Estadificación del carcinoma hepatocelular
Cambios introducidos en el BCLC Migración de estadio y en el estadio intermedio

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Maria Reig Disclossures

I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation.

- **Employment:** Head of Liver Oncology Unit. Hospital Clinic Barcelona. Director of BCLC group. IDIBAPS/CIBEREHD.
- **Consultant or Advisory Role:** AstraZeneca, Bayer, BMS, Eli Lilly, Geneos, Ipsen, Merck, Roche, Universal DX, Boston
- **Research Funding:** Yes (ISCIII, CIBER)
- **Speaking:** AstraZeneca, Bayer, BMS, Eli Lilly, Gilead, Roche
- **Grant Research Support (to the institution):** Bayer, Ipsen
- **Educational Support (to the institution):** Astrazeneca, Bayer, Roche, Eisai, Ipsen, Lilly, Terumo

BCLC 2022

Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

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

- Very early stage (0): Potential candidate for liver transplantation
  - No → Ablation
  - Yes → Portal pressure, bilirubin
- Early stage (A):
  - Single → Portal pressure, bilirubin
    - Normal → Resection
    - Increased^ → Contraindications to LT
  - ≤3 nodules, each ≤3 cm → Contraindications to LT
    - Yes^ → Ablation
    - No → Transplant
- Intermediate stage (B):
  - Extended liver transplant criteria (size, AFP) → Transplant
  - Well defined nodules, preserved portal flow, selective access → TACE
  - Diffuse, infiltrative, extensive bilobar liver involvement → Systemic treatment
- Advanced stage (C) → Systemic treatment
- Terminal stage (D) → BSC

1st Treatment option	Ablation	Resection	Ablation	Transplant	TACE	Systemic treatment	BSC
Expected survival	>5 years				>2.5 years	>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 → **TACE**, **Radioembolization** (only for single lesion ≤8 cm)

Successful downstaging → Transplant

Not feasible or failure → Systemic treatment

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

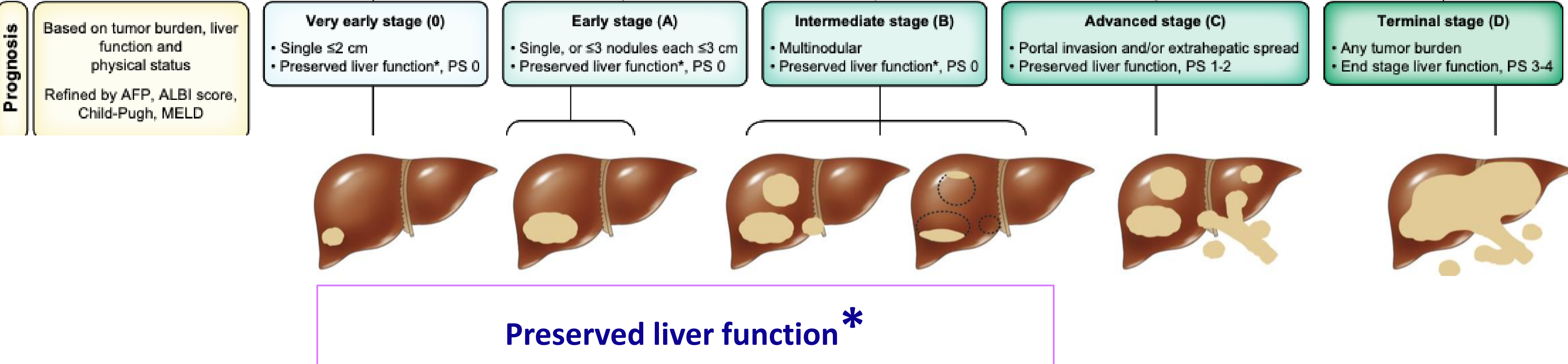
3rd Line
Cabozantinib

Not feasible → **Clinical trials**

Not feasible → BSC

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



Preserved liver function*

*Except for those with tumour burden acceptable for Transplant

Child-Pugh score

- **Ascites**
  - ✓ Minor ascites, easy to treat
  - ✓ Tense ascites, high diuretics dosing
  - ✓ Refractory ascites, hyponatremia
  - ✓ Spontaneous bacterial peritonitis
- **Encephalopathy**
  - ✓ Secondary due to infection, constipation, etc
  - ✓ Recurrent encephalopathy
- Bilirubin
- Prothrombin time
- Albumin

Pugh et al. Br J Surg 1973.

ALBI score

- Albumin
- Bilirubin

Johnson et al. J Clin Oncol 2015

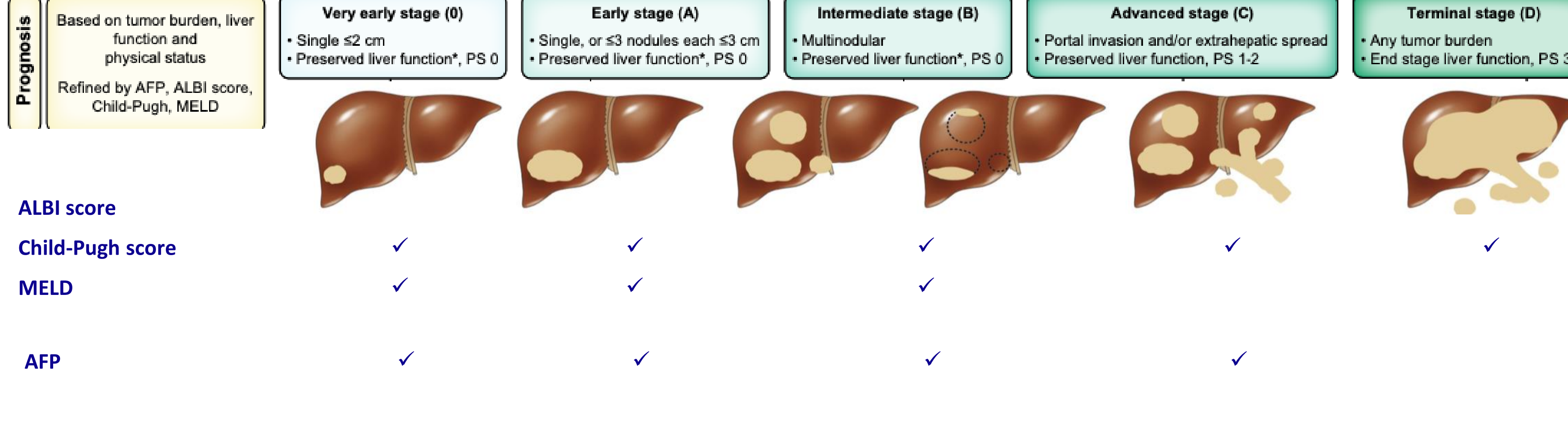
MELD/MELD-Na score

- Creatinine
- Bilirubin
- INR
- Sodium

Kamath et al. Hepatology 2001; Kim et al. N Engl J Med 2008

Alfafeto-Protein (AFP)

Takayasu et al Gastroenterology 20216;
et al. Gastroenterology 2021;
Cabibbo et al.World JHepatol 2012



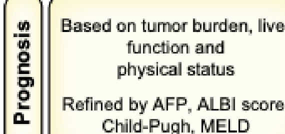
- Variceal bleeding
- Malnutrition
- Hepatorenal syndrome
- Arterial hypotension

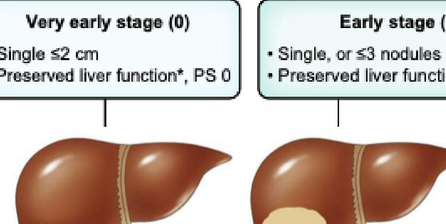
Child-Pugh, MELD, ALBI do not identify 100% of endstage patients

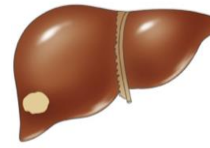
Clinical Decision-Making

Johnson et al. J Clin Oncol 2015; Pinato et a. J Hepatol 2017; Pugh et al. Br J Surg 1973; Kamath et al. Hepatology 2001; Kim et al. N Engl J Med 2008Kim et al. Gastroenterology 2021.

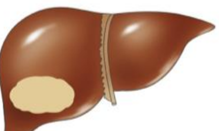
de Franchiset al.J Hepatol 2015; D'Amico et al. J Hepatol 2018;Garcia-Tsaoet al.Hepatology 2010;Tonon et al. Clin Gastroenterol Hepatol 2021; Llach J et al. Gastroenterology 1988



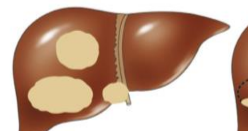
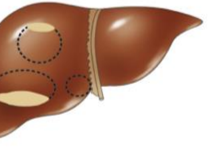




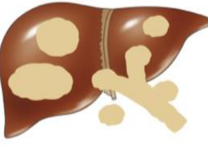
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0



Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0

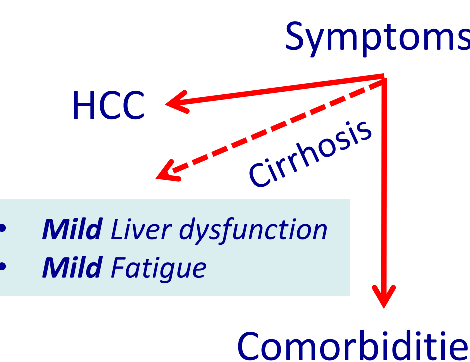
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2

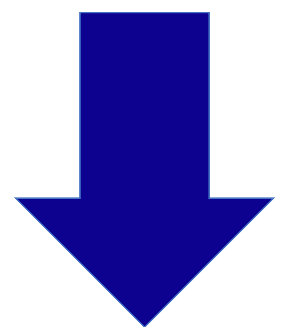


Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4

Performance Status, ECOG-PS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead





Tumour-related symptoms

Characterization of ECOG-PS can required more than 1 visit

HCC, hepatocellular carcinoma

BCLC 2022

Intermediate stage (B)
- Multinodular
- Preserved liver function*, PS 0

Duvoux et al. Gastroenterology 2012;
Mazzaferro et al. Gastroenterology 2018;
Mehta et al.Transplantation 2020
Toso et al. Hepatology 2015;
Mehta et al, Hepatology 2019

Lencioni et al. Cardiovasc Intervent Radiol 2012;
Kloeckner et al. Hepatology 2021

Reig et al. Semin Liver Dis 2014
El-Khoueiry et al. Lancet. 2017
Bruix et al. Lancet Oncology 2018
Kudo et al. Lancet Oncology 2018
Abou-Alfa et al. NEJM 2018
Zhu et al. Lancet Oncology 2019
Finn et al. J Clin Oncol. 2020
Finn at NEJM 2020
Yau et al.JAMA Oncol. 2020

Extended liver transplant criteria (size, AFP)

Well defined nodules, preserved portal flow, selective access

Diffuse, infiltrative, extensive bilobar liver involvement

TACE

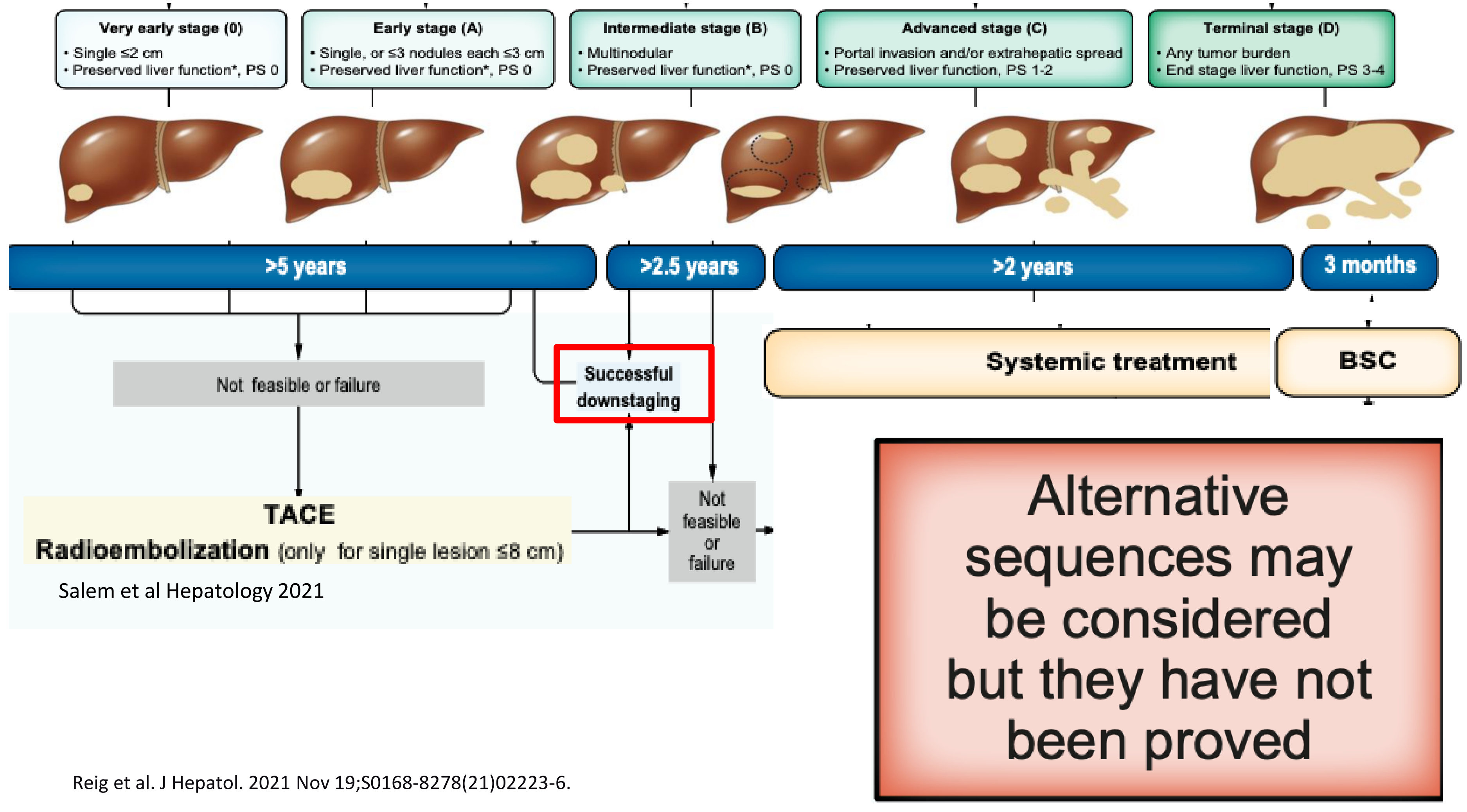
>2.5 years

Systemic treatment

>2 years

Several groups have established a concentration limit beyond which LT is not considered

A 1000 ng/dL cut-off value is currently applied as exclusion criteria.



Very early stage (0)
• Single ≤2 cm
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Early stage (A)
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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
>5 years
>2.5 years
>2 years
3 months
Not feasible or failure
Successful downstaging
Systemic treatment
BSC
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
Salem et al Hepatology 2021
Alternative sequences may be considered but they have not been proved
Reig et al. J Hepatol. 2021 Nov 19;S0168-8278(21)02223-6.

Clinical Decision-making – BCLC 2022

Physician – Multidisciplinary Team --> RESPONSABILITY

‘Shared-Decision Making’ and ‘Value-Based Healthcare’

Clinical decision-making

Treatment stage migration

primes lower priority options due to non-liver related clinical profile

(Age, comorbidities, patient values and availability)

- Age
- Comorbidities
- Patient values
- Treatment availability
- HCC location
- Techniques (type of ablation, surgery or material for loco-regional treatments)
- Type of systemic treatments
- Etc.

HCC, hepatocelular carcinoma; .

Reig et al. J Hepatol. 2022.

HCC treatment

Seminar

Hepatocellular carcinoma

Arndt Vogel, Tim Meyer, Gonzalo Sapisochin, Riad Salem, Anna Saborowski

Hepatocellular carcinoma is one of the most common cancers worldwide and represents a major global health-care challenge. Although viral hepatitis and alcohol remain important risk factors, non-alcoholic fatty liver disease is rapidly becoming a dominant cause of hepatocellular carcinoma. A broad range of treatment options are available for patients with hepatocellular carcinoma, including liver transplantation, surgical resection, percutaneous ablation, and radiation, as well as transarterial and systemic therapies. As such, clinical decision making requires a multidisciplinary team that longitudinally adapts the individual treatment strategy according to the patient's tumour stage, liver function, and performance status. With the approval of new first-line agents and second-line agents, as well as the establishment of immune checkpoint inhibitor-based therapies as standard of care, the treatment landscape of advanced hepatocellular carcinoma is more diversified than ever. Consequently, the outlook for patients with hepatocellular carcinoma has improved. However, the optimal sequencing of drugs remains to be defined, and predictive biomarkers are urgently needed to inform treatment selection. In this Seminar, we present an update on the causes, diagnosis, molecular classification, and treatment of hepatocellular carcinoma.

Treatment

Treatment options for patients with hepatocellular carcinoma are outlined in national and international guidelines, with slight differences in the therapeutic approach between Asia, Europe, and North America.[87–91] The Barcelona Clinic of Liver Cancer (BCLC) algorithm is the most widely used staging system and subdivides patients with hepatocellular carcinoma into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D).[92]

Vogel at a. Lancet . 2022 Sep 6;S0140-6736(22)01200-4.

BCLC approach for HCC patient management

What is the <u>profile</u> of the patient ?

Treatment stage migration

primes lower priority options due to non-liver related clinical profile

(Age, comorbidities, patient values and availability)

Compensated cirrhosis?

Prognosis defined by HCC

BCLC 2022 Algorithm

No

Meets the **RADIOLOGIC** LT criteria
or
Achieves the downstaging criteria for LT?

Comorbidities that contraindicate LT?

Male 60 years old
No comorbidities

Candidate to LT due to Liver Decompensation
BCLC 2022 Algorithm

LT, liver transplantation; BSC, Best Supportive Care

Reig et al. J Hepatol. 2022.

BCLC approach for patient management

What is the profile of the patient ?

Compensated cirrhosis

BCLC 2022 Algorithm

Doctor responsibility
Management

Male 92 years old
Alzheimer

Male 60 years old
Myocardial infraction

Treatment Stage Migration

Untreatable progression

Treatment Stage Migration

HCC

Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
• Single ≤2 cm • Preserved liver function*, PS 0	• Single, or ≤3 nodules each ≤3 cm • Preserved liver function*, PS 0	• Multinodular • Preserved liver function*, PS 0	• Portal invasion and/or extrahepatic spread • Preserved liver function, PS 1-2	• Any tumor burden • End stage liver function, PS 3-4

1st Treatment option: Ablation | Resection | Ablation | Transplant | TACE | Systemic treatment | BSC

Clinical decision-making

Treatment stage migration

primes lower priority options due to non-liver related clinical profile

(Age, comorbidities, patient values and availability)

Treatment Stage Migration

Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

Clinical Decision-making – BCLC 2022

EVOLUTIONARY EVENTS

BARCELONA CLINIC LIVER CANCER

Expected survival	>5 years	>2.5 years	>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

TACE
Radioembolization (only for single lesion ≤8 cm)

Successful downstaging

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

Treatment Stage Migration →

- Age
- Comorbidities
- Patient values,
- Treatment availability
- HCC location
- Etc.

Untreatable-Progression

Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

Untreatable progression concept

Patient's Selection

Start beyond BCLC-B
Associated to worse evolution

TACE
No objective response
Treatment failure
Second-line treatments
Objective response
(CR/PR)
Retreatment strategy
Disease progression
Impairment of liver
function and/or PS
TACE
Treatable
(i.e. new small
lesion)
Major progression
(i.e. vascular invasion,
extrahepatic spread or
liver involvement)
Objective response (CR/PR)
HCC-progression controlled
No objective response
Treatment failure
Untreatable progression
Consider second-line
treatments

UTP
Associated to worse
evolution

Bruix et al 2011; Forner et al 2015

Time to failure of treatment strategy

Time from randomization (treatment initiation) until death or need for a further therapeutic option

TACE

Discontinuation

Radiological Progression

Symptomatic Progression

Toxicity

Meeting Abstract | 2022 ASCO Gastrointestinal Cancers Symposium

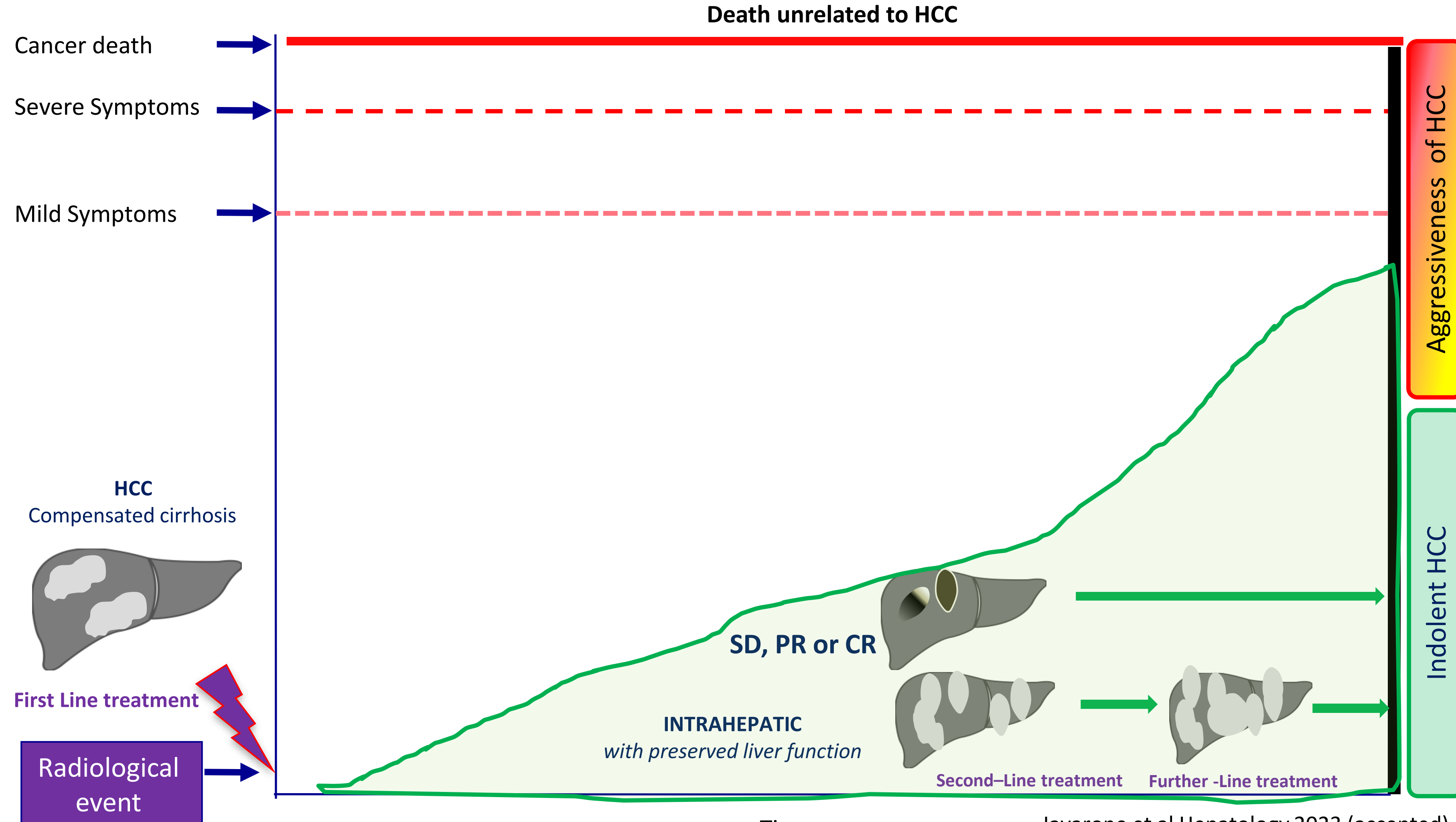
HEPATOBILIARY CANCER

ABC-HCC: A phase IIIb, randomized, multicenter, open-label trial of atezolizumab plus bevacizumab versus transarterial chemoembolization (TACE) in intermediate-stage hepatocellular carcinoma.

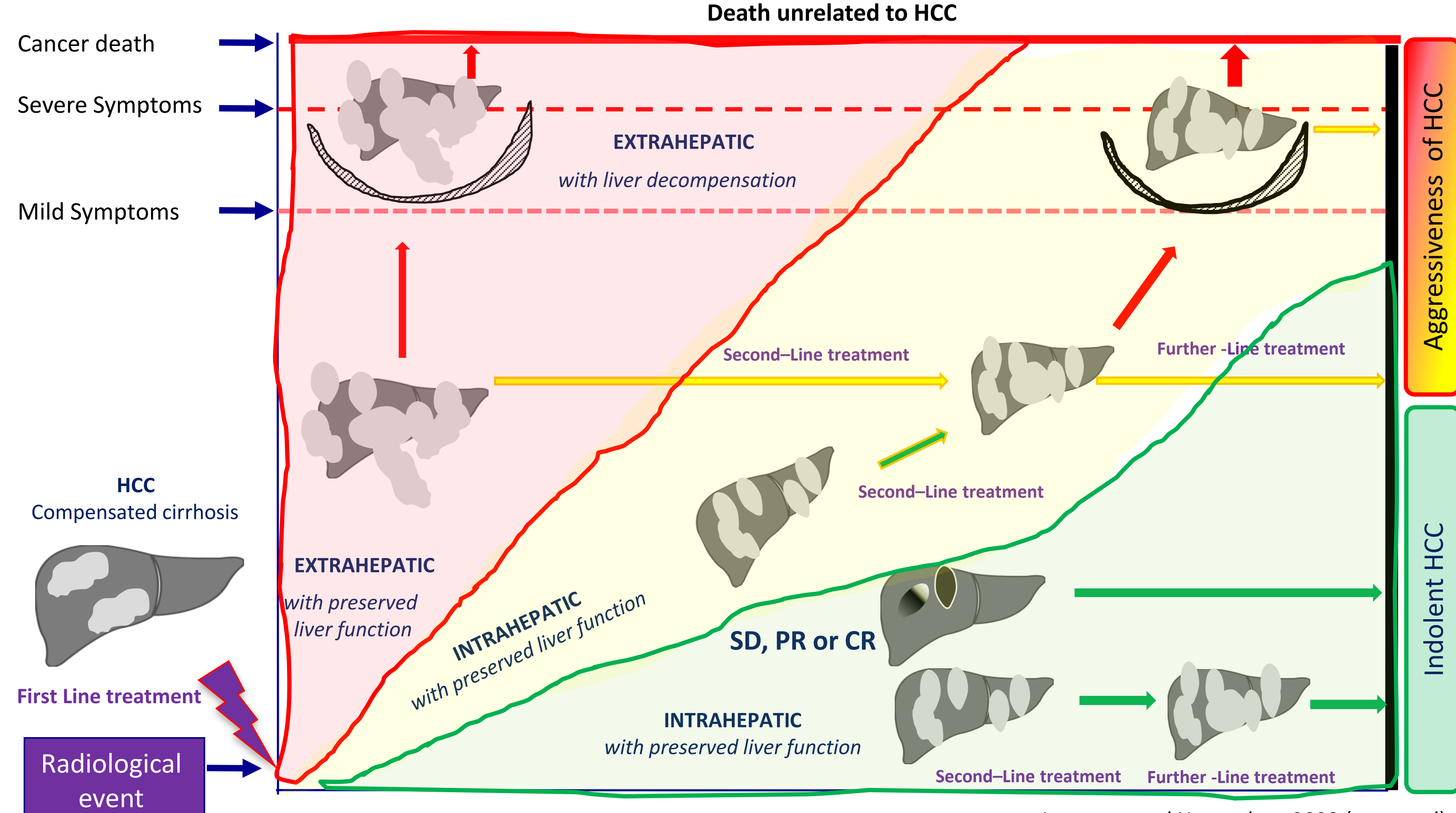
Check for updates

Friedrich Foerster, Roman Kloeckner, Maria Reig, Stephen Lam Chan, Jin Wook Chung, Philippe Merle, Joong-Won Park, Fabio Piscaglia, Arndt Vogel, Vincent Gaillard, Jordi Bruix, Peter R. Galle

ABC-HCC trial: NCT04803994



Death unrelated to HCC
Cancer death
Severe Symptoms
Mild Symptoms
Aggressiveness of HCC
Indolent HCC
HCC
Compensated cirrhosis
First Line treatment
Radiological event
SD, PR or CR
INTRAHEPATIC
with preserved liver function
Second–Line treatment
Further -Line treatment
Time
Iavarone et al Hepatology 2023 (accepted)


Death unrelated to HCC
Cancer death
Severe Symptoms
Mild Symptoms
EXTRAHEPATIC
with liver decompensation
Second–Line treatment
Further -Line treatment
Aggressiveness of HCC
HCC
Compensated cirrhosis
EXTRAHEPATIC
with preserved
liver function
Second–Line treatment
INTRAHEPATIC
with preserved liver function
SD, PR or CR
Indolent HCC
First Line treatment
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event
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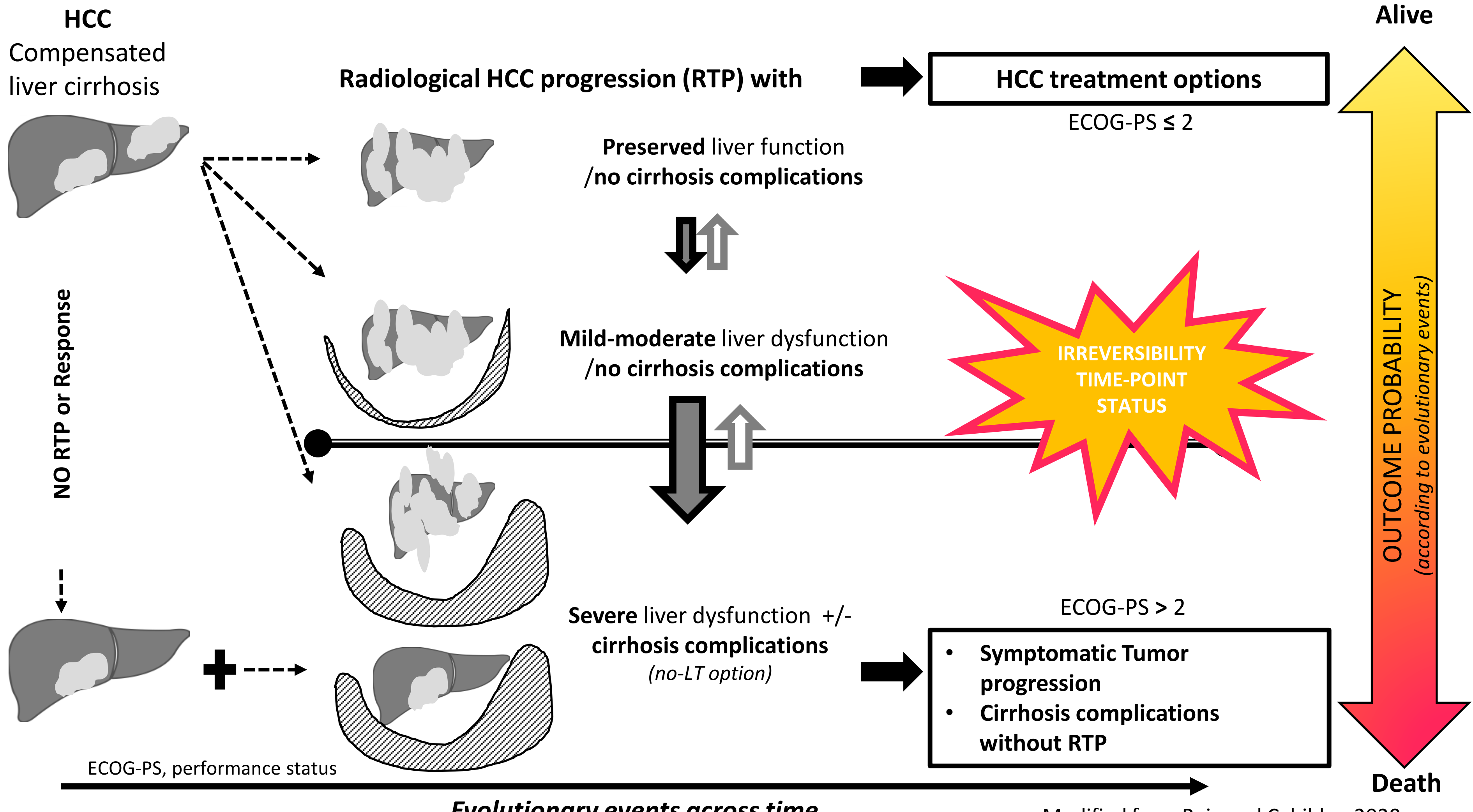
Iavarone et al Hepatology 2023 (accepted)



HCC
Compensated liver cirrhosis
Radiological HCC progression (RTP) with
HCC treatment options
ECOG-PS ≤ 2
Alive
Preserved liver function /no cirrhosis complications
NO RTP or Response
Mild-moderate liver dysfunction /no cirrhosis complications
IRREVERSIBILITY TIME-POINT STATUS
OUTCOME PROBABILITY
(according to evolutionary events)
Severe liver dysfunction +/- cirrhosis complications
(no-LT option)
ECOG-PS > 2
Symptomatic Tumor progression
Cirrhosis complications without RTP
ECOG-PS, performance status
Death
Evolutionary events across time
Modified from Reig and Cabibbo, 2020

HCC treatment selection process when more than one option improves the overall survival of patients.

Number of factors and their priority order according to diferent physicians when propose treatments

Factors considering for treatment selection:

- Safety
- Rationality
- Response
- Real-World data
- HRQoL

P Physician

P1. Safety, Rationality, Response, Real-World data, HRQoL

P2. Rationality, Response, Real-World data, HRQoL

P3. Real-World data

P4. Response, Real-World data

P5. Safety, Rationality, Response

P6. HRQoL, Real-World data, Response

⋮

n^x

Tailored treatment depending on patient profile and local availability

Discuss options with patient

Patient decision based on information recivied

Muñoz-Martinez et al. Current Opinion in Pharmacology 2021

Reason for considering a sequential treatments

Clinical decision-making

Treatment stage migration

primes lower priority options due to non-liver related clinical profile

(Age, comorbidities, patient values and availability)

Treatment indication

Treatment discontinuation

Radiological progression

AE/complications

Less tumour burden

Patient Decision

When is the right time for discontinuing?

?

Treatment failure

?

?

Substantial response

Special populations

Symptomatic progression

Intolerance

Downstaging/CR

The BCLC staging system

Treating HCC outside the BCLC strategy: should we change the treatment algorithm?

If you want …

- Rise the idea
- Develop a protocol
- Demonstrate the benefits of the change

KEEP in mind that 'CLINICAL DESICION-MAKING' IS …

Physician – Multidisciplinary Team --> ***RESPONSABILITY***

BCLC 2022 consider the following points

'Treatment Stage Migration concept' and 'Untreatable progression'

'Shared-Decision Making' and 'Value-Based Healthcare'

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M. Reig, A. Forner, J. Rimola, J. Ferrer-Fabrega, M. Burrel, A. Garcia-Criado, R.K. Kelley, P.R. Galle, V. Mazzaferro, R. Salem, B. Sangro, A.G. Singal, A. Vogel, J. Fuster, C. Ayuso, J. Bruix

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BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update

M. Reig * • A. Forner • J. Rimola • ... J. Fuster • C. Ayuso • J. Bruix * • Show all authors •