. Intense, non-correctable hepato-pulmonary shunt

and the procedure (Figure 1) was well tolerated by most patients and mortality was less than 3 % during the study period.

The above mentioned widely variable outcomes reported after TACE would indicate the importance of appropriate patient selection and expertise in the procedure. Liver function is the major determinant for selecting patients for TACE and survival benefits only have been documented in Child Pugh A or B7 patients in absence of ascites. Further, such patients should have clearly identified feeding vessels to the tumor which can be microcatheterised and can be isolated angiographically so that selective TACE can be performed for the segment in which the tumor is present. Such a strategy limits the hepatotoxicity and prevents embolization of the artery supplying the whole lobe of the liver, but needs expertise. An expert group recently recommended the absolute and relative contraindications for TACE treatment of HCC patients in the intermediate stage (Table 3).[10] One of the absolute contraindication of TACE is main portal vein thrombosis (PVT), because arterial blockage in such patents may cause liver failure due to ischemic liver injury. However, many centers use TACE in selected patients with segmental portal vein branch invasion, though survival benefits in such patients is unclear. At our center and most other tertiary centres, if even after two sessions of TACE adequate tumor response (evidenced by absence of arterial enhancement of at least more than 50% of the viable tumor tissue as evaluated by Triple phase MR or CT) is not achieved, additional therapies are considered- including systemic agent sorafenib. With careful planning of technique, patient selection and strategy a median overall survival in excess of 20 months is usually achievable.

The recent studies using DEB-TACE however have shown a marginal edge over TACE with reported median

Table 4: Milan's Criteria for Liver Transplant in HCC (This does not include liver function status)[11]

- One lesion smaller than 5 cm
- Up to 3 lesions smaller than 3 cm
- No extrahepatic manifestations
- No vascular invasion

Table 5: The UCSF criteria for liver transplantation in patients with HCC[12]

- Single lesion ≤ 6.5 cm
- Multiple lesions ≤ 3 cm
- Largest tumor diameter if multiple ≤ 4.5 cm
- Total tumor diameter if multiple ≤ 8 cm

survival of about 48 to 52 months and distinctly lower side effects than the latter therapeutic procedure.

Transarterial radioembolisation (TARE)

HCC patients with PVT are not suitable for TACE, as mentioned earlier. Such patients have been found to have beneficial therapeutic outcomes in terms of survival and quality of life with internal radiotherapy. A radioisotope delivered to the tumor with a dose to cause tumor necrosis with minimal radiation injury to surrounding hepatic parenchyma is the aim of such therapies. A variety of radioisotopes, such as Iodine-131, Yttrium-90, Rhenium-188, Holmium-166 etc have been shown to be effective in HCC. The TARE procedure is similar to TACE. Very small particles of glass or resin containing Yttrium-90 – a beta emitter with a tissue penetration of around 2.5 mm – are injected into the hepatic artery supplying the tumor and the isotope ultimately gets lodged in the tumor. Such treatment is safe and within first two weeks, maximum and optimal radiation is emitted from Yittrium-90 resulting in tumor necrosis. However, about 1 to 2 week prior to such therapy a thorough angiographic evaluation of coeliac, superior mesenteric, gastrodudenal, pancreaticoduodenal artery is done to assess the arterio-portal shunt. Macro aggregated albumin (MAA) is used to evaluate the shunt fraction going to lungs. These precautions are undertaken to avoid isotope induced pneumonitis, gastric ulcers and pancreatitis etc. This may exclude a significant number of patients and also add to the cost. TARE has shown comparable efficacy in terms of local response, time to progression and superiority in terms of downstaging tumors when compared toTACE.

In a multicenter trial from India, TARE using Rhenium-188 was found to be a safe, effective, and promising therapeutic option in patients with inoperable HCC with PVT. However, Rhenium is not available widely and Yittrium-90 microspheres have been commercialized and are used widely by now globally, including in India.

Patients usually receive a single TARE treatment. The two main absolute contraindications to TARE are liver decompensation (serum total bilirubin > 2 mg/dL) and untreatable arteriovenous shunting. Based on current evidence, a recent expert consensus endorsed that TARE could be first-line therapy for the sub-group of intermediate stage patients who have well-preserved liver function (Child A) and high tumor burden (beyond the up-to-7 rule) even with PVT. The reported results of TARE in the literature included patients with PVT, failure to TACE and patients with high tumor burden. These patients at best could have been treated by oral multikinase inhibitor sorafenib which has been reported to provide 3 month survival benefit in about 40 to 44%. However, the median survival with TARE has been reported to be more than 12 months.

Both TACE and TARE have been used to downstage the HCC to satisfy the criteria for LR and LT. The downstaging of HCC has gained immense attention even for those who have been listed for LT. While waiting for LT, about up to a quarter of patients can be delisted due to progression of the tumor, other tumor related complications and distant spread. Therefore, the present recommendations state that patients who are or are not being listed for LT should be tried for down staging, provided the liver function in them is good. Here, we will enumerate the two criteria for LT which are used worldwide. However in the present review, details of these criteria, their results and benefits are not being discussed.

Some have argued that the Milan criteria (Table 4) are too restrictive for liver transplantation and that acceptable outcomes can still be achieved using more liberal tumor criteria. The liver transplant group at the University of California at San Francisco (UCSF) has championed the use of LT for larger tumor sizes and achieved outcomes similar to those achieved when the Milan criteria are used (Table 5).

Over time with more expertise acquired in all the aspects of liver transplant and with above criteria to include patients with HCC for transplant has substantially improved recurrence free 5 survival rate up to 65-80 %. Such improved results have also resulted in bolder approach for Liver Transplant. One such example is "Rule of 7" in which tumor number is 7 and up to 7 cm in size who are transplanted with good results.[13]

Treatment of Advanced Hepatocellular Cancer

Before the promising results of TARE, patients with BCLC-C were only recommended to be treated with oral multikinase inhibitor Sorafenib. However, with increasing availability of TARE in India and as the cost is being gradually reduced with increasing expertise, it is being used more often. However, the results of such therapy in Indian patients are not yet available. None of the guidelines have recommended TARE in BCLC-C with good liver function, but such recommendations are likely to be included in future refreshed guidelines.

Sorafenib

Sorafenib is a multikinase inhibitor and down regulates various kinases responsible for hepatic cell proliferation. It acts against the serine–threonine kinases, Raf-1 and B-Raf downstream signals for Epidermal Growth Factor

(EGF) receptors, vascular endothelial growth factor receptors (VEGFRs)- 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR-β). Each of these receptors and signals emanating there off are associated with limitless proliferative property of the HCC. All guidelines, including the INASL guidelines,[2] recommend Sorafenib in BCLC-C HCC. These recommendations are based on two pivotal RCTs, (one conducted in west[14]) and the other one in Asia[15] which documented an increase in median survival of between 2-3 months over placebo. The SHARP trial conducted in America and Europe included majority of patients with good liver functions (Child A in 95%) as well with good performance status (PS 0-1), and recruited 602 patients. The median survival in Sorafenib treated patients was 10.7 months in comparison to 7.9 months in those who received placebo {HR 0.69 (0.55–0.87) P < 0.001}. The Asian trial included 216 patients (Sorafenib-150 and Placebo-76) but included also Child B patients and patients with distant metastasis. The median survival with Sorafenib and placebo was 6.5 and 4.2 months {HR 0.68 (95% CI 0.50–0.93); P = 0.014}.The most common side effects in both the studies were fatigue, diarrhoea and hand/foot skin reaction.

Sorafenib has subsequently been evaluated as adjunctive therapy after RFA or LR in randomized studies but adjuvant treatment with Sorafenib was not found to improve the median recurrence free survival over RFA or LR. Additionally, sorafenib has been explored in combination with TACE and, while it appears safe, there is currently no data confirming that the combination confers an improvement over TACE alone.[3]

Presently there is no evidence that a combination of Sorafenib with other cytotoxic agents or targeted agents or hormonal therapy is superior to Sorafenib alone. The use of systemic chemotherapy (Dauxorubicin, Adriamycin, Oxaliplatin, Fluorouracil) has not been found to be reproducibly effective in management of HCC in randomized controlled trials.

Other Targeted therapies

Since the approval of sorafenib, a number of randomised first and second line trials have been reported using many molecular targeted therapy (brivanib, sunitinib, linifinib and the combination of sorafenib and erlotinib) in HCC, however with disappointing results.[16]

Immunotherapy for HCC

Cancer immunotherapy has been a subject of intense investigation for many decades. Recent understanding of tumor regulation by the immune microenvironment has advanced substantially which has led to identification of molecules that can block inhibitory signals and enable a cell-mediated anti-tumor response. So-called checkpoint inhibitors which block negative regulatory molecules such as the cytotoxic T-lymphocyte protein 4 (CTLA-4), the programmed cell death protein 1 (PD-1) and its ligand PD-L1, have revolutionized the treatment of melanoma and lung cancer. An initial report of 20 HCC patients treated with the CTLA-4 inhibitor tremelimumab, reported a good safety profile and a radiological response rate of 18%[17] The PD1 inhibitor nivolumab in HCC reported a response in around 20% in an initial report from an ongoing phase I study. Pivotal randomized trials comparing nivolumab with sorafenib are in progress and the combination of nivolumab with the CTLA-4 inhibitor ipilimumab are ongoing. Other immunotherapeutic approaches include vaccine strategies, adoptive cell therapy and gene therapy all of which are being explored.

External beam Radiotherapy

Better understanding of partial liver tolerance of radiation therapy and technological advances have improved the ability to deliver tumoricidal doses of radiation safely to HCCs, and have led to a resurgence of interest in curative-intent treatment of HCC using radiation therapy. Promising clinical data from multiple studies suggest that HCCs are indeed radiosensitive. Sustained local control rates ranging from 71% to 100% have been reported following 30–90 Gy delivered over 1–8 weeks. It is suggested that doses greater than 75 Gy result in more durable in-field local control than lower doses. 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. However, till more trials are available, radiation therapy cannot be recommended for management of HCC outside of clinical trials.

Supportive Care

In very advanced HCC such as in BCLC-D, the median survival is around 3 months and there is no therapy with evidence to treat these patients with an aim to improve their survival. However, all efforts should be made to improve the quality of life in such patients. These include management of pain using various narcotic and non narcotic agents. Radiotherapy can be used to alleviate pain in patients with bone metastasis and for relief of symptoms from pulmonary or lymph node metastases.[3]

Besides the pain, nutritional support and psychological support in such patients are important to improve quality of life. Further, the therapy in such patients should also include the treatment for underlying cause of the liver disease such as antivirals for HBV or HCV, which may improve the liver function status in general and thereby may improve the quality of life. However, evidence of such therapy in improving quality of life is needed in adequately designed trials. Similarly treatment of portal hypertension, ascites, infections and renal dysfunction may be needed in such patients depending upon individual patients' need.

CONCLUSION

Advancements in knowledge about HCC biology, etiology, diagnosis, screening, staging and management have enhanced considerably during last 3 decades. Most important risk factor of HCC is cirrhosis of liver, irrespective of its etiology. Screening high risk patients to detect HCC in early stages when the tumor burden is small

with associated preserved liver function allows curative therapy in such patients, which includes liver resection, RFA and liver transplant. However, patients with HCC often present to tertiary care referral centers with onset of symptoms when the HCC is at an advanced stage. In such patients also, non-curative palliative care such as TACE, TARE and Sorafenib have been associated with improved survival benefit. Even palliative supportive care for very advanced HCC has improved. There are many efforts now to develop tumor biology specific therapy using targeted treatment at the molecular level, which in future is likely to provide further benefit to such patients.

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