

HEPATOCELLULAR CARCINOMA

GENERAL OVERVIEW, DIAGNOSIS AND BCLC STAGING

GENERAL OVERVIEW

- **Epidemiology.** HCC is the predominant primary liver malignancy. Most cases arise in chronic liver disease/cirrhosis, but HCC can also occur without cirrhosis, particularly with chronic hepatitis B and MASLD.
- **Surveillance.** Patients with cirrhosis and other established high-risk groups should undergo HCC surveillance every 6 months, usually with liver ultrasound; AFP can be added according to local practice.
- **Fibrolamellar carcinoma.** Rare, biologically distinct primary liver tumour, typically affecting younger patients without cirrhosis.

DIAGNOSIS AND STAGING

- **Imaging.** Use multiphasic contrast-enhanced CT or MRI of the liver. Add chest imaging for staging when HCC is confirmed or strongly suspected.
- **Non-invasive diagnosis.** In patients at high risk for HCC (e.g. cirrhosis), a typical radiological pattern can establish the diagnosis without biopsy.
- **Biopsy.** Indicated when imaging is indeterminate/atypical or when histology will influence management; histological confirmation is generally required in non-cirrhotic liver.
- **Integrated staging.** Assess tumour burden, macrovascular invasion and extrahepatic spread together with liver function (Child-Pugh and preferably ALBI), ECOG performance status and portal hypertension. Use BCLC (see table below) for integrated staging and treatment allocation.
- **AFP.** Not sufficiently sensitive or specific to diagnose HCC alone, but useful for surveillance in some settings, prognosis, and treatment selection (e.g. ramucirumab evidence for AFP ≥ 400 ng/mL).

Stage	Tumour pattern	Clinical context	Usual treatment direction
0 — very early	Solitary ≤ 2 cm	Preserved liver function; PS 0	Ablation or resection; transplant in selected cases
A — early	Solitary tumour or up to 3 nodules ≤ 3 cm	Preserved liver function; PS 0	Resection, ablation or transplantation according to liver reserve/portal hypertension
B — intermediate	Multifocal, beyond stage A; no vascular invasion/EHS	Preserved liver function; PS 0	TACE/TARE in selected patients; systemic therapy when TACE-unsuitable
C — advanced	Macrovascular invasion and/or extrahepatic spread	Usually preserved liver function; PS 1–2 from cancer	Systemic therapy
D — terminal	Any tumour burden	Poor PS and/or end-stage liver dysfunction without transplant option	Best supportive care

IMPORTANT UZA PRACTICE PRINCIPLES

- **MDT.** Management should be discussed in a multidisciplinary liver tumour board. BCLC stage guides treatment, but treatment-stage migration is appropriate when the preferred option is unsuitable.
- **Liver reserve.** Preserve liver function throughout the pathway. Reassess Child-Pugh/ALBI and ECOG at every major treatment transition.
- **Potential resection.** Assess clinically significant portal hypertension and future liver remnant. HVPG measurement, volumetry and functional liver testing (e.g. mebrofenin scintigraphy) may be useful in selected patients.

HEPATOCELLULAR CARCINOMA

BCLC 0 / A / B — LOCALISED AND INTERMEDIATE DISEASE

BCLC 0 / A — CURATIVE-INTENT TREATMENT

- **Surgical resection.** Preferred for appropriate solitary tumours when adequate liver reserve/future liver remnant are present and clinically significant portal hypertension is absent or acceptable.
- **Thermal ablation.** MWA/RFA is a curative alternative for small tumours, particularly when surgery is not appropriate. MWA is often preferred for technical reasons and larger ablation zones.
- **Liver transplantation.** Preferred for suitable patients with cirrhosis and transplant-appropriate tumour burden (classically Milan criteria: single tumour ≤5 cm or up to 3 tumours each ≤3 cm), including after successful downstaging in selected patients.
- **Other local options.** SBRT or selective radioembolisation/radiation segmentectomy can be considered when resection or thermal ablation is not feasible, depending on expertise and anatomy.

BCLC B — INTERMEDIATE STAGE

- **TACE.** Remains a standard option for multinodular, liver-limited HCC with preserved liver function when selective embolisation is feasible.
- **TARE/SIRT.** Valid alternative in selected patients, especially for unilobar/solitary disease, favourable anatomy and preserved liver reserve.
- **TACE-unsuitable disease.** Avoid repeated ineffective TACE. With high tumour burden, bilobar diffuse disease, impaired reserve or early TACE failure, switch to systemic therapy rather than persisting with locoregional treatment.
- **Combination strategies.** EMERALD-1 and LEAP-012 improved PFS by adding systemic therapy to TACE; EMERALD-3 (ASCO 2026) also met its PFS endpoint with STRIDE + lenvatinib + TACE. Align use with regulatory/reimbursement status and MDT selection.

BCLC C — FIRST-LINE SYSTEMIC THERAPY

PATIENT SELECTION BEFORE FIRST LINE

- **Preferred population.** Pivotal first-line trials predominantly enrolled Child-Pugh A patients with preserved performance status.
- **Child-Pugh B.** Not an automatic absolute contraindication to all systemic therapy, but evidence is weaker; individualise cautiously after MDT discussion.
- **Liver transplant.** Immune checkpoint inhibitors should generally be avoided after liver transplantation because of graft-rejection risk.
- **Autoimmune disease.** Requires individual risk-benefit assessment rather than a blanket exclusion.

Regimen	Key evidence	Practical selection
Durvalumab + tremelimumab (STRIDE)	HIMALAYA: OS benefit vs sorafenib; durable long-term survival	Avoid/individualise with high risk for severe immune toxicity or post-transplant
Atezolizumab + bevacizumab	IMbrave150: OS/PFS benefit vs sorafenib	Requires bleeding-risk/variceal assessment; caution with uncontrolled hypertension/proteinuria
Nivolumab + ipilimumab	CheckMate 9DW: mOS 23.7 vs 20.6 months; HR 0.79	High response rate; consider immune-toxicity profile and need for rapid/deep response
Lenvatinib or sorafenib	REFLECT / SHARP	Evidence-based first line when an ICI-based regimen is unsuitable

HEPATOCELLULAR CARCINOMA

AFTER PROGRESSION, BCLC D AND ADJUVANT THERAPY

TREATMENT AFTER PROGRESSION

- **After first-line immunotherapy.** There is no prospective phase III-defined optimal sequence. In fit patients with preserved liver function, a TKI is commonly used; choice is individualised according to prior therapy and toxicity.
- **Regorafenib.** Supported by RESORCE after progression on and tolerance of sorafenib.
- **Cabozantinib.** Supported by CELESTIAL after prior sorafenib and can be considered later-line.
- **Ramucirumab.** Phase III evidence after sorafenib in patients with AFP ≥ 400 ng/mL; use depends on availability/reimbursement.
- **Chemotherapy.** GEMOX has limited evidence and should be reserved for highly selected patients when established options are exhausted or contraindicated.

BCLC D — TERMINAL STAGE

- **Best supportive care.** Patients with poor performance status and/or end-stage liver dysfunction who are not candidates for transplantation or other disease-directed therapy should receive proactive palliative and supportive care, including symptom and liver-failure management.

ADJUVANT THERAPY AFTER RESECTION / ABLATION

- **Current standard.** There is no established adjuvant systemic therapy after curative-intent resection or ablation.
- **IMbrave050.** Adjuvant atezolizumab + bevacizumab initially improved RFS, but updated follow-up no longer showed sustained RFS benefit and no OS benefit has been demonstrated; routine use is not recommended.
- **STORM.** The phase III trial was negative for adjuvant sorafenib.

HEPATOCELLULAR CARCINOMA

BELGIAN REIMBURSEMENT — QUICK REFERENCE

Treatment	HCC situation	Belgian practical note
Durvalumab + tremelimumab	1L unresectable/advanced HCC	Reimbursed
Atezolizumab + bevacizumab	1L unresectable/advanced HCC	Reimbursed
Nivolumab + ipilimumab	1L unresectable HCC	Not reimbursed
Lenvatinib / sorafenib	1L when ICI unsuitable	Established TKI options.
Regorafenib	After sorafenib	Evidence-based after sorafenib progression/tolerance
Cabozantinib	Later line	Evidence-based after prior sorafenib..Not reimbursed
Ramucirumab	After sorafenib, AFP ≥400 ng/mL	Not reimbursed

WHAT'S NEW? — 2025–2026

PRACTICE-CHANGING / PRACTICE-INFORMING UPDATES

- **BCLC 2026.** Retains the 2022 staging structure but updates treatment recommendations to incorporate recent systemic and locoregional-systemic evidence.
- **CheckMate 9DW.** Nivolumab + ipilimumab is an active first-line immunotherapy option for unresectable HCC; mOS 23.7 vs 20.6 months versus lenvatinib/sorafenib (HR 0.79).
- **EMERALD-1 / LEAP-012.** Support adding systemic therapy to TACE through improved PFS in selected intermediate-stage disease.
- **EMERALD-3.** Positive PFS result reported in 2026 for STRIDE + lenvatinib + TACE; OS maturity, toxicity, selection and reimbursement remain important before broad adoption.
- **IMbrave050.** Updated analysis does not support adjuvant atezolizumab + bevacizumab as routine standard after resection/ablation.

UZA TAKE-HOME

- **Early HCC.** Prioritise curative-intent resection, ablation or transplantation according to tumour burden, portal hypertension and liver reserve.
- **Intermediate HCC.** Use selective locoregional therapy when appropriate; move early to systemic treatment when TACE-unsuitable or TACE-refractory.
- **Advanced HCC.** ICI-based therapy is preferred for suitable Child-Pugh A patients; treatment choice should integrate bleeding risk, immune toxicity, transplant status, liver reserve and Belgian access.

HEPATOCELLULAR CARCINOMA

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