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Discrepancies between EASL, AASLD and APASL Guidelines

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The Major International HCC Guidelines

AASLD Heimbach JK et al. Hepatology – January 2018.

APASL Omata M et al. Hepatology International – July 2017.

EASL Galle PR et al. Journal of Hepatology – July 2018.

Differences in Concept and Focus

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	AASLD	APASL	EASL
Structure	▪ 10 key questions ▪ Recommendation(s) – Technical remarks – background – evidence and rationale – future research	▪ 5 chapters ▪ Bullet point recommendations where applicable	▪ 14 chapters ▪ Bullet point recommendations followed by detailed explanation
Length	▪ 23 pp. ▪ 98 refs.	▪ 54 pp. ▪ 605 refs.	▪ 55 pp. ▪ 636 refs.
General concept	▪ Focused on most relevant issues	▪ Overview of the available evidence with focus on Asia-Pacific	▪ Extensive overview of the available evidence

Rating of the Quality of Evidence and Strength of Recommendation

	AASLD	APASL	EASL
System	▪ GRADE	▪ GRADE	▪ GRADE
Quality of evidence	▪ High ▪ Moderate ▪ Low ▪ Very low	▪ High ▪ Moderate ▪ Low or very low	▪ High ▪ Moderate ▪ Low
Strength of recommen-dation	▪ Strong ▪ Conditional	▪ Strong ▪ Weaker	▪ Strong ▪ Weak

Prevention

	AASLD	APASL	EASL
HBV vaccination	▪ Not covered	▪ All infants	▪ All new-borns and high-risk groups
Antiviral therapy	▪ Not covered	▪ Chronic hepatitis B infection and active liver disease ▪ No explicit recommendation of DAA therapy in HCV patients	▪ Chronic hepatitis B and C
Coffee	▪ Not covered	▪ No explicit recommendation	▪ ...should be encouraged in patients with chronic liver disease

Surveillance

	AASLD	APASL	EASL
Target	▪ Adults with cirrhosis ▪ Exception: patients with Child-Pugh class C cirrhosis unless they are on the transplant waiting list	▪ High-risk groups (cirrhotic hepatitis patients and chronic HBV carriers)	▪ Patients at high risk of developing HCC ▪ Patients on the waiting list for liver transplantation
Mode	▪ Ultrasound with or without AFP every 6 months	▪ Combination of ultrasound and serum AFP measurement every 6 months	▪ Ultrasound every 6 months

Populations recommended for Surveillance

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APASL

Table 3 Groups where HCC surveillance is recommended

	HCC risk (per year)
Cirrhotic hepatitis patients	
HBV	3–5%
HCV	2–7%
NASH	2–4%
Genetic hemochromatosis	Unknown, but probably >1.5%
Primary biliary cirrhosis	2–3%
Alpha 1 antitrypsin (A1AT) deficiency	Unknown, but probably >1.5%
Autoimmune hepatitis	
Other etiologies	Unknown
Chronic HBV carriers	
Noncirrhotic (HBsAg positive)	
Asian females >50 years	0.3–0.6%
Asian males >40 years	0.4–0.6%
Africans aged >20 years	NA
History of HCC in the family	NA

Omata M et al. Hepatology International 2017.

EASL

Table 3. Recommendations for HCC surveillance: Categories of adult patients in whom surveillance is recommended.

- Cirrhotic patients, Child-Pugh stage A and B **(evidence low; recommendation strong)**
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

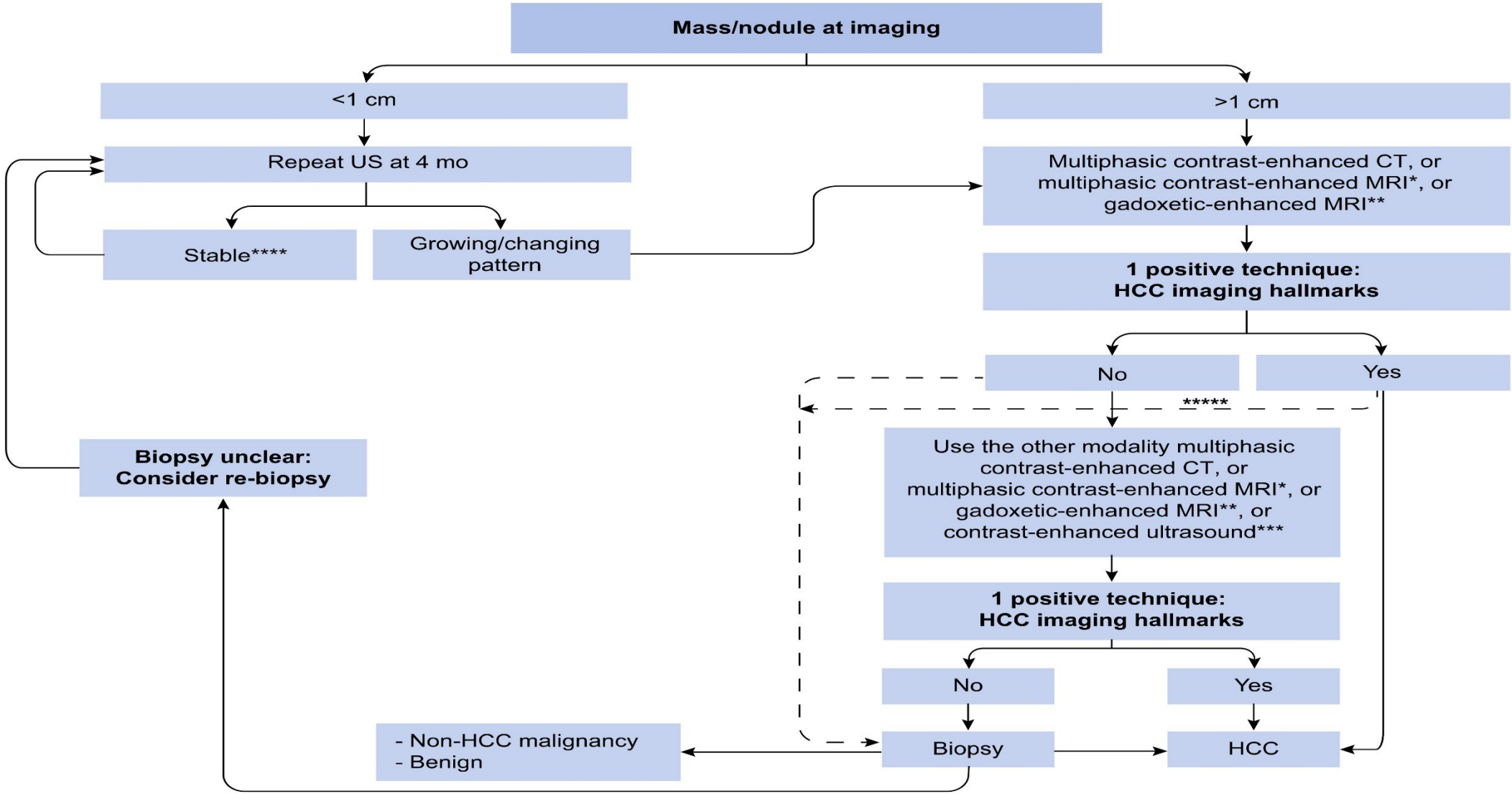
*Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at least yearly to verify progression of HCC risk.
†PAGE-B (Platelet, Age, Gender, hepatitis B) score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70 = 10), gender (M = 6, F = 0) and platelet count (≥200,000/μl = 0, 100,000–199,999/μl = 1, <100,000/μl = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years).[114]

Galle PR et al. Journal of Hepatology 2018.

Diagnosis

	AASLD	APASL	EASL
Imaging	▪ Either CT or MRI	▪ CT, MRI, or Gd-EOB-DTPA-enhanced MRI ▪ CEUS is as sensitive as CT or MRI	▪ First choice: CT or MRI ▪ CT, MRI or CEUS sufficient for nodules ≥1 cm in cirrhotic patients
Indeterminate nodules	▪ Follow-up imaging, alternative imaging modality, alternative contrast agent, or biopsy – no preference	▪ Further examination	▪ Use other imaging modality ▪ If still negative -> biopsy
Biopsy	▪ Against routine biopsy of every indeterminate nodule	▪ For indeterminate nodules ≥1 cm	▪ Cirrhotic patients: Optional ▪ Non-cirrhotic patients: Required for confirmation

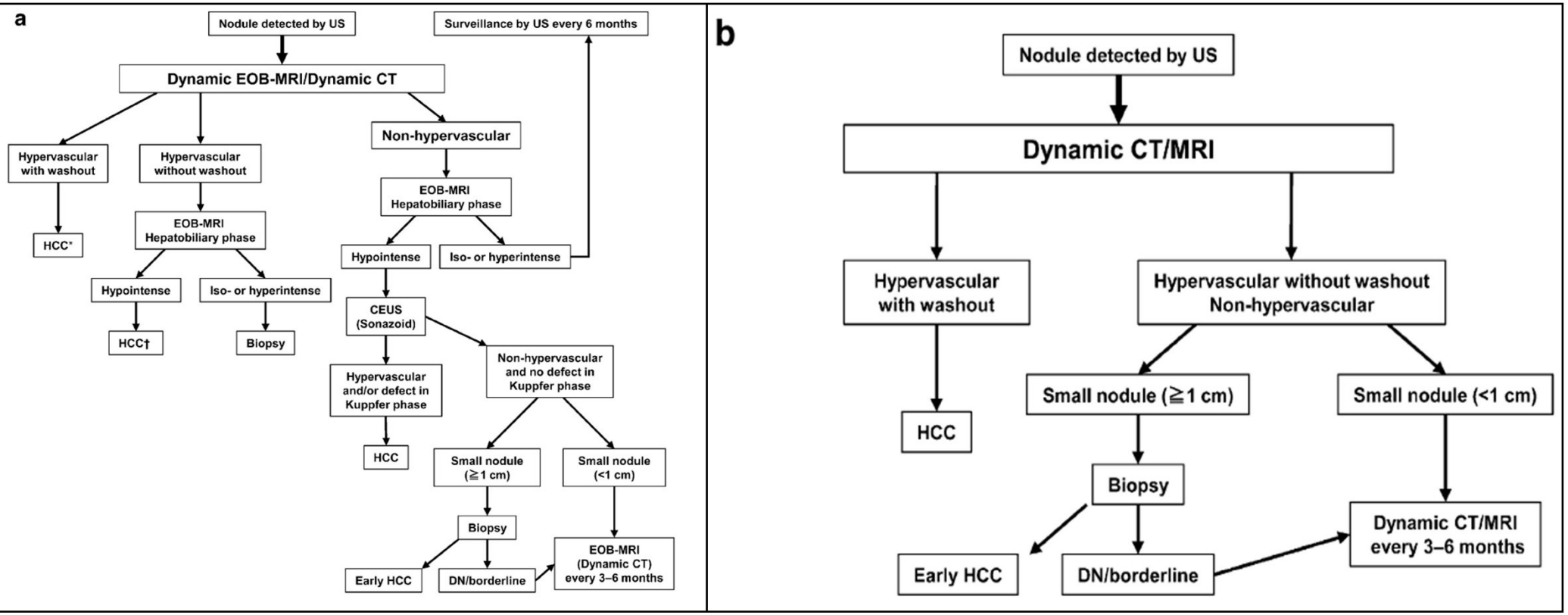
Diagnostic Algorithm by EASL



Galle PR et al. Journal of Hepatology 2018.

Diagnostic Algorithm by APASL

Fig. 1 Diagnostic algorithm for hepatocellular carcinoma using multiple modalities (**a**) and only dynamic CT/MRI (**b**) (APASL 2016). *Cavernous hemangioma sometimes shows hypointensity on the equilibrium (transitional) phase of dynamic Gd-EOB-DTPA MRI (pseudo-wash-out). It should be excluded by further MRI sequences and/or other imaging modalities. †Cavernous hemangioma usually shows hypointensity on the hepatobiliary phase of Gd-EOB-DTPA MRI. It should be excluded by other MRI sequences and/or other imaging modalities



Omata M et al. Hepatology International 2017.

Treatment – liver resection

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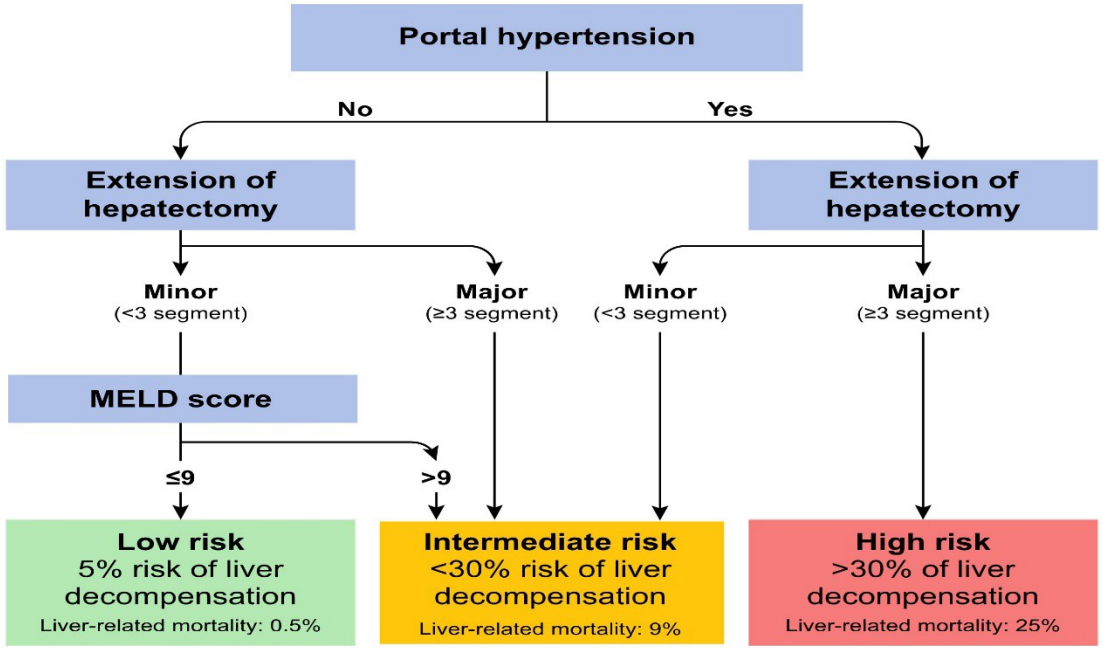
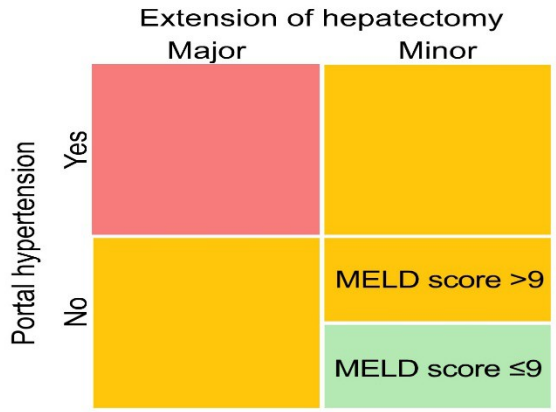
	AASLD	APASL	EASL
Liver resection	▪ Adults with Child-Pugh class A cirrhosis and resectable T1 or T2 HCC should undergo resection over radiofrequency ablation	▪ First-line curative treatment for Child–Pugh class A patients when resectability is given (including BCLC B and C)	▪ Treatment of choice in non-cirrhotic patients ▪ For single HCC of any size and for tumours >2 cm if feasible
Adjuvant treatment	▪ Not recommended	▪ Not recommended	▪ Not recommended

EASL Assessment of the Risk of Liver Decompensation after Resection in Cirrhosis





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Treatment – Liver Transplantation

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	AASLD	APASL	EASL
Liver transplantation	▪ Recommended for OPTN 1 and 2 (Milan) ▪ Observation with follow-up imaging over treatment for patients with cirrhosis awaiting liver transplantation who develop T1 HCC	▪ Best curative treatment for all HCC patients ▪ Recommended as first-line treatment for Child–Pugh class B and C patients	▪ Recommended as the first-line option for HCC within Milan criteria but unsuitable for resection ▪ Contraindications: Macrovascular invasion and extrahepatic metastases
Bridging	▪ Recommended for patients within OPTN T2 (Milan) ▪ No recommendation regarding modality	▪ No recommendation	▪ Recommended if feasible
Down-staging	▪ Patients beyond the Milan criteria should be considered for LT after successful downstaging	▪ TACE recommended as first-line therapy	▪ Patients beyond the Milan criteria can be considered for LT after successful downstaging

Treatment – Ablation & PEI

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	AASLD	APASL	EASL
Ablation	▪ LRT is recommended over no treatment in cirrhotic HCC patients (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation	▪ Recommended for Child–Pugh class A or B patients with ≤3 tumours, each ≤3 cm as an alternative to resection ▪ First-line treatment for HCCs ≤2 cm in Child–Pugh class A or B cirrhosis	▪ Standard of care for unresectable BCLC 0 and A tumours ▪ Alternative to resection in single tumours 2 to 3 cm in size ▪ Potential first-line therapy in BCLC-0 in favourable locations even in surgical patients
Ethanol injection	▪ The AASLD does not recommend one form of LRT over another	▪ Treatment of choice when RFA cannot be performed safely	▪ An option in some cases where ablation is not technically feasible, especially in tumours <2 cm

Treatment – TACE

	AASLD	APASL	EASL
TACE	▪ LRT is recommended over no treatment in cirrhotic HCC patients (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation ▪ The AASLD does not recommend one form of LRT over another	▪ First-line treatment for unresectable, large/multifocal HCCs with no vascular invasion or extrahepatic spread ▪ Selective TACE for patients with small tumors where ablation is difficult ▪ Drug-eluting beads have similar efficacy but less AEs than cTACE ▪ Change treatment strategy for HCC patients who are not suitable for or do not response to repeated TACE	▪ For BCLC B HCCs without hepatic decompensation, advanced kidney failure, macroscopic vascular invasion or extrahepatic spread ▪ Should be carried out in a selective manner ▪ Either with drug-eluting beads or as cTACE ▪ Insufficient evidence for bland embolisation, selective intraarterial chemotherapy or lipiodolisation ▪ Insufficient evidence for scores that help selecting candidates for first/subsequent TACE

Treatment – SIRT & Radiotherapy

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	AASLD	APASL	EASL
SIRT	▪ LRT is recommended over no treatment in cirrhotic HCC patients (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation	▪ Alternative treatment for unresectable HCC	▪ Good safety profile and local tumour control but no overall survival benefit ▪ The subgroup of patients benefitting from SIRT needs to be defined
Radio-therapy	▪ The AASLD does not recommend one form of LRT over another	▪ Reasonable option for patients who have failed other local therapies ▪ May be considered for symptomatic bone metastases	▪ No robust evidence to support this approach for HCC

Treatment - Sorafenib

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	AASLD	APASL	EASL
Sorafenib	▪ Recommended use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child- Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease	▪ First-line treatment for advanced HCCs (macrovascular invasion or extrahepatic metastasis) which are not suitable for locoregional therapy and in patients with Child–Pugh class A liver function ▪ May be used with caution in patients with Child–Pugh class B liver function	▪ Standard first-line systemic therapy for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies ▪ No clinical or molecular biomarkers for predicting the response to first or second-line systemic treatments

Treatment – Lenvatinib

	AASLD	APASL	EASL
Lenvatinib	▪ Recommended use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child- Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease	▪ No recommendation	▪ Non-inferior to sorafenib ▪ Recommended as first-line therapy in patients with well-preserved liver function (Child-Pugh class A), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or tumours progressing upon or unsuitable for loco-regional therapies

Treatment – other Systemic Agents

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	AASLD	APASL	EASL
Regora-fenib	▪ Recommended use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child- Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease	▪ No recommendation	▪ Recommended as second-line treatment for patients progressing on sorafenib and with Child-Pugh class A liver function and good performance status
Cabozan-tinib		▪ No recommendation	▪ Cabozantinib has shown survival benefits vs. placebo as second-line
Nivolumab		▪ No recommendation	▪ The data are not mature enough to give a clear recommendation

Treatment Algorithm by EASL

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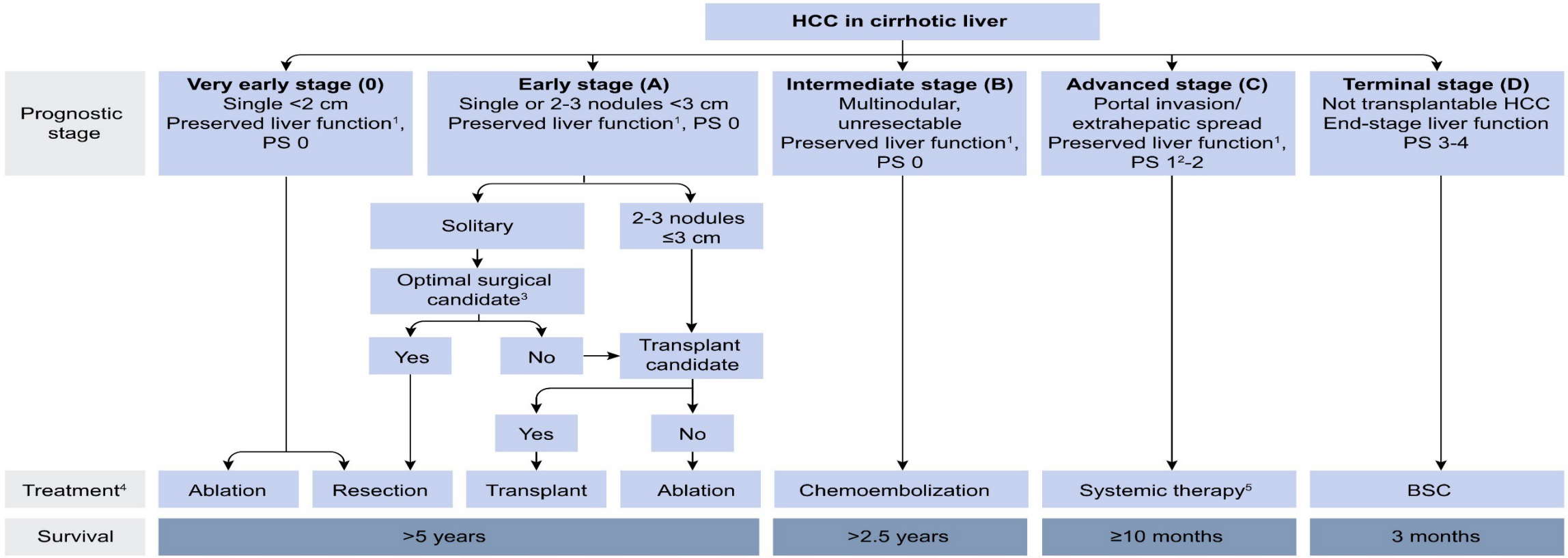
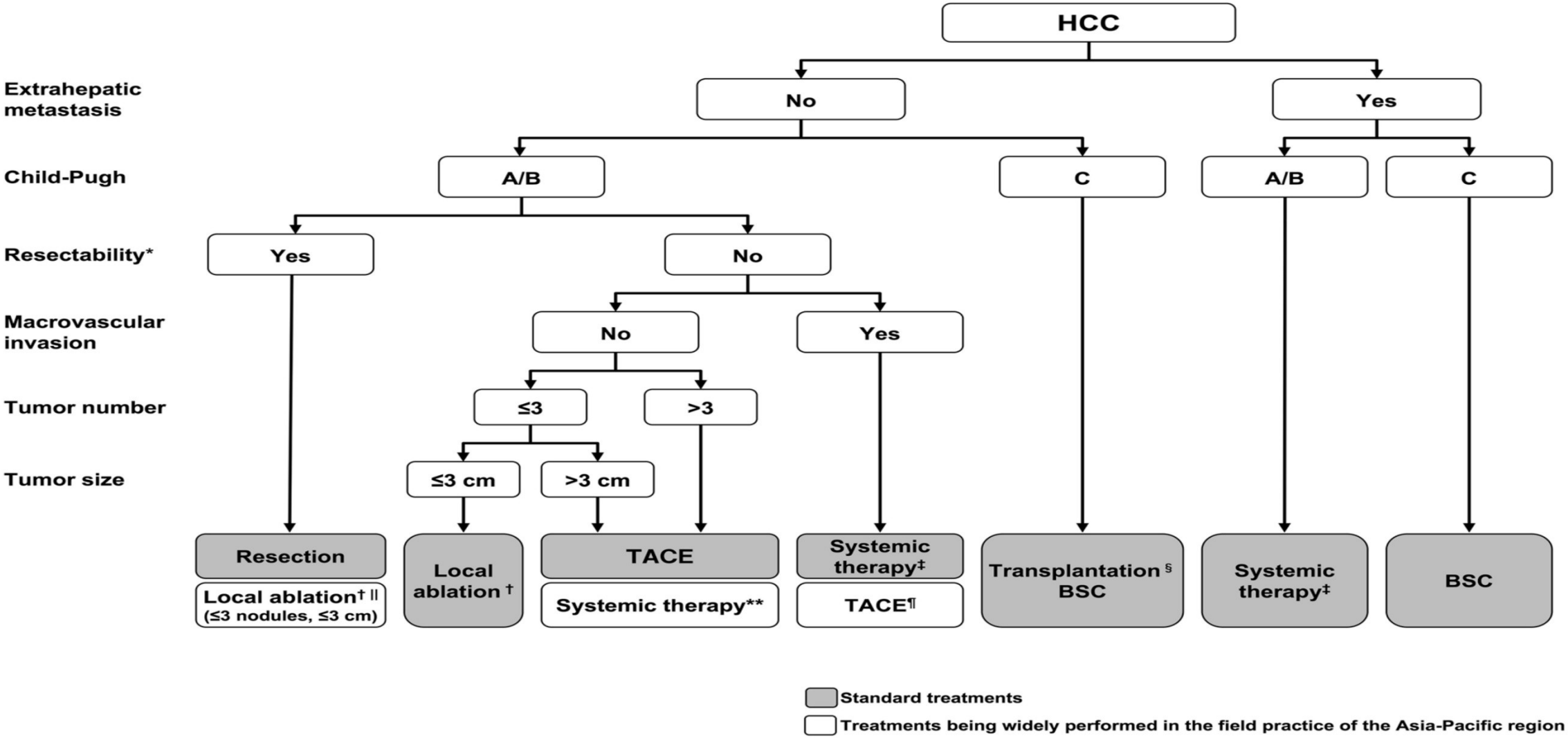


Galle PR et al. Journal of Hepatology 2018.

Treatment Algorithm by APASL



Omata M et al. Hepatology International 2017.

EASL Recommendations for the Treatment of HCC

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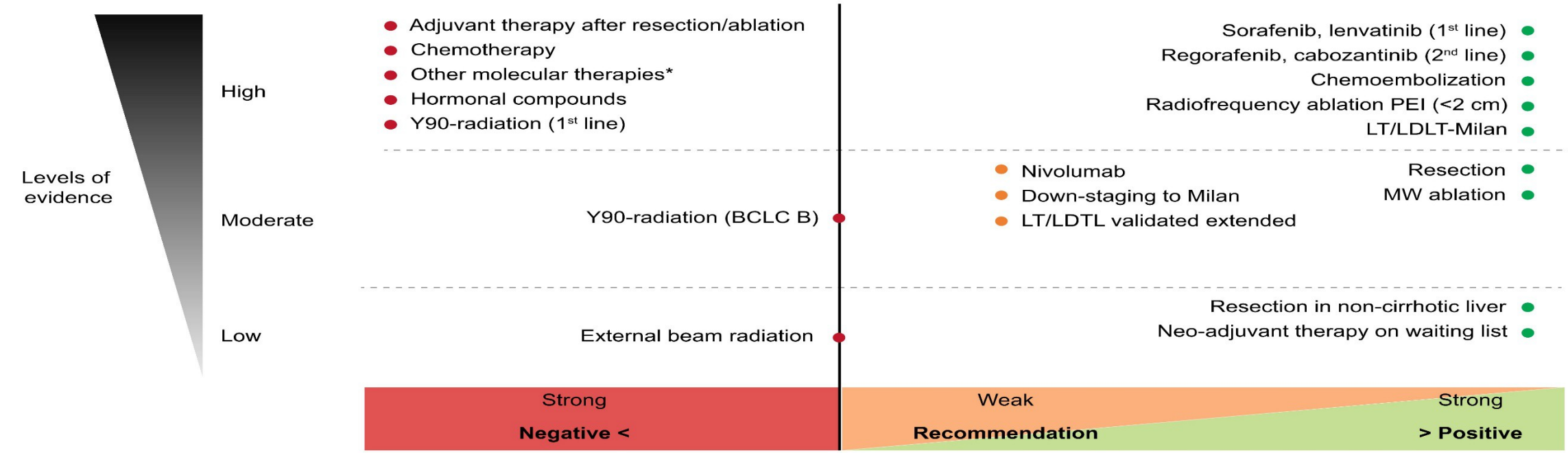

- *Other molecular therapies (sunitinib, linifanib, brivanib, tivantinig, erlotinib, everolimus, ramucirumab)
- Weak recommendation: more evidence needed

Galle PR et al. Journal of Hepatology 2018.

Additional Themes covered by EASL

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Response assessment

- Based on multiphasic CT / MRI
- mRECIST for loco-regional therapies
- Both mRECIST and RECIST1.1 for systemic therapies
- Serum biomarkers are under investigation

Best supportive care

- Acetaminophen (paracetamol) up to 3 g/day, NSAID should be avoided
- Opioids can be utilised, caution with psychoactive drugs / benzodiazepines
- Palliative radiotherapy for bone metastases
- Psycho-oncological support and adequate nutrition is recommended

Trial design

- Primary endpoints:
  - OS for loco-regional and systemic therapies
  - RFS or TTP for adjuvant therapies
  - OS, cancer-related deaths and waiting list drop-out rates for neoadjuvant treatments
  - No suitable surrogate endpoints for OS (exception: ORR and complete response by mRECIST for thermal ablation and TACE)
- BCLC staging system, Child-Pugh class and ECOG for patient selection
- Stratification for prognostic factors prior to randomisation
- Standard of care / placebo as control arm
- Upfront liver biopsy and blood sampling is recommended

Summary

	AASLD	APASL	EASL
Surveillance	▪ US +/- AFP every 6 months	▪ US + AFP every 6 months	▪ US every 6 months
CEUS	▪ Not recommended	▪ CEUS as sensitive as CT / MRI	▪ CEUS for nodules ≥1 cm in cirrhosis
Biopsy	▪ No routine use	▪ For indeterminate nodules ≥1 cm	▪ Required in noncirrhotic HCC
Bridging	▪ Recommended for T2	▪ No recommendation	▪ Recommended if feasible
LT after downstaging	▪ Recommended	▪ No recommendation	▪ Possible
LRT	▪ Recommended in cirrhotic non-surgical patients (T2 or T3, no vascular involvement) ▪ No preference re. modality	▪ Ablation: For HCCs ≤2 cm in CP-A/-B ▪ TACE: For unresectable, large/multifocal HCCs ▪ SIRT: Alternative	▪ Ablation: For unresectable BCLC 0 and A + selected surgical patients ▪ TACE: For BCLC B

Summary continued

	AASLD	APASL	EASL
Systemic therapy	▪ For patients with CP-A cirrhosis or well-selected patients with CP-B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease ▪ No preference re. drug	▪ Sorafenib for advanced HCC with CP-A liver function (possible with caution in CP-B)	▪ Sorafenib & Lenvatinib: 1st line for BCLC-C ▪ Treatment stage migration ▪ Regorafenib: 2nd line ▪ Cabozantinib: Benefit as 2nd line ▪ Nivolumab: No recommendation yet

- Many commonalities
- Differences in concept and focus
- A few striking differences in the management of HCC – a cause for intersocietal discussion & exchange

BACKUP

Additional points by EASL

- Treatments that failed to meet their endpoints in randomised trials are not recommended. Further clinical trials are needed to confirm claims of non-inferiority, or any trends of better outcome identified in subgroup analysis. TARE in combination with systemic therapy is under investigation.
- Patients at BCLC D stage, who are not candidates for liver transplantation should receive palliative support, including management of pain, nutrition and psychological support. In general, they should not be considered for clinical trials