

# Update

## EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma

Peter R. Galle

# Disclosure of Conflict of Interest

Peter R. Galle

**I have the following financial relationships to disclose.**

- (1) Advisory role fee: **Bayer, Lilly, AstraZeneca, BMS, MSD, Merck, SIRTEX, Eisai**
- (2) Stockholder: No
- (3) Patents and royalties: No
- (4) Honoraria ( lecture fee): **Bayer, SIRTEX**
- (5) Honoraria(manuscript fee) : No
- (6) Research funding from: Bayer





# EASL–EORTC Guidelines

- Official Clinical Practice Guidelines of the EASL, published in **Journal of Hepatology**<sup>1</sup>

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

- Official Clinical Practice Guidelines of the EORTC, published in **European Journal of Cancer**<sup>2</sup>

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



Available at [www.sciencedirect.com](http://www.sciencedirect.com)

SciVerse ScienceDirect

journal homepage: [www.ejconline.com](http://www.ejconline.com)



Clinical Practice Guidelines

## EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma<sup>☆</sup>

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

# **Update EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma**

**European Association for the Study of the Liver**

**Clinical Practice Guideline Panel:**

Peter R. Galle (chair)

Alejandro Forner (EASL governing board representative)

Josep M Llovet

Vincenzo Mazzaferro

Valerie Vilgrain

Fabio Piscaglia

Jean-Luc Raoul

Peter Schirmacher

# Clinical Practice Guideline Panel



Josép M Llovet  
(Hepatologist)



Fabio Piscaglia  
(Hepatologist)



Alejandro Forner  
(EASL GB,  
Hepatologist)



Valérie Vilgrain  
(Radiologist)



Peter R. Galle  
(Chair,  
Hepatologist)



Jean-Luc Raoul  
(Oncologist)



Vincenzo  
Mazzaferro  
(Surgeon)



Peter  
Schirmacher  
(Pathologist)

# Grading evidence and recommendations (adapted from GRADE system)

Grade of evidence	
<b>High</b> level of Evidence	Further research is very unlikely to change our confidence in the estimate of effect
<b>Moderate</b> level of evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
<b>Low</b> level of evidence	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
Grade of Recommendation	
<b>Strong</b> recommendation	Recommendations were reached by consensus of the panel and included the quality of evidence, presumed patient important outcomes and costs
<b>Weak</b> recommendation	

# EPIDEMIOLOGY, RISK FACTORS AND PREVENTION

- *The incidence of HCC is increasing in Europe and worldwide and it is amongst the leading causes of cancer death (**evidence high**).*
- *Vaccination against Hepatitis B reduces the risk of HCC and is recommended to all new-borns and high-risk groups (**evidence high; recommendation strong**).*
- *Governmental health agencies should implement policies for preventing HCV/HBV transmission, counteracting chronic alcohol abuse, and encouraging life styles preventing obesity and metabolic syndrome (**evidence moderate; recommendation strong**).*
- *In general, chronic liver disease should be treated to avoid progression of liver disease (**evidence high; recommendation strong**).*
- *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 HCC development (**evidence high; recommendation strong**).*
- *Once cirrhosis is established, anti-viral therapy is beneficial in preventing cirrhosis progression and decompensation but there are no robust data on its impact on the risk of HCC development (**evidence moderate**). Antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection.*
- *Patients with HCV associated cirrhosis and HCC treated with curative intend maintain a high rate of HCC recurrence even after subsequent directly acting antiviral (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. Thus, further research is encouraged. Currently, in these patients close surveillance is advised and the benefit of viral cure must be outweighed against a potentially higher recurrence risk. (**evidence low; recommendation high**).*
- *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 (**evidence moderate; recommendation strong**).*

# EPIDEMIOLOGY, RISK FACTORS AND PREVENTION

- *The incidence of HCC is increasing in Europe and worldwide and it is amongst the leading causes of cancer death (**evidence high**).*
- *Vaccination against Hepatitis B reduces the risk of HCC and is recommended to all new-borns and high-risk groups (**evidence high; recommendation strong**).*
- *Governmental health agencies should implement policies for preventing HCV/HBV transmission, counteracting chronic alcohol abuse, and encouraging life styles preventing obesity and metabolic syndrome (**evidence moderate; recommendation strong**).*
- *In general, chronic liver disease should be treated to avoid progression of liver disease (**evidence high; recommendation strong**).*
- *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 HCC development (**evidence high; recommendation strong**).*
- *Once cirrhosis is established, anti-viral therapy is beneficial in preventing cirrhosis progression and decompensation but there are no robust data on its impact on the risk of HCC development (**evidence moderate**). Antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection.*
- *Patients with HCV associated cirrhosis and HCC treated with curative intend maintain a high rate of HCC recurrence even after subsequent directly acting antiviral (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. Thus, further research is encouraged. Currently, in these patients close surveillance is advised and the benefit of viral cure must be outweighed against a potentially higher recurrence risk. (**evidence low; recommendation high**).*
- *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 (**evidence moderate; recommendation strong**).*



# SURVEILLANCE

- *Implementation of screening programs to identify at-risk candidate populations should be improved and are a public health goal to decrease HCC-related and overall liver related deaths (**evidence low; recommendation strong**).*
- *Patients at high risk for developing HCC should be entered into surveillance programs. Government health policy and research agencies should address these needs. Groups at high-risk are depicted in Table 3 (**evidence moderate; recommendation strong**).*
- *The role of surveillance for patients with NAFLD without cirrhosis is unclear (**evidence low**).*
- *Surveillance should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every 6 months (**evidence moderate; recommendation strong**).*
- *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 (**evidence low**).*
- *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 (**evidence low; recommendation strong**).*

# SURVEILLANCE

- *Implementation of screening programs to identify at-risk candidate populations should be improved and are a public health goal to decrease HCC-related and overall liver related deaths (**evidence low; recommendation strong**).*
- *Patients at high risk for developing HCC should be entered into surveillance programs. Government health policy and research agencies should address these needs. Groups at high-risk are depicted in Table 3 (**evidence moderate; recommendation strong**).*
- *The role of surveillance for patients with NAFLD without cirrhosis is unclear (**evidence low**).*
- *Surveillance should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every 6 months (**evidence moderate; recommendation strong**).*
- *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 (**evidence low**).*
- *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 (**evidence low; recommendation strong**).*

# Recommendations for HCC surveillance:

## Categories of adult patients in whom surveillance is recommended

1. Cirrhotic patients, Child-Pugh stage A and B (**evidence low; recommendation strong**)
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
3. Non-cirrhotic HBV patients at intermediate or high risk of HCC<sup>1</sup> (according to PAGE-B<sup>2</sup> classes for Caucasian subjects, respectively 10-17 and  $\geq 18$  score points) (**evidence low; recommendation weak**).
4. 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 6 months surveillance have to be reassessed at latest on a yearly basis 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,  $\geq 70=10$ ), gender (M=6, F=0) and platelet count ( $\geq 200.000=0$ , 100.000-199.999=1,  $<100.000=2$ ): a total sum of  $\leq 9$  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  $\geq 18$  is at high risk (17% HCC at 5 years) (Papatheodoritis J Hep 2015)

# DIAGNOSIS

- *Diagnosis of HCC in cirrhotic patients is based on non-invasive criteria or/and pathology (**evidence high; recommendation strong**).*
- *In non-cirrhotic patients diagnosis of HCC should be confirmed by pathology (**evidence moderate; recommendation strong**).*
- *Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistological analyses (**evidence high; recommendation strong**).*
- *Non-invasive criteria can only be applied to cirrhotic patients for nodule(s)  $\geq 1$  cm in the light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI (**evidence high; recommendation strong**) or contrast-enhanced ultrasound (CEUS) (**evidence moderate; recommendation weak**). Diagnosis should be based on the identification of the typical hallmarks of HCC which differ according to imaging techniques or contrast agents (arterial phase hyper-enhancement (APHE) with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid, APHE with late onset ( $>60$  sec) of washout of mild intensity on CEUS).*
- *Due to their higher sensitivity and the analysis of the whole liver, CT or MRI should be used first (**evidence high; recommendation strong**).*
- *FDG PET-scan is not recommended for early diagnosis of HCC due to the high rate of false negative cases (**evidence low; recommendation strong**).*

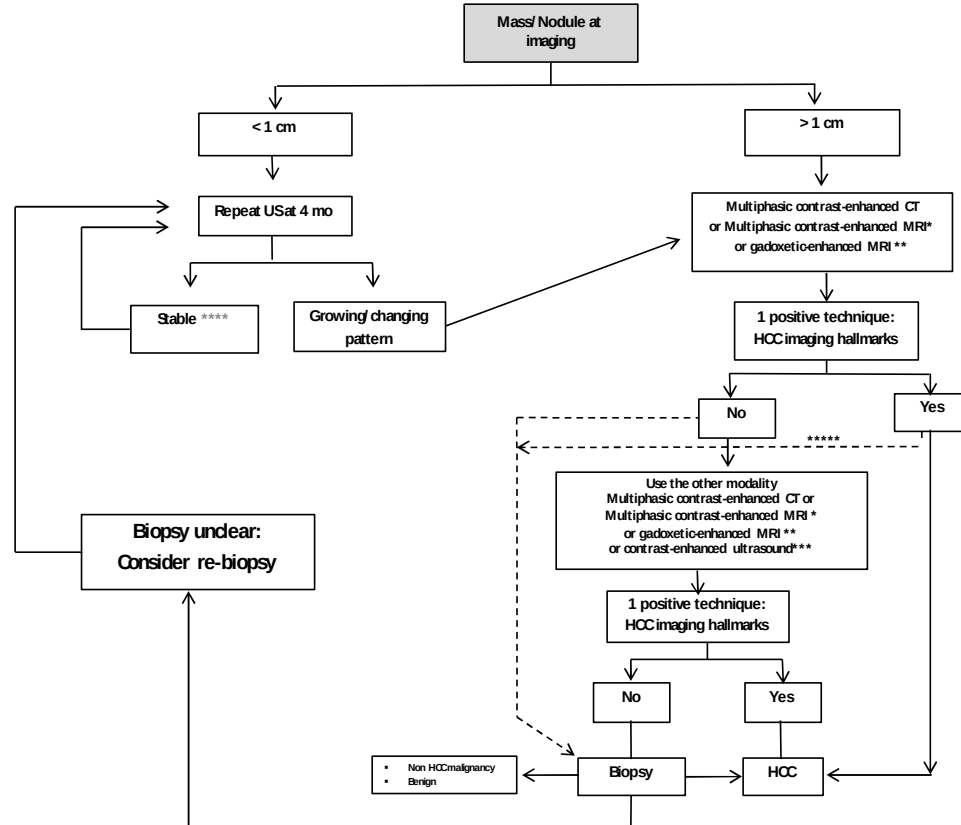
# DIAGNOSIS

- *Diagnosis of HCC in cirrhotic patients is based on non-invasive criteria or/and pathology (**evidence high; recommendation strong**).*
- *In non-cirrhotic patients diagnosis of HCC should be confirmed by pathology (**evidence moderate; recommendation strong**).*
- *Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistological analyses (**evidence high; recommendation strong**).*
- *Non-invasive criteria can only be applied to cirrhotic patients for nodule(s)  $\geq 1$  cm in the light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI (**evidence high; recommendation strong**) or **contrast-enhanced ultrasound (CEUS) (evidence moderate; recommendation weak)**. Diagnosis should be based on the identification of the typical hallmarks of HCC which differ according to imaging techniques or contrast agents (arterial phase hyper-enhancement (APHE) with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid, APHE with late onset (>60 sec) of washout of mild intensity on CEUS).*
- ***Due to their higher sensitivity and the analysis of the whole liver, CT or MRI should be used first (evidence high; recommendation strong).***
- *FDG PET-scan is not recommended for early diagnosis of HCC due to the high rate of false negative cases (**evidence low; recommendation strong**)*

# RECALL POLICY

- *In patients at high risk to develop HCC, nodule(s) less than 1 cm in diameter detected by ultrasound should be followed at  $\leq 4$  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 (**evidence weak; recommendation weak**).*
- *In cirrhotic patients, diagnosis of HCC for nodules of  $\geq 1$  cm in diameter can be achieved with non-invasive criteria or/and biopsy-proven pathological confirmation (**evidence strong; recommendation strong**).*
- *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 (**evidence low; recommendation strong**).*

# Diagnostic algorithm and recall policy in cirrhotic liver



# STAGING SYSTEMS and TREATMENT ALLOCATION

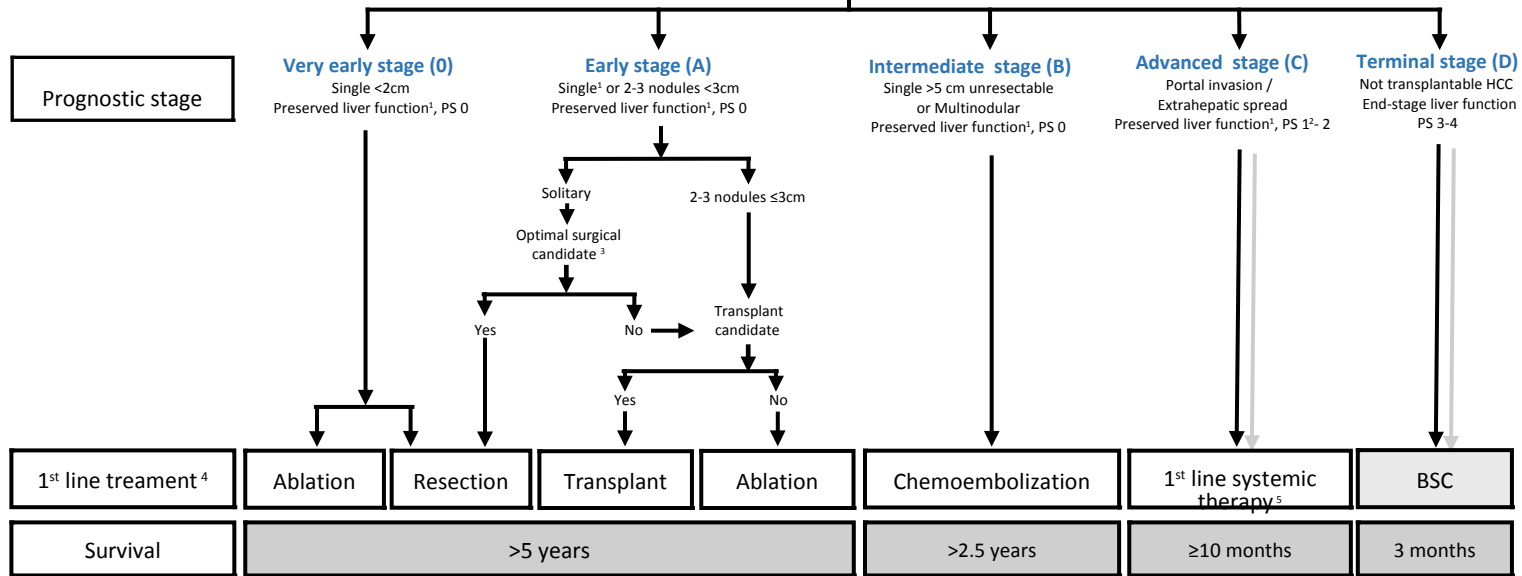
- *Staging systems for clinical decision making in HCC should include tumour burden, liver function and performance status (**evidence high; recommendation strong**).*
- *The BCLC staging system has been repeatedly validated and is recommended for prognostic prediction and treatment allocation (**evidence high; recommendation strong**).*
- *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 (**evidence low; recommendation strong**).*



# STAGING SYSTEMS and TREATMENT ALLOCATION

- *Staging systems for clinical decision making in HCC should include tumour burden, liver function and performance status (**evidence high; recommendation strong**).*
- *The BCLC staging system has been repeatedly validated and is recommended for prognostic prediction and treatment allocation (**evidence high; recommendation strong**).*
- *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 (**evidence low; recommendation strong**).*

# HCC in cirrhotic liver



<sup>1</sup> “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.

<sup>2</sup> PS 1 refers to tumor induced (as per physician opinion) modification of performance capacity.

<sup>3</sup> **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%.

<sup>4</sup> The **stage migration strategy** is a therapeutical 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.

<sup>5</sup> 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 in first line, but no effective second line option after lenvatinib has been explored. Cabozantinib was announced to be superior to placebo in 2nd or 3rd line, but no data has been presented as of December 2017.

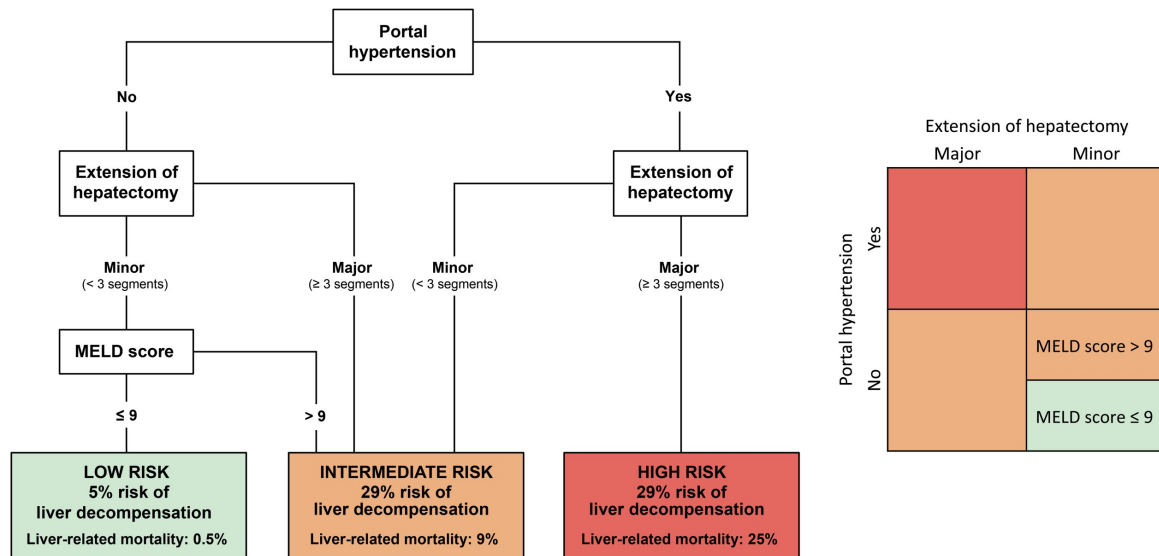
# RESPONSE ASSESSMENT

- *Assessment of response in HCC should be based on the modified RECIST (mRECIST) for loco-regional therapies (**evidence moderate; recommendation strong**). As per systemic therapies both mRECIST and RECIST1.1 are recommended (**evidence moderate; recommendation weak**). 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 (**evidence moderate; recommendation weak**). Follow-up strategies for detection of recurrence after different treatments are outlined in the specific treatment sections.*

# LIVER RESECTION (LR)

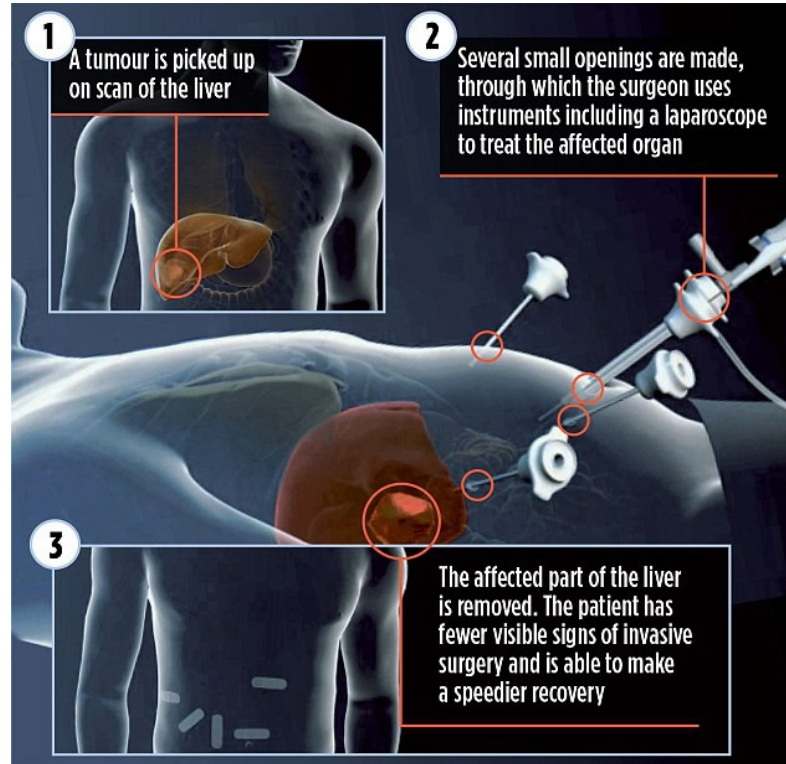
- *Surgical resection is recommended as treatment of choice in patients with HCC arising on a non-cirrhotic liver (**evidence low; recommendation strong**).*
- *Indication to LR for HCC in cirrhosis should be based on multi-parametric, composite assessment of liver function, portal hypertension, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' comorbidities (**evidence high; recommendation strong**).*
- *Perioperative mortality of liver resection in cirrhotic patients should be less than 3% (**evidence high; recommendation strong**).*
- *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 (**evidence moderate; recommendation strong**).*
- *In properly trained centres, LR should be considered via laparoscopic/minimal-invasive approaches, especially for tumours in anterolateral and superficial locations (**evidence moderate; recommendation weak**).*
- *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 (**evidence low; recommendation weak**).*
- *HCC-related macrovascular invasion is a contraindication to LR. Intervention on distal portal invasion – at segmental or sub-segmental level – deserves investigations within prospectively designed protocols (**evidence moderate**).*
- *Neoadjuvant or adjuvant therapies are not recommended because they have not proven to improve outcome of patients treated with resection (**evidence high; recommendation strong**). Further clinical trials with new agents are encouraged.*
- *Follow-up after resection in curative intent is recommended because of high rates of treatable recurrence. Follow-up intervals are not clearly defined (**evidence high; recommendation strong**). In the first year 3-4 months intervals are practical.*

# 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.

# Principles of mini-invasive / laparoscopic liver resection for HCC



# LIVER TRANSPLANTATION (LT)

- *Liver transplantation (LT) is recommended as first-line option for HCC within Milan criteria unsuitable for resection (**evidence high; recommendation strong**). 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 within defined protocols (**evidence low; recommendation weak**).*
- *Composite criteria defining transplantability considering surrogates of tumour biology – among which AFP is the most relevant – 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. Composite criteria should be investigated and determined a priori, validated prospectively and auditable at any time (**evidence low; recommendation strong**).*
- *Tumour vascular invasion and extra-hepatic metastases are absolute contraindication to LT for HCC (**evidence high**).*
- *There is no contraindication to the use of marginal cadaveric grafts\* for LT in patients with HCC (**evidence moderate**). 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 (**evidence moderate; recommendation strong**).*
- *LT for HCC may add Transplant Benefit (TB) considerations to the conventional transplant principles of Urgency and Utility in decision-making on patient selection and prioritization, depending on list composition and dynamics (**evidence moderate; recommendation weak**).*
- *In LT candidates with HCC, the use of pre-transplant (neo-adjuvant) loco-regional therapies (LRT) is recommended if feasible as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence - particularly when complete or partial tumour response are achieved (**evidence low; recommendation strong**).*
- *Although the contribution of living donation to LT for HCC in Europe is still marginal, LDLT for HCC remains an option to be explored in selected patients and in experienced centres, according to wait-list time and dynamics and with donor-recipient double equipoise principles (**evidence low**).*

# LIVER TRANSPLANTATION (LT)

- *Liver transplantation (LT) is recommended as first-line option for HCC within Milan criteria unsuitable for resection (**evidence high; recommendation strong**). 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 within defined protocols (**evidence low; recommendation weak**).*
- *Composite criteria defining transplantability considering surrogates of tumour biology – among which AFP is the most relevant – 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. Composite criteria should be investigated and determined a priori, validated prospectively and auditable at any time (**evidence low; recommendation strong**).*
- *Tumour vascular invasion and extra-hepatic metastases are absolute contraindication to LT for HCC (**evidence high**).*
- *There is no contraindication to the use of marginal cadaveric grafts\* for LT in patients with HCC (**evidence moderate**). 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 (**evidence moderate; recommendation strong**).*
- *LT for HCC may add Transplant Benefit (TB) considerations to the conventional transplant principles of Urgency and Utility in decision-making on patient selection and prioritization, depending on list composition and dynamics (**evidence moderate; recommendation weak**).*
- *In LT candidates with HCC, the use of pre-transplant (neo-adjuvant) loco-regional therapies (LRT) is recommended if feasible as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence - particularly when complete or partial tumour response are achieved (**evidence low; recommendation strong**).*
- *Although the contribution of living donation to LT for HCC in Europe is still marginal, LDLT for HCC remains an option to be explored in selected patients and in experienced centres, according to wait-list time and dynamics and with donor-recipient double equipoise principles (**evidence low**).*



# LOCAL ABLATION AND EXTERNAL RADIATION

- *Thermal ablation with radiofrequency is considered the standard of care for patients with BCLC 0 and A tumours not suitable for surgery (**evidence high; recommendation strong**). 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 location could be adopted as first line therapy even in surgical patients (**evidence moderate; recommendation strong**).*
- *Thermal ablation with microwave showed promising results for local control and survival (**evidence low**). 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 (**evidence high; recommendation strong**)*
- *External beam radiotherapy is under investigation, and, so far there is no robust evidence to support this therapeutic approach in the management of HCC (**evidence low; recommendation weak**).*

# LOCAL ABLATION AND EXTERNAL RADIATION

- *Thermal ablation with radiofrequency is considered the standard of care for patients with BCLC 0 and A tumours not suitable for surgery (**evidence high; recommendation strong**). 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 location could be adopted as first line therapy even in surgical patients (**evidence moderate; recommendation strong**).*
- *Thermal ablation with microwave showed promising results for local control and survival (**evidence low**). 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 (**evidence high; recommendation strong**)*
- *External beam radiotherapy is under investigation, and, so far there is no robust evidence to support this therapeutic approach in the management of HCC (**evidence low; recommendation weak**).*

# TRANSARTERIAL THERAPIES

- *Trans Arterial Chemo Embolization (TACE) is recommended for patients with BCLC stage B and should be carried out in a selective manner (**evidence high; recommendation strong**). The use of drug-eluting beads has shown similar benefit as conventional TACE (cTACE; gelfoam-lipiodol particles) and either of the two can be utilized (**evidence high; recommendation strong**). TACE should not be used in patients with decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion or extrahepatic spread (**evidence high; recommendation strong**). There is insufficient evidence to recommend bland embolization, selective intra-arterial chemotherapy and lipiodolization (**evidence moderate**).*
- *Transarterial Radioembolization (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 overall survival benefit compared to sorafenib in BCLC B and C patients. The subgroup of patients benefitting from TARE needs to be defined (**evidence moderate**).*
- *There is insufficient evidence to recommend scores to better select BCLC B patients' candidates to first TACE or for subsequent sessions (**evidence moderate**).*

# TRANSARTERIAL THERAPIES

- *Trans Arterial Chemo Embolization (TACE) is recommended for patients with BCLC stage B and should be carried out in a selective manner (**evidence high; recommendation strong**). The use of drug-eluting beads has shown similar benefit as conventional TACE (cTACE; gelfoam-lipiodol particles) and either of the two can be utilized (**evidence high; recommendation strong**). TACE should not be used in patients with decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion or extrahepatic spread (**evidence high; recommendation strong**). There is insufficient evidence to recommend bland embolization, selective intra-arterial chemotherapy and lipiodolization (**evidence moderate**).*
- *Transarterial Radioembolization (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 overall survival benefit compared to sorafenib in BCLC B and C patients. The subgroup of patients benefitting from TARE needs to be defined (**evidence moderate**).*
- *There is insufficient evidence to recommend scores to better select BCLC B patients' candidates to first TACE or for subsequent sessions (**evidence moderate**).*

# SYSTEMIC THERAPIES

- *Sorafenib is the standard systemic therapy for HCC in first 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 (**evidence high; recommendation strong**).*
- *Lenvatinib has been shown to be non-inferior to sorafenib and can be used in first line for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumours - BCLC C without main portal vein invasion - or those tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).*
- *There are no clinical or molecular biomarkers established to predict response to first or second line systemic treatments (**evidence moderate**).*
- *Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (**evidence high; recommendation strong**). 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 second-line, pending phase III data for conventional approval. At present, the data are not matured enough to give a clear recommendation (**evidence moderate; recommendation weak**).*
- *Treatments that failed to challenge sorafenib in first line or placebo in second line are not recommended. Further clinical trials are needed to confirm claims of non-inferiority or any trends of better outcome identified in sub-group analysis (**evidence high**). TARE in combination with systemic therapy is under investigation.*
- *Patients at BCLC D stage and no candidates for liver transplantation should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials (**evidence low; recommendation strong**).*

# SYSTEMIC THERAPIES

- *Sorafenib is the standard systemic therapy for HCC in first 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 (**evidence high; recommendation strong**).*
- *Lenvatinib has been shown to be non-inferior to sorafenib and can be used in first line for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumours - BCLC C without main portal vein invasion - or those tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).*
- *There are no clinical or molecular biomarkers established to predict response to first or second line systemic treatments (**evidence moderate**).*
- *Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (**evidence high; recommendation strong**). 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 second-line, pending phase III data for conventional approval. At present, the data are not matured enough to give a clear recommendation (**evidence moderate; recommendation weak**).*
- *Treatments that failed to challenge sorafenib in first line or placebo in second line are not recommended. Further clinical trials are needed to confirm claims of non-inferiority or any trends of better outcome identified in sub-group analysis (**evidence high**). TARE in combination with systemic therapy is under investigation.*
- *Patients at BCLC D stage and no candidates for liver transplantation should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials (**evidence low; recommendation strong**).*

# PALLIATIVE AND BEST SUPPORTIVE CARE

- *In HCC on cirrhosis acetaminophen (paracetamol) up to 3gr/day can be utilized for the management of pain of mild intensity. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided whenever possible in patients with underlying cirrhosis. Opioids can be utilized for the management of pain of intermediate or severe intensity, paying attention to proactively avoid constipation (**evidence low; recommendation strong**).*
- *Bone metastasis causing pain or at significant risk of spontaneous secondary fracture benefit from palliative radiotherapy (**evidence low**).*
- *In patients with advanced cirrhosis the use of psychoactive drugs and particularly of 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 (**evidence low; recommendation strong**).*
- *Psycho-oncological support and adequate nutrition should be considered according to patients' condition (**evidence low; recommendation strong**).*

# TRIAL DESIGN and ENDPOINTS

- *The primary end point for clinical phase III trials testing primary treatments (either loco-regional or systemic therapies) should be overall survival (OS), while for adjuvant therapies after resection/ablation should be recurrence-free survival (RFS) or time to recurrence (TTR) (**recommendation strong**).*
- *For neoadjuvant treatments in the waiting list of liver transplantation, OS, cancer related deaths and waitlist drop-out rates are recommended as end-points (**recommendation strong**).*
- *There are no optimal surrogate end-points able to recapitulate overall survival in HCC. Time to progression (TTP) and progression-free survival (PFS) are not recommended as primary end-points (**evidence high; recommendation weak**).*
- *Objective response rate (ORR) and in particular CR by mRECIST correlate with OS in patients treated with thermal ablation and TACE (**evidence high**). For phase II trials testing TACE ORR and testing thermal ablation CR may be considered as primary endpoint (**recommendation weak**). Conversely, ORR and disease control rate (DCR) have not robustly been shown to correlate with OS in patients receiving systemic therapies.*
- *Phase II studies testing systemic therapies are recommended to be randomized and should target OS as primary endpoint (**recommendation strong**). ORR, TTP and RFS can be assessed as secondary end-points.*
- *Assessment of response in HCC treated with systemic therapy is suggested to be based on both RECIST1.1 and mRECIST (**recommendation weak**). 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 system, Child-Pugh class and ECOG performance status (**recommendation strong**).*
- *Stratification for prognostic factors prior randomization is critical in randomized studies and is recommended (**evidence high; recommendation strong**).*
- *The control arm of randomized phase II and III studies should be the standard of care established in the current guidelines. When no standard of care is available (adjuvant trials, 3<sup>rd</sup> line setting) a placebo-control arm is recommended (**recommendation strong**).*
- *Upfront liver biopsy and blood sampling is recommended for clinical and diagnostic trials (**recommendation strong**).*



## Levels of evidence

High

- Adjuvant therapy after resection/ablation
- Chemotherapy
- Other molecular therapies\*
- Hormonal compounds
- Y90- radiation (1<sup>st</sup> line)

- Sorafenib, Lenvatinib (1<sup>st</sup> line)
- Regorafenib, cabozantinib (2<sup>nd</sup> line)
- Chemoembolization
- Radiofrequency Ablation  
PEI (<2 cm)
- LT/LDLT-Milan

Moderate

Y90- radiation  
(BCLC B)

- Nivolumab
- Down-staging to Milan
- LT/LDLT validated extended
- Resection
- MV Ablation

Low

External beam radiation

- Resection in non-cirrhotic liver
- Neo-adjuvant therapy on waiting list

Strong

Weak

Strong

Negative

Recommendation

Positive

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

● Weak recommendation: more evidence needed