CLINICAL PRACTICE GUIDELINES

An ESMO Product

Hepatocellular carcinoma

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

A. Vogel, A. Cervantes, I. Chau, B. Daniele, J. M. Llovet, T. Meyer, J.-C. Nault, U. Neumann, J. Ricke, B. Sangro, P. Schirmacher, C. Verslype, C. J. Zech, D. Arnold & E. Martinelli, on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Gastrointestinal-Cancers

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Diagnosis work-up

Based on histological analysis and/or contrast-enhanced imaging findings

History and clinical examination
Risk factors for chronic liver disease: • IV drug abuse • alcohol intake • metabolic syndrome (obesity, diabetes, arterial hypertension)
Symptoms and signs of chronic liver disease (jaundice, ascites, encephalopathy, bleeding, splenomegaly)
PS (distinguish cancer-related symptoms of recent onset with long-standing symptoms associated with cirrhosis) and nutritional state
Laboratory analysis
Aetiology of liver disease: HBV (at least HBsAg and anti-HBc), HCV (at least anti-HCV), iron status, autoimmune disease
Liver function: Prothrombin, albumin, bilirubin
Complete blood cell count including platelets
Tumour marker: Serum AFP

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Diagnosis work-up

Assessment of portal hypertension, imaging studies & tumour biopsy

Assessment of portal hypertension
Upper endoscopy: Varices and/or hypertensive gastropathy
Optional: Transjugular measurement of hepatic-venous pressure gradient
Imaging studies
Liver dynamic (multiple phase) MRI or CT studies for diagnosis and evaluation of tumour extent inside the liver (number and size of nodules, vascular invasion, extrahepatic spread)
CEUS can also be used for the non-invasive diagnosis of HCC if CT scan or MRI are not possible, but is not considered appropriate for tumour staging
CT of the chest, abdomen and pelvis to rule out extrahepatic spread
Tumour biopsy
Useful for nodules with non-diagnostic at imaging
Required to diagnose HCC in non-cirrhotic liver
Should be carried out according to national or institutional policy in all clinical trials and may support centre-based innovative treatment approaches
Ideally, should evaluate tumour and non-tumour tissue when used for scientific purposes

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Diagnosis and pathology / Molecular biology

Diagnosis by imaging
Diagnosis requires identification by multiphasic contrast-enhanced CT or MRI of typical vascular hallmarks of HCC in a nodule of > 1 cm diameter
Multiphasic MRI is more sensitive than multiple detector CT
MRI with diffusion-weighted imaging and hepatobiliary contrast agents may identify high-risk nodules
Diagnosis by pathology
Histopathological diagnosis of tumour biopsies relies on H&E staining and may be supplemented with IHC, which is also recommended in unclear cases
Significant CK19 expression indicates a poor prognosis
In highly differentiated HCC, additional histological and cytological criteria can support the diagnosis and additional IHC markers can improve diagnosis

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Staging and risk assessment

Summary of recommendations
Staging should be conducted according to the BCLC system and includes: • Assessment of tumour extent • AFP level • Liver function • Portal pressure • Clinical PS
Contrast-enhanced MRI or helical CT are recommended to evaluate tumour extent FDG-PET scanning is not recommended
Liver function is assessed by the Child–Pugh scoring system and the ALBI score can distinguish between good- and poor-prognosis patients
Oesophageal varices and/or splenomegaly with blood platelet counts of 100 × 10^9 cells/L suggest clinically important portal hypertension

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BCLC Staging and treatment options

Stages 0-A, B

BCLC Stage		Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment
0-A	Single tumour any size or up to 3 nodules ≤ 3 cm Preserved liver function ECOG PS 0	Resection	Adequate size and function of remnant liver	SBRT HDR brachytherapy SIRT
		Transplantation	Size ≤ 5 cm, number ≤ 3	
		Thermal ablation	Size ≤ 3 cm, not adjacent to vessels or bile duct	
		TACE	Contraindications against resection and thermal ablation. Bridging to transplantation	
B	Multinodular Preserved liver function ECOG PS 0	TACE	Size 5–10 cm, tumour nodules accessible to supra-selective catheterisation	Transplantation Resection Systemic therapy (not suitable for local therapies) SIRT (liver-confined, good liver function, no systemic therapy feasible)

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BCLC Staging and treatment options

Stages C, D

BCLC Stage		Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment
C	Portal invasion Extrahepatic spread Preserved liver function ECOG PS 0–2	Atezolizumab + Bevacizumab (first-line) Option: Sorafenib (first-line) Lenvatinib (first-line)	Child–Pugh A	SIRT (liver confined, good liver function, no systemic therapy feasible)
		Standard after sorafenib: Cabozantinib Regorafenib Ramucirumab Option after atezolizumab + bevacizumab/lenvatinib: Sorafenib Lenvatinib Cabozantinib Regorafenib Ramucirumab	Child–Pugh A Tolerability to sorafenib (regorafenib) AFP ≥ 400 ng/ml for ramucirumab	
D	End-stage liver function ECOG PS 3–4	BSC		

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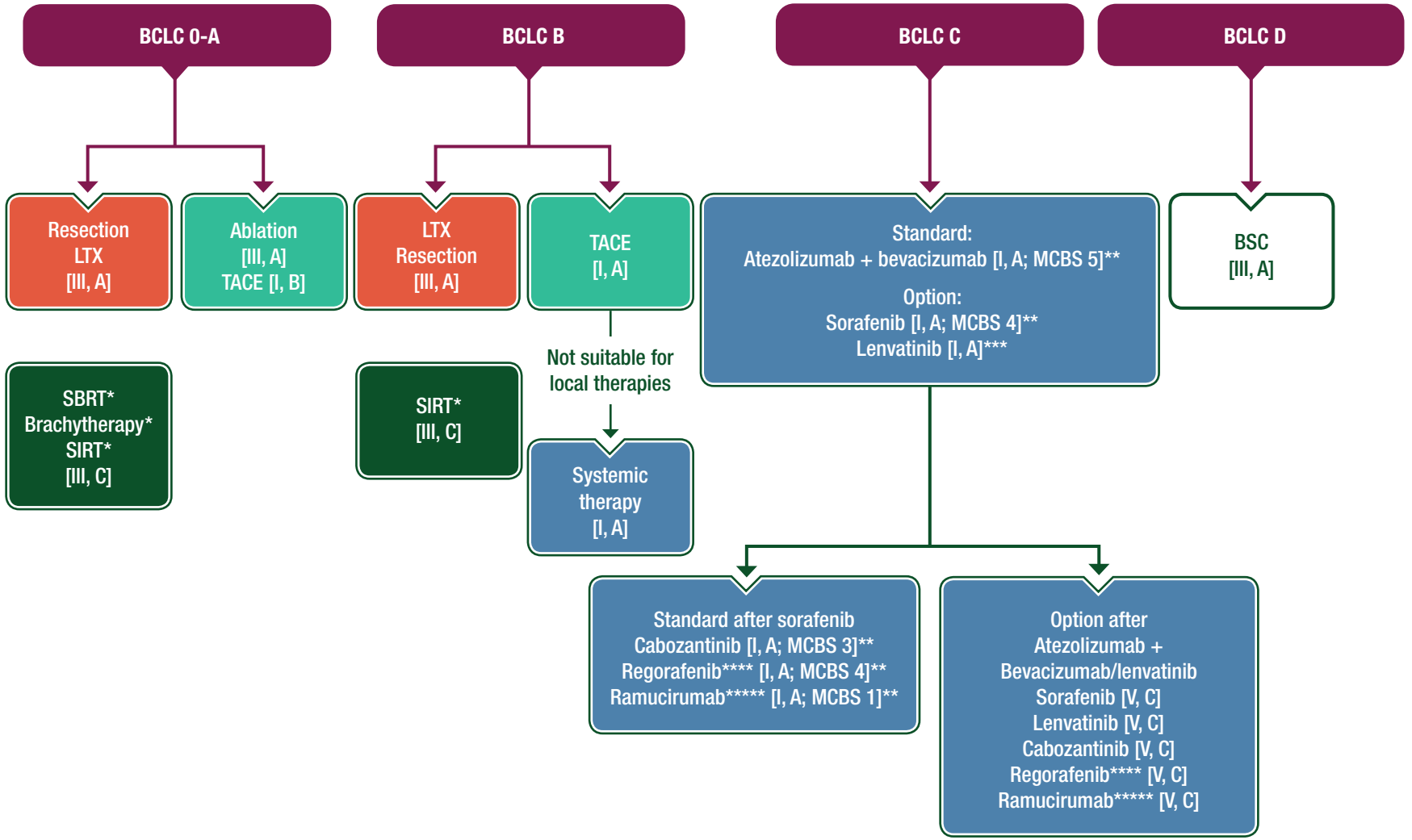
HCC Treatment options

BCLC Stages



* Non-standard, alternative treatment

** ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016

*** Non-inferiority to sorafenib established; no evaluable benefit

**** Regorafenib is not recommended in TKI-naive patients

***** Ramucirumab is only recommended in patients with an AFP level ≥ 400 ng/ml

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Management of early and intermediate HCC

Liver resection, orthotopic liver transplantation and adjuvant therapies

All patients should be discussed in an MDT tumour board (including liver and transplant surgeon)

* provided it can be carried out without causing postoperative liver failure

Summary of recommendations	
LR	• R0 LR is recommended for single tumours in patients with well-preserved liver function* • Child–Pugh A patients without significant portal hypertension are considered good candidates for minor/major LRs • Carefully selected patients with Child–Pugh B and/or portal hypertension may be candidates for minor surgical resection • Child–Pugh C patients are not suitable for surgical therapy • In cirrhosis, LR should preferably be carried out as laparoscopic resection
OLT	• Recommended for patients meeting the Milan criteria and where < 10% recurrence and 70% 5-year survival are expected, with the UCSF for patients with HCC beyond Milan criteria • When a long waiting time is anticipated, bridging resection, local ablation or TACE may be considered
Adjuvant therapies	• Adjuvant therapy outside of clinical trials is not recommended for HCC patients after OLT, LR or local ablation

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Management of early and intermediate HCC

Thermal T ablation; High conformal, HDR radioablation (SBRT; HDR brachytherapy); TACE; SIRT

All patients should be discussed in an MDT tumour board (including liver and transplant surgeon)

* who are not amenable to surgery or local ablation

Summary of recommendations	
Thermal T ablation	• First-line treatment options for very early-stage disease (BCLC 0): RFA or MWA • RFA is an alternative first-line option in early-stage HCC (up to three lesions up to 3 cm)
High conformal, HDR radioablation (SBRT; HDR brachytherapy)	• Options for tumours with a high risk of local failure after thermal ablation due to location • EBRT can be used to control pain in patients with bone metastases
TACE	• Lipiodol-based TACE prolongs OS in BCLC A to early intermediate BCLC B asymptomatic patients with maintained liver function and a small tumour burden* • Therapeutic algorithms based on prognostic scores of unknown predictive values are not recommended for candidate selection • DEB-TACE may reduce ChT side effects • The combination of TACE with systemic agents is not recommended
SIRT	• First-line SIRT is not recommended for intermediate- and advanced-stage HCC, but can be considered in exceptional circumstances

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Management of advanced disease

Systemic therapies for advanced HCC

ChT is not recommended as a standard of care

* Not eligible for, or progressing despite, locoregional therapies

** Not tested in patients with tumour burden over 50%

Targeted first-line therapies	
Sorafenib	• Is recommended for patients with advanced HCC and those with intermediate stage disease* • Is recommended for patients with well-preserved liver function and ECOG PS 0–2
Lenvatinib**	• Can be considered as a front-line systemic treatment in ECOG PS 0–1 patients with advanced HCC without main PV invasion
Targeted second-line therapies	
Regorafenib	• For patients with advanced HCC who have tolerated sorafenib but progressed • Recommended for patients with well-preserved liver function and ECOG PS 0–1
Cabozantinib	• Can be considered for patients with PD on one or two systemic therapies with well-preserved liver function and ECOG PS 0–1
Ramucirumab	• Can be considered as second-line treatment for patients with baseline AFP ≥ 400 ng/mL, well-preserved liver function and ECOG PS 0–1
Immunotherapies	• Atezolizumab + bevacizumab, nivolumab (first-line) and pembrolizumab (second-line) have been evaluated for patients with irresectable hepatoma. In view of the positive results of the atezolizumab + bevacizumab combination, the regimen has been approved by the EMA and the FDA

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Response assessment by RECIST v1.1 and mRECIST for HCC

	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoural arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions (lymph nodes of 1.5 cm diameter), taking as reference the smallest sum of the diameters of target lesions recorded since treatment started Development of new ascites	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions (lymph nodes of 2 cm diameter), taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started Development of new ascites with positive cytology

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Follow-up, long-term implications and survivorship

Summary of recommendations
Viable tumour must be assessed using dynamic CT or MRI studies
mRECIST are recommended for the assessment of response/progression to locoregional therapies
Patients undergoing resection or RFA should have, during the first year: • 3-monthly clinical evaluation of liver decompensation • dynamic CT or MRI 6-monthly surveillance thereafter
Patients with more advanced stages of HCC, receiving TACE or systemic agents, should have: • 3-monthly clinical evaluation of liver decompensation • dynamic CT or MRI to guide treatment

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This slide set provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of hepatocellular carcinoma. Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up.

The ESMO CPGs are intended to provide you with a set of recommendations for the best standards of care, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

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