

# INDIAN COUNCIL OF MEDICAL RESEARCH



## CONSENSUS DOCUMENT FOR MANAGEMENT OF HEPATOCELLULAR CARCINOMA

*Prepared as an outcome of  
ICMR Subcommittee on Hepatocellular Carcinoma*



Division of Non Communicable Diseases  
Indian Council of Medical Research  
2019

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Division of Non Communicable Diseases  
Indian Council of Medical Research  
Ansari Nagar, New Delhi – 110029  
2019

### **Disclaimer**

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. Balram Bhargava  
Secretary,  
Department of Health Research  
and Director General, ICMR

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# Foreword

I am glad to write this foreword for Consensus Document for Management of Hepatocellular Carcinoma. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines which worked tirelessly in formulating site-specific guidelines. The purpose of consensus document is to provide clear, consistent, succinct, evidence-based guidance for management of various cancers. I appreciate and acknowledge support extended by each member of the subcommittees for their contribution towards drafting of the document.



Hepatocellular Carcinoma require specialized multi-disciplinary care and treatment for better outcome. This document consolidates the modalities of treatment including the diagnosis, risk stratification and treatment. Hope that it would provide guidance to practicing doctors and researchers for the management of patients suffering from Hepatocellular Carcinoma and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on the subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this Consensus Document for Management of Hepatocellular Carcinoma would serve desired purpose.

*Balram Bhargava*

(Dr. Balram Bhargava)  
Secretary, Department of Health Research  
and Director-General, ICMR

# Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.



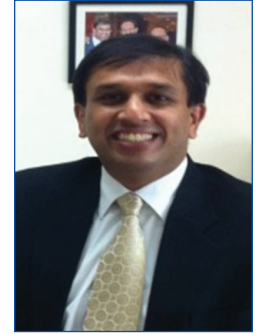
The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome, Pediatric Lymphoma, Pancreatic Cancers, Hepatocellular Carcinoma and Neuroendocrine Tumours. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till October 2015 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)  
Chairperson  
ICMR Task Force Project

# Preface



Hepatocellular Cancer remains an aggressive cancer with a dismal long term prognosis. With the rise of non alcoholic fatty liver disease and hepatitis B being endemic in India, this is a major health concern. Radical surgery, currently the only option for cure, is feasible in only a fraction of patients since the vast majority present to the clinician in advanced stages of the disease. Fortunately, the past two decades have not only seen tremendous refinements in surgical technique, liver transplantation with improved short and long term outcomes, and better molecular understanding has progressed enormously. Simultaneously, medical and radiation oncology has witnessed excellent progress that has clearly resulted in a paradigm shift in the management of liver cancer.

India with a population of 1.2 billion records a low incidence of this cancer but increasing awareness and urbanization is changing this picture and the prevalence has markedly increased in the past decade. This cancer requires specialized multi-disciplinary care and should be ideally treated in centers of excellence for better outcomes. This has been proven worldwide and our nation needs to take steps in the same direction. On this backdrop, the ICMR Guidelines have the potential to go a long way in improving standards of care across India.

We take this opportunity to congratulate the ICMR leadership and the various members and contributors for publishing this excellent resource.



Dr Bhawna Sirohi  
Chairperson, Sub-committee on Hepatocellular Cancer  
Director, Medical Oncology  
Max Healthcare, New Delhi



Prof Shailesh V Shrikhande  
Co-chairperson  
Deputy Director  
Tata Memorial Centre, Mumbai

# Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.



The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.



(Dr. R.S. Dhaliwal)  
Head, NCD Division



## Acknowledgement

The Consensus Document on Management of Hepatocellular Carcinoma is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma, pancreatic, hepatocellular & neuroendocrine tumours. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.



This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee. Dr Bhawna Sirohi, is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Balram Bhargava, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to benefits the cancer patients.

I would like to thank Dr. R.S. Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

A handwritten signature in blue ink that reads "Tanvir Kaur".

(Dr. Tanvir Kaur)  
Programme Officer & Coordinator



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## Members of the Sub-Committee

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### ***Chairperson***

**Dr. Bhawna Sirohi**

Max Healthcare, National Capital Region

### ***Co-Chairperson***

**Prof Shailesh V. Shrikhande**

Deputy director, Tata Memorial Centre, Mumbai

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## Members

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- |  |  |
|--|--|
| 1) Dr. Mahesh Goel<br>Tata Memorial Centre, Mumbai | 6) Dr. Vikram Bhatia<br>Institute of Liver and Biliary Sciences<br>New Delhi |
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| 3) Dr. Munita Bal<br>Tata Memorial Centre, Mumbai  | 8) Dr. Deep Narayan Srivastava<br>AIIMS, New Delhi                           |
| 4) Dr. Atul Kumar<br>AIIMS, New Delhi              | 9) Dr. GK Rath<br>AIIMS, New Delhi   |
| 5) Dr. Raj Kumar Shrimali<br>AIIMS, New Delhi      | 10) Dr. Shraddha Patkar<br>Tata Memorial Centre, Mumbai                      |

Support: Dr Chaitali Nashikkar, CTMH, Mumbai

# Categories of Evidence and Consensus

## *Levels of Evidence*

**Level 1:** High quality randomized controlled trials (RCTs) showing (a) a statistically significant difference or (b) no statistically significant difference with narrow confidence intervals; systematic reviews of Level I RCTs

**Level 2:** Lesser quality RCTs (e.g. <80% follow-up, no blinding, or improper randomization); prospective comparative studies; systematic reviews of Level II studies or of Level I studies with inconsistent results

**Level 3:** Case control studies; retrospective comparative studies; systematic reviews of Level III studies; retrospective studies

**Level 4:** Case series

**Level 5:** Expert opinions

Grading A to C has been done by the sub-committee. Grade A is to be assigned to a treatment or regimen that is easy to administer, has the highest level of evidence, and is cost effective as evaluated by the National Institute for Health and Clinical Excellence or as deemed so by the task force experts on the particular cancer.

On consideration of peripheral oncology centres, regional cancer centres, and tertiary cancer centres in major cities, the set of recommendations can be divided into 2 categories:

**Desirable/Ideal:** Tests and treatments that may not be available at all centres but the centres should aspire to have them in the near future.

**Essential:** Bare minimum that should be offered to all patients by all centres treating patients with cancer.



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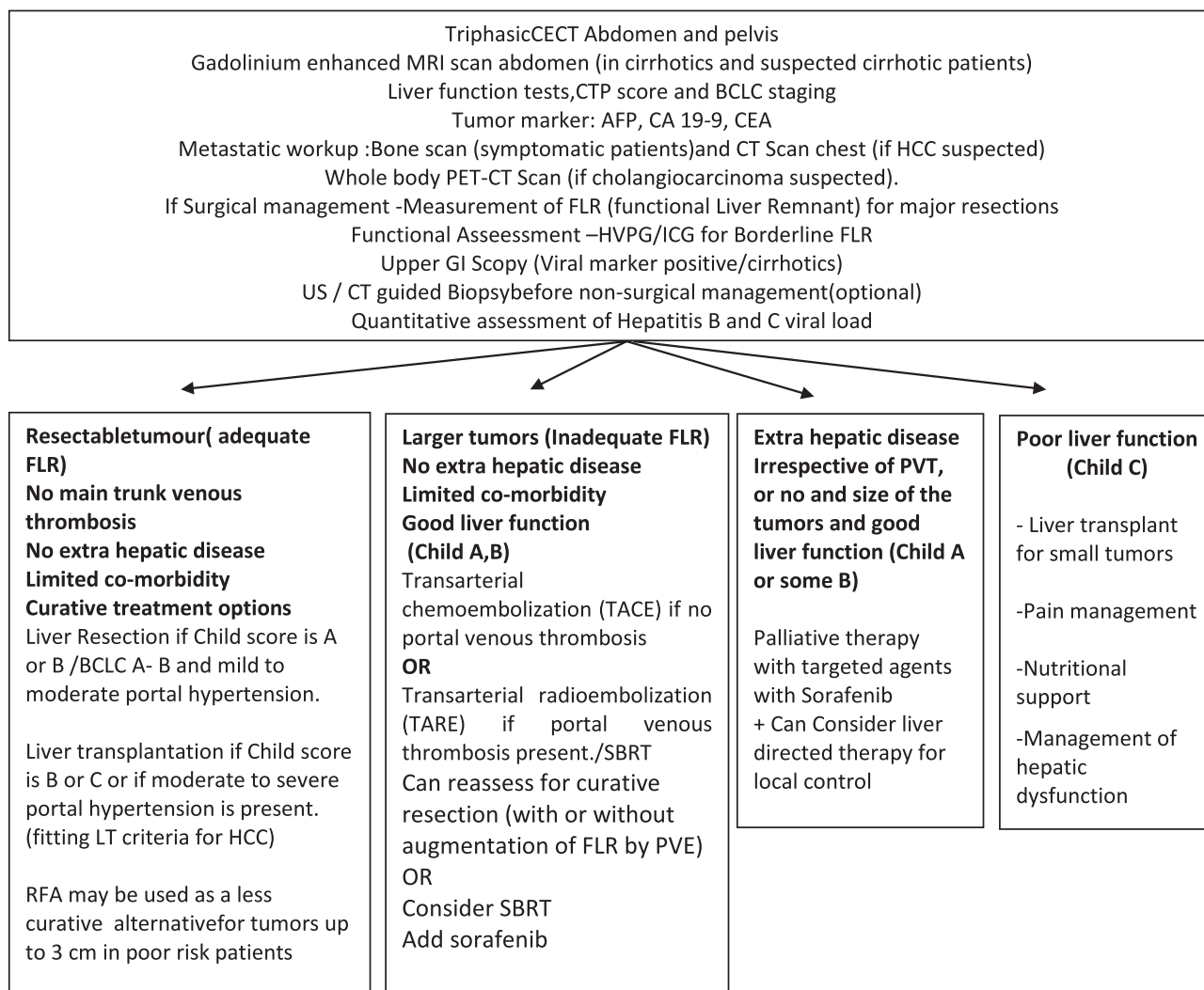
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**Management of Hepatocellular carcinoma**

Incidentally diagnosed at screening/follow up of chronic liver disease

Right upper Quadrant pain/mass, Jaundice, Nausea, weight loss, symptoms related to metastasis



*Sorafenib 400 mg twice daily is the standard dose. However many Indian patients are unable to tolerate this dose and hence need dose reduction.*

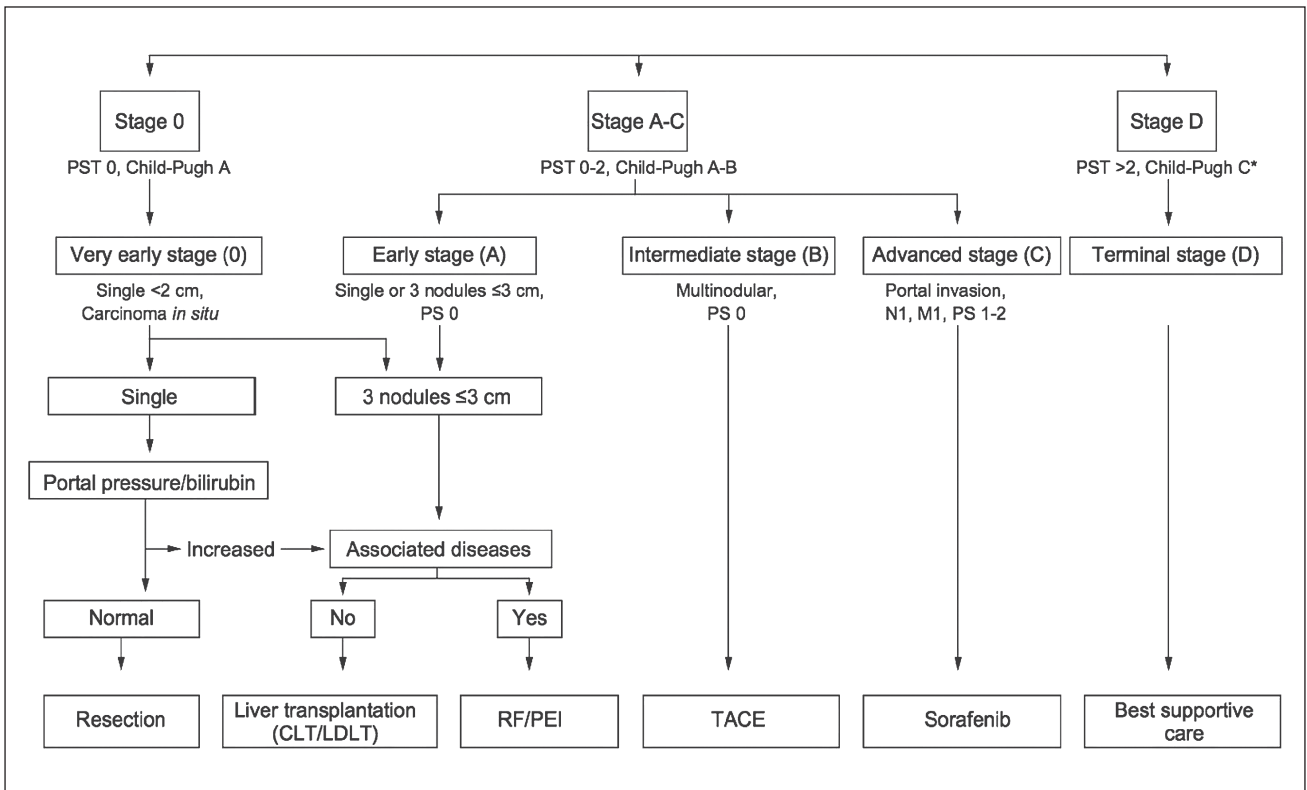
*All patients with chronic HBV and HCV infection need prophylactic therapy to control viral replication before and after interventions*

**Surveillance**

Patients must be followed every 3 months with LFT, relevant tumor marker and CECT Scan chest, abdomen and pelvis

Local recurrence with good liver function would necessitate complete work up for potentially curable treatments.

## BCLC Staging for HCC





# 2

## EXECUTIVE SUMMARY

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This consensus document may be used as framework for more focused and planned research programmes to carry forward the process. The aim of the Indian Council of Medical Research (ICMR) Consensus document is to assist oncologists in making major clinical decisions encountered while managing their patients, while realizing the fact that some patients may require treatment strategies other than those suggested in these guidelines.

- Non-invasive diagnosis can be established by demonstration of the typical HCC radiological hallmark by one of the imaging technique in nodules > 2 cm, and by two coincidental techniques with nodules of 1-2 cm in diameter (dynamic CT or dynamic MRI). If a suspicious nodule measuring >1cm fails to show typical enhancement pattern on both dynamic CT and dynamic MRI, image guided sampling is indicated. AFP estimation is no longer part of diagnostic algorithm of HCC. A PET scan is not routinely recommended.
- Various staging systems can be used but should include (1) tumour size, number, and location (2) liver function (3) performance status of the patient
- The most commonly used is the BCLC staging system which includes patient performance, Child status, number of nodules, size of nodules, portal vein invasion, and metastasis.
- Patients should receive multidisciplinary care under the care of a surgical, medical, radiation oncologist and interventional radiologist, if applicable.
- Surgery (resection/transplant) forms the mainstay of definitive treatment. Small tumours (<3 cm) in patients who are not candidates for surgical resection (Child B & C) can be offered ablative techniques.
- Patients with advanced HCC should be assessed on an individual basis to determine whether targeted therapy, interventional radiology procedures like TACE, TARE or best supportive care should be provided.
- Patients should be offered regular surveillance after completion of curative resection or treatment of advanced disease.
- Encourage participation in institutional and ethical review board-approved, registered controlled clinical trials.
- Refer for early palliative care, if indicated.

# 3

## EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) accounts for 90% of cancers of the liver worldwide with a growing incidence in most countries.<sup>1</sup> Globally, HCC is the fifth most common cancer (7.5 lac new cases per year) and is the third leading cause of annual deaths due to cancer (7 lac death per year) after lung and stomach cancer.<sup>1</sup> Several large international working groups have drafted consensus guidelines,<sup>1-4</sup> which differ among themselves based on the unique concerns of clinical circumstances and population affected.

The Indian Council of Medical Research (ICMR) consensus document for the management of HCC provides an evidence-based approach to the diagnosis, staging, and treatment of HCC pertinent to India. These guidelines aim to maximize healthcare resources, standardize diagnosis methodology, and strengthen the multidisciplinary approach regarding the treatment of HCC.

### **Epidemiology in India**

There is insufficient nationally representative data, so we must depend on autopsy studies, national cancer registries, and population based surveillance data to estimate the frequency of HCC in India. Since cancer is not a reportable disease in India, an increasing number of both rural and urban centers must be encouraged to document cancer related data to assist in building a reliable national cancer registry.

A large-scale verbal autopsy study in 2010 reported liver cancer to be the fourth leading cause of cancer related deaths in men (14,000 deaths) with an age standardized mortality rate (AMSR) of 6.8/100,000 population. In women, liver was the eighth highest cause of cancer related deaths (12,000 deaths) with an AMSR of 5.1/100,000 population.<sup>5</sup> (*Level 2b, Grade B*)

In 2014, the National Cancer Registry Program (NCRP) of the ICMR has expanded to 27 population based cancer registries (PBCRs) covering 34 geographical areas.<sup>6</sup> It also includes 8 hospital based cancer registries (HBCRs). The age adjusted incidence rate (AAIR) of liver cancer in men ranges from 1.2-38 per 100,000 and in women ranges from 0.2 – 2.2 per 100,000. (*Level 2a, Grade B*) In males, the areas covered by Naharlagun PBCR reported the highest AAIR (38.0 in Papumpare district). The incidence of liver cancer increased with increasing age, with a median age at presentation of 40-70 years. (*Level 2a, Grade B*) The International Agency for Research on Cancer (IARC-WHO) also reported similar incidences. Among HBCRs, AIMSRC-Kochi reports liver cancer as the most frequent site of cancer in males (11.3%), which is interesting since in most other centers liver cancer does not figure within the 10 most frequently reported cancers. Based on a prospective observation study, the annual incidence rate of HCC in cirrhotic patients (child A and B) was 1.6%.<sup>7</sup> (*Level 2b, Grade B*) Overall, there has been a significant increase in the reporting/incidence of liver cancer in India over the last 2 decades.<sup>8</sup> (*Level 1b, Grade A*)

### **Risk factors**

70-90% of HCC has been reported in cirrhotic patients globally, making cirrhosis of any etiology the

single most important risk factor for developing HCC.<sup>9,10</sup> Other more common risk factors are chronic hepatitis B infection, chronic hepatitis C infection, heavy alcohol consumption, male gender, increasing age, non-alcoholic fatty liver disease (NAFLD) and aflatoxin exposure. Less common risk factors are obesity, diabetes, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, autoimmune hepatitis, porphyrias, wilson's disease, tobacco use, and family history.<sup>9-12</sup> *(Level 1a, Grade A)*

Risk factors corroborated in Indian studies are cirrhosis, hepatitis B infection, hepatitis C infection, alcohol consumption, aflatoxin exposure, smoking, diabetes, NAFLD, and age.<sup>13-17</sup> In India, HBV genotype D was the most commonly implicated genotype for the development of HCC.<sup>18</sup> Isolated reports implicating genetic risk factors are available from Indian researchers. The involvement of CDKN2B, SOCS1, CDH1, GSTP1, and MYC was shown to alter DNA methylation in the molecular pathogenesis of hepatitis virus-related HCC.<sup>19</sup> Shorter telomeres have also been found in telomerase-positive HCC patients. Variants in low penetrance genes such as GSTM1 and GSTT1 and mEPHX as well as genetic variations of p53 and XRCC1 have also been associated with HCC risk.<sup>20</sup> In the near future, HBV genotype variant analysis and genome-wide association studies may assist in predicting HCC in chronic hepatitis B infected patients.<sup>21</sup> *(Level 3b, Grade C)*

### **Prevention**

Among cancers as a whole, HCC is particularly amenable to prevention given a detailed understanding of risk factors. Primary prevention entails reducing exposure to various carcinogenic hepatotoxins. Secondary prevention aims at managing the chronic necro-inflammatory state of the liver brought about by the carcinogenic hepatotoxin. Tertiary prevention focuses on preventing recurrence after the successful initial treatment of HCC.<sup>17</sup>

The most feasible and cost effective strategy in the Indian scenario appears to be primary prevention.<sup>22</sup> The most easily applicable modality is the hepatitis B vaccination, which is strongly recommended in newborns and health care workers.<sup>22,23</sup> *(Level 1b, Grade A)* Precise testing of blood and blood products for hepatitis B and C prior to administration is also imperative.<sup>24</sup> *(Level 1b, Grade A)* A healthy lifestyle in order to prevent obesity and diabetes along with the control of other related metabolic conditions is beneficial.<sup>24</sup> *(Level 2b, Grade B)*

For secondary prevention, for chronic hepatitis B patients antiviral therapies aimed at maintaining hepatitis B virus suppression and for chronic hepatitis C patients achieving sustained viral response should be recommended to all those who are candidates for antiviral therapy.<sup>25</sup> *(Level 1a, Grade A)* These measures have been shown to successfully prevent progression to cirrhosis and HCC. Patients with a high viral load in HBV cirrhosis, antiviral therapy assists in preventing HCC development and is therefore recommended.<sup>26,27</sup> *(Level 1b, Grade A)*

### **Surveillance**

All patients at risk of developing HCC and who are eligible for HCC therapy are candidates for regular surveillance.<sup>28</sup> *(Level 1b, Grade A)* This will ensure early detection of tumours that are amenable to treatment. Candidates for surveillance are categorized into those with cirrhosis and those without cirrhosis. Cirrhotic patients of any etiology with Child A and B cirrhosis or Child C patients on the waiting list for a liver transplantation are candidates. Noncirrhotic patients with chronic hepatitis B (males >40 years and females >50 years), chronic HBV infection of any age with family history of HCC, or chronic HCV with advanced fibrosis are candidates for surveillance.<sup>29</sup> *(Level 1a, Grade A)* The recommended surveillance test is a six-monthly ultrasound abdomen by an experienced radiologist.<sup>30</sup> *(Level 1a, Grade A)* Serum alpha-fetoprotein has no role in surveillance.<sup>30</sup> *(Level 1a, Grade A)*

### Diagnostic strategies

#### *Non-invasive lesion characterization*

For lesion characterization in the liver it is useful to divide detected nodules as per size into those <1cm, and larger nodules. Small nodules <1cm cannot be characterized by existing imaging techniques, and are difficult to target by biopsy. These nodules should be subjected to a 3-6 monthly follow-up using the same technique, which detected the nodule, for a period of 2 years.<sup>31</sup> Note that this recommendation only refers to nodules detected in cirrhotic livers. Pathology studies show that most small nodules <1cm that are detected in a cirrhotic liver are not HCCs.<sup>32</sup> Evaluation by gadolinium-ethoxybenzyl- diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)- enhanced MRI scan, or a SonoVue contrast enhanced ultrasound are alternative strategies. Gd-EOB-DTPA MRI is not available in India.

For nodules >1cm in size, a dynamic (3-phase or 4-phase) CT or MRI is recommended, including late arterial phase and portal venous phase. The HCC radiological hallmark includes hyper-enhancement on arterial phase and wash-out on porto-venous (delayed phase). Those nodular lesions, which do not show this typical enhancement pattern on one of the dynamic scans, should undergo the other scan (CT or MRI). Contrast-enhanced USG (CE-USG) is unable to distinguish HCC from intra-hepatic cholangiocarcinoma.<sup>33</sup> Hence the use of CE-EUS has declined for non-invasive diagnosis of HCC.

Non-invasive diagnosis can be established by demonstration of the typical HCC radiological hallmark by one of the imaging technique in nodules > 2 cm, and by two coincidental techniques with nodules of 1-2 cm in diameter (dynamic CT or dynamic MRI).<sup>34</sup> Updated AASLD guidelines have proposed that demonstration of typical imaging features of HCC by either dynamic CT or dynamic MRI may suffice for diagnosing tumors 1-2 cm in diameter.<sup>35</sup> However, non-invasive diagnosis of nodules 1-2cm in diameter remains difficult. The false positive and false negative results with current imaging modalities for nodules 1-2cm in diameter are substantial, and biopsy confirmation may be required.<sup>36</sup>

PET scan has limited role in diagnosis of HCC. PET scan is not accurate for diagnosis of small HCCs. Overall, the FDG-PET sensitivity in detecting HCC is lower (50%-70%) than other liver tumors. The tumor FDG uptake is influenced by cellular differentiation, with the lowest performance in well-differentiated HCC.<sup>37</sup>

#### *Tissue diagnosis*

If a suspicious nodule measuring >1cm fails to show typical enhancement pattern on both dynamic CT and dynamic MRI, image guided sampling is indicated. Indian guidelines recommend that biopsy samples should be obtained, and cytology may be inadequate. NCCN guidelines also recommend that biopsy is 'preferred'. However, cytology with cell-block preparation may be adequate in many cases. Both core-biopsies and cytology have advantages and disadvantages in this setting. Obtaining cytology samples are

easier and may be safer than histology cores. Cytology diagnosis of HCC may be difficult in the subsets of well-differentiated HCC, sclerotic type of tumors, and in hepato-cholangiocarcinomas. In these cases, a core biopsy may be required for evaluation of tissue architecture. Note that if the patient is a surgical or transplant candidate, surgical evaluation should be done before any biopsy.

Immunohistochemical markers useful for diagnosing HCC include glypican-3 (GPC-3), glutamine synthase (GS), and heat shock protein-70 (HSP-70).<sup>38</sup> These are markers of malignancy and are useful for distinguishing HCC from nodules with high-grade dysplasia (dysplastic nodules).

For distinguishing poorly differentiated HCC from metastatic cancer, staining by liver specific markers is useful. These include Hep-Par 1, pCEA, arginase, and CD10 antibodies.

### ***Serological markers***

When used as a diagnostic test, AFP levels at a value of 20 ng/ml show good sensitivity but low specificity, whereas at higher cut-offs of 200 ng/ml the sensitivity drops to 22% with high specificity.<sup>39</sup> AFP values greater than 400 ng/mL are more diagnostic, but are observed only in a small percentage of patients with HCC. AFP can also be elevated in intrahepatic cholangiocarcinoma, and some metastases from colon cancer. For these reasons AFP estimation is no longer part of diagnostic algorithm of HCC.

Des-gamma-carboxy prothrombin (DCP) – also known as prothrombin induced by Vitamin K absence II (PIVKA II), lens culinaris agglutinin-reactive AFP (AFP-L3), alpha-fucosidase, and glypican 3 are other serological tests used for surveillance and diagnosis of HCC. Both DCP and AFP-L3 fractions are associated with PV invasion and advanced tumor stage.<sup>40</sup>

### **Initial workup**

Besides assessing the functional status, co-morbidities, and staging (detailed below), the following workup should be considered in a patient with HCC:

1. Serology for HBV and HCV (HBsAg, IgG/total-HBc, anti-HBs, anti-HCV).
2. HIV serology.
3. Biochemistry panel, including LFT and AFP.
4. Assessment of complications of portal hypertension (upper gastrointestinal endoscopy for varices, abdominal collaterals, hepatic venous pressure gradient/HVPG).
5. Chest CT.
6. Bone scan, if indicated clinically.
7. Assessment of liver function (Child score, MELD score, Indocyanine green clearance test)

If HBsAg is positive, then HbeAg, anti-HBe antibody, and HBV-DNA levels are estimated. If anti-HCV is positive, then HCV genotype and HCV-RNA levels are estimated.

### **Staging and treatment allocation**

In HCC, co-existence of cancer and cirrhosis complicates prognostic assessment. Three factors should be considered when planning treatment for HCC:

1. Tumor size, number, and location.
2. Liver function.
3. Performance status of the patient.

The different staging systems in use for HCC are: TNM, Okuda, Cancer of the Liver Italian Program (CLIP), Barcelona -Clinic Liver Cancer (BCLC), Chinese University Prognostic Index (CUPI score), and Japan Integrated Staging (JIS) system. The underlying etiology does not influence prognosis of HCC beyond the severity of liver disease. The AJCC TNM system does not take into regards the liver functional status, and has limited usefulness, since most patients with HCC do not undergo surgery.

BCLC staging system includes patient performance, child status, number of nodules, size of nodules, portal vein invasion, and metastasis. It has been externally validated in different clinical settings. The BCLC classification was first endorsed by the EASL <sup>41</sup>, and thereafter by the AASLD guidelines for the management of HCC . In India BCLC staging system is most commonly used for prognostic information and treatment allocation. BCLC system divides HCC patients into 5 stages (0, A, B, C, and D). Stage 0 is very early, stage A is early, stage B is intermediate, stage C is advanced, and stage D is terminal stage HCC. [Algorithm 2]

Pathology report should include essential, reproducible and uniform information that provides correct diagnosis and allows accurate decision-making by a multidisciplinary team.

The minimum essential data items of a pathology report of hepatocellular carcinoma that facilitate accurate diagnosis, classification, staging and decision-making for optimal treatment include:

**Macroscopic**

1. Type of specimen
2. Specimen dimensions, (all 3 dimensions)
3. Tumor number
4. Tumor size
5. Presence of satellite lesions (considered multiple tumors for staging)
6. Macroscopic involvement of vessels (specify main, left or right portal vein; or main, left or right hepatic vein)
7. Diameter of vessel involved
8. Capsular surface (including bare area)
9. Presence of adherent tissues/organs
10. Number of lymph nodes submitted

**Microscopic**

1. Tumor type
2. Tumor grade
3. Tumor extension
4. Minimum distance to resection margin- hepatic parenchymal, and where appropriate bile duct or vascular) Microscopic involvement (R1) is generally defined as a clearance of < 1mm
5. Capsular invasion
6. Vascular invasion, including confirmation of macroscopic vessel involvement
7. Perineural invasion
8. Prior therapy related response (in post neoadjuvant therapy resections)



9. Background pathology-(cirrhosis/severe fibrosis, chronic hepatitis (specify etiology), low-grade or high-grade dysplastic nodule, steatosis, iron overload, other)

10. Lymph node status (total number and total involved)

### **Explanatory notes**

#### ***Relevant surgical anatomy***

Surgically, liver is divided into eight segments based on watershed boundaries created by main branches of hepatic artery and portal vein. Since the boundary of segments is defined by the course of intrahepatic vessels, segmental divisions cannot be assigned from surface landmarks. The surgeon should provide this information.

#### ***Types of specimen***

1. Wedge resection (non-anatomic)
2. Right hepatectomy
3. Left hepatectomy
4. Right extended hepatectomy (right trisectionectomy)
5. Left extended hepatectomy (left trisectionectomy)
6. Total hepatectomy
7. Other (specify):

#### **Tumor multifocality**

Frequent occurrence of multiple tumor nodules is a characteristic feature of HCC. This is either reflective of intra-hepatic metastasis or synchronous independent primaries. Presence of solitary or multiple tumor nodules should be noted and dimensions of each must be recorded. Satellite nodules, defined as microscopic nodules of HCC separated by a non-tumoral hepatic parenchyma, have been shown to be prognostically important following liver resection and liver transplantation for HCC<sup>42</sup>. For staging purposes, multifocal tumor nodules or smaller satellite tumor nodules are regarded as multiple tumors<sup>43</sup>.

#### **Histologic types of HCC**

Typical histologic features of HCC are: wide cell plates (>3 cells thick), pseudoacinar pattern, small cell change, cytologic atypia, mitotic activity, vascular invasion, reticulin loss and invasion of the adjacent stroma.

Histologic variants of HCC are as follows:

1. Fibrolamellar carcinoma
2. Clear cell HCC
3. Schirrous HCC
4. Sarcomatous HCC
5. Lymphoepithelial-like HCC
6. Steatohepatic HCC

Fibrolamellar type is seen in young non-cirrhotic patients and is associated with better prognosis than classical HCC <sup>44</sup>. Only carcinomas showing exclusive fibrolamellar features should be classified as fibrolamellar carcinoma as opposed to hybrid tumors with areas of both fibrolamellar carcinoma and typical hepatocellular carcinoma. Sarcomatous and schirrous types are associated with worse survival.

### Tumor grade

The grading system of Edmondson and Steiner <sup>45</sup> is recommended for hepatocellular carcinomas by the AJCC Cancer Staging Manual, 7th edition [2] (Table 1).

**Table 1: Edmondson and Steiner grading system for hepatocellular carcinoma [2]**

Grade	Features
<b>Grade I</b>	Reserved for hepatocellular carcinomas where the difference between the tumor cells and hyperplastic liver cells is so minor that a diagnosis of carcinoma rests upon the demonstration of more aggressive growths in other parts of the neoplasm.
<b>Grade II</b>	Cells show marked resemblance to normal hepatic cells. Nuclei are larger and more hyperchromatic than in normal cells. Cytoplasm is abundant and acidophilic. Cell borders are sharp and clear cut. Acini are frequent and variable in size. Lumina are often filled with bile or protein precipitate.
<b>Grade III</b>	Nuclei are larger and more hyperchromatic than in grade II cells. The nuclei occupy a relatively greater proportion of the cell (high nuclear to cytoplasmic [N:C] ratio). Cytoplasm is granular and acidophilic, but less so than grade II tumors. Acini are less frequent and not as often filled with bile or protein precipitate. More single-cell growth in vascular channels is seen than in grade II
<b>Grade IV</b>	Nuclei are intensely hyperchromatic. Nuclei occupy a high percentage of the cell. Cytoplasm is variable in amount, often scanty. Cytoplasm contains fewer granules. The growth pattern is medullary in character, trabeculae difficult to find, and cell masses seem to lie loosely without cohesion in vascular channels. Only rare acini are seen. Spindle cell areas have been seen in some tumors. Short plump cell forms, resembling “small cell” carcinoma of the lung, are seen in some grade IV tumors.

Use of other validated grading systems is not precluded. However, the grading system employed must be specified in the report. Tumors should be graded according to the least differentiated area <sup>43</sup>. Histologic grade has been shown to have a relationship to tumor size, tumor presentation, and metastatic rate <sup>46</sup>.

### Vascular invasion

Vascular invasion is an important prognostic factor and is an important component of the pT stage. Vascular invasion includes both macroscopic and microscopic invasion of vessels. Both are associated with lower survival post-resection.

Stage pT2 includes any vascular invasion (gross or microscopic involvement) but less than a major vessel involvement (main left or right or middle branch of the portal or hepatic vein). Major vessel involvement is classified as stage pT3b. Distinguishing satellite nodules from a completely plugged vessel is often difficult. Presence of a tumor nodule within a portal tract or at a site corresponding to a portal vein favors vascular invasion, however is subject to inter-observer variation. Tumors > 5cm or multiple tumors are more likely to exhibit vascular invasion than solitary smaller tumors. In TNM 7 classification, vascular invasion is only confirmed if one can clearly identify the lumen and endothelium of a portal vein. Both presence of satellite nodules and intra-hepatic venous dissemination are classified as multiple tumors, and are therefore equivalent for staging purposes (i.e. pT2, when no tumor is >5cm).

## Resection margin

Margins evaluation depends on the method and extent of resection. Minimum distance to resection margin (hepatic, and where appropriate bile duct or vascular) should be measured and sections examined microscopically. Microscopic involvement (R1) is generally defined as a clearance of < 1mm. When parenchymal transected margin is large, judicious sampling of the cut surface is needed. If the margin is grossly positive, one section is adequate for microscopic confirmation. If tumor is near the margin or grossly free, sections from the areas where tumor is closest should be taken after measuring the minimum distance. For multiple tumors, the distance from the nearest tumor should be reported.

## TNM and Anatomic Stage/Prognostic Groupings

According to the AJCC/UICC TNM staging, the pT stage depends on the maximum tumor size (of the largest nodule), the number of tumor nodules, and presence or absence of venous invasion. The TNM classification does not make a distinction between multiple independent primaries and intra-hepatic metastasis from a single primary HCC. Vascular invasion includes both microscopic and macroscopic involvement of vessels. Portal vein invasion is an important adverse prognostic factor and should be reported.

**Table 2: pT staging (AJCC/UICC) of hepatocellular carcinoma**

Primary Tumor (T)	
<b>Tx</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>T1</b>	Solitary tumor without vascular invasion
<b>T2</b>	Solitary tumor with vascular invasion; or multiple tumors, none more than 5 cm in greatest dimension
<b>T3</b>	Multiple tumors more than 5 cm in greatest dimension or tumor involving a major branch of the portal or hepatic veins(s)
<b>T3a</b>	Multiple tumors more than 5 cm
<b>T3b</b>	Tumor(s) any size involving a major branch of the portal or hepatic vein(s)
<b>T4</b>	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

## Regional Lymph Nodes (N)

Histologic examination of a regional lymphadenectomy specimen usually involves examination of 3 or more lymph nodes. The regional lymph nodes of the hepatic region include the hilar, hepatoduodenal ligament, inferior phrenic, and caval lymph nodes. Metastasis to lymph nodes distal to the hilar, hepatoduodenal ligament, and caval lymph nodes are considered as indicative of distant metastasis (pM1).

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

## Preoperative ablative therapy

Specimens removed from patients after pre-operative ablative therapy can show variable effects that may be visible macroscopically and/or identified on microscopy. To establish complete tumor necrosis, extensive tumor sampling is necessary; tumors should be sampled entirely through their largest diameter if the tumor/nodule size is  $\geq 2$  cm. For every additional 1 cm, an additional section should be taken. No

standardized regression scores are available for post-ablative therapy resections; however an estimate of the ration of the viable tumor to overall tumor may be helpful to oncologists.

### Background liver disease

Presence and severity of underlying chronic liver disease strongly impacts prognosis following resection of HCC of underlying chronic liver disease. The pathology report should include information about the background liver. Sampling of peritumoral area should be avoided and sections should be taken from parenchyma distant from the tumor. The presence of chronic liver disease (hepatitis, haemochromatosis, alcoholic liver disease and non-alcoholic steatohepatitis etc) as well as the stage of fibrosis and the nature and intensity of inflammation/hepatocytic damage should be documented.

Cirrhosis or severe fibrosis (Ishak score 5, 6) should be specifically reported as it adversely affects outcome<sup>47</sup>. Because of its prognostic importance, stage of fibrosis of underlying chronic liver disease forms a core data item. The etiology may be unknown to the pathologist, and is hence considered a non-core (optional) item. The scoring system described by Ishak<sup>48</sup> is recommended by the AJCC Cancer Staging Manual, 7th ed [2].

**Table 3: Fibrosis score [6]**

Degree of Fibrosis	Score
None	0
Fibrous expansion of most portal areas	1
Fibrous expansion of some portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal-portal bridging	3
Marked bridging with occasional nodules (incomplete cirrhosis)	4
Fibrous expansion of portal areas with marked bridging as well as portal-to-central bridging	5
Cirrhosis	6

### Dysplastic Nodules

Dysplastic nodules (DN) are generally regarded as important precursors to development of HCC. Nodules with presence of cytological or architectural dysplasia that is insufficient for a diagnosis of HCC are considered DN. DNs are further histologically categorized into low-grade (LGDN) and high-grade (HGDN) dysplastic nodules. Reporting of dysplastic changes in cirrhotic nodules is optional in specimens with HCC, although it may be helpful in assessing risk for second primary tumors in patients undergoing partial hepatectomy. Distinguishing HGDN from small HCC (<2 cm) can be challenging. The International Consensus Group for Hepatocellular Neoplasia has defined nomenclature for small <2cm lesions (Table 4).

**Table 4: The International Consensus Group for Hepatocellular Neoplasia nomenclature for small < 2 cm hepatocellular lesions** <sup>49</sup>.

#### **Dysplastic foci (microscopic lesion)**

Cluster of dysplastic hepatocytes, < 1 mm in size and is a microscopic lesion. It may be characterized by small cell change (SCC) or large cell change (LCC).

#### **Dysplastic nodules (DN) (macroscopic lesions)**

DNs are defined grossly as large hepatic nodules that are distinct from the surrounding liver parenchyma in terms of size, color, texture, or the degree to which they bulge from the cut surface of the liver. Confirmation that a nodule is in fact a DN comes with histologic examination and the identification of intact portal structures distributed through the lesion. The number of these portal structures may be mildly or greatly reduced compared to a similar area of non-diseased hepatic parenchyma. Histologically, DNs are categorized as follows:

1. **Low grade dysplastic nodules (LGDN):** a clonal cell population with mild increase in cellularity in comparison to the surroundings but without architectural atypia; portal structures are identified within LGDN.
2. **High grade dysplastic nodule (HGDN):** frank cytological and architectural atypia but insufficient for diagnosis of hepatocellular carcinoma; portal tracts detectable within HGDN albeit reduced.

#### **Small HCC**

1. **Early HCC:** vaguely nodular lesion with indistinct margins, well differentiated histology, and a few portal tracts identifiable.
2. **Progressed HCC:** a distinctly nodular lesion with well to moderately differentiated histology in which malignancy is easy to recognize; no portal tracts are identified.

### **Role of immunohistochemistry in diagnosis of hepatocellular carcinoma**

IHC may be employed to resolve diagnostic issues encountered on morphology. The two most common scenarios where distinction of HCC from its mimics requires IHC are:

A. Distinguishing poorly differentiated HCC from HCC from metastatic carcinoma, intra-hepatic cholangiocarcinoma (IHCC), mixed hepatocellular-cholangiocarcinoma, poorly differentiated neuroendocrine carcinomas and other rare primary hepatic malignancies.

B. Segregating well differentiated HCC from hepatic adenoma (HA), focal nodular hyperplasia (FNH) and DN.

#### **A. Poorly differentiated carcinoma**

This category includes lesions which are clearly malignant and epithelial; however their cellular differentiation or origin is not apparent. IHC markers of hepatocellular lineage, i.e. Arginase1 (ARG-1), HepPar1, alpha fetoprotein, glypican-3 (GPC3) and albumin (detected by in-situ hybridization), help to distinguish poorly differentiated HCC from its differential diagnoses in problematic cases. ARG-1 shows 100% sensitivity and 82.6% specificity for the diagnosis of HCC whereas GPC-3 demonstrated 97.7% sensitivity and 91.3% specificity for the diagnosis of this tumor <sup>50</sup>

**Table 5: Immunohistochemistry panels in differential diagnoses of HCC**

Problem	Diagnosis	Primary panel	Additional antibodies	Remarks
HCC vs MA	HCC	ARG-1+ / MOC 31-	HepPar 1+ / GPC3+ / canalicular pCEA+ / mCEA-	AE1/E3 and CAM 5.2 not useful
	MA	MOC 31+ / ARG-1 -	CK7 / CK20 (colorectal) / CK19 / TTF1 (lung) / GATA3 (breast) / PAX8 (ovary) / PSA (prostate)	
HCC vs IHCC	HCC	ARG-1 + / MOC 31- / CK19-	HepPar1+ / GPC3+ / canalicular pCEA+ / mCEA-	AE1/E3 and CAM 5.2 is not useful. Non-peripheral cholangiocarcinoma are CK20+ whereas peripheral IHCC are CK20-
	IHCC	MOC31+ / CK19+ / ARG-1-	CK7+ / CK20+ / HepPar1-	
HCC vs NEC	HCC	ARG-1+ / Synaptophysin- / chromogranin-	HepPar1+ / GPC3+ / pCEA+	CD56 not useful
	NEC	Synaptophysin+ / chromogranin+ / Arginase 1-	MOC31+	
HCC vs Melanoma	HCC	ARG-1+ / HMB45- / Melan A-	GPC3+	GPC3 is not useful
	Melanoma	HepPar 1- / HMB45+ / Melan A+	S100+	
HCC vs RCC	HCC	ARG-1+ / PAX8-	GPC3+ / pCEA+	CD10, RCC antigen not useful
	RCC	ARG-1- / PAX8+	Vimentin+	
HCC vs ACC	HCC	ARG-1+ / Inhibin- / Melan A-	GPC3+ / pCEA+	
	ACC	ARG-1+ / Inhibin- / Melan A-	CK-	

*Abbreviations: MA- metastatic adenocarcinoma; IHCC- intra-hepatic cholangiocarcinoma; NEC- neuroendocrine carcinoma; RCC- renal cell carcinoma; ACC- adrenocortical carcinoma; ARG-1- Arginase-1; GPC3- glypican-3; pCEA- polyclonal carcinoembryonic antigen; mCEA- monoclonal carcinoembryonic antigen; CK- cytokeratin.*

## B. Well differentiated hepatocellular lesions

Distinction of well differentiated HCC from HA, FNH and DN can be challenging, especially in limited tissue specimens. Endothelial marker, CD34 and the smooth muscle antigen, (SMA) for muscularized unpaired arteries can help recognize neovascularization typical of HCC. Stromal invasion into portal tracts or septae, characteristic of HCC, can be highlighted by the lack of immunoreactivity for CK7/19 (in contrast to Ck7/19 positive ductular reaction in DN).

For distinction between benign and malignant Well Differentiated Hepatocellular Lesions, three most useful markers are: Glypican-3, Glutamine synthetase (GS) and heat shock protein 70 (HSP-70). Positivity for any two out of three of these markers provides sensitivity of 72% and specificity of 100% for HCC <sup>51</sup>.



**Table 6 : Immunohistochemical markers helpful in distinguishing well-differentiated HCC from benign differential diagnostic entities**

Antibody	Finding	Diagnosis
<b>CK7/19</b>	Absent ductular reaction around tumor cells of stromal invasion	HCC
<b>CD34</b>	Extensive/diffuse capillarization of hepatic sinusoids	Progressive increase through LGDN, HGDN, HCC
<b>Glypican-3 (GPC-3)</b>	Diffuse strong cytoplasmic	HCC (more in less differentiated); <10% HGDN
<b>Heat Shock Protein 70 (HSP-70)</b>	Nuclear and cytoplasmic	HCC (more in less differentiated); <10% HGDN
<b>Beta-catenin</b>	Nuclear positivity	HCC HA with $\beta$ -catenin mutations
<b>Glutamine synthetase (GS)</b>	Diffuse cytoplasmic granular	HCC; more in less differentiated; 14% HGDN  HA with $\beta$ -catenin mutations
	Map-like areas of positivity	FNH

*Abbreviation: HCC- hepatocellular carcinoma; LGDN-low grade dysplastic nodule; HGDN-high grade dysplastic nodule; HA- hepatic adenoma; FNH- focal nodular hyperplasia*

### Steps of grossing

1. State the type of specimen
2. Identify if there is an adherent tissue (such as diaphragm)
3. Take dimensions
4. Examine the capsular aspect for tumor infiltration or breach. Document if the background liver is nodular/cirrhotic.
5. Paint the parenchymal resection margin with ink
6. Serially slice the specimen at an interval of about 1 cm and keep for fixation for 24-48 hours.
7. Document the number of nodules and take dimensions of each nodule
8. Distance between nodules is also measured and documented.
9. Closest distance from the tumor nodule(s) is recorded.
10. Background liver texture or macroscopic pathology, if any is also recorded
11. Presence or absence of macroscopic vascular involvement by tumor of main left, right branches of portal vein or hepatic vein is looked for and documented.
12. Lymph nodes are dissected from the specimen



## Sections

1. Take a minimum of 4 sections of tumor
  - a. All tumor nodules should be sampled and examined
  - b. All macroscopically varied areas should be sampled to better assess tumor differentiation
  - c. Complete (if small tumor)/extensive sampling should be done in post-ablative resections with abundant necrosis and no/little residual tumor
2. Tumour with closest hepatic resection margin (when this is close enough to the tumour to be included in the block)
3. Hepatic parenchymal margin (if the tumor is far and cannot be included in the same section)
4. Tumor with adjacent liver parenchyma (for microscopic vascular invasion)
5. Liver capsule –from areas where there is a subjacent tumour , or an overlying adherent tissue or macroscopic capsular invasion.
6. Any site macroscopically suggestive of vascular or bile duct invasion
7. Gall bladder bed where there is adjacent intrahepatic tumour.
8. Background liver (taken as far away as possible from the tumour).
9. Lymph nodes, along the specimen and those sent separately.

Multidisciplinary care remains at the core of treating all cancers—such treatment relies upon an effective multidisciplinary network including surgical, medical, and radiation oncologists; gastroenterologists; pathologists; radiologists (for interventional and nuclear medicine); nurse specialists, and palliative care physicians.

All new cases should be discussed at the tumour board or in multidisciplinary team meetings, and the treatment strategy should be confirmed. In most patients with localised disease, resection will be the treatment of choice. More commonly, in India, patients present with locally advanced disease (evident on imaging).

**Recommendation:**

- (Level 1A)

**SURGICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA (HCC)****Introduction:**

Surgical management is the main stay of definitive treatment for HCC. Treatment of HCC essentially involves treating two pathologies viz. the tumour itself and the underlying liver disorder like cirrhosis. Pre-operative assessment both in terms of tumour and liver related factors is important and should be targeted at achieving adequate anatomical and functional liver reserve with clear resection margins. Improvements in pre-operative assessment, techniques to control intra-operative blood loss and better post-operative care have contributed to decreased morbidity as well as mortality and established safety of liver resections even in cirrhotic patients.<sup>52, 53</sup>

**Resection:**

Surgical management for HCC is guided by various staging criteria. Currently, Barcelona clinic liver cancer (BCLC) staging is the most commonly used staging system guiding resections<sup>1</sup>. This system broadly divides patients into the following stages:

1. Early (A): single nodule or 3 nodules < 3cm
2. Intermediate (B): Multi-nodular HCC
3. Advanced (C): vascular invasion/ extra -hepatic disease
4. Terminal (D): End stage liver disease, poor performance status

According to this system, surgical resection is advocated only in early stage disease. i.e. tumours < 3 cm with preserved liver function ( Child Pugh A) without evidence of portal hypertension. Whereas, in patients with decompensated liver disease or portal hypertension, transplant is the treatment of choice as it not only treats the tumor but also the underlying predisposing liver pathology.<sup>54</sup>

Though the BCLC staging is widely accepted by the western countries to guide treatment philosophy, there has been a reluctance on the part of the eastern countries regarding its acceptance. Many surgeons from the east believe that these criteria are too restrictive and that size and number should not be the only factors to deem a patient unresectable especially if oncological clearance can be achieved with safety. Resection remains the only hope of cure for large tumours and hence clinical discretion is warranted in their treatment. Five year survival rates up to 39 % for large/ multinodular HCC have been shown in study by *Ng et al.*<sup>55</sup> There is now a definite shift towards moving beyond BCLC criteria for most countries especially in the east.<sup>56</sup>

### Issues in Hepatic resection for HCC:

- 1. Anatomical resection (AR) vs. non-anatomical resection (NAR)** Complete oncological clearance ideally warrants an anatomical resection for negative margins. However, this may not be always possible either due to location of the tumour or due to the need to preserve as much parenchyma as possible in cirrhotic patients. Meta- analyses of non randomised trials have shown AR to have better survival outcomes than NAR<sup>57,58</sup>. Hence, an attempt to perform AR must always be made. Newer imaging technologies like 3-D reconstruction and virtual hepatectomies, which better delineate segmental anatomy may make AR feasible even in patients with poor hepatic reserve.<sup>59</sup>
- 2. Role of Laparoscopic resection:** The First International Position statement on Laparoscopic Liver Surgery, 2008 Louisville, defined acceptable indications for laparoscopic liver resection (LLR) as solitary lesions < 5 cm, segment II to VI and considered laparoscopic left lateral sectionectomy as standard practice<sup>60</sup>. Six years later, the second international consensus conference 2014, held at Marioka, Japan defined minor LLR as the one in which two or fewer segments are removed. Minor LLR was confirmed to be standard practice as per the recommendations of this conference. However, major LLR was considered an innovative procedure still in its learning phase<sup>61</sup>.
- 3. Role of ablative procedures: Radiofrequency ablation (RFA) / Percutaneous ethanol injection (PEI):** Small tumours (<3 cm) in patients who are not candidates for surgical resection (Child B & C) can be offered ablation either by thermal (RFA) or chemical (PEI) methods either as a definitive treatment modality or as a bridging therapy prior to liver transplantation. The role of ablation as compared to resection has been addressed in few randomised trial and several non randomised studies<sup>62, 63</sup>. Meta-analysis of these studies showed that RFA was as effective as surgical resection with fewer complications albeit with a higher recurrence rate<sup>64</sup>. The difference in survival was more pronounced after 5 years and in larger tumors. The superiority of RFA over PEI has been shown in several studies and PEI is currently recommended only when facilities for thermal ablation are not available<sup>65-67</sup> The role of other ablative procedures viz; microwave ablation, cryoablation, irreversible electroporation (IRE) remains investigational.
- 4. Transplantation Vs Resection:** Orthotopic Liver Transplantation (OLT) provides an attractive treatment option for patients with early stage HCC and decompensated liver disease as it treats not only the tumour with widest oncological margin but also the underlying liver. The Milan criteria for liver transplantation in HCC were established by *Mazzaferro et al* in 1996<sup>68</sup>. This landmark

study demonstrated excellent overall and recurrence free survival rates for patients with early stage HCC who satisfied the criteria viz. solitary tumour < 5 cm, or up to 3 nodules all < 3 cm, without vascular invasion or extra-hepatic spread. Any patient with deranged liver functions or evidence of portal hypertension should ideally undergo transplant. On the other hand, resection is best suited for larger but otherwise operable tumours with no vascular invasion. There has been no randomized trial comparing the two treatment modalities. Evidence from meta-analysis of retrospective series on intention to treat basis shows no significant difference in outcomes<sup>69</sup>. Hence, the choice of treatment offered is primarily decided by the degree of underlying liver dysfunction in an otherwise resectable lesion.

### **LIVER TRANSPLANTATION:**

Mazzaferro's study established the role of liver transplantation for HCC. These criteria were further extended by the University of California at San Francisco (UCSF) group to include larger tumours up to or less than 6.5 cm for solitary lesion or up to 3 nodules with the largest lesion < 4.5 cm and cumulative tumour size up to 8 cm<sup>70</sup>. However, the main problem in offering liver transplantation is the limited availability of organ and long waiting list with inherent risk of disease progression leading to drop outs. To circumvent this problem a number of strategies have been proposed like living donor related transplant (LDLT), use of bridging therapy and role of salvage transplantation.

1. LDLT has the advantage of practically no waiting list if a suitable donor is available. However, it does have an inherent risk of morbidity to the donor. Two meta-analyses of deceased donor liver transplant (DDLT) vs. LDLT have shown no difference in survival outcomes.<sup>71, 72</sup>
2. In an effort to minimize the drop outs in the waiting period, the use of bridging therapies such as Transarterial chemoembolisation / RFA have gained popularity. Though helpful in reducing the drop rate, their effect on long term outcomes remains to be seen.<sup>73</sup>
3. Another alternative to primary OLT is the policy of salvage transplanatation in which the patient undergoes surgical resection first and a transplant is offered later for recurrence or deterioration of liver functions. Though primary transplantation has better long term outcomes than salvage transplantation it is still a feasible option in centres with resource constraints for transplant.<sup>74, 75</sup>

### **LOCOREGIONAL THERAPY FOR HEPATOCELLUAR CARCINOMA:**

Various interventional radiological procedures are effective therapeutic options for patients with HCC and they play important role in the locoregional management of HCC which are not suitable for surgery or transplant. They are as follows:

#### **Interventional radiological therapies for HCC:**

- 1) Thermal ablation
  - i) Radiofrequency ablation
  - ii) Microwave ablation.
- 2) Chemical ablation:
  - i) Percutaneous ethanol ablation (PEI)

- 3) Trans-arterial therapies
  - i) Transarterial chemoembolisation (TACE)
    - a) Conventional lipiodol TACE
    - b) Drug eluting beads TACE
  - ii) Transarterial radioembolisation (TARE)
    - a) Yttrium-90 microspheres
    - b) Rhenium-188 lipiodol

5) Portal vein embolisation.

The choice of the modality is decided by taking into consideration the performance status of the patient, functional status of the liver parenchyma, anatomical location and size of the lesion and overall staging of the disease. A multidisciplinary tumor board evaluation is helpful to ascertain the best treatment option for the patient .

The percutaneous ablative therapies have role in the very early stage (BCLC 'O') & early stage (BCLC A) HCC, while the trans-arterial therapies are (generally) indicated in the intermediate stage (BCLC B, C) of HCC.

**Ablative Therapy:** Radiofrequency ablation is indicated when the lesion is not suitable for resection, the size of the lesion is upto 3 cm and number of lesions are upto 3 lesions <sup>76,77</sup>. The randomized control trial performed by Feng K et al has shown equivalent outcome with ablation and surgery in 'very early' BCLC grade 0 patients, in terms of overall survival and disease free survival rates <sup>78,79</sup>. RFA is a safe and effective modality for patients on waiting list for liver transplantation <sup>80</sup>

The ablative modalities have following advantages:

1. They are minimally invasive, so the recovery is fast and morbidity is less.
2. Ablation can be performed percutaneously under suitable imaging guidance.
3. Ablation can be done as OPD procedure which reduces the hospitalization cost.
4. Ablation can be complementary to surgery for example in a situation where during hepatic resection if a small lesion is detected intraoperatively, it can be treated by ablation.

RFA usually causes complete necrosis in 83 % of tumors less than 3 cm in size and upto 88% of tumors located in non-perivascular liver parenchyma.<sup>81</sup>

The 5 year survival of 61 % is shown in patient with solitary HCC in CHILD Pugh class A <sup>82</sup>. In patients with early HCC with compensated cirrhosis, survival in the range of 43- 64% has been documented in different studies.<sup>83</sup>

The minor complication rate with radiofrequency ablation for inoperable HCC is 5% - 8.9% and major complication rate is 2.2% to 3.1%.The common complications are hemoperitoneum, infection and biliary injury. <sup>84</sup>

### Transarterial Chemoembolization

**(TACE)** is an endovascular procedure where the chemotherapeutic agent (doxorubicin, Cisplatin, mitomycin) is injected into the tumoral parenchyma through the arteries supplying the lesion.

This is a minimally invasive modality of treatment which has shown definitive survival benefits especially in patients who can be categorized as intermediate BCLC B patients.<sup>85, 86</sup> TACE provides statistically significant survival benefit as shown by Llovet et al (10) and Lo et al(11) in randomized control trial with 1 to 2 year survival of 82% and 63% for TACE versus 63% and 27% for supportive group respectively .

It is usually offered as palliative treatment; however it also has a role as a bridge to transplant in the patients who are in the waiting list for transplant <sup>87</sup>

For unresectable HCC systematic review of randomized trials have shown that patients undergoing TACE have got improved 2 year survival benefit as compared to control group<sup>88</sup>.

The meta analysis of the five randomized controlled trial has also shown reduction of the two year mortality in patients treated with TACE.<sup>89</sup>

Ablation can be combined with TACE when the size is between 3 to 5 cm, so that the patient gets advantage of both modalities of treatment . Various studies have shown better disease control and survival benefit with combined treatment as compared to single treatment modality <sup>90,91</sup>.

The complications that can happen after TACE are liver failure (5-10%), liver abscess (30%) and non-target embolization (<10%) and post-embolisation-syndrome. However the complications can be avoided if adequate risks mitigation measures are undertaken.

### **Transarterial radio-embolization (TARE)**

Radioembolisation is the loco-regional therapy where the tumoricidal dose of radioactive isotope like yttrium <sup>90</sup> microspheres are injected by the Trans arterial route into the tumor vascularity. The yttrium <sup>90</sup> which is a beta emitter has a half life of 64.1 hours. They cause irradiation of the tumor from within and so also called as 'Selective Intrarterial Brachytherapy ' (SIRT).

TARE is indicated in patients who are not upfront resectable as

1. For palliation of the unresectable tumor.
2. As a bridge to definitive treatment like transplant.
3. In patients with portal vein thrombosis.

The microspheres being small in size can even penetrate the vascularity of the tumor thrombus, which helps to recanalise or to cause necrosis of the tumor thrombus.

The microspheres are made up of glass or resin with Y<sup>90</sup> embedded into the microspheres. The procedure is contraindicated in case of severe liver dysfunction (Sr bilirubin >3mg %), angio architecture not suitable to prevent non target embolization or if the hepato pulmonary shunt fraction is more than 20 %.

TARE has shown response rate between 35-47%. <sup>92,93</sup>.

Median survival between 5 to 24 months according to the stage of the disease, have been shown in the literature <sup>94,95</sup>

It is a safe and effective modality for patients of HCC with portal vein invasion where it has shown to offer median survival between 8-14 months <sup>96</sup>

TARE is a quite safe procedure with one of the most common complication being fatigue .Infection, ulceration or radiation cholecystitis are known complications of the procedure however they are not very common and usually managed conservatively.<sup>97,98</sup>

### **Percutaneous ethanol injection (PEI)**

PEI is a method of chemical ablation of the tumor performed by directly puncturing the tumor percutaneously and injecting ethanol into the tumor parenchyma. It is quite effective in small tumors and most important is that it is a very cost effective modality of treatment for small HCC <sup>99</sup>.

However after the advances in ablative therapies PEI is less commonly practiced than before. Randomized control trials have shown that RFA offers a better local control of the tumor as well as survival benefit as compared to PEI <sup>100</sup>. The major limitation of this technique is a high recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm. <sup>101</sup>

### **Portal vein embolization (PVE)**

PVE is a technique where percutaneously the portal vein on the side of liver which is planned to be resected is embolised, so that opposite lobe of liver gets hypertrophied.

This procedure is offered in patients where the Future Liver Remnant (FLR) to Total Estimated Liver Volume (TELV) ratio is less than 25 % for non-cirrhotic patients and less than 40% for cirrhotic patients, who are otherwise the potential candidates for hepatic resection <sup>102,103</sup>.

Usually hypertrophy of the opposite lobe is at peak by 2 weeks and occurs upto 4 weeks. Recent meta analysis has shown 11.9 % increase in FLR after PVE with only 2.2% major complications <sup>104</sup>.

This is a useful procedure in patients with inadequate FLR which has shown to reduce the post op complications and reduce the hospital stay as well.



**General approach:**

Unfortunately, most patients will present with advanced disease not amenable to resection. In these cases, curative treatment is not possible, but many patients will benefit in terms of both quality of life and survival from the use of systemic treatment, interventional procedures like TACE, TARE, rarely chemotherapy and supportive measures.

**External Beam Radiation Therapy (EBRT) for Hepatocellular carcinoma (HCC)**

Historically, the role of radiotherapy for HCC has been limited by the radio-sensitivity and low tolerance of the liver to radiation. Furthermore, underlying liver morbidity made EBRT difficult. EBRT was limited to the palliation of bone <sup>105,106</sup>, soft tissue <sup>107</sup> and lymph nodes <sup>108,109</sup> metastases from HCC. EBRT can be used to control pain in patients with bone metastases [II, B].

However, recent technological advancements, including computed tomography based radiotherapy planning and delivery, respiratory-motion management and image-guided radiation therapy (IGRT), have allowed for more precise and targeted delivery of radiation to the liver. These have made conformal liver irradiation feasible for treating focal HCC. Several phase II studies have shown benefit of radiotherapy in local control and OS for patients with locally advanced HCC unsuitable for standard loco-regional therapies <sup>110,111</sup>. Three-dimensional conformal radiotherapy (3D-CRT), IMRT and SBRT make high-dose radiation to HCC possible with sparing of the surrounding non-tumour liver parenchyma [III, C].

**Different roles of external beam radiotherapy, described in the literature:**

1. Definitive treatment in patients where locally advanced HCC unsuitable for standard loco-regional therapies.
2. Feasible in patients with portal vein thrombosis (PVT), who have been shown to respond to RT in about 45% of the cases <sup>112,113</sup>.
3. Possible in patients unsuitable for TACE owing to severe tumour-induced arteriovenous shunts; in a study 20% of these patients were able to undergo TACE successfully after radiation therapy-induced vascular occlusion <sup>114</sup>.
4. EBRT combined with TACE as definitive therapy: A meta-analysis of 5 randomized and 12 non-randomized trials reports that the use of TACE in combination with EBRT improves the 3-year survival rate by 10%–28% compared to TACE monotherapy <sup>115</sup>.
5. EBRT combined with TACE as local neo-adjuvant therapy: Reported as a local neo-adjuvant treatment for larger HCCs with the aim of improving resectability and enabling safe surgery post-RT, resulting in an effective response to neo-adjuvant radiotherapy <sup>116</sup>.
6. EBRT can be considered a bridging treatment for patients awaiting liver transplantation <sup>117,118</sup>.

Reported toxicity include gastric or duodenal ulcer or perforation <sup>119, 120</sup>. Target volume should be about 2cm away from the bowels <sup>121</sup>. The non-tumoural liver is the main dose-limiting organ, and the radiation induced liver disease (RILD) is the most feared toxicity. Dose constraints for Liver SBRT are:

- The liver volume receiving 30 Gy (ie, V30) must be limited to 60% of the total liver volume 3D-CRT planning-based dose-volume (DVH) analysis <sup>122</sup>.
- For SBRT consisting of 10 fractions, the normal liver volume receiving <15 Gy must be 700 mL (<sup>123</sup>) and the dose to the normal liver volume excluding the tumor must be limited to 28 Gy (corrected to 2 Gy per fraction-equivalent dose) <sup>124</sup>.
- Used in SBRT studies for 3-fraction regimes <sup>125</sup>:
  - 17.1 Gy (700 cm<sup>3</sup>) (RTOG 1021).
  - 15 Gy (700 cm<sup>3</sup>) (VU Group, Amsterdam).

Radiation-induced Liver Disease (RILD) is defined as a clinical syndrome of anicteric hepatomegaly, ascites and elevated liver enzymes (particularly serum alkaline phosphatase) occurring from 2 weeks to 4 months after radiotherapy <sup>126</sup>. Notable aspects of RILD are:

- Patients with (HCC) usually have underlying cirrhosis, increasing the risk of RILD.
- Incidence of (RILD) is generally low in clinical trials and retrospective studies <sup>127, 128</sup>.
- The sparing of normal liver parenchyma is possible using highly conformal isodose distribution of SBRT.
- With radiation dosing using risk-adapted approach in Child-Pugh class A, no RILD was seen <sup>128</sup>.
- In another dose-escalation trial, no patient with Child-Pugh class A developed RILD. Two patients with Child-Pugh class B developed RILD when dose was escalated from 36Gy to 42Gy in 3 fractions. The dose was eventually changed to 40Gy in 5 fractions, with 1 additional case of RILD <sup>129</sup>.
- A Child-Pugh score 8 was identified as the strongest predictor of RILD <sup>118, 129</sup>.
- Poor liver function with a Child-Pugh B or C score, prior TACE, portal vein thrombosis, and hepatitis B carrier status are known to be associated with a higher risk of RILD <sup>130, 131</sup>.
- To manage the risk of RILD, radiation dose modification is recommended according to the liver function, the relative size of the tumour to the whole liver, and the normal liver dose. More advanced techniques for radiotherapy in order to spare more normal tissue and reduce the normal liver dose is also recommended <sup>131, 132</sup>. Therefore, more advanced RT techniques (such as IMRT and SBRT) are often warranted to improve the clinical outcomes in terms of tumour control and normal tissue toxicity.

The Korean Practice Guidelines for the Management of Hepatocellular Carcinoma summarize the recommendations for RT as follows <sup>133</sup>:

1. RT can be performed in HCC patients if liver functions indicate Child-Pugh class A or B and the irradiated total liver volume receiving 30 Gy is 60% (evidence level B1);
2. RT can be considered for HCC patients ineligible for surgical resection, liver transplantation, RFA, percutaneous ethanol injection, or TACE (evidence level C1);
3. RT can be considered for HCC patients who show incomplete response to TACE when the dose-

volume criteria in Recommendation 1 are met (evidence level B2);

4. RT can be considered for HCC patients with portal vein invasion when the dose-volume criteria in Recommendation 1 are met (evidence level C1); and
5. RT is performed to alleviate symptoms caused by primary HCC or its metastases (evidence level B1).

The different modalities of EBRT are as follows:

1. Three-dimensional conformal radiotherapy (3D-CRT).
2. Intensity modulated radiation therapy (IMRT).
3. Stereotactic body radiotherapy (SBRT).

### **Three-dimensional conformal radiotherapy (3D-CRT)**

3D-CRT makes high-dose radiation to HCC possible by using multiple coplanar or non-coplanar fields in order to reduce the high-dose exposure of normal tissues including the liver and bowels and to increase the tumour dose coverage. With the use of (CT) images for RT planning and a computerized treatment planning system, the tumour and surrounding normal liver can be delineated accurately, beam arrangements and dosimetry calculations are reliable; the delivered dose and irradiated volume of the tumour and normal liver can be precisely evaluated using dose volume histograms (DVH).

In a French phase 2 trial conducted in 27 patients (16 patients with Child-Pugh class A or 11 with Child-Pugh class B liver function) with a single tumour sized 5 cm or 2 tumours sized 3 cm after 66 Gy of 3D-CRT delivered in 33 fractions. A 92% response rate (80% complete response and 12% partial response) was achieved <sup>134</sup>. A large multicenter retrospective study conducted in 398 HCC patients showed that a biologic effective dose of 53.1 Gy<sub>10</sub> was associated with an improved 2-year overall survival <sup>135</sup>. Seong et al, treated 158 unresectable HCC patients with a dose of 25.2-60 Gy (1.8 Gy per fraction). Local RT was combined with TACE as primary treatment (107 patients) or as salvage after failure of repeated TACE (51 patients). In this study, the RT dose was identified by multivariate analysis as the only significant factor for survival. The median survival times in patients who received < 40 Gy, 40-50 Gy, and > 50 Gy were 6, 8, and 13 months, respectively <sup>136</sup>.

Other studies also showed that a total RT dose of > 40-50 Gy achieved higher response or survival rates <sup>137-140</sup>. The reported overall response rates and median survival after EBRT are 40%–90% and 10–25 months, respectively <sup>141</sup>.

TACE alone cannot always achieve complete tumour necrosis (range 40%-100%) and remaining viable tumours increase the possibility of recurrence <sup>142</sup>. Besides, TACE is relatively contraindicated for patients with main portal vein thrombosis. To overcome these limitations, the combination of TACE with EBRT is used with the rationale that radiotherapy can either eradicate residual hepatic tumour after TACE or increase the effectiveness of TACE by eradicating portal vein thrombi <sup>143</sup>. Various studies have reported EBRT with TACE, and the literature supports the feasibility and efficacy of this combined approach for HCC patients with or without portal vein thrombosis <sup>115, 132, 144-147</sup>.

Recommendation: Aim for a dose of 50Gy or above, keeping the liver dose within constraints.

### **Intensity modulated radiation therapy (IMRT)**

In HCC patients previously diagnosed with RILD after 3D-CRT, dosimetric studies comparing IMRT to 3D-CRT have suggested that IMRT enables dose escalation without the risk of increased liver toxicity and potentially reduced the normal tissue complication probability <sup>131, 148</sup>. Some studies reported that

the mean liver dose was higher for fixed-angle IMRT or VMAT plan compared to 3D-CRT<sup>131, 149</sup>, these results could be caused by suboptimal IMRT beam configuration<sup>150</sup>. Comparison of dose-volumetric parameters of VMAT vs fixed-angle IMRT differed according to the target location within the liver; central tumours showed higher mean liver dose and lower liver volume receiving 30 Gy for VMAT than for IMRT<sup>151</sup>. With fixed-angle coplanar IMRT, using fields entering the body near the tumour is possibly better at reducing the normal liver dose compared to the equidistant beam array<sup>152</sup>. Numerous clinical series have been reported with doses to the tumour ranging from 45Gy to 66Gy<sup>153-157</sup> highlighting the potential of dose escalation for HCC without an increased risk of RILD, which signals the potential for improved survival and quality of life in patients with HCC. However, because there is no standard technique for IMRT delivery and because the IMRT plan is not always better than the 3D-CRT plan, it is important to evaluate the DVH data carefully and individualize the treatment plan for every patient<sup>150</sup>.

Recommendation: Aim for a dose of 50Gy or over, keeping the liver dose within constraints.

### **Stereotactic body radiotherapy (SBRT)**

SBRT delivers a high dose of radiation to the target in a few fractions (typically 1-5 fractions) with a high degree of precision. As a single modality, or combined with TACE, SBRT is emerging as a preferred option in patients with localized HCC who may not fit criteria for the more established curative treatments (Surgery, transplantation, TARE or TACE)<sup>133, 158</sup>. The philosophy and biological effects of this treatment are very different from conventionally fractionated treatments.

SBRT has been used for the treatment of a few, small HCCs (< 5-6 cm) in patients with Child-Pugh class A or B disease<sup>110,118,129,159-163</sup>. Local control rates at 2-3 years were 84%-100%, excluding two studies in which a relatively low dose was used<sup>159</sup> or large tumours were treated<sup>110</sup>.

Wahl et al,<sup>160</sup> in a recent retrospective comparison of SBRT and RFA in (predominantly) early-stage HCC (median, 2.2 cm; range, 0 to 10 cm) found no significant difference between SBRT and RFA with similar local control overall and survival. One-year freedom from liver progression of SBRT compared with RFA was 95% v 84% ( $P = .005$ ), and 2-year freedom from liver progression and 2-year overall survival rates were 83% v 79% ( $P = .69$ ) and 45% v 55% ( $P = .26$ ), respectively. Local control with RFA was significantly lower compared with SBRT for tumours larger than 2 cm (hazard ratio, 3.43; 95% CI, 1.03 to 11.41;  $P = .045$ ). SBRT was well tolerated with an excellent side-effect profile. Increase in tumour size was a predictor of local progression in patients who underwent RFA, but not in patients who underwent SBRT.

Despite the growing evidence of a potential curative role of 3D-CRT and SBRT in the multidisciplinary approach of HCC,<sup>121, 160</sup> radiotherapy often remains a palliative option in the many international guidelines<sup>164</sup>. Moreover, this study confirms that SBRT can be safe and efficient in the management of HCC, despite a relatively short follow-up<sup>160</sup>.

SBRT alone (or after TACE) has been used as a curative treatment in the management of early-stage HCC disease in single institutional studies from Japan<sup>162</sup> and Korea<sup>159, 161</sup>, with 3-year survival rates of 54% and 70%, respectively. The response to SBRT can be delayed, and continuous HCC shrinkage and gradual loss of arterial enhancement can be seen over months, and sometimes years, post SBRT. HCC lesions up to 10 cm are potential targets for SBRT, and SBRT may even control tumours greater than 10 cm, although this is more technically challenging and has a higher risk of side effects. Radiotherapy is not yet an accepted standard of care in most international HCC treatment guidelines<sup>164</sup>. Although there are no phase III data as yet to support SBRT, it is an accepted treatment option for early-stage HCC at multidisciplinary HCC management

## Technological considerations and requirements for Liver SBRT

A unique set of technological considerations are associated with targeting liver lesions with narrow margins. Particular issues of concern are:

- Large intra-fraction excursions: As the liver is a sub-diaphragmatic organ the intra-fraction position of liver and therefore HCC can be affected by respiratory motion, which must be characterized during treatment simulation<sup>165, 166</sup>. Respiratory-correlated computed tomography (retrospective 4DCT) should be obtained for all patients, to obtain the internal target volume (ITV) and to consider gating for larger excursions.
- Organ deformation and changing anatomy and poor visibility of liver lesions: The position of liver tumours with respect to bony anatomy can change between fractions<sup>106</sup>. The liver tumours also exhibit low contrast relative to surrounding liver parenchyma. Therefore, daily localization of soft tissue in or near the target volume, using an online (IGRT) option (volumetric kilovoltage imaging and/or implanted fiducials) is important<sup>166, 167</sup>.

Apart from the standard linear accelerators and Helical Tomotherapy (Accuray, Inc., Sunnyvale, CA, United States), specialized machines for SBRT include the CyberKnife system (Accuray, Inc., Sunnyvale, CA, United States) and the VERO system (Brainlab AG, Feldkirchen, Germany).

Recommendation: fixed doses are employed for smaller tumours with a median diameter of approximately 3 cm, *e.g.*, 36 Gy/3 fractions or 40 Gy/5 fractions<sup>121</sup>. In contrast, modified doses were employed for larger targets according to normal liver tolerance based on tumour size and normal liver volume, in a clinical trial. The SBRT dose range was 24 to 54 Gy in six fractions<sup>110</sup>.

### Medical treatment of hepatocellular cancer (HCC):

Systemic therapy includes chemotherapy and targeted therapy. Systemic treatment for advanced and unresectable patients who are not suitable for liver directed therapy are discussed here.

Though systemic chemotherapy has been used and tried in advanced HCC encouraging results were not found. Despite observation of objective response rates median survival is not more than 12 months. The plausible reasons for this may be presence of higher rate of expression of several drug resistance genes like, p-glycoprotein (pgp), glutathione-S-transferase, heat shock proteins (HSP), and mutations in p53 genes. Important cause of mortality is deteriorating liver functions. In three phase III studies doxorubicin was compared with other agents including VP-16, 5-FU and combinations. Though response rates were higher but survival was not different.<sup>168-170</sup>

Combination chemotherapy also has been tried. In two phase II reports from India gemcitabine based combinations were evaluated. Parikh et al reported 20% partial response rates and median overall survival of 21 weeks using combination of gemcitabine and cisplatin.<sup>171</sup> In another study, Pande et al reported a partial response rate of 25% and median overall survival of 7.5 months.<sup>172</sup> Combination of gemcitabine and oxaliplatin also has been tried with limited success.<sup>173</sup> However, in the absence of trials showing distinct benefit, the use of systemic chemotherapy in management of HCC is not recommended outside of clinical trials.<sup>174</sup> Systemic chemotherapy may be an option for patients who progress on sorafenib and are in good physical health.

Number of monoclonal antibodies and small molecules have been evaluated and are being evaluated in clinical trials. The only drugs with proven survival benefit is Sorafenib and Regorafenib in first and second line therapy respectively.



In the pivotal study of sorafenib, SHARP trial, inoperable HCC and Child Pugh (CP) A cirrhotic patients were randomly assigned to sorafenib (400 mg twice daily) or placebo. 602 patients were randomized and overall survival, the primary endpoint, was significantly longer in the sorafenib-treated patients (10.7 versus 7.9 months), so was the time to radiologic progression (5.5 versus 2.8 months). Though objective response rates were low (7 partial responses [2% only]).<sup>175</sup> Treatment was tolerated well with manageable side effects. Grade 3 or 4 diarrhea (8 versus 2 percent) and hand-foot skin reaction (8 versus <1 percent) occurred significantly more often in the treated group were. Based on this study sorafenib was approved as first line monotherapy in advanced HCC and became standard of care. As per personal communications, many Indian physicians feel that Indian patients mostly do not tolerate dose of 400 mg twice a day very well and they start with 200 mg BID and gradually increase the dose. To best of knowledge any pharmacokinetic and pharmacodynamic in Indian subjects is not reported. A second study was conducted in Asian patients (non-Indians). Here, total 226 patients with CP A cirrhosis and no prior systemic therapy for HCC received sorafenib 400 mg twice daily or placebo. Median overall survival (6.5 Vs 4.2 months) and TTP (2.8 Vs 1.4 months) were significantly better in sorafenib arm.<sup>176</sup> However, these results were inferior to European study. Reportedly patients in Asian study were sicker at the start of therapy than those in the SHARP trial.

Recently, regorafenib has been found to be superior to placebo in a double blind phase III randomized trial in sorafenib failures.<sup>(177)</sup> In this study 573 were randomized in a 2:1 ratio to regorafenib and placebo. Regorafenib improved overall survival with a hazard ratio of 0.63 (95% CI 0.50–0.79; one-sided  $p < 0.0001$ ). Median survival was 10.6 months (95% CI 9.1–12.1) for regorafenib versus 7.8 months (6.3–8.8) for placebo. Understanding that this is second line therapy after sorafenib failure, these results are impressive. Whether Indian patients will be able to tolerate recommended dose of 160 mg 3 weeks on and 1 week off is to be seen.

The Indian National Association for Study of the Liver (INASL) has brought out a consensus statement in 2014.<sup>174</sup> This consensus statement advocates that, Sorafenib is indicated in patients of HCC, and that there is no evidence that combination Sorafenib with other cytotoxic agents or targeted agents or hormonal therapy is superior to Sorafenib alone. The data on levatinib and nivolumab looks promising.

Supportive care involves providing support at all stages of a person's experience with cancer. The primary aim of treatment is to bring about symptomatic benefit and improvement in the quality of life of patients with incurable malignancies and support patients while receiving chemotherapy.

### Treatment of Hepatitis B , C

HCC is often diagnosed at advanced stages and prognosis is generally poor.<sup>178</sup> This extremely guarded prognosis is frequently coupled with occurrence of severe symptom like pain, fatigue, anorexia, and ascites.<sup>11</sup> These symptoms impair quality of life as well as functional, psychological, and emotional status.

About a quarter of newly diagnosed patients of HCC and about 25-50% of progressive HCC patients after initial management will develop some of these symptoms requiring supportive and terminal care.<sup>178</sup>

The terminally sick patients are those who presents with Barcelona Clinic Liver cancer (BCLC) stage D, or presenting with ECOG status III-IV or Child –Pugh C but transplant ineligible. They should receive symptoms care and palliative care. The median life expectancy of such patients is 3-4 months.<sup>179</sup> The aim of such treatment should include, management of pain, nutrition, psycho-social support, and management of ascites, bleeding etc.

**Pain management:** Pain is a common cause of morbidity. A numeric pain scale should be used to assess pain and, knowing its often transient in nature needs to be reassessed frequently.

NSAIDs (including aspirin) should generally be avoided in patients with advanced chronic liver disease or cirrhosis as they may increase risk of bleeding and impair renal functions. Opioid analgesia should be used for pain management in terminal stage HCC. Number of opioids like morphine, hydromorphone, levorphanol, methadone, buprenorphine, fentanyl, and transdermal fentanyl can be safely used in patients with cirrhosis and patients with HCC.<sup>180</sup> However, one should keep in mind that there is increased bio-availability of oral morphine and delayed clearance in presence of hepatic dysfunctions and cirrhosis. Thus, necessitating dose modification of morphine. Up-to 2 gm of acetaminophen or paracetamol may be added to opioids. One may use step ladder approach for management of pain as recommended by WHO. An approach to assessment and management of cancer patient is shown in figure 1.<sup>181</sup>

For patients who develop or present with symptomatic bone metastases, lung metastases or pressure symptoms because of lymph nodes, appropriate short course palliative radio-therapy should be offered.<sup>182</sup>

**Ascites:** Ascites is a common symptom in progressive HCC. Progressive ascites causes abdominal wall discomfort, anorexia, early satiety, nausea and vomiting etc. abdominal paracentesis may be used for immediate relief. For medical management potassium sparing diuretics in combination with a loop diuretic is useful. Typically, spironolactone up-to a dose of 100mg/day and frusemide 40 mg/day are recommended. If facility available, for intractable ascites peritono-venous shunt may be offered.

**Nutrition:** Malnutrition is commonly encountered in HCC patients. It may be due to decompensating liver or malignancy related. However, current data do not recommend routine use of parenteral, enteral, or oral nutritional supplement.<sup>183</sup> However, in individual cases, dietary counseling, and artificial nutrition can slow down nutritional deprivation, avoid dehydration and improve the quality of life.<sup>174</sup>

**Bleeding:** One of common cause of mortality is GI bleed. Transhepatic arterioembolization (TAE) may be helpful in such situations.<sup>184</sup>

TAE is also effective in controlling bleeding from ruptured HCC in the acute phase.

The Indian National Association for Study of the Liver (INASL) has brought out a consensus statement in 2014.<sup>174</sup> This consensus statement advocates that:

- a). patients with BCLC stage D have a poor survival and should be offered palliative and supportive care including pain, nutritional, and psychological support
- b). for pain management opioids analgesics and in appropriate settings palliative radiation should be used
- c). routine use of artificial nutrition is not supported by good evidence
- d). TAE may be useful in controlling bleeding from tumour



**Follow-up schedule after surgery or localised procedure**

Year	Time from start of chemotherapy (months)	Clinical examination	Elevated tumour marker levels, AFP	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓		
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓		
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓		
5	60	✓	✓		✓

**Advanced HCC**

- Following completion of therapy, review every 3 months (may be extended if the patient is stable)
- Measure the AFP level (whichever is elevated at diagnosis) at each clinic visit
- No routine imaging is indicated, unless symptom driven
- Consider CT if signs/symptoms suggest disease progression or increasing tumour marker levels
- Ensure that all patients receive palliative care support if possible (desirable)
- If no further treatment can be offered following evidence of disease progression, the patient should be discharged from the clinic with adequate psychological/palliative support, if possible.

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# 11

## ABBREVIATIONS

AAIR	Age Adjusted Incidence Rate	INASL	Indian National Association for Study of the Liver
AASLD	American Association for the Study of Liver Diseases	IRE	Irreversible Electroporation
ACC	Adrenocortical Carcinoma	ITV	Internal Target Volume
AFP	Alfa Feto Protein	LCC	Large Cell Change
AFP-L3	Lens Culinaris Agglutinin-reactive AFP	LDLT	Living Donor Liver Transplant
AJCC	American Joint Committee on Cancer	LGDN	Low Grade Dysplastic Nodule
AMSR	Age Standardized Mortality Rate	LLR	Laparoscopic Liver Resection
AR	Anatomical Resection	MA	Metastatic Adenocarcinoma
ARG	Arginase 1	mCEA	Monoclonal Carcinoembryonic Antigen
BCLC	Barcelona Clinic Liver Cancer	MELD	Model of End-stage Liver Disease
Ca19-9	Carbohydrate Antigen 19-9	MRI	Magnetic Resonance Imaging
CEA	Carcinoembryonic Antigen	NAFLD	Non Alcoholic Fatty Liver Disease
CECT	Contrast Enhanced Computed Tomography	NAR	Non-anatomical Resection
CE-USG	Contrast Enhanced Ultrasonography	NCCN	National Comprehensive Cancer Network
CK	Cytokeratin	NCRP	National Cancer Registry Program
CLIP	Cancer of the Liver Italian Program	NEC	Neuroendocrine Carcinoma
CLT	Cadaveric Liver Transplant	NSAID	Non Steroidal Anti-inflammatory Drugs
CTP	Child Turcottte Pugh	OLT	Orthotopic Liver Transplantation
CUPI	Chinese University Prognostic Index	OPD	Out-patient Department
DDLT	Deceased Donor Liver Transplant	PBCR	Population Based Cancer Registry
DN	Dysplastic nodules	PCEA	Polyclonal Carcinoembryonic Antigen
EASL	European Association for the Study of the Liver	PEI	Percutaneous Ethanol Injection
EBRT	External Beam Radiation Therapy	PET	Positron Emission Tomography
ECOG	Eastern Cooperative Oncology Group	PIVKA	Prothrombin Induced by Vitamin K Absence II
FLR	Future Liver Remnant	PVE	Portal Vein Embolization
FNH	Focal Nodular Hyperplasia	RCC	Renal Cell Carcinoma
GPC3	Glypican-3	RCT	Randomized Controlled Trial
GS	Glutamine synthetase	RFA	Radiofrequency Ablation
HA	Hepatic Adenoma	RILD	Radiation Induced Liver Disease
HBV	Hepatitis B Virus	SBRT	Stereotactic Body Radiation Therapy
HCC	Hepatocellular Carcinoma	SCC	Small Cell Change
HCV	Hepatitis C Virus	SIRT	Selective Intraarterial Brachytherapy
HGDN	High Grade Dysplastic Nodule	SMA	Smooth Muscle Antigen
HSP	Heat Shock Protein	TACE	Transarterial Chemoembolization
HVPG	Hepatic Venous Pressure Gradient	TARE	Transarterial Radioembolization
IARC	International Agency for Research on Cancer	TELV	Total Estimated Liver Volume
ICG	Indocyanine Green	TNM	Tumor Node Metastasis
ICMR	Indian Council of Medical Research	UCSF	University of California at San Francisco
IGRT	Image-Guided Radiation Therapy	UICC	Union for International Cancer Control
IHC	Immuno Histo Chemistry	US	Ultrasound
IHCC	Intra-Hepatic Cholangiocarcinoma	VMAT	Volumetric Arc Therapy
IMRT	Intensity Modulated Radiation Therapy	WHO	World Health Organization



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