Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

L'epatocarcinoma nel 2018

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- EASL – 2018 HCC Guidelines

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

European Association for the Study of the Liver*

Summary

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem. The following Clinical Practice Guidelines will give up-to-date advice for the clinical management of patients with hepatocellular carcinoma, as well as providing an in-depth review of all the relevant data leading to the conclusions herein.

Introduction

In 2012, the previous guidelines for the management of hepatocellular carcinoma (HCC) were published as a result of a joint effort by the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC).[1] Since then several clinical and scientific advances have been achieved. Thus, an updated version of the document is needed.

Objectives of the guideline

These EASL Clinical Practice Guidelines (CPGs) are the current update to the previous EASL-EORTC CPGs.[1] These EASL CPGs define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with HCC.

The purpose of this document is to assist physicians, patients, healthcare providers and health-policy makers from Europe and worldwide in the decision making process, based on the currently available evidence. Users of these guidelines should be aware that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available. Thus, they should adapt the recommendations to their local regulations and/or team capacities, infrastructure and cost-benefit strategies. Finally, this document sets out some recommendations that should be instrumental to advancing the research and knowledge of this disease, and ultimately contributing to improved patient care.

Methodology

Composition of the guidelines group

The guideline development group (GDG) of this guideline project is composed of international experts in the field of HCC, comprising the areas of hepatology (PRC, AF, JL, FP), surgery (VM), radiology (VV), oncology (JJR) and pathology (PS). Initially, the EASL governing board nominated a chair (PRG) and a governing board member (AF) to propose a panel of experts and finally nominated the above GDG. Additionally, a guideline methodologist was appointed to support the GDG (MF).

Funding and management of conflict of interests

This guideline project has kindly been supported by EASL. The financial support did not influence the development of this guideline. Key questions to be answered and outcomes were chosen in accordance with the consensus of the expert panel. Recommendations were reached by consensus of the expert panel and based on clinical expertise and existing evidence. A declaration of conflicts of interest was required to participate in the guideline development. The ethical committee of EASL assessed the individual interests and decided that there were no substantial conflicts of interest.

Generation of recommendations

In a first step the panel identified, prioritised and selected relevant topics and agreed on key questions to be answered. These questions were clustered and distributed according to the defined working groups, which are reflected in the different chapters.

According to the key questions, a literature search was performed. The studies identified and included were assessed and assigned to categories related to study design and strength of evidence according to endpoints. Based on this evidence, the drafts for recommendation and chapters were created.

Consent was provided for all recommendations during the consensus conference, moderated by Markus Follmann, MD MPH MSc, a certified moderator for the German Association of Scientific Medical Societies (AWMF). Formal consensus

* Clinical practice guideline panel: Peter R. Galle (chair), Alejandro Forner (EASL governing board representative), Josep M. Llovet, Vincenzo Mazzaferro, Fabio Piscaglia, Jean-Luc Raoul, Peter Schirmacher, Violette Vilgrain.

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EASL The Home of Hepatology

Topics

1. **Epidemiology and risk factors**
2. **Prevention**
3. **Surveillance**
4. Diagnosis
5. Recall policy
6. **Staging**
7. Treatment: liver resection
8. **Treatment: liver transplantation**
9. Treatment: systemic therapy
10. Assessment of treatment response
11. Palliative and best supportive care

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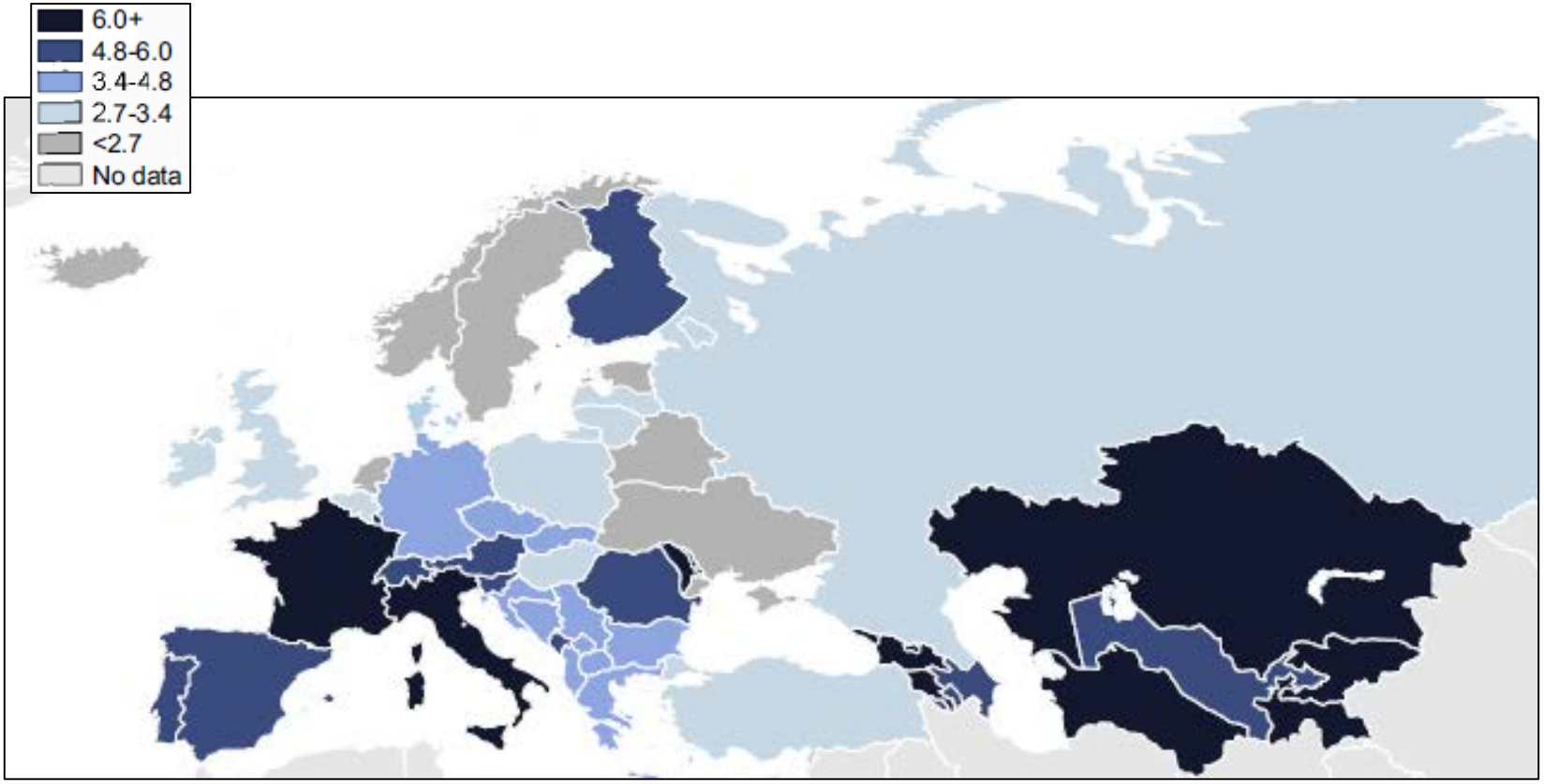
Background

- Liver cancer
  - Fifth most common cancer
  - Second most frequent cause of cancer-related death globally
    - 854,000 new cases and 810,000 deaths per year
  - 7% of all cancers
- HCC
  - Accounts for approximately 90% of primary liver cancers
  - Constitutes a major global health problem

Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91 ;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Incidence of primary liver cancer in Europe

Incidence rates per 100,000



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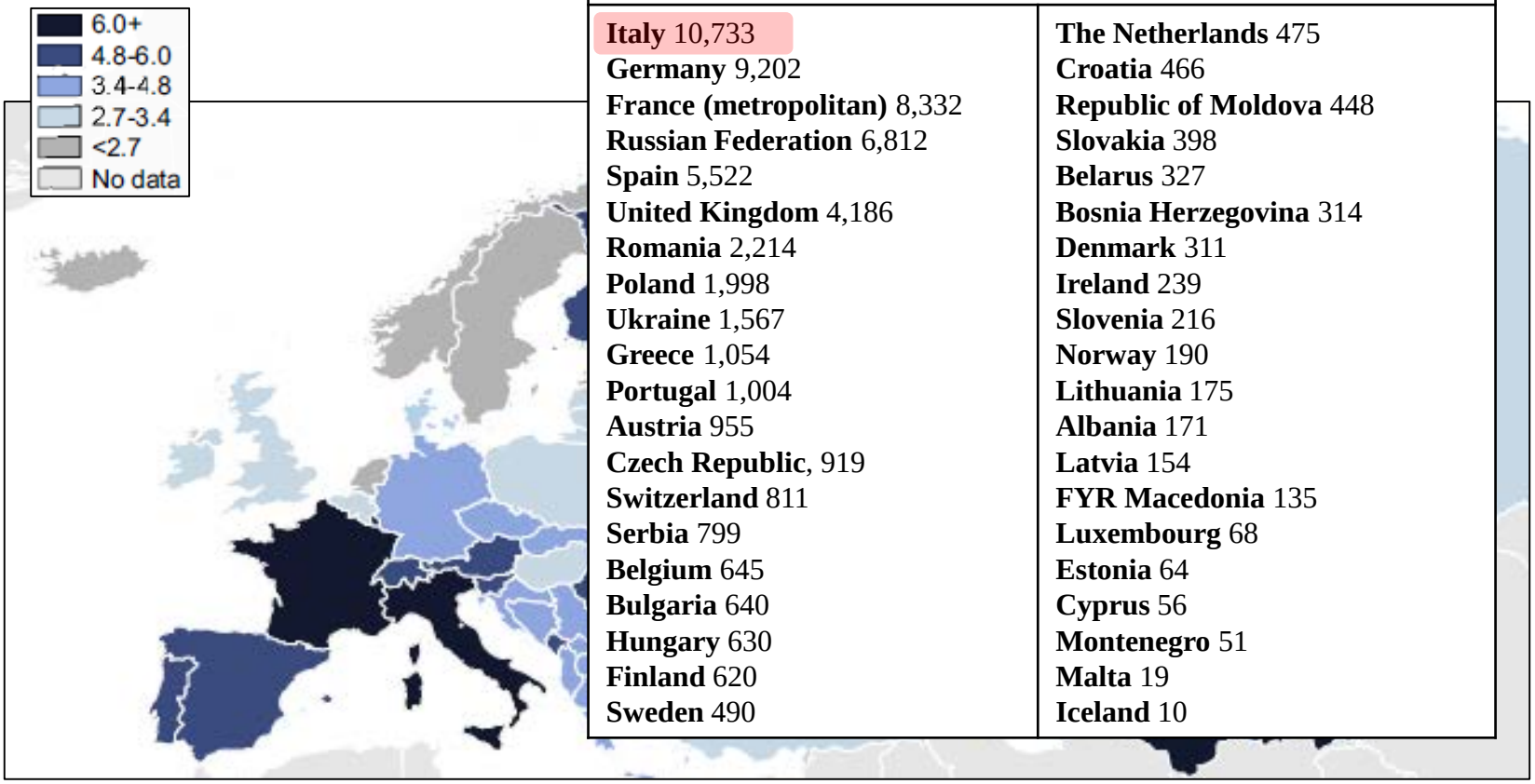

Total number per country	
Italy 10,733	**The Netherlands** 475
Germany 9,202	**Croatia** 466
France (metropolitan) 8,332	**Republic of Moldova** 448
Russian Federation 6,812	**Slovakia** 398
Spain 5,522	**Belarus** 327
United Kingdom 4,186	**Bosnia Herzegovina** 314
Romania 2,214	**Denmark** 311
Poland 1,998	**Ireland** 239
Ukraine 1,567	**Slovenia** 216
Greece 1,054	**Norway** 190
Portugal 1,004	**Lithuania** 175
Austria 955	**Albania** 171
Czech Republic, 919	**Latvia** 154
Switzerland 811	**FYR Macedonia** 135
Serbia 799	**Luxembourg** 68
Belgium 645	**Estonia** 64
Bulgaria 640	**Cyprus** 56
Hungary 630	**Montenegro** 51
Finland 620	**Malta** 19
Sweden 490	**Iceland** 10

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Main risk factors for primary liver cancer worldwide*

~90% of HCCs are of known underlying aetiology[1]

– Most frequently HCV, HBV, alcohol and aflatoxin exposure

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15		10
Eastern	53	15		8
North America	37		31	23
Andean Latin America	23		12	20
Asia				
East Asia		41	9	18
Asia-Pacific		22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

And NASH ????

*Contribution of hepatitis B, C, alcohol and other causes on absolute liver cancer deaths, both sexes, globally and by region 2015. Data refer to all primary liver cancers (HCC, intrahepatic CCA and liver cancer of mixed differentiation)

1. Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91; EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Epidemiology and risk factors

- Incidence of HCC has been rising
  - Driven by increases in chronic viral infections and lifestyle-related risk factors
- **Cirrhosis is an important risk factor for HCC**
  - Multiple causes, including viral hepatitis, chronic alcohol use, NAFLD
  - Up to 90% of HCC arises on a background of cirrhosis in the Western world[1]

Recommendations	Level of evidence	Grade of recommendation
The **incidence of HCC is increasing** both in Europe and worldwide; it is amongst the leading causes of cancer death globally	High	
Chronic liver disease should be treated to avoid progression	High	Strong

1 Forner A, et al. Lancet 2018;391:1301–1314;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Prevention

- Primary prevention of HCC can be achieved with universal vaccination against HBV
- Progression to cirrhosis and HCC can be prevented by:
  - Antiviral treatment in patients with chronic hepatitis B and C*
  - Adoption of healthy lifestyle measures

Recommendations	Level of evidence	Grade of recommendation
Vaccination against hepatitis B reduces the risk of HCC and is **recommended for all newborns and high-risk groups**	High	Strong
Governmental health agencies should **implement policies** that: • Prevent **HBV/HCV** transmission • Counteract **chronic alcohol abuse** • Promote lifestyles that prevent **obesity** and **metabolic syndrome**	Moderate	Strong
In patients with chronic hepatitis, use antiviral therapies to: • Maintain HBV suppression in chronic hepatitis B • Maintain SVR in chronic hepatitis C	High	Strong

*Level of evidence high, grade of recommendation strong

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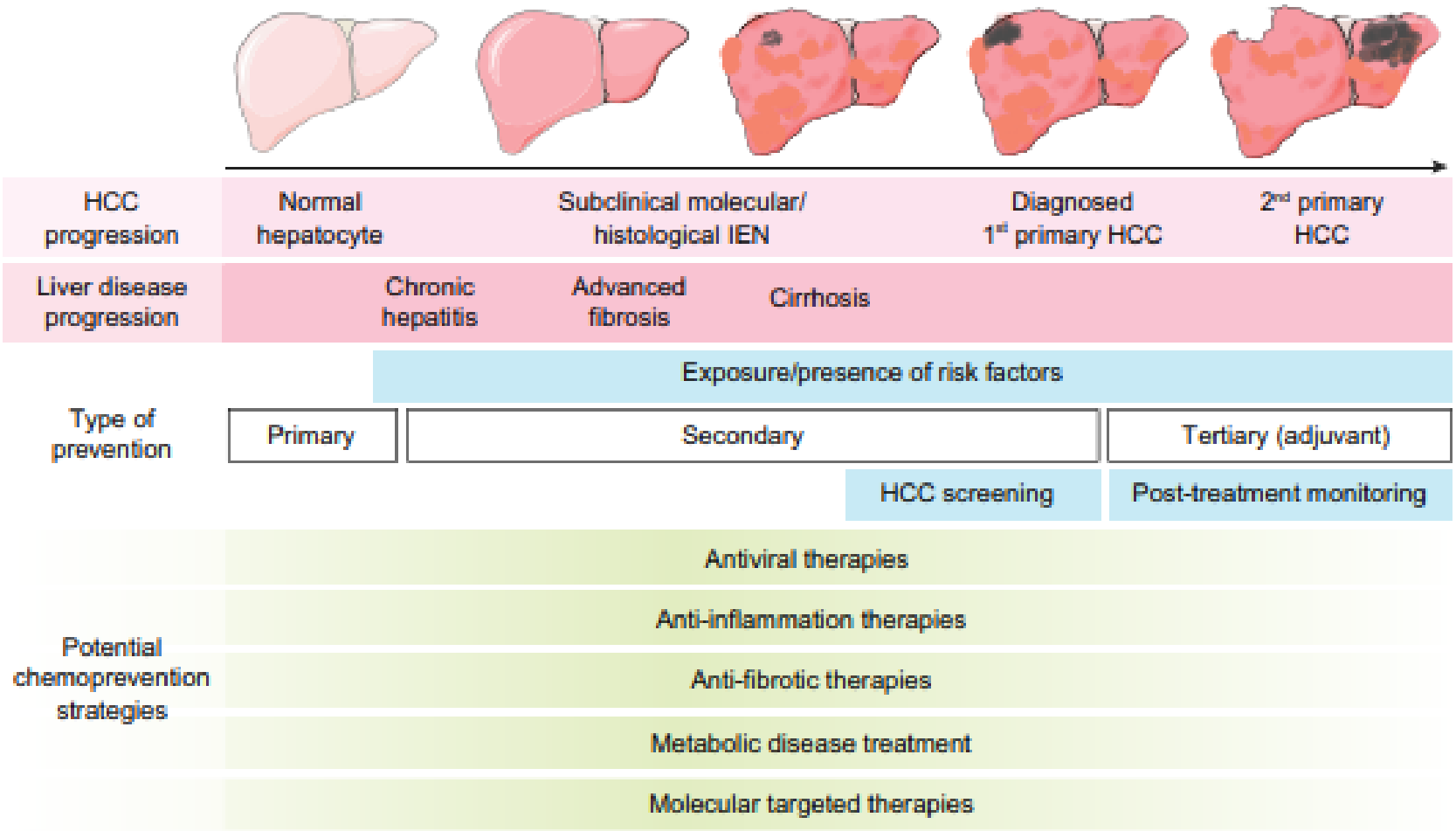
HCC preventive interventions



Fujiwara N, et al. J Hepatol 2018;68:526–49
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Role of DAAs for HCV in HCC

- Effect of DAAs on HCC in patients with cirrhosis is debated
  - Robust conclusion impeded by retrospective assessment, absence of HCC screening, short follow-up and loss to follow-up

Recommendations	Level of evidence	Grade of recommendation
Once cirrhosis is established: • **Antiviral therapy*** is beneficial in **preventing cirrhosis progression** and decompensation • Successful **antiviral therapy reduces but does not eliminate** the risk of **HCC** development	Moderate	
For patients with HCV-associated cirrhosis and treated HCC: • **HCC recurrence rate is high** even after SVR with DAA therapy† • **Close surveillance is advised** in these patients • The benefit of viral cure must be weighed against a potentially higher recurrence risk	Low	Strong

*Antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection;
†It is unclear whether this represents the inherent risk of HCC development in advanced cirrhosis, or if DAA therapy increases recurrence rates

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Impact of coffee on HCC development

- Numerous epidemiological studies have addressed the prevention
  of HCC in patients with chronic liver disease
  - Trials analyzing the effect of coffee consumption have shown a consistently positive effect with regard to lowering HCC incidence

Recommendations	Level of evidence	Grade of recommendation
Coffee consumption has been shown to decrease the risk of HCC in patients with **chronic liver disease** In these patients, **coffee consumption** should be **encouraged**	Moderate	Strong

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Surveillance

- Utility of and applicability of surveillance is influenced by a number of factors
  - Incidence of HCC in **target populations**
  - Availability of efficient diagnostic tests at acceptable costs
  - Availability and effectiveness of treatments

- Definition of target populations must consider
  - Incidence of HCC in subsets of patients
  - Probability that effective therapies, particularly radical ones, are suitable

HCC incidence is **higher** in patients with **more advanced** cirrhosis
Probability of receiving **effective therapy** is **lower***
Different incidence thresholds may apply to different target populations

*Because of lower applicability of surgery

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Surveillance

- High rate of HCC in certain risk groups makes surveillance a cost-effective route to reducing mortality
  - Conventional threshold is US $50,000 per year of life saved*

Recommendations	Level of evidence	Grade of recommendation
• **Implementation** of screening programmes to identify at-risk candidate populations **should be improved** • Such programmes are a public health goal, aiming to decrease HCC-related and overall liver-related deaths	Low	Strong
Patients at **high risk** of developing HCC should be entered into **surveillance** programmes. Government health policy and research agencies should address these needs	Moderate	Strong

*Slightly lower (£30,000) or significantly higher levels (up to $150,000) have been proposed to account for inflation, specific national healthcare resources and other factors

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Surveillance in patients at high risk of HCC

- Surveillance is recommended in specific target populations

Recommendations	Level of evidence	Grade of recommendation
• Cirrhotic patients, **Child–Pugh stage A and B**	Low	Strong
• Cirrhotic patients, **Child–Pugh stage C awaiting LT**	Low	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)*	Low	Weak
• Non-cirrhotic F3 patients, based on an individual risk assessment	Low	Weak

- Interval should be dictated by rate of tumour growth and tumour incidence in target population
  - **6-month interval is reasonable and cost-effective**
    - **3 months**: no clinical benefit
    - **12 months**: fewer early stage diagnoses and shorter survival

**Patients at low HCC risk left untreated for HBV and without regular 6-month surveillance must be reassessed at latest on a yearly basis to verify progression of HCC risk.*

[†]PAGE-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, 100,000–199,999µl = 1, <100,000 = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at 5 years) a score of 10–17 at intermediate risk (3% incidence HCC at 5 years) and ≥18 is at high risk (17% HCC at 5 years)

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Uncertainties in surveillance strategy

- Benefit of surveillance has not been established in all risk groups
- US remains the method of choice
  - Serological tests are not currently cost-effective

Recommendations	Level of evidence	Grade of recommendation
Role of **surveillance for patients with NAFLD** without cirrhosis is **unclear**	Low	
Surveillance should be performed by **experienced personnel** in all **high-risk populations** using **abdominal US every 6 months**	Moderate	Strong
Tumour **biomarkers** for accurate early detection are **still lacking***	Low	-
Patients on the **waiting list for LT** should **undergo surveillance for HCC** • To detect and manage tumour occurrence or tumour response • To help **define priority policies** for transplantation	Low	Strong

**Available data show that the biomarkers tested (i.e. AFP, AFP-L3 and DCP) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC*

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Diagnosis

- Diagnosis generally relies on pathology
- Non-invasive criteria can be used in patients with cirrhosis
  - Peculiar vascular derangement occurs during hepatic carcinogenesis
  - High pre-test probability of HCC

Recommendations	Level of evidence	Grade of recommendation
Diagnosis of **HCC in cirrhotic** patients should be based on **non-invasive criteria and/or pathology**	High	Strong
In **non-cirrhotic** patients, diagnosis of HCC should be confirmed by **pathology**	Moderate	Strong
Pathological diagnosis of HCC should be **based on International Consensus recommendations**[1,2] using the required histological and immunohistological analyses	High	Strong

1. International Consensus Group for Hepatocellular Neoplasia. Hepatology 2009;49:658–64;
2. Bosman FT, et al. WHO Classification of Tumours of the Digestive System. Fourth Edition. IARC press; 2010;

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Staging systems and treatment allocation

- Prognostic assessment is critical in the management of HCC
  - Complicated by co-existence of HCC and cirrhosis
- Staging for HCC should be based on:
  - Prognostic variables from studies on natural history of HCC and cirrhosis
  - Variables from evidence-based studies on therapeutic rationale

Recommendations	Level of evidence	Grade of recommendation
Staging systems for clinical decisions in HCC **should include**: • Tumour burden • Liver function • Performance status	High	Strong
BCLC staging system has been **repeatedly validated** and **is recommended** for prognostic prediction and treatment allocation • The treatment '**stage migration**'* concept applies	High	Strong
Patients should be discussed in **multidisciplinary teams** to fully capture and tailor **individualized treatment options**	Low	Strong

**The stage migration strategy is a therapeutic choice by which a treatment theoretically recommended for a different stage is selected as the best first-line treatment option: usually offering the effective treatment option recommended for the subsequent more advanced tumour stage, which occurs when patients are not suitable for their first line therapy. However in highly selected patients, with parameters close to the thresholds, a lower-stage migration strategy could be the best option, given a multidisciplinary decision*

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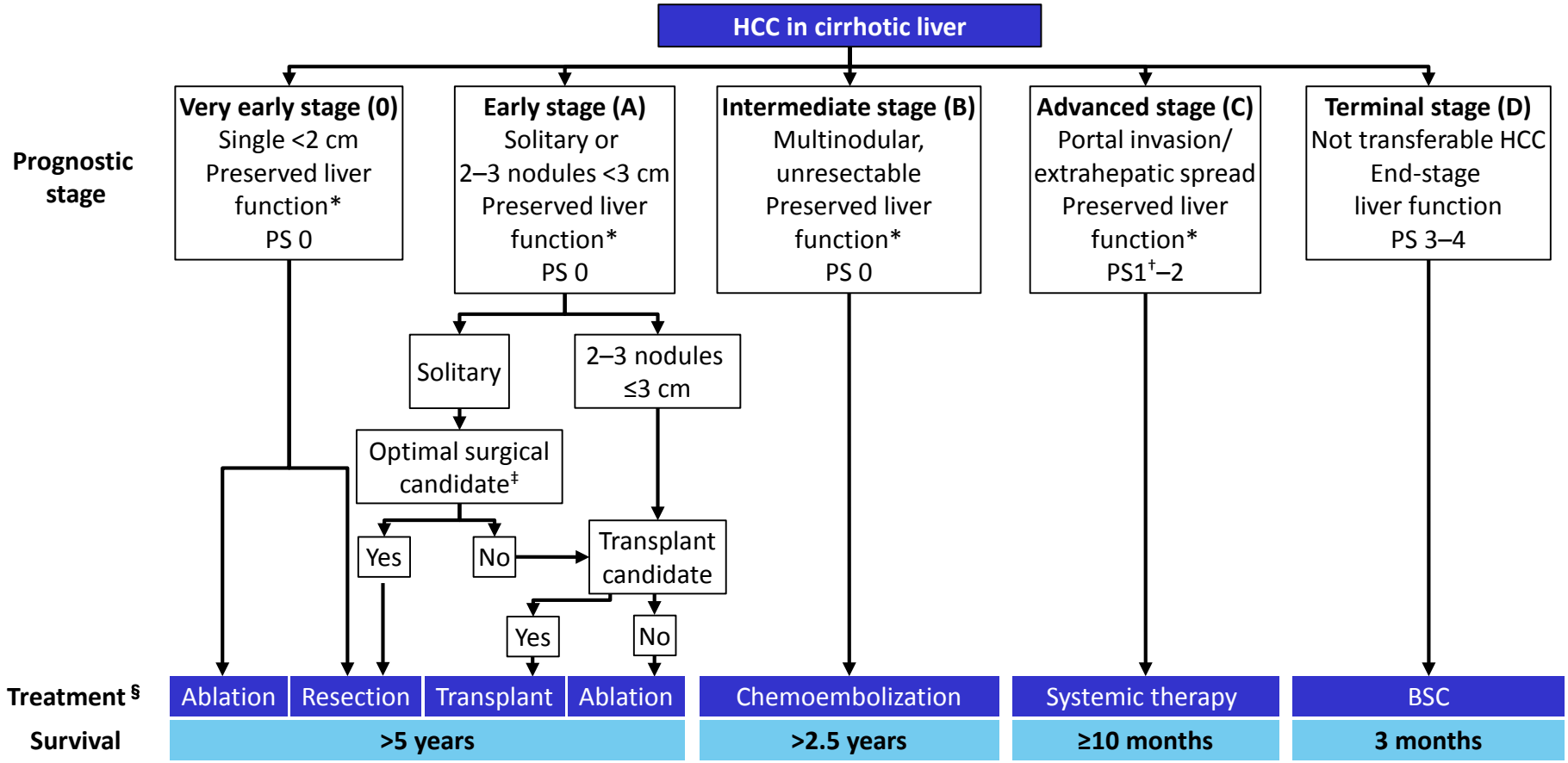
Modified BCLC staging system and treatment strategy



**Child–Pugh A without ascites. Applies to all treatment options apart from LT; †PS 1; tumour-induced modification of performance capacity; ‡Multiparametric evaluation: compensated Child–Pugh class A liver function with MELD score <10, matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach; §The stage migration strategy applies;*

‖Sorafenib has been shown to be effective in first line, while regorafenib is effective in second line in case of radiological progression under sorafenib. Lenvatinib has been shown to be non-inferior to sorafenib in first line, but no effective second-line option after lenvatinib has been explored. Cabozantinib has been demonstrated to be superior to placebo in 2nd or 3rd line with an improvement in OS. Nivolumab has been approved in second line by FDA but not EMA based on uncontrolled Phase 2 data. Please see notes for full details.

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Treatment of HCC: liver transplantation

- Together with **NAFLD/NASH, HCC** is the fastest growing indication for LT
- Milan criteria are the benchmark for selecting patients for LT
  - Basis for comparison with other suggested criteria

Recommendations	Level of evidence	Grade of recommendation
LT is recommended as the **first-line option** for HCC **within Milan criteria** but **unsuitable for resection**	High	Strong
Consensus on expanded criteria for LT in HCC has not been reached • Patients outside Milan criteria can be considered for LT after successful downstaging to within Milan criteria, within defined protocols	Moderate	Weak
Composite criteria,* are **likely** to **replace conventional criteria** for defining transplant feasibility	Low	Strong
Tumour vascular invasion and extrahepatic metastases are an **absolute contraindication** for LT in HCC	High	

**That consider surrogates of tumour biology and response to neoadjuvant treatments to bridge or downstage tumours in combination with tumour size and number of nodules: these criteria should be investigated and determined a priori,validated prospectively and auditable at any time*

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Organ allocation and priority for HCC

- LT is the therapy with the highest chance of curing HCC
  - Always consider unless age and co-morbidities advise against LT
- Major limiting factor is scarcity of donated organs
  - Including relative priority with other LT indications

Cirrhosis	HCC + cirrhosis
High pre-transplant mortality	Low pre-transplant mortality
High post-transplant long-term recovery	Variable post-transplant cure, depending on tumour stage at operation
Predictable outcome with no transplant (MELD)	Composite prognostic factors and variable biology influencing outcome
No competitive options besides transplantation ↓ **Urgency principle**	Competitive options in selected patient subgroups ↓ **Utility principle**
Focused on pre-LT risk of dying	Focused on maximization of post-LT

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Liver transplant prioritization

- Prioritization of cadaveric graft allocation is challenging

Recommendations	Level of evidence	Grade of recommendation
The use of **marginal cadaveric grafts** for LT in patients with HCC has **no contraindication**	Moderate	
Prioritizing a cadaveric graft allocation, for patients with or without HCC, within a common waiting list, is complex: • **No system can serve all regions** • Prioritization **criteria** for HCC **should at least include:** – *Tumour burden* – *Tumour biology indicators* – *Waiting time* – *Response to tumour treatment*	Moderate	Strong
Transplant **benefit** may need to be considered **alongside** the conventional transplant principles of **urgency** and **utility** in decision making, depending on list composition and dynamics	Moderate	Weak

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AASLD Guidelines for the Treatment of Hepatocellular Carcinoma

Julie K. Heimbach,[1] Laura M. Kulik,[2] Richard S. Finn,[3] Claude B. Sirlin,[4] Michael M. Abecassis,[5] Lewis R. Roberts,[6] Andrew X. Zhu,[7] M. Hassan Murad,[8] and Jorge A. Marrero[9]

4. SHOULD ADULTS WITH CHILD-PUGH CLASS A CIRRHOSIS AND EARLY-STAGE HCC (T1 OR T2) BE TREATED WITH RESECTION OR LOCOREGIONAL THERAPY?

4. The AASLD suggests that adults with Child-Pugh class A cirrhosis and resectable T1 or T2 HCC undergo resection over radiofrequency ablation.

Quality/Certainty of Evidence: Moderate

Strength of Recommendation: Conditional

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5. SHOULD ADULTS WITH CIRRHOSIS AND HCC THAT HAS BEEN RESECTED OR ABLATED SUCCESSFULLY UNDERGO ADJUVANT THERAPY?

Recommendation

5. The AASLD suggests against the routine use of adjuvant therapy for patients with HCC following successful resection or ablation.

Quality/Certainty of Evidence: Low

Strength of Recommendation: Conditional

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6. SHOULD ADULTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION AND T1 HCC BE TREATED OR UNDERGO OBSERVATION?

Recommendation

6. The AASLD suggests observation with follow-up imaging over treatment for patients with cirrhosis awaiting liver transplantation who develop T1 HCC.

Quality/Certainty of Evidence: Very Low

Strength of Recommendation: Conditional

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7. SHOULD ADULTS WITH CIRRHOSIS AND OPTN T2 HCC AWAITING LIVER TRANSPLANTATION UNDERGO TRANSPLANT ALONE OR TRANSPLANT WITH BRIDGING THERAPY WHILE WAITING?

Recommendations

7A. The AASLD suggests bridging to transplant in patients listed for liver transplantation within OPTN T2 (Milan) criteria to decrease progression of disease and subsequent dropout from the waiting list.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

7B. The AASLD does not recommend one form of liver-directed therapy over another for the purposes of bridging to liver transplantation for patients within OPTN T2 (Milan) criteria.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

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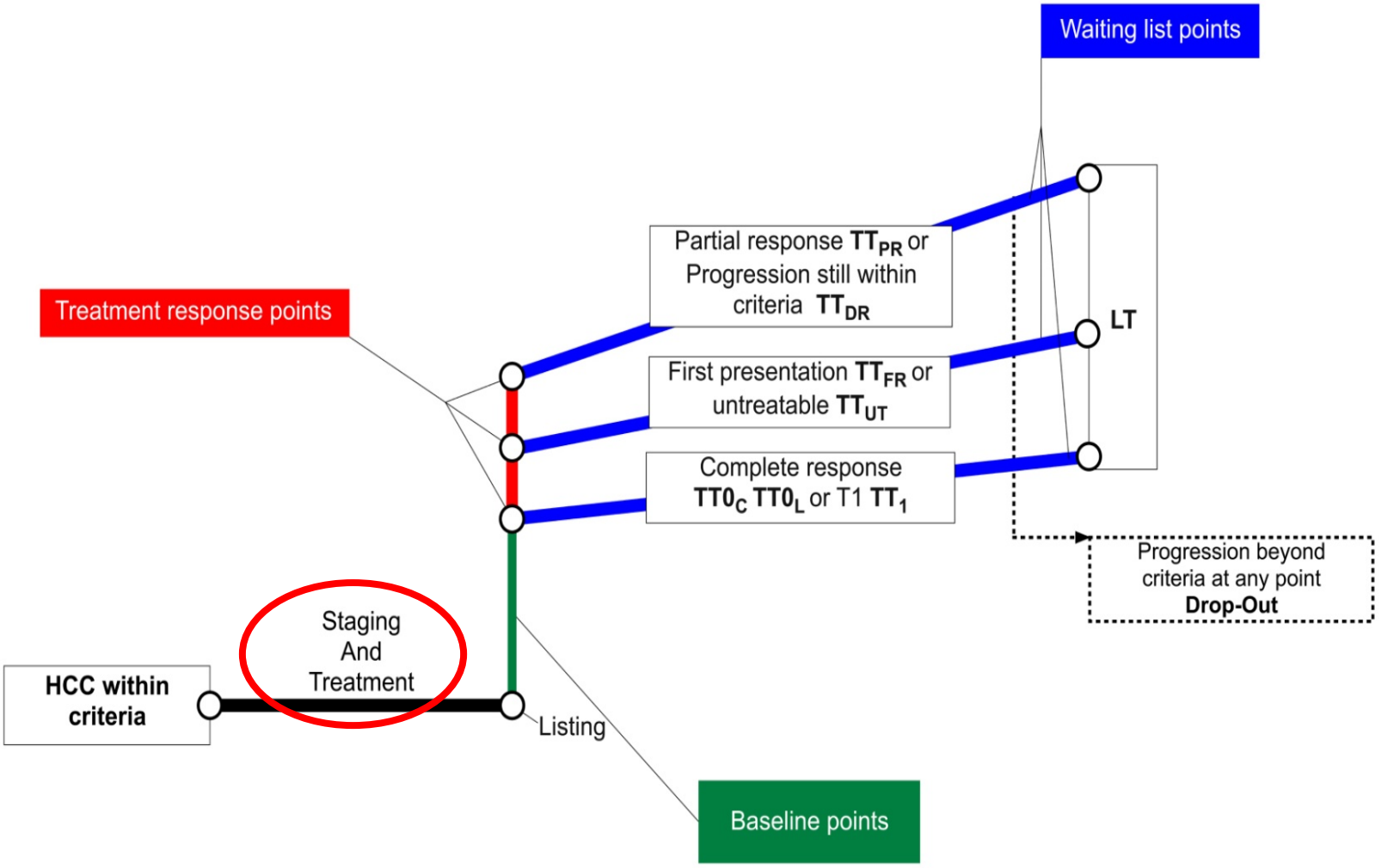
8. SHOULD ADULTS WITH CIRRHOSIS AND HCC BEYOND MILAN CRITERIA (T3) BE TRANSPLANTED FOLLOWING DOWNSTAGING TO WITHIN MILAN CRITERIA?

Recommendation

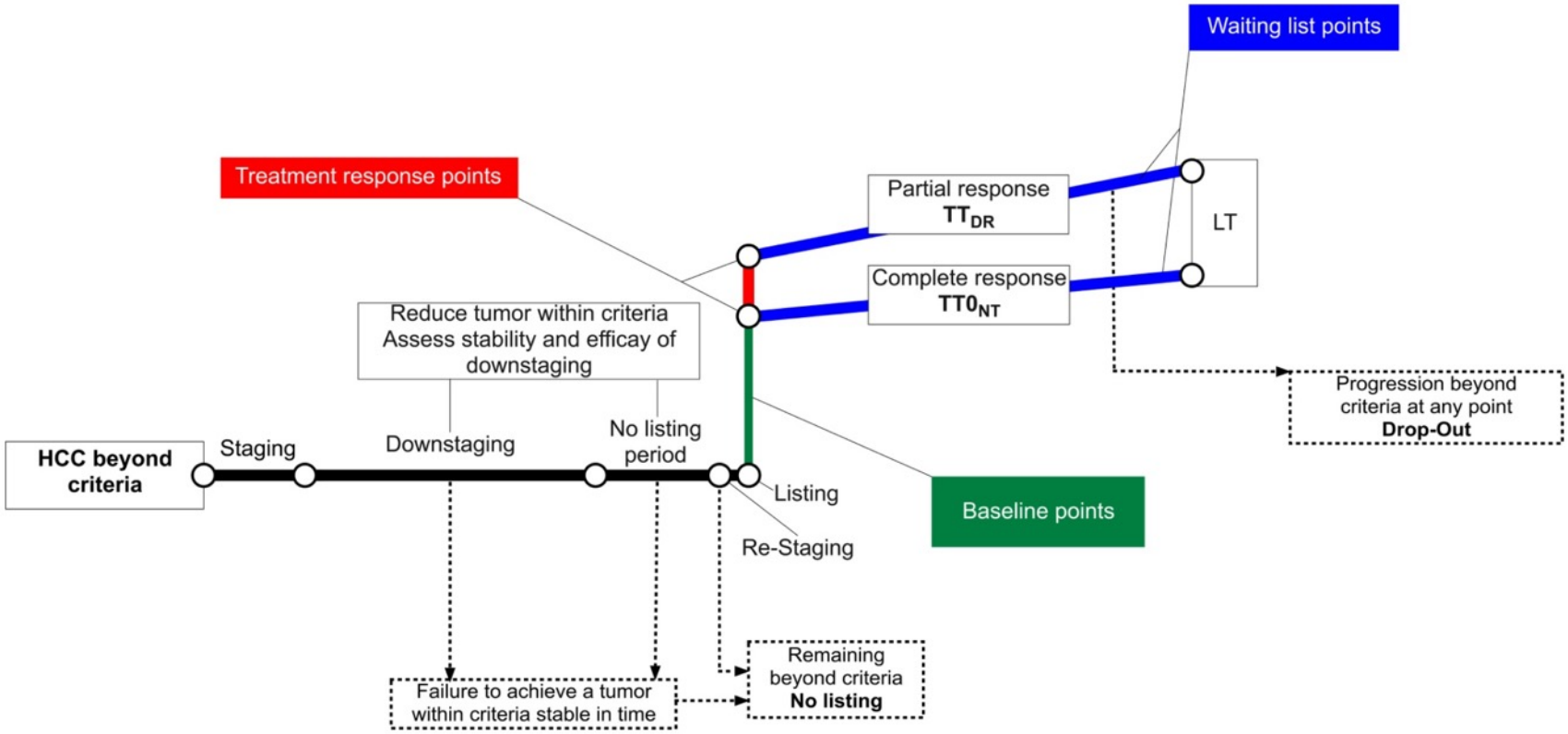
8. The AASLD suggests that patients beyond the Milan criteria (T3) should be considered for liver transplantation after successful downstaging into the Milan criteria.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Lombardy model



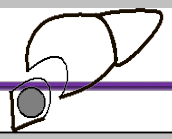
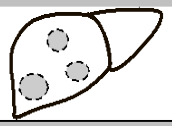
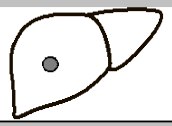
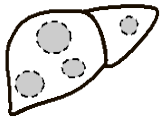
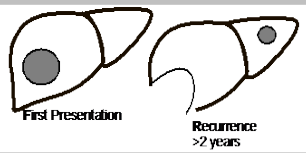
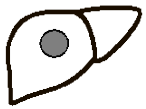
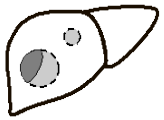
HCC Beyond Criteria (Downstaging)

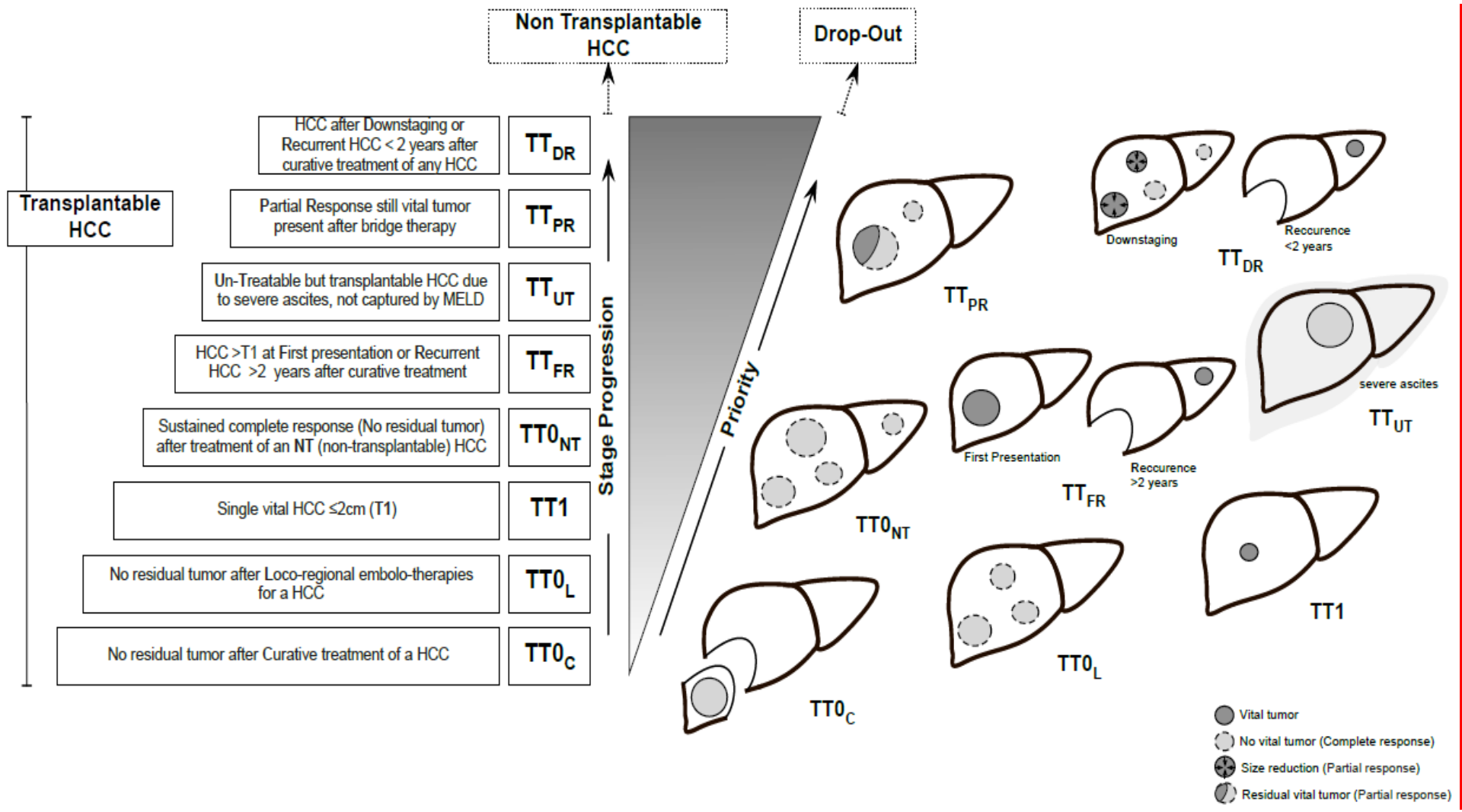


In presenza di adeguato compenso epatico quindi il paziente con HCC deve essere trattato per tale neoplasia, in accordo alle migliori opzioni terapeutiche disponibili secondo le vigenti linee guida. Deviazioni da tale condotta (no treatment policy) sono accettabili solo se frutto di una decisione multidisciplinare la cui motivazione deve essere documentata e tracciabile. Le no-treatment policy devono essere contenute in non più del 10-15% anno.

Schema riassuntivo di attribuzione punteggio per pazienti con HCC

*HCC-MELD: 1.27 x MELD - 0.51 x log AFP + 4.59

Transplantable Tumor (TT): HCC categories	Radiology Stage	Punteggio Base	Risposta ai trattamenti	Coefficiente attesa in lista
$TT0_C$				
No residual tumor after Curative treatment of a HCC				
$TT0_L$				
No residual tumor after Loco-regional embolo-therapies for a transplantable HCC		HCC -MELD*	0 Punti	1 punto ogni 3 mesi
TT1				
Single HCC ≤2cm				
$TT0_{NT}$				
No residual tumor after treatment of a Non-Transplantable HCC (successful downstaging)				
TT_{FR}				
transplantable HCC > T1 at First presentation or Recurrent HCC >2yrs after curative treatment		HCC-MELD*	2 punti	1 punto ogni 2 mesi
TT_{UT}				
Transplantable HCC judged Un-Treatable for reasons not captured by MELD (i.e. ascites)				
TT_{PR}				
Partial Response after complete bridge therapy in a transplantable tumor				
TT_{DR}				
Transplant eligibility after Downstaging (sustained partial response) or Recurrent HCC <2yrs after curative treatment of any HCC		HCC-MELD*	4 punti	1 punto ogni mese


Non Transplantable HCC
Drop-Out
Transplantable HCC
HCC after Downstaging or Recurrent HCC < 2 years after curative treatment of any HCC
TT DR
Partial Response still vital tumor present after bridge therapy
TT PR
Un-Treatable but transplantable HCC due to severe ascites, not captured by MELD
TT UT
HCC >T1 at First presentation or Recurrent HCC >2 years after curative treatment
TT FR
Sustained complete response (No residual tumor) after treatment of an NT (non-transplantable) HCC
TT0 NT
Single vital HCC ≤2cm (T1)
TT1
No residual tumor after Loco-regional embolo-therapies for a HCC
TT0 L
No residual tumor after Curative treatment of a HCC
TT0 C
Stage Progression
Priority
Downstaging
Reccurence <2 years
First Presentation
Reccurence >2 years
severe ascites
Vital tumor
No vital tumor (Complete response)
Size reduction (Partial response)
Residual vital tumor (Partial response)

HEPATOLOGY
PRACTICE GUIDELINE | HEPATOLOGY, VOL. 67, NO. 1, 2018

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9. SHOULD ADULTS WITH CIRRHOSIS AND HCC (T2 OR T3, NO VASCULAR INVOLVEMENT) WHO ARE NOT CANDIDATES FOR RESECTION OR TRANSPLANTATION BE TREATED WITH TACE, TARE, OR EXTERNAL RADIATION?

Recommendations

9A. The AASLD recommends LRT over no treatment in adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation.

Quality/Certainty of Evidence:
TACE: Moderate
Transarterial Bland Embolization: Very Low
TARE: Very Low
External Radiation: Very Low
Strength of Recommendation: Strong

9B. The AASLD does not recommend one form of LRT over another.

Quality/Certainty of Evidence: Very low
Strength of Recommendation: Conditional

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Technical Remarks

1. The available evidence is for Child-Pugh class A and highly selected Child-Pugh class B. There are no data to support the use of LRT for patients with Child-Pugh class C or poor performance status, and use of LRT should be weighed against the risk of harm.
2. The data for the use of TARE and external beam radiotherapy is emerging. As discussed below, the results to date are encouraging but inadequate to make a recommendation.
3. RFA is another treatment strategy that may be used for selected patients with unresectable T2 HCC, depending on the size, location, and number of lesions.

Local ablation and external radiation

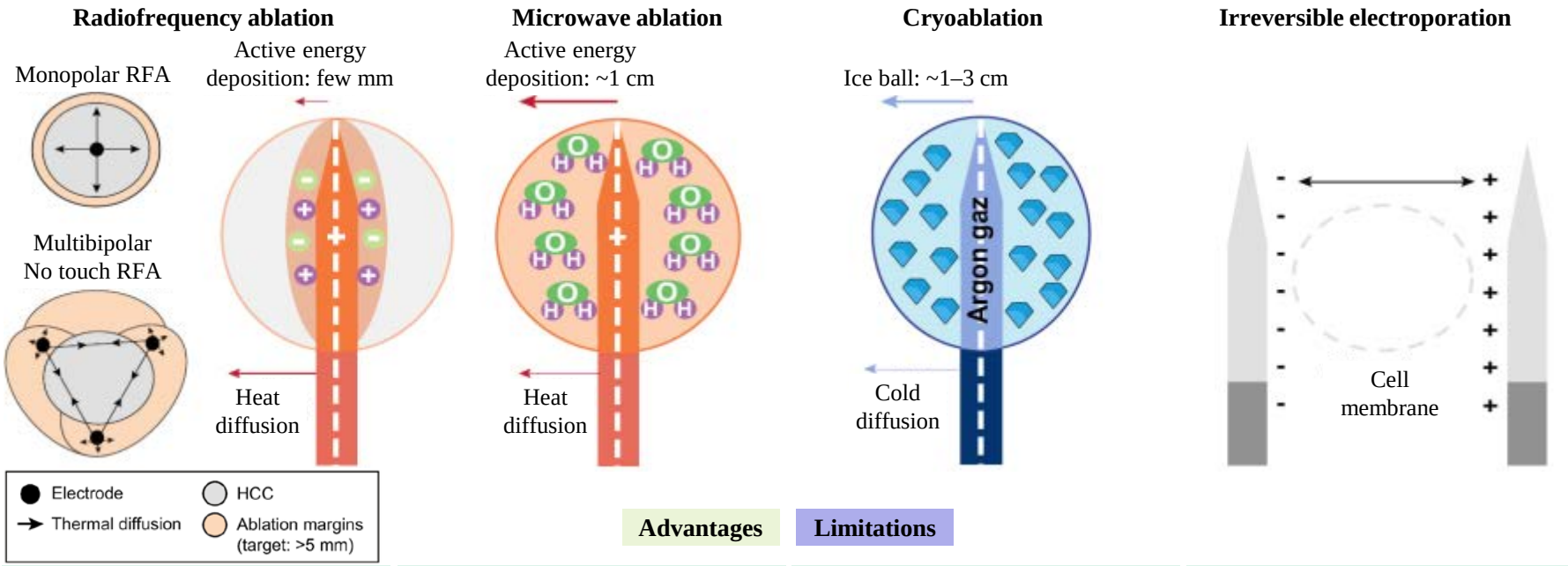
- Tumour ablation techniques have improved along with the imaging-guidance tools required to ensure their successful application

Recommendations	Level of evidence	Grade of recommendation
Thermal ablation with **radiofrequency** is the **standard of care** for patients with BCLC-0 and A tumours **not suitable for surgery***	High	Strong
In patients with **very early stage HCC** (BCLC-0) **radiofrequency ablation** in **favourable locations** can be adopted as **first-line therapy** even in **surgical patients**	Moderate	Strong
Microwave ablation showed promising results for local control and survival	Low	
Ethanol injection is an option in some cases **where thermal ablation** is **not technically feasible**, especially in tumours <2 cm	High	Strong
External beam radiotherapy is under investigation • So far there is no robust evidence to support this therapeutic approach in the management of HCC	Low	Weak

**Thermal ablation in single tumours 2–3 cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions*

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Percutaneous ablation



	Advantages	Limitations	
Radiofrequency ablation	• Well-evaluated treatment (reference) • Multibipolar mode: increases volume and predictability (margin) of ablation zone	• Thermal injury of adjacent structure • Heat sink effect (near major vessels) • Multibipolar mode is less sensitive to heat sink effect
Microwave ablation	• Higher and faster temperature picks reached than with RFA (less sensitive to heat sink effect than monopolar RFA)	• No reliable endpoint to set the amount of energy deposition
Cryoablation	• Easy monitoring with imaging of ice ball progression	• Cryoshock with first device • Limited clinical data available with new devices
Irreversible electroporation	• Limited risk of thermal injury to neighbouring critical structures • Unsensitive to heat sink effect • Advantage of multibipolar mode (no touch technique, predictability of margins)	• Only preliminary clinical data • General anaesthesia using curare and major analgesic drugs is mandatory

Nault J-C, et al. J Hepatol 2018;68:783–97
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Transarterial therapies

- Benefits of **TACE** in appropriately selected patients have been robustly demonstrated

Recommendations	Level of evidence	Grade of recommendation
TACE is recommended for patients with **BCLC stage B** and should be carried out in a selective manner	High	Strong
The use of **drug-eluting beads** has shown **similar benefit** to **conventional TACE** and **either** of the two **can be utilized**	High	Strong
TACE should not be used in patients with: • Decompensated liver disease • Advanced liver and/or kidney dysfunction • Macroscopic vascular invasion • Extrahepatic spread	High	Strong

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Transarterial therapies in development

- Potential benefits of other transarterial therapies **have yet to be sufficiently demonstrated**

Recommendations	Level of evidence
There is **insufficient evidence** to recommend bland embolization, selective intra-arterial chemotherapy and lipiodolization	Moderate
TARE/SIRT using yttrium-90 microspheres has been investigated in: • Patients with BCLC-A for bridging to transplantation • Patients with BCLC-B to compare with TACE • Patients with BCLC-C to compare with sorafenib Current data: • Show good safety profile and local tumour control • Fail to show overall survival benefit compared to sorafenib in BCLC-B and -C patients **The subgroup of patients benefitting from TARE needs to be defined**	Moderate
There is **insufficient evidence** to recommend **scores** that **better select BCLC-B candidates** for first TACE or for subsequent sessions	Moderate

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First-line systemic therapies

- VEGFR and multi-kinase inhibitors have shown survival benefits in advanced HCC
  - First line: **sorafenib and lenvatinib**

Recommendations	Level of evidence	Grade of recommendation
Sorafenib is the standard first-line systemic therapy for HCC, indicated for patients with: • Well-preserved liver function (Child–Pugh A) and with advanced tumours (BCLC-C) • Earlier stage tumours progressing upon, or unsuitable for, loco-regional therapies	High	Strong
Lenvatinib is non-inferior to sorafenib and is **also recommended in first-line therapy** for patients with: • Well-preserved liver function, good performance status and advanced tumours (BCLC-C) without main portal vein invasion • Tumours progressing with, or unsuitable for, loco-regional therapies	High	Strong
There are no clinical or molecular biomarkers established to predict response to first- or second-line systemic treatments	Moderate	

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Second-line systemic therapies

- VEGFR and multi-kinase inhibitors have shown survival benefits in advanced HCC
  - First line: sorafenib and lenvatinib
  - Second line: **regorafenib** (and cabozantinib and ramucirumab*)
- Another agent that has shown some promise is the checkpoint inhibitor nivolumab

Recommendations	Level of evidence	Grade of recommendation
Regorafenib is **recommended** as **second-line** treatment for patients: • **Tolerating** and **progressing** on **sorafenib** • With well-preserved liver function (Child–Pugh class A) • With good performance status	High	Strong
Cabozantinib and ramucirumab* have shown survival benefits vs. placebo in this setting	-	-
Based on uncontrolled but promising data, **immune therapy** with **nivolumab** has received **FDA approval** in **second-line treatment**, pending Phase 3 data for conventional approval • At present, the data are not mature enough to give a clear recommendation	Moderate	Weak

*In patients with high baseline alpha-fetoprotein (> 400 ng/ml)

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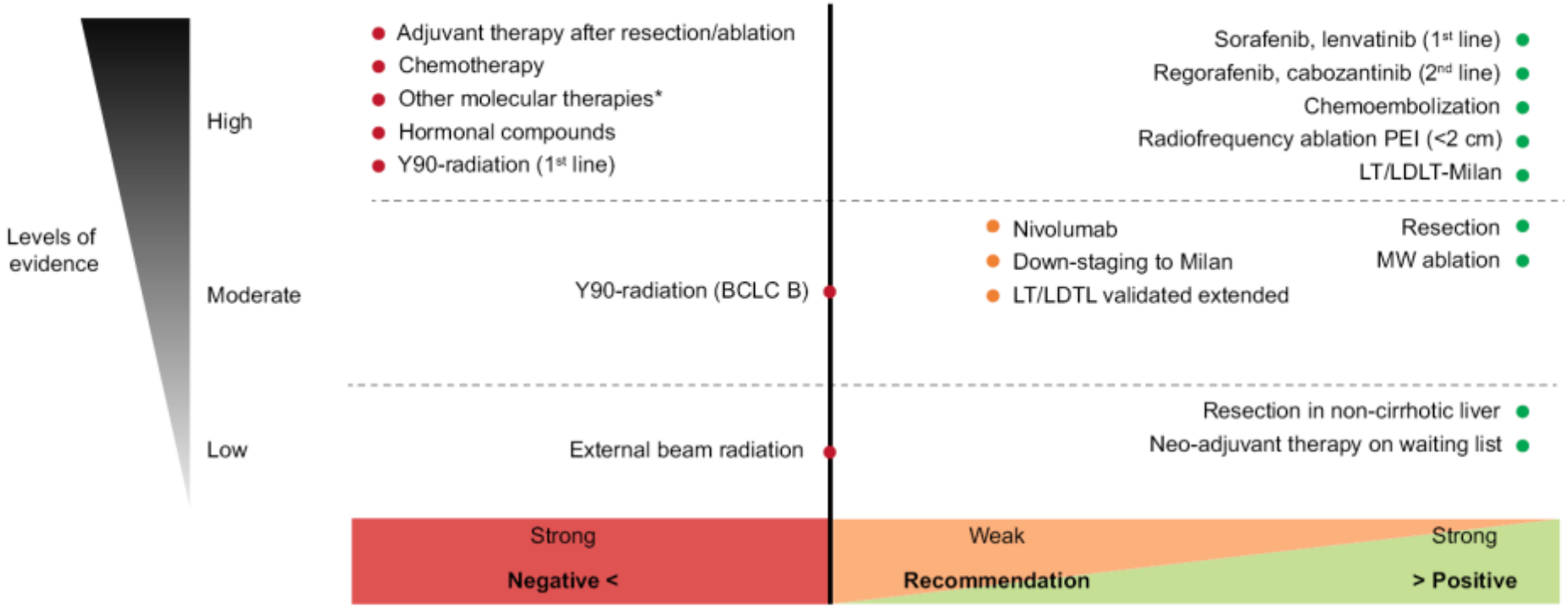
10. SHOULD ADULTS WITH CHILD-PUGH CLASS A/B CIRRHOSIS AND ADVANCED HCC WITH MACROVASCULAR INVASION AND/OR METASTATIC DISEASE BE TREATED WITH SYSTEMIC THERAPY OR LRT OR NO THERAPY?

Recommendation

10. The AASLD recommends the 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.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Overview of EASL recommendations for treatment



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

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Assessment of response to treatment

- Different methods of response assessment are appropriate for different treatments

Recommendations	Level of evidence	Grade of recommendation
Assessment of response **in HCC** should be based on **mRECIST** for **loco-regional therapies**	Moderate	Strong
For systemic therapies both mRECIST and RECIST1.1 are recommended	Moderate	Weak
Multiphasic contrast-enhanced CT or MRI are recommended for assessment of response after resection, loco-regional or systemic therapies	Moderate	Weak

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Palliative and best supportive care

- Management of end-stage disease is only symptomatic
  - **No tumour-directed treatment is indicated**

Recommendations	Level of evidence	Grade of recommendation
In HCC on cirrhosis: • **Acetaminophen** ≤3 g/day to manage pain of mild intensity • **NSAIDs should be avoided** whenever possible in patients with underlying cirrhosis. • **Opioids** to manage pain of intermediate or severe intensity (proactively avoid constipation)	Low	Weak
Bone metastases causing pain, or at significant risk of spontaneous secondary fracture, benefit from palliative radiotherapy	Low	

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Unmet needs to achieve EASL future goals

- Major health policy interventions to secure:
  - Universal vaccination against HBV
  - Universal treatment of HCV if indicated
  - Prevention of heavy alcohol intake and obesity
- Universal implementation of surveillance programmes
- New tools for early detection, including assessment of liquid biopsy
- Transition to biopsy for HCC in all instances once a tissue biomarker predicting response is available
- Development of new therapies for improving outcome, including adjuvant therapies, combination trials with checkpoint inhibitors and other drugs, and modalities (TKIs, loco-regional therapies, radiation)
- Development of third-line therapies in advanced stage
- Define optimal sequencing of systemic therapy

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Unmet needs to achieve EASL future goals

- Surrogate markers recapitulating OS
- Translate molecular knowledge into precision medicine, linking response rates in trials to molecular subgroups
- Assess the role of prognostic and predictive markers in surgical and interventional therapies within prospective investigations
- Understand the impact of minimal invasive surgery on HCC recurrence and post-progression survival
- Define and evaluate reliable quality of life assessment tools in HCC
- Stratify patients at risk for hepatocellular carcinoma and the utilization of chemopreventive strategies

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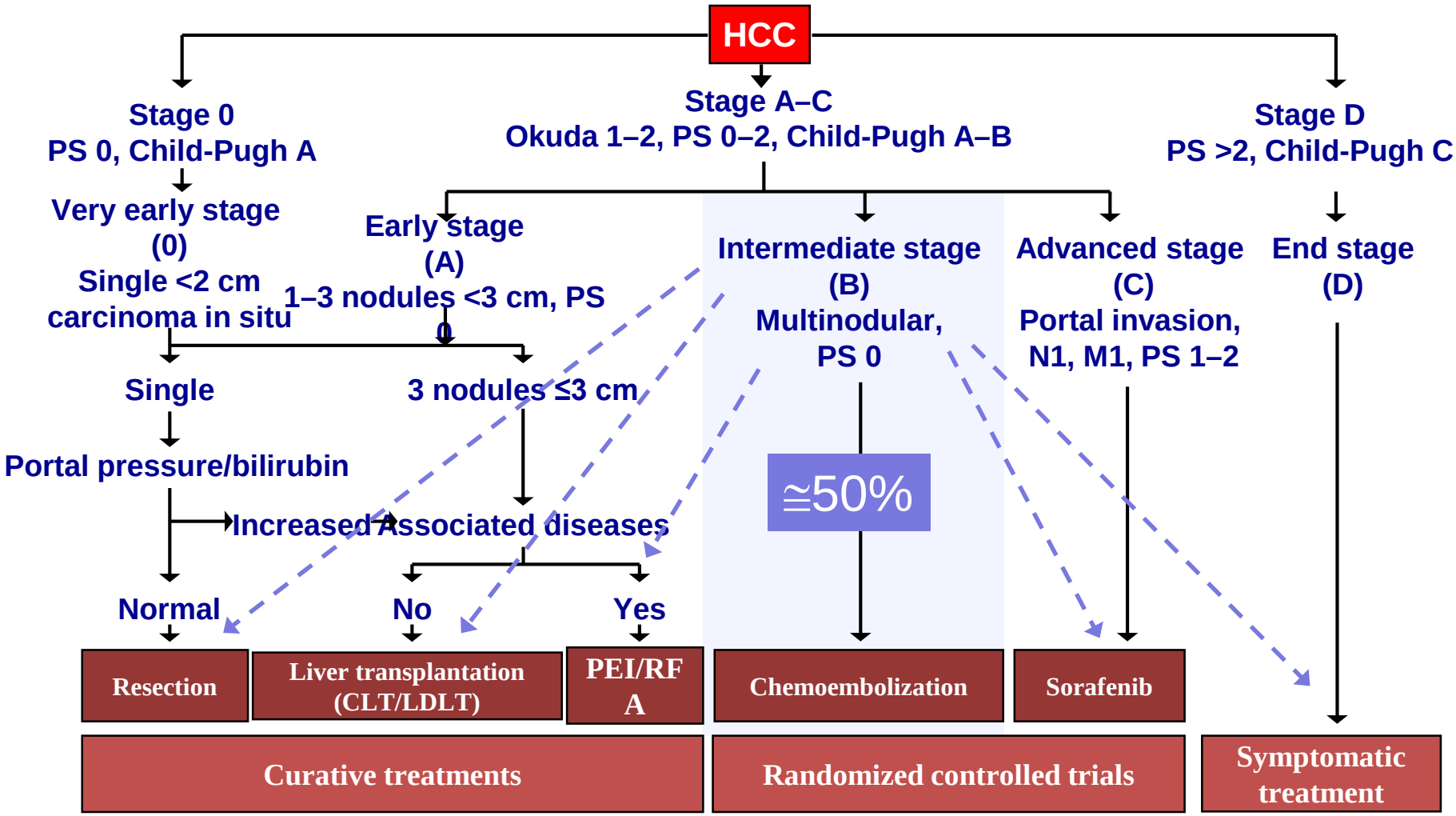
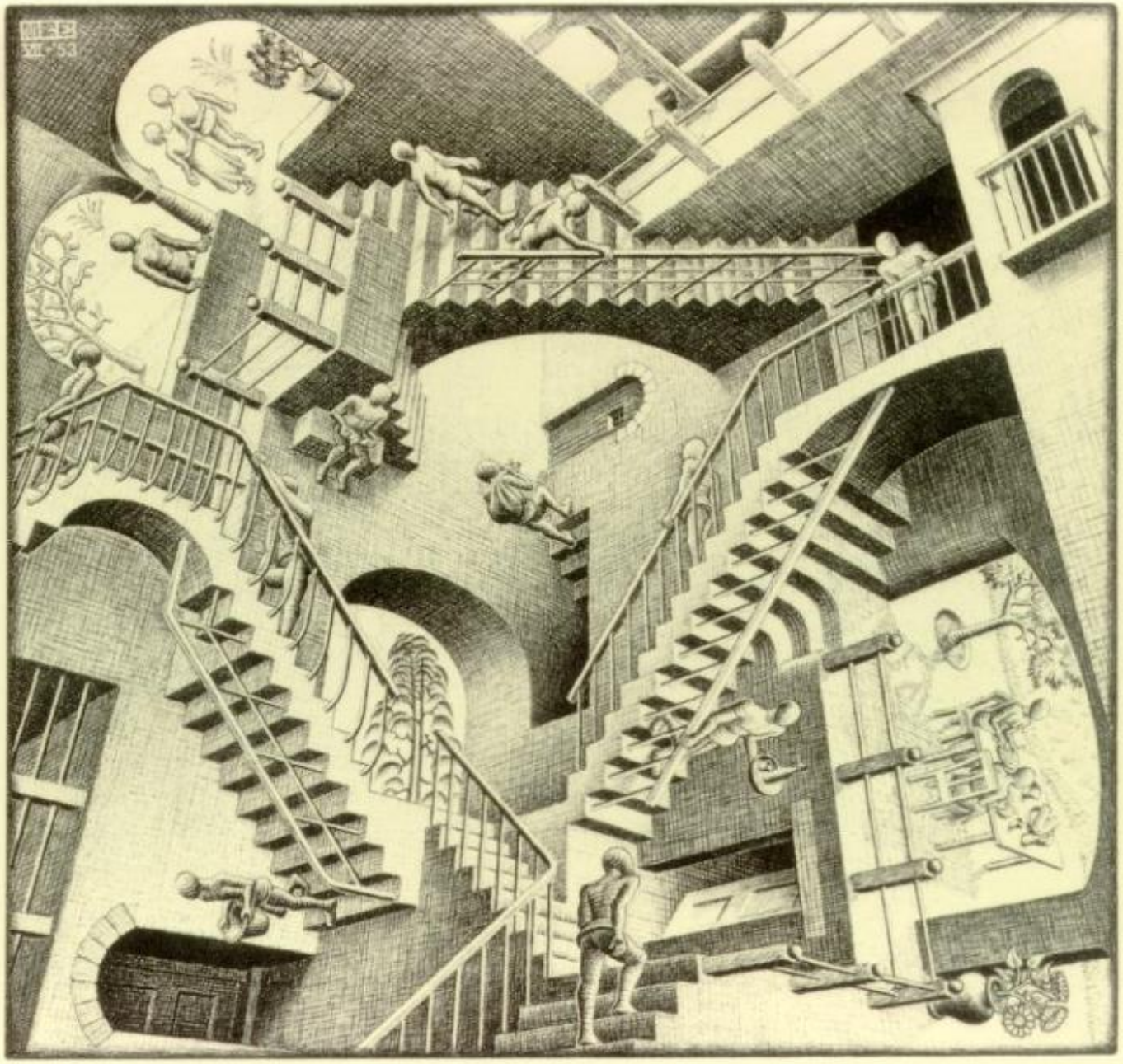
BCLC B patients

The evolving treatment paradigm



Grazie dell'attenzione



Escher