CLINICAL PRACTICE GUIDELINES: PARADIGMS IN MANAGEMENT OF HCC

EASL-EORTC Guidelines

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Levels of Evidence

Strength of evidence			
according to study design		according to end-points	
1	RCTs or meta-analysis of RCTs	A	Total mortality (or OS from a defined time)
2	Non-randomized CT or subset analysis of RCTs	B	Cause-specific mortality
3	Case series (prospective or retrospective studies) • Population based, consecutive series • Consecutive cases (not pop.-based) • Non-consecutive cases	C	Carefully assessed quality of life
		D	Indirect surrogates * • Event-free survival • Disease-free survival • Progression-free survival • Tumor response rate

National Cancer Institute: PDQÒ Levels of Evidence for Adult and Paediatric Cancer Treatment Studies.

Grading of Evidence and Recommendations

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	2

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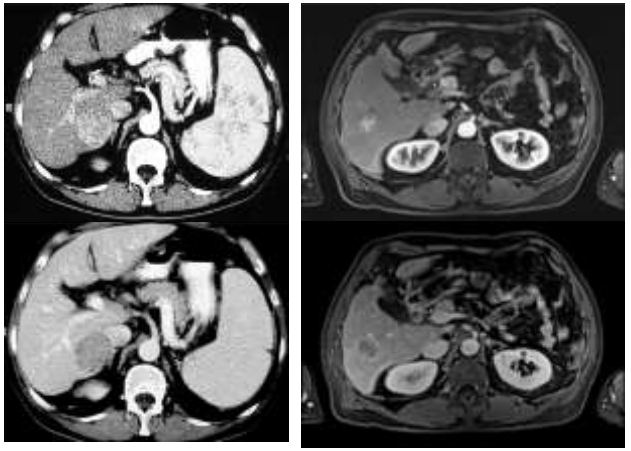
HCC Surveillance
recommendation 1A/B

	Evidence		Strength	
Patient population	Western	Asian	Western	Asian
Cirrhotic patients. Child-Pugh A and B.	3A		B1	
Cirrhotic patients. Child-Pugh C awaiting LT.	3D		B1	
Non-cirrhotic HBV carriers with active hepatitis or family history of HCC	3D	**1B**	C1	**A1**
Non-cirrhotic patients with chronic hepatitis C and liver fibrosis F3	3D	3D	B2	B1

Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months (evidence 2D; recommendation 1B)

Non-Invasive Criteria for Diagnosis

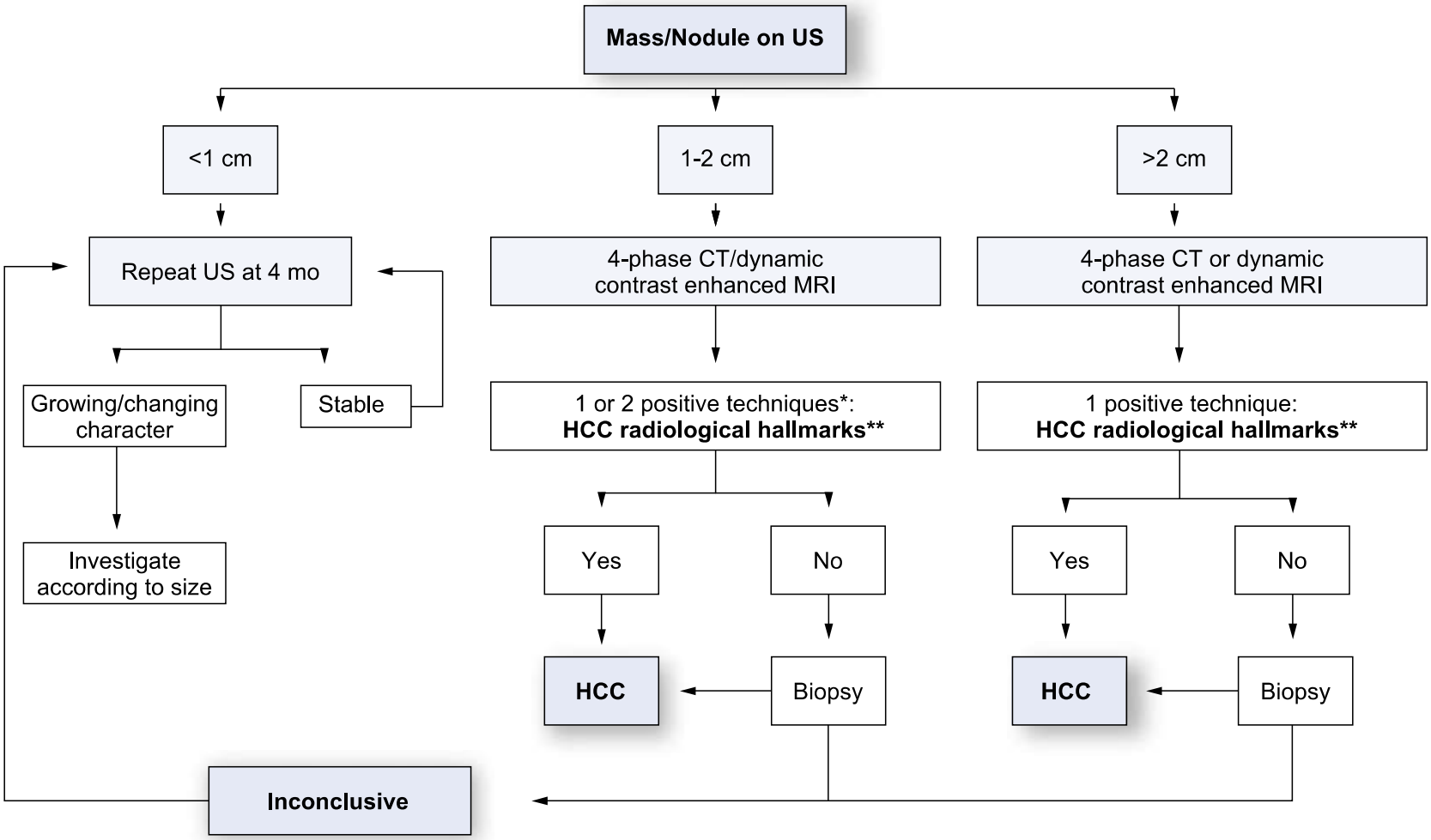
- can only be applied to **cirrhotic** patients
- 4-phase multidetector **CT or** dynamic contrast-enhanced **MRI**
- identification of the typical hallmark of HCC (**hypervascular** in the arterial phase with **washout** in the portal venous or delayed phases).



CT MRI

- 1 technique required for nodules >1 cm (evidence 2D; recommendation 2B)
- 2 techniques in suboptimal settings
- CEUS and angiography are controversial.
- PET is not accurate

Diagnostic Algorithm and Recall Policy



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Treatment Guidelines for HCC

AASLD PRACTICE GUIDELINE

Management of Hepatocellular Carcinoma: An Update

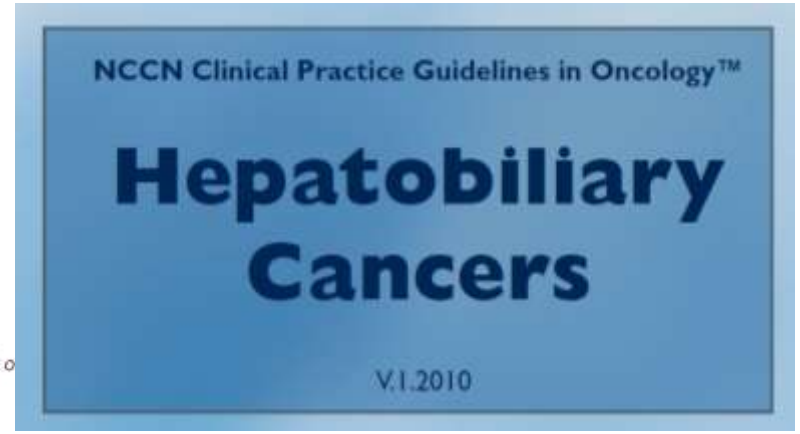
Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

GUIDELINES

Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma

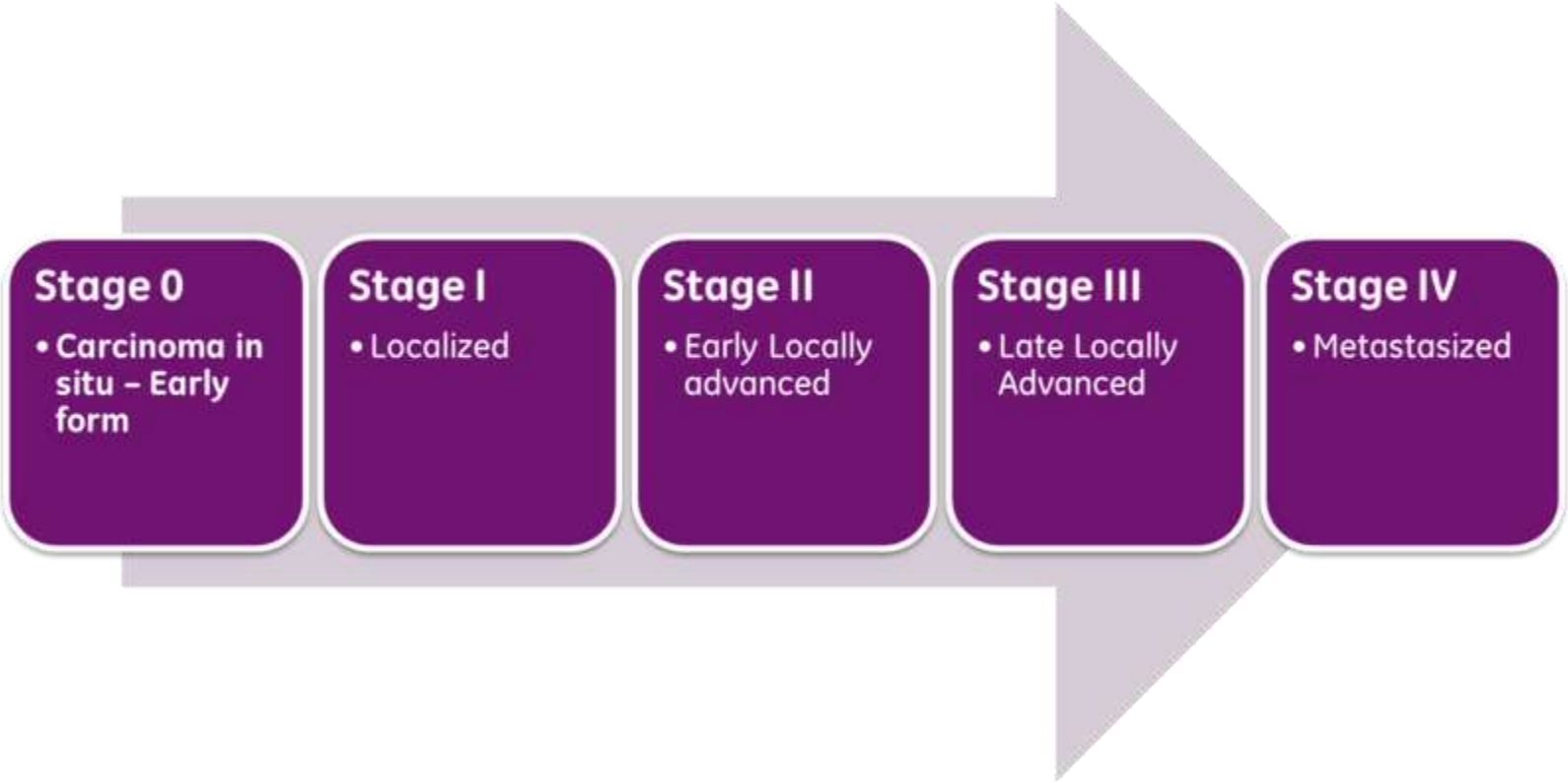


clinical practice guidelines

Annals o

Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Cancer Staging



Define subgroups of patients in order to:

- Establish prognosis (natural history of the disease)
- Select the best treatment option

Scoring and Staging Systems for HCC





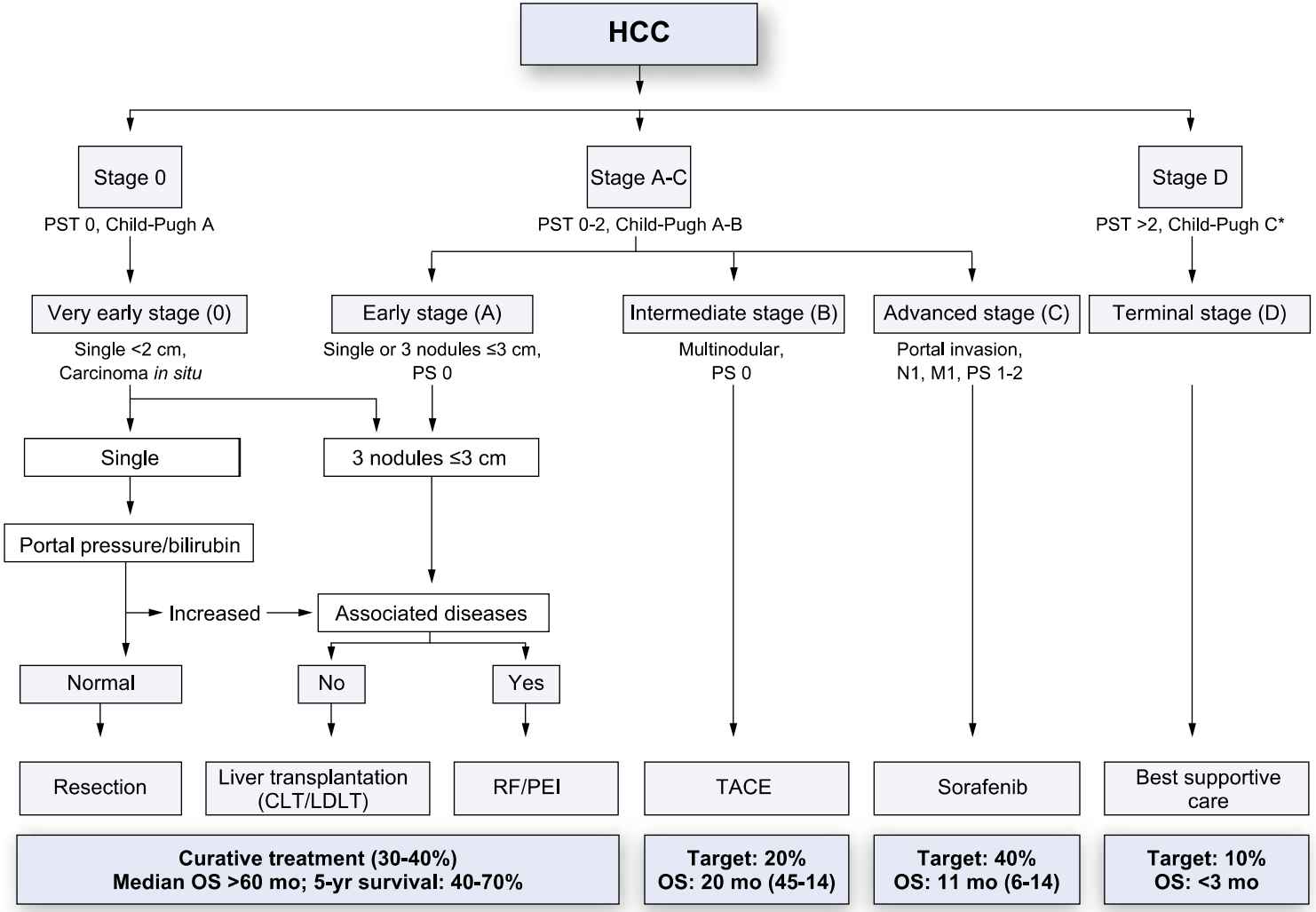

	Tumor Burden	Liver Function	Health Status
French	PVI, AFP	Bili, Alk Ph	Karnofsky Index
CLIP	PVI, AFP, >50% Inv	Child-Pugh	
CUPI	TNM, AFP	Bili, Alk Ph, Ascites	Symptoms
JIS	TNM	Child/Pugh	
Okuda	>50% Inv	Bili, Albumin, Ascites	
TNM	Size&Nod, VI, Mets	Fibrosis	
BCLC	Size&Nod, PVI, Mets, Okuda	Child-Pugh	ECOG PS

PVI: portal vein invasion, AFP: alpha-fetoprotein, VI: vascular invasion

Staging of HCC

- **BCLC is recommended** for prognostic prediction and treatment allocation (**evidence 2A; recommendation 1B**).
- Specific considerations for special subpopulations (**liver transplantation**) should be incorporated.
- Calls for **refinement of BCLC class C** by clinical or biomarker tools.
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice.

BCLC Staging System



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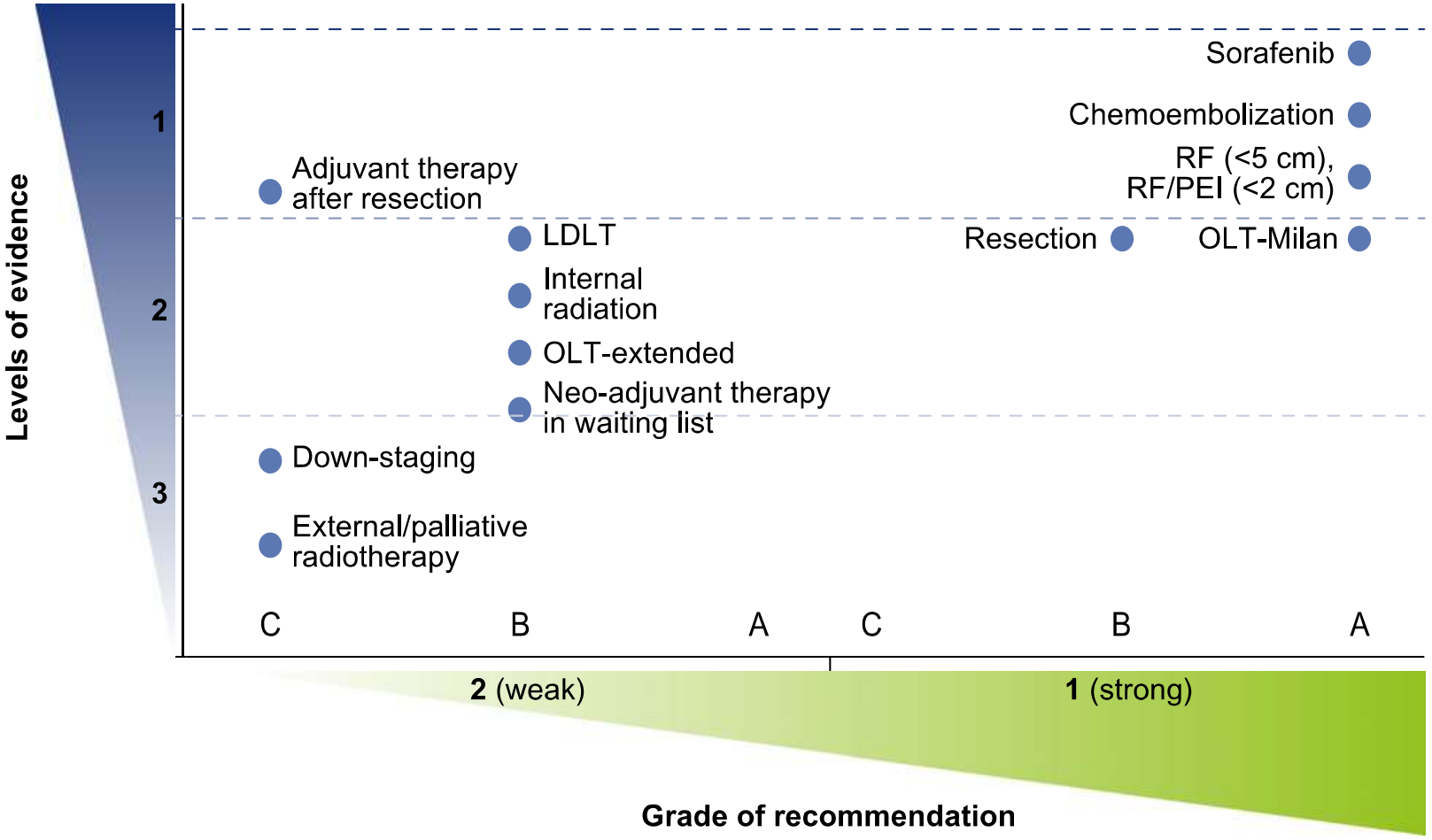
the strength of evidence for most interventions in HCC is far behind the most prevalent cancers worldwide



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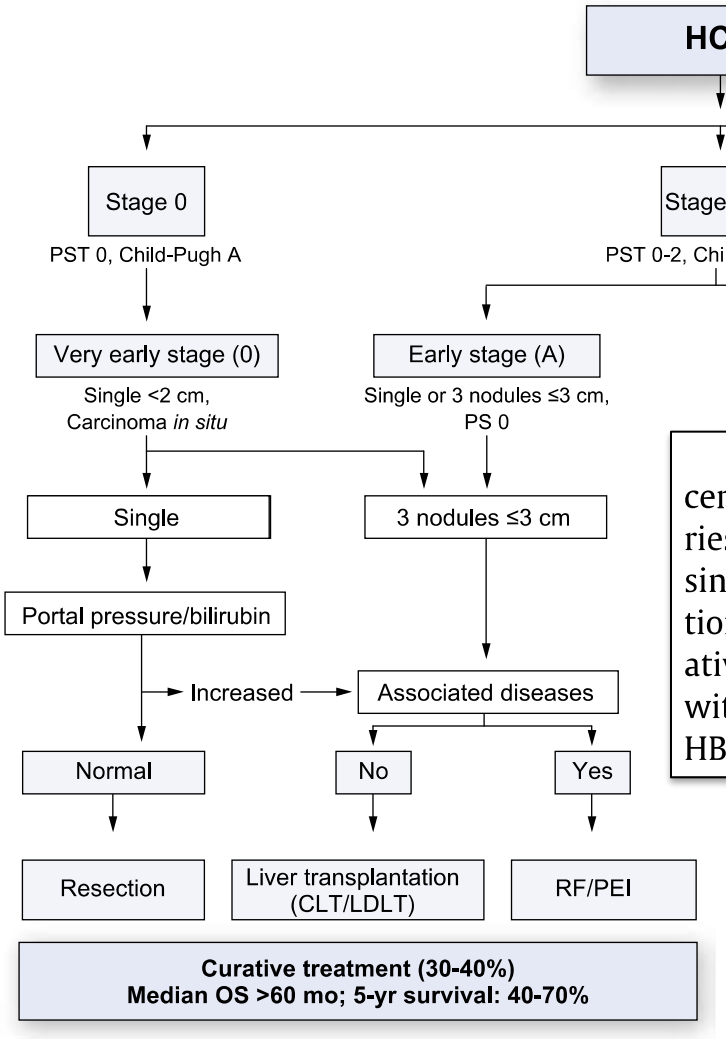
Resection

	EASL-EORTC	NCCN	APASL
Tumor Burden	Solitary tumors	Suitable tumor location	Solitary or multifocal
Liver Function	Normal bilirubin	Child A	Satisfactory
Others	Platelets ≥100,000 or HVPG ≤10 mmHg	No portal hypertension suitable liver remnant • 20% if non-cirrhotic • 30-40% if Child A	Anatomically resectable
Evidence	2A, 1B		2b, B

- Additional indications for patients with multifocal tumors meeting **Milan criteria** (≤3 nodules ≤3 cm) or with **mild portal hypertension** not suitable for liver transplantation require **prospective comparisons with loco-regional treatments** (evidence 3A; recommendation 2C)

Early Stages 0 and A



Tumor status is defined by size of the main nodule and multicentricity (single 2–5 cm, 3 nodules $\leqslant$3 cm), each of these categories showing significantly different outcomes. As discussed below, single tumors beyond 5 cm are still considered for surgical resection as first option, because if modern MRI is applied in pre-operative staging, the fact that solitary large tumors remain single and with no macrovascular involvement – which might be common in HBV-related HCC – reflects a more benign biological behavior.

Transplantation

	EASL-EORTC	NCCN	APASL
Tumor Burden	Milan	Milan	Milan
Liver Function			Child-Pugh C
Others	Not suitable for resection		
Evidence	2A, 1A		2b, B

- Extension of tumor limit criteria has not been established.
- Modest expansion applying the **"up-to-seven" requires prospective validation** (evidence 2B; recommendation 2B)

Percutaneous Ablation

	EASL-EORTC	NCCN	APASL
Tumor Burden	BCLC 0 or A	Optimal≤ 3 cm TACE+ablation for Tumors 3-5 cm	Milan
Liver Function			Child-Pugh A-B
Others	Not suitable for resection Uncertain if it can be considered an alternative to resection for tumors ≤ 2 cm		Acceptable alternative to resection for small HCC (<3 cm) in Child A cirrhosis.
Evidence	2A, 1B		2b, B

- Other ablative therapies, such as **microwave or cryoablation, still under investigation**
- Ethanol injection is recommended in cases where RFA is not technically feasible

Embolization

	EASL-EORTC	NCCN	APASL
Tumor Burden	**Multinodular asymptomatic** tumors without vascular invasion or mets (BCLC B)	**All tumors** if arterial supply may be isolated and main PVT absent	**Unresectable, large/multifocal** tumors without main PV invasion or metastasis
Liver Function	Child A or B	Child A or B	Child C
Others	Discouraged if decompensated cirrhosis or advanced liver dysfunction. Y90-RE not recommended	Relative contraindication if T Bil>3 mg/dl unless segmental TACE, bland embolization or Y90-RE	
Evidence	2A, 1B		1b, A

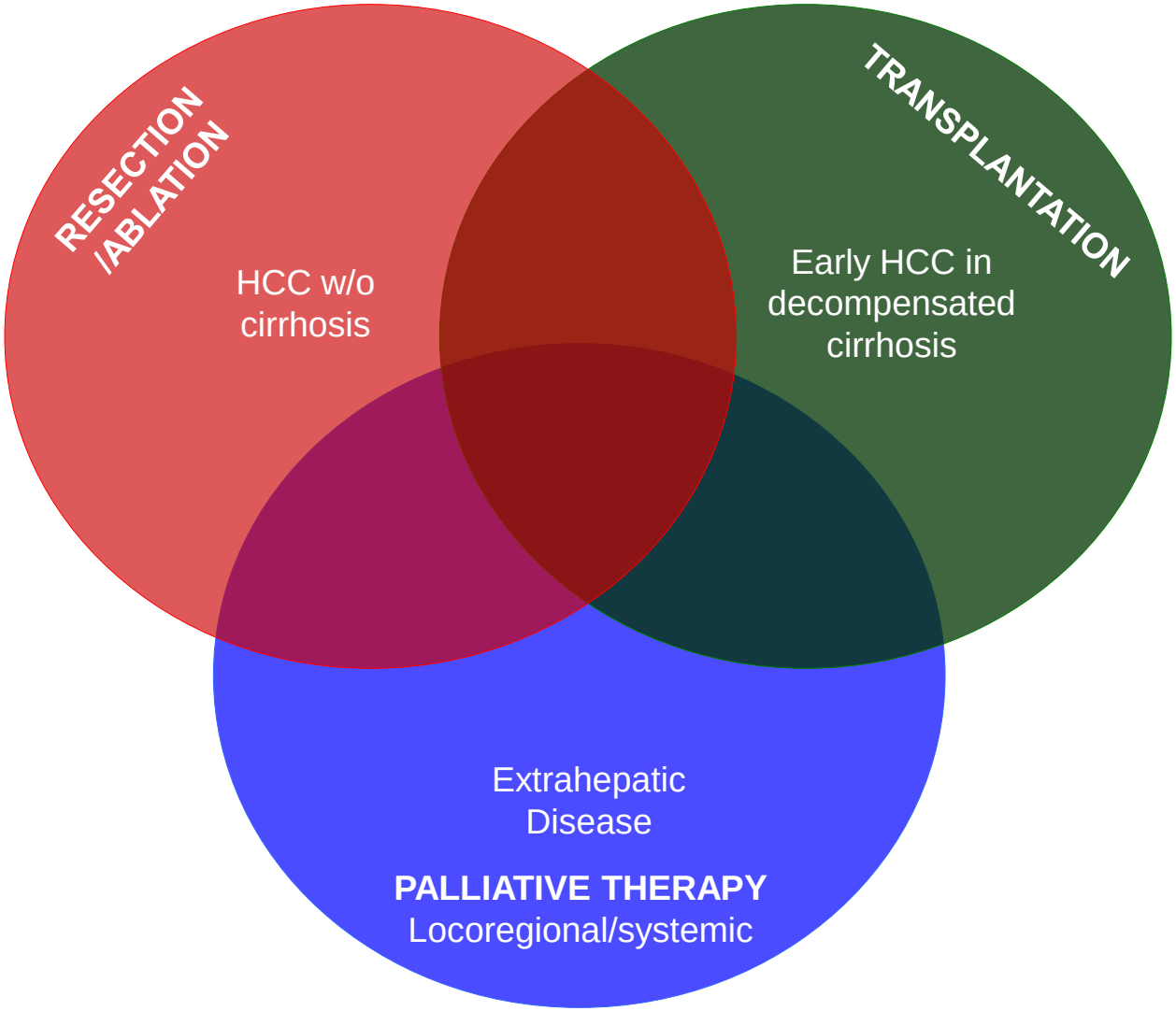
- IA chemotherapy or lipiodolization are not recommended (evidence 2A; recommendation 2B)

Systemic Therapy

	EASL-EORTC	NCCN	APASL
Tumor Burden	Advanced tumors (BCLC C) or those progressing upon loco-regional therapies	No specific indication (unresectable and untransplantable)	Advanced stage patients (PVT or mets) who are not suitable for locoregional therapy
Liver Function	Child A		Child A
Others			
Evidence	1A, 1A		2b, B

- Systemic chemotherapy, immunotherapy, anti-androgen, and herbal drugs are not recommended (evidence 1-2A; recommendation 1A/B)
- There is no available second-line treatment for patients with intolerance or failure to sorafenib. Best supportive care or the inclusion in CTs is recommended (recommendation 2B)

The Grey Areas



The Grey Areas