Selecting the first line treatment in non-metastatic hepatocellular carcinoma - comparing clinical practice guidelines

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Abstract

Primary malignancy of the liver or hepatocellular carcinoma (HCC) is unique in its presentation, disease process, and management. Unlike breast or colon cancer, the staging of HCC depends on performance status and baseline liver function along with pathological characteristics. Apart from traditional options like surgery and systemic therapy, effective management can be achieved in selected cases with liver transplant and locoregional therapy (LRT) like transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and ablation. Liver study societies and cancer groups across the globe proposed guidelines to aid the treating physicians in choosing first-line treatment for liver cancer. It is tough to compare these guidelines as they differ not only in treatment recommendations but also in risk assessment (and staging). The approach to the same patient may be different in the country he or she is managed. In clinical practice, decisions are usually taken on the consensus of multidisciplinary tumor boards and do not necessarily adhere to any guidelines. In the early (and very early) stage HCC, curative options like surgery, transplant, and ablation are recommended. In intermediate stage HCC, LRT (TACE and TARE) is preferred in the first line and systemic therapy for treatment failure or residual disease. Systemic therapy, including the atezolizumab/bevacizumab combination and tyrosine kinase inhibitors (TKI) like sorafenib and lenvatinib, is used for advanced stages. Supportive care is advised for terminal stage HCC.

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Introduction

Hepatocellular carcinoma (HCC) ranks fourth in cancer-related mortality worldwide, with only an 18% five-year survival rate.[1] HCC from North America contributes to only 5% of the cases worldwide, but its rising incidence in recent years is concerning.[2] Cirrhosis is frequently associated with HCC, and other common risk factors include viral infections (hepatitis B and hepatitis C virus), life-style related like alcohol and tobacco use, metabolic disorders like diabetes, obesity and nonalcoholic steatohepatitis, and rare genetic diseases like acute intermittent porphyria.[3-10] HCC not related to HBV or HCV infections are usually diagnosed in later stages and have a worse prognosis.[11]

In the current clinical practice, there is much ambiguity in the ideal first-line treatment of non-metastatic HCC. In the majority of institutions, decisions are taken through multidisciplinary tumor board consensus involving medical oncologists, hepatologists, radiation oncologists, interventional radiologists, and surgeons. Various liver study groups and cancer networks across the globe proposed clinical practice guidelines that aid in screening, diagnosing, and treating HCC. These guidelines are based on either consensus or evidence and are tailor-made to the respective populations. Interestingly, there are disparities among them not only in proposed treatment options but also in risk assessment. The aim of this review is to compare the available options around the world to treat non-metastatic HCC so that physicians can make an informed decision suitable to their patients. For this purpose, we studied different guidelines and try to lay out the major difference in them for treating non-metastatic HCC. The practical challenges in adhering to the guidelines and the gaps in the current practice were also discussed in this review briefly.

Clinical practice guidelines for managing hepatocellular carcinoma

According to our literature search, the oldest clinical practice guidelines for HCC were out of England and were explicitly for transplant eligibility in 1999.[12] In the following 10-15years, several such guidelines covering all aspects of HCC (screening, diagnosis and management) were proposed. In 2014, Wang *et al.* assessed the quality of various guidelines proposed to manage HCC and liver metastases.[13] It was a comprehensive study with more than 40 guidelines (and updates). At that time, proposals

from the American Association for the Study of Liver Disease (AASLD) (2011), European Association for the Study of the Liver (EASL) (2012), Japanese Ministry of Health (2008), Association of Upper Gastrointestinal Surgeons (2006), and Netherlands (2007) were considered to be of high quality.

The rationale for selecting the guidelines

During our literature, we identified 63 guidelines for the management of liver-related cancers or metastatic diseases. For our literature review, the guidelines selected were: i) related to the management of primary liver cancer; ii) published or updated in the last three years; iii) evidence-based proposals. We excluded guidelines: i) restricted only to guide liver transplants; ii) related to the management of liver metastases; and iii) consensus-based proposals.

Older guidelines used more traditional locoregional treatment (LRT) options like surgical resection, ablation, liver transplant, and transarterial chemoembolization (TACE). The cut-off of three years was to compare the utilization of newer treatment modalities like transarterial radioembolization (TARE), stereotactic radiation therapy (SBRT), immune-checkpoint inhibitors (ICI), and tyrosine-kinase inhibitors (TKI).

After applying our selection criteria, we ended up with seven guidelines. These include the American Association for the Study of Liver Disease (AASLD); European Association for the Study of the Liver (EASL); Japanese Society for Hepatology (JSH), Asian Pacific Association for the Study of the Liver (APASL); Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines (KLCSG); National Comprehensive Cancer Network (NCCN); European Society for Medical Oncology (ESMO) Clinical Practice Guideline.[14-20]

Both AASLD and JSH proposed their first guidelines in 2005, and current guidelines are from the updates in 2018 and 2019, respectively. The EASL's first guidelines were published in 2012 and were updated in 2018. The APASL proposed recommendations for the first time in 2010, and last updated them in 2017. KLSCG guidelines were earlier published in 2014 and updated in 2018. ESMO guidelines were first published in 2018 and updated in June 2020. NCCN guidelines are updated continuously, and at the time of writing this review, they were updated in June 2020.

Comparing guidelines

The common theme in all the practice guidelines discussed below is to stratify the patients based on individual risk factors (staging) and recommend an appropriate treatment modality for it. There is no good evidence in favor of administering adjuvant or adjunct therapy in the management of HCC. To better understand the differences in the approach among the discussed guidelines, two sample non-metastatic HCC patients, AB and XY, are used in the review.

First sample patient, AB is a 46-year-old African-American lady with a history of hepatitis B and hepatitis C who presented to the hospital with unbearable RUQ abdominal pain (No ascites or encephalopathy). The computed tomography (CT) scan of the abdomen showed heterogeneous, multiloculated, hypoattenuating lesion measuring 5×10×8 cm without portal vein tumor thrombosis (PVTT) or lymph node extension or extra-hepatic disease. Her Child-Pugh (CP) score is B7, and the performance status (PS) on the Eastern Cooperative Oncology Group scale (ECOG) scale is 0.

The second patient, XY, is a 65-year-old Caucasian male with no history of hepatitis C or hepatitis B present with LLQ pain and intractable vomiting. He does not have ascites or encephalopathy. The magnetic resonance imaging (MRI) of the abdomen showed an invasive lesion involving both left and right lobes with PVTT but no lymph nodes and extra-hepatic disease. His CP score is A, and PS is ECOG 1. In the following text, these patients are stratified according to each guideline, and their recommended treatment is discussed. The HCC with favorable features (like small solitary lesion <2 cm with ECOG 0 and CP A) and worse clinical features (like metastasis, CP C, PS ≥2) were not chosen deliberately for this exercise as the approach (risk stratification and treatment) of such extreme patients is similar across the guidelines.

Risk assessment and staging

Algorithms for managing HCC proposed by all the guidelines are based on accurate risk stratification, and hence it is a critical step in treating a new HCC patient. For risk assessment, three categories of risk-factors are used: i) hepatic functional reserve; ii) PS; iii) pathological factors (size and number of primary liver lesions, vascular invasion, nodal extension, and extra-hepatic metastasis). Some guidelines use all three factors, while others may use only one or two of them.

The Barcelona clinic liver cancer (BCLC) staging system is unique to HCC, where all three risk factors are used to stage the patient.[21] For staging, patients are first classified based on the liver functional status (CP score), then by PS, and lastly, the pathological features. The CP score is used to assess the hepatic functional reserve in this system. It has five stages (BCLC 0, A to D) with BCLC 0 at one end of the spectrum (very early stage) and BCLC D at the other end representing the terminal stage. This staging system was proposed in the late 2000s and is adopted across the globe. The EASL strictly follows this staging system, while societies like AASLD and Dutch modified modified the parameters for the liver function (CP score) and PS.

European Association for the Study of the Liver and European Society for Medical Oncology

In EASL guidelines, the term *preserved liver function* (as in BCLC staging) strictly refers to patients with CP A and without ascites. HCC patients with CP B or C and those with ascites are considered the terminal stage (BCLC D). The PS of ECOG 0 is essential to put the patients in early and intermediate groups. The ECOG of 1 places patients directly in the advanced stage (BCLC C). According to this system, AB is the terminal stage (BCLC D) just based on the CP score of B, while XY is an advanced stage (BCLC C) given the ECOG of 1 (and also PVTT). Pathological features used in staging patients are size and number of primary tumor lesions, macro-vascular invasion (MVI), and metastasis (lymph node or distant). In this system, they are only useful in staging the patients among very-early, early and intermediate stages (ECOG 0 and CPA). A single lesion ≤2 cm is very early (BCLC 0), and a multinodular tumor (>3) is the intermediate stage (BCLC B), while early-stage (BCLC A) is an HCC where the primary is >2 cm or there 2-3 nodules all ≤3 cm. It is important to note that an HCC with ECOG >2 is a terminal stage irrespective of liver function and pathological features. The ESMO guidelines use the same BCLC staging as EASL except for one small difference. It considers the BCLC stages 0 and A as one low-risk group, Stage 0-A. The staging of our sample patients, AB and XY would be the same as that according to EASL staging.

American Association for the Study of Liver Disease

The AASLD guidelines are generous in classifying the HCC for liver function and PS. Even though the terminology for staging is the same as in EASL, the characteristics of the stratification are

different. HCC with CP B (along with CP A) is classified as early (BCLC 0), intermediate (BCLC A), or advanced stage (BCLC C). The CP C patients are categorized as the terminal stage (BCLC D). Patients in stages BCLC 0-C (up to the advanced stage) can have an ECOG of 1. Pathological features for grouping the HCCs are similar to EASL guidelines. The patient AB is early-stage (BCLC A) secondary to CP B and ECOG 0, while XY is an advanced stage (BCLC C) due to PVTT. Patient AB will be treated as an advanced stage HCC in Europe and an early-stage HCC in the US while XY would be an advanced stage in both the regions.

Japanese Society for Hepatology and Asian Pacific Association for the Study of the Liver

Risk assessment is similar in the guidelines proposed by *JSH and APASL.* They do not use PS to stratify the patients but use the comparable parameters for liver functional status (CP score) and pathological factors (2/3 risk factors of the BCLC system). There are no designated risk groups as in EASL or AASLD, but there is an algorithm that has CP A or B patients with ≤3 primaries and ≤3 cm on one end and CP C patients at the other (terminal) end. The

Table 1. Comparing risk assessment and management in guidelines.

		AASLD	EASL	JSHd	APASLd	KLCSGf	NCCN
Risk assessment	PS	Y[1]	Y[2]	N	N	N	N
	Liver function	Y	Y	Y	Y	N	N
	Pathological factors	Y	Y	Y	Y	Y	Y
	AB	Early-stage	Advanced stage	Low-risk[3]	Low-risk3	Stage II	Stage IIIA
	XY	Advanced stage	Advanced stage	Intermediate risk[3]	Intermediate risk[3]	Stage III	Stage IIIB
Management of HCC	OLT	Early[a] Terminal[a] Intermediatea[b]	Early	Terminal	Terminal stage (without mets)	Stage II/III (Milan's criteria)	UNOS criteria
	Ablation	Very early[a] Early[a]	Very early	Early	Early	Stage I Stage II (without VI)	Unresectable/ Non-operable/ Transplant-ineligible
	Surgery	Very early Early[a]	Very early	Early Advanced	No specific stage	Stage I Stage II (single lesion without VI)	Resectable
	TACE	Early[a] Intermediate	Intermediate	Early Intermediate Advanced	Intermediate Advanced (alternative)	Stage II (except single lesion without V) Stage III	Unresectable/ Non-operable/ Transplant-ineligible
	TARE	Early[a] Intermediate[a] Advanced[ac]	NR	NR	NR	NR	Unresectable/ Non-operable/ Transplant-ineligible
	SBRT	Early[a]	NR	NR	NR	Stage II/III (VI+)	NR
	EBRT	NR	NR	NR	NR	Stage II/III/IV (VI+)	Unresectable/ Non-operable/ Transplant-ineligible
	HAIC	NR	NR	Intermediate Advanced	NR	Any Stage III	NR
	TKI	Advanced	Advanced	Intermediate Advanced	Intermediate[e] Advanced	Stage II/III (VI+) Stage IV	Unresectable/ Non-operable/ Metastatic
	ICI	Advanceda	NR	NR	NR	NR	Unresectable/ Non-operable/ Metastatic
	BSC	Terminal	Terminal	CP C not transplantable	CP C with mets	NR	CP C with mets
	AB	Ablation TACE TARE SBRT	Best supportive care	TACE	TACE TKI for residual disease	TACE ABLATION	Ablation/TACE /TARE EBRT/BSC/TKI/ICI
	XY	TKI ICI and TARE are alternatives	TKI	TACE TKI HAIC	TKI TACE	TACE TACE + SBRT TKI	Ablation/TACE /TARE EBRT/BSC/TKI/ICI

AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of the Liver; JSH, Japanese Society for Hepatology; APASL, Asian Pacific Association for the Study of the Liver; KLCSG, Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines; NCCN, National Comprehensive Cancer Network; PS, performance status; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; SBRT, stereotactic radiation therapy; EBRT, external radiation therapy; HAIC, hepatic artery infusion chemotherapy; TKI, tyrosine kinase inhibitors; ICI, immune-checkpoint inhibitors; BSC, best supportive care; NR, not recommended; VI, vascular invasion. a= Level 2 evidence; b= to downstage c= level 3 evidence; d= comparable groups with AASLD or EASL; e= if TACE is ineffective; f= only CP A with no portal hypertension and ECOG 0-1. 1= Early and intermediate stage can have ECOG of 1; 2= ECOG of 1, places a patient in an advanced stage; 3= comparable to AASLD/EASL stratification.

APASL guidelines differ with JSH in recommendations for resection in that they are vague by leaving it to the MDTB consensus (for CP A or B). According to both the systems, AB and XY can be staged in groups comparable to intermediate (due to size) and advanced stage (PVTT), respectively.

Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines

KLCSG guidelines use all three risk factors used in the BCLC, but the recommendations are only to CP A HCC without portal hypertension and ECOG of 0-1. For pathological factors, it uses modified Union for International Cancer Control (mUICC) staging system that use three criteria to stage the patient: i) Number of lesions- solitary; ii) Size of the lesion is ≤ 2 cm); iii) no vascular or bile duct invasion.

Staging is depends on the number of criteria a HCC patient meets, Stage I (comparable to the very early stage in EASL) patients meet all three criteria; Stage II meets 2/3; Stage III meets 1/3; Stage IV (similar to the terminal stage) does not meet any criteria (0/3) or have lymph node/distant metastasis. Sample patient, AB is Stage II (T2N0M0) - 2/3 criteria (single lesion >2 cm and no MVI) and XY is Stage III (T3N0M0) - 1/3 criteria (single lesion >2 cm and MVI+)

National Comprehensive Cancer Network

The NCCN guidelines are strictly based on pathological factors (1/3 of the risk factors used in BCLC). It uses the TNM staging from AJCC Cancer Staging Manual, eight edition.[22] Resectability (Solitary lesion in CPC A without portal hypertension; an adequate future liver remnant, and no vascular invasion) and transplant eligibility (UNOS criteria) are the main principles among all the factors for non-metastatic diseases.[23] Patient AB is Stage IIIA (T3N0M0), while XY is Stage IIIB (T4N0M0) according to it, and both of them are unresectable.

In 2019, Pan-Asian adapted ESMO Clinical Practice Guidelines were proposed based on concise of the Hepatology societies of Taiwan, China, India, Japan, Korea, Malaysia, and Singapore for management of intermediate and advanced-stage cancers (based on BCLC).[24] For risk stratification, it proposes dividing the CP A patients into two groups based on the albumin-bilirubin (ALBI) grading system based on the data of combined stage HCCs of different ethnic cohorts. ALBI is prognostic scoring based on a formula [ALBI = (log10 bilirubin ×0.66) + (albumin × -0.085), where bilirubin is in μmol/L and albumin in g/L].

Other prognostic scoring systems (like ALBI) were proposed that combine clinical and pathological factors like NIACE score (tumor nodularity, infiltrative nature of the tumor, serum alpha-fetoprotein level, CP, and PS) calculated by a certain formula like ALBI gives a prognostic score to stratify the patients.[25] The Cancer of the Liver Italian Program (CLIP) score based on CP score, tumor morphology and extension, serum AFP levels, and PVT.[26] The Chinese University Prognostic Index (CUPI) uses TNM staging and clinical factors like an asymptomatic disease on presentation, ascites, AFP level, total bilirubin, and alkaline phosphatase (ALP).[27] Japan Integrated Staging (JIS) score combines CP score and tumor-node-metastasis staging.[23]

Management of hepatocellular carcinoma

Management of the very early-stage tumors is similar across the guidelines with the preference of orthotropic liver transplant (in APASL living donor transplant is allowed), surgery or ablation depending on the size (of the primary). For early and intermediate HCCs, there are some notable differences. TARE and SBRT are conspicuously absent in recommendations of EASL, JSH, APASL, and KLCSG [use external beam radiation (EBRT) instead] as there is no robust data that supports its efficacy. ESMO guidelines recommend TARE in early and intermediate stages and SBRT for early-stage HCC. AASLD proposes TARE in early, intermediate, and advanced stages (it is important to note that they are level 2 and level 3 recommendations). It also has SBRT for early-stage HCC (level 2 evidence). Systemic therapy (TKI and atezolizumab plus bevacizumab) for intermediate stage HCC that fail LRT. Advanced cancers are treated with systemic therapy with exceptions like TARE (level 3) in AASLD; hepatic artery infusion chemotherapy (HAIC) in JSH; Combination of TACE and EBRT in KLCG; TACE as an alternative to systemic therapy in APASL (and KLCG). AASLD and ESMO have updated their guidelines to include atezolizumab plus bevacizumab combination in their recommendations for systemic therapy.

The NCCN guidelines do not give any clear recommendations as other guidelines for management and include everything from ablation to TACE, TARE, EBRT, and systemic therapy (TKI and ICI) for unresectable tumors. In clinical practice, NCCN guidelines are not used to guide treatment decisions. Even though the KLCSG guidelines outline the management only for healthy patients (CPA and ECOG 0–1), fine print mentions the use of EBRT, Sorafenib, and resection (if eligible) in CP B7patients.

In Pan-Asian adopted guidelines, TACE is preferred for intermediate stage HCC while TARE and TKI can be used in the second line. For advanced stages, even though systemic treatment with TKI is preferred, LRT was proposed for non-metastatic patients. Updated HKLC guidelines are similar to APASL except for proposal for the TACE and ablation combination for solitary nodule between 3-5 cm.[28]

The sample patient AB receives the best supportive care if treated in Europe (EASL and ESMO), any LRT in the USA (AASLD or NCCN), TACE in most of the countries, and can get EBRT or Sorafenib in Korea. In other words, depending on the country where she is treated, she might be sent to supportive care on the presentation or aggressively managed. On the other hand, XY would have got systemic therapy (TKI or newer options like atezolizumab plus bevacizumab) in all these countries. He could have also got TARE (AASLD), TACE, or EBRT (NCCN) in the US; HAIC or TACE alone in Asian countries (along with EBRT in Korea).

Which guidelines are better? Why are the guidelines different?

All seven guidelines discussed above were drafted based on evidence (not just on consensus), but they vary in their approach to managing HCC. The next valid question is, which guidelines are better? There are no convincing trials that validate the superiority of one guideline over the other in terms of survival (or response). For a meaningful comparison of the guidelines, it is essential to stratify the patients into comparable groups. This is challenging as the risk factors (and their parameters) used for staging is different among the guidelines. The EASL and ESMO guidelines stand apart from the rest of them as they strictly follow the BCLC staging system, specifically the PS and liver function (based on CP score). Inclusion of PS, as in AASLD and EASL, makes them incomparable to JSH, APSAL, and NCCN. Even though the ECOG scale is fairly standardized, it is a subjective assessment, and to some extent, the differences between ECOG 0 and 1 are subtle. The impact of such differences is underestimated.

The use of CP score for risk stratification by liver function makes AASLD, JSH, and APSAL comparable, but it is very different from EASL and ESMO. Such differences should be taken into

account while choosing one recommendation over the other. More differences are explained in Table 1.

The differences in the proposals can be attributed the effectiveness of a particular approach in the respective populations (as all of them are evidence based). The underappreciated factor here is the differences in etiology of the most common underlying chronic liver diseases across the different populations. This may impact the success of a particular approach. The criteria for surgical resection may be attributed to local practices. The Milan's criteria is common for selecting ideal transplant candidates cross the guidelines, but the feasibility of transplantation (based on available donors and the resources) in the countries different countries played a role in its usage for managing HCC. TARE and ICI are not a popular modalities in the Asian and European countries. For TARE, there are a very few randomized prospective trials with comparative arms.

AASLD and ESMO guidelines added a combination of atezolizumab and bevacizumab in the first line based on the success of IMbrave 50 trial.[29] In Checkmate 40 trial, an open-label, non-comparative, phase 1/2 dose escalation and expansion trial, Nivolumab showed durable response even in patients treated with Sorafenib (added in the expansion phase of the trial).[30] It was approved for the second line use (after sorafenib) in 2017. Later, in the Checkmate 459 trial, a phase III trial, Nivolumab did not reach the pre-determined median overall survival threshold compared to Sorafenib even though it had a better response rate and fewer adverse effects. In Keynote 224, a non-randomized, multicenter, open-label, phase II trial, Pembrolizumab was effective and tolerable in patients previously treated with Sorafenib, earning its approval as a second-line agent in 2018.[31] But, in Keynote 240, a randomized, double-blind, phase III study, pembrolizumab did not reach a pre-specified target as a second line after Sorafenib compared to placebo despite having a reasonable response rate.[32]

Practical challenges in adherence to guidelines

In the institutions where MDTB is available, the treatment decisions are usually based on its consensus, which may not adhere to any guidelines. Some older studies in the literature looked at adherence rate to the guidelines, but they are obsolete in the current context due to accessibility of TARE, newer TKIs, and ICI, which were not available then.[33,34] Even when they were relevant, the overall adherence to AASLD guidelines was in the range of 60-65%, and interestingly, the adherence dropped with the increasing stages.[35] In a study accepted for ASCO this year, we looked at adherence to the current AASLD proposals by our MDTB consensus and its impact on survival. After retrospectively staging the patients based on their PS, CP score, and pathological features, the overall adherence rate (for all stages of HCC) was 83%; the adherence rate of BCLC stage 0, A, B, C, and D was 100%, 97%, 77%, 77%, and 38% respectively.[36]

The expertise, as well as the preference of the surgeons, availability of TARE, or TACE, which may, in turn, depend on the financial resources (like insurance) and clinical trials, influence the decision making in an MDTB setup. The scarcity of cadaver livers for transplant and also institutes that run such successful programs virtually removes that option from the table in many practices. LRT, like TACE and TARE are allowed downgrading the patient or as bridging therapy, but it is not uncommon for patients to progress before they are up for transplant.

In summary, surgical resection, ablation, and transplant are considered curative in HCC. If a patient is ineligible for either of them, options that should be considered are TACE, TARE, SBRT or EBRT, and systemic therapy, including TKI, atezolizumab bevacizumab combination. Appropriate therapy is chosen based on the patient characteristics (liver function, PS, and pathological features) and options locally feasible (usually based on MDTB consensus). It should be noted that the etiology of HCC (viral *vs* non-viral), age, gender, and, more importantly, the histopathology of HCC is not a part of either risk assessment or treatment recommendations in any guidelines.

Future directions

In recent years, we learned a lot about the molecular markers and histological classification of HCC.[37-42] None have them used for risk-assessment or treatment. There is no convincing evidence that supports the use of adjunct therapy (systemic or otherwise) in HCC.[43] If the clinical trials which are using ICI show any positive results, that might change the landscape of this disease. For advanced cancers with PVTT, systemic therapy (TKI and atezolizumab/bevacizumab combination) are known to be effective.[44] The role of procedures like SBRT, TACE, and TACE are questionable and need clarity as there is no consensus among the present guidelines.

Conclusions

Selecting an effective first-line treatment option in HCC is a challenge. Given the poor prognosis and high treatment failure rates, particularly in the intermediate and advanced stage HCC, it is essential to build a comprehensive algorithm that takes liver function, pathological features, and appropriate biomarkers to stratify the patient.

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