Hepatocellular carcinoma

General Overview

- Hepatocellular carcinoma (HCC) is 6th most common cancer worldwide (GLOBACAN 2018) and accounts for 90% of all primary liver cancer.
- 80% of all HCC occurs in a background of cirrhosis, regardless of cause (viral or non-viral), due to the pro-inflammatory and fibrotic microenvironment created by cirrhosis.
- Given the high risk of HCC development, all patients with cirrhosis should undergo 6-monthly surveillance with ultrasound and alpha-fetoprotein (AFP)
- HCC in non-cirrhotic liver is most often associated with chronic hepatitis B but is also seen in patients with NAFLD or without underlying liver disease.
- A rare subtype of HCC (<1%) is fibrolamellar HCC, affecting young individuals (typically <40 years old) without underlying liver disease or cirrhosis

Diagnosis and staging (BCLC)

- Diagnosis through triphasic (arterial, portal venous, and delayed phases) CT thorax/abdomen and MRI liver (with or without liver-specific contrast)
- In cirrhotic patients, diagnosis can be made using only imaging for lesions > 1 cm according to AASLD/Li-RADS, although a biopsy is recommended
- In non-cirrhotic patients a biopsy is **always** needed

AASLD Imaging criteria for HCC diagnosis

Criterion	Description
Arterial Phase Hyperenhancement	Increased enhancement of the lesion during the arterial phase
Washout appearance	Reduced contrast in the venous or delayed phase compared to surrounding liver parenchyma
Capsule appearance	Smooth, enhancing peripheral rim visible in the delayed phase
Threshold growth	≥ 50% increase in lesion size within 6 months

- Most common staging algorithm used in Europe is the Barcelona Clinic Liver Cancer (BCLC) staging – AJCC TNM is rarely used

BLCLC stage	0	A	B	C	D
Tumor	Single nodule ≤ 2 cm.	Single nodule > 2 cm or ≤ 3 nodules ≤ 3 cm	Multiple nodules without vascular invasion or extrahepatic spread	Evidence of vascular invasion or distant metastasis	Extensive disease
Liver function	Child Pugh A	Child Pugh A or B	Child Pugh A or B	Child Pugh A or B	Child Pugh C
Performance status	PS 0	PS 0	PS 0	PS 1-2	PS ≥3

- AFP is elevated in 60% of HCC and is a marker of poor prognosis (≥400 ng/mL in those patients)

- Transjugular portal venous pressure measurement to determine level of portal hypertension, MRI-based volumetry and technetium (99mTc) mebrofenin clearance can be used to select patients for surgery.

Treatment

BCLC Stage 0 (Very Early Stage)

- Surgical Resection is first-line option for patients without clinically significant portal hypertension and adequate liver remnant after surgery with median overall survival (mOS) of > 90% at 5 years
- Radiofrequency ablation (RFA) or microwave ablation (MWA) is a good alternative for non-surgical candidates with limited side effects and mOS of ~80% at 5 years

BCLC Stage A (Early Stage)

- Liver Transplantation is preferred for cirrhotic patients within Milan Criteria (single tumor ≤ 5 cm or up to 3 tumors ≤ 3 cm) with a mOS 70–80% at 5 years as it also cures the underlying liver disease with high risk of second primary
- Surgical Resection is preferred for non-cirrhotic patients or those with sufficient liver reserve with a mOS: ~50–70% at 5 years.
- RFA/MWA for patients unfit for surgery or awaiting transplantation with a mOS ~50–60% at 5 y.

BCLC Stage B (Intermediate Stage)

- Transarterial Chemoembolization (TACE) and transarterial radioembolization (TARE / SIRT) are standard of care for intermediate-stage patients, improving survival but not leading to cure (median OS ~20–26 months).
- Conventional TACE (cTACE), drug-eluting-beads TACE (DEB-TACE) and TARE are supported by BCLC guidelines. In practice, DEB-TACE and TARE are most often used with TARE being preferred for single lesions ≤8 cm due to the higher objective response rates and thus downstaging.
- In patient with advanced stage B – especially multifocal and bilobar disease beyond “up to 7 criteria” – use of systemic immunotherapy as in BCLC stage C can be considered instead of TARE/TACE
- In case of sufficient downstaging, liver transplantation can be considered in BCLC B patients

BCLC Stage C (Advanced Stage)

- Based upon the results of the IMBRAVE-150 with atezolizumab-bevacizumab (mOS 19.2 months) and HIMALAY trial with durvalumab-tremelimumab (mOS 16.4 months – 5-year-OS 20%), all patients should be treated with an immunotherapy (IO)-based regimen in first-line unless contra-indications exist. Relevant contra-indications include Child-Pugh status B and above, active auto-immune disease and status post-liver transplant.
- Selection of the type of IO-based first-line regimen should be based upon the different toxicity-profile of both combinations (e.g. bleeding complications for bevacizumab vs. higher risk for immunotherapy-related toxicity with dual IO) as there is no consensus on predictors of efficacy (e.g. etiology).
- For patients with contra-indications for IO-based treatment, oral tyrosine-kinase inhibitors (TKI) sorafenib (SHARP trial) and lenvatinib (REFLECT trial) are recommend with median overall survival ranging from 12-22 months. Given the improved tolerability and limited real-world evidence on efficacy, lenvatinib is often the preferred TKI in first-line.

- In patients progressing under IO, treatment with TKI (e.g. sorafenib) can be considered based upon retrospective data
- For patients progressing on TKI in first-line, treatment with regorafenib (RESORCE trial – reimbursed in Belgium) and cabozantinib (CELESTIAL trial – only available in Belgium through medical samples) lead to a modest improvement in OS.
- Chemotherapy with gemcitabine and oxaliplatin should be reserved for selected populations when no other treatment options are available.

BCLC Stage D (Terminal Stage)

- Patient with BCLC stage D should receive best supportive care with focus on symptom control and improving quality of life as mOS is limited to 3-4 months

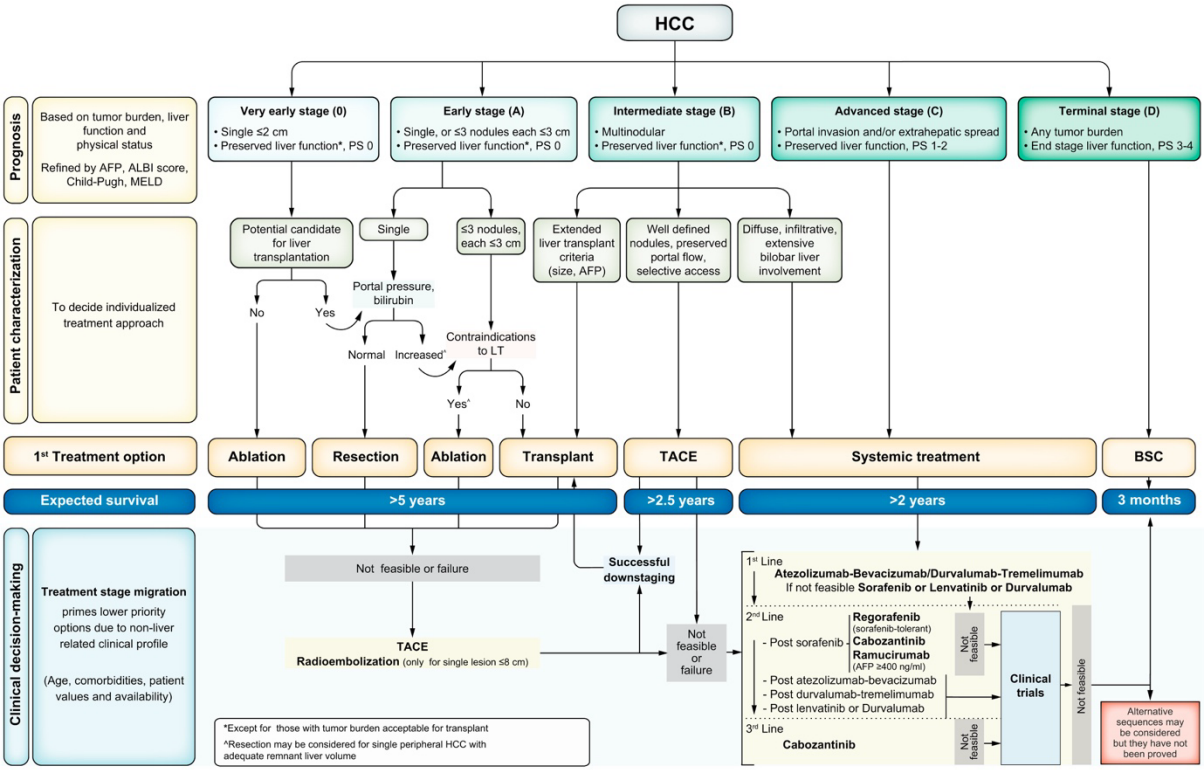

Figure 1. BCLC treatment algorithm (2022) – adapted from Reig et al. J Hep; 76(3)681-693

References

1) IMBRAVE-150 trial: Finn R et al. N Engl J Med 2020;382:1894-1905
2) HIMALAYA trial: Abou-Alfa G et al NEJM Evid 2022;1(8)
3) SHARP trial: Llovet J et al. N Engl J Med 2008;359:378-390
4) REFLECT trial: Kudo J et al. Lancet 2018; 391(10126):1163-1173
5) CELESTIAL: Abou-Alfa G et al. N Engl J Med 2018;379:54-63
6) RESORCE: Bruix J et al. Lancet 2017

What's new ?

- Ongoing development of novel immunotherapy combinations including anti-TIGIT in BCLC C patients and combination therapies of TACE +/- immunotherapy in BCLC B.