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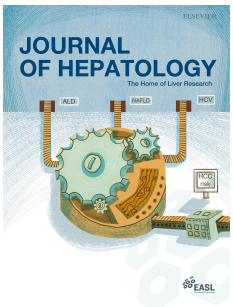

BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update

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BCLC strategy for prognosis prediction and treatment recommendation

Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update

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Keywords: HCC, survival, BCLC, ablation, surgery, liver transplantation TACE, TARE, systemic treatment, ALBI score, AFP.

Key Points

- The updated BCLC strategy for prognosis prediction and treatment recommendation has been updated according to advancements in knowledge
- Stratification of patients into stages has kept its simplicity adding further refinement according to patient characterization
- Staging is linked to the 1st option to be considered according to scientific evidence
- Personalized treatment indication is established according to an expert clinical decision-making process where all dimensions of the patients are taken into account.
- Therapeutic process in BCLC B patients has to be tailored according to tumor burden and effective downstaging may allow liver transplantation.
- Evaluation and management of patients with liver cancer has to integrate baseline patients' profile as well as evolutionary events
- Tumor progression and/or treatment related adverse events may induce to recommend the treatment for a more advanced stage even if BCLC stage has not changed (treatment stage migration)

Brief summary

Treatment for hepatocellular carcinoma (HCC) has experienced major advancements since the last update of the official Barcelona Clinic Liver Cancer (BCLC) prognosis and treatment strategy published in 2018. Advancements in the field have emerged in all areas, but in this manuscript, we present those that have primed a change in the strategy and comment why some encouraging data in select interventions are still considered immature and in need of further research to gain their incorporation into an evidence-based model for clinicians and researchers. Finally, we describe the critical insight and expert knowledge that is needed to take clinical decisions in individual patients so that the recommendation takes into account all the needed parameters to allow a personalised approach.

Treatment for hepatocellular carcinoma (HCC) has experienced major advancements since the last update of the official Barcelona Clinic Liver Cancer (BCLC) prognosis and treatment strategy published in 2018 [1–7]. Advancements in the field have emerged in all areas, but in this manuscript, we will present those that have induced a change in the strategy and comment why some encouraging data in select interventions are still considered immature and in need of further research to gain their incorporation into an evidence-based model for clinicians and researchers. Scientific evidence should be properly graded according to study design and while observational studies are informative, their limitations for robust causality inference should be acknowledged [8]. While prior updates were developed by BCLC members, we have now included expert authors beyond the BCLC group to integrate different expertise insights and knowledge in this updated version.

Prognosis prediction and patient characterization

While there is no controversy in the current stratification of patients according to tumour burden and cancer related symptoms [9,10] in prognosis prediction, the evaluation of the underlying liver function already induced to abandon the Child-Pugh classification [11] in the last BCLC version; this aspect deserved again an update. Decompensation of liver disease (jaundice, ascites, encephalopathy) reflects non-preserved liver function irrespective of the Child-Pugh or MELD points [12,13], for which several improvements have been proposed [14], but compensated liver function could be stratified with additional granularity by using the Albumin-Bilirubin (ALBI) score [15–17], while also adding AFP concentration irrespective of tumour burden [18,19]. These parameters are now included in the 2022 BCLC model (Figure 1), but while they may impact prognosis, they may not abolish the treatment benefit if the degree of liver dysfunction does not exceed the established selection criteria for an optimal outcome. Prior variceal bleeding also reflects more advanced liver disease with clinically significant portal hypertension [20–22], but history thereof does not necessarily warrant its incorporation into prognosis prediction in patients with liver cancer, while it could still be an

important aspect in treatment indication. The degree of ascites and response to therapy also impact prognosis: small radiographic ascites or fluid retention that is controlled by a low sodium diet differs from tense ascites regardless of medical treatment (diuretics and/or paracentesis) with or without renal failure [23,24]. Regarding performance status (PS) assessment [9,10], it is important to highlight that PS assessment should incorporate tumour-related symptoms but not baseline symptoms already present prior to cancer diagnosis and thus, related to pre-existing comorbidities. This can be difficult to differentiate when PS impairment is related to liver dysfunction, which may or may not be related to tumour burden. Clinical research trials include BCLC staging in the definition of the target population, while at the same time they establish inclusion/exclusion criteria to define the patient's profile. In clinical practice the evaluation of patients to characterise their status also uses the BCLC staging and simultaneously, includes the expert and insightful personalised approach by the treating physician and multidisciplinary tumour board. This will also consider tumour extension and burden, nutritional status, comorbidities and frailty, age, social status and human values and beliefs. There is still no molecular profiling that may predict a different patients outcome or a higher risk of recurrence after successful surgery or ablation [25] nor predict the best treatment option [18].

As known, clinical practice guidelines and algorithms such as BCLC model [1–7], expose the current status of knowledge and the degree of scientific evidence available for each intervention [26–30], but the ultimate decision is to be taken by the responsible physician and tumour board who needs to assimilate all variables and recommend a given path of care for the patient as an individual [31]. The multidisciplinary approach is key from the initial diagnosis and tumour staging until the definition of the best initial and sequential treatment definition. Expert radiologists, interventional radiologists, radiation oncologist, pathologists, nurses, clinicians, surgeons in the field of HCC and palliative care specialists and social workers need to work together for this purpose. Health care teams are responsible for performing and/or interpreting imaging techniques and pathology samples, to ultimately integrate all those data

with the individual patient's medical profile. In this regard, the personalised management of patients exceeds the needed assessment of the factors related to HCC and liver function. Thereby, clinical decision-making and treatment recommendation should not be merely based on a simplified figure but is rather a quite elaborated process that requires expert decision making.

Treatment

In the following paragraphs we describe the proposed treatment options for each BCLC stage. We also emphasize that while at first sight a given option is the first to be considered, the expert evaluation blending all the clinical and sociocultural information may result in two important concepts: The Treatment Stage Migration (TSM) and the UnTreatable Progression (UTP) [6,32,33]. TSM is applied when a specific patient profile may induce a shift of the recommendation to the option that would be considered a priority for a more advanced stage. UTP was developed for patients under transarterial chemoembolizaton (TACE) [32,33] but applies to all BCLC stages and treatments applied. It represents failure of the selected treatment strategy [34]. It emerges when patients present treatment failure or progression but still fit into their initial BCLC stage, thus warranting the consideration of a therapy corresponding to a more advanced stage. The 2022 BCLC treatment strategy (Figure 1) incorporates a specific section to describe the proposed Clinical Decision-Making for an individualised approach according to the available data on September 15, 2021. Clinical trials affecting any stage to improve the current benefits are encouraged to induce further advancements.

It is worth stressing that while at first sight the BCLC figure displays a given option as the initial one to be considered, a specific profile of an individual patient may induce to shift the recommendation to another one considered a priority for a more advanced stage (TSM

concept) [6]. In some cases, treatment may shift from that recommended at first for early stage, to that recommended to advanced stage, or even to no treatment.

Very early stage (BCLC 0)

This is defined as a solitary HCC ≤ 2cm without vascular invasion or extrahepatic spread in a patient with preserved liver function and no cancer-related symptoms.

BCLC-0 management varies according to the potential access to LT and specific profiles as depicted in the clinical decision-making section. The potential of transplant indication because of high recurrence risk is taken into account as already described in the last BCLC model [5]. Therefore, If transplant would be an option and patients fulfil the criteria for surgery, resection would be the first option. Pathology pattern of increased recurrence risk (microscopic vascular invasion, satellites) may induce their consideration for LT because of such risk [35–37]. However, local regulations for enlistment and priority policies may preclude effective transplant for BCLC-0 until recurrence is apparent. If LT is not feasible, the first treatment approach would be ablation, with resection having given similar survivals between both options [38–41]. Those patients with such small HCC who present with severe liver dysfunction/decompensation may be considered for LT if they fulfil the enlistment criteria [42–47]. If not eligible for LT due to non-HCC factors, patients should be classified as BCLC-D stage because of their dismal survival expectation. Indeed, patients may receive priority because of their end-stage liver status, while the presence of very early HCC is not considered as the reason for enlistment and/or for priority allocation.

Early stage (BCLC A)

This is defined as solitary HCC irrespective of size or as a multifocal HCC up to 3 nodules (none of them > 3 cm), without macrovascular invasion, extrahepatic spread or cancer related symptoms (PS-0). Liver function has to be preserved and not have reached LT criteria, at

which point the patient would be classified as BCLC stage D because of dismal prognosis outside of LT eligibility. As mentioned above, those patients with liver disease deserving LT consideration should be evaluated in the framework of end-stage liver disease. In such setting, HCC diagnosis could become an exclusion criterion for LT if exceeding the enlistment criteria [42–47]. If LT is contraindicated due to non-HCC factors, there is no effective option to be offered. Thus, the patient should be classified as BCLC D stage.

Treatment approach for BCLC A patients varies according to tumour number and degree of liver function impairment.

Solitary HCC

Treatment selection in these patients requires a multiparametric approach.[48] Liver function assessment should be stratified according to the degree of portal hypertension as it has been established that the presence clinically significant portal hypertension (CSPH) (defined by a hepatic venous pressure gradient (HVPG) > 10 mmHg) predicts a higher rate of postoperative complications and a lower long-term survival [49–51]. It is important to note that the accuracy of HVPG measurement is controversial in patients with NAFLD [52,53].

- In the absence of CSPH, patients are considered for resection, and the recommendation should consider tumour burden and location, as well as potential candidacy for LT if the pathology profile of a resected HCC would predict a high risk of recurrence [35–37]. Thereby, microvascular invasion and satellites are well-known recurrence predictors and because of such increased risk, LT may be considered [35–37]. If no decision is to be derived from pathology examination, the survival offered by ablation in patients with HCC $\leq$ 3 cm may be competitive with that offered by resection [38–40,54–56]. Because of less invasiveness and cost, ablation could be given priority. However, larger size and some risky locations for ablation (for instance, adjacent to the gallbladder) may induce resection (see Clinical Decision-making section) [57].

- If patients present with CSPH, surgical resection should be considered of significant risk [50,58] and LT offers improved medium and long-term survival. However, patients may not be considered for LT because of any characteristic and ablation has limited efficacy for large HCC. Therefore, this may induce consideration for the potential benefit of laparoscopic resection if HCC is in proper locations and there is a minor degree of CSPH [27,48,59–63]. Unfortunately, no portal pressure cut-off value may be given for such decision and no robust recommendation can be made.

Multifocal within Milan criteria (up to 3 HCC nodules, each ≤ 3 cm)

Multifocal disease still within the Milan criteria (MC) [42] is better served by LT as ablation and resection are hampered by a high risk of HCC recurrence [64–66]. If LT is not feasible, it is a matter of debate if outcome after surgery or ablation is better than that offered by TACE [67,68]. Prospective clinical research is mandatory to define when surgical resection or ablation should be given priority in up to 3 nodules over TACE. This may provide very competitive survival figures in early-stage patients with preserved liver function and health status, as it is usually requested to proceed with resection.

Intermediate stage (BCLC-B)

Patients with multifocal HCC (exceeding BCLC-A criteria) with preserved liver function, no cancer related symptoms (PS 0) and no vascular invasion or extrahepatic spread conform the intermediate BCLC B stage. As well known, the magnitude of tumour burden may be quite heterogeneous in this stage, and prognosis is also influenced by AFP concentration [69] and the degree of liver function impairment even if still belonging to Child-Pugh class A [16]. However, robust cut-offs to be applied are not available. This individualised profile of the patients may also determine a separate treatment decision favouring LT, TACE or systemic

therapy [70,71]. The 2022 BCLC version stratifies the BCLC-B into 3 groups of patients according to tumour burden and liver function.

The first subgroup within BCLC B stage includes patients with well-defined HCC nodules. These patients could be candidates for LT if they meet the 'Extended Liver Transplant criteria' according to the criteria of the Institution [72]. Expansion of the criteria for LT has been proposed for several years [42–47]. A minor increase in tumour size or number may provide competitive survival figures hampered by a slight increase in recurrence that impairs long term survival [73]. The same has been reported if patients are allowed to develop a limited asymptomatic progression beyond MC [74]. Survival may be competitive as compared with those patients within MC, but always at a cost of higher recurrence and lower long-term survival. Accordingly, the decision to accept extended criteria is defined by the impact of such expansion in the transplant access for other indications and the minimal outcome to be achieved in each indication [75]. Elevated AFP value predicts a higher risk of HCC recurrence and thus, lowered survival. Several groups have established a concentration limit beyond which LT is not considered [45,46,76]. A 1000 ng/dL cut-off value is currently applied as exclusion criteria. While downstaging therapy may induce a reduction of AFP, there are no robust data to define the magnitude and /or duration of the reduction [77].

The second subgroup is conformed by patients without option for LT but who have preserved portal flow and defined tumour burden suggesting the feasibility of selective access to feeding tumour arteries. They are candidates for TACE. If patients do neither meet the 'Extended liver transplant criteria' nor the TACE criteria to secure optimal outcomes [5,27,71], they should be considered for systemic therapy.

The third subgroup within BCLC B includes patients with diffuse, infiltrative, extensive HCC liver involvement. They do not benefit from TACE [6], and systemic therapy should be the recommended option, although there is no strict cut-off when this is the case.

Advanced stage (BCLC C)

This stage includes HCC patients presenting with vascular invasion or extrahepatic spread and still relatively fit as reflected by a PS $\leq$ 2 at staging work-up and a preserved liver function. BCLC C patients should be evaluated for systemic therapy [29]. Different effective options for first-, second- and following lines are currently available if patients fulfil the characteristics defined in the registration trials that led to regulatory approval [29].

The combination of atezolizumab with bevacizumab (Atezo-Bev) is currently the first line treatment to be considered since it surpasses the survival benefit offered by sorafenib [78–80], while it has not been evaluated head-to-head versus Lenvatinib [81]. To benefit from Atezo-Bev patients must present preserved liver function (compensated Child-Pugh A if there is underlying cirrhosis) and absence of high-risk stigmata for bleeding on upper endoscopy, e.g., properly treated oesophageal varices and no history of variceal bleeding, in order to minimize bleeding risk. Additional requirements that may prevent treatment include vascular disorders and arterial hypertension, as well as severe autoimmune disorders and prior transplantation [29]. On October 15, 2021 the HIMALAYA Phase III trial using a single priming dose of tremelimumab added to durvalumab was announced to provide a statistically significant survival benefit versus sorafenib in 1st-line [82]. Hence, availability of all the study data will sure impact in clinical decision in such setting.

After disease progression or toxicity leading to treatment interruption, the treatment landscape has gained complexity [29]. Prior to 2020 sorafenib was the single effective option in 1st line where evidence-based treatment sequencing can be proposed [83–86]. Patients transitioning to the 2nd line setting benefit from regorafenib if they are tolerant to sorafenib [83], from cabozantinib irrespective of tolerance to sorafenib [84], or ramucirumab if AFP level is > 400 ng/dl and irrespective of tolerance to sorafenib [86]. Cabozantinib is also effective as 3rd line [84]. A Western trial comparing pembrolizumab vs placebo in 2nd line did not met his OS primary end-point [87], but an Asian trial in a similar population has reported significant survival improvement [88].

End-stage (BCLC D)

Patients with major cancer related symptoms (PS >2) and/or impaired liver function without option of LT due to HCC burden or non-HCC related factors present poor survival at short term and belong to BCLC D stage [1]. Development of HCC in patients with advanced liver disease who would otherwise be considered for LT may mandate their enlistment if tumour burden does not exceed the established criteria. Accordingly, treatment of HCC will not change the survival expectancy due to chronic liver disease and cancer treatment would be of no benefit. In such instance, symptomatic management and coordination of palliative care is mandatory.

According to the BCLC proposal the expected median survival of HCC patients should be more than 5 years, 2.5 years, 2 years and 3 months for BCLC 0/A, B, C and D; respectively.

Clinical Decision-Making

The 2022 BCLC strategy incorporates the Expert Clinical Decision-Making component (Figure 1). It exposes the different concepts and parameters that physicians and multidisciplinary tumour boards responsible for the patients should integrate to propose a personalised HCC treatment indication.

BCLC-0 patients

Decision in BCLC 0 may be modulated by several factors that preclude their feasibility and justify a different recommendation from that proposed in the patient characterization block of the figure.

Ablation through radiofrequency (RF) or microwave (MW) is the preferred technique [89,90], while ethanol injection (PEI) is still applied in selected patients when there are technical or safety concerns. If ablation (percutaneous or laparoscopic if needed) is not feasible because of any reason (location, availability etc.),[57] the patient may be considered for surgical resection with the feasibility and safety assessment detailed in the BCLC A section. When this option is not feasible, TACE is the preferred option.[91] Transarterial radioembolization (TARE) is equally effective [92]. Stereotactic body radiation bears antitumoral activity but further prospective studies are needed to define it role [93,94]. However, while safety and efficacy data are well established for RF and MW, TARE could be considered in patients with single nodules $\leq$ 8 cm. This new BCLC recommendation is based on the results of the Legacy study [92], which included patients with singles nodules less than 8 cm, Child-Pugh A and ECOG-PS 0/1. It is important to emphasize that the median tumour size of the patients included in that study was 2.6 cm (range 0.9-8.1). If the patient is not a candidate for locoregional treatment, the option of systemic treatment should be considered, but always aligned with the inclusion and exclusion criteria for the available agents with proven survival benefit.

BCLC-A patients

Resection and ablation by radiofrequency offer the same survival expectancy in HCC $\leq$ 2 cm [38,39]. Ablation beyond this size is less effective and the lower rate of complete responses and higher rate local recurrences gives priority to resection in such cases. MW achieves a more extensive tumour necrosis as compared to RF and is potentially the best option for those patients with HCC $\leq$ 4 cm [95–97]. Larger tumours may still benefit from resection as size alone should not be considered as a limiting factor for surgical resection, as long as imaging has not identified vascular invasion and the remnant liver volume permits adequate postoperative liver function [98,99]. Radiation lobectomy by TARE may increase remnant liver volume and could be considered in some patients [100]. Major hepatectomy carries excessive

risk in patients with cirrhosis and thus, specific tumour locations may also prevent resection and induce consideration for LT [48]. In such instances, size may be a limiting factor for LT according to the expanded criteria that may be in place. Finally, large tumours are frequently associated to cancer related symptoms (ex: pain) and this portends poor outcome after resection.

Upon enlisting patients for LT and if the expected waiting time exceeds 6 months, it is recommended to consider treatment to prevent tumour progression leading to exclusion from transplantation. Ablation, chemoembolization and TARE are the most widely used option for this purpose.

Laparoscopic/robotic resection allows adequate margins and has a reduced invasiveness with lower postoperative complications and potential non-significant impact in liver function even if there exists CSPH [59–63,101]. These encouraging results may induce a resection recommendation in patients who would be initially selected for ablation, but in whom the peripheral tumour location may contraindicate such approach because of risk of tract seeding if punctured without a protective rim of non-tumoral liver or risk of neighbouring organ damage [60]. While an acceptable increased CSPH value has not been defined, it is worth considering that postoperative mortality increases and one year survival decreases in parallel to portal hypertension even if the surgery does not involve the liver [102].

As proposed for BCLC 0 stage, if a patient is not a candidate for any of the mentioned approaches the concept of TSM should be applied and treatment with TACE should be considered, as well as TARE in patients who meet the Legacy inclusion criteria [92]. This is a retrospective cohort study in which median tumour size was < 3cm and thus, validation by other groups is eagerly awaited. If TARE is also not feasible, patients should be considered for systemic therapy.

The 2022 version of BCLC staging system does not recommend resection for multinodular HCC within MC. Cohort studies of resection report encouraging survival results [103], but

prospective data are needed to establish the effectiveness of such approach as compared to locoregional approaches. Thus, TACE is the preferred option if the first treatment option is not feasible. However, large tumours exceeding 8-10 cm are reported to be associated to worse outcome after TACE [70,104], this potentially being related to the potential impairment of portal venous flow due to invasion or compression, rather than to the impact of major tumour necrosis. Furthermore, large tumours are rarely free of symptoms. If these are present the patients should be classified as BCLC C. Indeed, survival of symptomatic patients (PS 1) after TACE is significantly lower than that of patients without them [105].

BCLC-B patients

For patients to be a candidate for TACE, liver function has to be well preserved. Increased bilirubin beyond 2 mg or slight fluid retention requiring diuretic treatment are associated with increased risk of adverse events and suboptimal survival after TACE [70]. It is not possible to define strict evidence-based criteria to recommend TSM favouring systemic treatment and hence, expert assessment is key to secure optimal care. Currently on-going trials in BCLC B stage comparing TACE vs systemic therapy have detailed inclusion and exclusion criteria and may produce highly useful information that will guide clinical practice.

TACE might be performed using chemotherapy emulsified in lipiodol followed by gelfoam or any other material injection (conventional TACE) or using drug eluting microspheres (DEB-TACE) [104]. The first is associated to a peak of chemotherapy in the systemic circulation that may increase toxicity and to a higher post-procedural pain, while DEB-TACE has a favourable pharmacokinetic profile.[106] Response rate and survival are not different between the two techniques [105,107]. Thus, each team has to define its preference. Available clinical trials comparing bland embolization to TACE are not informative as the population included does not match the profile of patients who would be recommended to receive TACE treatment

[108,109]. Metanalytic assessment is hampered by an excessive heterogeneity of the trials available for such evaluation [110].

Systemic treatment is the recommended option for those BCLC-B patients who are not candidates for TACE for any reason [78–81,83,84,86]. If not candidates for systemic treatment, the option of clinical trials should be considered.

Although the MC are still largely applied to select HCC patients for LT, an increasing number of studies have shown that acceptable post-LT may be obtained in a selected group of patients at BCLC B stage beyond MC. Several selection criteria that sought to expand the MC have been proposed and revised elsewhere [72]. Consensus on expanded criteria for LT in HCC has not been reached. However, composite criteria that consider surrogates of tumour biology (AFP being the most frequently explored) and response to neoadjuvant treatments, are likely to replace conventional morphological criteria for defining transplant feasibility. Several AFP cut-offs have been used for exclusion from LT [45,46,76,111], with value beyond 1000 ng/mL widely accepted as a contraindication for LT [45,46,111]. Patients with an AFP >1000 ng/mL who experienced biochemical response (at least a decrease to less than 500 ng/mL) to locoregional therapies (LRT) have a post-LT outcome comparable to the reported within MC [77]. Downstaging has emerged as a reliable tool for selecting patients for LT. The goal of downstaging is to reduce tumour burden in order for residual viable tumours to fall within acceptable LT criteria, with MC being the commonest endpoint of downstaging [112,113]. The upper limit of where a downstaging approach is considered varies across LT regions. This also affects the specific imaging criteria used to define baseline and post-treatment staging and evaluation of response. There is need to develop further studies to validate such approach and establish how to best apply a downstaging protocol. It is important to note that the need to careful establish the patient profile that defines a good transplant candidate is due to the shortage of donors. It implies a demand to use the available donors to provide the best outcome for the community and not solely focus on individual benefit. Live donation may avoid

the donor shortage and the decision to use the same criteria as for cadaveric donors or to accept a moderate expansion or a down-staging success is still controversial [72]. Again, survival may be competitive but the balance between the donor risk and the patient benefit is not homogeneously perceived in different cultural settings.

BCLC-C patients.

Atezo-Bev provides survival benefit over sorafenib with some patients exhibiting prolonged complete responses. Real-life data will inform about the proportion of patients excluded from the IMBRAVE 150 clinical trial due to comorbidities or CSPH with risk of bleeding. The combination of tremelimumab and durvalumab has been announced superior to sorafenib and hence, this adds another option for 1st line [82]. A significant proportion of patients with advanced HCC may not be appropriate candidates for both options and still be considered for TKI (sorafenib or lenvatinib) which have lower risk of significant bleeding [29]. In this regard, selection of the most adequate option relies in the careful analysis of the clinical and biochemical profile of the patients so that they fit into the target population enrolled in the trials where safety and efficacy was demonstrated. Prospective studies of data in real life may broaden the treatment indication, but in its absence, the recommendation is to retain the clinical and biochemical profile defined in registration trials [29]. Furthermore, real world data may be informative but will never replace the strength of randomised trials to prove survival benefit [114]. Safety in specific populations may be established but survival benefit in the absence of randomized trials will remain as a suggestion.

Even though Atezo-Bev is the preferred first-line treatment [78], and lenvatinib is as effective as sorafenib [81], there is a major need to assess if the available second line alternatives retain their effectiveness in patients initially receiving any of these two options. Further, it needs to be evaluated if sorafenib and lenvatinib should be considered as “de facto” 2nd line options or if their effectiveness could be modified after Atezo-Bev [29,114]. No robust

information is available, thus preventing evidence-based recommendation. Several trials that may clarify some of the current unknowns are currently ongoing and, they may or may not increase the 1st line alternatives and/or change the sequential treatment schedule currently in place [29]. In that sense, as the efficacy of new strategies increases in terms of response and reduction of tumour burden, the registered downstaging may allow some patients to benefit from potentially curative options that were initially discarded because of excessive tumour load [115].

TARE has also been suggested to be as effective as sorafenib in patients with liver-only involvement [116–118]. However, prospective phase 3 trials comparing it with sorafenib or combining it with sorafenib vs sorafenib alone have failed to demonstrate its superiority and they were not designed to proof non-inferiority [119–121]. Thereby, no evidence-based recommendation may be made until positive trials are available.

Evolutionary events and Clinical-Decision making process

BCLC staging upon progression after initial diagnosis

It is conventional in Oncology to consider tumour progression as a dismal event that is taken as a reflection of treatment failure and need to transition to another line of therapy [114]. However, it is well established that patients treated with surgical resection, ablation or TACE may present progression as new intrahepatic sites after successful treating the first tumour nodule. In some instances, treatment may be repeated, and the tumour be again under control with potential complete response [6]. Indeed, progression may have different patterns with sharply different meaning in terms of prognosis and potential treatment [122]. This concept was raised years ago for patients treated by TACE [33]. Treatment may be successful, but new tumour sites may appear during follow-up. These may be amenable to new TACE if just

intrahepatic and the patient profile has not changed in terms of liver function and physical status [32]. Contrarily, if progression is due to portal vein invasion or extrahepatic spread or cancer related symptoms or liver function is significantly impaired, new TACE sessions are not recommended. In such instance, the patient is registered as presenting untreatable progression and systemic therapy may be considered [6,33]. This specific progression scenario implies a different prognosis and a different treatment recommendation and hence, offers more clinical insight than the commonly used “progression” term. The heterogeneity of tumor progressions and individual patient profiles at progression mandates that the best treatment option requires multidisciplinary team discussion.

The same need to stratify the pattern of progression has emerged in patients undergoing systemic therapy. Prospective studies have demonstrated that prognosis after progression due to increased growth of known tumour sites or new intrahepatic sites is significantly better than progression due to new extrahepatic involvement or vascular invasion [122]. This primed the proposal of a BCLC prognostic model upon progression that is depicted in Figure 2 [6]. As shown, patients may start systemic therapy either in BCLC stage B or C. Those initially at stage B may progress but still stay within the B definitions being classified a BCLCp-B. Those initially at BCLC stage C may show growth of existing lesions or new intrahepatic sites and be classified as BCLCp-C1 or develop new vascular invasion or extrahepatic spread and then be registered as BCLCp-C2 [6].

The prognostic stratification offered by the classification of patients according to their pattern of progression has been repeatedly validated [123–126]. While pattern of progression is not a predictor of treatment benefit, it has become a relevant parameter to inform patients and to design and analyse clinical trials where a sound survival assumption of the patients recruited is key to establish the potential impact of new agents in life expectancy [114].

In summary, we have here updated the BCLC prognostic and treatment strategy. It has incorporated the several novelties in the field of clinical management of HCC and clearly delineated the three steps for patients diagnosed with this cancer. Initial staging serves to stratify patients according to their evolutionary status and is linked to the first treatment option to be recommended. This should be based on the amalgamation of all different patient characteristics that are key to propose the option that is expected to provide the best survival. While the initial recommendations are based on robust scientific evidence the “Clinical Decision Making” displays the complexity at the individual level and the need to personalize decisions at the tumor board level incorporating treatment stage migration and the untreatable progression concepts. However, no algorithm should be expected to be able to provide guidance for each patient. A multiparametric evaluation should be in place for every patient and this should be integrated in Multidisciplinary Tumor Boards where all partners involved in care are actively incorporated. For an effective output of such boards, it is key to have a clearly established initial approach to patients from where to reach individual decisions. The updated BCLC model and its regular update serves this purpose.

REFERENCES:

[1] Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–38.

[2] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–17.

[3] Forner A, Reig M, Rodriguez De Lope C, Bruix J, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61–74. https://doi.org/10.1055/s-0030-1247133.

[4] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245–55. https://doi.org/10.1016/S0140-6736(11)61347-0.

[5] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;31:1301–14. https://doi.org/10.1016/S0140-6736(18)30010-2.

[6] Reig M, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Systemic Therapy for Hepatocellular Carcinoma: The Issue of Treatment Stage Migration and Registration of Progression Using the BCLC-Refined RECIST. Semin Liver Dis 2014;34:444–55. https://doi.org/10.1055/s-0034-1394143.

[7] Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology 2016;150:835–53. https://doi.org/10.1053/j.gastro.2015.12.041.

[8] Hernán MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med 2021;385. https://doi.org/10.1056/NEJMp2113319.

[9] Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187–93.

[10] Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 1993;67:773–5.

[11] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

[12] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.

[13] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and Mortality among Patients on the Liver-Transplant Waiting List. N Engl J Med 2008;359:1018–26. https://doi.org/10.1056/nejmoa0801209.

[14] Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, et al. MELD 3.0: The Model for End-stage Liver Disease Updated for the Modern Era. Gastroenterology 2021. https://doi.org/10.1053/j.gastro.2021.08.050.

[15] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550–8. https://doi.org/10.1200/JCO.2014.57.9151.

[16] Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 2017;66:338–46. https://doi.org/10.1016/j.jhep.2016.09.008.

[17] Scheiner B, Pomej K, Kirstein M, Hucke F, Finkelmeier F, Waidmann O, et al. Predicting the outcome of patients with hepatocellular carcinoma treated with immunotherapy-the CRAFITY score. J Hepatol 2021;75:S236–7.

[18] Singal AG, Hoshida Y, Pinato DJ, Marrero J, Nault JC, Paradis V, et al. International Liver Cancer Association (ILCA) White Paper on Biomarker Development for Hepatocellular Carcinoma. Gastroenterology 2021;160:2572–84. https://doi.org/10.1053/J.GASTRO.2021.01.233.

[19] Cabibbo G, Maida M, Genco C, Parisi P, Peralta M, Antonucci M, et al. Natural history of untreatable hepatocellular carcinoma: A retrospective cohort study. World J Hepatol 2012;4:256–61. https://doi.org/10.4254/wjh.v4.i9.256.

[20] de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension. J

Hepatol 2015;63:743–52. https://doi.org/10.1016/j.jhep.2015.05.022.

[21] D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563–76. https://doi.org/10.1016/j.jhep.2017.10.020.

[22] Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445–9. https://doi.org/10.1002/hep.23478.

[23] Tonon M, Piano S, Gambino CG, Romano A, Pilutti C, Incicco S, et al. Outcomes and Mortality of Grade 1 Ascites and Recurrent Ascites in Patients With Cirrhosis. Clin Gastroenterol Hepatol 2021;19:358-366.e8. https://doi.org/10.1016/j.cgh.2020.03.065.

[24] Llach J, Ginès P, Arroyo V, Rimola A, Titó L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482–7. https://doi.org/10.1016/0016-5085(88)90441-6.

[25] Pinyol R, Montal R, Bassaganyas L, Sia D, Takayama T, Chau G-Y, et al. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. Gut 2019;Jun;68:1065-1075. https://doi.org/10.1136/gutjnl-2018-316408.

[26] Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2018;29:iv238–55. https://doi.org/10.1093/annonc/mdy308.

[27] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182–236. https://doi.org/10.1016/j.jhep.2018.03.019.

[28] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–80. https://doi.org/10.1002/hep.29086.

[29] Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of

hepatocellular carcinoma. An EASL position paper. J Hepatol 2021;Oct(75):960–74. https://doi.org/10.1016/j.jhep.2021.07.004.

[30] Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. J Clin Oncol 2020;38:4317–45. https://doi.org/10.1200/JCO.20.02672.

[31] Pocock SJ, Stone GW. The Primary Outcome Is Positive — Is That Good Enough? N Engl J Med 2016;375:971–9. https://doi.org/10.1056/nejmra1601511.

[32] Forner A, Gilabert M, Bruix J, Raoul J-L. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014;11:525–35. https://doi.org/10.1038/nrclinonc.2014.122.

[33] Bruix J, Reig M, Rimola J, Forner A, Burrel M, Vilana R, et al. Clinical decision making and research in hepatocellular carcinoma: Pivotal role of imaging techniques. Hepatology 2011;54:2238–44. https://doi.org/10.1002/hep.24670.

[34] Templeton AJ, Amir E, Tannock IF. Informative censoring — a neglected cause of bias in oncology trials. Nat Rev Clin Oncol 2020;17:327–8. https://doi.org/10.1038/s41571-020-0368-0.

[35] Sala M, Fuster J, Llovet JM, Navasa M, Sole M, Varela M, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004;10:1294–300.

[36] Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology 2012;55:132–40. https://doi.org/10.1002/hep.24680.

[37] Ferrer-Fàbrega J, Forner A, Liccioni A, Miquel R, Molina V, Navasa M, et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology 2016;63:839–49. https://doi.org/10.1002/hep.28339.

[38] Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency

ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology 2010;51:1284–90. https://doi.org/10.1002/hep.23466.

[39] Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol 2013;59:300–7. https://doi.org/10.1016/j.jhep.2013.04.009.

[40] Izumi N, Hasegawa K, Nishioka Y, Takayama T, Yamanaka N, Kudo M, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial). J Clin Oncol 2019;37:4002–4002. https://doi.org/10.1200/JCO.2019.37.15_SUPPL.4002.

[41] Doyle A, Gorgen A, Muaddi H, Aravinthan AD, Issachar A, Mironov O, et al. Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3 cm in potentially transplantable patients. J Hepatol 2019;70:866–73. https://doi.org/10.1016/j.jhep.2018.12.027.

[42] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.

[43] Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–403.

[44] Mazzaferro V, Llovet JMJM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43. https://doi.org/10.1016/S1470-2045(08)70284-5.

[45] Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:985–6. https://doi.org/S0016-5085(12)00941-9 [pii] 10.1053/j.gastro.2012.05.052.

[46] Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death Following Liver Transplantation for Hepatocellular Carcinoma. Gastroenterology 2018;154:128–39. https://doi.org/10.1053/j.gastro.2017.09.025.

[47] Herrero JI, Sangro B, Pardo F, Quiroga J, Inarrairaegui M, Rotellar F, et al. Liver transplantation in patients with hepatocellular carcinoma across Milan criteria. Liver Transpl 2008;14:272–8.

[48] Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma. JAMA Surg 2016;151:846. https://doi.org/10.1001/jamasurg.2016.1121.

[49] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–40.

[50] Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology 2015;61:526–36. https://doi.org/10.1002/hep.27431.

[51] Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018–22.

[52] Ferrusquía-Acosta J, Bassegoda O, Turco L, Reverter E, Pellone M, Bianchini M, et al. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. J Hepatol 2021;74:811–8. https://doi.org/10.1016/j.jhep.2020.10.003.

[53] Baffy G, Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: Is it real and how to measure it? J Hepatol 2021. https://doi.org/10.1016/j.jhep.2021.09.029.

[54] Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321–8.

[55] Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg 2017;Dec;104:1775–84. https://doi.org/10.1002/bjs.10677.

[56] Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012;57:794–802. https://doi.org/S0168-8278(12)00361-3 [pii]10.1016/j.jhep.2012.05.007.

[57] Nault J-C, Sutter O, Nahon P, Ganne-Carrié N, Séror O. Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations. J Hepatol 2018;68:783–97. https://doi.org/10.1016/j.jhep.2017.10.004.

[58] Berardi G, Morise Z, Sposito C, Igarashi K, Panetta V, Simonelli I, et al. Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in Child-Pugh B cirrhosis. J Hepatol 2020;Jan(1):75–84.

[59] Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. Br J Surg 2016;103:871–80. https://doi.org/10.1002/bjs.10137.

[60] Molina V, Sampson-Dávila J, Ferrer J, Fondevila C, Díaz del Gobbo R, Calatayud D, et al. Benefits of laparoscopic liver resection in patients with hepatocellular carcinoma and portal hypertension: a case-matched study. Surg Endosc 2018;32:2345–54. https://doi.org/10.1007/s00464-017-5930-1.

[61] Witowski J, Rubinkiewicz M, Mizera M, Wysocki M, Gajewska N, Sitkowski M, et al. Meta-analysis of short- and long-term outcomes after pure laparoscopic versus open liver surgery in hepatocellular carcinoma patients. Surg Endosc 2019;33:1491.

https://doi.org/10.1007/S00464-018-6431-6.

[62] Morise Z, Ciria R, Cherqui D, Chen K-H, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 2015;22:342–52. https://doi.org/10.1002/jhbp.215.

[63] Ciria R, Cherqui D, Geller DA, Briceno J, Wakabayashi G. Comparative Short-term Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. Ann Surg 2016;263:761–77. https://doi.org/10.1097/SLA.0000000000001413.

[64] Pompili M, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. J Hepatol 2013;59:89–97. https://doi.org/10.1016/j.jhep.2013.03.009.

[65] N'Kontchou G, Mahamoudi A, Aout M, Ganne-Carrie N, Grando V, Coderc E, et al. Radiofrequency ablation of hepatocellular carcinoma: Long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 2009;50:1475–83. https://doi.org/10.1002/hep.23181.

[66] Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107:569–77. https://doi.org/10.1038/ajg.2011.425.

[67] Cucchetti A, Djulbegovic B, Tsalatsanis A, Vitale A, Hozo I, Piscaglia F, et al. When to perform hepatic resection for intermediate-stage hepatocellular carcinoma. Hepatology 2015;61:905–14. https://doi.org/10.1002/hep.27321.

[68] Forner A, Gilabert M, Bruix J, Raoul J-L. Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery. Nat Rev Clin Oncol 2014;12:10–10. https://doi.org/10.1038/nrclinonc.2014.122-c2.

[69] Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, et al. Prospective cohort study

of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461–9. https://doi.org/S0016-5085(06)01075-4 [pii]10.1053/j.gastro.2006.05.021.

[70] Galle PR, Tovoli F, Foerster F, Wörns MA, Cucchetti A, Bolondi L. The treatment of intermediate stage tumours beyond TACE: From surgery to systemic therapy. J Hepatol 2017;67:173–83. https://doi.org/10.1016/j.jhep.2017.03.007.

[71] Kloeckner R, Galle PR, Bruix J. Local and Regional Therapies for Hepatocellular Carcinoma. Hepatology 2021;73:137–49. https://doi.org/10.1002/hep.31424.

[72] Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020:1136–42. https://doi.org/10.1097/TP.0000000000003174.

[73] Kwong A, Mehta N. Expanding the Limits of Liver Transplantation for Hepatocellular Carcinoma: Is There a Limit? Clin Liver Dis 2021;25:19–33. https://doi.org/10.1016/J.CLD.2020.08.002.

[74] Ferrer-Fàbrega J, Sampson-Dávila J, Forner A, Sapena V, Díaz A, Vilana R, et al. Limited tumour progression beyond Milan criteria while on the waiting list does not result in unacceptable impairment of survival. J Hepatol 2021. https://doi.org/10.1016/J.JHEP.2021.06.015.

[75] Navasa M, Bruix J. Multifaceted perspective of the waiting list for liver transplantation: the value of pharmacokinetic models. Hepatology n.d.;51:12–5. https://doi.org/10.1002/hep.23332.

[76] Toso C, Meeberg G, Hernandez-Alejandro R, Dufour J-F, Marotta P, Majno P, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 2015;62:158–65. https://doi.org/10.1002/hep.27787.

[77] Mehta N, Dodge JL, Roberts JP, Hirose R, Yao FY. Alpha-fetoprotein Decrease from >1000 to <500 ng/ml in Patients with Hepatocellular Carcinoma Leads to Improved

Post-Transplant Outcomes. Hepatology 2019;Mar;69:1193–205. https://doi.org/10.1002/hep.30413.

[78] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894–905. https://doi.org/10.1056/NEJMoa1915745.

[79] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.

[80] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90. https://doi.org/10.1056/NEJMoa0708857.

[81] Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–73. https://doi.org/10.1016/S0140-6736(18)30207-1.

[82] https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-and-tremelimumab-improved-os-in-liver-cancer.html n.d.

[83] Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;Jan 7;389:56–66. https://doi.org/10.1016/S0140-6736(16)32453-9.

[84] Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54–63. https://doi.org/10.1056/NEJMoa1717002.

[85] Finn RS, Merle P, Granito A, Huang Y-H, Bodoky G, Pracht M, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. J Hepatol 2018;69:353–8.

https://doi.org/10.1016/j.jhep.2018.04.010.

[86] Zhu AX, Kang Y-K, Yen C-J, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282–96. https://doi.org/10.1016/S1470-2045(18)30937-9.

[87] Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2020;38:193–202. https://doi.org/10.1200/JCO.19.01307.

[88] https://www.merck.com/news/merck-announces-keytruda-pembrolizumab-met-primary-endpoint-of-overall-survival-os-in-patients-with-advanced-hepatocellular-carcinoma-previously-treated-with-sorafenib/ n.d.

[89] Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–30.

[90] Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. J Hepatol 2010;52:380–8. https://doi.org/S0168-8278(09)00805-8 [pii] 10.1016/j.jhep.2009.12.004.

[91] Burrel M, Reig M, Forner A, Barrufet M, Lope CRD, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56:1330–5. https://doi.org/10.1016/j.jhep.2012.01.008.

[92] Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology 2021. https://doi.org/10.1002/hep.31819.

[93] Chen CP. Role of External Beam Radiotherapy in Hepatocellular Carcinoma. Clin Liver Dis 2020;24:701–17. https://doi.org/10.1016/j.cld.2020.07.006.

[94] Shanker MD, Moodaley P, Soon W, Liu HY, Lee YY, Pryor DI. Stereotactic ablative radiotherapy for hepatocellular carcinoma: A systematic review and meta-analysis of local control, survival and toxicity outcomes. J Med Imaging Radiat Oncol 2021. https://doi.org/10.1111/1754-9485.13309.

[95] Yu J, Yu X, Han Z, Cheng Z, Liu F, Zhai H, et al. Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomised controlled trial. Gut 2017;66:1172–3. https://doi.org/10.1136/gutjnl-2016-312629.

[96] Vietti Violi N, Duran R, Guiu B, Cercueil J-P, Aubé C, Digklia A, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol 2018;3:317–25. https://doi.org/10.1016/S2468-1253(18)30029-3.

[97] Han J, Fan YC, Wang K. Radiofrequency ablation versus microwave ablation for early stage hepatocellular carcinoma: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e22703. https://doi.org/10.1097/MD.0000000000022703.

[98] Chan AWH, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018;Dec(69):1284–93. https://doi.org/10.1016/j.jhep.2018.08.027.

[99] Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol 2015;62:617–24. https://doi.org/10.1016/j.jhep.2014.10.037.

[100] Vouche M, Lewandowski RJ, Atassi R, Memon K, Gates VL, Ryu RK, et al. Radiation

lobectomy: Time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol 2013;59:1029. https://doi.org/10.1016/J.JHEP.2013.06.015.

[101] Troisi RI, Berardi G, Morise Z, Cipriani F, Ariizumi S, Sposito C, et al. Laparoscopic and open liver resection for hepatocellular carcinoma with Child–Pugh B cirrhosis: multicentre propensity score-matched study. Br J Surg 2021;108:196–204. https://doi.org/10.1093/BJS/ZNAA041.

[102] Reverter E, Cirera I, Albillos A, Debernardi-Venon W, Abraldes JG, Llop E, et al. The prognostic role of hepatic venous pressure gradient in cirrhotic patients undergoing elective extrahepatic surgery. J Hepatol 2019;71:942–50. https://doi.org/10.1016/j.jhep.2019.07.007.

[103] Fukami Y, Kaneoka Y, Maeda A, Kumada T, Tanaka J, Akita T, et al. Liver Resection for Multiple Hepatocellular Carcinomas: A Japanese Nationwide Survey. Ann Surg 2020;272:145–54. https://doi.org/10.1097/SLA.0000000000003192.

[104] Raoul J-L, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 2019;Jan;72:28–36. https://doi.org/10.1016/j.ctrv.2018.11.002.

[105] Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255–64. https://doi.org/10.1038/bjc.2014.199.

[106] Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474–81. https://doi.org/10.1016/j.jhep.2006.10.020.

[107] Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of

hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Interv Radiol 2010;33:41–52. https://doi.org/10.1007/s00270-009-9711-7.

[108] Meyer T, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. Br J Cancer 2013;108:1252–9. https://doi.org/10.1038/bjc.2013.85.

[109] Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, et al. Randomized Trial of Hepatic Artery Embolization for Hepatocellular Carcinoma Using Doxorubicin-Eluting Microspheres Compared With Embolization With Microspheres Alone. J Clin Oncol 2016;34:2046–53. https://doi.org/10.1200/JCO.2015.64.0821.

[110] Facciorusso A, Bellanti F, Villani R, Salvatore V, Muscatiello N, Piscaglia F, et al. Transarterial chemoembolization vs bland embolization in hepatocellular carcinoma: A meta-analysis of randomized trials. United Eur Gastroenterol J 2017;5:511–8. https://doi.org/10.1177/2050640616673516.

[111] Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver Transpl 2014;20:945–51. https://doi.org/10.1002/lt.23904.

[112] Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R, De Carlis L, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging: a randomised, controlled, phase 2/3 trial. Lancet Oncol 2020;Jul;21:947–56.

[113] Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: Long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968–77. https://doi.org/10.1002/hep.27752.

[114] Bruix J. End-points in clinical trials for liver cancer and their value in evidence based clinical decision making: an unresolved Gordian knot. J Hepatol 2021. https://doi.org/10.1016/j.jhep.2021.01.033.

[115] Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, et al. Neoadjuvant

cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity. Nat Cancer 2021;2:891–903. https://doi.org/10.1038/s43018-021-00234-4.

[116] Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 2011;54:868–78. https://doi.org/10.1002/hep.24451.

[117] Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology 2013;57:1826–37. https://doi.org/10.1002/hep.26014.

[118] Hilgard P, Hamami M, Fouly A El, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 2010;52:1741–9. https://doi.org/10.1002/hep.23944.

[119] Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol 2018;36(19):1913–21. https://doi.org/10.1200/JCO.2017.76.0892.

[120] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017;Dec;18:1624–36. https://doi.org/10.1016/S1470-2045(17)30683-6.

[121] Ricke J, Klümpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol 2019;Dec;71:1164–74. https://doi.org/10.1016/j.jhep.2019.08.006.

[122] Reig M, Rimola J, Torres F, Darnell A, Lope CR-, Forner A, et al. Post-progression

survival of patients with advanced hepatocellular carcinoma. Rationale for second line trial design. Hepatology 2013;58:2023–31. https://doi.org/10.1002/hep.26586.

[123] Iavarone M, Cabibbo G, Biolato M, Della Corte C, Maida M, Barbara M, et al. Predictors of survival of patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015;Sep;62:784–91. https://doi.org/10.1002/hep.27729.

[124] Reig M, Galle PR, Kudo M, Finn R, Llovet JM, Metti AL, et al. Pattern of progression in advanced hepatocellular carcinoma treated with ramucirumab. Liver Int 2021;41:598–607. https://doi.org/10.1111/liv.14731.

[125] Rimassa L, Assenat E, Peck-Radosavljevic M, Pracht M, Zagonel V, Mathurin P, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. Lancet Oncol 2018;May;19:682–93. https://doi.org/10.1016/S1470-2045(18)30146-3.

[126] de la Torre-Aláez M, Jordán-Iborra C, Casadei-Gardini A, Bilbao JI, Rodriguez-Fraile M, Sancho L, et al. The Pattern of Progression Defines Post-progression Survival in Patients with Hepatocellular Carcinoma Treated with SIRT. Cardiovasc Intervent Radiol 2020;43:1165–72. https://doi.org/10.1007/s00270-020-02444-2.

Figures Legends

Figure 1: Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy in 2022

The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. The Clinical Decision-Making for an individualised approach according to the available data on September 15, 2021 is defined by teams responsible for integrating all those data with the individual patient's medical profile

Note that liver function should be evaluated beyond the conventional Child-Pugh staging

AFP, alfa-fetoprotein; **ALBI,** Albumin-Bilirubin Child-Pugh; **MELD,** Model of End-stage Liver

Disease; **ECOG PS,** Eastern Cooperative Oncology Group Performance Status; **LT,** Liver Transplantation; **TACE,** transarterial chemoembolization; **BSC,** Best Supportive Care.

*****Except for those with tumor burden acceptable for Transplant

^ Resection may be considered for single peripheral HCC with adequate remnant liver volume

++ Full availability of the trial testing the combination of tremelimumab and durvalumab, may incorporate these agents in the first line alternatives.

Figure 2: BCLC up on progression

BCLC stratification upon radiology progression. This "BCLC upon progression" (BCLCp) proposal classifies as BCLCp-B those patients who present radiologic progression due to growth of existing nodules 20% or new intrahepatic sites but are still within BCLC-B because of the absence of vascular invasion or extrahepatic spread or cancer-related symptoms (PS 0). Those patients who present radiologic progression and evolve to BCLC-C or progress within BCLC-C are divided at the time of progression into: BCLCp-C1: those patients who present radiologic progression due to growth of existing nodules 20% or new intrahepatic sites, and BCLCp C2: those patients who present progression due to new extrahepatic lesion and/or vascular invasion.

FIGURE 1

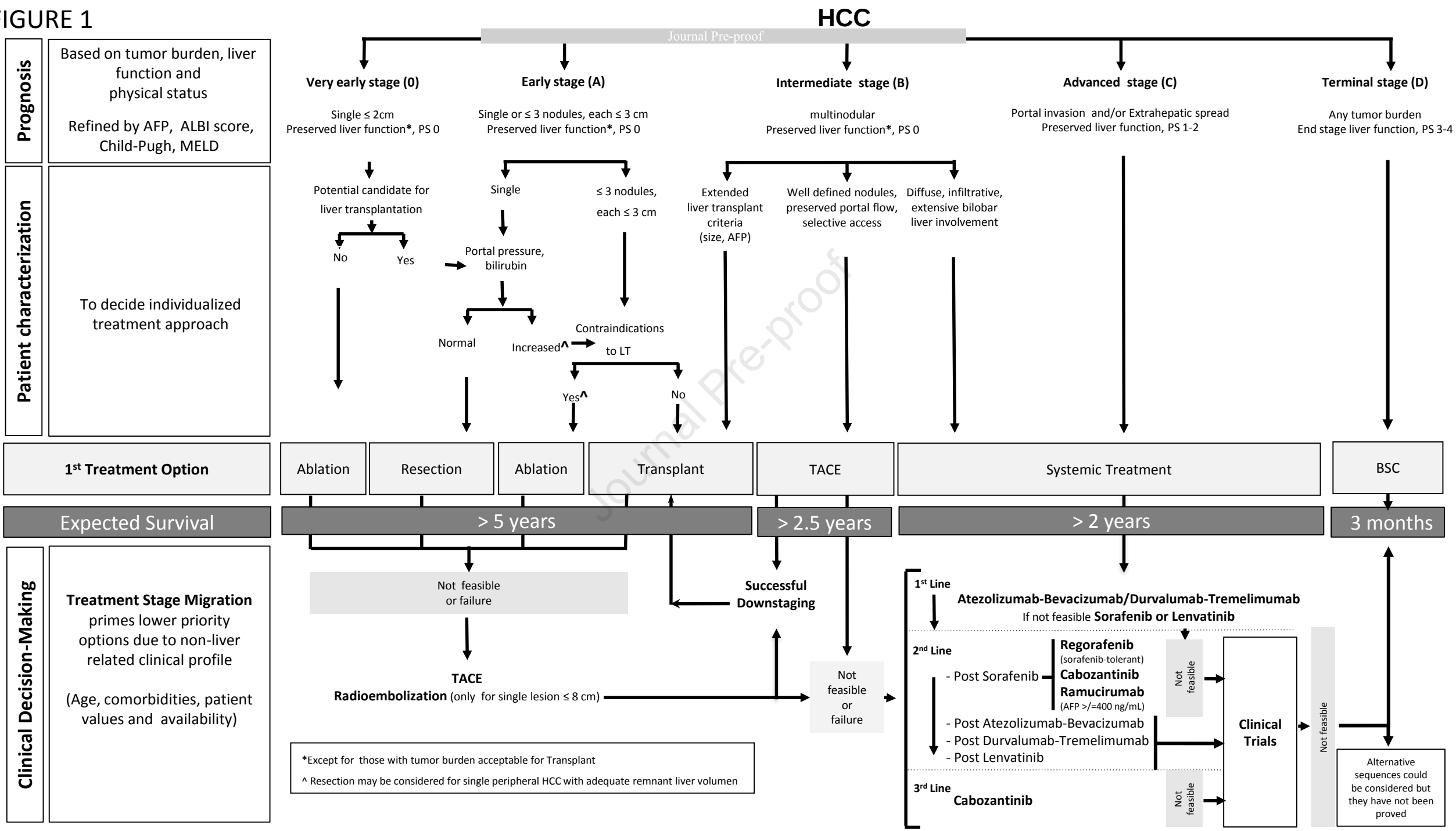
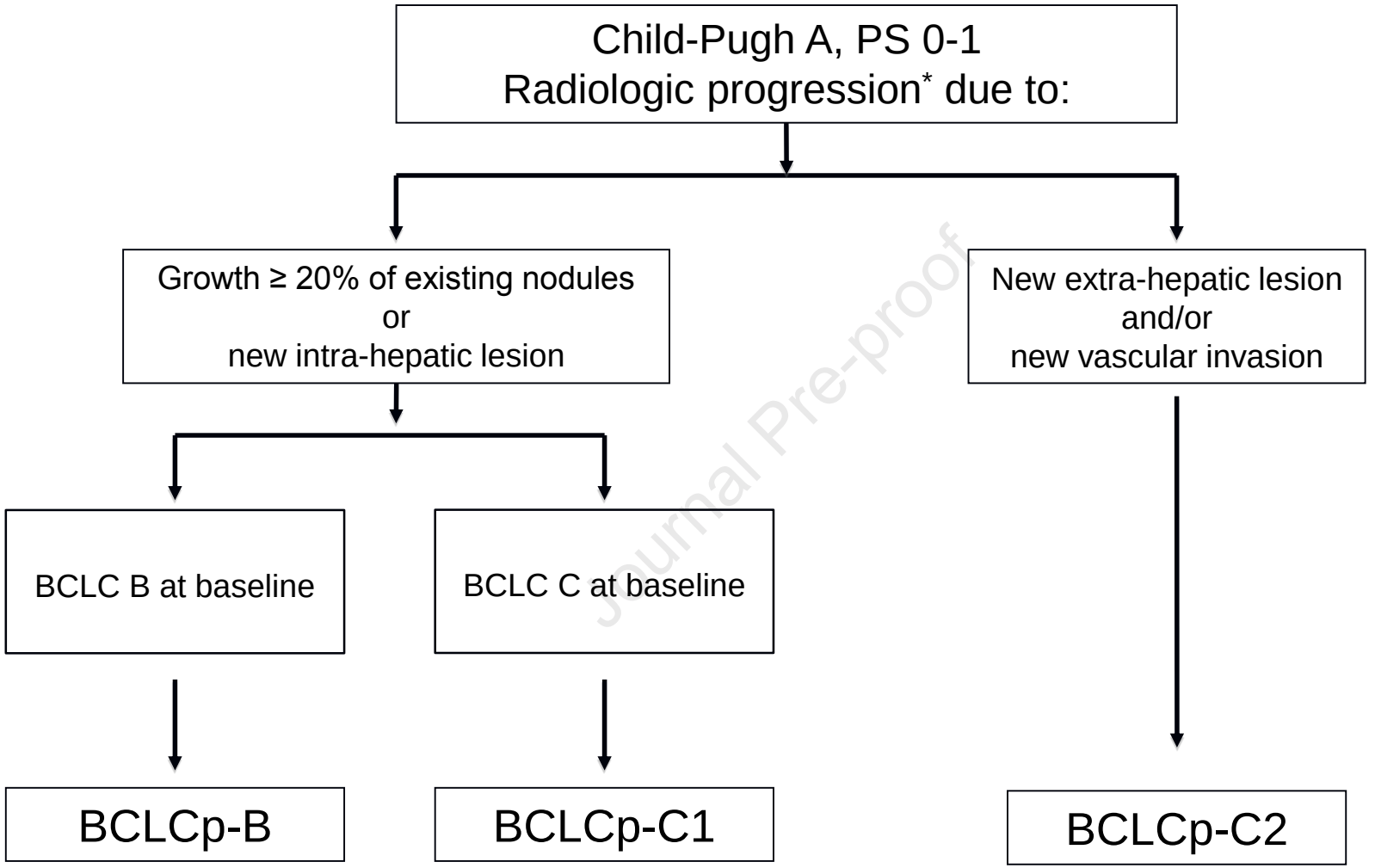

HCC
Journal Pre-proof
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Patient characterization
To decide individualized treatment approach
Very early stage (0)
Single ≤ 2cm
Preserved liver function*, PS 0
Early stage (A)
Single or ≤ 3 nodules, 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
Potential candidate for liver transplantation
No
Yes
Single
≤ 3 nodules, each ≤ 3 cm
Portal pressure, bilirubin
Normal
Increased^
Contraindications to LT
Yes^
No
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
1st Treatment Option
Ablation
Resection
Ablation
Transplant
TACE
Systemic Treatment
BSC
Expected Survival
> 5 years
> 2.5 years
> 2 years
3 months
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
2nd Line
- Post Sorafenib
Regorafenib (sorafenib-tolerant)
Cabozantinib
Ramucirumab (AFP >/=400 ng/mL)
Not feasible
- Post Atezolizumab-Bevacizumab
- Post Durvalumab-Tremelimumab
- Post Lenvatinib
Clinical Trials
Not feasible
3rd Line
Cabozantinib
Not feasible
Alternative sequences could be considered but they have not been proved
Clinical Decision-Making
Treatment Stage Migration primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
*Except for those with tumor burden acceptable for Transplant
^ Resection may be considered for single peripheral HCC with adequate remnant liver volumen

FIGURE 2



*RECIST criteria v1.1