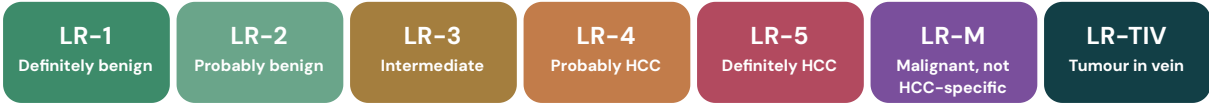


Hepatocellular carcinoma: tests, treatment by setting, systemic regimens and side effects

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A. Diagnosis and staging tests and what they change

LI-RADS CT/MRI categories (high-risk patients only: cirrhosis, chronic hepatitis B, or current/prior HCC)



LR-5 (no biopsy needed in a high-risk liver)

Observation ≥ 1 cm with non-rim arterial phase hyperenhancement, PLUS

- non-peripheral washout (portal venous or delayed phase), and/or
- enhancing capsule, and/or
- threshold growth (≥50% in ≤6 months)

Size and number of features decide LR-4 versus LR-5

The same picture in a NON-cirrhotic liver is only "suspicious": biopsy

What to do next

LR-3: repeat CT/MRI in 3–6 months

LR-4: MDT; biopsy, repeat imaging or treat as HCC

LR-5: stage and treat

LR-M: biopsy (cholangio-carcinoma, combined HCC-CCA, metastasis)

LI-RADS turns imaging into a probability. HCC is one of the few cancers that can be diagnosed without tissue, but only in a high-risk liver and only when the imaging is classic. Rim enhancement, targetoid features or a normal background liver call for a biopsy.

Table A. Diagnosis and staging tests and what they change

Test	When	What it changes	Pitfalls
Ultrasound + AFP	Every 6 months in at-risk adults	Finds HCC while curable; a nodule ≥1 cm or AFP ≥20 ng/mL triggers contrast CT/MRI	Operator-dependent; poor views in obesity and fatty or coarse livers
Multiphase CT or MRI (liver protocol)	Any suspicious nodule or rising AFP; staging	LI-RADS category; LR-5 = HCC without biopsy in a high-risk liver	A routine portal-phase CT misses small HCC; MRI better after treatment
AFP	Surveillance, baseline, response	>400 ng/mL in a high-risk patient nearly confirms HCC; >1000 lowers transplant eligibility; ramucirumab needs ≥400	Normal in most early HCC; raised in active hepatitis and in pregnancy and germ cell tumours
Core biopsy	Non-cirrhotic liver; LR-4/LR-M; before systemic therapy if imaging atypical	Separates HCC from cholangiocarcinoma, combined HCC-CCA and metastasis	Track seeding ~0.6%; bleeding risk in cirrhosis; a negative biopsy does not exclude HCC

Test	When	What it changes	Pitfalls
CT chest	All patients at staging	Lung is the commonest distant site; changes BCLC to C	PET-CT is not routine (HCC is often FDG-negative)
Child-Pugh, ALBI, MELD	Every decision point	Child-Pugh A for most treatments; B7 borderline; C supportive or transplant	Child-Pugh mixes subjective items; ALBI is objective
Portal hypertension (platelets, varices, elastography, HVPg)	Before resection; before bevacizumab	Clinically significant portal hypertension steers away from major resection; varices must be treated before bevacizumab	Endoscopy within 6 months before atezolizumab-bevacizumab
HBsAg, anti-HBc, HBV DNA; anti-HCV, HCV RNA	Every patient at diagnosis	Antiviral therapy reduces recurrence and liver failure; prophylaxis prevents HBV reactivation on immunotherapy or TACE	Anti-HBc positive alone still needs a reactivation plan
NTRK fusion (RNA NGS)	Rare; consider in young, non-cirrhotic or treatment-refractory cases	TRK inhibitor (larotrectinib, entrectinib, repotrectinib)	No other routine predictive biomarker in HCC; PD-L1 does not select

B. Treatment by setting

BCLC staging (2026 update): tumour burden + liver function + performance status → treatment

O Very early	Single ≤2 cm ECOG 0 · liver function preserved	Resection or ablation; transplant if needed
A Early	Single >2 cm, or ≤3 nodules each ≤3 cm ECOG 0 · preserved	Resection, transplant or ablation
B Intermediate	Multinodular beyond A ECOG 0 · preserved	Transplant (if downstaged), TACE/TARE, or systemic if burden large
C Advanced	Portal invasion and/or spread outside liver ECOG 1–2 · preserved	Systemic therapy (immunotherapy combinations first)
D Terminal	Any tumour ECOG 3–4 or end-stage liver	Best supportive care; transplant only if otherwise eligible

BCLC now allows "treatment stage migration": if the stage–default fails or is unsuitable, move to the next option that fits.

BCLC links stage to treatment. Unlike TNM, it builds in liver function and fitness, which often decide survival more than the tumour itself. The 2026 update keeps the five stages; Indian (INASL) and Asian guidelines accept more aggressive local treatment in selected B and C patients.

Table B. Treatment by setting (no doses)

Setting	Standard	Alternatives / notes	Evidence
BCLC O (single ≤2 cm)	Thermal ablation or resection	Transplant if liver function poor and eligible; SBRT if ablation not feasible	SURF , Chen 2006
BCLC A, resectable (single, Child–Pugh A, no portal hypertension)	Resection (laparoscopic where possible)	Ablation for ≤3 cm when surgery is riskier; transplant if liver reserve inadequate	Shin 2021
BCLC A, not resectable (liver function, location)	Transplant if within Milan/UCSF	Ablation ≤3 cm; TACE + ablation 3–5 cm; TARE for solitary large; SBRT	Milan 1996 , LEGACY
BCLC B (multinodular, liver-confined)	TACE (DEB–TACE) or TARE	Downstaging to transplant; systemic first if burden large or TACE–unsuitable; TACE + immunotherapy investigational	Llovet 2002 , EMERALD–1 , LEAP–012
Branch PVTT (Vp1–Vp2)	Local (TARE, SBRT, TACE + RT) or systemic	Choose local when later resection or transplant is possible	Yoon 2018
Main or lobar PVTT (Vp3–Vp4), metastatic (BCLC C)	Atezolizumab–bevacizumab or tremelimumab–durvalumab	Nivolumab–ipilimumab (fit); lenvatinib; single-agent immunotherapy; HAIC in expert centres	IMBrave150 , HIMALAYA , CheckMate 9DW
Child–Pugh B advanced HCC	Single-agent immunotherapy (ECOG 0–1)	Sorafenib with cautious start; supportive care if B8–9 and frail	Xie 2023

Setting	Standard	Alternatives / notes	Evidence
Recurrence after transplant	Lenvatinib or sorafenib	Local therapy for oligometastases; NO checkpoint inhibitors (graft rejection)	Kumar 2020
After resection or ablation	Surveillance + antiviral therapy	No adjuvant systemic therapy outside trials	STORM, IMbrave050, Yin 2013
BCLC D	Best supportive care; palliative RT for pain	Transplant only if otherwise eligible (liver failure, not tumour, is the problem)	CCTG HE1

C. Systemic regimens: evidence and best fit

First-line systemic therapy for advanced HCC (Child-Pugh A, ECOG 0–1, no prior liver transplant)

Atezolizumab + bevacizumab

- IMbrave150: OS 19.2 vs 13.4 mo
- Response ~30%: bulky or symptomatic disease
- Endoscopy ± banding within 6 months first

Tremelimumab + durvalumab

- HIMALAYA: 5-yr OS 20% vs 9%
- No bevacizumab: suits bleeding risk
- One-off tremelimumab dose; low burden

Nivolumab + ipilimumab

- CheckMate 9DW: OS 24 vs 21 mo
- Response 36%; more immune toxicity
- ECOG 0, few comorbidities

When combinations are not suitable

Lenvatinib

- REFLECT: OS non-inferior to sorafenib
- Higher response; preferred TKI

Sorafenib

- SHARP: OS 10.7 vs 7.9 mo
- Start low, build up

Single immunotherapy

- Durvalumab, tislelizumab or pembrolizumab
- Also first choice in Child-Pugh B

After liver transplant

- TKI only (lenvatinib or sorafenib)
- No checkpoint inhibitors: rejection

Three immunotherapy combinations beat a tyrosine kinase inhibitor for survival; choose by bleeding risk, tumour burden, fitness and access. Before any of them: screen and treat hepatitis B (reactivation risk), check varices if bevacizumab is planned. No doses shown.

Table C. Systemic regimens: evidence and best fit (no doses)

Regimen	Key trial and result	Best for	Avoid or caution
Atezolizumab + bevacizumab	IMbrave150 : OS 19.2 vs 13.4 mo (HR 0.66); response 30%	Bulky or symptomatic disease; Vp3–Vp4 PVTT	Untreated varices, recent bleeding, arterial thrombosis, uncontrolled hypertension, proteinuria, anticoagulation
Tremelimumab + durvalumab (STRIDE)	HIMALAYA : OS 16.4 vs 13.8 mo; 5-year 20% vs 9%	Low burden; bleeding risk; wants fewer visits	Autoimmune disease; organ transplant
Nivolumab + ipilimumab	CheckMate 9DW : OS 24 vs 21 mo (HR 0.79); response 36%	ECOG 0, few comorbidities	More grade 3–4 immune toxicity; early progression in some
Lenvatinib	REFLECT : OS 13.6 vs 12.3 mo (non-inferior); response 24 vs 9%	Immunotherapy unsuitable; after transplant; second line after immunotherapy	Hypertension, proteinuria, fatigue, bleeding; trial excluded >50% liver involvement and main portal vein invasion
Sorafenib	SHARP : OS 10.7 vs 7.9 mo; Asia-Pacific trial similar relative gain	Lowest cost in India (generics); Child-Pugh B with care	Hand-foot skin reaction, diarrhoea; start low and build up

Regimen	Key trial and result	Best for	Avoid or caution
Durvalumab, tislelizumab or pembrolizumab alone	HIMALAYA durvalumab arm and RATIONALE-301 : OS non-inferior to sorafenib; KEYNOTE-394 : OS gain after sorafenib	Not fit for combinations; Child-Pugh B	Transplant recipients
Regorafenib	RESORCE : OS 10.6 vs 7.8 mo after sorafenib	Second line if sorafenib was tolerated	Sorafenib intolerance
Cabozantinib	CELESTIAL : OS 10.2 vs 8.0 mo after sorafenib	Second or third line	Hand-foot reaction, diarrhoea, hypertension
Ramucirumab	REACH-2 : OS 8.5 vs 7.3 mo; AFP ≥ 400 only	AFP ≥ 400 ng/mL; no hand-foot reaction	Bleeding risk, proteinuria
Not established	CheckMate 459 (nivolumab vs sorafenib) and COSMIC-312 (cabozantinib + atezolizumab) missed OS; CARES-310 and ORIENT-32 positive but agents mostly unavailable in India	—	—

D. Managing common problems during treatment

Table D. Managing common problems during treatment

Problem	Think of	First steps	When to stop or refer
Rising ALT/AST on immunotherapy	Immune hepatitis vs HBV/HCV flare vs tumour progression vs drug or alcohol injury	Check HBV DNA, HCV RNA, imaging, bilirubin, INR; hold drug at grade 2+; steroids per irAE grade	Grade 3–4 or bilirubin rise: stop, high-dose steroids, hepatology input
HBV reactivation	HBsAg+ or anti-HBc+ patient on immunotherapy, TACE or chemotherapy without prophylaxis	Prevent with entecavir or tenofovir started before treatment; monitor HBV DNA	Any rise in DNA with ALT flare: urgent antiviral and hepatology
Bleeding on bevacizumab or TKI	Varices, tumour bleed, peptic ulcer	Endoscopy before bevacizumab; band large varices; stop drug for major bleeding	Variceal bleed: stop bevacizumab permanently in most
Hypertension, proteinuria	Bevacizumab, lenvatinib, ramucirumab	Home BP; urine dipstick each cycle; ACE inhibitor or ARB	Nephrotic-range proteinuria: hold
Hand-foot skin reaction, diarrhoea	Sorafenib, regorafenib, cabozantinib (less with lenvatinib)	Urea cream, soft footwear, early dose reduction; loperamide	Grade 3: hold until grade ≤ 1 , restart lower
Fever, pain, vomiting after TACE	Post-embolisation syndrome (common, self-limiting)	Analgesia, antiemetics, fluids	Fever beyond a week or rigors: liver abscess (higher risk after biliary procedures)
Jaundice, ascites, confusion	Liver decompensation (treatment- or tumour-related), PVT obstruction, biliary obstruction	Recalculate Child-Pugh/ALBI; ultrasound; treat precipitant (infection, bleed)	Child-Pugh C: move to supportive care unless transplant candidate
Fatigue, weight loss, low mood	Disease, TKI, hypothyroidism, hypoadrenalism after immunotherapy	TSH, cortisol; nutrition (late-evening snack in cirrhosis); exercise	Persistent: dose reduce TKI; endocrine review