

# Hepatocellular carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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## incidence

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and eighth most common cancer in women worldwide. Its crude incidence in the European Union is 8.29/100 000. It is four to eight times more common in men and usually associated with chronic liver injury (hepatitis B, hepatitis C and alcoholic cirrhosis). Median age at diagnosis is between 50 and 60 years.

## diagnosis

Diagnosis is usually made by history, physical examination, imaging (ultrasound, MRI or CT scan showing a liver mass consistent with HCC) and elevated serum  $\alpha$ -fetoprotein (AFP 400 ng/ml). Confirmation of diagnosis is made by fine needle aspiration or biopsy. Elevation of AFP >400 ng/ml can be used instead of fine needle cytology for diagnosis of HCC in patients with liver cirrhosis and a focal hypervascular liver lesion (>2 cm) in at least one imaging technique. Patients with potentially resectable liver mass and AFP >400 ng/ml should undergo surgery without preoperative FNAC or biopsy.

## staging and risk assessment

Staging should include X-ray of chest and CT scan of the abdomen. Tumors should be staged according to AJCC staging criteria/TNM system. The fibrolamellar variant is not associated with cirrhosis and has a more favorable prognosis.

- Staging systems such as CLIP or BCLC that include staging of liver cirrhosis may improve prediction of the ultimate prognosis of HCC patients.
- Risk assessment is based on Pugh's modification of Child's grading of liver function.
- For patients being considered for liver transplantation, MELD score is also useful.

- Child–Pugh grade C patients should be offered only supportive care. Child–Pugh grade A and favorable grade B should be evaluated for specific treatment options.

## treatment plan

This should be based on extent of disease, growth pattern of tumor, hepatic functional reserve and patient's performance status.

### localized resectable tumors (T1, T2, T3 and selected T4; N0; M0)

Standard treatment is surgical resection (partial hepatectomy) for patients without liver cirrhosis [II, A]. For patients with liver cirrhosis, surgical resection or liver transplantation may be considered depending on hepatic functional reserve.

### localized unresectable tumors (selected T2, T3 and T4; N0; M0)

Total hepatectomy with liver transplantation should be considered first [II, A]. Other options include [IV, B]:

- Chemoembolization for patients with adequate hepatic functional reserve and multifocal HCC.
- Percutaneous ethanol injection for patients with fewer than three or four tumor nodules, maximum 5 cm in size.
- Radiofrequency ablation also for tumors <5 cm in size and/or fewer than four in number.
- Inclusion in clinical trials.
- Best supportive care.
- Systemic chemotherapy containing anthracyclines, cisplatin and 5-FU with a prospect of a 10% response rate and no survival benefit (if bilirubin normal and hepatic reserve adequate).

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In a phase II study Sorafenib induced response in 8% and disease control in 41% of patients. In a phase III study it extended survival for 2.8 months.

**Table 1.** TNM staging criteria for HCC

T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
T3	Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
N0	Indicates no nodal involvement
N1	Indicates regional nodal involvement
M0	Indicates no distant metastasis
M1	Indicates metastasis presence beyond the liver
Stage grouping	
Stage I	T1 + N0 + M0
Stage II	T2 + N0 + M0
Stage IIIA	T3 + N0 + M0
Stage IIIB	T4 + N0 + M0
Stage IIIC	TX + N1 + M0
Stage IVB	TX + NX + M1

**Table 2.** CLIP classification

Parameter	Score
<b>Child–Pugh</b>	
A	0
B	1
C	2
<b>Tumour morphology</b>	
Uninodular and extension <50% of tumour	0
Multinodular and extension <50% of tumour	1
Massive or extension ≥50% of tumor	2
<b>Alpha fetoprotein</b>	
<400 ng/ml	0
>400 ng/ml	1
<b>Macro vascular invasion</b>	
No	0
Yes	1

**advanced tumors (any T; N+; M1)**

There is no established standard of care. Systemic chemotherapy, inclusion in clinical trials and best supportive care should be considered

**follow-up**

Patients undergoing curative resection should be followed up 3- to 6-monthly with AFP determination and liver imaging (for 2 years)—since curative therapy can still be offered at relapse, to a minority. The indications for antiviral/IFN therapy for patients positive for hepatitis C and hepatitis B virus should depend on the degree of hepatitis and/or liver cirrhosis and viral replicative status. For other patients, follow-up aims to prevent and/or treat hepatic decompensation.

**Table 3.** Child–Pugh classification of severity of liver disease

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirrubin, mg/dl	≤ 2	2–3	>3
Albumin, g/dl	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds over control	1–3	4–6	>6
INR	<1.8	1.8–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

A total score of 5–6 is considered grade A (well-compensated disease); 7–9 is grade B (significant functional compromise); and 10–15 is grade C (decompensated disease).

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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