

ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Hepatocellular Carcinoma

A mini review for clinicians

For postgraduate residents (medical, surgical and radiation oncology, gastroenterology and hepatology, general and hepatobiliary surgery, interventional radiology, medicine), practising clinicians and medical students

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Updated 15 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Hepatocellular Carcinoma

Hepatobiliary cancers, part 1 · Surveillance · LI-RADS · BCLC · Resection · Ablation · TACE/TARE · SBRT · Transplant · Immunotherapy · Key points for clinicians · Last updated 15 October 2026

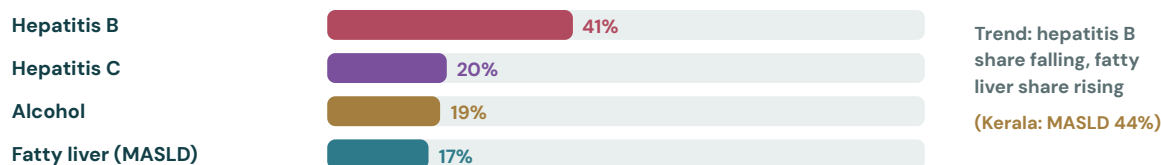
01 At a glance

- Hepatocellular carcinoma (HCC) is the main primary liver cancer (roughly three-quarters or more of cases). In India, GLOBOCAN 2022 estimates about **38,700 new liver cancers and 37,000 deaths a year**, with men affected more than twice as often as women. Deaths almost equal new cases: most patients are diagnosed when cure is no longer possible.
- In Indian series the underlying cause is **hepatitis B in about 41%**, hepatitis C 20%, alcohol 19% and fatty liver disease (MASLD) 17%; the hepatitis B share is falling and the fatty-liver share rising ([Praharaj 2024^{\[1\]}](#)). In Kerala, fatty liver was present in 44% of more than 1,200 patients ([Koshy 2023^{\[2\]}](#)).
- HCC is **two diseases at once**: the tumour and the liver that produced it. Tumour burden, liver function (Child–Pugh, ALBI) and performance status together decide treatment; BCLC staging builds in all three ([BCLC 2026^{\[3\]}](#)).
- Cure (resection, ablation, transplantation) is possible mainly when HCC is found by **6-monthly surveillance** of people at risk. India's National Viral Hepatitis Control Programme offers free testing and treatment for hepatitis B and C: preventing and treating viral hepatitis is the most effective HCC control measure available.
- Advanced HCC is no longer a sorafenib-only disease: three immunotherapy combinations improve survival, with about one in five patients alive at 5 years in HIMALAYA ([Rimassa 2025^{\[4\]}](#)).

India, GLOBOCAN 2022: about 38,700 new liver cancers and 37,000 deaths a year

Deaths almost equal new cases: most patients are found when cure is no longer possible.

Underlying cause in Indian HCC series (pooled proportions; causes overlap, so they do not add to 100%)



Who gets it

- Cirrhosis of any cause (about 4 in 5)
- Hepatitis B even without cirrhosis
- Men about 3 times more than women

Why it is found late

- No symptoms until advanced
- Cirrhosis often unknown
- Surveillance rarely done

Two diseases at once

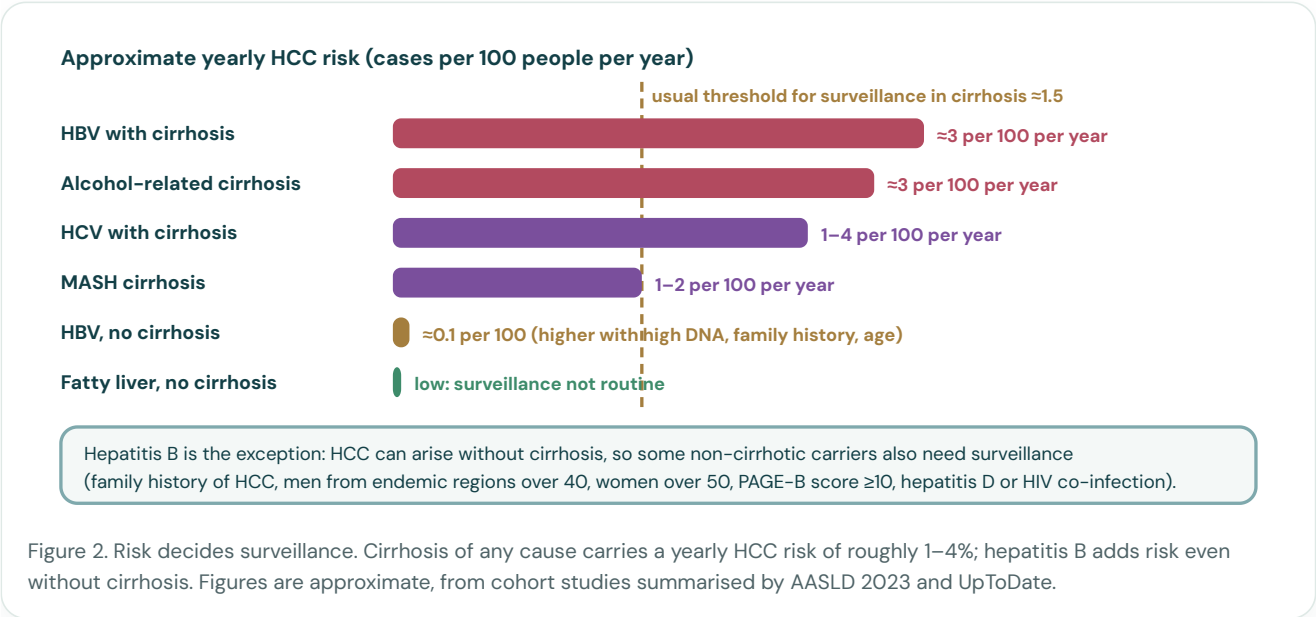
- Cancer stage AND liver function decide treatment
- Treat the virus as well as the tumour
- Team care: hepatology + oncology + IR + surgery

Figure 1. Hepatocellular carcinoma (HCC) at a glance. In India viral hepatitis still causes most HCC, but fatty liver is rising. Because deaths nearly match new cases, finding HCC early through surveillance is the main lever for cure (GLOBOCAN 2022; Praharaj 2024 meta-analysis).

02 Clinical presentation, common traps & causes

Who is at risk

Cause	HCC risk	Clinical note
Hepatitis B	With cirrhosis about 3 per 100 a year; without cirrhosis about 0.1, higher with high HBV DNA, HBeAg positivity, older age, family history, hepatitis D	HCC can arise in a non-cirrhotic liver; risk rises with viral load (REVEAL 2006^[5]); antivirals lower but do not abolish it (Liaw 2004^[6])
Hepatitis C	Almost only with advanced fibrosis or cirrhosis: 1–4% a year	Cure (SVR) cuts risk by about two-thirds but not to zero: keep surveillance if F3–F4 before cure (Lockart 2022^[7])
Alcohol	Alcohol-related cirrhosis about 3 per 100 a year; heavy drinking raises risk by about 87%	Synergy with viral hepatitis, diabetes and smoking
MASLD (fatty liver)	MASH cirrhosis 1–2% a year; low without cirrhosis	Diabetes and obesity add risk; a growing share in India; poor ultrasound views make surveillance harder
Aflatoxin	Contaminated stored grains and groundnuts	Multiplies risk in hepatitis B carriers
Other	Haemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease, glycogen storage disease, acute hepatic porphyria; tobacco (heavy smoking ~55% higher)	Ask about family liver disease and drugs (anabolic steroids: hepatic adenoma that can transform)
Associated with lower risk (observational)	Coffee (relative risk about 0.66), statins, aspirin	Not a reason to start a drug for prevention; treat the liver disease



How HCC presents

Presentation	Typical story	What to do
Surveillance finding	Asymptomatic nodule or rising AFP in a known cirrhotic or hepatitis B carrier	Multiphase CT/MRI, LI-RADS, MDT: the best chance of cure

Presentation	Typical story	What to do
Decompensation of known cirrhosis	New ascites, variceal bleed, jaundice or encephalopathy in a previously stable patient	Look for HCC and portal vein tumour thrombus on contrast imaging
Advanced tumour	Right upper abdominal pain, weight loss, early satiety, palpable mass, fever	Stage fully; check liver function before discussing options
Rupture	Sudden severe abdominal pain, distension, falling haemoglobin, shock	Resuscitate; CT (plain + contrast); urgent angio-embolisation; staged resection later if feasible
Obstructive jaundice	Tumour in a bile duct or hilar compression	Separate from cholangiocarcinoma (biopsy); drainage if needed
Paraneoplastic	Hypoglycaemia, erythrocytosis, hypercalcaemia, watery diarrhoea, skin changes	Usually advanced disease; hypoglycaemia can be severe with IGF-II secretion

- **Normal liver function tests do not exclude HCC**, and AFP is normal in most small tumours. A clinician should not wait for jaundice or a high AFP before imaging an at-risk liver.
- **"Liver abscess" or "TB" labels:** a febrile patient with a solid liver lesion and hepatitis B or cirrhosis needs contrast imaging read as HCC until proven otherwise.
- **A routine portal-venous CT can miss small HCC:** request a multiphase liver protocol (arterial, portal venous, delayed).
- **HCC without cirrhosis:** think of hepatitis B, MASLD, and, in adolescents and young adults with a large mass and a normal liver, fibrolamellar carcinoma.
- **Not every liver lump is cancer:** haemangioma, focal nodular hyperplasia and regenerative nodules are common; cholangiocarcinoma and metastases from bowel, stomach, pancreas, breast and lung are more common than HCC in a non-cirrhotic liver.

SHARE WITH PATIENTS: PRESENTATION AND CAUSES

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Only people who drink alcohol get liver cancer?](#)

[Fatty liver is harmless and cannot cause cancer?](#)

[Liver cancer always causes pain or jaundice?](#)

[Normal liver function tests mean there is no liver cancer?](#)

[Every lump in the liver is cancer?](#)

[Liver cancer cannot be prevented?](#)

[Liver cancer can spread to family members who live or eat together?](#)

03 Screening, workup & staging essentials

At-risk adult (cirrhosis Child–Pugh A–B, or C if listed for transplant; selected hepatitis B; HCV with advanced fibrosis)
Ultrasound by an experienced operator + serum AFP every 6 months

Normal

- Continue 6-monthly
- Liver poorly seen (obesity, fatty or coarse liver)? Use multiphase CT or abbreviated contrast MRI

Nodule < 1 cm, AFP normal

- Probably benign
- Repeat ultrasound every 3–6 months for two scans
- Stable or gone: back to 6-monthly

Nodule ≥1 cm or AFP ≥20

- AFP ≥20 ng/mL or rising, even with no nodule
- Multiphase contrast CT or MRI (liver protocol)
- Report with LI-RADS
- Discuss in the liver tumour board

Six-monthly beats yearly (more early cancers found); three-monthly adds nothing. A randomised trial in hepatitis B carriers showed about one-third fewer HCC deaths with 6-monthly ultrasound + AFP (Zhang 2004).

Figure 3. Surveillance in three outcomes. The commonest failure is not the test but the gap: patients with cirrhosis who are never enrolled or who stop attending. Surveillance is pointless when liver failure would prevent any HCC treatment (Child–Pugh C not listed for transplant).

Who should have surveillance (ultrasound + AFP every 6 months)

Group	Notes
Cirrhosis of any cause, Child–Pugh A or B	Child–Pugh C only if on a transplant list (otherwise HCC treatment would not be possible)
Hepatitis B without cirrhosis, with any of	family history of HCC; African origin; men over 40 or women over 50 from an endemic country; PAGE–B score ≥10; hepatitis D co-infection; HIV co-infection
Hepatitis C with advanced fibrosis (F3) or cirrhosis	Continue after cure: the risk falls but persists
Acute hepatic porphyria	Rare; high HCC risk

- **Evidence:** in a randomised trial of about 19,000 Chinese hepatitis B carriers, 6-monthly ultrasound + AFP reduced HCC mortality by 37% ([Zhang 2004](#)^[8]). Six-monthly finds more early tumours than yearly ([Santi 2010](#)^[9]); three-monthly adds nothing ([Trinchet 2011](#)^[10]).
- **When ultrasound views are poor** (obesity, fatty or very coarse liver), use multiphase CT or abbreviated contrast MRI.

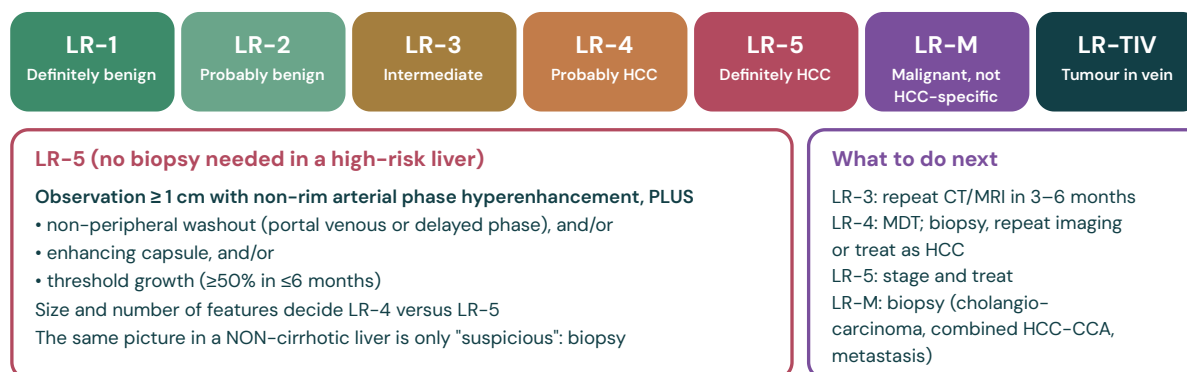
LI-RADS CT/MRI categories (high-risk patients only: cirrhosis, chronic hepatitis B, or current/prior HCC)

Figure 4. 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.

Diagnosis

- **Imaging diagnosis:** in a high-risk liver (cirrhosis, chronic hepatitis B, current or prior HCC), an observation ≥ 1 cm with non-rim arterial phase hyperenhancement plus washout, capsule or threshold growth is LR-5 and is treated as HCC without biopsy. The same features in a non-cirrhotic liver are only suspicious.
- **AFP:** above 400 ng/mL in a high-risk patient is nearly diagnostic, but fewer than 20% of HCCs reach that level; AFP is not a stand-alone diagnostic test. It is useful for prognosis, response, transplant selection (above 1000 ng/mL excludes routine priority listing) and ramucirumab eligibility.
- **Biopsy:** for a non-cirrhotic liver, LR-M or atypical lesions, persistent LR-4, and before systemic therapy if imaging is not classic. Needle-track seeding is rare (about 0.6% in a systematic review); bleeding and other complications occur in about 2% of cirrhotic patients. A negative biopsy does not exclude HCC.
- **Staging workup:** liver tests, INR, albumin, creatinine, full blood count, AFP, HBV and HCV serology; multiphase CT or MRI of the abdomen and pelvis; CT chest. PET-CT is not routine. Bone scan or brain imaging only for symptoms.
- **Multidisciplinary review** (hepatology, hepatobiliary surgery, interventional radiology, radiation and medical oncology, transplant team) before the first treatment improves survival and avoids "one-specialty" decisions.

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.

Figure 5. 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.

Child–Pugh score (5–15 points)

	1 point	2 points	3 points
Bilirubin	<2 mg/dL	2–3	>3
Albumin	>3.5 g/dL	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	none	slight	moderate+
Encephalopathy	none	grade 1–2	grade 3–4

Class A (5–6 points) 1-yr ≈100%, 2-yr ≈85%

Class B (7–9 points) 1-yr ≈80%, 2-yr ≈60%

Class C (10–15 points) 1-yr ≈45%, 2-yr ≈35%

ALBI grade (albumin + bilirubin only)

Objective; no subjective ascites or encephalopathy scoring

Grade 1: score ≤ -2.60 (best)

Grade 2: -2.60 to -1.39

Grade 3: > -1.39 (worst)

Splits Child–Pugh A into two groups with different survival; increasingly used to select TACE, TARE, SBRT and systemic therapy (Johnson 2015)

Figure 6. Liver function is the second staging axis. Most curative and systemic treatments were tested in Child–Pugh A; class B7 is borderline, B8–9 rarely benefits, and class C (unless a transplant candidate) is a supportive-care situation. Survival figures are for cirrhosis overall.

- **AJCC 8th edition TNM:** T1a solitary ≤2 cm; T1b solitary >2 cm without vascular invasion; T2 solitary >2 cm with vascular invasion or multiple ≤5 cm; T3 multiple, any >5 cm; T4 major portal or hepatic vein branch, or direct invasion of adjacent organs. TNM is validated after resection and transplant but ignores liver function.
- **ALBI** (albumin and bilirubin only) is objective and separates Child–Pugh A patients with different survival ([Johnson 2015^{\[11\]}](#)).
- **Portal hypertension** (platelets below about 100,000, varices, splenomegaly, elastography, hepatic venous pressure gradient ≥10 mmHg) matters as much as Child–Pugh before resection.

SHARE WITH PATIENTS: SURVEILLANCE AND TESTS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

If you have hepatitis B but feel completely well, you do not need regular check-ups?

Once hepatitis C is cured, there is no more risk of liver cancer?

A normal AFP blood test rules out liver cancer?

A liver biopsy makes cancer spread through the body?

04 Biomarkers that change treatment

- **No routine targeted therapy:** HCC is genetically diverse (TERT promoter mutations in about 40–65%, CTNNB1 and TP53, which are mutually exclusive, AXIN1, ARID1A/2), but none of these selects a drug today. Do not delay treatment waiting for a gene panel.
- **NTRK fusions** are very rare; when found, a TRK inhibitor (larotrectinib, entrectinib, repotrectinib) is preferred first line. Consider RNA-based testing in young patients, non-cirrhotic livers or unusual histology.
- **PD-L1, TMB and MSI do not select immunotherapy in HCC;** responses occur regardless of PD-L1.
- **AFP** is the only blood marker with treatment consequences: ≥ 400 ng/mL qualifies for ramucirumab after sorafenib ([REACH-2](#) ^[12]); persistently >1000 ng/mL argues against transplant; a falling AFP supports response and can precede imaging changes.
- **Viral status is a "biomarker":** HBV DNA and HCV RNA decide antiviral therapy, which improves survival after curative treatment and prevents reactivation during immunotherapy, TACE or chemotherapy.
- **Liver function (Child–Pugh, ALBI) predicts benefit** from almost every treatment and is re-checked at every decision point.

Pathology or marker	What it tells you	Consequence
Arginase-1, HepPar1, glypican-3 (IHC)	Hepatocellular origin; arginase-1 is the most sensitive, glypican-3 helps in poorly differentiated tumours	Separates HCC from metastatic adenocarcinoma and cholangiocarcinoma
Combined HCC–cholangiocarcinoma	Both lineages in one tumour; behaves more aggressively; classified with biliary tumours	Higher recurrence after transplant; systemic options borrowed from both diseases
Fibrolamellar carcinoma (<i>DNAJB1::PRKACA</i> fusion)	Adolescents and young adults, normal liver, normal AFP, central scar	Resection with lymph node dissection; HCC drugs work poorly
Steatohepatic, scirrhous, macrotrabecular–massive subtypes	WHO 2019 subtypes; macrotrabecular–massive carries a worse prognosis	Prognostic, not yet treatment–selecting
Grade, microvascular invasion, satellite nodules (resection specimen)	Main predictors of early recurrence	Closer follow-up; trial referral; no proven adjuvant drug
NTRK fusion	Rare driver	TRK inhibitor

05 Local therapy: surgery, liver-directed treatments & transplant

In this section

A. Surgery: [who to operate on](#) · [workup](#) · [future liver remnant](#) · [the operation](#) · [enhanced recovery](#) · [complications](#) · [outcomes](#) · [resection or ablation?](#)

B. Liver-directed therapies: [thermal ablation](#) · [TACE](#) · [TARE](#) · [SBRT](#) · [at a glance](#) · [portal vein thrombus](#) · [transplantation](#)

A. Surgery: from patient selection to complication management

A1. Who should have a resection?

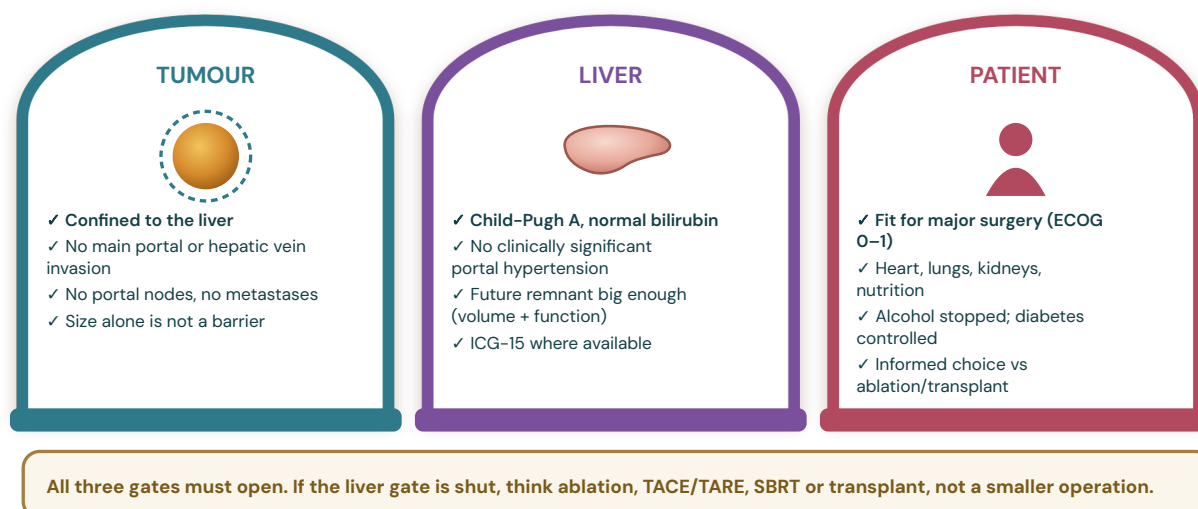


Figure 7. Three gates before resection. Tumour extent, liver reserve and general fitness are assessed separately; failure at any one gate redirects the patient to another curative or palliative option rather than to a riskier operation (UpToDate; AASLD 2023; EASL 2025).

- **Tumour gate:** disease confined to the liver. Regional (portal) node involvement is generally taken to rule out curative resection, except in fibrolamellar carcinoma, where nodes are removed as part of the operation; nodal spread occurs in only 1–8%, and benign enlarged portal nodes are common in cirrhosis, so suspicious nodes need tissue confirmation before they change the plan. Invasion of a major portal or hepatic vein, other organs or the peritoneum (AJCC IIIB) and distant spread are usually considered incurable by resection in Western practice.
- **Size and number:** size alone is not a contraindication (large solitary tumours without vascular invasion do about as well as small ones), but microvascular invasion becomes more likely as tumours grow. Up to three nodules can be resected with a median 5-year survival around 49%; beyond three, about 23%.
- **Liver gate:** Child-Pugh A with a normal bilirubin; no clinically significant portal hypertension (platelets below about 100,000, varices, splenomegaly, HVPg ≥ 10 mmHg); and an adequate future remnant by volume and, ideally, function. MELD is not useful for this decision because it ignores portal hypertension; ALBI separates risk within Child-Pugh A.

- **Patient gate:** performance status, cardiopulmonary reserve, kidney function, nutrition and muscle mass (sarcopenia predicts complications), diabetes control, and alcohol: heavy drinkers should stop at least 4–8 weeks before surgery ([ERAS Society 2022^{\[13\]}](#)).
- **Shared decision:** for a small tumour, discuss ablation and, in a decompensated or borderline liver, transplantation, alongside resection (see "Resection or ablation?" below).

A2. Preoperative workup checklist

Test	Why it matters	Practical note
Multiphase CT or gadoteric acid MRI of the liver	Number of nodules, vascular relations, satellite lesions	Arterial-phase imaging finds 30–40% more nodules than a routine CT; MRI is best for small nodules
CT chest; bone scan only if symptoms	Excludes spread	PET-CT is not routine for HCC
CT volumetry ± 3D reconstruction	Future liver remnant (FLR) as % of total or standardised liver volume	Repeat after portal vein embolisation to measure growth
Function: ICG-15 or hepatobiliary scintigraphy	Function can lag behind volume in cirrhosis	In cirrhosis, PVE was used when FLR <40% with ICG-15 <10%, or FLR <50% with ICG-15 10–20% (Glantzounis 2017^[14])
Portal hypertension: platelets, spleen size, elastography, endoscopy, HVPG where available	The strongest predictor of post-hepatectomy liver failure after cirrhosis itself	Band large varices before surgery
HBV DNA, HCV RNA	Active hepatitis raises operative and long-term risk	Start entecavir or tenofovir before surgery; hepatitis C cure can follow
Cardiopulmonary, renal and nutritional assessment	Fitness for major surgery and anaesthesia	Prehabilitation and nutritional support for frail patients
Biopsy	Only if imaging is not diagnostic or the liver is non-cirrhotic	Not needed for an LR-5 lesion in a cirrhotic liver

A3. The future liver remnant and how to grow it

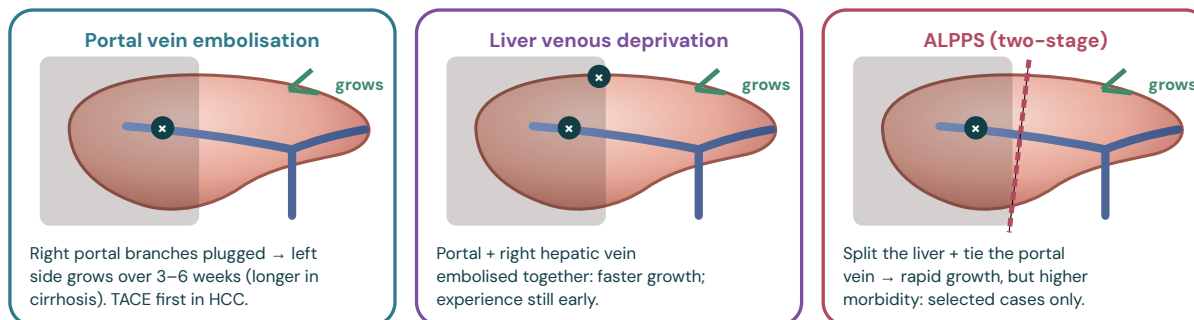
How much liver must remain? (standardised future liver remnant, % of total)

Figure 8. Grow the remnant before you cut. Volumetry (CT) plus a function test sets the safe limit; when the remnant is too small, portal vein embolisation is the standard way to enlarge it. A growth rate below about 2% a week warns that the liver may not cope (thresholds from published series; UpToDate PVE meta-analysis used <40% with ICG-15 <10%, or <50% with ICG-15 10–20%, in cirrhotic HCC).

- **Thresholds** (standardised FLR, % of total liver volume): at least about 20% for a normal liver, 30% after prolonged chemotherapy or with steatosis, and 40% (some centres 50%) in cirrhosis. In cirrhosis the operation is generally limited to under a quarter of the functional parenchyma; a non-cirrhotic liver can lose up to about two-thirds in a young patient.
- **Portal vein embolisation (PVE)**: percutaneous transhepatic occlusion of the portal branches to the tumour side diverts portal flow to the remnant, which grows over about 3–6 weeks (longer in cirrhosis). In HCC, **TACE before PVE** stops the tumour growing meanwhile and blocks arteriportal shunts; the sequence improves hypertrophy and was linked to better survival ([Glantzounis 2017](#)^[14]).
- **Why it matters**: in one series, major resection for HCC in cirrhosis without PVE carried mortality up to 18%, versus under 3% with PVE ([Palavecino 2009](#)^[15]).
- **Read the response, not just the volume**: a kinetic growth rate below about 2% per week warns that the liver may not cope even if the final volume looks adequate. Roughly one in five patients never reach resection after PVE because of poor growth or tumour progression.
- **Faster options**: liver venous deprivation (PVE plus hepatic vein embolisation) accelerates growth but experience is early; ALPPS (liver partition plus portal vein ligation, two operations) grows the remnant within days but carries higher morbidity and is rarely used in cirrhotic HCC. Radiation lobectomy with TARE is an alternative in HCC (see Part B).

A4. The operation

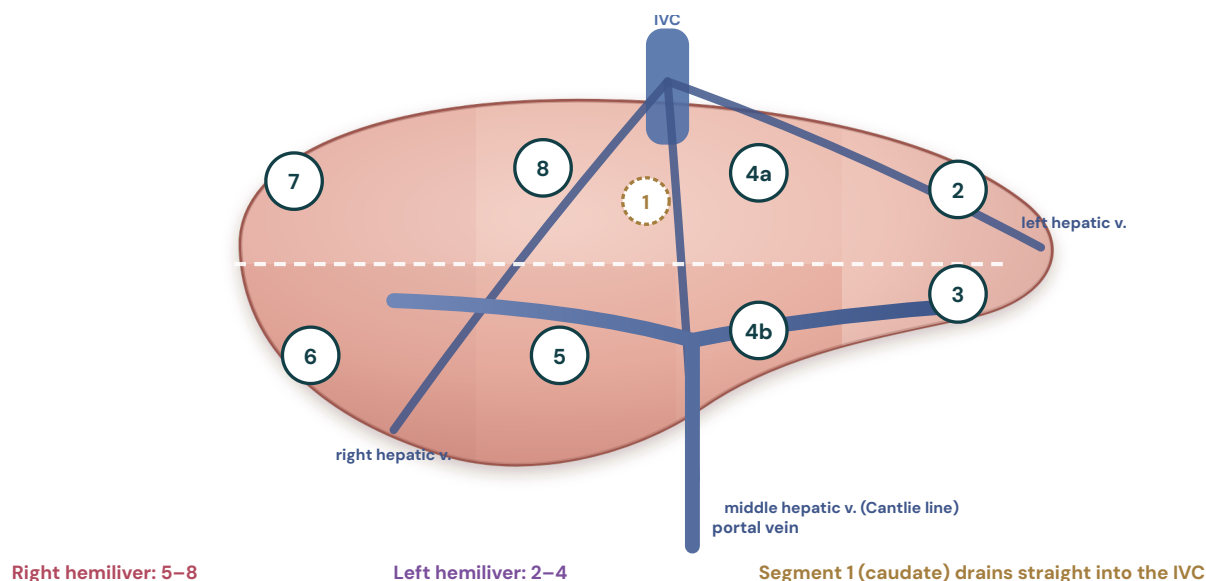


Figure 9. The surgeon's map. Hepatic veins divide the liver vertically and the portal bifurcation horizontally, giving eight functional segments, each with its own inflow and drainage. Anatomical resection removes whole segments; in cirrhosis, parenchyma-sparing resections keep more of the precious liver.

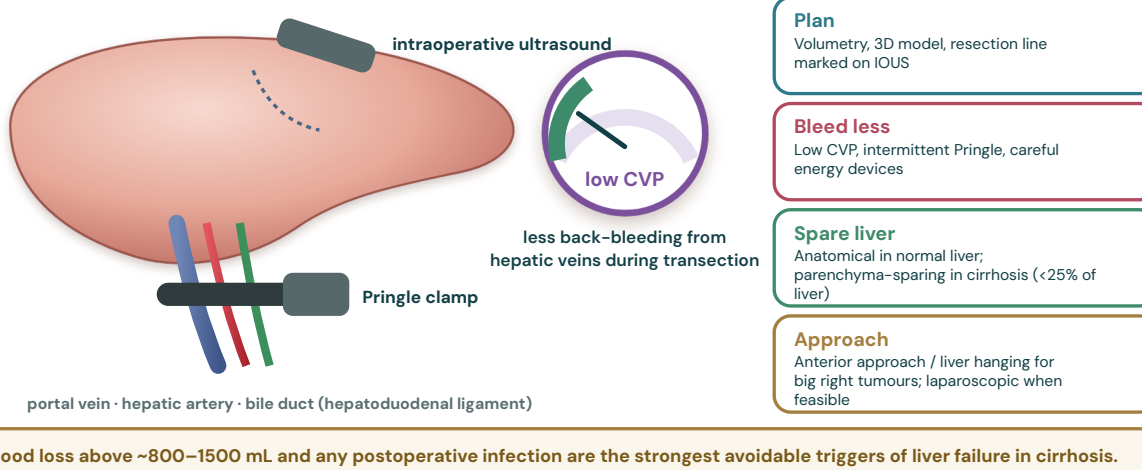


Figure 10. Bleed less, spare more. The Pringle manoeuvre clamps inflow; a low central venous pressure (goal-directed fluids, anaesthetist-led) reduces outflow bleeding; intraoperative ultrasound finds satellite nodules and guides the plane. Minimally invasive resection lowers morbidity in experienced hands (El-Gendi 2018 RCT; ERAS Society 2022).

- **Anatomical or not:** most surgeons prefer anatomical resection (whole Couinaud segments, ligating the segment's portal inflow and venous outflow) in a non-cirrhotic liver; in cirrhosis, parenchyma-sparing (non-anatomical or limited) resection may be needed to protect liver function, and an oncological advantage of anatomical resection has not been proven there.
- **Approach:** the anterior approach, often with the liver-hanging manoeuvre, controls inflow, divides the parenchyma and controls outflow before mobilising a large right-sided tumour, reducing tumour handling and the risk of tearing the vena cava. Central hepatectomy spares parenchyma for central tumours but is technically demanding.
- **Minimally invasive resection:** in experienced centres laparoscopic or robotic resection is safe, with equal or better outcomes. A randomised trial in Child-Pugh A cirrhosis (solitary peripheral HCC <5 cm) showed shorter hospital stay with comparable cancer outcomes (El-Gendi 2018^[16]). Fewer adhesions also simplify later transplantation.

- **Intraoperative ultrasound** maps vessels, finds satellite nodules and guides subsegmental resection (counter-staining of the segmental portal branch defines the territory).
- **Bleeding control:** intermittent inflow occlusion (Pringle manoeuvre), low central venous pressure during parenchymal transection with goal-directed fluids, and energy and stapling devices. Blood loss above about 800 mL is linked to early death, and loss above 1500 mL plus postoperative infection are the main triggers of liver failure in cirrhosis; avoid transfusion where possible.

A5. Enhanced recovery (ERAS Society 2022)

- Before: counselling and expectation-setting, prehabilitation and nutrition for frail or sarcopenic patients, alcohol and smoking cessation, short fasting with carbohydrate drinks where allowed.
- During: minimally invasive surgery when feasible, goal-directed fluid therapy with a low central venous pressure during transection, normothermia, prevention of nausea, opioid-sparing analgesia.
- After: early oral feeding and mobilisation, oral laxatives (quicker bowel recovery), thromboprophylaxis, early removal of lines and catheters, and audit of outcomes ([ERAS Society 2022](#)^[13]).
- **In cirrhosis:** avoid NSAIDs and sedatives, watch sodium and fluid balance closely (ascites), and treat infection early because sepsis precipitates liver failure.

A6. Complications and how to manage them

When complications appear after hepatectomy (typical windows)

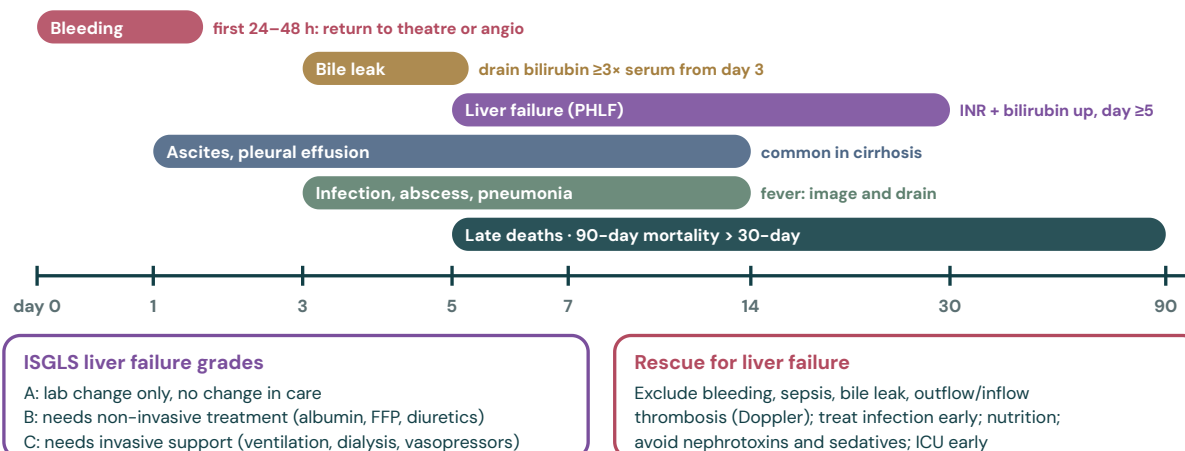


Figure 11. Know the clock. About half of patients have some complication after resection for HCC, but only 7–11% a major one; liver failure is the main cause of death and typically shows from day 5 onward (ISGLS 2011; 50–50 criteria; UpToDate).

Complication	How it is recognised	What to do
Post-hepatectomy liver failure (PHLF)	ISGLS: rising INR and bilirubin on or after day 5, compared with preoperative values; graded A (no change in care), B (non-invasive treatment), C (invasive support) (Rahbari 2011 ^[17]). The "50–50" criteria (prothrombin activity <50% and bilirubin >50 $\mu\text{mol/L}$ on day 5) flag high mortality (Balzan 2005 ^[18])	Look for a reversible cause first: bleeding, sepsis, bile leak or collection, hepatic artery or portal vein thrombosis and outflow obstruction (Doppler, CT). Support: fluids and albumin, vitamin K, plasma only for bleeding or procedures, lactulose for encephalopathy, enteral nutrition, glucose monitoring, early antibiotics if infection is possible; avoid nephrotoxins and sedatives; early ICU. Salvage transplantation only in highly selected patients

Complication	How it is recognised	What to do
Haemorrhage	First 24–48 hours: falling haemoglobin, blood in drain, shock	Correct coagulopathy; CT angiography; angioembolisation or return to theatre
Bile leak	ISGLS: drain bilirubin at least 3 times serum on or after day 3, or a bile collection needing treatment; grade A (no change), B (drainage or ERCP), C (relaparotomy) (Koch 2011^[19])	Keep or place a drain; most close; ERCP with stent for persistent leaks; drain infected bilomas
Ascites and wound leak	Common after resection in cirrhosis	Salt restriction, diuretics, albumin after large-volume drainage; meticulous wound closure
Right pleural effusion	Breathlessness, low oxygen	Usually reactive; tap if symptomatic or infected
Infection, abscess, pneumonia	Fever, raised inflammatory markers, collection on imaging	Image early; percutaneous drainage and targeted antibiotics; infection also worsens survival
Portal vein or hepatic artery thrombosis	Sudden rise in enzymes, PHLF, abnormal Doppler	Urgent imaging; anticoagulation or re-intervention
Kidney injury, venous thromboembolism	Rising creatinine; leg swelling or breathlessness	Avoid nephrotoxins and contrast where possible; thromboprophylaxis by protocol

A7. Outcomes of resection

- **Mortality:** 30-day 0–2% in modern series; 90-day mortality is the better measure (late liver failure kills outside hospital): 1.9–4.5% for non-cirrhotic or Child-Pugh A patients and 1.7–22% for Child-Pugh B. Most deaths are from liver failure; fewer than 10% from bleeding.
- **Morbidity:** about half of patients have a complication, but only 7–11% a major one (ascites, liver insufficiency, biliary fistula, abscess, haemoperitoneum, pleural effusion).
- **Survival:** up to about 78% at 5 years in ideal candidates (solitary ≤ 5 cm, no vascular invasion, clear margin); lower with microvascular invasion, high AFP, rupture or poor differentiation. Recurrence in the liver is common, so surveillance and antivirals continue for life.

Resection or ablation for small HCC?

- Randomised trials from China, Japan and Hong Kong are mixed ([Chen 2006^{\[20\]}](#)). A Cochrane analysis found no clear all-cause survival difference but lower cancer mortality with surgery, at the cost of far more serious adverse events (about 23% vs 2%). A later meta-analysis found similar 5-year overall survival but better recurrence-free survival and local control with resection ([Shin 2021^{\[21\]}](#)).
- Japan's SURF trial (tumours ≤ 3 cm, up to three) showed no significant difference between surgery and radiofrequency ablation in recurrence-free survival ([SURF 2022^{\[22\]}](#)) or overall survival ([SURF 2025^{\[23\]}](#)).
- **Practical rule:** resection when it is straightforward (especially laparoscopic) and the liver is good; ablation for ≤ 2 –3 cm tumours that are deep, in patients with portal hypertension or comorbidity, or when the patient prefers a less invasive option.

B. Liver-directed therapies: selection, technique, risks and results

B1. Thermal ablation

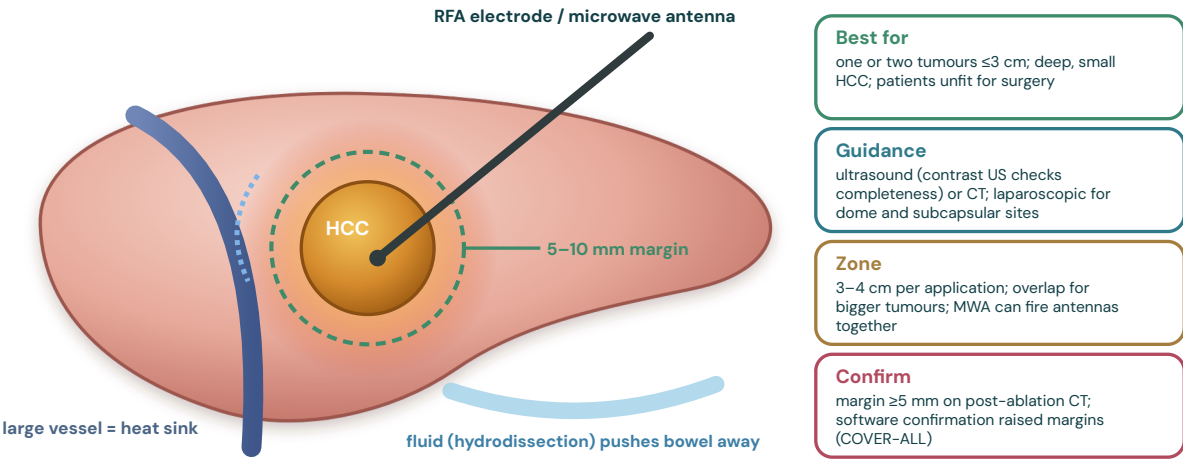


Figure 12. Thermal ablation. A needle electrode (RFA) or antenna (MWA) cooks the tumour plus a 5–10 mm rim of liver. Blood flow in a large vessel carries heat away and leaves viable cells; fluid can be injected to protect bowel or diaphragm. Major complications 2–11%, procedural death 0.1–0.8% (UpToDate).

Step	Key points
Who	One or two tumours ≤ 3 cm (best results), not resectable or preferring a less invasive option; 3–5 cm only combined with TACE; Child-Pugh A–B; bridging to transplant. Typical procedural limits: platelets $\geq 50,000$ and INR ≤ 1.5 . Caution: tumours at the hilum next to central bile ducts, bilioenteric anastomosis or biliary stent (abscess risk), uncorrectable coagulopathy.
How it is done	Usually percutaneous under ultrasound or CT guidance, with sedation or general anaesthesia; laparoscopic or open for dome, subcapsular or bowel-adjacent tumours. RFA passes alternating current through tissue around an electrode; MWA agitates water molecules around an antenna. One application makes a 3–4 cm zone; larger tumours need overlapping ablations (in a large series, about 1.5 insertions for nodules < 2 cm versus 4.2 for 3–5 cm; Tateishi 2005 ^[24]). Contrast ultrasound at the end checks for residual flow; CT or MRI at 4–8 weeks confirms complete ablation.
Technical nuances	Aim for a 5–10 mm rim of ablated liver around the tumour (minimal margin ≥ 5 mm). Software-based margin confirmation with deformable image registration raised the mean margin from 2.2 to 5.9 mm in a randomised trial and lowered 2-year local progression (about 5% vs 16%) (COVER-ALL ^[25]). Large vessels act as heat sinks; MWA is less affected and can drive several antennas together. Hydrodissection or artificial ascites protects bowel and diaphragm; track ablation on withdrawal limits seeding. One dose of prophylactic antibiotic; 24 hours IV plus a week orally after a bilioenteric anastomosis or with a biliary stent. Ethanol injection remains useful near the gallbladder or hilum and where thermal devices are not available.
Risks	Major complications 2.2–11%, procedural death 0.1–0.8% (de Baère 2003 ^[26]): liver abscess, biloma or bile duct stricture, pleural effusion, skin burn, pneumothorax, subcapsular haematoma, haemoperitoneum, bowel perforation, portal vein thrombosis and needle-track seeding. A self-limiting post-ablation syndrome (fever, malaise, pain) occurs in about a third.
Outcomes	Local tumour progression 3–29% at 3 years (higher next to large vessels); MWA and RFA were equivalent in a randomised trial (5-year local progression 11% vs 20%, not significant; 5-year survival 67% vs 73%) (Yu 2017 ^[27]). Within Milan criteria, 3- and 5-year survival 67–91% and 40–77%.

B2. Transarterial chemoembolisation (TACE)

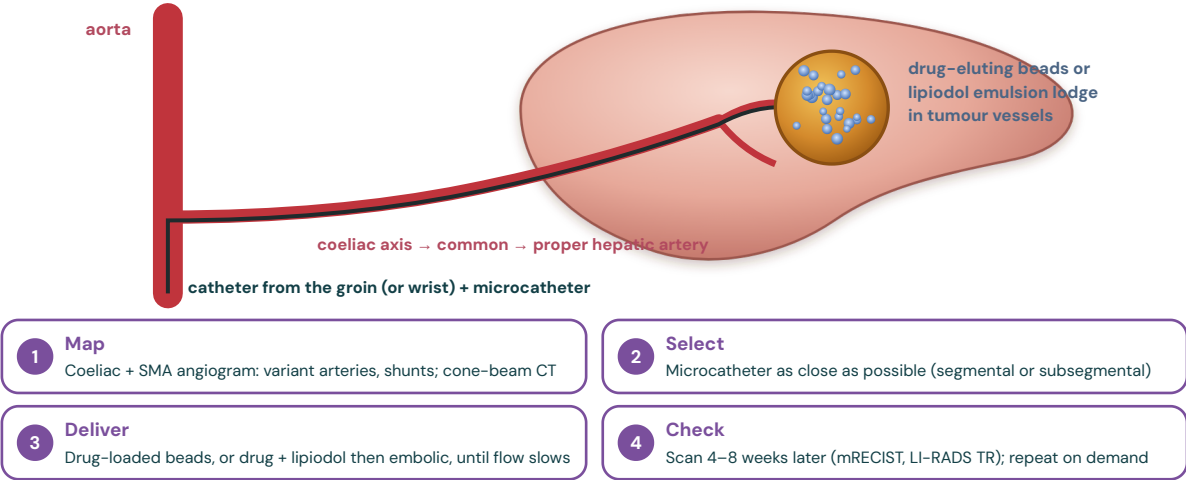
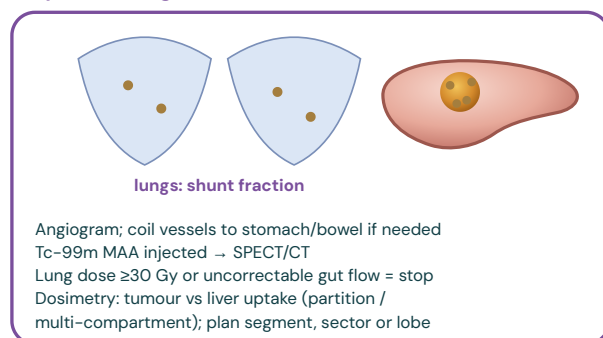
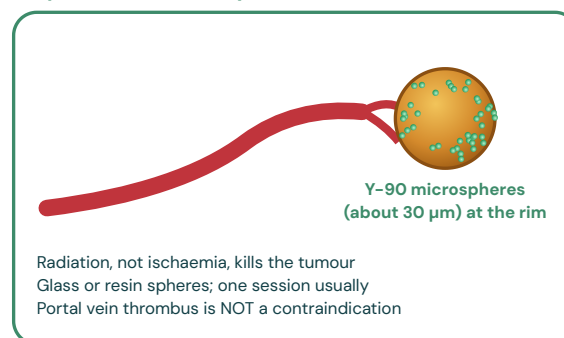


Figure 13. TACE exploits the tumour’s arterial blood supply: HCC is fed by the hepatic artery, normal liver mainly by the portal vein. Superselective delivery treats the tumour and spares liver; post-embolisation syndrome is expected in 60–80%, liver decompensation is the main serious risk (UpToDate).

Step	Key points
Who	Multinodular liver-confined HCC (BCLC B), Child-Pugh A or B7, ECOG 0, no main or lobar portal vein thrombus, no extrahepatic spread; bridging and downstaging; before portal vein embolisation; with ablation for 3–5 cm tumours. Do not treat: absent portal flow, Child-Pugh C or B >8, jaundice, refractory ascites, encephalopathy, biliary obstruction or bilioenteric anastomosis, uncorrectable bleeding tendency, kidney failure.
How it is done	Arterial access from the groin or wrist; coeliac and superior mesenteric angiography maps variants (replaced right hepatic artery, accessory left from the left gastric) and shunts; cone-beam CT helps find feeders. A microcatheter is advanced as close to the tumour as possible. Conventional TACE: doxorubicin, epirubicin or cisplatin emulsified with lipiodol, then an embolic agent. DEB-TACE: beads loaded with doxorubicin delivered until flow slows. Analgesia, antiemetics, hydration, antiviral prophylaxis in hepatitis B carriers.
Technical nuances	Superselective delivery spares liver and lowers decompensation. Protect gastric and duodenal branches to avoid ulcers. Beads stay in the arteries, whereas lipiodol can pass into portal venules ("dual embolic hit"), one reason DEB-TACE is better tolerated (PRECISION V ^[28]). Repeat on demand for viable or new tumour (judged by mRECIST or LI-RADS treatment response), not on a fixed schedule; stop when the tumour no longer responds or liver function falls, and move to systemic therapy.
Risks	Post-embolisation syndrome in 60–80% (pain, fever, nausea, ileus, enzyme rise; settles in 3–4 days, recovery 7–10 days). Acute hepatic decompensation after about 20% of sessions, irreversible in about 3% (Chan 2002 ^[29]); liver abscess about 2%; bile duct injury 0.5–2%; gastroduodenal ulcer 3–5%; kidney dysfunction about 2%; rare lipiodol embolism to lung or brain. Treatment-related death under 1% (2–3% with very large tumours, from tumour lysis).
Outcomes	Survival gain over supportive care in selected patients (Llovet 2002 ^[30] , Lo 2002 ^[31]). In a network meta-analysis, estimated median survival was about 18 months with TACE and 21 months with DEB-TACE, and best when TACE was combined with ablation or radiotherapy. Adding immunotherapy ± antiangiogenic drugs (EMERALD-1, LEAP-012, EMERALD-3) prolongs progression-free survival; overall survival data are maturing.

B3. Transarterial radioembolisation (TARE, yttrium-90)

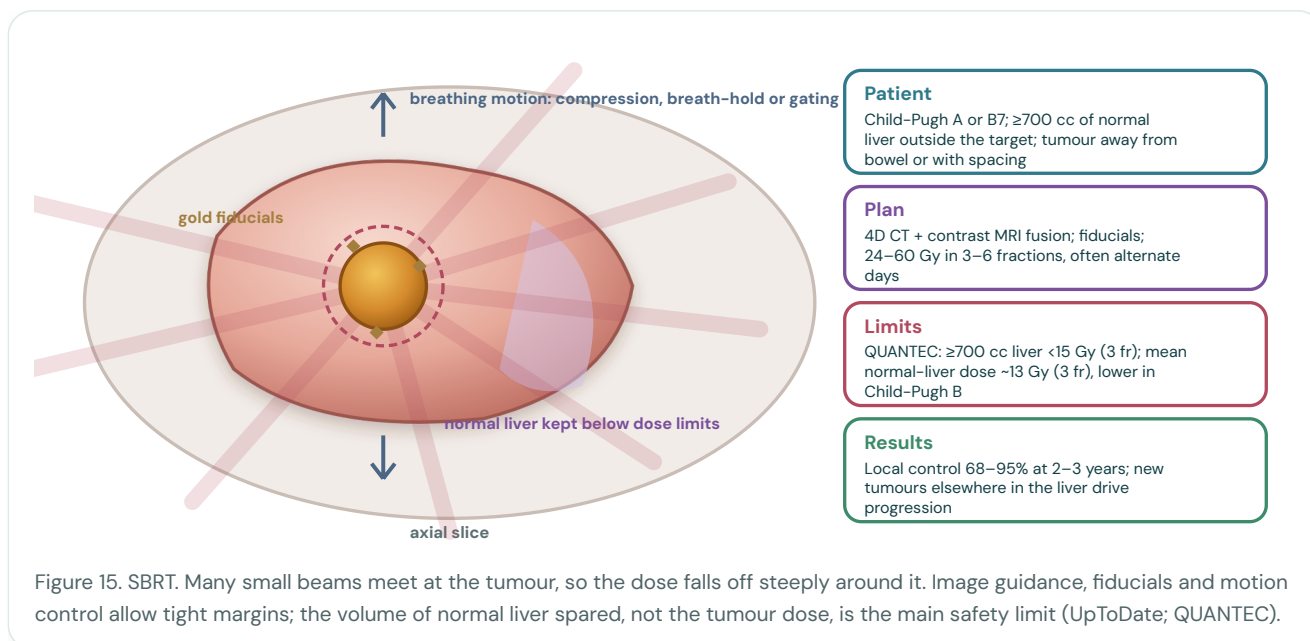
Step 1 · Planning (1–2 weeks before)**Step 2 · Treatment (day case)**

Dose matters: personalised dosimetry (≥ 205 Gy to the index tumour) vs standard (120 Gy to the lobe) doubled response (71% vs 36%) and lengthened survival in DOSISPHERE-01 (phase 2). Radiation segmentectomy: very high dose to 1–2 segments, little liver toxicity. Radiation lobectomy shrinks the treated lobe and grows the other, like portal vein embolisation.

Figure 14. Radioembolisation (TARE, SIRT) is planned like radiotherapy and delivered like TACE. The planning study protects the lungs and gut; personalised dosimetry decides how much activity to give. Toxicity is mainly fatigue and, uncommonly, radioembolisation-induced liver disease.

Step	Key points
Who	Solitary large HCC unsuitable for resection or ablation (LEGACY ^[32] : tumours ≤ 8 cm, Child-Pugh A, ECOG 0–1); selected BCLC B; branch or lobar portal vein thrombus (unlike TACE, portal thrombus is not a contraindication); bridging and downstaging; radiation lobectomy to grow the future remnant. Do not treat: predicted lung dose ≥ 30 Gy, uncorrectable flow to the gut, prior liver radiotherapy, encephalopathy, biliary obstruction, Child-Pugh C; caution with bilirubin > 2 mg/dL or ascites.
How it is done	Two steps. Planning: angiography, coil embolisation of vessels feeding the stomach or bowel if needed, and technetium-99m macroaggregated albumin (MAA) with SPECT/CT to measure lung shunting and tumour-to-liver uptake. Treatment, usually 1–2 weeks later as a day case: glass or resin microspheres (about 30 μm) delivered through a microcatheter to a segment, sector or lobe; post-treatment imaging confirms where the spheres went.
Technical nuances	Personalised (multi-compartment) dosimetry matters: aiming ≥ 205 Gy at the index tumour, versus a standard 120 Gy to the lobe, doubled response (71% vs 36%) and lengthened median survival (26.6 vs 10.7 months) in the phase 2 DOSISPHERE-01 ^[33] trial. Radiation segmentectomy gives very high doses to one or two segments with less liver toxicity (Riaz 2011 ^[34]). Glass and resin products are dosed differently. Responses are slower than after TACE, so the first assessment is at about 3 months.
Risks	Milder post-embolisation syndrome than TACE (20–70%: fatigue, pain). Radioembolisation-induced liver disease (jaundice and ascites 1–2 months later without progression), mainly in cirrhosis; in one series, ursodeoxycholic acid plus a short steroid course lowered it from 23% to 5% (Gil-Alzugaray 2013 ^[35]). Radiation pneumonitis under 1% with proper lung-shunt limits; gastric or duodenal injury under 5%; fibrosis, portal hypertension and lymphopenia.
Outcomes	LEGACY: response 72%, no local progression at 2 years, 3-year survival 87%. As a replacement for systemic therapy in advanced HCC, TARE did not improve survival over sorafenib (SIRveNIB ^[36]), although those trials did not use personalised dosimetry.

B4. Stereotactic body radiotherapy (SBRT) and proton therapy



When SBRT is indicated

- **Guideline position:** ASTRO 2022 strongly recommends external beam radiotherapy as a potential first-line treatment for liver-confined HCC when curative treatment is not possible, as consolidation after incomplete response to another liver-directed treatment, and as salvage for local recurrence; it conditionally recommends it for multifocal or unresectable disease and macrovascular invasion (sequenced with systemic or catheter therapy), as a bridge to transplant or surgery, and for palliation ([ASTRO 2022^{\[37\]}](#)).
- **Best candidates:** 1–3 tumours, ideally ≤5 cm (best local control under 3 cm), Child–Pugh A or B7, ECOG 0–2, at least about 700 cc of uninvolved liver, no extrahepatic disease, and a tumour that is hard to ablate (dome, subcapsular, next to large vessels or the hilum, after TACE failure).
- **Special roles:** branch or lobar portal vein tumour thrombus (often with TACE); bridging on the transplant waiting list; residual tumour after TACE; painful bulky tumour (single 8 Gy fraction).
- **Avoid or refer:** Child–Pugh B8 or worse (trial or bridge only), tumour abutting bowel that cannot be spaced, very large or diffuse tumours that leave too little spared liver, prior liver irradiation (expert centre only), uncontrolled ascites.

Platforms: photons and protons

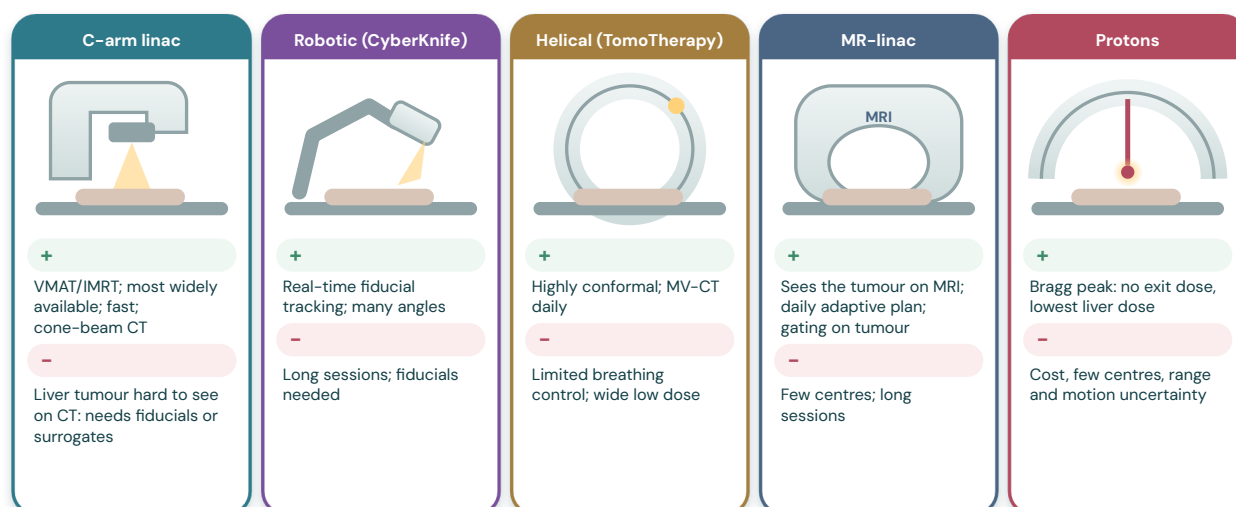


Figure 16. One technique, five machines. Any modern platform can deliver liver SBRT if it combines motion management, daily image guidance and liver-sparing planning; protons or IMRT are recommended for dose-escalated or hypofractionated treatment (ASTRO 2022). The best machine is the one the team uses well every day.

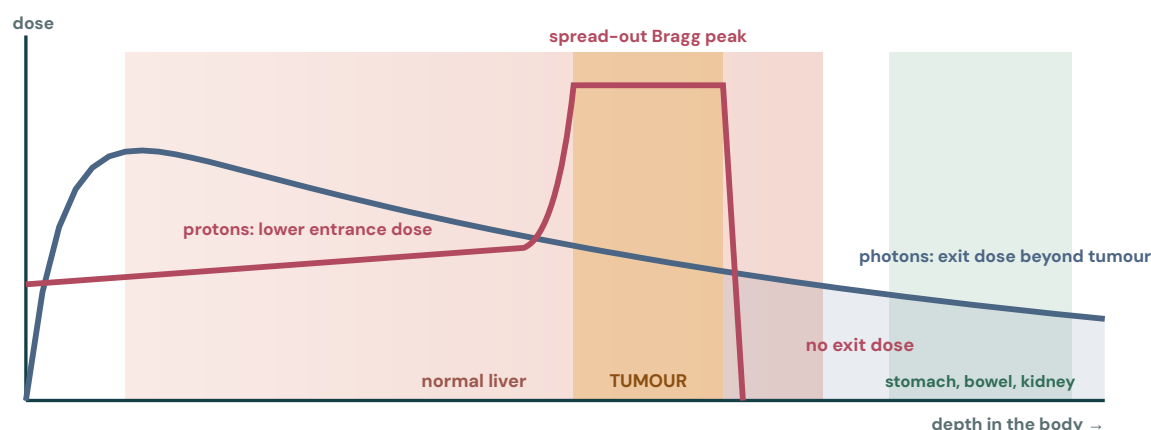


Figure 17. Photons versus protons. A photon beam deposits dose all the way through the body; a proton beam stops at a depth set by its energy, releasing most of its dose in the Bragg peak. Spreading the peak across the tumour spares liver and gut behind it. Proton doses are written in Gy(RBE) or GyE (1 Gy of protons ≈ 1.1 Gy of photons in effect).

Platform	What it offers	Limitations
C-arm linac with VMAT or IMRT and cone-beam CT	Available in most Indian radiotherapy centres; fast delivery; gating or breath-hold possible	HCC is barely visible on cone-beam CT: needs fiducials, lipiodol from prior TACE, or diaphragm surrogates
Robotic linac (CyberKnife)	Real-time tracking of implanted fiducials; many non-coplanar angles; no breath-hold needed	Fiducial placement (bleeding risk in coagulopathy); long sessions; wide low-dose spread
Helical (TomoTherapy)	Very conformal dose; daily MV-CT	Limited respiratory management on many units; larger low-dose volume
MR-linac	Sees the tumour and liver on MRI at every session; daily re-planning (adaptive); gating on the tumour itself	Few machines; long sessions; claustrophobia; implants

Platform	What it offers	Limitations
Proton therapy (pencil-beam scanning preferred)	No exit dose: lowest mean liver dose, helpful for large tumours, portal vein thrombus, Child–Pugh B7 and re-irradiation; randomised data versus RFA and TACE	Few centres in India and high cost; range uncertainty; interplay with breathing (needs gating, breath-hold or rescanning); doses in Gy(RBE)

- **Proton evidence:** in recurrent or residual HCC (1–2 tumours ≤ 3 cm), protons (66 GyE in 10 fractions) were non-inferior to RFA for 2-year local progression-free survival (about 95% vs 84%), with similar survival ([APROH, Kim 2021^{\[38\]}](#)). In a randomised trial versus TACE for tumours within transplant criteria, protons (70.2 Gy in 15 fractions) gave better local control and progression-free survival, similar 2-year survival (68% vs 65%) and far fewer hospital days (24 vs 166) ([Bush 2023^{\[39\]}](#)). A multi-institutional phase 2 study (up to 67.5 GyE in 15 fractions) reported 2-year local control of 95% ([Hong 2016^{\[40\]}](#)); a large Japanese series reported 87% 5-year local control ([Chiba 2005^{\[41\]}](#)).
- **Photons or protons?** No completed randomised trial compares them in HCC. Protons matter most when photon SBRT cannot meet liver limits (large tumour, thrombus, poor reserve, re-treatment); for small tumours in a good liver, well-delivered photon SBRT achieves similar local control.

Pros and cons

Advantages	Disadvantages
Non-invasive, outpatient, 3–6 short sessions; no anaesthesia	Needs good liver reserve (Child–Pugh A or B7) and enough spared liver
No needle: no track seeding, little bleeding risk (fiducials apart); works in "risky" sites (dome, near vessels, hilum)	Limited by nearby stomach, duodenum and bowel
Not affected by heat-sink; can treat tumour thrombus	Response is slow and hard to read (enhancement can persist for months)
Can follow failed TACE or ablation; compatible with transplant and systemic therapy	Can lower liver function (Child–Pugh rise); out-of-field progression is common
Repeatable for new lesions if dose limits allow	Few randomised survival comparisons with RFA or resection; expertise and (for protons) access and cost

Technical nuances

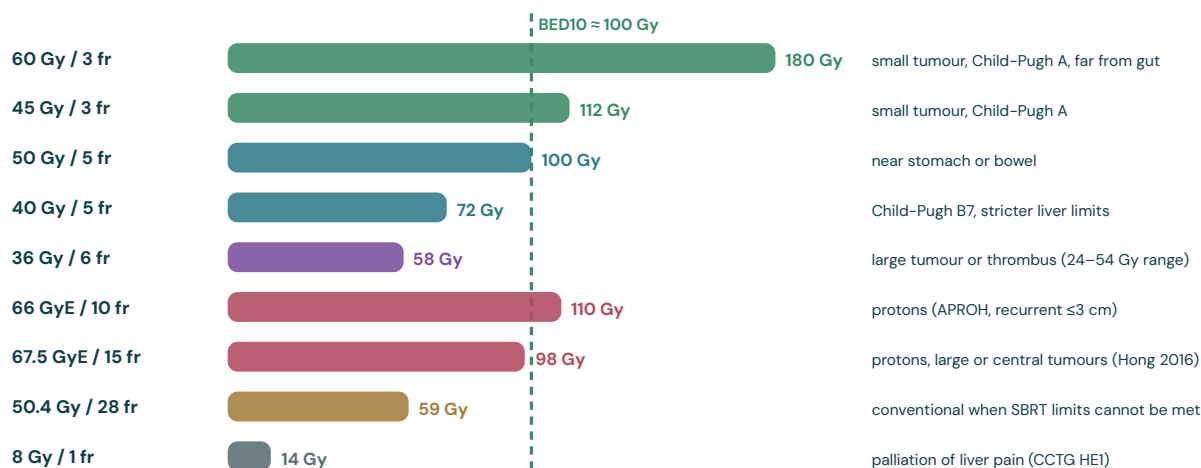
- **Simulation:** fasting before each session (consistent stomach filling); arms up; 4D-CT with intravenous contrast in arterial and portal-venous phases, because HCC is often seen only in the arterial phase; fuse a contrast MRI (hepatobiliary phase helps define the tumour).
- **Motion:** the liver moves 1–2 cm or more with breathing. Options: abdominal compression, breath-hold (deep inspiration or exhale), respiratory gating, real-time tracking, or an internal target volume covering the whole motion path.
- **Markers:** gold fiducials placed under ultrasound or CT about a week before; retained lipiodol after TACE is a natural marker; otherwise the diaphragm dome or liver edge as a surrogate.
- **Volumes:** GTV = enhancing tumour + any tumour thrombus; HCC has little microscopic spread, so the CTV margin is small (0–5 mm); PTV usually 3–5 mm with good image guidance.
- **Organs at risk:** uninvolved liver (liver minus GTV), stomach, duodenum, bowel, oesophagus, central bile ducts, kidneys, chest wall and ribs, heart, spinal cord. Where tumour touches the gut, the dose can be

lowered in the overlapping part ("simultaneous integrated protection") rather than abandoning SBRT.

- **Image guidance:** cone-beam CT, MV/kV imaging or MRI before every fraction, matched to fiducials or the tumour; alternate-day treatment lets acute effects settle.
- **Combinations:** TACE before SBRT (TACE + SBRT) for 3–5 cm tumours or thrombus; the lipiodol then helps targeting. Keep hepatitis B suppressed throughout.
- **Response:** first CT/MRI at about 3 months; use the LI-RADS radiation treatment-response algorithm. Arterial enhancement can persist for 6–12 months without viable tumour, and the surrounding liver may enhance too: do not re-treat on a single early scan; AFP trend helps.

Dosing paradigm

Common schedules and their biologically effective dose to the tumour ($BED_{10} = \text{total dose} \times (1 + \text{dose per fraction} / 10)$)



Isotoxic principle: the dose is set by the liver (spared volume, mean dose, Child-Pugh), then pushed as high as limits allow.

Figure 18. Dosing paradigm. Ablative three-fraction schedules for small tumours in good livers deliver a BED₁₀ above about 100 Gy; five or six fractions protect nearby gut or a poorer liver; protons use 10–15 fractions to similar biological doses. Values are calculated ($\alpha/\beta = 10$) for orientation, not prescriptions.

Situation	Typical schedules	Comments
Small tumour (≤3–5 cm), Child-Pugh A, away from gut	45–60 Gy in 3 fractions	Ablative; a phase 2 trial (45–60 Gy/3) reported 2- and 3-year local control of 97% and 95%
Tumour near stomach, duodenum or bowel	40–50 Gy in 5 fractions	Gut limits drive fractionation; simultaneous integrated protection
Child-Pugh B7	More conservative, for example 40 Gy in 5 fractions with stricter liver limits (mean normal-liver dose under about 6 Gy in some protocols)	Higher risk of Child-Pugh decline; select carefully
Large tumour or tumour thrombus	Individualised 24–54 Gy in 6 fractions (Princess Margaret approach; median 36 Gy/6 in large tumours, median 7.2 cm)	Dose chosen from the effective liver volume irradiated (isotoxic) (Bujold 2013^[42])
Protons	66 GyE/10 (small recurrent), 58–67.5 GyE/15 (larger or central), 70.2 GyE/15 (Loma Linda)	Hypofractionated; dose in Gy(RBE)
Limits cannot be met for SBRT	Moderately hypofractionated or conventional IMRT (for example 50.4 Gy in 28 fractions)	Lower BED; often with TACE or systemic therapy

Situation	Typical schedules	Comments
Pain palliation	8 Gy single fraction	Improved liver pain at 1 month (CCTG HE1^[43])

- **Liver limits** (QUANTEC; [Pan 2010^{\[44\]}](#)): at least 700 cc of normal liver below 15 Gy in 3 fractions; mean normal-liver dose about 13 Gy in 3 fractions or 18 Gy in 6 for primary liver cancer; lower for Child–Pugh B.
- **Rule of thumb**: ablative schedules give a BED10 above about 100 Gy (for example 45 Gy in 3 fractions = 112.5 Gy). When liver or gut limits prevent that, accept a lower dose rather than exceed the limits: liver failure costs more than a marginal recurrence.

Complications and their management

When side effects appear after liver SBRT

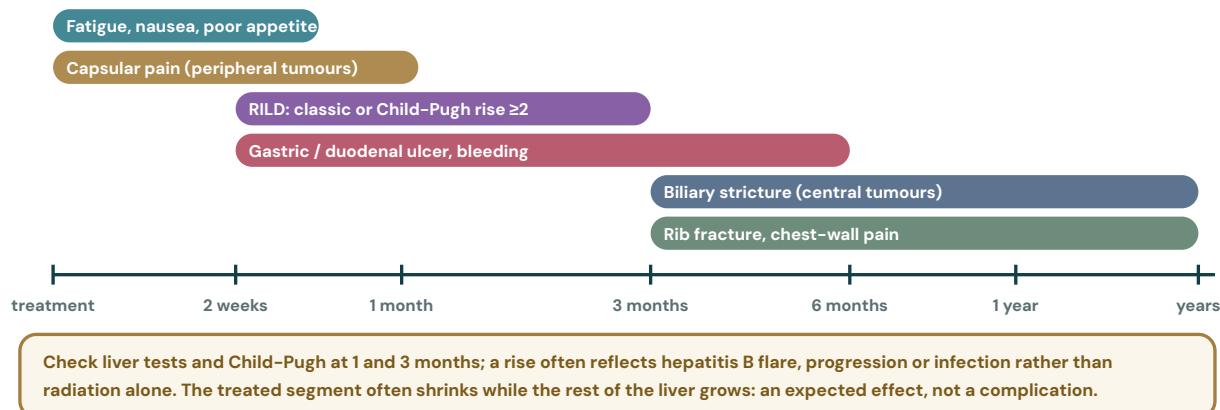


Figure 19. Side effects by time. Acute effects are mild and short; the window for radiation-induced liver disease is about 2 weeks to 3 months; gut, bile duct and rib problems appear later and depend on dose to those structures (UpToDate; QUANTEC).

Complication	When and how it shows	Prevention and management
Fatigue, nausea, poor appetite	During treatment and 1–2 weeks after	Prophylactic antiemetic when stomach is in the low-dose field; small frequent meals; settles in weeks
Capsular (right upper abdominal) pain	Peripheral tumours; days to weeks	Paracetamol in a liver-safe amount; avoid NSAIDs
Classic radiation-induced liver disease	2 weeks to 3 months: tender enlarged liver, ascites, raised alkaline phosphatase with near-normal bilirubin	Rare with modern limits. Supportive: salt restriction, diuretics, paracentesis; exclude tumour progression and vein thrombosis; usually resolves over weeks but can be fatal
Non-classic toxicity (Child–Pugh rise ≥ 2 or transaminases $>5\times$ normal)	Within 3 months, mainly in cirrhosis or hepatitis B	Check HBV DNA (reactivation), infection, progression; continue antivirals; supportive care; delay further liver-directed treatment until recovery
Gastric or duodenal ulcer, bleeding	Weeks to months; pain, melaena, anaemia	Respect gut limits; consider a proton-pump inhibitor when stomach or duodenum receive high dose; endoscopy for symptoms; avoid NSAIDs
Biliary stricture	Months to years after central (hilar) treatment: cholestatic tests, jaundice	Limit dose to central bile ducts; MRCP; endoscopic or percutaneous stenting
Chest-wall pain, rib fracture	Months to years, peripheral tumours	Limit rib dose; simple analgesia; usually heals

Complication	When and how it shows	Prevention and management
Radiation pneumonitis	Dome tumours, 1–6 months	Rare; steroids if symptomatic

Outcomes

- Local control 68–95% at 2–3 years. A phase 2 trial (45–60 Gy in 3 fractions; median tumour 2.4 cm) reported 2- and 3-year local control of 97% and 95%. In a pooled series of 297 patients, local recurrence was 6.3% at 1 year and 13.3% at 3 years, survival 77%, 39% and 24% at 1, 3 and 5 years, and no classic liver disease despite 22% Child–Pugh B or C ([Mathew 2020](#)^[45]). Observational comparisons favour SBRT over RFA for tumours ≥ 2 cm ([Wahl 2016](#)^[46]).
- Progression is mostly new tumours elsewhere in the liver, so SBRT is combined with surveillance and treatment of the underlying liver disease. SBRT added to sorafenib improved progression-free survival ([NRG/TOG 1112](#)^[47]).

B5. Local control and toxicity at a glance

Local control and toxicity at a glance (selected patients; not head-to-head comparisons)

Treatment	Local control	Main risks	Survival signal
Resection	Lowest local recurrence	90-day mortality 2–5% (Child–Pugh A); up to 22% in Child–Pugh B	up to ~78% 5-yr survival (ideal)
RFA / MWA ≤ 3 cm	Local progression 3–29% at 3 yr	Major complications 2–11%; death 0.1–0.8%	3-yr survival 67–91% (Milan)
TACE	Partial control; repeat on demand	Decompensation ~20% of sessions (mostly reversible); death <1%	Median survival ~18–21 mo in trials
TARE	No local progression at 2 yr in LEGACY	Fatigue; REILD (fewer with prophylaxis); pneumonitis <1%	3-yr survival 87% (solitary ≤ 8 cm)
SBRT	Local control 68–95% at 2–3 yr	Child–Pugh decline ≥ 2 points in a minority; GI ulcer if near bowel	3-yr survival ~39% in pooled series

Numbers come from different populations and eras (UpToDate topic reviews, LEGACY, Mathew 2020): use them to explain, not to rank.

Figure 20. One table, five tools. Local control is highest after resection and ablation of small tumours; TACE controls but rarely eradicates; TARE and SBRT achieve high local control in selected tumours. Liver toxicity, not tumour control, usually limits all of them.

Portal vein tumour thrombus

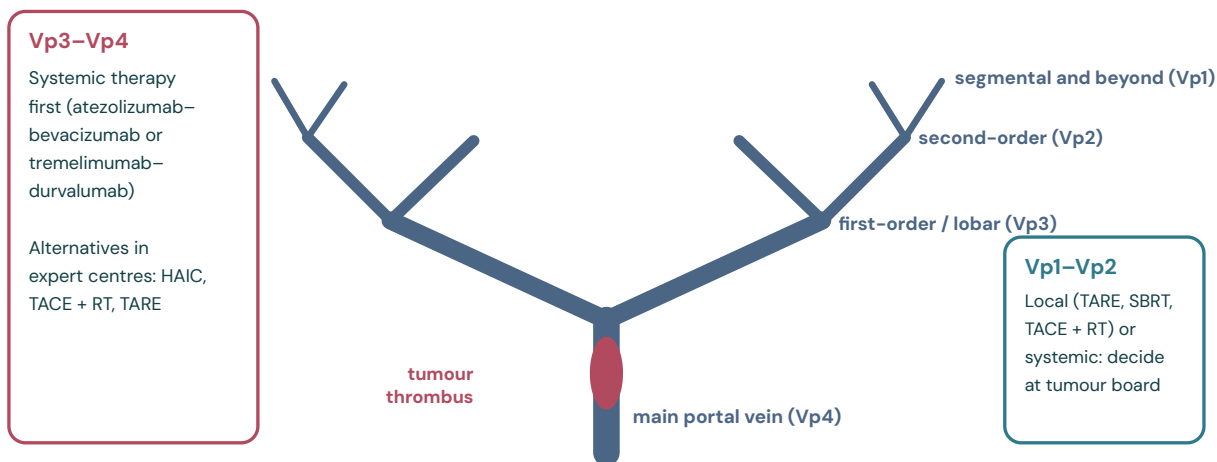


Figure 21. Portal vein tumour thrombus (PVTT) is a frequent finding when HCC is diagnosed without surveillance. Its level (Vp1–Vp4) guides treatment: main or lobar thrombus usually means systemic therapy; branch thrombus leaves room for radioembolisation or radiotherapy, sometimes as a route to later surgery.

Liver transplantation

Who can be cured by liver transplantation?

Milan	One tumour ≤ 5 cm, or 2–3 tumours each ≤ 3 cm; no vascular invasion, no spread 5-year survival $\geq 75\%$ (Mazzaferro 1996)
UCSF	One ≤ 6.5 cm, or 2–3 tumours, largest ≤ 4.5 cm and total ≤ 8 cm Similar outcomes in selected centres
Downstaged	Beyond Milan, brought within Milan by TACE/TARE/ablation and kept there; AFP falling 10-year survival 52% vs 61.5% within Milan (Tabrizian 2022)
Exclude	Macrovascular invasion, extrahepatic spread, AFP persistently >1000 ng/mL Recurrence too likely
India: about 4 in 5 liver transplants are living–donor (3,183 of 3,920 in 2022); most centres select HCC patients by UCSF or centre-specific criteria. Bridging (ablation or TACE) is used when the wait for a graft is likely to exceed about 6 months.	

Figure 22. Transplant treats both the tumour and the cirrhosis that caused it. The randomised XXL trial showed that, after successful downstaging, transplantation gave far better 5-year survival than non-transplant treatment (78% vs 31%), although the trial was small and stopped early.

- **Why it works:** it removes the tumour and the cirrhotic liver. Within the Milan criteria (one tumour ≤ 5 cm, or two to three ≤ 3 cm; no vascular invasion or spread) 4-year survival was 75% ([Mazzaferro 1996](#)^[48]); 5-year survival of 75% or more is expected with strict selection.
- **Resect first when possible:** for a resectable HCC in a good liver, resection is preferred; transplantation is for those who cannot be resected because of liver function or tumour distribution. Salvage transplantation is possible after recurrence.
- **Beyond Milan:** UCSF criteria, Metroticket 2.0 ([Metroticket 2.0](#)^[49]) and downstaging extend eligibility. After downstaging into Milan, 10-year survival was 52% (vs 61.5% always within Milan; recurrence 21% vs 13%) ([Tabrizian 2022](#)^[50]). In the randomised [XXL](#)^[51] trial, transplant after successful downstaging gave 5-year overall survival of 78% vs 31% with non-transplant treatment (small trial, stopped early).

- **Exclusions:** macrovascular invasion, extrahepatic spread, AFP persistently >1000 ng/mL, and failure to respond to downstaging.
- **Living donor transplantation** (about 4 in 5 liver transplants in India; India performs the most living-donor transplants in the world) avoids the waiting list, but exposes a healthy donor to surgery: tumour biology must justify it.
- **After transplant:** keep immunosuppression at the lowest effective level; no adjuvant anticancer therapy outside trials; imaging + AFP surveillance. Checkpoint inhibitors cause graft rejection in about four in ten recipients ([Kumar 2020^{\[52\]}](#)) and are avoided.

SHARE WITH PATIENTS: TREATMENT OPTIONS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Surgery is the only way to cure liver cancer?](#)

[If liver cancer cannot be operated on, nothing can be done?](#)

[A liver transplant needs a liver from someone who has died, so the wait never ends?](#)

[Fever, pain and vomiting after TACE mean the treatment has failed?](#)

[Herbal medicines or liver tonics can cure liver cancer or cirrhosis?](#)

o6 Systemic therapy: indications & options

Who should receive systemic therapy

- Extrahepatic spread; main or lobar portal vein thrombus (Vp3–Vp4); large or diffuse intrahepatic tumour unsuitable for TACE; or progression after liver-directed therapy. Requires Child–Pugh A (selected B7) and ECOG 0–1 for the combination regimens.
- **Before starting:** HBsAg and anti–HBc (start entecavir or tenofovir if positive, to prevent reactivation and treat the liver); HCV RNA; upper endoscopy within 6 months before any bevacizumab-containing regimen, banding large varices; thyroid, cortisol and glucose baseline; autoimmune disease and any history of organ transplant.

Recurrent disease: treat locally again, or start systemic therapy?

- Most recurrences after resection or ablation are confined to the liver, and many can still be treated with curative or local intent; surveillance exists to find them while they are small. Extrahepatic spread carries a poorer outlook and is treated systemically.

Recurrence pattern	Usual first step	Notes
Solitary or few intrahepatic nodules, late (more than about 2 years), good liver	Repeat resection, thermal ablation, or salvage transplantation	Late recurrences are often new tumours in the same liver and behave like a first HCC
Early (within about 2 years), multinodular intrahepatic	TACE or TARE if liver-confined and TACE-suitable; systemic therapy if burden is large or TACE fails	Early multifocal recurrence signals aggressive biology (spread from the first tumour)
Macrovascular invasion (Vp3–Vp4) or extrahepatic spread	Systemic therapy (first line below)	Add radiotherapy for painful bone metastases or symptomatic sites
Limited extrahepatic disease (a few lung or adrenal nodules) with a controlled liver	Systemic therapy first; resection or SBRT of the few lesions considered in an expert MDT if disease stays limited	Evidence is observational; select carefully
Recurrence after liver transplant	Lenvatinib or sorafenib; resection or SBRT of isolated lesions where feasible	No checkpoint inhibitors (graft rejection); lowest effective immunosuppression, some teams switch to an mTOR inhibitor-based regimen
Progression during or soon after first-line systemic therapy	Second-line therapy (below)	Re-check liver function first: many patients slip to Child–Pugh B

Systemic therapy by line: first, second and third line

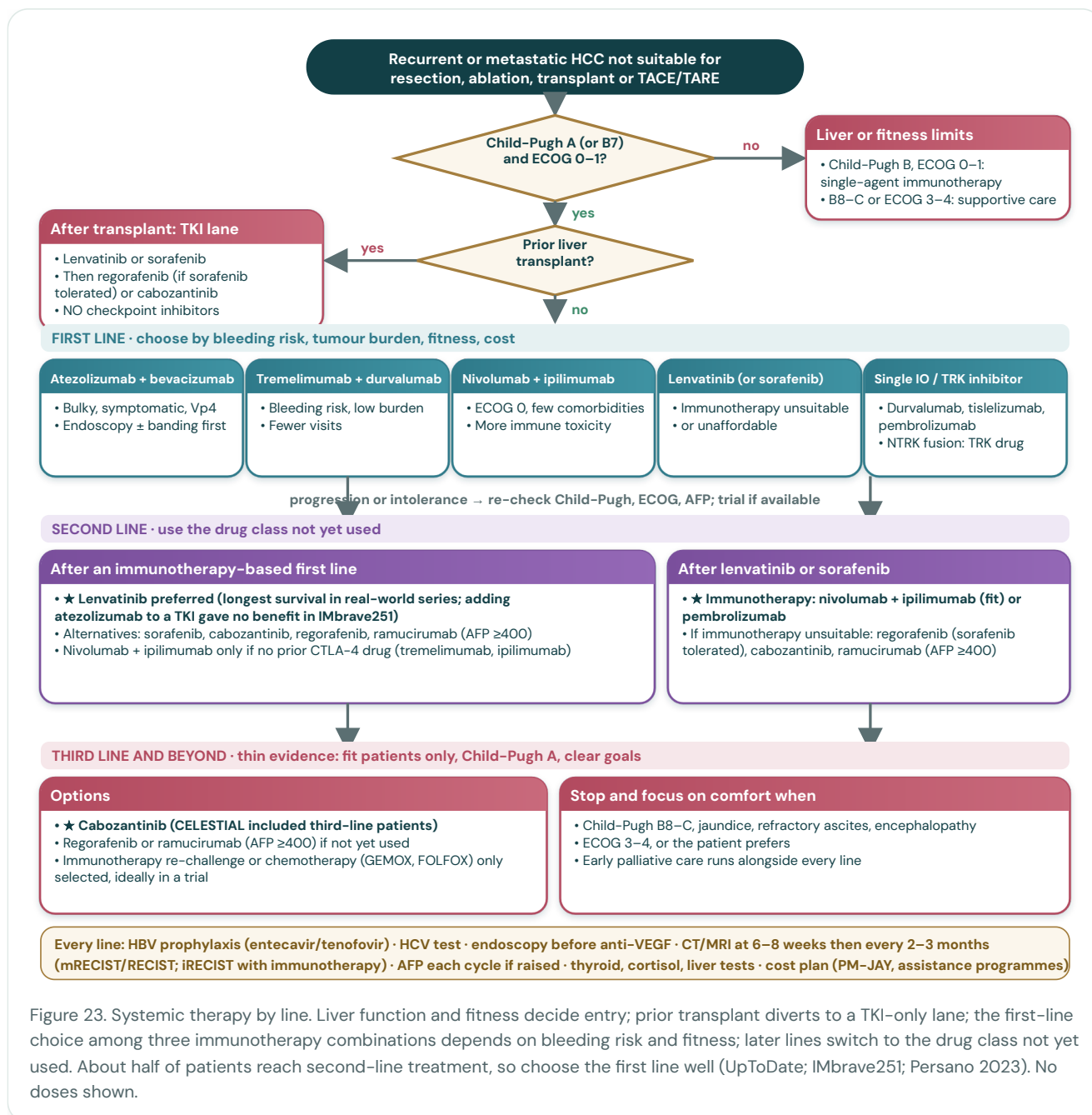


Figure 23. Systemic therapy by line. Liver function and fitness decide entry; prior transplant diverts to a TKI-only lane; the first-line choice among three immunotherapy combinations depends on bleeding risk and fitness; later lines switch to the drug class not yet used. About half of patients reach second-line treatment, so choose the first line well (UpToDate; IMbrave251; Persano 2023). No doses shown.

Before any line

- Child-Pugh and ALBI, ECOG, AFP baseline; HBsAg and anti-HBc (start entecavir or tenofovir if positive), HCV RNA; upper endoscopy within 6 months before any anti-VEGF drug (band large varices); thyroid, cortisol and glucose; autoimmune disease; history of organ transplant.
- A cost and access plan at the start (scheme eligibility, patient-assistance programmes, generic TKIs), because interrupted treatment is a common reason for failure; early palliative care alongside, not after, active treatment.

First line

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

Figure 24. 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.

Regimen	Evidence (vs sorafenib unless stated)	Choose when	Avoid or caution
Atezolizumab + bevacizumab	IMbrave150 ^[53] : median OS 19.2 vs 13.4 months (HR 0.66); response 30% vs 11%	Bulky, symptomatic or rapidly growing disease; main portal vein thrombus (Finn 2024 ^[54])	Untreated varices, recent bleeding or arterial thrombosis, therapeutic anticoagulation, uncontrolled hypertension or proteinuria
Tremelimumab + durvalumab (STRIDE)	HIMALAYA ^[55] : median OS 16.4 vs 13.8 months; 20% vs 9% alive at 5 years (Rimassa 2025 ^[41])	Bleeding risk or contraindication to bevacizumab; low tumour burden; fewer hospital visits	Active autoimmune disease; organ transplant
Nivolumab + ipilimumab	CheckMate 9DW ^[56] (vs lenvatinib or sorafenib): median OS 24 vs 21 months (HR 0.79); response 36% vs 13%	ECOG 0 and few comorbidities; response wanted	More grade 3–4 immune toxicity; some early progression in the first months
Lenvatinib	REFLECT ^[57] : OS non-inferior (13.6 vs 12.3 months); response 24% vs 9%	Immunotherapy unsuitable or unaffordable	Hypertension, proteinuria, bleeding; trial excluded more than 50% liver involvement and main portal vein invasion
Sorafenib	SHARP ^[58] : OS 10.7 vs 7.9 months vs placebo; Asia-Pacific trial ^[59] similar relative benefit	Lowest-cost option; cautious use in Child–Pugh B	Hand–foot skin reaction, diarrhoea; start low and build up
Durvalumab, tislelizumab or pembrolizumab alone	Durvalumab arm of HIMALAYA and RATIONALE-301 ^[60] : OS non-inferior; KEYNOTE-224 ^[61] : durable responses	Not fit for combinations; Child–Pugh B with ECOG 0–1	Transplant recipients
TRK inhibitor	Larotrectinib, entrectinib or repotrectinib: high, durable responses	NTRK fusion (rare)	—

- **Not adopted:** nivolumab alone ([CheckMate 459](#)^[62]) and cabozantinib + atezolizumab ([COSMIC-312](#)^[63]) did not improve survival; camrelizumab + rivoceranib ([CARES-310](#)^[64]) and sintilimab + a bevacizumab biosimilar ([ORIENT-32](#)^[65]) were positive in largely Chinese, hepatitis B populations and are not generally available in India.

Second line

First line received	Preferred second line	Alternatives	Evidence
Immunotherapy-based (atezolizumab + bevacizumab, STRIDE, nivolumab + ipilimumab, single agent)	Lenvatinib	Sorafenib, cabozantinib, regorafenib, ramucirumab (AFP ≥400 ng/mL); nivolumab + ipilimumab only if no prior CTLA-4 drug	No positive randomised trial after immunotherapy. Real-world data favour lenvatinib after atezolizumab + bevacizumab (Persano 2023 ^[66]). Adding atezolizumab to lenvatinib or sorafenib gave no survival gain (IMbrave251: median OS about 15 vs 13 months in the preliminary report; the 2026 final analysis did not meet its survival endpoint)
Lenvatinib or sorafenib (no transplant)	Immunotherapy: nivolumab + ipilimumab (fit) or pembrolizumab	If immunotherapy unsuitable: regorafenib (only if sorafenib was tolerated), cabozantinib, ramucirumab (AFP ≥400)	CheckMate 040 ^[67] : durable responses with nivolumab + ipilimumab; pembrolizumab improved OS in Asia (KEYNOTE-394 ^[68] : 15 vs 13 months) after a borderline KEYNOTE-240 ^[69] ; RESORCE ^[70] 10.6 vs 7.8, CELESTIAL ^[71] 10.2 vs 8.0, REACH-2 ^[12] 8.5 vs 7.3 months
Any first line after liver transplant	Second TKI: regorafenib (if sorafenib tolerated) or cabozantinib	Ramucirumab (AFP ≥400); supportive care	Immunotherapy avoided: graft rejection in about 4 in 10 (Kumar 2020 ^[52])
Any first line, now Child-Pugh B (ECOG 0–1)	Single-agent immunotherapy if not yet used	Sorafenib with caution; supportive care	Pooled response about 12%, median OS about 6 months (Xie 2023 ^[72])

- **Principle:** switch to the class not yet used (antiangiogenic TKI after immunotherapy; immunotherapy after a TKI). Only about half of patients ever reach second-line treatment, mostly because liver function or fitness declines, so a well-chosen first line matters most.
- **Regorafenib** was tested only in patients who tolerated sorafenib; do not use it after sorafenib intolerance. **Ramucirumab** needs AFP ≥400 ng/mL and avoids hand-foot skin reaction.

Third line and beyond

- **Evidence is thin.** Cabozantinib is the only drug with randomised data that included third-line patients ([CELESTIAL](#)^[71]: up to two prior systemic regimens, one of them sorafenib). Other choices are extrapolated.
- **Practical sequence:** give an agent not yet used: cabozantinib; regorafenib (if sorafenib or lenvatinib was tolerated); ramucirumab if AFP ≥400 ng/mL; nivolumab + ipilimumab after an anti-PD-1/PD-L1 regimen only in selected fit patients (responses in a minority in retrospective series; [Alden 2023](#)^[73]).
- **Chemotherapy** (gemcitabine–oxaliplatin, FOLFOX) gives modest responses: reserve for fit patients without access to other agents, or in trials.

- **Who should not get a third line:** Child–Pugh B8–C, jaundice, refractory ascites or encephalopathy, ECOG 3–4, or a patient who prefers comfort. Median survival in these situations is short, and supportive care (pain control including single–fraction liver RT, nutrition, ascites and encephalopathy management) is active treatment.
- **Clinical trials** should be offered at every progression, and repeat molecular testing considered only if it could reveal a targetable alteration (NTRK).

Special situations

Situation	Approach
Main portal vein thrombus (Vp4)	Atezolizumab + bevacizumab after variceal banding, or STRIDE; local therapy (TARE, TACE + RT) in expert centres
High bleeding risk (varices, recent bleed, anticoagulation)	STRIDE or nivolumab + ipilimumab; avoid bevacizumab and ramucirumab
ECOG 2 or frail elderly	Single-agent immunotherapy or a TKI at a reduced starting dose; reassess after 6–8 weeks
Bone metastases	Radiotherapy for pain or cord risk; bone-protecting drug if multiple sites; continue systemic therapy
Active hepatitis B or C	Antiviral therapy throughout; HBV prophylaxis is mandatory with immunotherapy and TKIs
Autoimmune disease	Prefer a TKI; immunotherapy only after specialist discussion

Response, switching and stopping

- CT or MRI after 6–8 weeks, then every 2–3 months; mRECIST (viable enhancing tumour) or RECIST 1.1 for TKIs; iRECIST with immunotherapy, where early apparent progression can occasionally be followed by response (confirm with a repeat scan if the patient is well).
- A rising AFP can precede radiological progression by weeks; a falling AFP supports response. Neither alone defines progression.
- Switch at confirmed progression or unacceptable toxicity; at every switch recalculate Child–Pugh, ALBI and ECOG, because liver function, not the tumour, most often ends systemic treatment.

Before and after curative treatment

- **No adjuvant drug is standard.** Sorafenib did not reduce recurrence ([STORM^{\[74\]}](#)); atezolizumab + bevacizumab improved recurrence-free survival at the first analysis but the benefit was not sustained ([IMbrave050^{\[75\]}](#)); adjuvant pembrolizumab did not improve recurrence-free survival (KEYNOTE-937, reported in 2026). Adjuvant hepatic arterial FOLFOX improved disease-free but not overall survival in a Chinese trial ([Li 2023^{\[76\]}](#)). Neoadjuvant therapy belongs to trials.
- **Antiviral therapy is the proven "adjuvant":** for hepatitis B-related HCC with active viral replication, nucleos(t)ide analogues improve recurrence-free and overall survival ([Yin 2013^{\[77\]}](#)). For hepatitis C, direct-acting antivirals after curative treatment improve liver outcomes and do not increase recurrence ([Singal 2019^{\[78\]}](#)); many centres give them 4–6 months after HCC treatment, once complete response is confirmed.

India: access and cost

- Generic sorafenib and lenvatinib are much cheaper than immunotherapy combinations; when cost decides, a well-chosen TKI with good supportive care is a reasonable first line, and immunotherapy can follow at progression.
- Check eligibility under Ayushman Bharat PM-JAY and state schemes, and patient-assistance programmes, before the first cycle; cost-driven interruptions are a common cause of treatment failure.

Quick-reference tables

Printable as a landscape PDF from the Printable Teaching Resources page. No doses: check current product information and Indian approvals.

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
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

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 ^[22] , Chen 2006 ^[20]
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 ^[21]
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 ^[48] , LEGACY ^[32]
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 ^[30] , EMERALD–1 ^[79] , LEAP–O12 ^[80]
Branch PVTT (Vp1–Vp2)	Local (TARE, SBRT, TACE + RT) or systemic	Choose local when later resection or transplant is possible	Yoon 2018 ^[81]
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 ^[53] , HIMALAYA ^[55] , CheckMate 9DW ^[56]
Child–Pugh B advanced HCC	Single-agent immunotherapy (ECOG 0–1)	Sorafenib with cautious start; supportive care if B8–9 and frail	Xie 2023 ^[72]
Recurrence after transplant	Lenvatinib or sorafenib	Local therapy for oligometastases; NO checkpoint inhibitors (graft rejection)	Kumar 2020 ^[52]
After resection or ablation	Surveillance + antiviral therapy	No adjuvant systemic therapy outside trials	STORM ^[74] , IMbrave050 ^[75] , Yin 2013 ^[77]
BCLC D	Best supportive care; palliative RT for pain	Transplant only if otherwise eligible (liver failure, not tumour, is the problem)	CCTG HE1 ^[43]

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

Regimen	Key trial and result	Best for	Avoid or caution
Atezolizumab + bevacizumab	IMbrave150 ^[53] : 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 ^[55] : 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 ^[56] : 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 ^[57] : 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 ^[58] : OS 10.7 vs 7.9 mo; Asia-Pacific trial ^[59] 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 ^[60] : OS non-inferior to sorafenib; KEYNOTE-394 ^[68] : OS gain after sorafenib	Not fit for combinations; Child–Pugh B	Transplant recipients
Regorafenib	RESORCE ^[70] : OS 10.6 vs 7.8 mo after sorafenib	Second line if sorafenib was tolerated	Sorafenib intolerance
Cabozantinib	CELESTIAL ^[71] : OS 10.2 vs 8.0 mo after sorafenib	Second or third line	Hand–foot reaction, diarrhoea, hypertension
Ramucirumab	REACH-2 ^[12] : 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 ^[62] (nivolumab vs sorafenib) and COSMIC-312 ^[63] (cabozantinib + atezolizumab) missed OS; CARES-310 ^[64] and ORIENT-32 ^[65] positive but agents mostly unavailable in India	—	—

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 progression, 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

SHARE WITH PATIENTS: MEDICINES AND SIDE EFFECTS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Medicines for advanced liver cancer always cause hair loss and severe vomiting, like chemotherapy?](#)

[People with hepatitis B cannot have chemotherapy, immunotherapy or other cancer treatment?](#)

Yellow eyes, dark urine or more tiredness during treatment always mean the cancer is spreading?

People with liver cancer or cirrhosis must stop eating protein foods such as dal, eggs, fish and meat?

Every painkiller damages the liver, so pain from liver cancer just has to be endured?

07 Management algorithms

These decision paths pull together sections 02–06. Colours: teal for favourable paths, purple for intermediate, rose for advanced or high-risk paths.

ALGORITHM 1

Liver nodule or raised AFP in an at-risk patient

Surveillance ultrasound shows a nodule, or AFP ≥ 20 ng/mL or rising → multiphase contrast CT or MRI (liver protocol) → **LI-RADS category** → liver tumour board

LR-1 / LR-2 / LR-3

LR-1-2 → back to 6-monthly surveillance

LR-3 → repeat CT/MRI in 3–6 months

Nodule <1 cm on ultrasound: repeat ultrasound 3-monthly × 2

LR-4 / LR-M

LR-4 → MDT: biopsy, short-interval imaging, or treat as HCC

LR-M → biopsy (cholangiocarcinoma, combined HCC-CCA, metastasis)

Non-cirrhotic liver: biopsy any suspicious lesion

LR-5 / LR-TIV

HCC confirmed without biopsy

Stage: CT chest, Child-Pugh, ALBI, ECOG, portal hypertension, HBV/HCV status

Go to Algorithm 2 or 3 by BCLC stage

All patients: treat the hepatitis B or C · stop alcohol · varices screening if cirrhotic · surveillance continues for life, even after cure.

ALGORITHM 2

Liver-confined HCC (BCLC 0–B)

HCC confined to the liver, no main or lobar portal vein thrombus → Child-Pugh, portal hypertension, future liver remnant, transplant eligibility → MDT

BCLC 0–A

Resectable, Child-Pugh A, no portal hypertension → resection

≤3 cm, resection riskier → RFA or MWA

3–5 cm, not resectable → TACE + ablation, TARE or SBRT

Poor liver function within Milan/UCSF → transplant (ablate or TACE as bridge)

BCLC B

Multinodular, Child-Pugh A–B7 → DEB-TACE or TARE

Downstaged within Milan → transplant evaluation

TACE refractory or liver worse → systemic therapy

Large diffuse burden → systemic therapy first (or HAIC/TACE + lenvatinib in expert centres)

SPECIAL SITUATIONS

Ruptured HCC → embolise, stabilise, stage → delayed resection if feasible

Child-Pugh C → transplant evaluation or supportive care

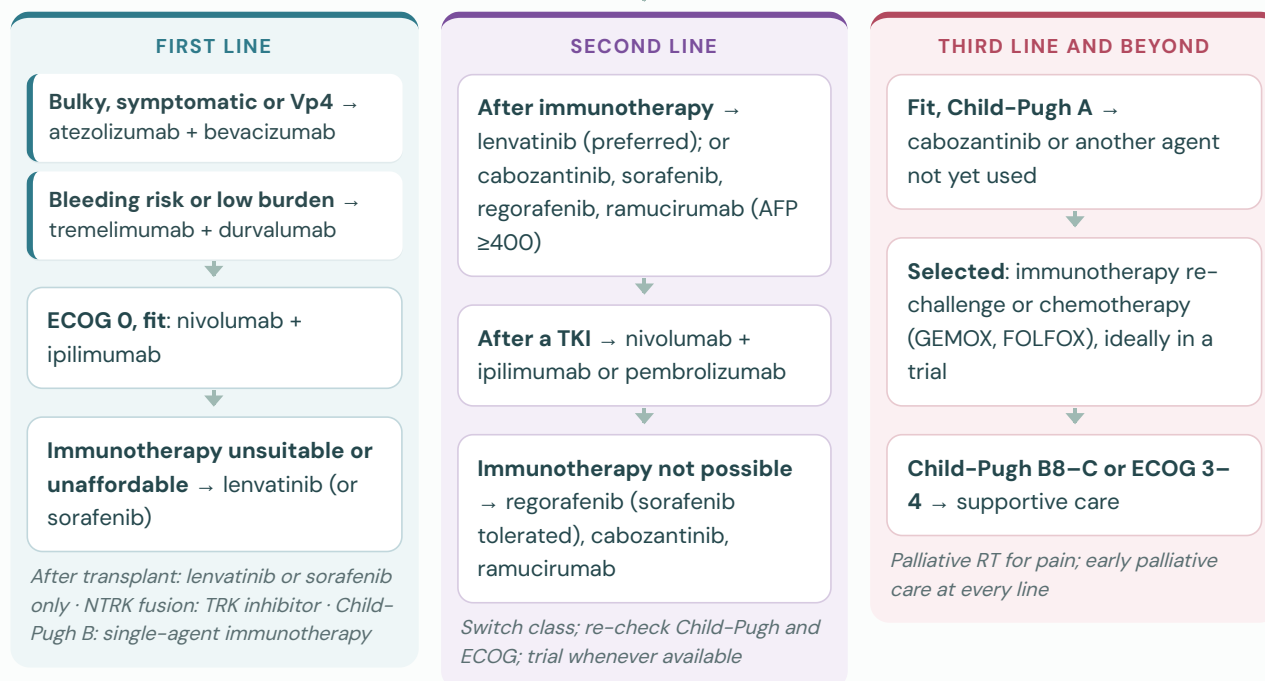
Every curative treatment: antivirals, surveillance 3–6-monthly for 2 years

All patients: no adjuvant drug outside trials · hepatitis B antivirals for life · hepatitis C cure after HCC treatment · recurrence can often be treated again.

ALGORITHM 3

Recurrent or metastatic HCC: systemic therapy by line

Not suitable for local therapy → Child-Pugh A (or B7) and ECOG 0–1? → prior liver transplant? → HBV prophylaxis, HCV test, endoscopy if anti-VEGF planned

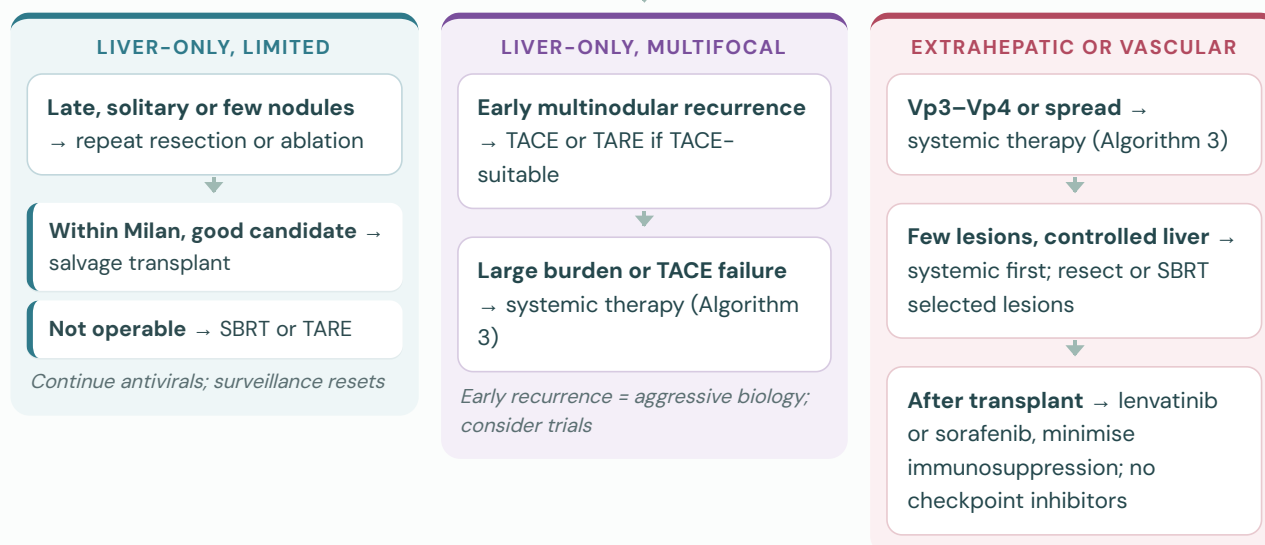


All patients: CT/MRI at 6–8 weeks then every 2–3 months · AFP · liver tests, thyroid, cortisol · nutrition · cost plan · goals of care discussed at each progression.

ALGORITHM 4

Recurrence after curative treatment (resection, ablation or transplant)

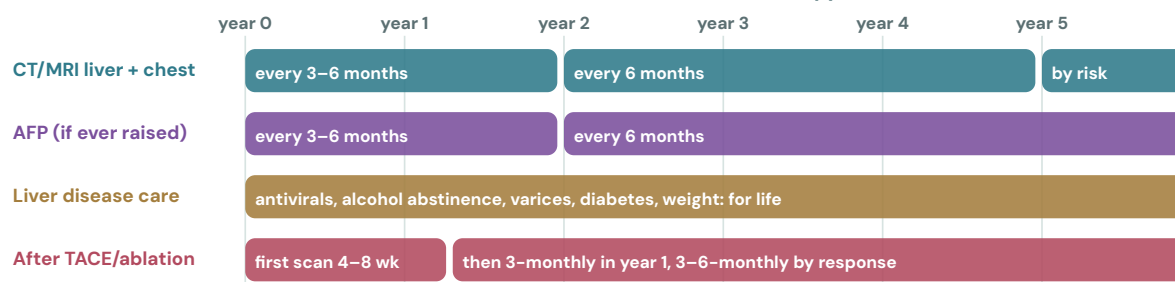
Recurrence on surveillance → multiphase CT/MRI + CT chest + AFP → is it liver-only? → liver function and fitness → MDT



All patients: hepatitis B suppression and hepatitis C cure · alcohol abstinence · re-stage liver function before every decision.

o8 Survivorship, follow-up & reducing recurrence

Years after curative treatment (resection, ablation) or after liver-directed therapy



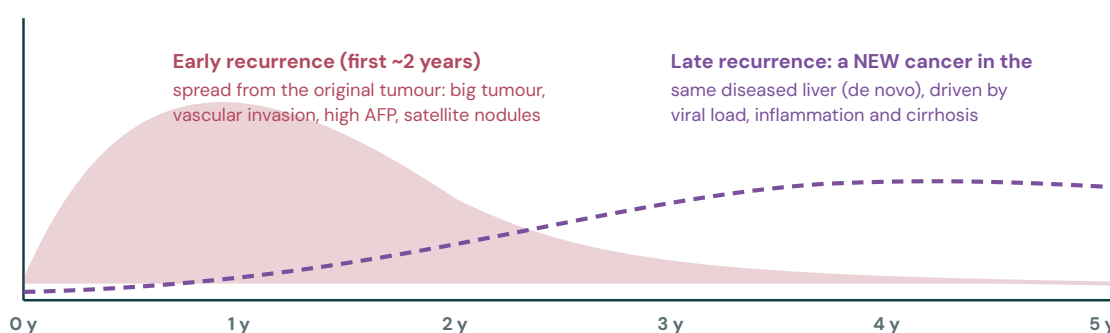
Response after locoregional therapy is read with LI-RADS treatment response (viable enhancement), after systemic therapy with mRECIST or RECIST 1.1 (iRECIST with immunotherapy). After TARE or SBRT wait about 3 months for the first scan.

Figure 25. A simple follow-up rhythm (NCCN, AASLD, UpToDate). Continue for at least 5 years and then keep lifelong HCC surveillance, because the cirrhotic liver that produced the first cancer can produce a second one.

Follow-up protocol (NCCN, AASLD, UpToDate; adapt to resources)

Situation	Imaging and AFP	Notes
After resection or ablation	Multiphase CT or MRI + AFP every 3–6 months for 2 years, then 6-monthly; at least 5 years, then lifelong surveillance	Most recurrences are in the liver and can be treated again
After TACE, TARE or SBRT	First scan 4–8 weeks after TACE/ablation (about 3 months after TARE or SBRT), then 3-monthly in the first year	Read with LI-RADS treatment response; persistent nodular enhancement = viable tumour
On systemic therapy	CT/MRI after 6–8 weeks, then every 2–3 months; AFP each cycle or monthly if raised	mRECIST or RECIST 1.1; iRECIST with immunotherapy
After liver transplant	CT/MRI + AFP, typically 3–6-monthly for 2–3 years, then less often	Yearly skin examination; age-appropriate cancer screening; lowest effective immunosuppression

Recurrence after resection or ablation (illustrative shape, not to scale)



Reduce it: suppress hepatitis B (nucleos(t)ide analogue), cure hepatitis C, stop alcohol, control diabetes and weight. No adjuvant drug has proven benefit (STORM, IMbrave050, KEYNOTE-937); repeat resection, ablation or transplant can still cure.

Figure 26. When relapses happen. Early recurrences reflect the first tumour; late ones are new tumours in a liver that still carries the original risk. That is why antiviral therapy and liver care matter as much as the scan schedule.

- **Treat the liver for life:** hepatitis B antivirals do not stop after HCC treatment; cure hepatitis C; complete alcohol abstinence; weight, diabetes and lipid control in MASLD; vaccinate against hepatitis A and B if not immune; carvedilol for clinically significant portal hypertension to reduce decompensation; screen and band varices.
- **Family:** test household members and sexual partners of hepatitis B carriers (HBsAg, anti-HBs) and vaccinate if negative; first-degree relatives of HCC patients with hepatitis B need surveillance.
- **After transplant:** higher risk of skin cancer, lymphoma and other cancers; sun protection and yearly skin checks; report new lumps or symptoms early; no checkpoint inhibitors without transplant team input.
- **Symptoms and quality of life:** fatigue, muscle wasting and itch are common; late-evening carbohydrate snack and adequate protein help in cirrhosis; avoid NSAIDs and sedatives; early palliative care for advanced disease.
- **Prevention for the next generation:** hepatitis B birth dose within 24 hours and the full vaccine course; universal vaccination cut childhood HCC in Taiwan ([Chang 1997^{\[82\]}](#)).

SHARE WITH PATIENTS: FOLLOW-UP AND LIFE AFTER TREATMENT

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

Once liver cancer is treated, it cannot come back?

If scans stay clear for two years after treatment, check-ups are no longer needed?

A little alcohol is fine once liver cancer or cirrhosis has been treated?

After a liver transplant, the anti-rejection medicines can be stopped once you feel well?

If the AFP blood test goes up once during treatment, the treatment has failed?

Once liver cancer has been treated and the hepatitis B virus is undetectable, the antiviral tablets can be stopped?

After part of the liver is removed, you can never live or work normally again?

If liver cancer cannot be operated on, nothing can be done?

09 Landmark trials

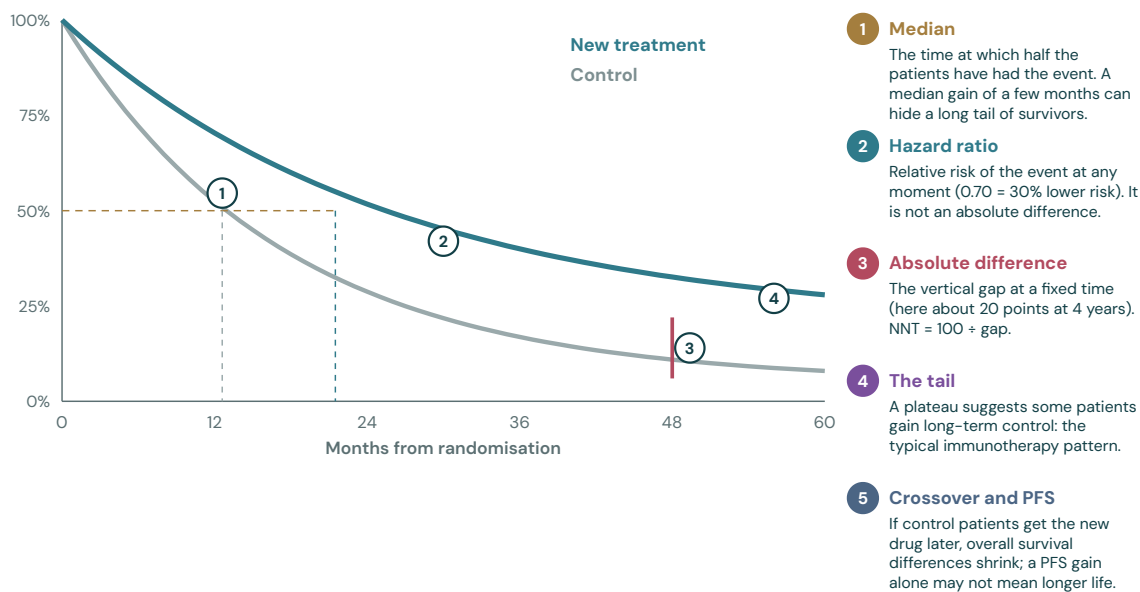


Figure 27. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

- **Milan (Mazzaferro 1996)**^[48]: transplant restricted to small HCC → 4-year survival 75% → the selection standard worldwide.
- **Zhang 2004**^[8]: 6-monthly ultrasound + AFP vs none in hepatitis B carriers → HCC mortality down 37% → surveillance for high-risk groups.
- **Llovet 2002**^[30] and **Lo 2002**^[31]: chemoembolisation vs supportive care → survival gain → TACE for intermediate HCC.
- **SHARP**^[58]: sorafenib vs placebo → median survival 10.7 vs 7.9 months → first systemic therapy for HCC.
- **REFLECT**^[57]: lenvatinib vs sorafenib → non-inferior survival, higher response → second TKI option.
- **IMbrave150**^[53]: atezolizumab + bevacizumab vs sorafenib → 19.2 vs 13.4 months → immunotherapy era begins.
- **HIMALAYA**^[55]: tremelimumab + durvalumab vs sorafenib → 5-year survival 20% vs 9% → durable long-term survivors.
- **CheckMate 9DW**^[56]: nivolumab + ipilimumab vs lenvatinib/sorafenib → 24 vs 21 months → third first-line combination.
- **RESOURCE**^[70], **CELESTIAL**^[71], **REACH-2**^[12]: second-line regorafenib, cabozantinib and ramucirumab (AFP ≥ 400) after sorafenib → modest survival gains.
- **STORM**^[74] and **IMbrave050**^[75]: adjuvant sorafenib and atezolizumab + bevacizumab → no lasting benefit → surveillance plus antivirals remains standard.
- **XXI**^[51]: transplant vs non-transplant after successful downstaging → 5-year survival 78% vs 31% → downstaging is a route to cure.
- **EMERALD-1**^[79] and **LEAP-012**^[80]: TACE plus systemic therapy → longer progression-free survival → overall survival awaited.

- [Yin 2013^{\[77\]}](#): antivirals after resection of hepatitis B-related HCC → better recurrence-free and overall survival → treat the virus.

10 Practice pearls & pitfalls

- Every patient with cirrhosis or chronic hepatitis B needs a named person responsible for their 6-monthly ultrasound; most "late" HCC in India is a missed surveillance problem.
- Ask for a multiphase liver protocol CT or MRI. A routine portal-venous CT can miss a small HCC.
- In a cirrhotic liver, an LR-5 lesion is HCC: do not biopsy just for confirmation if it would delay treatment, but do biopsy atypical lesions and non-cirrhotic livers.
- Normal liver function tests and a normal AFP do not rule out HCC.
- A febrile patient with a liver "abscess" that does not drain pus, in a hepatitis B carrier, needs contrast imaging for HCC.
- Stage the liver as carefully as the tumour: Child-Pugh, ALBI, platelets, varices and ascites decide what is safe.
- Check HBsAg and anti-HBc in every patient before TACE, immunotherapy or chemotherapy; start antiviral prophylaxis when needed. Hepatitis B flares can kill.
- Endoscopy before bevacizumab: band large varices first, or choose tremelimumab + durvalumab.
- Resection is still the default for a single tumour in a good liver; ablation is an excellent alternative for $\leq 2-3$ cm.
- Keep transplantation in mind for every Child-Pugh B/C patient within criteria, and for selected patients after downstaging; refer early.
- Never give checkpoint inhibitors after a liver transplant without the transplant team.
- When cost decides, lenvatinib or sorafenib with good supportive care is a reasonable first line; do not let the "perfect" regimen block any treatment.
- In Child-Pugh C, the liver, not the tumour, will decide survival: transplant evaluation or supportive care, not chemotherapy.
- Prevention is the biggest win: hepatitis B birth dose, vaccinating families, free NVHCP treatment for hepatitis B and C, alcohol counselling and weight control.

11 Case vignettes: lines of management

Seven cases, written for postgraduates and practising clinicians. Read the presentation, decide on diagnosis, workup and plan, then open the line of management. No doses are given.

CASE 1 Surveillance · hepatitis B · resection

A hepatitis B carrier with a new nodule

46 years, man

HBsAg positive, no cirrhosis

Single 3 cm nodule

A 46-year-old farmer, known HBsAg positive for 10 years with a father who died of liver cancer, has never been treated. Surveillance ultrasound shows a 3 cm nodule; AFP 38 ng/mL. Platelets 210,000, bilirubin and albumin normal.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

Multiphase MRI: 3 cm segment VI observation with arterial hyperenhancement, washout and capsule. In chronic hepatitis B this is LR-5: HCC without biopsy.

2

STAGE

CT chest clear; Child-Pugh A5; no portal hypertension; HBV DNA 4.8 log IU/mL; HCV negative. BCLC A.

3

TREAT THE VIRUS

Start tenofovir (or entecavir) now, for life.

4

TREAT THE TUMOUR

Laparoscopic anatomical segment VI resection; clear margin; no microvascular invasion.

5

FOLLOW-UP

Multiphase CT or MRI + AFP every 3–6 months for 2 years, then 6-monthly; screen and vaccinate the family.

TEACHING POINTS

- Hepatitis B causes HCC without cirrhosis, especially with family history.
- LR-5 in a high-risk liver needs no biopsy.
- Antiviral therapy is part of the cancer treatment.

See: Sections O3, O5, O8 · Algorithms 1–2 · [Zhang 2004](#)^[8], [Yin 2013](#)^[77]

CASE 2 Hepatitis C cirrhosis · ablation

Two small nodules and a low platelet count

58 years, woman

HCV cirrhosis, Child-Pugh A6

2.2 cm + 1.4 cm

A 58-year-old woman with untreated hepatitis C cirrhosis has two nodules on surveillance (2.2 cm in segment VIII and 1.4 cm in segment III). Platelets 78,000; small oesophageal varices; AFP 9 ng/mL.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

MRI: the 2.2 cm lesion is LR-5; the 1.4 cm lesion has arterial enhancement and washout (LR-5 by size and features).

2

ASSESS THE LIVER

Clinically significant portal hypertension (platelets, varices): major resection is risky. Both lesions within Milan.

3

TREAT

Percutaneous microwave ablation of both lesions in one session; start carvedilol for portal hypertension.

4

VIRUS

Direct-acting antivirals once complete ablation is confirmed on the 4–8-week MRI.

5

PLAN AHEAD

Transplant assessment if recurrence or decompensation; lifelong surveillance even after SVR.

TEACHING POINTS

- Portal hypertension, not just Child–Pugh, decides resection.
- Thermal ablation is curative for small HCC.
- Curing hepatitis C after HCC treatment does not raise recurrence.

See: Sections 05, 06, 08 · Algorithm 2 · [Yu 2017](#)^[27], [Singal 2019](#)^[78]

CASE 3 MASLD cirrhosis · BCLC B · TACE**Diabetes, fatty liver and four tumours**

63 years, man

MASH cirrhosis, Child–Pugh A6

4 nodules up to 4 cm

A 63-year-old man with diabetes and obesity (BMI 32) had "fatty liver" on scans for years but no surveillance. He now has four HCC nodules (largest 4 cm) in both lobes, no vascular invasion, no extrahepatic disease; AFP 210 ng/mL; ECOG 0.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STAGE

BCLC B: multinodular, liver-confined, preserved function.

2

TREAT

Selective DEB-TACE, repeated on demand; endoscopy and HBV/HCV tests done.

3

ASSESS

MRI at 6 weeks (LI-RADS treatment response): three nodules non-viable, one partially viable → repeat TACE.

4

CONSIDER CURE

Within UCSF after treatment, AFP falling: living-donor transplant evaluation (his daughter volunteers).

5

IF IT FAILS

TACE refractoriness or liver deterioration → systemic therapy (Algorithm 3).

TEACHING POINTS

- MASLD cirrhosis needs the same surveillance as viral cirrhosis.
- TACE is for liver-confined multinodular HCC with good function.
- Successful downstaging can lead to transplant.

See: Sections 05, 06 · Algorithm 2 · [Llovet 2002](#)^[30], [PRECISION V](#)^[28], [Tabrizian 2022](#)^[50]

CASE 4 Advanced · portal vein thrombus · immunotherapy**New ascites in a drinker**

55 years, man

Alcohol, Child–Pugh A6

9 cm HCC + Vp4

A 55-year-old man who drinks daily presents with abdominal distension. Ultrasound: ascites (now controlled on diuretics) and a 9 cm right-lobe mass. Contrast CT: HCC with tumour thrombus in the main portal vein (Vp4); no extrahepatic disease. AFP 14,800 ng/mL. ECOG 1.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STAGE

BCLC C (portal invasion); Child–Pugh A6 after diuretics; HBsAg and anti-HBc negative.

2

BEFORE THERAPY

Upper endoscopy: large varices → banding; alcohol abstinence support.

3

CHOOSE

Atezolizumab + bevacizumab after banding (bulky disease, Vp4 thrombus, needs a response); tremelimumab + durvalumab if banding is incomplete or bleeding risk is high.

4

MONITOR

CT at 6–8 weeks, AFP each cycle, liver tests, thyroid and cortisol; watch for immune hepatitis versus progression.

5

AT PROGRESSION

Lenvatinib if still Child–Pugh A; supportive care if the liver fails.

TEACHING POINTS

- Sudden decompensation in cirrhosis can be the first sign of HCC with portal vein thrombus.
- Main portal vein thrombus means systemic therapy.
- Endoscopy and banding come before bevacizumab.

See: Sections 05, 06 · Algorithm 3 · [IMbrave150](#)^[53], [Finn 2024](#)^[54], [HIMALAYA](#)^[55]

CASE 5 Emergency · rupture**Sudden abdominal pain and shock**

42 years, man

HBsAg positive

Haemoperitoneum

A 42-year-old man collapses with sudden severe abdominal pain. BP 80/50, haemoglobin 7.2 g/dL. He was told years ago he "has jaundice virus" but never followed up.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

RESUSCITATE

Blood, fluids, correct coagulopathy.

2

IMAGE

CT (plain and contrast): 7 cm left-lobe HCC with surrounding haemoperitoneum and active contrast blush.

3

STOP THE BLEEDING

Urgent transarterial embolisation by interventional radiology.

4

STAGE AND PLAN

Child–Pugh A, no portal hypertension, no metastases; tenofovir started; staged left hepatectomy 6 weeks later.

5

FOLLOW-UP

Higher risk of peritoneal recurrence: close imaging; peritoneal nodules may be resectable.

TEACHING POINTS

- Rupture is an emergency first, an oncology problem second.
- Embolisation then delayed resection can still cure selected patients.
- Untreated hepatitis B carriers fall through the gaps: link them to care.

See: Sections 02, 05 · Algorithm 2

CASE 6 Young patient · normal liver**A big mass in a young woman**

24 years, woman

Normal liver, HBV/HCV negative

11 cm, central scar

A 24-year-old student has right upper abdominal discomfort. CT: an 11 cm well-defined left-lobe mass with a central calcified scar in an otherwise normal liver; enlarged nodes at the porta hepatis. AFP normal; HBV and HCV negative.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

THINK

Fibrolamellar carcinoma; also focal nodular hyperplasia (central scar, but usually no calcification or nodes) and hepatic adenoma.

2

CONFIRM

Core biopsy: fibrolamellar carcinoma (DNAJB1::PRKACA fusion).

3

TREAT

Left hepatectomy with portal lymph node dissection (nodal spread is common).

4

FOLLOW-UP

Imaging every 3–6 months; recurrences are often resectable again. Systemic options are poorly effective: trial referral.

TEACHING POINTS

- A normal liver and a normal AFP do not exclude primary liver cancer.
- Fibrolamellar carcinoma is a surgical disease; lymph nodes matter.
- Do not apply cirrhotic-liver LI-RADS rules to a normal liver: biopsy.

See: Sections 02, 04, 05

CASE 7 After transplant · recurrence**Lung nodules two years after transplant**

51 years, man

DLT for HCC beyond Milan

Lung metastases

A 51-year-old man had a living-donor liver transplant 2 years ago for hepatitis B-related HCC slightly beyond Milan (explant: microvascular invasion). AFP has risen from 6 to 340 ng/mL; CT shows five lung nodules up to 1.5 cm. Graft function is normal on tacrolimus.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

CONFIRM

CT-guided biopsy of a lung nodule: metastatic HCC.

2

TALK TO THE TRANSPLANT TEAM

Reduce immunosuppression to the lowest safe level; some teams switch to an mTOR inhibitor-based regimen.

3

SYSTEMIC THERAPY

Lenvatinib (or sorafenib). No checkpoint inhibitors: graft rejection risk is about 40%.

4

LOCAL OPTIONS

Few slow lesions: resection or SBRT of metastases can be considered.

5

SUPPORT

Hepatitis B prophylaxis continues; palliative care input.

TEACHING POINTS

- Immunotherapy is avoided after liver transplantation.
- Recurrence risk is higher beyond Milan and with microvascular invasion.
- AFP is a useful early marker after transplant.

See: Sections 05, 06 · Algorithm 3 · [Kumar 2020](#)^[52], [REFLECT](#)^[57]

12 References & guidelines

- AASLD Practice Guidance on prevention, diagnosis and treatment of HCC (Hepatology 2023;78:1922) ([PubMed](#)^[83]); EASL Clinical Practice Guidelines on the management of HCC (J Hepatol 2025;82:315) ([PubMed](#)^[84]).
- Indian National Association for the Study of the Liver: 2023 update of the consensus on intermediate and advanced HCC, the Puri III recommendations (J Clin Exp Hepatol 2024;14:101269) ([PubMed](#)^[85]); National Viral Hepatitis Control Programme (Ministry of Health and Family Welfare), national guidelines for viral hepatitis.
- BCLC strategy, 2026 update; ACR LI-RADS v2018 (diagnostic) and LI-RADS treatment response algorithms v2024; AJCC Cancer Staging Manual, 8th edition (liver); WHO Classification of Digestive System Tumours, 5th edition; NCCN Guidelines: Hepatocellular Carcinoma (current version).
- GLOBOCAN 2022 (IARC Global Cancer Observatory) for Indian incidence and mortality; Liver Transplantation Society of India survey (Natl Med J India 2025) for transplant activity.
- Cross-checked in October 2026 against 24 UpToDate topic reviews (epidemiology and risk factors; surveillance; clinical features and diagnosis; pathology of malignant liver tumours; staging and prognostic factors; overview of treatment; surgical resection; neoadjuvant and adjuvant therapy and post-treatment surveillance; local ablation; liver-directed therapy for patients not eligible for ablation; liver transplantation for HCC and transplant candidate evaluation; systemic therapy for advanced HCC; assessment of tumour response; cirrhosis; hepatitis B in adults and children; hepatitis C antiviral selection; cancer and skin problems after organ transplantation; and, for the colorectal module, colorectal liver metastases and pulmonary metastasectomy). Facts only; no text, tables or figures were copied; dose tables were not used.
- KEYNOTE-937 (adjuvant pembrolizumab) and the IMbrave251 final analysis (second line after atezolizumab + bevacizumab) are cited from 2026 meeting presentations, which have no PubMed record yet.

Core trials cited on this page (85)

Journal, year, volume and first page (or DOI); each links to the PubMed record by exact citation.

NUMBERED IN ORDER OF FIRST CITATION IN THE TEXT

1. **HCC aetiology in India (Praharaj 2024)**: Praharaj DL, Singh A, Vaidya A, et al. Changing etiological spectrum of hepatocellular carcinoma in India: a systematic review and meta-analysis. J Clin Exp Hepatol. 2024. doi:10.1016/j.jceh.2024.101391. [PubMed](#)
Epidemiology, prevention and surveillance
2. **Kerala HCC survey (Koshy 2023)**: Koshy A, Devadas K, Panackel C, et al. Multi-center prospective survey of hepatocellular carcinoma in Kerala: more than 1,200 cases. Indian J Gastroenterol. 2023. doi:10.1007/s12664-022-01314-8. [PubMed](#)
Epidemiology, prevention and surveillance
3. **BCLC 2026 update**: Reig M, Sanduzzi-Zamparelli M, Forner A, et al. BCLC strategy for prognosis prediction and treatment recommendations: the 2026 update. J Hepatol 2026;84:631. [PubMed](#) Staging and response assessment
4. **HIMALAYA 5-year (Rimassa 2025)**: Rimassa L, Chan SL, Sangro B, et al. Five-year overall survival update from the HIMALAYA study of tremelimumab plus durvalumab in unresectable HCC. J Hepatol 2025;83:899. [PubMed](#) Systemic therapy
5. **HBV DNA and HCC risk (REVEAL, Chen 2006)**: Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65. [PubMed](#) Epidemiology, prevention and surveillance
6. **Lamivudine in advanced HBV disease (Liaw 2004)**: Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521. [PubMed](#) Epidemiology, prevention and surveillance
7. **SVR and HCC in advanced fibrosis (Lockart 2022)**: Lockart I, Yeo MGH, Hajarizadeh B, et al. HCC incidence after hepatitis C cure among patients with advanced fibrosis or cirrhosis: a meta-analysis. Hepatology 2022;76:139. [PubMed](#)
Epidemiology, prevention and surveillance
8. **Surveillance RCT (Zhang 2004)**: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417. [PubMed](#) Epidemiology, prevention and surveillance

9. **6-monthly vs annual surveillance (Santi 2010):** Santi V, Trevisani F, Gramenzi A, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. *J Hepatol* 2010;53:291. [PubMed](#)
Epidemiology, prevention and surveillance
10. **3- vs 6-monthly surveillance (Trinchet 2011):** Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. *Hepatology* 2011;54:1987. [PubMed](#) Epidemiology, prevention and surveillance
11. **ALBI grade (Johnson 2015):** Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach, the ALBI grade. *J Clin Oncol* 2015;33:550. [PubMed](#)
Staging and response assessment
12. **REACH-2:** Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α -fetoprotein concentrations (REACH-2). *Lancet Oncol* 2019;20:282. [PubMed](#) Systemic therapy
13. **ERAS liver surgery 2022:** Joliat GR, Kobayashi K, Hasegawa K, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations 2022. 2022. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
14. **PVE systematic review (Glantzounis 2017):** Glantzounis GK, Tokidis E, Basourakos SP, et al. The role of portal vein embolization in the surgical management of primary hepatobiliary cancers: a systematic review. *Eur J Surg Oncol* 2017;43:32. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
15. **Major resection with or without PVE (Palavecino 2009):** Palavecino M, Chun YS, Madoff DC, et al. Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: perioperative outcome and survival. *Surgery* 2009;145:399. [PubMed](#) Surgical technique, complications and liver-directed therapy technique
16. **Laparoscopic vs open resection RCT (El-Gendi 2018):** El-Gendi A, El-Shafei M, El-Gendi S, Shawky A. Laparoscopic versus open hepatic resection for solitary hepatocellular carcinoma less than 5 cm in cirrhotic patients: a randomized controlled study. *J Laparoendosc Adv Surg Tech A* 2018;28:302. [PubMed](#) Surgical technique, complications and liver-directed therapy technique
17. **ISGLS liver failure (Rahbari 2011):** Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;149:713. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
18. **50-50 criteria (Balzan 2005):** Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005;242:824. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
19. **ISGLS bile leakage (Koch 2011):** Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 2011;149:680. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
20. **Resection vs ablation (Chen 2006):** Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243:321. [PubMed](#)
Surgery, ablation and transplantation
21. **Resection vs ablation meta-analysis (Shin 2021):** Shin SW, Ahn KS, Kim SW, et al. Liver resection versus local ablation therapies for hepatocellular carcinoma within the Milan criteria: a systematic review and meta-analysis. *Ann Surg* 2021;273:656. [PubMed](#)
Surgery, ablation and transplantation
22. **SURF trial:** Takayama T, Hasegawa K, Izumi N, et al. Surgery versus radiofrequency ablation for small hepatocellular carcinoma: a randomized controlled trial (SURF trial). *Liver Cancer* 2022;11:209. [PubMed](#) Surgery, ablation and transplantation
23. **SURF trial (2025):** Kawaguchi Y, Hasegawa K, Kashiwabara K, et al. Surgery versus ablation for hepatocellular carcinoma: a randomized controlled trial (SURF-RCT) and a nonrandomized prospective observational trial (SURF-Cohort). *J Clin Oncol* 2025;43:2628. [PubMed](#) Surgery, ablation and transplantation
24. **RFA 1000 cases (Tateishi 2005):** Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma: an analysis of 1000 cases. *Cancer* 2005;103:1201. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
25. **COVER-ALL:** Odisio BC, et al. Software-based versus visual assessment of the minimal ablative margin in patients with liver tumours undergoing percutaneous thermal ablation (COVER-ALL): a randomised phase 2 trial. *Lancet Gastroenterol Hepatol*. 2025. [PubMed](#) Surgical technique, complications and liver-directed therapy technique
26. **RFA adverse events (de Baère 2003):** de Baère T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *AJR Am J Roentgenol* 2003;181:695. [PubMed](#) Surgical technique, complications and liver-directed therapy technique
27. **MWA vs RFA (Yu 2017):** Yu J, Yu XL, Han ZY, et al. Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomised controlled trial. *Gut* 2017;66:1172. [PubMed](#)
Surgery, ablation and transplantation

28. **PRECISION V:** Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33:41. [PubMed](#)
Arterial and radiation therapies
29. **TACE complications (Chan 2002):** Chan AO, Yuen MF, Hui CK, et al. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. *Cancer* 2002;94:1747. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
30. **TACE vs symptomatic care (Llovet 2002):** Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734. [PubMed](#) Arterial and radiation therapies
31. **TACE RCT Hong Kong (Lo 2002):** Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164. [PubMed](#) Arterial and radiation therapies
32. **LEGACY:** Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. *Hepatology* 2021;74:2342. [PubMed](#) Arterial and radiation therapies
33. **DOSISPHERE-01:** Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol* 2021;6:17. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
34. **Radiation segmentectomy (Riaz 2011):** Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys* 2011;79:163. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
35. **REILD prevention (Gil-Alzugaray 2013):** Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology* 2013;57:1078. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
36. **SIRveNIB:** Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913. [PubMed](#) Arterial and radiation therapies
37. **ASTRO liver RT guideline 2022:** Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract Radiat Oncol* 2022;12:28. [PubMed](#) Radiotherapy and proton therapy
38. **APROH (protons vs RFA):** Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. *J Hepatol* 2021;74:603. [PubMed](#) Radiotherapy and proton therapy
39. **Protons vs TACE RCT (Bush 2023):** Bush DA, Volk M, Smith JC, et al. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: results of a randomized clinical trial. *Cancer* 2023;129:3554. [PubMed](#)
Radiotherapy and proton therapy
40. **Proton phase II (Hong 2016):** Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2016;34:460. [PubMed](#) Radiotherapy and proton therapy
41. **Proton therapy 162 patients (Chiba 2005):** Chiba T, Tokuyue K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res* 2005;11:3799. [PubMed](#) Radiotherapy and proton therapy
42. **SBRT phase I-II (Bujold 2013):** Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
43. **CCTG HE1:** Dawson LA, Ringash J, Fairchild A, et al. Palliative radiotherapy versus best supportive care in patients with painful hepatic cancer (CCTG HE1): a multicentre, open-label, randomised, controlled, phase 3 study. *Lancet Oncol* 2024;25:1337. [PubMed](#) Arterial and radiation therapies
44. **QUANTEC liver (Pan 2010):** Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 2010;76:S94. [PubMed](#) Surgical technique, complications and liver-directed therapy technique
45. **SBRT long-term outcomes (Mathew 2020):** Mathew AS, Atenafu EG, Owen D, et al. Long term outcomes of stereotactic body radiation therapy for hepatocellular carcinoma without macrovascular invasion. *Eur J Cancer* 2020;134:41. [PubMed](#)
Surgical technique, complications and liver-directed therapy technique
46. **SBRT vs RFA (Wahl 2016):** Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 2016;34:452. [PubMed](#) Arterial and radiation therapies
47. **NRG/ROG 1112:** Dawson LA, Winter KA, Knox JJ, et al. Stereotactic body radiotherapy vs sorafenib alone in hepatocellular carcinoma: the NRG Oncology/ROG 1112 phase 3 randomized clinical trial. *JAMA Oncol* 2025;11:136. [PubMed](#)
Arterial and radiation therapies
48. **Milan criteria (Mazzaferro 1996):** Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693. [PubMed](#) Surgery, ablation and transplantation

49. **Metroticket 2.0:** Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2018;154:128. [PubMed](#) **Surgery, ablation and transplantation**
50. **Downstaging 10-year outcomes (Tabrizian 2022):** Tabrizian P, Holzner ML, Mehta N, et al. Ten-year outcomes of liver transplant and downstaging for hepatocellular carcinoma. *JAMA Surg* 2022;157:779. [PubMed](#) **Surgery, ablation and transplantation**
51. **XXL:** Mazzaferro V, Citterio D, Bhoori S, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol* 2020;21:947. [PubMed](#) **Surgery, ablation and transplantation**
52. **Checkpoint inhibitors after transplant (Kumar 2020):** Kumar V, Shinagare AB, Rennke HG, et al. The safety and efficacy of checkpoint inhibitors in transplant recipients: a case series and systematic review of literature. *Oncologist* 2020;25:505. [PubMed](#) **Surgery, ablation and transplantation**
53. **IMbrave150:** Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894. [PubMed](#) **Systemic therapy**
54. **IMbrave150 Vp4 subgroup (Finn 2024):** Finn RS, Galle PR, Ducreux M, et al. Efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in hepatocellular carcinoma with main trunk and/or contralateral portal vein invasion in IMbrave150. *Liver Cancer* 2024;13:655. [PubMed](#) **Systemic therapy**
55. **HIMALAYA:** Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. 2022. doi:10.1056/EVIDoa2100070. [PubMed](#) **Systemic therapy**
56. **CheckMate 9DW:** Yau T, Galle PR, Decaens T, et al. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW). *Lancet* 2025;405:1851. [PubMed](#) **Systemic therapy**
57. **REFLECT:** Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163. [PubMed](#) **Systemic therapy**
58. **SHARP:** Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378. [PubMed](#) **Systemic therapy**
59. **Sorafenib Asia-Pacific (Cheng 2009):** Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25. [PubMed](#) **Systemic therapy**
60. **RATIONALE-301:** Qin S, Kudo M, Meyer T, et al. Tislelizumab vs sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a phase 3 randomized clinical trial. *JAMA Oncol* 2023;9:1651. [PubMed](#) **Systemic therapy**
61. **KEYNOTE-224:** Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018;19:940. [PubMed](#) **Later-line systemic therapy**
62. **CheckMate 459:** Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459). *Lancet Oncol* 2022;23:77. [PubMed](#) **Systemic therapy**
63. **COSMIC-312:** Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312). *Lancet Oncol* 2022;23:995. [PubMed](#) **Systemic therapy**
64. **CARES-310:** Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310). *Lancet* 2023;402:1133. [PubMed](#) **Systemic therapy**
65. **ORIENT-32:** Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32). *Lancet Oncol* 2021;22:977. [PubMed](#) **Systemic therapy**
66. **Second-line after atezolizumab-bevacizumab (Persano 2023):** Persano M, Rimini M, Tada T, et al. Sequential therapies after atezolizumab plus bevacizumab or lenvatinib first-line treatments in hepatocellular carcinoma patients. *Eur J Cancer* 2023;189:112933. [PubMed](#) **Later-line systemic therapy**
67. **CheckMate 040 5-year (Melero 2024):** Melero I, Yau T, Kang YK, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040. *Ann Oncol* 2024;35:537. [PubMed](#) **Later-line systemic therapy**
68. **KEYNOTE-394:** Qin S, Chen Z, Fang W, et al. Pembrolizumab versus placebo as second-line therapy in patients from Asia with advanced hepatocellular carcinoma. *J Clin Oncol* 2023;41:1434. [PubMed](#) **Systemic therapy**
69. **KEYNOTE-240:** Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240. *J Clin Oncol* 2020;38:193. [PubMed](#) **Systemic therapy**
70. **RESORCE:** Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE). *Lancet* 2017;389:56. [PubMed](#) **Systemic therapy**
71. **CELESTIAL:** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 2018;379:54. [PubMed](#) **Systemic therapy**

72. **ICI in Child–Pugh B meta-analysis (Xie 2023):** Xie E, Yeo YH, Scheiner B, et al. Immune checkpoint inhibitors for Child–Pugh class B advanced hepatocellular carcinoma: a systematic review and meta-analysis. *JAMA Oncol* 2023;9:1423. [PubMed](#)
Systemic therapy
73. **Salvage nivolumab–ipilimumab after PD–1 (Alden 2023):** Alden SL, Lim M, Kao C, et al. Salvage ipilimumab plus nivolumab after anti-PD–1/PD–L1 therapy in advanced hepatocellular carcinoma. *Cancer Res Commun* 2023;3:1312. [PubMed](#)
Later-line systemic therapy
74. **STORM:** Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM). *Lancet Oncol* 2015;16:1344. [PubMed](#) **Adjuvant therapy and antivirals after treatment**
75. **IMbrave050:** Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050). *Lancet* 2023;402:1835. [PubMed](#)
Adjuvant therapy and antivirals after treatment
76. **Adjuvant HAIC–FOLFOX (Li 2023):** Li SH, Mei J, Cheng Y, et al. Postoperative adjuvant hepatic arterial infusion chemotherapy with FOLFOX in hepatocellular carcinoma with microvascular invasion: a multicenter, phase III, randomized study. *J Clin Oncol* 2023;41:1898. [PubMed](#) **Adjuvant therapy and antivirals after treatment**
77. **Antiviral therapy after resection (Yin 2013):** Yin J, Li N, Han Y, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol* 2013;31:3647. [PubMed](#) **Adjuvant therapy and antivirals after treatment**
78. **DAA and HCC recurrence (Singal 2019):** Singal AG, Rich NE, Mehta N, et al. Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. *Gastroenterology* 2019;156:1683. [PubMed](#)
Adjuvant therapy and antivirals after treatment
79. **EMERALD–1:** Sangro B, Kudo M, Erinjeri JP, et al. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD–1). *Lancet* 2025;405:216. [PubMed](#) **Arterial and radiation therapies**
80. **LEAP–012:** Kudo M, Ren Z, Guo Y, et al. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP–012). *Lancet* 2025;405:203. [PubMed](#)
Arterial and radiation therapies
81. **TACE + RT vs sorafenib (Yoon 2018):** Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized clinical trial. *JAMA Oncol* 2018;4:661. [PubMed](#) **Arterial and radiation therapies**
82. **HBV vaccination and childhood HCC (Chang 1997):** Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997;336:1855. [PubMed](#)
Epidemiology, prevention and surveillance
83. **AASLD HCC guidance 2023:** *Hepatology* 78:1922. [PubMed](#) **Other studies cited in the text**
84. **EASL HCC guidelines 2025:** *J Hepatol* 82:315. [PubMed](#) **Other studies cited in the text**
85. **INASL Puri III (2023):** INASL Puri III (2023). [PubMed](#) **Other studies cited in the text**

FURTHER READING (NOT CITED IN THE TEXT ABOVE)

- **mRECIST (Lencioni 2010):** Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52. [PubMed](#) **Staging and response assessment**
- **EMERALD–3:** Kudo M, Abou-Alfa GK, Ren Z, et al. Durvalumab and tremelimumab, with or without lenvatinib, combined with transarterial chemoembolisation in embolisation-eligible hepatocellular carcinoma (EMERALD–3). *Lancet Oncol* 2026;27:1077. [PubMed](#) **Arterial and radiation therapies**
- **LAUNCH:** Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (LAUNCH). *J Clin Oncol* 2023;41:117. [PubMed](#) **Arterial and radiation therapies**
- **IMbrave150 updated (Cheng 2022):** Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;76:862. [PubMed](#)
Systemic therapy

Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Biliary tract cancers (gallbladder cancer, cholangiocarcinoma) will be added to this module as part 2. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.