HEPATOCELLULAR CARCINOMA

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Introduction and Epidemiology :

Liver cancer is the sixth leading cause of cancer and the third leading cause of cancer-related deaths globally.

Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem.

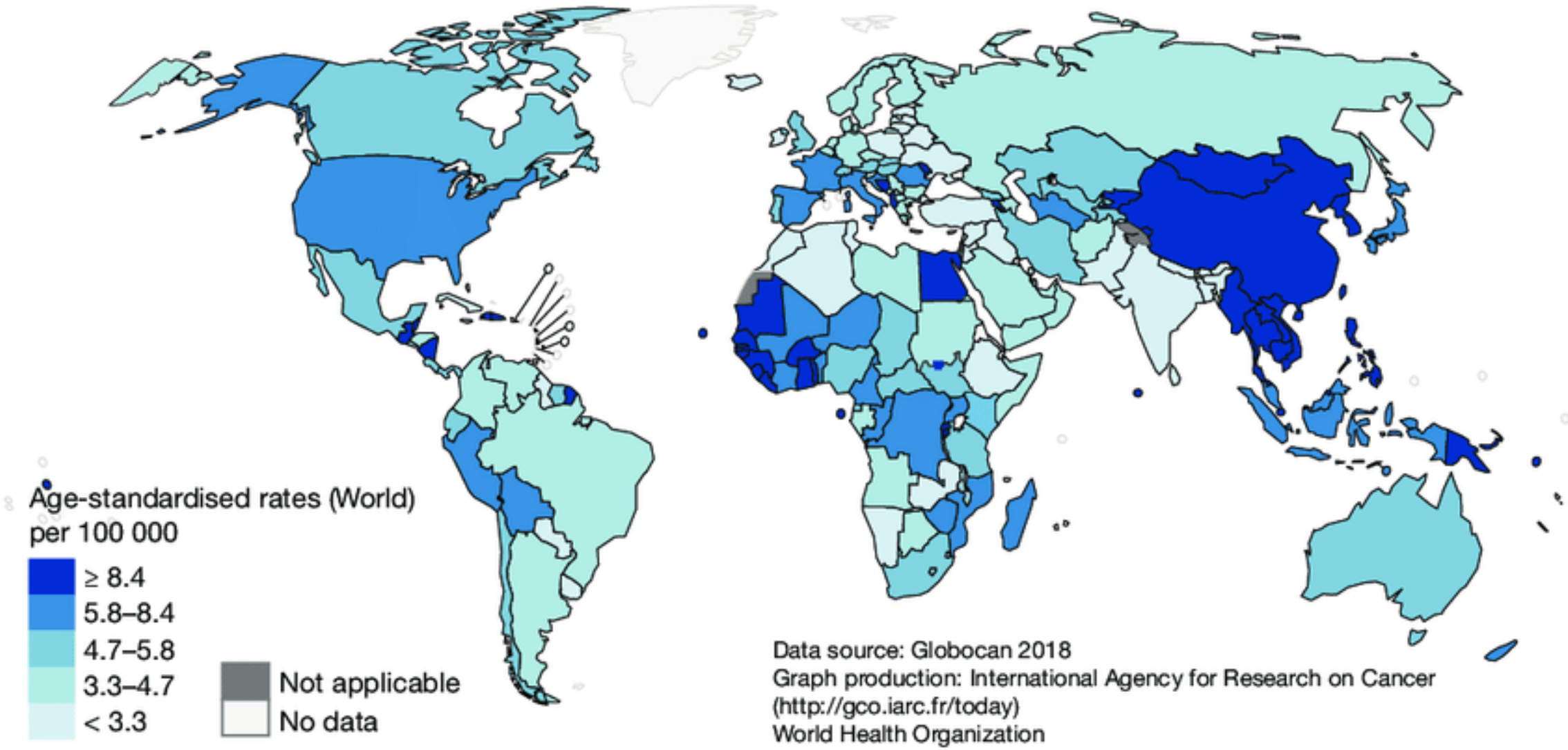
- 80% of all HCC emanate from SSA and East Asia

HCC account for 8.3% of all cancer death in 2020.

- Ranking the 3rd cancer mortality with shortest survival of any cancer in both gender.

HCC in SSA

- incidence range 4:1 Male to Female ratio
- Is 2nd and 3rd leading cancer in men and women respectively .
- Increased number of newly diagnosed cases with shorter survival


Age-standardised rates (World)
per 100 000
≥ 8.4
5.8–8.4
4.7–5.8
3.3–4.7
< 3.3
Not applicable
No data
Data source: Globocan 2018
Graph production: International Agency for Research on Cancer
(http://gco.iarc.fr/today)
World Health Organization

Aetiology and Risk Factors :

- **Cirrhotic**
  - HBV
  - HCV
  - NASH
  - Alcohol
- Others
  - Aflatoxin
- Autoimmune hepatitis
-
  - Wilson
  - Tyrosinemia
  - Citrullinemia
  - Alfa 1 antitrypsin

. **Noncirrhotic**

  - HBV
  - NAFLD
  - Haemochromatosis

Organization	Risk Factors	Aetiology
EASL	- Chronic hepatitis B and C infections	- Cirrhosis due to chronic hepatitis B and C2
	- Alcohol consumption	- Alcoholic liver disease2
	- Nonalcoholic fatty liver disease (NAFLD)	- NAFLD2
	- Aflatoxin exposure	- Aflatoxin-induced liver damage2
AASLD	- Chronic hepatitis B and C infections	- Cirrhosis due to chronic hepatitis B and C4
	- Alcohol consumption	- Alcoholic liver disease4
	- Nonalcoholic fatty liver disease (NAFLD)	- NAFLD4
	- Metabolic dysfunction-associated steatotic liver disease (MASLD)	- MASLD
APASL	- Chronic hepatitis B and C infections	- Cirrhosis due to chronic hepatitis B and C7
	- Alcohol consumption	- Alcoholic liver disease7
	- Nonalcoholic fatty liver disease (NAFLD)	- NAFLD7

HBV :

- Hepatitis B Virus :
- 350-400 million infected worldwide
- 50% of all HCC
- Nearly all childhood cases
- May occur in the absence of cirrhosis
- 80-90% of HBV patients have cirrhosis
- Risk increased in those exposed to aflatoxin , alcohol , tobacco , HCV coinfection , high level of HBV replication .
- High-risk seronegative people should be vaccinated against HBV to decrease HCC incidence and HCC-related death and improve overall survival
- (Tenofovir and entecavir) significantly decrease the risk of HCC development in CHBV

HCV

- Hepatitis C Virus
- 3-4% of world population infected
- Risk of HCC increased 15 – 20 % X
- Limited to those with advance fibrosis or cirrhosis
- HCC occur at rate of 2-5% year
- Conflicting studies regarding risk of HCC following antiviral therapy (J Hepatomegaly 65:663)
- HCV infection and liver fibrosis should be treated with (DAA) to reduce the risk of cirrhosis-related complications, including HCC

MASLD

- MASLD and HCC
- NAFLD (MASLD) perhaps the most common liver disease worldwide
- 80 million affected in US
- 2002-2012 4 fold increase in liver transplant due to NASH
- NASH second cause of HCC related liver transplantation 8.3 to 13.5%
- MASLD cause HCC in both cirrhotic and noncirrhotic liver especially with steatosis and F3 fibrosis.
-

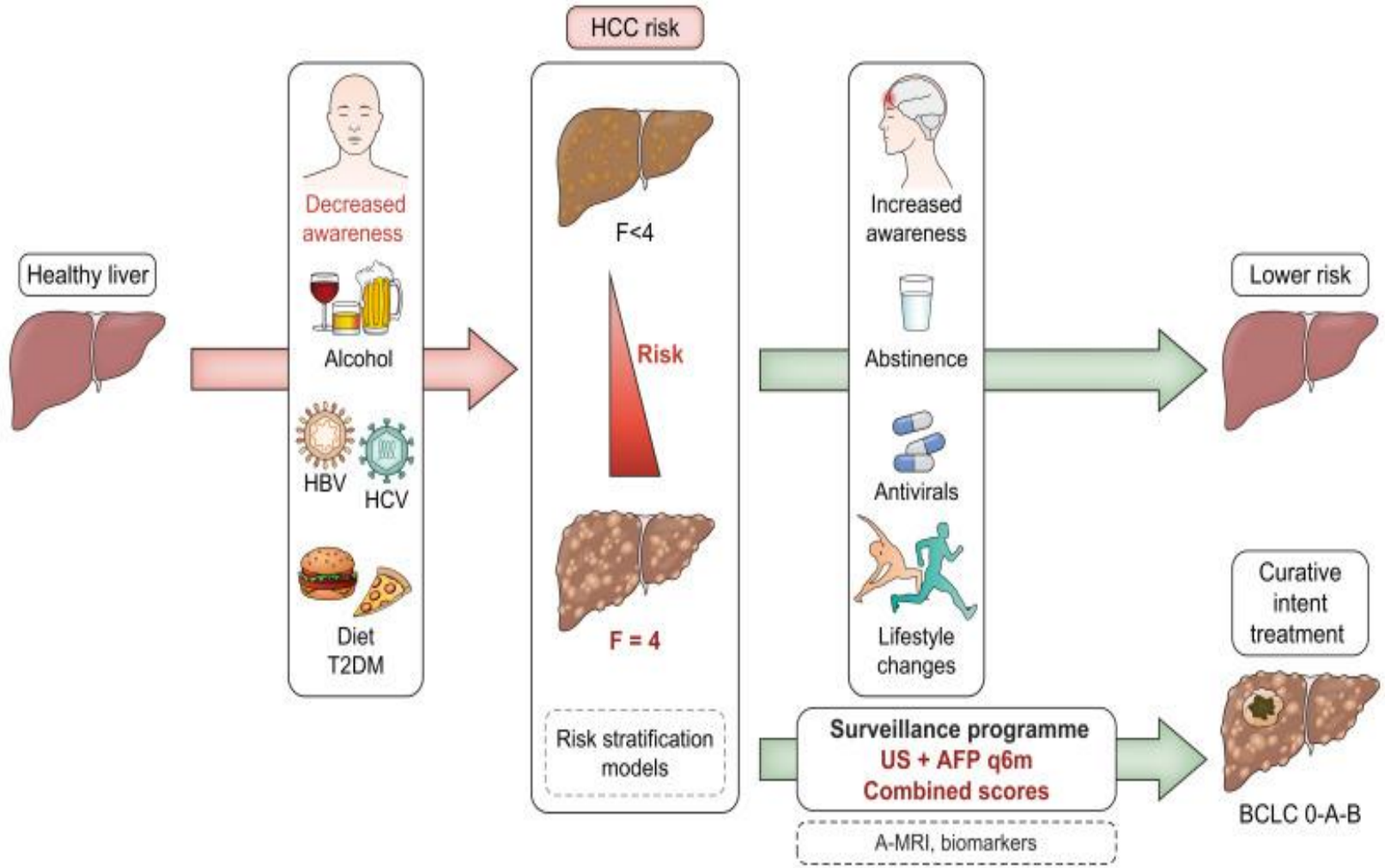
Prevention :

- Weight loss in obese patients ,
- alcohol and tobacco cessation

  are recommended to reduce the risk of HCC
- Coffee consumption

  may be recommended to reduce the risk of HCC
- the use of statins, aspirin and metformin

  cannot currently be recommended to reduce the risk of HCC


HCC risk
Healthy liver
Decreased awareness
Alcohol
HBV
HCV
Diet
T2DM
F<4
Risk
F = 4
Risk stratification models
Increased awareness
Abstinence
Antivirals
Lifestyle changes
Lower risk
Curative intent treatment
Surveillance programme
US + AFP q6m
Combined scores
A-MRI, biomarkers
BCLC 0-A-B

Clinical Manifestations :

- Asymptomatic in early stage , patient usually present at advance stages.
- However, due to widespread used of imaging (US , CT , MRI)more HCC are found incidentally in early stages.
- Symptoms and signs of advance liver cirrhosis :
- Impaired LFTs
- Paraneoplastic syndrome

-

Screening Tools :

USG :

Low sensitivity of detecting small lesion (27.3 %) and (63%) for lesion > 2cm with limited visualization in AFLD , MASLD and Ascites.

Alfa fetoprotein :

- At cutoff 20 ng/ml sensitivity and specificity are (49.1, 87.9%)
- AFP 21-400 ng/ml we miss 50% of cases
- AFP more than 400 ng/ml effective in early dx.
- AFP Is not specific for HCC ,

. USG+ Alfa fetoprotein increase sensitivity74% with decrease specificity

New Screening Modalities :

Future test

- Lens culinaris agglutination -reactive fraction of AFP (AFP-L3)
- Des-gamma- carboxy prothrombin (DCP)
- Combination of the above
- Abbreviated MRI
- combine AFP with both clinical and serum biomarkers in different models such as VA, ASAP, male-ABCD,HEB, HES or GALAD.

Surveillance :

- High risk patients

- chronic and active HBV infection esp. African and Asian .
- liver cirrhosis.
- Screening us +/- alfa-fetoprotein of the liver q6 months
- HCC surveillance is associated with improved early-stage detection (or 2.08 95% ci 1.80-2.37)
- Curative treatment rate (2.4 95% ci 1.9-2.52)
- HCC surveillance was associated with significant survival rate (OR 1.90 ci 95% 1.67-2.17)
- No role for CT or MRI for screening
- With aggressive screening resect-ability is reaching 30 – 50%

Surveillance :

Guidelines	Surveillance population	Surveillance modality	Surveillance interval
AASLD 2018[40]	All patients with liver cirrhosis except patients with Child–Pugh stage C cirrhosis unless on transplant waiting list	US ± AFP	6 months
APASL 2017[41]	All patients with cirrhosis Chronic HBV carriers without cirrhosis • Asian females >50 years • Asian males >40 years • Africans >20 years • Family history of HCC	US + AFP	6 months
EASL 2018[24]	Cirrhosis Child–Pugh stage A and B Cirrhosis Child–Pugh stage C awaiting liver transplant Chronic HBV without cirrhosis at intermediate (10–17) or high risk (≥18) of HCC according to PAGE-B score Non-cirrhotic patients with Metavir F3 fibrosis regardless of etiology	US	6 months
ESMO 2018[42]	All patients with cirrhosis as long as liver function and comorbidities allow curative or palliative treatment Chronic HBV and HCV carriers with Metavir F3 fibrosis Asian chronic HBV carriers with serum HBV-DNA above 10,000 copies/mL	US ± AFP	6 months

Abbreviations: AASLD, American Association for the Study of Liver Disease; AFP, alpha fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PAGE-B score, Platelets, Age, Gender, Hepatitis B; US, ultrasound.

Diagnosis and Staging :

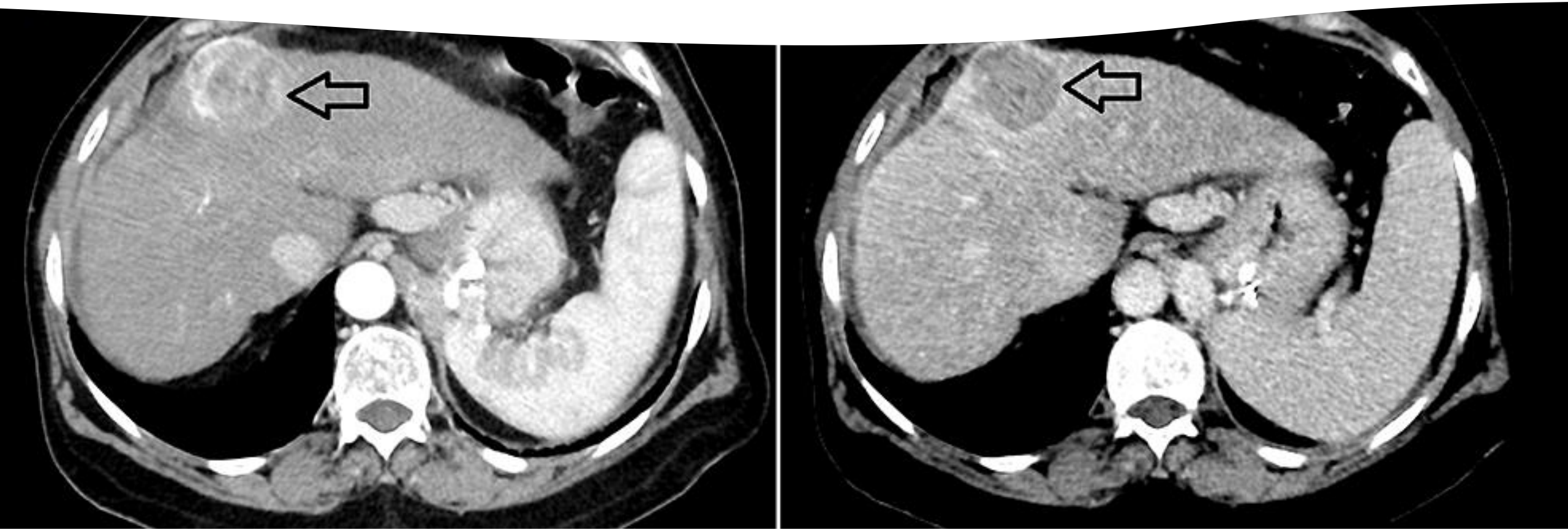
- ✓ Histopathology plays a crucial role in confirmation and providing essential tissue characteristics of the tumor.
- ✓ In the pathway from benign to dysplastic to malignant liver nodules, changes in vascularization occur that can be captured by contrast-enhanced imaging and are the basis of the non-invasive diagnosis of HCC.
- ✓ In patients with cirrhosis, HBV infection or a previous diagnosis of HCC, a liver nodule can be diagnosed non-invasively as HCC when major features are observed with dynamic contrast-enhanced CT, MRI or (CEUS) .
- ✓ The terminology and criteria used to describe liver nodules should follow the LI-RADS v2018 recommendations

LIRADS

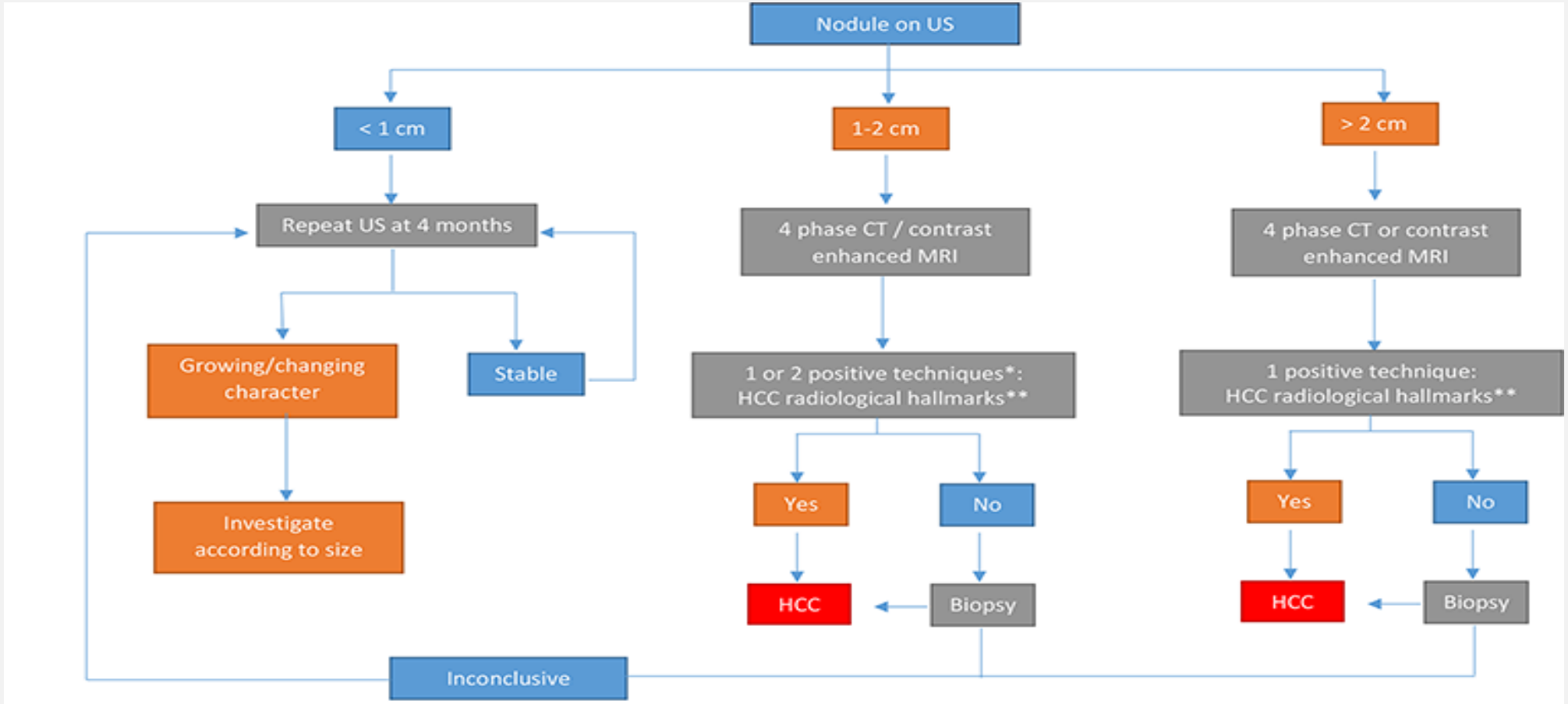
- Two diagnostic LI-RADS algorithms have been developed, one for CT/MRI and another one for CEUS
- The LI-RADS CT/MR diagnostic algorithm can be used in patients with cirrhosis or chronic HBV infection or current or prior HCC, regardless of lesion size
- CT/MRI, the following major imaging features are combined to reach the diagnosis:
  - tumor size,
  - rim and non rim arterial hyperenhancement
  - peripheral and non peripheral washout ,
  - enhancing capsule and
  - threshold growth.
- With CEUS,
  - non-rim arterial hyper enhancement with late-onset (>60 s) and washout of mild intensity are combined to reach the diagnosis

Diagnostic Approach

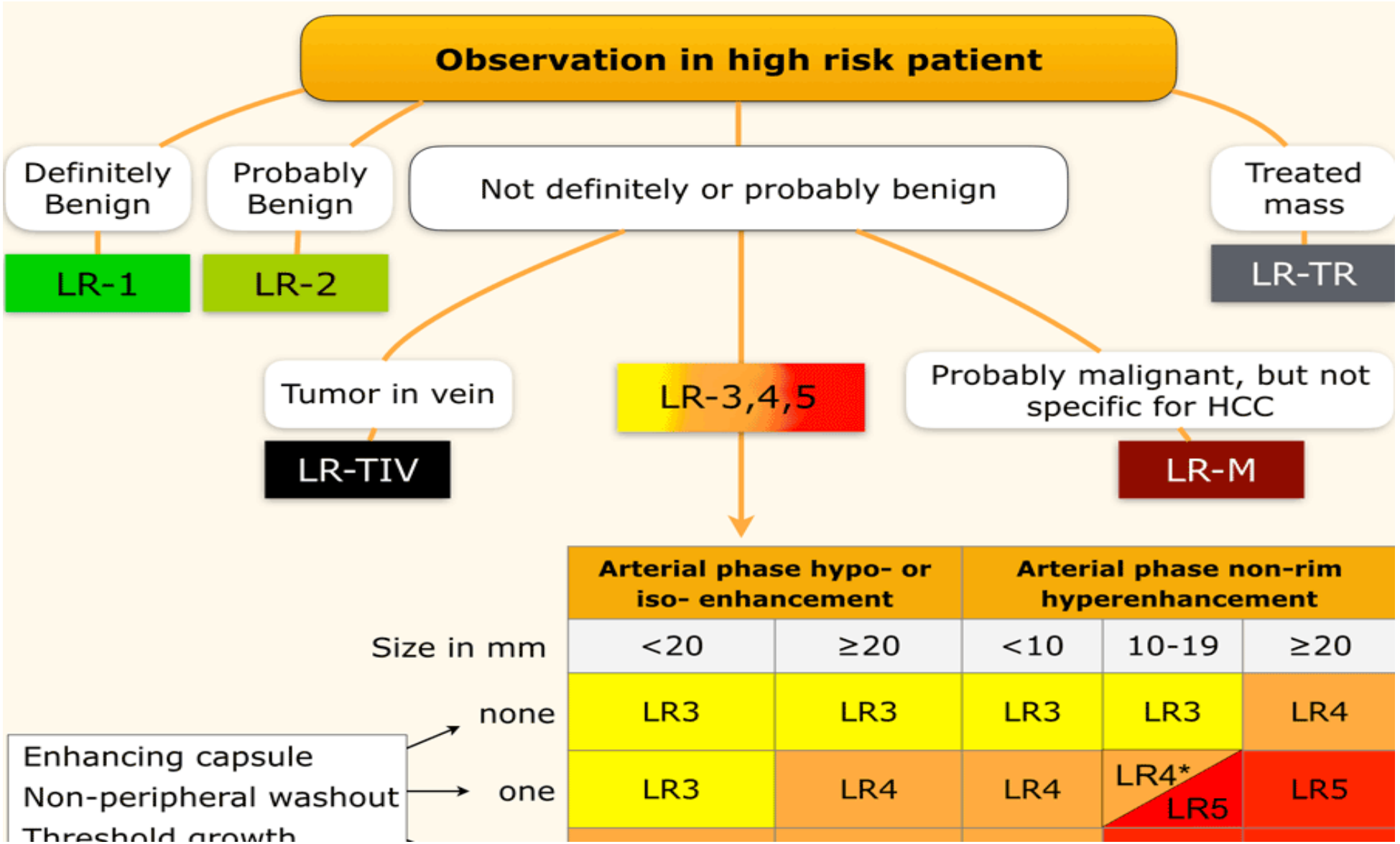
- Only tumor that can be diagnosed radiologically in the absence of biopsy but there is prerequisites ;
- underlying cirrhosis
- More than 1cm lesion size
- Showing typical feature of arterial phase hyperenhancement and portal venous washout .

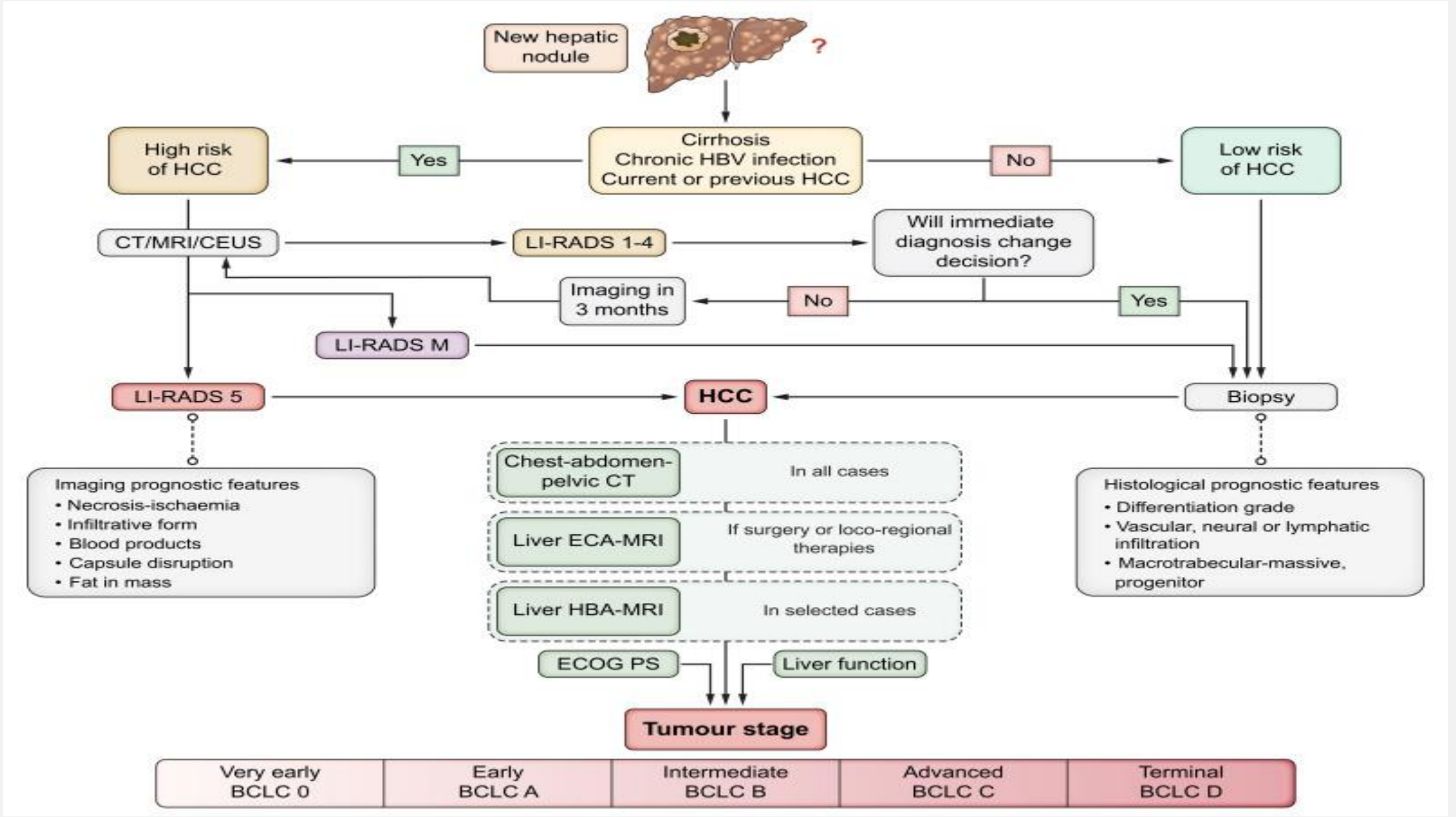


Diagnostic Algorhythm :



* One imaging technique only recommended in centers of excellence with high-end radiological equipment.
** HCC radiological hallmark arterial hypervascularity and venous/late phase washout.


Observation in high risk patient
Definitely Benign
Probably Benign
Not definitely or probably benign
Treated mass
LR-1
LR-2
LR-TR
Tumor in vein
LR-3,4,5
Probably malignant, but not specific for HCC
LR-TIV
LR-M
Arterial phase hypo- or iso- enhancement
Arterial phase non-rim hyperenhancement
Size in mm
<20
≥20
<10
10-19
≥20
Enhancing capsule
Non-peripheral washout
Threshold growth
none
LR3
LR3
LR3
LR3
LR4
one
LR3
LR4
LR4
LR4*
LR5
LR5


New hepatic nodule
?
Cirrhosis
Chronic HBV infection
Current or previous HCC
Yes
High risk of HCC
No
Low risk of HCC
CT/MRI/CEUS
LI-RADS 1-4
Will immediate diagnosis change decision?
Imaging in 3 months
No
Yes
LI-RADS M
LI-RADS 5
HCC
Biopsy
Imaging prognostic features
• Necrosis-ischaemia
• Infiltrative form
• Blood products
• Capsule disruption
• Fat in mass
Chest-abdomen-pelvic CT
In all cases
Liver ECA-MRI
If surgery or loco-regional therapies
Liver HBA-MRI
In selected cases
Histological prognostic features
• Differentiation grade
• Vascular, neural or lymphatic infiltration
• Macrotrabecular-massive, progenitor
ECOG PS
Liver function
Tumour stage
Very early BCLC 0
Early BCLC A
Intermediate BCLC B
Advanced BCLC C
Terminal BCLC D

Role of Biopsy in Diagnosis of HCC :

- If the criteria for the non-invasive diagnosis of HCC are not met (LI-RADS-5, TIV), a tumor biopsy is mandatory
- so it required in minority of cases
- LR-4 and LR-M (AASLD) ,
- Indeterminate nodule > 1cm (APASL)
- Noncirrhotic HCC inconclusive imaging (EASL)
- May be required of certain clinical trial
- Low risk of seeding (HCC)
- High risk of seeding (cholangiocarcinoma)
- When performed
    - Immunohistochemistry
    - Reticulin staining

Histological Classification :

- Depend on national consensus panel
- Macroscopically

    Nodular most common

    Large circumscribed mass

    Diffusely infiltrative type

Histological Classification : contd..

Microscopically :

- Well differentiated
- Moderately differentiated
- undifferentiated
- Progenitor cell HCC

Histological Classification : contd…

Fibrolamellar HCC ;

- Distinct type in younger age with equal gender distribution .
- Characterized by non-secretory AFP , occur in noncirrhotic liver , not caused by hepatitis b or c .
- Better prognosis
- Microscopically ; plump deeply eosinophilic hepatocytes surrounded by fibrous stoma , stain CK7+

Differential of Hepatocellular Nodules :

broad spectrum of lesions from regenerative to dysplastic nodule and early HCC

- Discriminating premalignant high-grade dysplastic nodules from malignant well-differentiated HCC is the main challenge.
- The most informative features include the presence of unpaired arteries, increased sinusoidal capillarization, stromal invasion and reticulin loss. .
- A panel of three immunohistochemical markers (glypican-3, glutamine synthetase and heat shock protein 70) was shown to have 100% specificity and 72% sensitivity for the diagnosis of HCC when all three markers are positive In malignant nodules

Differential of Hepatocellular Nodules : *contd..*

- In malignant nodules <2cm, 2 distinct subtypes are defined :
  - early HCC and
  - progressed HCC,
- based on their growth development (vaguely nodular vs. distinctly nodular) and
- histological differentiation (well vs. moderately to poorly differentiated)
- Among primary liver cancers, differential diagnosis depend on :
- Morphological analysis is always supported by IHC markers :
  - hepatocellular differentiation (CD10, pCEA, glypican 3 and) or
  - cholangiocytic differentiation (cytokeratin 7 and 19)

Staging :

- ,Tumor burden inside and outside the liver must be mapped in order to make sound therapeutic decisions
- Initial tumor staging should always include :
  - contrast-enhanced chest, abdominal and pelvic scans.
  - Gadoxetic acid-enhanced MRI (local tumor staging)
  - AFP as useful prognostic information provider
- The BCLC classification is recommended for tumor staging and provides important prognostic information

Multidisciplinary Approach Management of HCC :

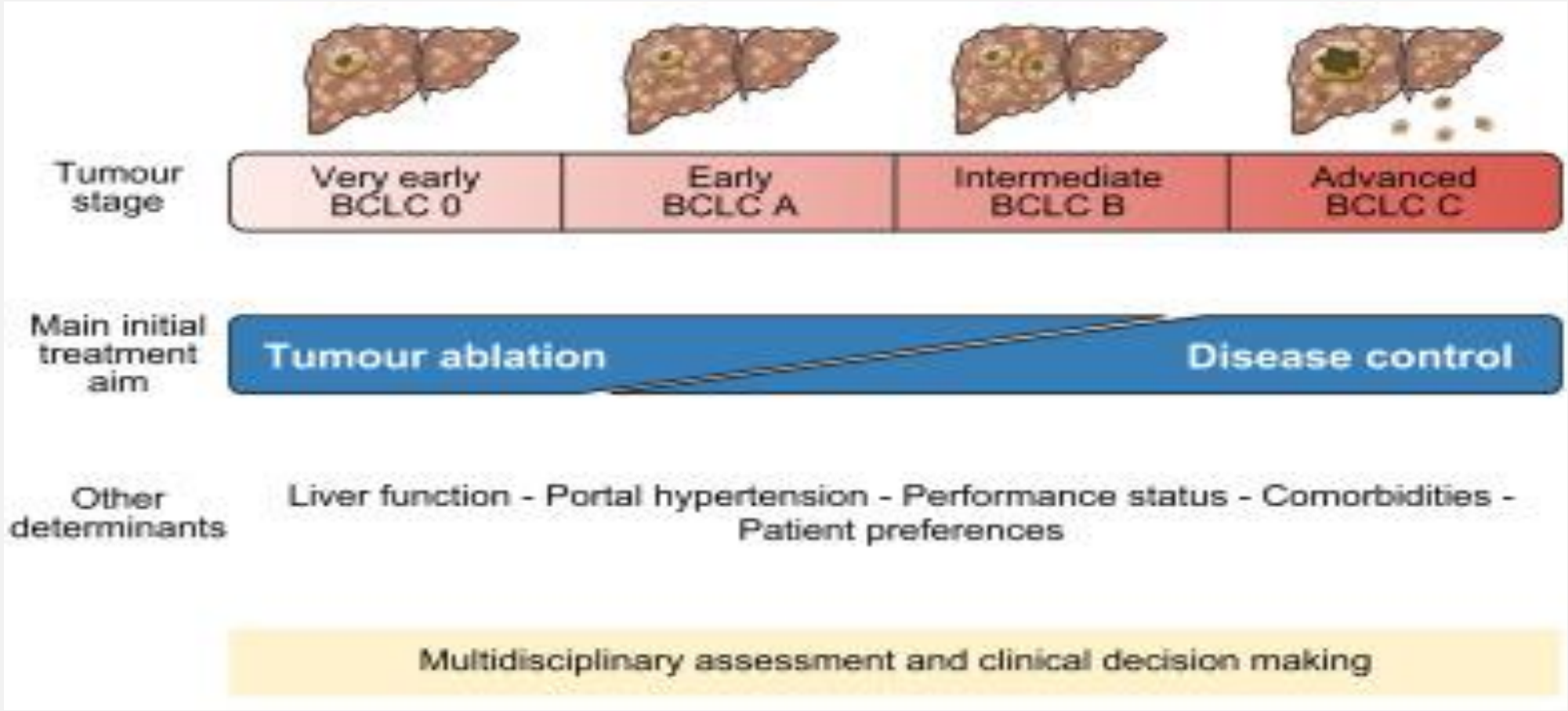
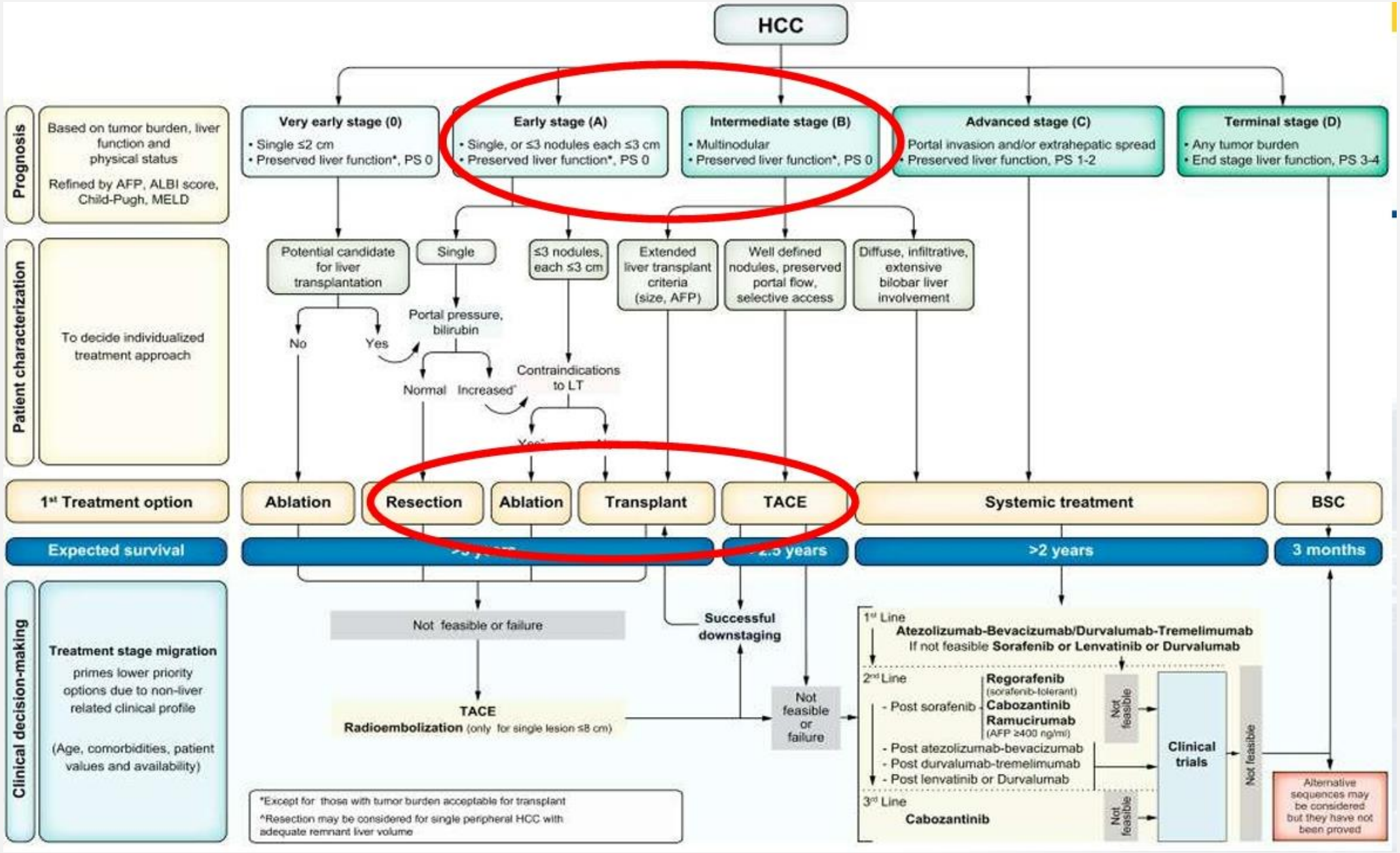


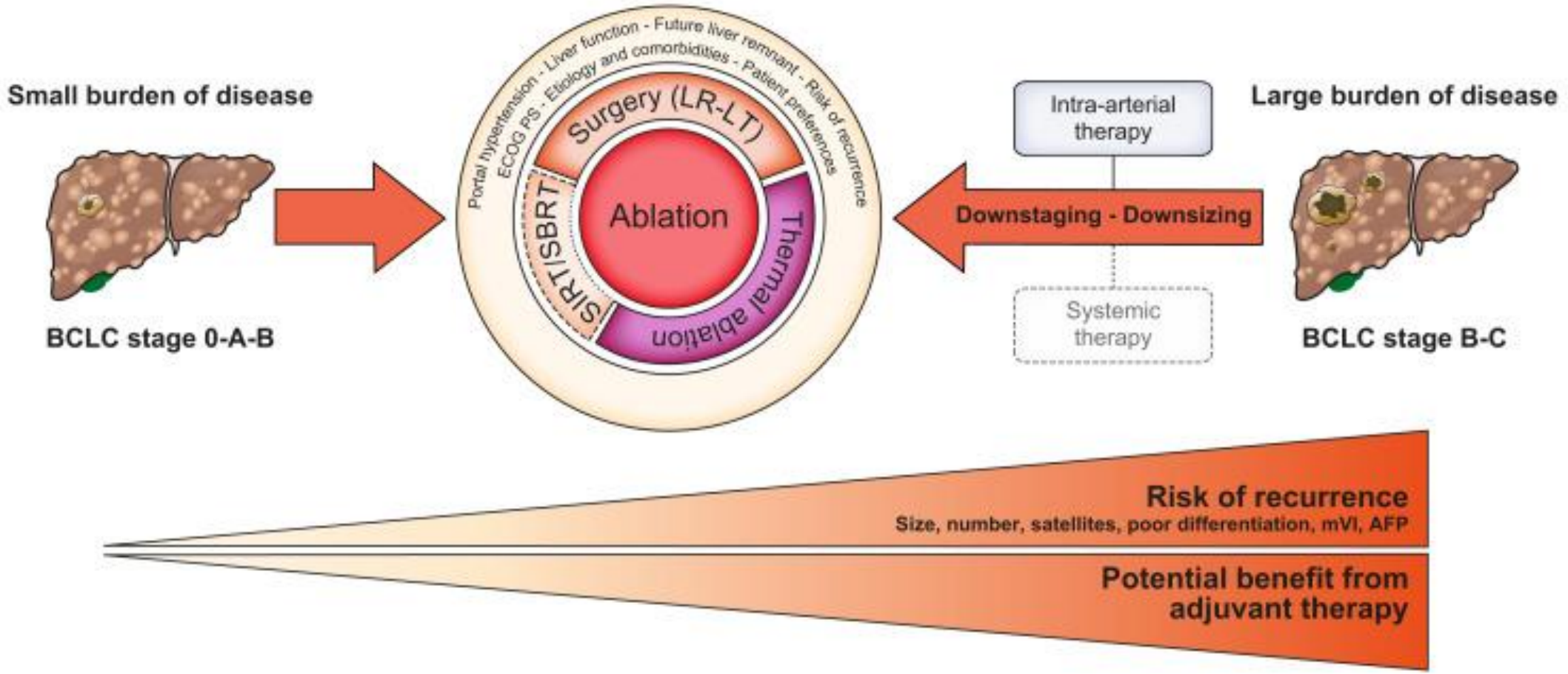
Fig. 3 Main determinants of the process of clinical decision-making

Treatment of HCC :

Based on BCLC 2025

- **Curative:**
  1. Resection,
  2. Ablation,
  3. Transplantation
- **Non-curative:**
  I. TACE,
  II. TARE, SBRT,
  III. Systemic Therapy


HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased^
Contraindications to LT
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib (sorafenib-tolerant)
Cabozantinib
Ramucirumab (AFP ≥400 ng/ml)
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
3rd Line
Cabozantinib
Not feasible
Clinical trials
Not feasible
Alternative sequences may be considered but they have not been proved
*Except for those with tumor burden acceptable for transplant
^Resection may be considered for single peripheral HCC with adequate remnant liver volume

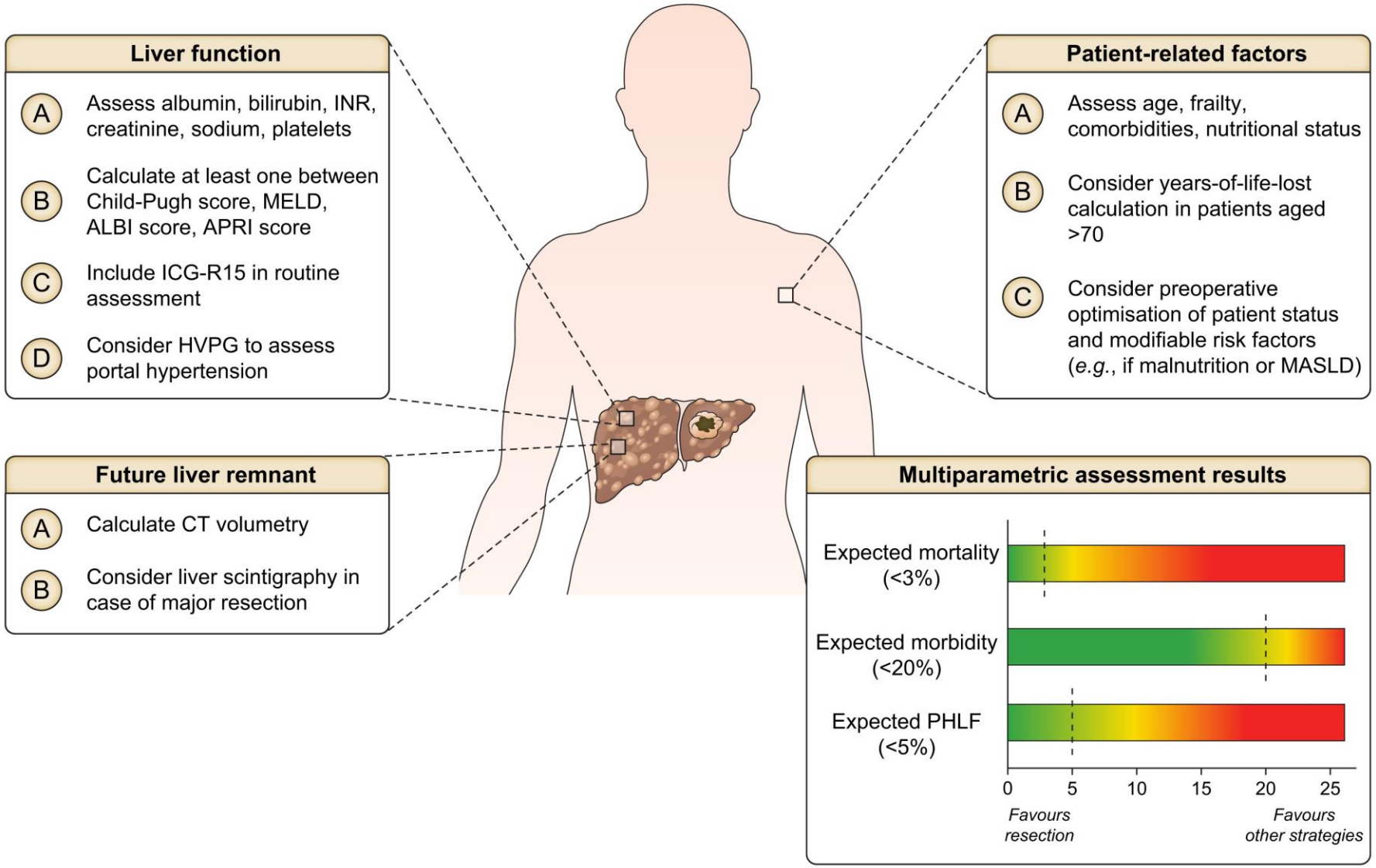


Therapeutic approach of patients with the aim of tumour ablation

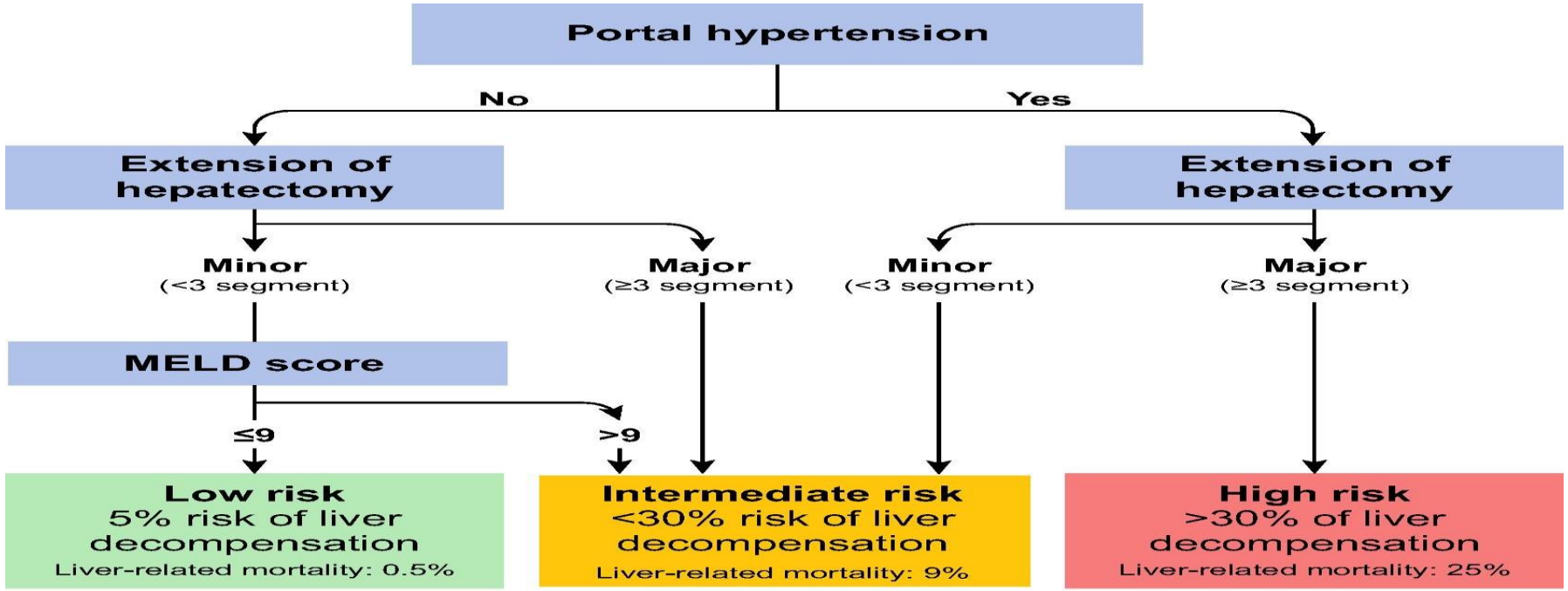
Liver Resection :

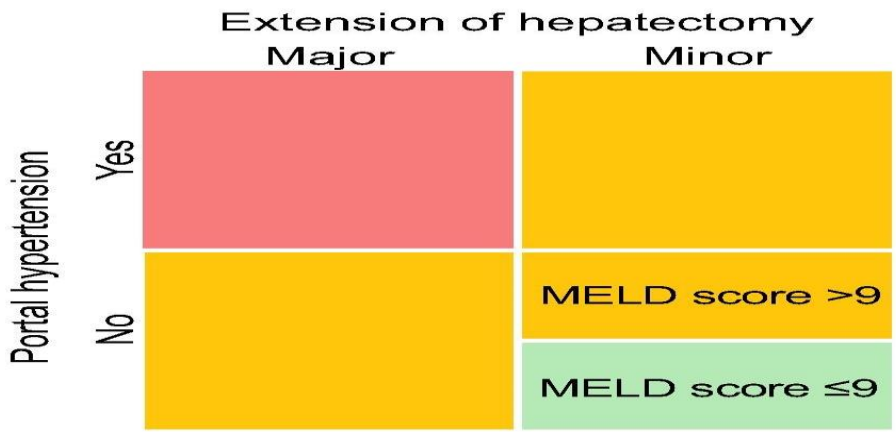
Highly selected patients

- Solitary tumour > 2cm
- Tumour >5cm high chance of extrahepatic spread (CT)
- Low MELD score (predict post-op mortality and prognosis)
- Normal bilirubin
- No evidence of significant portal hypertension (HVPG<10mmhg)
- Platelet count > 100000
- Spleen normal size



Multiparametric preoperative assessment for patients eligible for liver resection


Portal hypertension
No
Yes
Extension of hepatectomy
Extension of hepatectomy
Minor
(<3 segment)
Major
(≥3 segment)
Minor
(<3 segment)
Major
(≥3 segment)
MELD score
≤9
>9
Low risk
5% risk of liver decompensation
Liver-related mortality: 0.5%
Intermediate risk
<30% risk of liver decompensation
Liver-related mortality: 9%
High risk
>30% of liver decompensation
Liver-related mortality: 25%


Extension of hepatectomy
Major
Minor
Portal hypertension
Yes
No
MELD score >9
MELD score ≤9

Laparoscopic vs Open Surgery :

The benefits of laparoscopic resection:

- low complication rate , blood loss and duration hospital stay
- esp cirrhotic reduce the risk of post hepatectomy liver failure
- should be done in high volume centre with expertise
- lesion near the porta-hepatis , subcapsular and adjacent sticking of intestine should benefit where RFA has limitation
- for patient with HCC of 3cm or less , RFA may be an alternative to LR because of their comparable long-term efficacy

Prognosis of Liver Resection :

- 5 years survival 60 – 80 %
- Perioperative mortality 3-5%
- Low requirements for blood transfusion
- Only approximately 5-10% of patients HCC in meet resection requirements

Predictor of Survival :

- Tumor size as predictor of 5 years survival :
  - <2 cm – 66%
  - 2-5 cm -52%
  - >5 cm – 37%
- Tumor number as predictor of 5 years survival :
  - single tumor 57%
  - three or more 26%
- Vascular invasion and median survival :
  - none 87 month
  - microvascular invasion ; 38- 71 months
  - macrovascular invasion ; 8-12 months

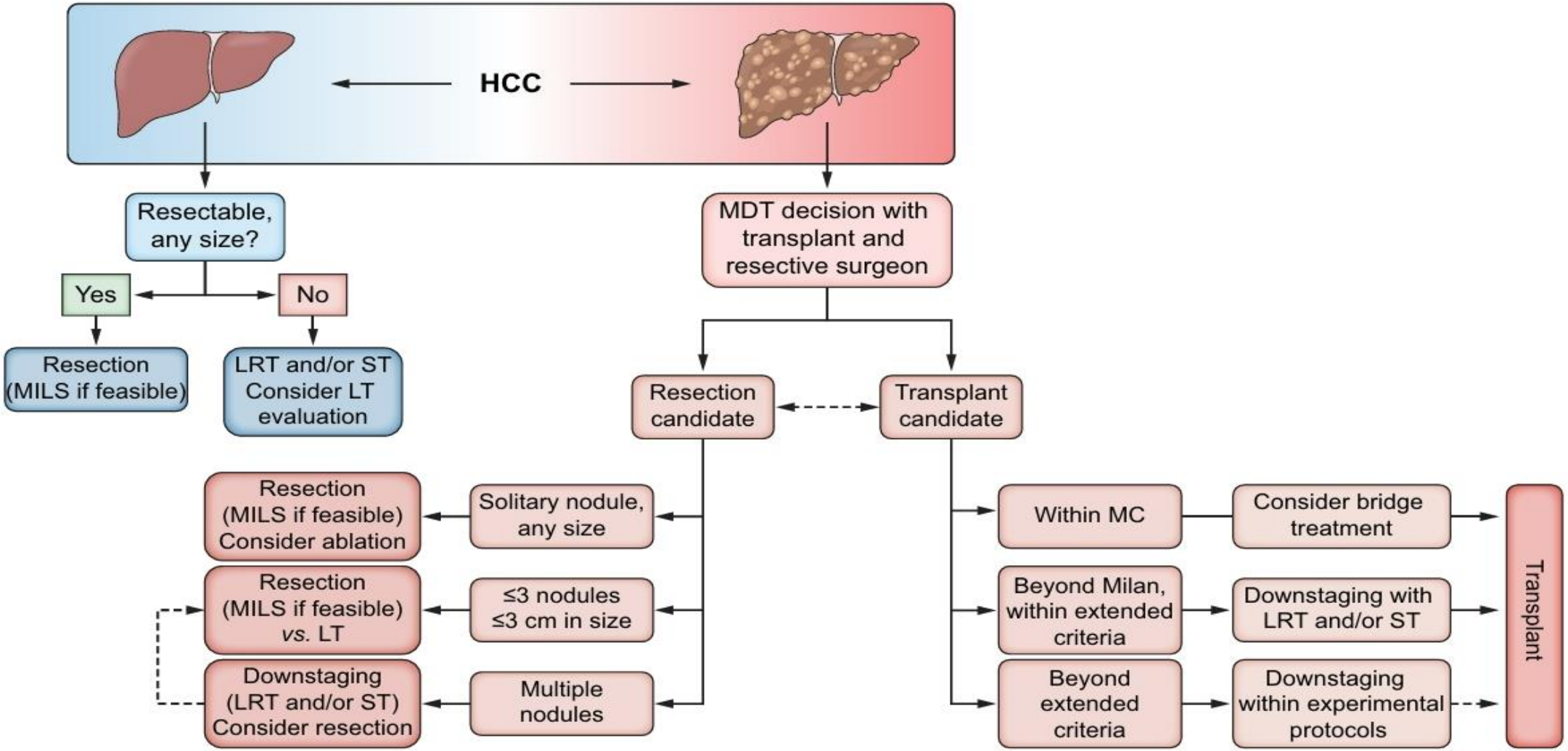


Fig. 6. Decision-making pathway in patients with HCC who are surgical candidates. HCC, hepatocellular carcinoma; LRT, loco-regional therapy; ST, systemic therapy; LT, liver transplantation; MC, Milan criteria; MDT, multidisciplinary team; MILS, minimally invasive liver surgery.

Ablations Therapy :

Percutaneous Ethanol Injection : (Chemical coagulative necrosis)

- Suitable for smaller lesion(2cm) with child A group
- high intrahepatic recurrence rates with PEI
- No beneficial in large lesion (>3cm) unlike surgery.
- # Ci / in the presence of gross ascites , severe thrombocytopenia or coagulopathy

Ablation Therapy :

- **Radiofrequency Ablation :** (Heat generated coagulative necrosis)

- Needle electrode under imaging or surgical guidance
- Not effective in lesions adjacent to blood vessels(heat sink)
- Perforation risk in lesions near hollow viscera
- Grounding bad required (can cause burns)
- Combined with other LRT for >3cm lesion
- RFA better than PEI .

Ablation Therapy :

- **Microwave Ablation :** (High local temperature)

✓ less peri-procedural pain

✓ More predictable ablation zone

✓ less susceptible to heat-sink effect

✓ Short procedure time

✓ Surgical clips or a pacemaker not contraindication

✓ No grounding park (no burn risk)

✓ Cost of RFA probe less than MWA.

Liver Transplantation :

- ✓ • LT is the treatment of choice for early-stage HCC (ie Milan) and patients with more advanced cirrhosis, CSPH, hepatic decompensation
- ✓ • LT should be a primary consideration for multifocal HCC
- ✓ • LT is a highly effective, efficient therapy for early-stage HCC because it offers optimal treatment of both the underlying liver disease and the tumor.
- ✓ • LT is associated with excellent long term survival rates for HCC within Milan criteria occurring in the setting of decompensated liver disease.

AASLD. Hepatology 2018, 68

Liver Transplantation :

- Most in the US are transplanted within Milan
- Expanded criteria
  - UCSF
- Extended Toronto Criteria – Any size or number!

Exclusions: cancer related symptoms, extrahepatic disease, vascular invasion, poorly differentiated

Downstaging to within Milan

- In highly selected cases can have excellent post-transplant outcomes similar to those within Milan
- Typically for unresectable, particularly due to background liver disease

Milan Criteria (Mazzaferro et al, 1996)

- Single tumor $\leq$ 5 cm, or
- 2-3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread

UCSF Criteria (Yao et al, 2001)

- Single tumor $\leq$ 6.5 cm, or
- 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter $\leq$ 8 cm
- No vascular invasion and/or extrahepatic spread

Criteria Beyond Milan

Dallas Criteria	Largest lesion ≤ 6 cm; no. of lesions ≤ 4
“Up to 7”	Largest tumor + number = 7 W/O microVI
Total tumor volume	≤115 cm^3 and AFP ≤ 400 ng/mL (1 lesion ≤ 6 cm or 3 lesions up to 4.2 cm)
Asian Criteria	Largest lesion ≤ 5 cm; no. of lesions ≤ 6
Kyoto Criteria	Largest lesion ≤ 5 cm; no. of lesions ≤ 10 PIVKA ≤ 400 m AU/mL
Kyushu University Criteria	All tumors < 5 cm OR DCP < 300 mAU/mL
Toronto Criteria	No restriction size/number: Tumor grade well or moderately differentiated in those > Milan; PS = 0

Outcome of the Liver Transplantation :

- US survival rates for patients transplanted for HCC are excellent (65-87%)
- Predictors of recurrence after transplant ;
  - microvascular invasion
  - AFP > 500 ng/ml at time of transplant
  - Sum of largest viable tumour and number of viable tumours at explant

Post Transplantation Surveillance :

- There is no consensus as to optimal approach posttreatment surveillance
- HCC recurrence estimated to occur in 8 – 20% of the patients
- Most cases of HCC recurrence are diagnosed within the first 2yrs after LT
- The risk of recurrence is directly related to pre- LT tumour stage and unfavourable tumour biology .
- Majority of HCC recurrence represent metastasis from the primary tumour rather than de novo cancer arising in the transplant graft.

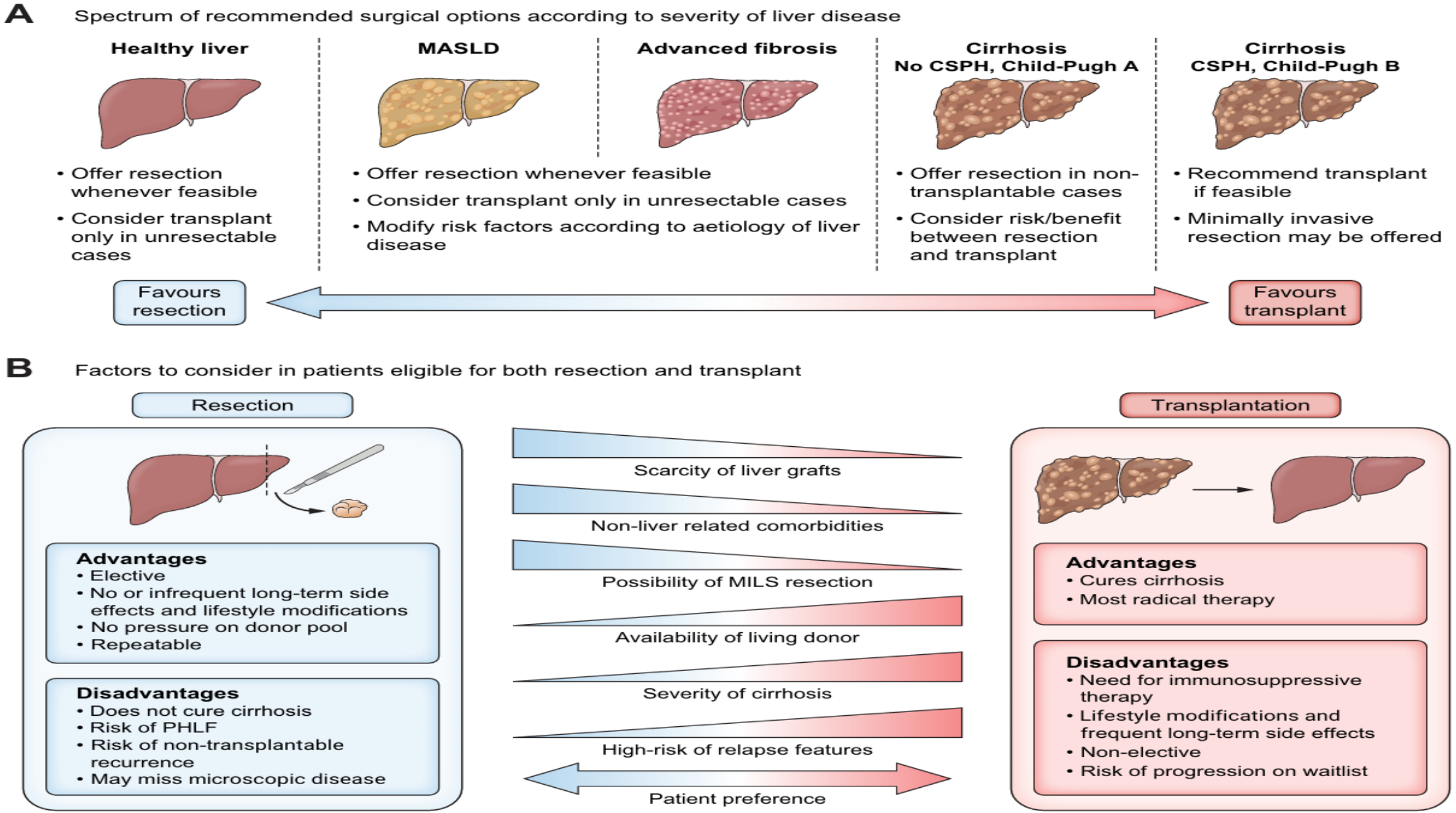


Fig. 7. Surgical decision-making framework for patients with HCC who are surgical candidates. CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MILS, minimally invasive liver surgery; PHLF, post-hepatectomy liver failure.

Locoregional Therapy :

Vascular interventional therapy

I. Trans-arterial chemo-embolization (TACE)

II. Trans-arterial radio-embolization (TARE)

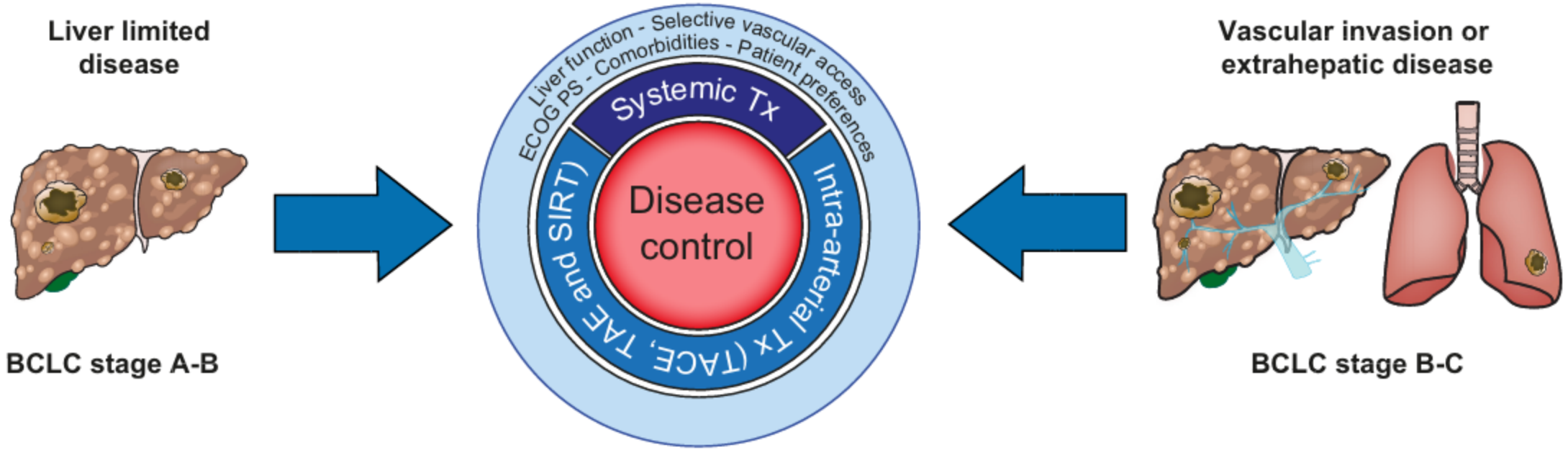


Fig. 8. Therapeutic approach of with the aim of disease control. BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TAE, transarterial embolization; TX, therapy.

Indication

I. Intermediate stage BCLC B: multifocal disease

II. Bridge to Transplantation

III. Pre-transplant downstaging

IV. Pre-resection downstaging

V. Advanced disease palliation in combination with systemic therapy

TACE :

Conventional TACE

- Selective – segmental hepatic artery

- Super selective – subsegmental hepatic artery

- Ultra selective –distal most subsegmental hepatic artery.

Drug Eluting Beads TACE.

- **PRECISION V Trial** : overall response similar DEB & c-TACE

Transarterial Radioembolization :

- Y90 Thersphers@
- 2 radioembolization agent available (SIR-Sphere & sera-sphere)
- Minimizing complication associated with radiation
- May be used in presence of PVT
- Lobar treatment
- Requires staging procedure
- Salvage therapy

Downstaging :

- Patients outside Milan criteria ;
- Defined as reduction in tumour burden to meet acceptable LT criteria
- Based on imaging of viable tumour
- No acceptable standard at this time

UNOS Downstaging Criteria

Inclusion Criteria

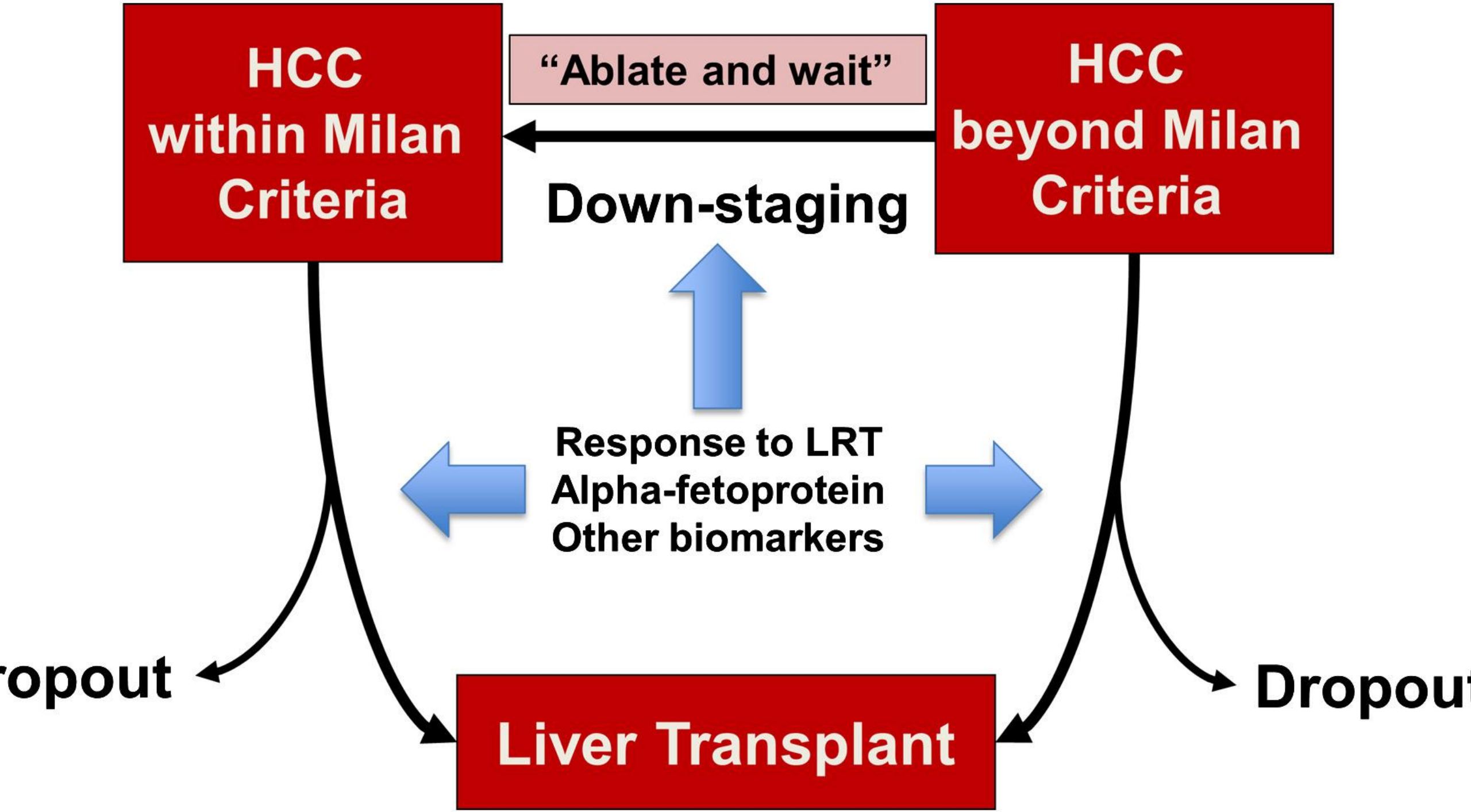
HCC exceeding Milan criteria but meeting one of the following:

Single lesion 5.1-8 cm

- 2-3 lesions each ≤ 5 cm with the sum of the maximal D ≤ 8 cm
- 4-5 lesions each ≤ 3 cm with the sum of the maximal D ≤ 8 cm
- Plus absence of vascular invasion or extrahepatic disease based on cross-sectional imaging

Criteria for Successful Down-Staging

- Residual tumor size and diameter within Milan criteria


HCC within Milan Criteria
"Ablate and wait"
HCC beyond Milan Criteria
Down-staging
Response to LRT
Alpha-fetoprotein
Other biomarkers
ropout
Liver Transplant
Dropout

Systemic Therapy :

Targeted Therapy (TKIs) /

target specific molecule essential for tumor growth. (RAF, FGFR, RET, KIT, TIE2 or MET)

- Sorafenib ; RAF kinase and Tyrosine kinase inhibitor of VEGF & PDGF
- Lenvatinib , Regorafenib , Cabozantinib ; Multi-kinase inhibitor of VEGF , FGFR , PDGFR , RIT and KIT.
- Bevacizumab ,Rivoceranib and Ramucirumab ; VEGF & VEGFR-2.
- Sorafenib and Lenvatinib was standard of care based on (SHARP+Asia Pacfic and REFLECT trials)

Systemic Therapy :

Immunotherapy Therapy (ICIs) :

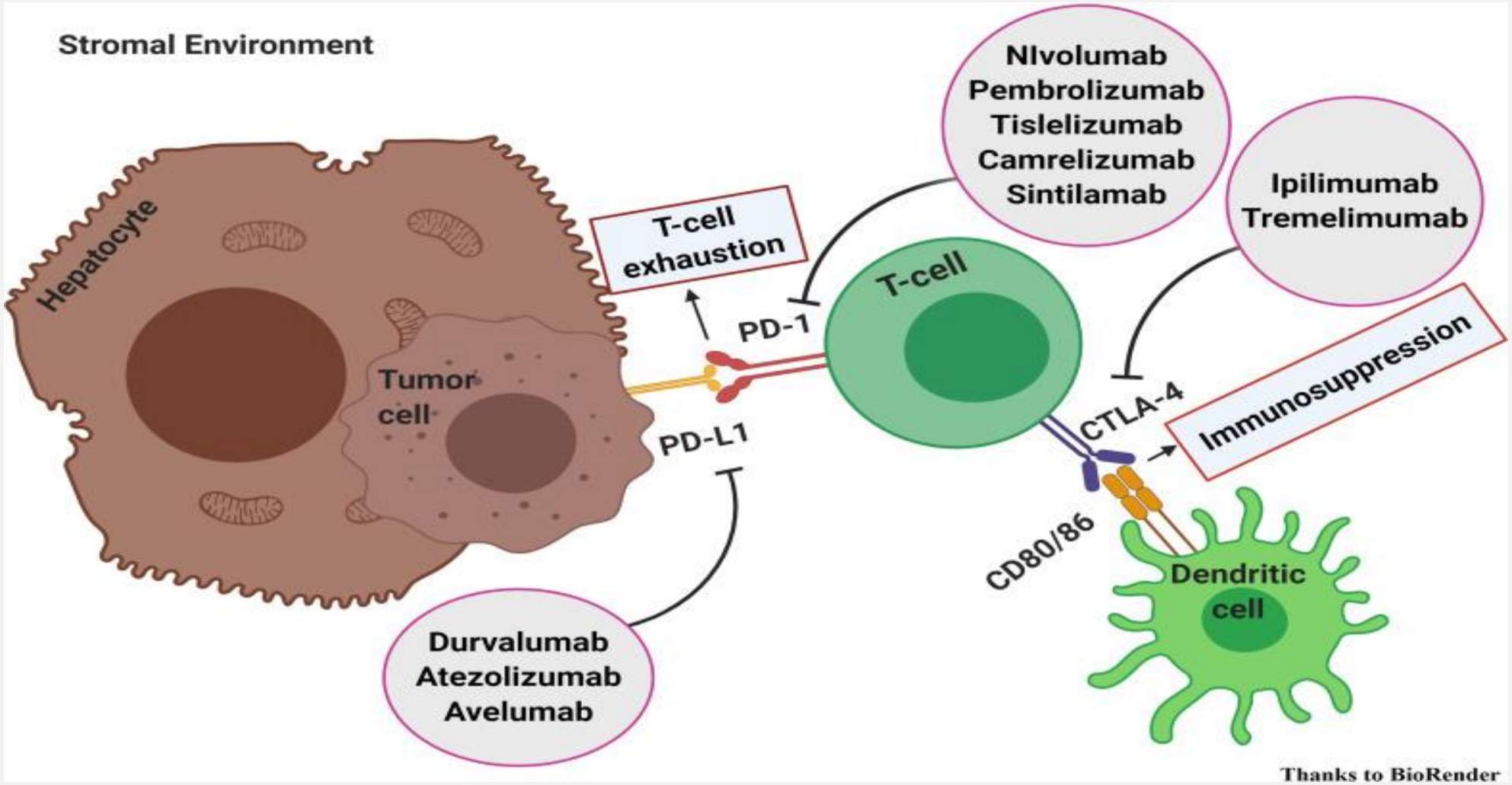
act by eliciting or strengthening ongoing antitumor response :

- PD-1 (nivolumab, pembrolizumab, sintilimab)
- PD-L1 (atezolizumab, durvalumab, tislelizumab)
- CTLA-4 (ipilimumab, tremelimumab)

Systemic Therapy :

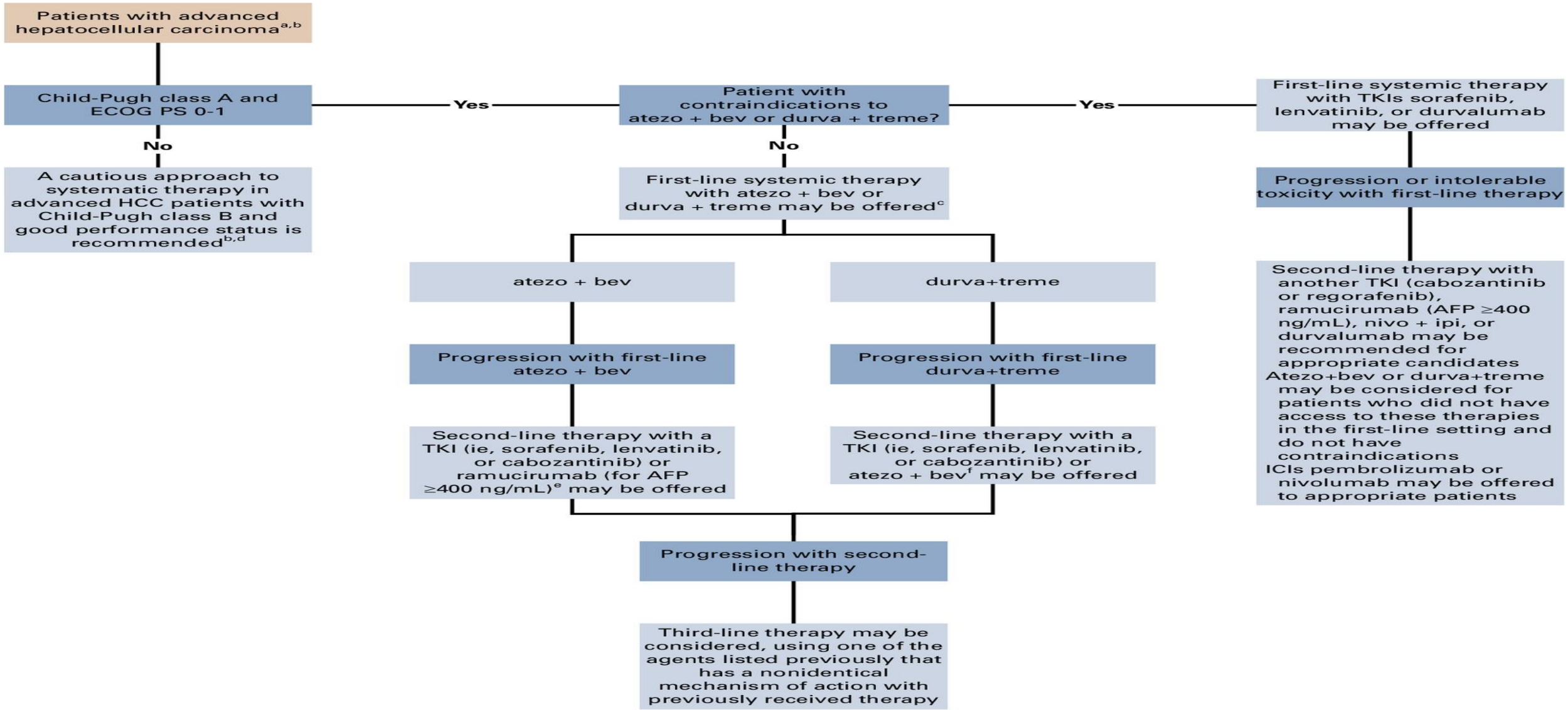
- **Combination immunotherapy and TKIs** are the main stay of systemic therapy in advance stage HCC .
- combinations including at least one PD-1 or PD-L1 inhibitor should be offered, provided there are no contraindications

- **Imbrave 150** (Atez+Beva vs Sorafenib) / OS 19.2 vs 13.4
- **HIMALAYA** trial (Tremeli+Durva vs Sorafenib) /OS 16.4 vs 13.7
- **CheckMate 9DW** trial,(Nivolu+ Ipilimu vs Lenvatinib) / OS 23.7 vs 20.6


Stromal Environment
NIvolumab
Pembrolizumab
Tislelizumab
Camrelizumab
Sintilamab
Ipilimumab
Tremelimumab
T-cell exhaustion
Hepatocyte
Tumor cell
PD-1
T-cell
PD-L1
CTLA-4
Immunosuppression
CD80/86
Dendritic cell
Durvalumab
Atezolizumab
Avelumab
Thanks to BioRender

ASCO® Guidelines

Systemic Therapy for Advanced Hepatocellular Carcinoma Algorithm



Summary :

- Primary liver cancer is a major health burden
- All patients with cirrhosis required screening
- We underperform at screening for HCC
- Outcomes for HCC are poor ,due in part to concomitant cirrhosis
- Curatives therapies exist when detected early
- New treatment are on horizon

Case Presentation

- 64 yrs old male known DM2 and HTN on metformin, enalapril and statin
- Present to casualty with fatigue and abdominal swelling
- Physical examination : jaundice and abdominal grade 2 ascites
- Blood test : mild impaired LFT + decrease albumin level
- Abd USC 2 liver lesion with background of coarse liver texture

What is your approach and management plan ?