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Clinical Practice Guidelines

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

European Association for the Study of the Liver*, European Organisation for Research and Treatment of Cancer

1. Introduction

EASL–EORTC Clinical Practice Guidelines (CPG) on the management of hepatocellular carcinoma (HCC) define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with this type of cancer. This is the first European joint effort by the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC) to provide common guidelines for the management of hepatocellular carcinoma. These guidelines update the recommendations reported by the EASL panel of experts in HCC published in 2001.[1] Several clinical and scientific advances have occurred during the past decade and, thus, a modern version of the document is urgently needed.

The purpose of this document is to assist physicians, patients, health-care providers and health-policy makers from Europe and worldwide in the decision-making process according to evidence-based data. Users of these guidelines should be aware that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available. Thus, they should adapt the recommendations to their local regulations and/or team capacities, infrastructure and cost–benefit strategies. Finally, this document sets out some recommendations that should be instrumental in advancing the research and knowledge of this disease and ultimately contribute to improve patient care.

The EASL–EORTC CPG on the management of hepatocellular carcinoma provide recommendations based on the level of evidence and the strength of the data (the classification of evidence is adapted from the National Cancer Institute[2]) (Table 1A) and the strength of recommendations following previously reported systems (GRADE systems) (Table 1B).

2. Clinical Practice Summary

The clinical practice guidelines below will give advice for up to date management of patients with HCC as well as providing an in-depth review of all the relevant data leading to the conclusions.

☆ These Guidelines were developed by the EASL and the EORTC and are published simultaneously in the *Journal of Hepatology* (volume 56, issue 4) and the *European Journal of Cancer* (volume 48, issue 5).

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Abbreviations: HCV, Hepatitis C virus; SNP, Single nucleotide polymorphism; PEG, Polyethylene glycol; HALT-C, Hepatitis C antiviral long-term treatment against cirrhosis; EPIC, Evaluation of PegIntron in control of hepatitis C cirrhosis; CT, Computed tomography; MR, Magnetic resonance; MRI, Magnetic resonance imaging; EpCAM, Epithelial cell adhesion molecule; PPV, Positive predictive value; qRT-PCR, Real-time reverse-transcription polymerase chain reaction; CUPI, Chinese university prognostic index; CLIP, Cancer of the Liver Italian program; SHARP, Sorafenib hepatocellular carcinoma assessment randomised protocol.

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Surveillance

- Patients at high risk for developing HCC should be entered into surveillance programs. Groups at high risk are depicted in Table 3
  (evidence 1B/3A; recommendation 1A/B)
- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months
  (evidence 2D; recommendation 1B)
  Exceptions: A shorter follow-up interval (every 3–4 months) is recommended in the following cases: (1) Where a nodule of less than 1 cm has been detected (see recall policy), (2) In the follow-up strategy after resection or loco-regional therapies
  (evidence 3D; recommendation 2B)
- Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumour progression and to help define priority policies for transplantation
  (evidence 3D; recommendation 1B)

Recall policy

- In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed every 4 months the first year and with regular checking every 6 months thereafter
  (evidence 3D; recommendation 2B)
- In cirrhotic patients, diagnosis of HCC for nodules of 1–2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. In the latter case, it is recommended that biopsies are assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow-up
  (evidence 2D; recommendation 1B)
- In cirrhotic patients, nodules more than 2 cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy
  (evidence 2D; recommendation 1A)

Diagnosis

- Diagnosis of HCC is based on non-invasive criteria or pathology
  (evidence 2D; recommendation 1A)
- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (*GPC3*, *LYVE1* and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC
  (evidence 2D; recommendation 2B)
  Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34).
- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter **(evidence 2D; recommendation 2B)**, a more conservative approach with 2 techniques is recommended in suboptimal settings. The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis.

Staging systems

- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumour stage, liver function and performance status.
- The BCLC staging system is recommended for prognostic prediction and treatment allocation
  (evidence 2A; recommendation 1B)
  This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated.
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice.