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REVIEW

# Clinical Management of Liver Cancer in India and Other Developing Nations: A Focus on Radiation Based Strategies

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## ABSTRACT

Hepatocellular carcinoma (HCC) is a global killer with preponderance in Asian and African countries. It poses a challenge for successful management in less affluent or developing nations like India, with large populations and limited infrastructures. This review aims to assess the available options and future directions for management of HCC applicable to such countries. While summarizing current and emerging clinical strategies for detection, staging and therapy of the disease, it highlights radioisotope- and radioactivity-based strategies as part of an overall program. Using the widely accepted Barcelona Clinic Liver Cancer (BCLC) staging system as a base, it evaluates the applicability of different therapeutic approaches and their synergistic combination(s) in the context of a patient-specific dynamic results-based strategy. It distills the conclusions of multiple HCC management-focused consensus recommendations to provide a picture of clinical strategies, especially radiation-related approaches. Additionally, it discusses the logistical and economic feasibility of these approaches in the context of the limitations of the burdened public health infrastructure in India (and like nations) and highlights possible strategies both at the clinical level and in terms of an administrative health policy on HCC to provide the maximum possible benefit to the widest swathe of the affected population.

**Keywords:** BCLC; Embolization; Hepatocellular carcinoma; Liver cancer; Radiation therapy; SIRT; TARE

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**Key Summary Points**

Hepatocellular carcinoma (HCC) is a global killer with preponderance in Asian and African regions. It poses a challenge for successful management in less affluent developing countries like India, with large populations and limited infrastructures.

This review aims to assess the available options and future directions for management of HCC. It describes current and emerging strategies for detection, staging and therapy of the disease emphasizing measures involving clinical use of radiation.

Using the widely accepted Barcelona Clinic Liver Cancer (BCLC) staging system as a base, it discusses different therapeutic approaches and their synergistic combinations in the context of a patient-specific dynamic results-based strategy, considering multiple HCC management consensus recommendations.

The review has a special focus on radiant therapies that can help downstage intermediate/advanced disease or extend patient lifespan while awaiting other therapies. Such therapies can be made more widely available through development of indigenous formulations and facility installations.

It also discusses the logistical and economic feasibility of these approaches in the context of the limitations of the burdened public health infrastructure in nations like India.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14573604.

## INTRODUCTION

Most major organ functions can at least hypothetically be substituted or supplemented by artificial means, but the liver is such a multifunctional powerhouse—purifying the blood, providing compartmentalized metabolism and directed transport of a vast array of substances, secreting metabolic regulators as well as vital proteins and hormones—that it is as yet impossible for a being to survive any meaningful span without a functioning liver [1]. This supposition is borne out by the fact that liver disease accounts for approximately 2 million deaths per year globally, of which half is attributed to viral hepatitis and hepatocellular carcinoma [2]. This review attempts to provide an overview on the current global status of liver cancer. It also discusses the modalities available for its detection, staging and clinical management, and the feasibility of their application in vulnerable countries like India. A special emphasis is made on radiation-based modalities that can be made locally available to serve the greatest fraction of the affected population.

## HEPATOCELLULAR CARCINOMA—A CAUSE FOR SERIOUS CONCERN

Liver cancer is the fifth most common cancer globally and the third most frequent cause of cancer-related death overall (second for men, sixth for women) [3, 4]. Developing nations account for > 80% of those deaths. About 70–85% of liver cancers are attributed to hepatocellular carcinoma (HCC), while intrahepatic bile duct cancer accounts for the remainder [5, 6]. In regions of greater prevalence (Asia, sub-Saharan Africa), HCC is present in > 50% of cases associated with endemic hepatitis B virus (HBV) infection. China, with ~ 84 million infected with HBV, accounts for roughly half of the primary liver cancer incidence in the world [7]. India has ~ 43–45 million chronic HBV sufferers [8], and the reported HCC incidence

ranges from 0.7 to 7.5 in men and 0.2 to 2.2 in women for every 100,000 persons per year [9]. Considering India's population of ~ 1.4 billion, the actual numbers would be on the order of tens of thousands of new cases annually. What confounds this situation is the high ratio of mortality to incidence (0.95) and a reported median survival period of only 2–3 months, even with the best supportive care [10]. The reasons for this situation are several:

### Patient Demographics and Causative Factors

There is a wide range for median age of liver cancer presentation, 40–70 years [9]. Apart from chronic HBV infection, several risk factors have been associated with HCC development, including HCV infection, alcoholism and exposure to fungal aflatoxin. Classically, 70–90% of HCC incidences have been seen with underlying liver cirrhosis, but the contribution of non-alcoholic fatty liver disease (NAFLD) independent of cirrhosis to HCC development is rising steeply. Increasingly prevalent chronic lifestyle conditions like obesity and diabetes mellitus, linked to NAFLD, are thus suspected to play a role in the malignant transformation of hepatocytes [11].

### Symptomatology and Screening

HCC develops initially as slow growing nodules (with estimated doubling time of 1–19 months), which may be asymptomatic for years. Diagnosis based on external symptoms is challenging—gross symptoms such as pain, abdominal discomfort, weight loss, fatigue, decompensatory jaundice or ascites often manifest only when the disease is in an advanced stage with multiple hepatic nodules and occasionally extra-hepatic lesions [12]. For such patients many potentially curative treatments are not applicable, unless the disease is successfully downstaged.

Multiple scientific reports have urged a regular HCC screening program for high-risk groups to help in early identification and improved disease prognosis [13–15]. They have recommended screening at least for cirrhotic patients with HBV/HCV infections, but also admitted the difficulty of lack of consensus on non-cirrhotic patients at risk. Even in the target group, screening logistics are complicated given patient numbers, clarity of diagnosis and awareness of screening programs among patients and physicians. For less affluent countries like India, with significant portions of the population in rural/semi-urban areas, a screening program with adequate penetration and follow-up is a major endeavor for already burdened public healthcare systems. Kumar et al. have proposed a three-fold program for curbing HCC in India, consisting of (1) reducing exposure to carcinogenic hepatotoxins, (2) treating the chronic necro-inflammatory state of liver produced by hepatotoxins and (3) preventing recurrence after initial curative treatment [9]. This calls for a major commitment from the public health infrastructure with adequate consideration of logistics and economics.

### Metastasis and Disease Recurrence

Due to delayed detection, HCC is curable in only a fraction of cases. HCC is mostly detected as a multi-focal phenomenon: Intra-hepatic metastases are common because of the spread of the primary lesions into the portal vein branches and the main portal vein; rarely, extra-hepatic metastases are observed in the lung or bone as well as porta-hepatic lymphadenopathy. Certain tumor foci may be missed, being undetectable by existing imaging techniques or a product of metastases that occurred prior to surgical intervention [4]. Post-treatment recurrence can be as high as 50% at 2 years and 70% at 5 years post-resection [9, 16]. Liver transplantation is the second most common transplantation procedure in most countries. Even so, < 10% of the requirement of organ donors is currently met [17].

## EARLY DETECTION AND DIAGNOSIS: THE KEY TO BETTER DISEASE MANAGEMENT

As symptomatic detection of HCC is often too late for simple curative strategies, anticipatory

screening of identified high-risk groups becomes a necessary strategy. Regardless of the approach, there are certain common techniques in in most countries diagnosis of hepatic malignancies.

### Ultrasonography

Ultrasonographic (USG) examination of the liver, with its non-invasive, safe and economical profile, would be one of the early tests for the distress symptoms of HCC. Several groups have recommended USG as a bi-annual surveillance tool for select groups, citing greater amenability to curative treatment and increased survival [18, 19], and advances such as microbubble contrast agents for contrast-enhanced USG have increased diagnostic value in terms of characterizing focal liver lesions [20]. But while it has been reported sensitive in detection of even asymptomatic tumors, factors like doubling time of the lesion and experience of the clinician in interpretation of the scan are critical for success. Different meta-analytic studies suggest that a combination of USG findings with clinico-pathological manifestations and other biomarkers, like p16 expression and serum alpha-fetoprotein (AFP), can have greater sensitivity for early-stage HCC than USG alone [21, 22]. In a retrospective analysis involving > 250 patients, Schwarze et al. showed that contrast-enhanced USG demonstrated remarkable accuracy compared to MRI as a diagnostic gold standard [23]. But even knowing the benefits of early detection, it remains a massive endeavor in terms of implementation for nations with strained public health resources.

### Serum Alpha-Fetoprotein and Other Biomarkers

Regarded as a fetal analog of serum albumin owing to its abundance in fetal plasma, AFP has been linked with HCC at least since 1977 when Chen et al. compared serum AFP between patients with HCC, other malignancies and other hepatic disorders [24]. They found that AFP levels were maximal in HCC, exceeding 400 ng/ml depending on the stage and differentiation of the tumor cells. Several practice guidelines have suggested high serum AFP (> 200 ng/ml) as a screening tool in combination with USG [22, 25] as a prognostic marker along with tumor volume [26] or to monitor tumor response to therapy [27]. As per the 2019 guidelines pertinent to the China Liver Cancer (CNLC) staging system, serum AFP along with USG is mandatory for surveillance [28]. However, other studies contend that variation in serum AFP across populations and different stages of the disease limit the utility of serum AFP as a diagnostic, prognostic or treatment monitoring aid [29, 30]. Generally, AFP is not recommended as a confirmatory diagnostic marker in small HCC, since its observed rise during tissue regeneration and necro-inflammation reduce its specificity as a screening aid in high-risk populations [25].

Apart from AFP, serum markers such as des-gamma-carboxyprothrombin (DCP) and glypican-3 (GPC3) have been studied. In selected instances they showed better performance than AFP for diagnosis of HCC, but implementation logistics must be considered before recommending them for mass screening [31].

### Imaging-based Diagnosis: Non-Radioactive and Radioactive

USG as previously described is the sole non-invasive diagnostic technique recommended as a screening tool for HCC. Other non-radioactive imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) cannot at present serve this role because of their limited availability and cost factor. However, they have a crucial part to play in confirmatory diagnosis and differential characterization/staging of suspect liver masses/lesions.

For patients with ≤ 1 cm nodules in the liver, contrast-enhanced CT or MRI showing hypervascularity in arterial phase and washout of contrast media in portal-venous phase is recommended as a first-line post-screening diagnostic and staging tool, showing near absolute positive predictive value especially for high-risk groups without an additional need for confirmation by histopathology [25, 31].

Techniques like perfusion/dual-energy CT and functional MRI modes like diffusion-weighted MRI, if correctly interpreted, can provide improved characterization of detected HCC lesions that can aid in personalized therapy: in fact, widely used staging systems including the BCLC are based on CT/MRI-based imaging results [20]. Dynamic MRI using Gd-based extracellular contrast agents/hepatobiliary agents and a minimum field strength of 1.5 T is regarded as having superior diagnostic value for lesions $\leq$ 2 cm (81% vs. 68% for CT), its cost and limited availability being the sole hindrance for large-scale use in less economically affluent nations with HCC incidence [32]. In the Chinese system, patients with chronic HBV/HCV can be diagnosed with HCC based on the findings of a single or two imaging techniques, depending on whether the nodules are $>$ or $<$ 2 cm in diameter. Perfusion imaging by CT or MRI can also be used to monitor response to loco-regional treatment procedures [20, 32]. These techniques thus form the bulwark of imaging-based confirmation/prognosis of hepatic malignancies.

In radioisotope imaging, positron emission tomography (PET) with the normally useful [$^{18}$F]-fluorodeoxyglucose ([$^{18}$F]FDG) diagnostic radiotracer finds only limited application in HCC staging because of its lower sensitivity here, which is less than half that of other liver tumors and highly dependent on the extent of tumor cell differentiation [33]. Haug reviewed the clinical utility of PET tracers in HCC, concluding that $^{11}$C-acetate and choline-based PET tracers showed higher sensitivity [34]. $^{68}$Ga-labeled prostate specific membrane antigen (PSMA) has shown potential as a marker superior to [$^{18}$F]FDG for extra-hepatic metastases [35, 36]. Recent reports have associated poor prognosis with PSMA expression in liver tumor vasculature [37, 38], but larger-scale multi-centric studies and comparative meta-analyses are needed. Of course, availability of tracers for diagnosis/screening programs needs to be considered before recommending any shift in testing. Single photon emission computed tomography (SPECT) with technetium-99m ($^{99m}$Tc) labeled mebrofenin and sulfur colloid is routinely employed for assessment of liver function. Multiple reports have concluded that this can be used in devising personalized therapy regimens for HCC, which are calculated to minimize decompensation of reserve hepatic function [39, 40].

Radioisotope imaging also helps to assess the safety of administering internalized particulate radiotherapies; scintigraphy with $^{99m}$Tc-labeled macroaggregated albumin (MAA) can assess the distribution and possible shunting out of the radiolabeled particles into other regions. This will be discussed in greater clarity in the section dealing with radiolabeled microparticles.

## Tissue Biopsy

Image-guided tissue biopsy followed by immunohistochemical testing is not useful for screening or asymptomatic testing, but it may serve to pathologically confirm the results of previously discussed protocols. In China, biopsy has been recommended for nodules $>$ 2 cm [28]. Testing should ideally be carried out with a panel of antibodies. Existing reports have recommended the inclusion of GPC-3, heat shock protein-70 and glutamine synthetase to differentiate HCC from hepatic adenomas and arginase-1, hepatocyte paraffin antigen (hep par-1) and polyclonal carcinoembryonic antigen among others to distinguish from metastatic carcinomas [41, 42]. For early stage HBV-associated HCC, a 7-marker plasma microRNA panel, reported to have good accuracy and better sensitivity than AFP, has been extensively adopted for large centers in China, which other nations can also consider for their screening [28]. Tissue biopsy carries a possible risk of bleeding and possible needle track metastasis, but the European Association for Study of Liver (EASL) recommendations suggest these risks are infrequent and do not affect disease progression or overall survival (OS) [43]. Tissue biopsy may have a role in patient selection for targeted therapy [44]. Biopsy is also done post-resection/transplantation to assess tumor cell lineage for prognostic investigation.

## STAGING AND PROGNOSIS OF HCC: A PRECURSOR TO THERAPY

Before discussing treatment strategies, it is important to emphasize that the selection of specific approaches is wholly dependent on the prognosis of the individual patient. For HCC, apart from tumor grading (considering morphology, portal invasion and AFP level), cirrhotic damage and reserve liver function play a role in determining suitable line(s) of therapy [45, 46]. Several systems exist for HCC prognosis, including Okuda, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer (BCLC), etc. [47]. Multiple reports have named BCLC as the most widely used staging system. One of its salient features is the matching of tumor prognosis with treatment strategy, making specific recommendations for each stage. This system provides overall prognosis of the patient based on three major criteria: (1) tumor staging from morphology, portal invasion, metastasis and liver involvement, (2) patient's performance status (PS) assessment on a 0–4 scale based on well-being and motility and (3) liver function grading from A-C on the Child-Pugh (C-P) score, a points system that tracks biochemical parameters, physiological kinetics and clinical factors [48]. A simplified representation of the BCLC staging system is provided in Fig. 1, which will be referred to in the discussions ahead. Based on the staging and demonstrated characteristics of the tumor lesion and liver function, a specific treatment regimen can be tailored to the patient. For the purpose of our discussion, therapeutic approaches to HCC have been divided into non-radioactive and radioactive approaches. Each of these is described in more detail in the following sections.

## NON-RADIOACTIVE THERAPIES: SURGICAL, LOCO-REGIONAL AND SYSTEMIC APPROACHES

### Surgical Resection/Transplantation

Surgical resection is the primary treatment for patients in BCLC Stage 0, typically a single $< 2$ cm diameter nodule with absent/minimal underlying cirrhosis, not located near any major intra-hepatic vessels. Other guidelines like from the Japanese Society of Hepatology, Hong Kong Liver Cancer (HKLC) staging system and Indian National Association for Study of the Liver (INASL) recommend resection even for selected cases of multi-focal lesions [9, 49, 50]. Omata et al. have stated that in routine clinical practice, liver resection may need to be a strategy even for intermediate (BCLC stage A/B) cancers [25]. Success in terms of post-treatment remission would largely depend on the initial staging. As per INASL consensus, even with strict selection there is a significant recurrence risk ($> 70\%$) at 5 years post-resection because of underlying liver disease [9]; a repeat of the resection may be called for if it meets eligibility criteria.

Transplantation offers greater survival benefit, since it allows for removal of both the tumor and cirrhotic liver tissue. Under the strict Milan criteria (BCLC stage A type single lesion $< 5$ cm in diameter or up to 3 lesions each $< 3$ cm, absence of vascular invasion and distant metastases), primary transplantation shows $< 75\%$ survival at 4–5 years in an arguably more cost-effective manner than salvage transplants/resection/loco-regional therapy [51, 52]. But guideline reviews from medical fraternities in India and abroad have suggested these criteria may be so restrictive as to serve only a small fraction of HCC patients [9, 25]; in countries where the ratio of donors to recipients is much lower, the procedure is likely recommended to more-at-risk intermediate stage patients (C-P score A/B). Simultaneously, they cite the findings of Volk et al., calling for measured relaxation of the requirements to prioritize patients who would obtain the highest survival benefit [53].

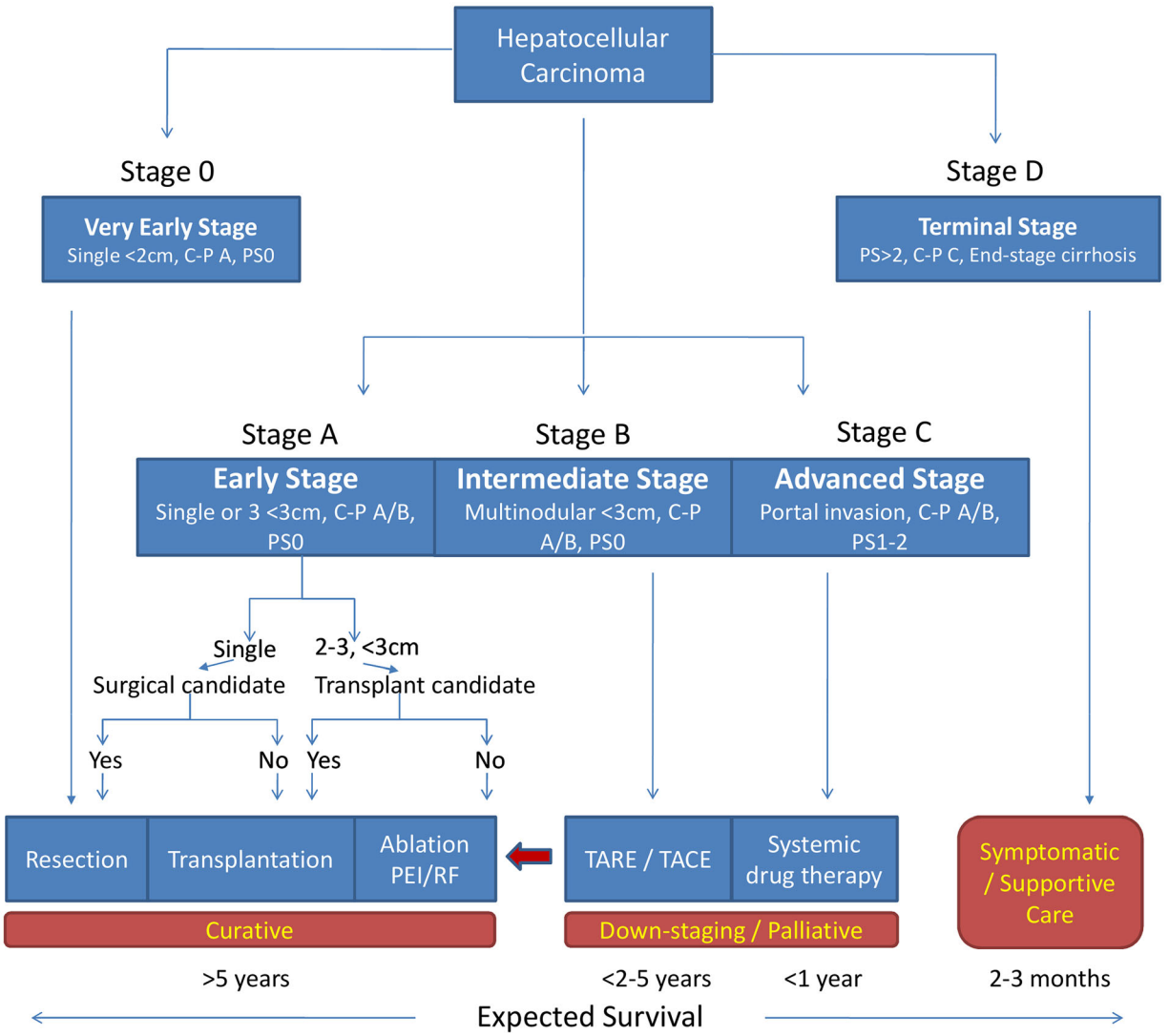


**Fig. 1** Schematic representation of the Barcelona Clinic Liver Cancer (BCLC) staging system

### Local Ablation Therapies: Ethanol and Radiofrequency Ablation (RFA)

Ablation therapies can serve as a mass alternative to resection and transplantation in eligible cases. The main types are (1) chemical ablation with percutaneous administration of ethanol/acetic acid to create a cytotoxic environment in tumor tissue and (2) radiofrequency or microwave ablation, with tissue localized electrodes generating heat for significant necrosis. Ablation therapies are minimally invasive, economical compared to surgical and embolic therapy options and can be repeated with lower probability of adverse effects. Effectiveness is dependent on staging. Patients having few detected hepatic lesions ($\leq 3$) with smaller diameter ($\leq 3$ cm) may be best benefited, showing 38–60% 5-year survival for percutaneous ethanol injection (PEI) and 40–70% for radiofrequency ablation (RFA) [54, 55]. Accordingly, they are recommended for BCLC Stage 0-A with C-P score A/B [9, 25]. While RFA appears generally superior to PEI for small lesions, the latter may be more suitable in certain cases (e.g. when lesions are located near major vessels or the biliary tree) [56]. Ablation is also suggested for post-resection local tumor

progression and distant recurrences [57]. An effective diagnostic program that can detect patients suitable for ablation can reduce the need for transplantation or other more invasive treatments.

## Systemic and Localized Chemotherapy

Chemotherapy is a useful modality in specific clinical situations involving non-resectable HCC. Chemotherapy for HCC falls into two categories: (1) conventional/systemic chemotherapy, with systemic administration of therapeutic drugs, and (2) trans-arterial chemoembolization, where the drug is encapsulated in an embolizing medium that gets trapped in the tumor-feeding vasculature, delivering a higher target dose with reduced toxicity to surrounding normal tissue.

### *Systemic Chemotherapy*

Systemic chemotherapy with agents such as tamoxifen and doxorubicin has long had limited effectiveness in HCC, being dismissed in previous reports as having no OS benefit [58]. Newer drugs, however, have proved useful in specific patient groups. Sorafenib has been reported in phase III trials to be well tolerated and efficacious for advanced HCC [59]. Dosage and duration also have a significant impact on the effectiveness of chemotherapy. A large-scale multi-institutional retrospective study of sorafenib with ~ 4900 patients showed that, compared to the standard prescribed regimen of 800 mg/day, patients initiated with reduced doses showed better tolerance with fewer adverse effects, reduced treatment costs and minimal change in OS values as per the study parameters [60]. Among combinatory drug cocktails, sequential sorafenib/regorafenib treatment has been proposed to offer survival benefit for C-P score A/B patients. A FOLFOX4 drug cocktail was approved in 2013 for treating advanced HCC patients in China and proclaimed in 2018 as a cost-effective, non-inferior alternative to sorafenib, after which it continues to be recommended to Chinese patients [28, 61]. Other potential drugs include the multikinase inhibitor lenvatinib, which was shown to be a suitable first-line alternative to sorafenib, and the anti-VEGFR2 antibody ramucirumab, which is seen as an adjunct to sorafenib therapy in specific cases of advanced HCC [25, 62–64]. Similarly, a phase III study of immunotherapy with cytokine-induced killer cells has been favorably compared to surgery and standard care [65]. However, these require more large-scale studies and are as such not currently included in clinical recommendations.

### *Trans-arterial Chemoembolization (TACE)*

TACE involves application of a therapeutic drug encapsulated in an embolic matrix, delivered to the tumor by selective hepatic arterial administration. While more tedious in application than systemic chemotherapy, it is advantageous, because 80–85% normal liver supply is drawn via the portal vein, whereas hepatic tumors are almost exclusively fed by the arterial supply, leading to targeted delivery at the site of action, minimizing collateral toxicity. The drug is gradually released from the matrix, giving an extended therapy window, and the embolism causes ischemic tumor necrosis by arterial occlusion [66]. Drugs like doxorubicin, cisplatin and mitomycin have been used alone or in various combinations for TACE. The use of drug eluting beads (DEBs) instead of free drug may further reduce liver toxicity [43]. Some consensus reports have proposed that TACE may be repeatedly given or used sequentially with systemic chemotherapy [25], and recent literature claims advantages for TACE in combination with RFA or radiation beam therapy [67], but others have advised against recommendations of such combinations in routine practice, claiming no additional survival benefit [56].

As there is a significant overlap in application between TACE and the radioisotopic therapy known as trans-arterial radioembolization (TARE), these aspects will be discussed and compared in detail in the section dealing with TARE. It may however be said that TACE is expressly contraindicated in concomitant portal vein thrombosis (PVT), where it may cause complete blockage of the blood supply and extensive collateral tissue necrosis [9]. In such cases, TARE may serve as a useful alternative.

## RADIOACTIVE THERAPIES: BEAM RADIATION AND RADIONUCLIDE ADMINISTRATION

With caveats, radiation is a useful therapeutic tool for liver cancers. Radioactive or radiation-based therapies for HCC fall in two categories: (1) external beam radiation therapy (EBRT), with x-rays/gamma radiation/proton beams and (2) selective internal radiation therapy (SIRT)/-trans-arterial radioembolization (TARE), using beta-emissions of therapeutic radioisotopes.

### External Beam Radiation Therapy

EBRT is the dominant radiation therapy for most cancers. HCC and liver metastases present a more complex situation, since normal liver is also radiosensitive. Radiation induced liver disease (RILD) is a real danger for HCC patients receiving EBRT, and this has limited the applicability of conventional radiotherapy [68]. The situation may be improved by image-guided 3D conformal radiation therapy (3D-CRT), where the volume of the tumor mass is considered, but a safer alternative would be stereotactic body radiation therapy (SBRT), in which multiple radiation beams converge upon a precise predetermined dose delivery point. Multiple reviews have suggested that SBRT can provide localized disease control where patients are ineligible for other therapy [69, 70], and several institutional studies reporting short- and long-term outcomes are now available [71–73], but greater validation through randomized trials is lacking. This is likely why some guidelines, like the American Association for Study of Liver Diseases (AASLD) and the EASL, have not yet prescribed radiation therapy for HCC management, citing lack of robust evidence for recommendation [25, 43]. But others such as the National Comprehensive Cancer Network (NCCN) and the Korean Liver Cancer Association (KLCA) have acknowledged it as an option for unresectable/refractory HCC [74, 75]. Similarly, the HKLC has proposed multi-fractional SBRT as a bridging therapy before resection, and as an alternative to ablation for critically located tumors in patients with a C-P score of B or lower [56]. To reduce the possibility of non-target radiation dosage from respiratory movement of organs, multiple techniques are developed for real-time tracking of moving tumors, coupled with dynamic collimation or use of a robotic arm to shift the radiation beam in sync [76]. Intensity-modulated radiation therapy (IMRT) applied as adjunct to conservative resection can reduce the frequency of recurrences and improve OS at least in a 3-year period [77, 78]. EBRT can additionally serve an important auxillary role for skeletal and lymph node metastases [79].

Proton beam therapy (PBT) with its dosimetric safety advantage has been suggested to show promise in disease control, OS and reduced adverse effects [80–82]. The American Society of Radiation Oncology (ASTRO) currently accepts HCC as a Group I indication for insurance coverage for PBT on the evidence available. PBT may especially help in patients with large tumors or PVT, where sparing of reserve function is paramount [83]. However, infrastructure and cost considerations must be accounted for before consideration as a mainstream option for HCC [84].

Mainland China possesses 1930 linear accelerators, 96 Co-60 teletherapy units, 173 X-knife units and 212 gamma-knife units available for radiation oncology services, which should make beam therapy very accessible for eligible HCC patients [85]. In India, > 540 teletherapy units are currently employed in adjunct radiotherapy, but there are just 22 advanced therapy units and only 1 PBT facility [86]. Though several linear accelerator-based units are also capable of stereotactic treatment, they are over-burdened for conventional radiotherapy requirements alone. Besides machines, skilled manpower is an essential requirement for safe and effective delivery of SBRT. Hence, for India, the infrastructure for EBRT for HCC is currently inadequate, and it may be wiser to place emphasis on internalized radiotherapy for patients with non-resectable liver cancers. SBRT is presently less expensive compared to imported microsphere-based TARE formulations, but this may change with greater clinical uptake of generic/indigenous radionuclide therapies. Although the Indian Council of Medical Research guidelines

acknowledge the option of SBRT for patients with early and advanced HCC, EBRT is not currently recommended in India for HCC outside of clinical trials by the INASL [87].

## Selective Internal Radiation Therapy/ Trans-arterial Radioembolization

SIRT/TARE is analogous to TACE, in that a radionuclide encapsulated inside or attached to an embolizing agent is administered intra-arterially to selectively localize in the tumor-feeding vasculature. Depending on tumor size and location, SIRT may be performed with a lobar, sectorial or segmental approach [43]. Radiation dose from adequate deposition of the radionuclide in the tumor causes destruction of malignant cells by DNA damage and cell signaling mechanisms [4]. It may be offered as an alternative to TACE for intermediate BCLC stage patients with large ($\geq$ 5 cm) or intermediate multi-focal ($\geq$ 3 cm, $\geq$ 3 tumors) lesions in the absence of vascular invasion or extra-hepatic spread, or as a bridge to transplantation. In terms of mainstream clinical guidelines from Western nations, the AASLD as of 2018 regards the data for radiation-based therapies such as EBRT and TARE as 'emerging' but not adequate to make a recommendation [88]. As per the EASL recommendations, TARE compared to TACE does not provide longer OS, but induces lower toxicity and shows better results in terms of time to progression, tumor control and quality of life. For advanced HCC (BCLC B and C stage), it does not show a survival benefit compared to sorafenib [43]. However, the Hong Kong Consensus Statements for management of unresectable HCC state that TARE is useful as a bridge therapy to liver transplantation in suitable candidates and for C-P A patients with multifocal or large burden HCC, and it can be considered for unresectable/unabalatable lesions > 5 cm [56]. TARE has also been suggested for patients with C-P score A/B that fail to respond to TACE, reported to score better on tumor response, safety and quality of life (QoL) parameters [25, 56, 87]. A 2016 meta-analysis comparing TARE and TACE suggested a long-term benefit of TARE in terms of delayed tumor progression [89]. As previously stated, PVT is a contraindication to chemoembolization, another area where TARE can improve QoL for the patient [87]. Reports have suggested that segmented TARE application can be prescribed for specific early BCLC stage patients not eligible for resection/ablation because of proximity of the hepatic lesions to vital viscera. They have also discussed TARE for patients with single lobe, multi-focal lesions as an alternative to surgical lobectomy, as TARE not only causes atrophy in the affected lobe, but initiates compensatory hypertrophy in the contralateral lobe, helping to shore up reserve liver function [90].

Unlike TACE, which requires release of the drug from the embolic matrix, SIRT radionuclides can exert cytotoxic action by beta-emission at the pre-capillary level bound within the matrix. Therefore, TARE agents can afford to be designed for greater stability with minimal leaching of radioactivity from the formulation. There are two categories of SIRT agents based on the type of embolic matrix: (1) radionuclide-tagged formulations of lipiodol and (2) radiolabeled microparticles.

### *Radionuclide-tagged Formulations of Lipiodol*

In clinical trials nearly 3 decades ago, lipiodol was assessed for TARE after substitution labeling with iodine-131 ($^{131}$I) [half-life 8 days, beta-energy (max) 0.6 meV, tissue penetration 0.6–2 mm], exhibiting good patient tolerance [91]. Long-term reports have shown up to 39 $\pm$ 8.3% OS at 3 years [92]. When applied in random selection trials as post-resection adjuvant therapy, it improved OS for up to 7 years (66.7% vs. 31.8% for control) [93]. Studies with [$^{131}$I]lipiodol TARE found lower adverse effects than with TACE [94]. In India, [$^{131}$I]lipiodol for TARE has been demonstrated capable of cost-effective indigenous preparation—using a semi-automated synthesis module and locally available reactor-produced radioisotope—of standard patient doses of 2.22 GBq $^{131}$I activity (as per European Association of Nuclear Medicine guidelines, corresponding to a mean liver dose of $\sim$ 50 Gy) [95, 96]. This can be replicated in any radiopharmacy with the suitable setup and is an economical SIRT solution. [$^{131}$I]lipiodol

has certain disadvantages because of the radioisotope. Preparation must be done in a suitable ventilated cabinet to prevent accidental $^{131}$I aerosol release to ambient atmosphere. The 364-keV penetrative gamma emissions with the long 8 day half-life call for additional precautions in patient management. For example, it must be ensured that no individual in public receives > 5 mSv external dose from the patient. Hence, the patient may be discharged only after the dose at 1 m away reduces to 0.07 mSv/h [97], and necessary precautions must be followed in handling/disposal of their body waste [98]. Thyroid uptake of free $^{131}$I is also reported, though there is no consensus on the need for measures to protect against this [96]. Thus, while [$^{131}$I]lipiodol has the advantage of being a well-known economical mode of TARE, it may not remain the first choice if other options become more widely available.

Lipiodol has also been prepared as a rhenium-188 ($^{188}$Re) labeled formulation. Here, the transition metal forms stable lipophilic complexes with suitable ligands, such as AHDD (acetylated 4-hexadecyl-4,7-diaza-1,10-decanedithiol), DEDC (diethyl dithiocarbamate) and SSS [(S3CPh)2(S2CPh)], which can then be extracted into lipiodol. Unlike with $^{131}$I, no covalent bond exists between $^{188}$Re and lipiodol. With greater therapeutic energy and penetration (beta-energy max 2.1 meV, penetration range 2–10 mm), safer imaging-friendly gamma emission (155 keV) and a shorter half-life (16.9 h), $^{188}$Re is more suitable for TARE than $^{131}$I. Additionally, the ligands mentioned can form rhenium-188 complexes in much higher yield than the substitution labeling process for $^{131}$I and be extracted into lipiodol phase with moderate to high efficiency. Its availability through a versatile application "Good Manufacturing Practice" (GMP)-certified tungsten-188/rhenium-188 ($^{188}$W/$^{188}$Re) radionuclide generator makes it convenient to elute rhenium-188 and prepare the radiopharmaceutical on demand in a radiopharmacy [99, 100]. Reports of $^{188}$Re-HDD in phase I and II trials indicate that escalation of administered radioactivity from 1.8–9.8 GBq showed good tolerance with minimal side effects, rapid renal clearance of blood radioactivity and regression/stabilization of the disease in an appreciable proportion of patients [101]. A multi-centric study by nuclear medicine departments in India and Vietnam found complete/partial disappearance of tumor or stable disease in > 68% of patients and survival rates of 58% at 24 months and 30% at 36 months, with a median survival of 980 days [99]. A more recent study showed the utility of $^{188}$Re-HDD/lipiodol for therapy in patients with solitary HCC not amenable to resection [102]. Moreover, post-administration SPECT imaging could be used to assess absorbed doses in target and normal tissue [103]. $^{188}$Re-HDD/lipiodol carries caveats of limited extraction (~ 60–70%) into lipiodol and adhesion to vial/syringe surfaces, making less therapeutic activity available for injection (50–60%) [103], but formulations like $^{188}$Re-DEDC/lipiodol and $^{188}$Re-SSS/lipiodol, capable of 80–90% extraction into lipiodol and lower surface adhesion tendencies, rectify this limitation. Phase I clinical studies with $^{188}$Re-labeled DEDC and SSS indicate good hepatic retention with minimal uptake in other tissues [104]. Automated synthesis modules for preparation of clinical scale doses of $^{188}$Re-lipiodol via DEDC and SSS have already been reported [105, 106]. In India, kits for formulating $^{188}$Re-lipiodol using DEDC have been indigenously developed, and preliminary clinical assessment at regional nuclear medicine centers has ascertained a favorable profile of the radiopharmaceutical [107]. The sole stumbling block to greater adoption of $^{188}$Re-lipiodol in India is the sparse local availability of $^{188}$W/$^{188}$Re generators, still imported at a significant cost and subject to international market vagaries. An earlier report by Bal and Kumar strongly advocated the need for affordable $^{188}$Re generator technology [108], and the know-how for making various types of $^{188}$W/$^{188}$Re generators in India using $^{188}$W raw material already exists [109, 110], but it would be a significant advantage for any future planned reactors to possess the requisite characteristics for indigenous $^{188}$W production for use in clinical-grade generators in India.

### *Radiolabeled Microparticles*

Microparticles labeled with beta-emitters such as yttrium-90 ($^{90}$Y) are the most widely

**Table 1** Technical comparison of clinically available yttrium-90 labeled microspheres for trans-arterial radioembolization—Therasphere™ and SIR-Sphere® (data sourced from [91, 110])

| Therasphere | SIR-Sphere |
|---|---|
| Non-biodegradable glass microspheres | Biodegradable resin microspheres |
| Diameter range 20–30 microns | Diameter range 20–60 microns |
| Radioactivity concentration 3 GBq in 1.2 million microspheres (2500 Bq per sphere) | Radioactivity concentration 3 GBq in 40–80 million microspheres (50 Bq per sphere) |
| Indicated for inoperable HCC as a bridge to transplantation and HCC complicated by PVT | Primarily indicated for unresectable liver metastases of colorectal cancers |

employed form of SIRT for HCC. Made of degradation-resistant material with sufficiently large particle diameter (> 20 micron), they embolize in the terminal arterioles of tumor-feeding vasculature permanently, or at least long enough for the radiation dose to be deposited almost entirely [111]. $^{90}$Y is the most common radioisotope to address primary and secondary liver malignancies. Its 2.28-meV (maximum energy) pure beta emission, 11-mm maximum penetration range and 64.2-h half-life can provide an effective therapeutic dose to large and/or multi-nodal lesions [94]. Despite being tested for liver cancer therapy as early as 1982 [112], there are only few commercially available $^{90}$Y-labeled microparticle therapies for HCC: (1) $^{90}$Y-impregnated glass microspheres—Therasphere® (BTG, Canada); (2) $^{90}$Y-labeled resin microspheres—SIR-sphere® (Sirtex Medical, USA) [113]. The major differences between them are outlined in Table 1.

Due to the greater radioactive concentration and higher specific gravity compared to SIR-Spheres® (3.2 g/cc vs. 1.6 g/cc), Therasphere® is less amenable to dose fractionation, which may be practiced for logistics in large-scale public healthcare facilities. The multi-fold higher particle count in SIR-spheres® also means higher embolism for a given radiation dose [114]. These aspects are expected to factor in when determining the specific eligibility criteria under which these agents may be prescribed.

As previously mentioned for imaging-based diagnosis, the administration of $^{90}$Y-labeled therapeutic microparticles is preceded 1–2 weeks by a safety scan using ~ 148-185 MBq of $^{99m}$Tc-labeled MAA to simulate deposition of therapeutic microparticles in the vascular bed. This is primarily to determine the lung shunt fraction (LSF), the potential extent of shunting of these microparticles to the lung because of arteriovenous anastomoses in the tumor vasculature. This helps minimize the risk of radiation pneumonitis as an adverse effect. Existing literature recommends maximum lung exposure of 30 Gy in a single session and 50 Gy across multiple sessions, beyond which dose reduction is made or TARE is contraindicated [111, 114]. It may however be noted that some reports have raised doubts over the accuracy of LSF calculated from $^{99m}$Tc-MAA scans [115]. For liver metastases from colorectal cancers, LSF is not usually of significant concern [94]. Dosimetric data from the $^{99m}$Tc-MAA scan are also useful to pre-determine the possible absorbed dose ratio of tumor to normal liver tissue.

The safe dosage for EBRT is only 30 Gy for conventional radiotherapy and 40-65 Gy for IMRT and SBRT in reported clinical studies [77, 116]. For SIRT, increased selectivity has made it possible to deposit an up to 150 Gy dose in a single session without serious instance of RILD in dose escalation studies [96]. In fact, reviews have cited studies with radiation doses of up to 748 Gy in a single session and 1580 Gy dose across multiple sessions targeted onto the tumor lesions without clinical evidence of radiation hepatitis or pneumonitis [117].

A systematic review of TARE with $^{90}$Y microspheres (both glass and resin) comparing 14 clinical studies with > 700 HCC patients with concomitant PVT showed a median survival rate of 9.7 months with 74.3% median disease control rate [118]. In these patients the attending adverse effects mostly did not require medical intervention. Vilgrain et al.'s report of the SARAH trial—a randomized controlled phase 3 trial with 459 patients comparing $^{90}$Y-labeled resin microspheres with systemic sorafenib for locally advanced and inoperable HCC—states that while OS did not appreciably vary between the groups, frequency of grade 3 or worse treatment-related adverse effects was lower in TARE [119]. Sangro et al. have highlighted that contrary to TACE's requirement of extended hospitalization, TARE has converted embolic therapy into an outpatient procedure logistically, economically and psychologically favorable to the patient [120]. Controversially, a 2018 review comparing patients receiving SIRT, 3D-CRT and SBRT showed no significant difference in OS between them at 1 year [121], but appropriate patient selection would be a deciding factor for this parameter. A recent UK-based report by Manas et al. evaluated the cost-effectiveness of TheraSphere against other embolic treatments such as conventional TACE (cTACE) or drug-eluting bead TACE (DEB-TACE) and found that for patients with early to intermediate HCC, treatment with TheraSphere is cost-effective, mostly because of its more successful downstaging ability [122]. In another multicentric cohort study, while transplant-free survival was similar between SIRT and DEB-TACE, SIRT's effectiveness was observed even with significantly larger median tumor size [123].

In India, Therasphere® was first tested in 2007 and has been used in major metropolitan nuclear medicine departments, but the high cost factor per dose and involved logistics of importing makes it accessible only to a select subset of patients that can benefit. Other resins and polymers have been tested for potential as TARE agents, and other radiolabeled microparticle formulations incorporating other isotopes such as $^{188}$Re and $^{166}$Ho have been reported, but apart from $^{166}$Ho-labeled polylactate microspheres (Quiremspheres®), these have not as yet progressed beyond preclinical evaluation or limited clinical studies [124, 125]. An advantage of $^{188}$Re/$^{166}$Ho-labeled formulations is that their image-able gamma emissions allow for pre-therapy safety assessment by microdosimetric study using the same preparation.

***Percutaneous/Trans-arterial Ho-166 Chitosan***

While not so far considered for any clinical recommendations, there are reports of limited phase II clinical trials in Korea for both percutaneous and trans-arterial application of $^{166}$Ho-labeled chitosan. In patients with tumors < 3 cm diameter and absence of portal vein invasion and extra-hepatic metastases (mostly BCLC stage A), they showed complete tumor necrosis in > 77% patients, with a 65% 3-year survival rate [126]. $^{166}$Ho-chitosan was also studied as a trans-arterial radiopharmaceutical in patients with a single large (3–13 cm) lesion and no vascular shunt, where around 57% showed complete response for a median of 27 months [127]. However, there have since been no reports of larger scale clinical trials for either approach. In India also, the development of a kit-based methodology for preparation of $^{166}$Ho-chitosan for liver cancer treatment has been reported [128], but there is no literature of clinical studies performed with this kit.

## RADIATION AND RADIOISOTOPES IN HCC MANAGEMENT: CAN THEY SERVE A GREATER ROLE?

The global threat of hepatocellular carcinoma (and liver cancers in general) calls for a multi-pronged defense strategy to tackle the disease. Integration of HBV vaccination into the Universal Immunization Programme in India is probably one of the most important and effective methods to reduce the incidence of viral hepatitis-related HCC and needs to be replicated in other developing countries. Early diagnosis and accurate staging are paramount in its effective treatment. While implementation of effective screening in developing countries with large populations—where ironically HCC is most prevalent—is no doubt arduous, it

may be an essential component of deterrence to interrupt HCC's prolonged period of asymptomatic development, beyond which it becomes exponentially less conquerable. Detection of cases in earlier stages of the disease (BCLC 0/A) will allow for less invasive, patient-friendly, relatively inexpensive therapies toward management and likely cure of the condition. Both tumor staging and residual liver function play a role in the staging and prognosis of the disease and determination of treatment strategies. Classification systems like the BCLC, which can link staging to a recommended therapy regimen, prove highly useful to clinicians. Of course, like any guideline, it must consider the individual patient's case history and availability of viable treatment options that will best support the case. Radiation in the form of x-rays from CT, while not suited for a general screening program, serves in the confirmatory diagnosis of suspected cases with near absolute positive predictive value. Nuclear medicine currently plays only a limited role in HCC diagnosis/prognosis: tracers such as $^{68}$ Ga-PSMA and general liver function tracers such as $^{99m}$Tc-labeled mebrofenin or sulfur colloid have found application in patient assessment, but without sufficient large-scale testing and meta-analysis, HCC detection and prognosis are expected to rely primarily on non-radioactive techniques.

There are myriad therapeutic techniques for HCC (and liver metastases): surgery, loco-regional ablation by physical/chemical means, embolic therapy delivering cell-killing drugs or radiation, external beam therapy and systemic chemotherapy. These are not necessarily competitors, but an array of tools from which the overseeing physician must choose the optimal implementation or combination thereof. EBRT and SIRT are the major applications of radiotherapy for HCC. While adhering to the ALARA (as low as reasonably achievable) safety principles for radiation applications, when such techniques offer specific advantages viz. scalable utilization and measurable patient benefits in QoL and OS, they must be more widely adopted in the HCC clinical scenario. A simplistic eye-view the BCLC staging suggests that surgery and ablative therapies are better suited to earlier stage cancers and potentially curative, while chemo-/radioembolization and systemic chemotherapy are advised for more advanced forms, primarily serving as palliatives. However, a meta-analysis of recent studies suggests a more layered application of these techniques in additive/synergistic combinations. Ablation and TARE/TACE applied in tandem to resection have increased the period of recurrence-free survival. SBRT and TACE combined have shown a greater progression-free survival and response rate than sorafenib alone [129]. SBRT and TARE/TACE have also helped to downstage multi-focal intermediate stage cancers to where they become eligible for resection/ablation or sustained patients during the waiting period for transplantation. The advantage of TARE over TACE in patients with concomitant PVT should be duly considered when preparing the treatment strategy in these cases. TARE and EBRT may be indicated in specific situations of post-resection adjuvant therapy where ablation is contraindicated. Multi-dose SBRT may prove useful in patients with single lesions where the location is not amenable to surgery and ablative measures might prove inadequate. A combination of TARE/TACE/SBRT with systemic chemotherapy can help patients with extra-hepatic metastases to downstage the disease to where it can be addressed with other tools. A critical potential application of radiotherapy is when HCC metastases infiltrate critical tissues like the brain [130]; most other modalities are of limited application here because of permeability/systemic toxicity issues and the potential danger of any invasive protocols. TARE (or any other approach) to treat the hepatic lesions may be paired with a targeted SBRT modality to specifically address the cranial metastases. Ready availability of specific techniques in terms of equipment and trained personnel at clinical centers is an important factor. In countries that have a significant HCC-afflicted population with limited public healthcare options, resective surgery, ablation, EBRT and selected embolic therapies (TARE/TACE) represent the major strategies available to patients. Since only a small proportion of HCC patients is at least initially eligible for resection, and ablative therapies are less useful for a significant proportion of diagnosed cases, there is a strong

case to enhance clinical utilization of SBRT or TARE/TACE to manage or downstage the disease till other therapy options become viable. SBRT in combination with measures like chemotherapy would be useful in countries like China, which have many beam therapy centers for the population, and has also generated many clinical data on newer drugs and drug combinations effective against HCC. India with its limited access to HCC therapy-capable beam therapy centers may have to lean more on internalized radionuclide therapies. One obstacle toward this is the currently high cost of SIRT formulations that are imported. To address this, there should be greater clinical adoption of indigenously developed solutions that can provide similar benefits with easier availability and lower cost, some of which are discussed in the relevant sections of this report. Simultaneously, the infrastructure related to their production and on-site delivery should be enhanced to keep up with the perceived demand and eventually have the capability to export to other countries at more cost-effective rates as a worldwide public health initiative. For advanced multi-focal HCC cases, China's advances in economically more favorable systemic chemotherapy can be adapted and followed by other nations with a large public healthcare burden. Similarly, depending on the proportion of patients with such needs, the technological means to deliver a targeted dose of EBRT for HCC or metastases in critical areas should also be made more widely available. Awareness in the clinical community regarding availability of these options for HCC is also essential in ensuring that appropriate patients receive the most optimal treatment/combination of treatments.

## CONCLUSION

When viewed from a holistic perspective, the various approaches to treatment of liver cancer are revealed to complement each other when applied after judicious tailoring on the strength of an effective screening/diagnosis program to the individual patient's requirements and careful monitoring of their impact to ensure optimal therapeutic benefit with minimal collateral damage. Radiation and radioisotope-based approaches are seen to be a necessary component of any holistic management protocol for HCC. What is required is strategic planning at both the level of the clinical institution and the level of national health policy to identify, promote and enhance availability of the specific approaches that can provide the best possible therapeutic benefit to the greatest proportion of patients that require it.

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***Compliance with Ethics Guidelines.*** This article is a review based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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