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UPDATE OF EASL CLINICAL PRACTICE GUIDELINES: MANAGEMENT OF HEPATOCELLULAR CARCINOMA*

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May 2018

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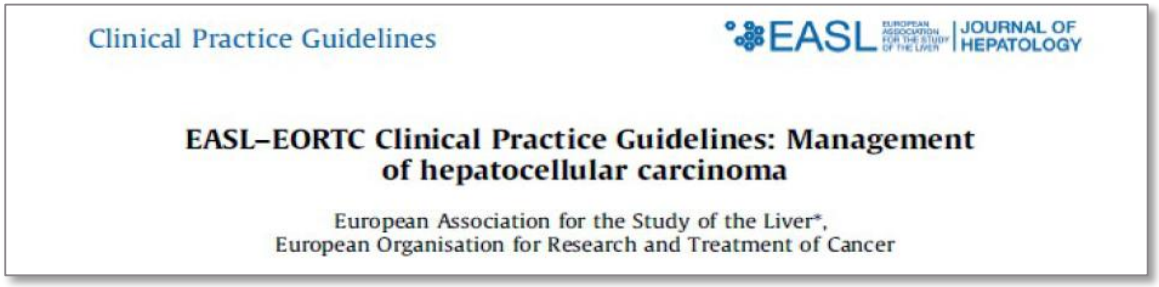
Please note:

The views expressed within this presentation are the personal opinion of the author. They do not necessarily represent the views of the author's academic institution or the rest of the HCC CONNECT group

1. EASL–EORTC GUIDELINES

- Official Clinical Practice Guidelines of EASL, published **in Journal of Hepatology** in 2012[1]


Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

European Association for the Study of the Liver*,
European Organisation for Research and Treatment of Cancer

- Official Clinical Practice Guidelines of EORTC, published **in European Journal of Cancer** in 2012[2]


European Journal of Cancer (2012) 48, 599–641

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ELSEVIER

EJC

Clinical Practice Guidelines

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

European Association for the Study of the Liver*, European Organisation for Research and Treatment of Cancer

1. EASL–EORTC. *J Hepatol* 2012; 56: 908-43. 2. EASL–EORTC. *Eur J Cancer* 2012; 48: 599-641
EASL, European Association for the Study of the Liver; EORTC, European Organisation for the Research and Treatment of Cancer

EPIDEMIOLOGY, RISK FACTORS AND PREVENTION

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Epidemiology:

- Incidence of HCC is increasing worldwide and it is amongst the leading causes of cancer death

Risk factors and Prevention:

- **Vaccination** against Hepatitis B reduces the risk of HCC and is recommended for all new-borns and high-risk groups
- Governmental health agencies should implement **policies** for preventing HCV/HBV transmission, counteracting chronic alcohol abuse, and encouraging life styles preventing obesity and metabolic syndrome
- In general, **chronic liver disease** should be treated to avoid progression of liver disease
- In patients with **chronic hepatitis**, antiviral therapies leading to maintained HBV suppression in chronic hepatitis B and sustained viral response in hepatitis C are recommended, since they have been shown to prevent progression to cirrhosis and development of HCC
- Once **cirrhosis** is established, anti-viral therapy is beneficial in preventing progression and decompensation but robust data on its impact on the risk of HCC development are lacking

HBV, Hepatitis B Virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C Virus

RISK FACTORS AND PREVENTION

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Risk factors and Prevention:

- Patients with **HCV-associated cirrhosis and HCC** treated with curative intent maintain a high rate of HCC-recurrence even after subsequent DAA therapy. It is presently unclear whether this presents the inherent risk of advanced cirrhosis to develop HCC or if DAA therapy increases recurrence rates. Currently, in these patients close surveillance is advised and the benefit of viral cure must be outweighed against a potentially higher recurrence risk

- **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

DAA, Directly Acting Antiviral therapy; HBV, Hepatitis B Virus; HCC, HepatoCellular carcinoma; HCV, Hepatitis C Virus

SURVEILLANCE

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- Implementation of **screening programs** to identify at-risk populations should be improved and are a public health goal to decrease HCC-related and overall liver-related deaths
- Patients **at high risk for developing HCC** should be entered into surveillance programs. Government health policy and research agencies should address these needs
- The role of surveillance for patients with **NAFLD without cirrhosis** is unclear
- Surveillance should be performed by experienced personnel in all high-risk populations using **abdominal ultrasound** every 6 months
- **Tumour biomarkers** for accurate early detection are still lacking. Data available with tested biomarkers (i.e. AFP, AFP-L3 and DCP) show that these tests are suboptimal in terms of cost effectiveness for routine surveillance to the aim of early HCC detection
- Patients on the **waiting list for liver transplantation** should be surveilled for HCC in order to detect and manage tumour occurrence or tumour response and to help define priority policies for transplantation

AFP, Alpha-FetoProtein; AFP-L3, lectin-reactive Alpha-FetoProtein; DCP, Des-gamma-Carboxy Prothrombin; HCC, Hepatocellular carcinoma; NAFLD, Non-Alcoholic Fatty Liver Disease

RECOMMENDATIONS FOR HCC SURVEILLANCE: CATEGORIES OF ADULT PATIENTS IN WHOM SURVEILLANCE IS RECOMMENDED

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1. Cirrhotic patients, Child-Pugh stage A and B
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation
3. Non-cirrhotic HBV patients at intermediate or high risk of HCC[1] (according to PAGE-B[2] classes for Caucasian subjects, respectively 10-17 and ≥18 score points)
4. Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment

PAGE-B risk score for prediction of HCC

Variable	Points
Age, years	
<30	-4
30-39	-2
40-49	0
50-59	2
60-69	4
≧70	6
Gender	
Male	5
Female	0
Platelets, mm^3	
≧200×10^3	0
100-<200×10^3	6
<100×10^3	11

1. Patients at low HCC risk left untreated for HBV and without regular 6 months surveillance have to be reassessed at latest on a yearly basis to verify progression of HCC risk.
2. 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 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). Papatheodoritis et al. *J Hepatol* 2015

F3, fibrosis stage 3; HBV, Hepatitis B Virus; HCC, Hepatocellular carcinoma

DIAGNOSIS

- Diagnosis of HCC in **cirrhotic patients** should be based on non-invasive criteria or/and pathology
- In **non-cirrhotic patients,** diagnosis of HCC should be confirmed by pathology
- Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistological analyses
- **Non-invasive criteria** can only be applied to cirrhotic patients for nodule(s) ⩾1 cm in the light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI or CEUS
- Due to their higher sensitivity and the analysis of the whole liver, **CT or MRI** should be used first
- **FDG PET-scan** is not recommended for early diagnosis of HCC due to the high rate of false negative cases

CT, Computerised Tomography; HCC, Hepatocellular carcinoma; CEUS, Contrast-Enhanced UltraSound; FDG PET-scan, FluoroDeoxyGlucose Positron Emission Tomography; MRI, Magnetic Reshepatoonance Imaging

RECALL POLICY

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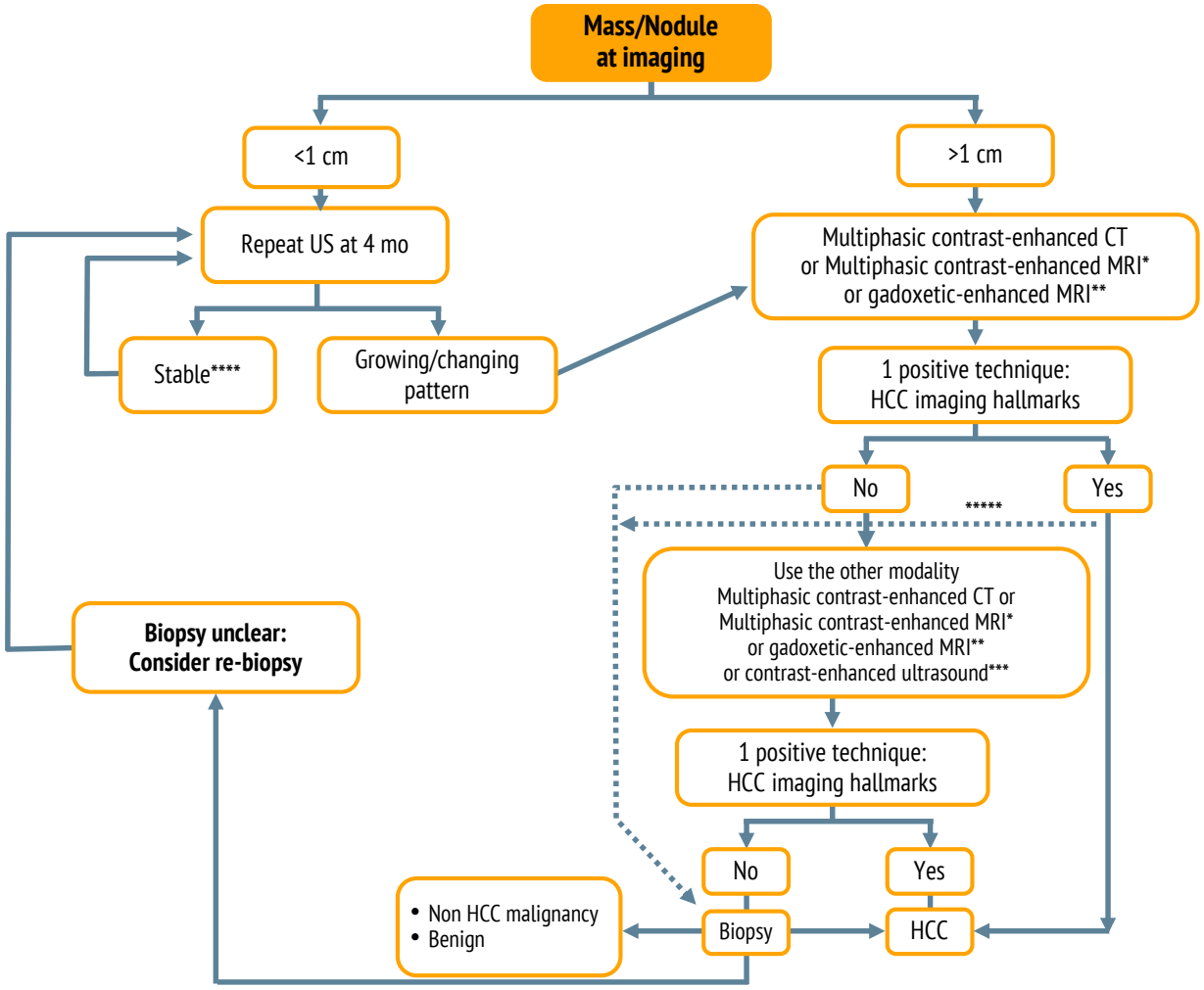
- In **patients at high risk** to develop HCC, nodule(s) <1 cm in diameter detected by US should be followed at ⩽4 months intervals in the first year. If no increase in either nodules size or number occurs, surveillance could be returned to the usual 6 months interval thereafter
- In **cirrhotic patients**, diagnosis of HCC for nodules of ⩾1 cm in diameter can be achieved with non-invasive criteria or/and biopsy-proven pathological confirmation
- **Repeated bioptic sampling** is recommended in case of inconclusive histological or discordant findings, or in case of growth or change in enhancement pattern identified during follow-up but with imaging still not diagnostic for HCC

HCC, Hepatocellular carcinoma; US, UltraSound

DIAGNOSTIC ALGORITHM AND RECALL POLICY IN CIRRHOTIC LIVER



* Using extracellular MR contrast agents or gadobenate dimeglumine

** Using the following diagnostic criteria: APHE and washout on the portal venous phase

*** Using the following diagnostic criteria: APHE and mild washout after 60 sec

**** Lesion <1 cm stable for 12 months (three controls after 4 months) can be shifted back to regular 6 months surveillance

***** Optional for center-based programs

APHE, Arterial Phase HyperEnhancement; CT, Computerised Tomography; HCC, Hepatocellular carcinoma; MRI, Magnetic Resonance Imaging; US, UltraSound

STAGING SYSTEMS AND TREATMENT ALLOCATION

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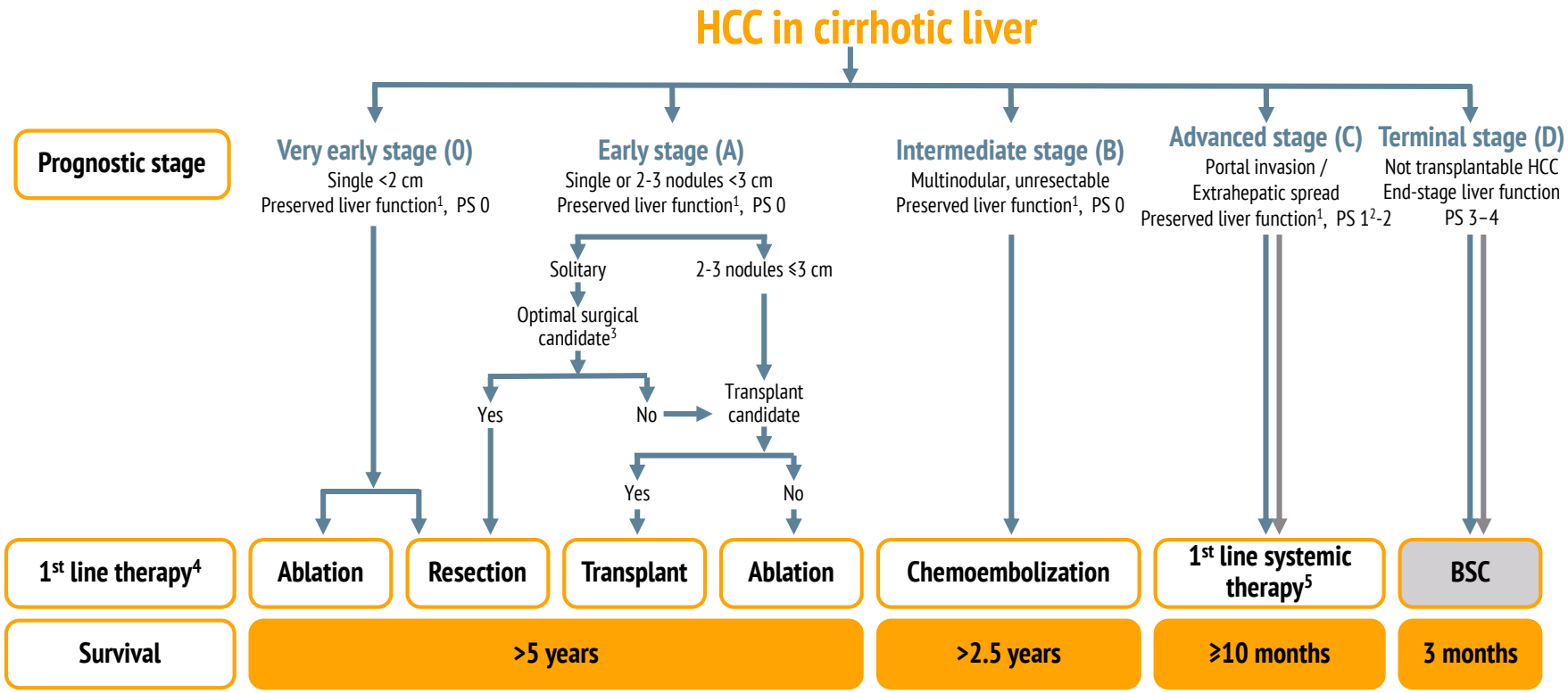
- Staging systems for clinical decision making in HCC should include tumour burden, liver function and performance status
- The **BCLC staging system** has been repeatedly validated and is recommended for prognostic prediction and treatment allocation
- Treatment stage migration concept applies
- **Refinement** of BCLC classes (particularly B and C) by clinical data, molecular classes or biomarker tools should further facilitate understanding of outcome data, treatment allocation and trial stratification and need to be validated in a clinical setting
- Patients should be discussed in **multidisciplinary teams** to fully capture and tailor individualized treatment options

BCLC, Barcelona Clinic Liver Cancer; HCC, Hepatocellular carcinoma



1. **"Preserved liver function"** refers to Child Pugh A without any ascites, considered conditions to obtain optimal outcomes. This prerequisite applies to all treatment options apart from transplantation, that is instead addressed primarily to patients with decompensated or end-stage liver function
2. **PS 1** refers to tumour induced (as per physician opinion) modification of performance capacity
3. **Optimal surgical candidacy** is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach. The combination of the previous factors should lead to an expected perioperative mortality <3% and morbidity <20% including a postsurgical severe liver failure incidence <5%
4. **The stage of migration strategy** is a therapeutic choice by which a treatment theoretically recommended for a different stage is selected as best 1st line treatment option. Usually it is applied with a left to right direction in the scheme (i.e. offering the effective treatment option recommended for the subsequent more advanced tumor stage rather than that forecasted for that specific stage). This occurs when patients are not suitable for their first-line therapy. However in highly selected patients, with parameters close to the thresholds defining the previous stage, a right to left migration strategy (i.e. a therapy recommended for earlier stages) could be anyhow the best opportunity, pending multidisciplinary decision
5. **As of 2017 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 as first-line but no effective second-line option after lenvatinib has been explored. Cabozantinib was announced to be superior to placebo in 2nd line or 3rd line, but no data has been presented as of December 2017

BSC, best supportive care; HCC, Hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; PS, Performance Status

RESPONSE ASSESSMENT

- Assessment of response in HCC should be based on the mRECIST for **loco-regional therapies**
- For **systemic therapies** both mRECIST and RECIST1.1 are recommended
- Use of changes in serum levels of **biomarkers** for assessment of response (i.e. AFP levels) is under investigation
- Multiphasic contrast-enhanced CT or MRI are recommended to assess response after resection, loco-regional or systemic therapies

AFP, Alpha-FetoProtein; CT, Computerised Tomography; HCC, Hepatocellular carcinoma; mRECIST, modified RECIST; MRI, Magnetic Resonance Imaging; RECIST, Response Evaluation Criteria in Solid Tumors

LIVER RESECTION

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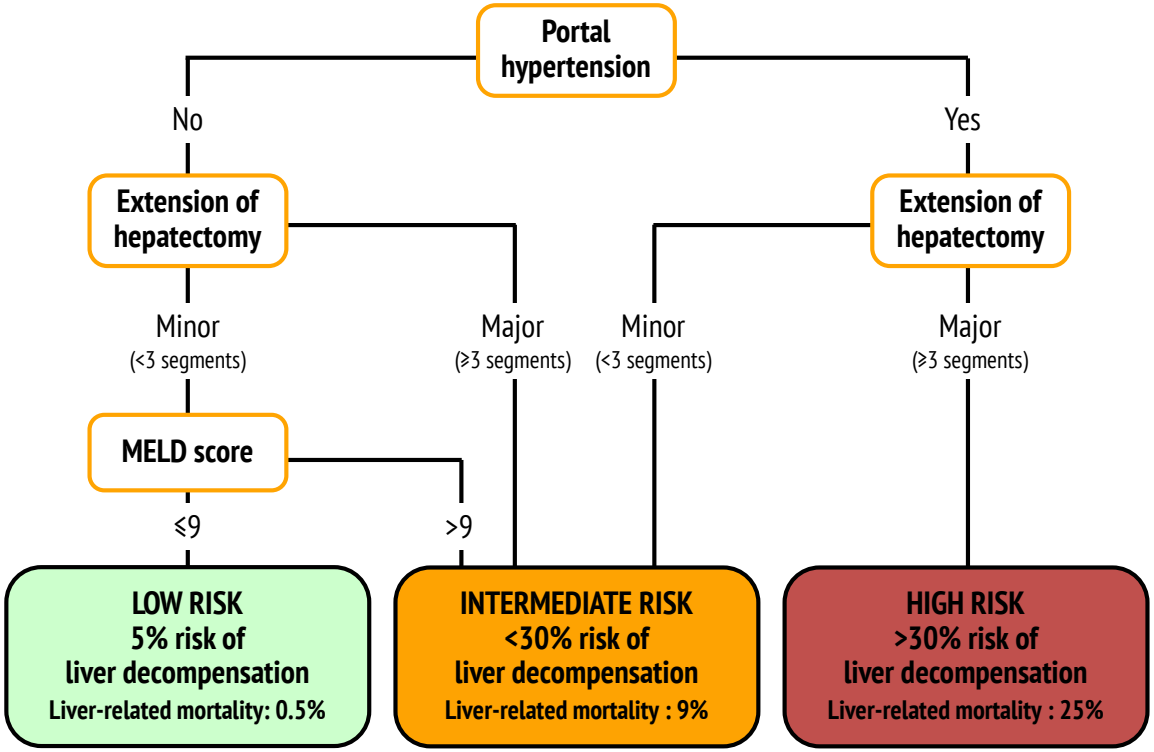
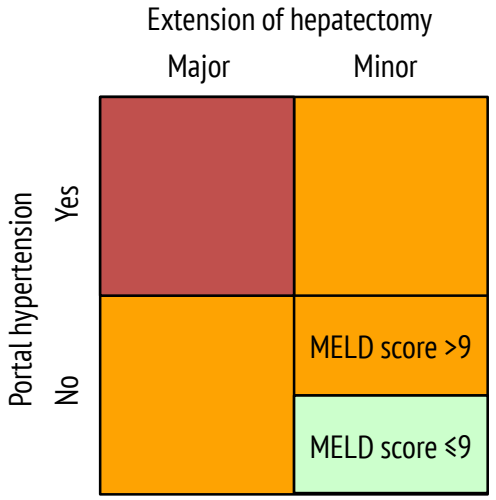
- Surgical resection is recommended as treatment of choice in patients with HCC arising on a **non-cirrhotic liver**
- Indication to LR for **HCC in cirrhosis** should be based on multi-parametric, composite assessment of liver function, portal hypertension, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' comorbidities
- Perioperative mortality of liver resection in cirrhotic patients should be <3%
- LR is recommended for single HCC of any size and in particular for tumours >2 cm, when hepatic function is preserved and sufficient remnant liver volume is maintained
- In properly trained centres, LR should be considered via laparoscopic/minimal-invasive approaches, especially for tumours in anterolateral and superficial locations
- HCC presenting with two or three nodules within Milan criteria may be eligible for LR according to patient performance status, comorbidities and preservation of liver function and remnant volume
- HCC-related macrovascular invasion is a **contraindication** to LR
- **Neoadjuvant or adjuvant therapies** are not recommended because they have not proven to improve outcome of patients treated with resection
- **Follow-up** after resection in curative intent is recommended because of high rates of treatable recurrence. Follow-up intervals are not clearly defined. In the first year, 3-4 months intervals are practical

HCC, Hepatocellular carcinoma; LR, Liver Resection

MULTI-PARAMETRIC ASSESSMENT OF THE RISK OF LIVER DECOMPENSATION AFTER LR FOR HCC

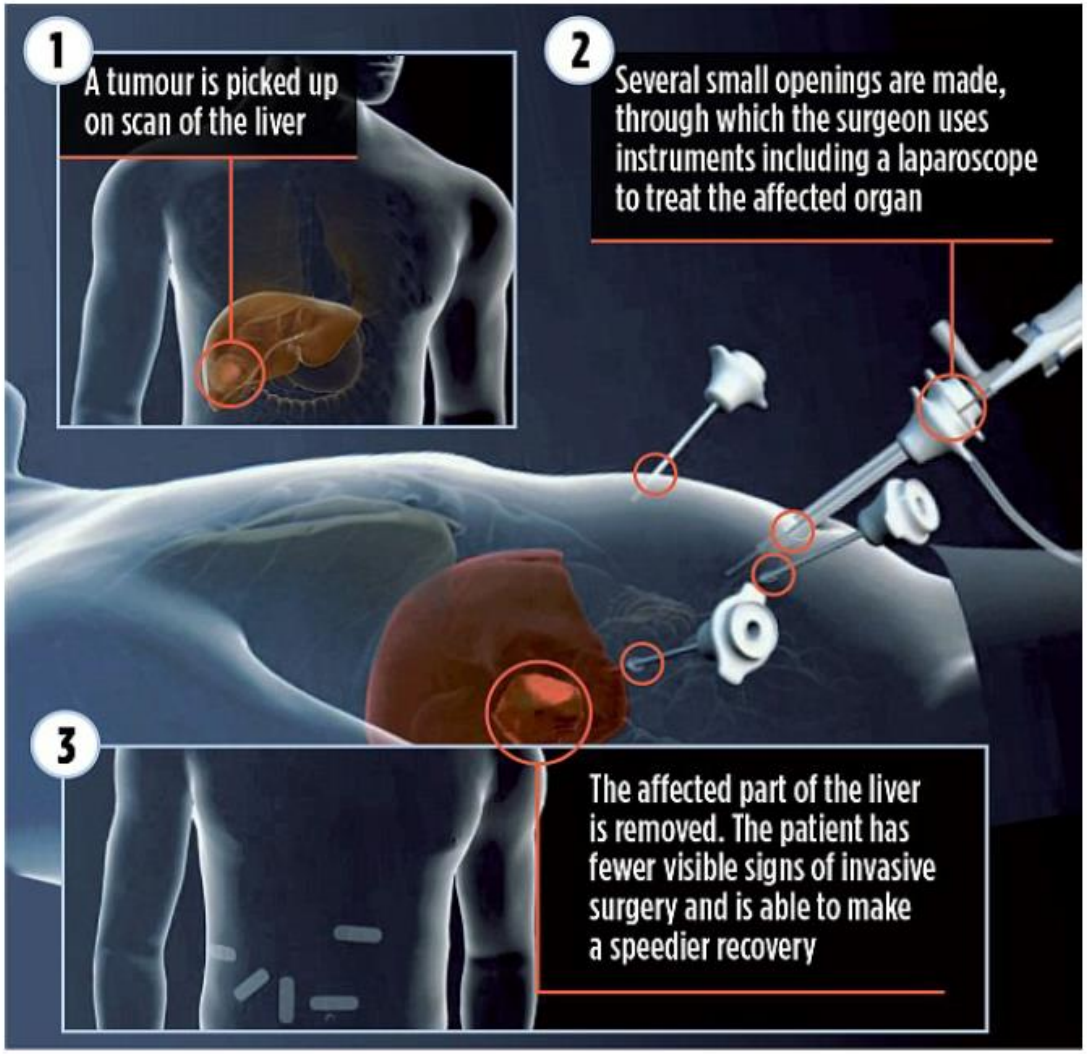




Simplified decisional algorithm identifying high (red), intermediate (yellow) and low (green) risk of liver decompensation, according to a hierarchic interaction of the 3 main determinants of liver insufficiency: portal hypertension, extent of resection and liver function

LR, Liver Resection; HCC, Hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease

PRINCIPLES OF MINI-INVASIVE/LAPAROSCOPIC LIVER RESECTION FOR HCC



LIVER TRANSPLANTATION

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- LT is recommended as first-line option for HCC within **Milan criteria unsuitable for resection**. Milan criteria are the benchmark for selection of HCC patients for LT and the basis for comparison with other suggested criteria
- Consensus on expanded criteria for LT in HCC is not reached. **Patients beyond the Milan criteria** can be considered for LT after successful down-staging within Milan criteria within defined protocols
- **Composite criteria defining transplantability** considering surrogates of tumour biology and response to neo-adjuvant treatments – to bridge or down-stage tumours – in combination with tumour size and number of nodules, are likely to replace conventional criteria
- Tumour vascular invasion and extra-hepatic metastases are absolute **contraindication** to LT for HCC
- There is no contraindication to the use of **marginal cadaveric grafts** for LT in patients with HCC. Decision-making on priority of a cadaveric graft allocation to HCC vs. non-HCC patients within a common waiting list is complex and no system is able to serve all regions. Prioritization criteria for HCC should take into account at least tumour burden, tumour biology indicators, waiting time and response to tumour treatment
- **Transplant benefit** of LT for HCC may need to be considered alongside the conventional transplant principles of Urgency and Utility in decision-making on patient selection and prioritization, depending on list composition and dynamics
- In LT candidates with HCC, the use of **pre-transplant (neo-adjuvant) LRTs** is recommended, if feasible, as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence

HCC, Hepatocellular carcinoma; LT, Liver Transplantation; TB, Transplant Benefit; LRT, Loco-Regional Therapies

LOCAL ABLATION AND EXTERNAL RADIATION

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- **Thermal ablation with radiofrequency** is considered the standard of care for patients with BCLC 0 and A tumours not suitable for surgery. **Thermal ablation** in single tumours 2 to 3 cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions
- In patients in the very early stage HCC (BCLC-0) **radiofrequency ablation** in favourable locations could be adopted as first-line therapy even in surgical patients
- Thermal ablation with **microwave** showed promising results for local control and survival. Other ablative therapies are under investigation
- **Ethanol injection** is an option in some cases where thermal ablation is not technically feasible, especially in tumours <2 cm
- **External beam radiotherapy** is under investigation, and, so far there is no robust evidence to support this therapeutic approach in the management of HCC

BCLC, Barcelona Clinic Liver Cancer; HCC, Hepatocellular carcinoma

TRANSARTERIAL THERAPIES

- **TACE** is recommended for patients with BCLC stage B and should be carried out in a selective manner. The use of **drug-eluting beads** has shown similar benefit as cTACE and either of the two can be utilised
- **TACE should not be used** in patients with decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion or extrahepatic spread. There is insufficient evidence to recommend bland embolization, selective intra-arterial chemotherapy and lipiodolisation
- **TARE** using Yttrium-90 microspheres has been investigated in BCLC A patients for bridging to transplantation, in BCLC B patients in comparison with TACE and in BCLC C patients in comparison with sorafenib. Current data show good safety profile and local tumour control but failed to show OS benefit compared with sorafenib in BCLC B and C patients. The subgroup of patients benefitting from TARE needs to be defined
- There is insufficient evidence to recommend scores to better select BCLC B patients' candidates to first TACE or for subsequent sessions

BCLC, Barcelona Clinic Liver Cancer; OS, Overall Survival; TACE, TransArterial ChemoEmbolization; cTACE, conventional TACE; TARE, TransArterial RadioEmbolization

SYSTEMIC THERAPIES

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- **Sorafenib** is the standard systemic therapy for HCC in 1st line. It is indicated 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
- **Lenvatinib** has been shown to be non-inferior to sorafenib and can be used in 1st line for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies
- No clinical or molecular biomarkers are established to predict response to 1st or 2nd line systemic treatments
- **Regorafenib** is recommended as 2nd line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status. **Cabozantinib** has also been announced to have shown survival benefits vs placebo in this setting
- Based on uncontrolled but promising data, immune therapy with **nivolumab** has been FDA-approved in 2nd line, pending phase III data for conventional approval
- Treatments that failed to challenge sorafenib in 1st line or placebo in 2nd line are not recommended. Further clinical trails are needed. TARE in combination with systemic therapy is under investigation

BCLC, Barcelona Clinic Liver Cancer; FDA, Food and Drug Administration; HCC, Hepatocellular carcinoma; TARE, TransArterial RadioEmbolization

PALLIATIVE AND BEST SUPPORTIVE CARE

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- In HCC on cirrhosis **acetaminophen** (paracetamol) up to 3gr/day can be utilised for the management of pain of mild intensity. **NSAIDs** should be avoided whenever possible in patients with underlying cirrhosis. **Opioids** can be utilised for the management of pain of intermediate or severe intensity, paying attention to proactively avoid constipation
- Bone metastasis causing pain or at significant risk of spontaneous secondary fracture benefit from **palliative radiotherapy**
- In patients with advanced cirrhosis, the use of **psychoactive drugs** and particularly benzodiazepines to treat psychological distress is associated with an increased risk of falls and injuries and altered mental status. Great caution should therefore be adopted in their use in patients with HCC with cirrhotic liver dysfunction
- Psycho-oncological support and adequate nutrition should be considered according to patients' condition

HCC, Hepatocellular carcinoma; NSAID, Non-Steroidal Anti-Inflammatory Drug

TRIAL DESIGN AND ENDPOINTS

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- The primary endpoint for clinical phase III trials testing **primary treatments** should be OS, while for **adjuvant therapies after resection/ablation** should be RFS or TTR
- For neoadjuvant treatments in the **waiting list of liver transplantation**, OS, cancer-related deaths and waitlist drop-out rates are recommended as end-points
- There are not optimal **surrogate endpoints** able to recapitulate OS in HCC. TTP and PFS are not recommended as primary endpoints
- ORR and in particular CR by mRECIST correlate with OS in patients treated with **thermal ablation and TACE**. For phase III trials testing TACE ORR and testing thermal ablation CR may be considered as primary endpoint. Conversely, ORR and DCR have not robustly been shown to correlate with OS in patients receiving systemic therapies
- **Phase II studies with systemic therapies** are recommended to be randomized and should target OS as primary endpoint. ORR, TTP and RFS can be assessed as secondary endpoints
- Assessment of response in HCC treated with systemic therapy is suggested to be based on both **RECIST1.1 and mRECIST**. Use of changes in serum levels of biomarkers for assessment of response (i.e. AFP levels) is under investigation
- **Selection of the target population** for clinical trials should consider BCLC staging, Child-Pugh class and ECOG performance status

AFP, Alpha-FetoProtein; BCLC, Barcelona Clinic Liver Cancer; CR, Complete Response; DCR, Disease Control Rate; ECOG, Eastern Cooperative Oncology Group; HCC, Hepatocellular carcinoma; mRECIST, Modified Response Evaluation Criteria in Solid Tumours; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; RFS, Recurrence-Free Survival; TTR, Time To Recurrence; TTP, Time To Progression

REPRESENTATION OF EASL RECOMMENDATIONS FOR TREATMENT ACCORDING TO LEVELS OF EVIDENCE AND STRENGTH OF RECOMMENDATION

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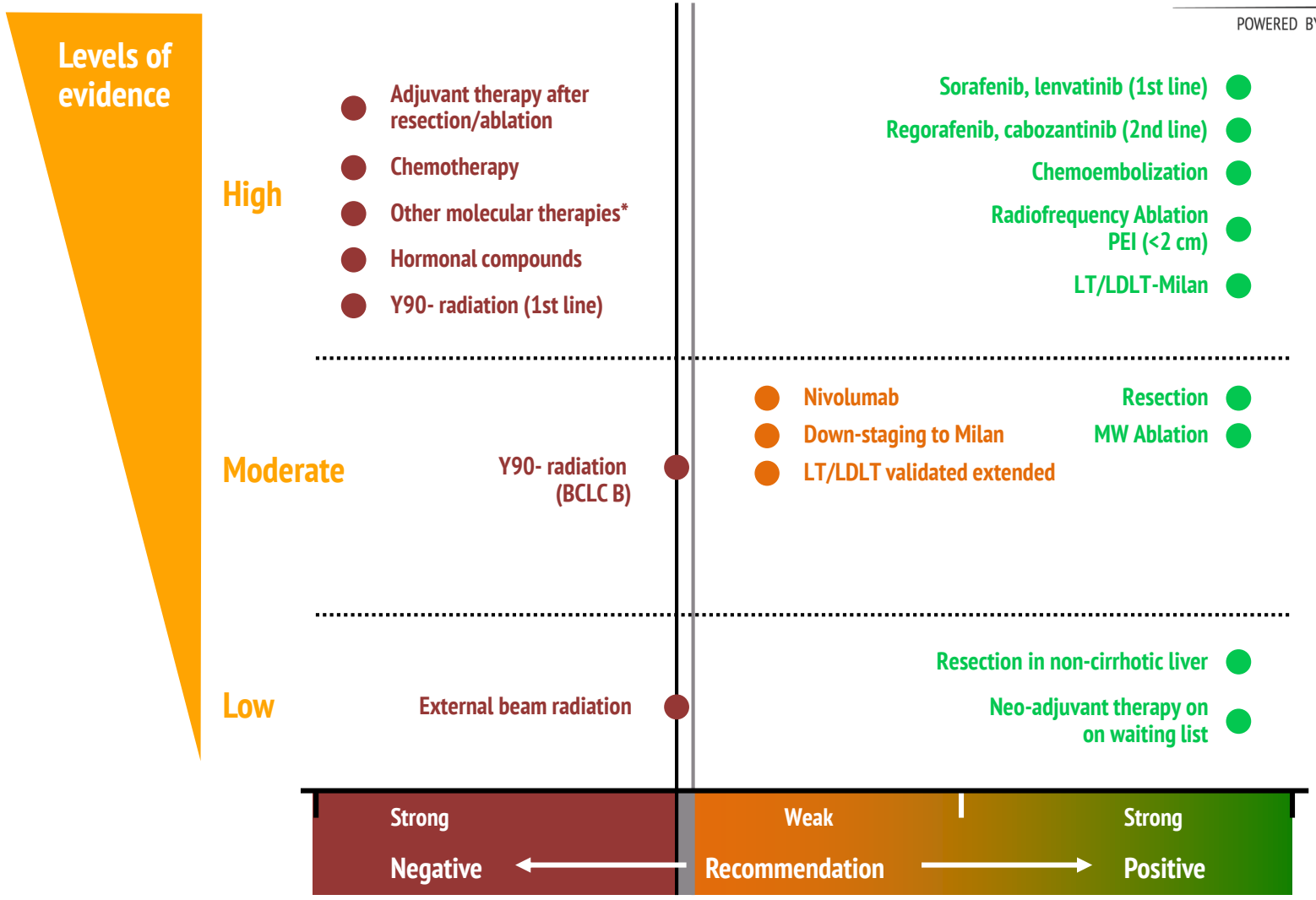

Other molecular therapies (sunitinib, linifanib, brivanib, tivantinib, erlotinib, everolimus, ramucirumab)

Weak recommendation: more evidence needed

BCLC, Barcelona Clinic Liver Cancer; LT, Liver Transplantation; LDLT, Living Donor Liver Transplantation; MW, MicroWave; PEI, Percutaneous Ethanol Injection

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