Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

EDITORIAL

Access to Medical Research is a Basic Human Right: A Roadmap to Research Integration Into a Practical Hepatocellular Carcinoma Treatment Allocation Algorithm (HCC-TAA)

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, representing the fifth most common cancer globally, and the annual number of new liver cancer cases is predicted to increase by 55.0% between 2020 and 2040.[1] In fact, HCC is the fastest growing cause of cancer-related death in the United States since the early 2000s and is projected to become the third leading cause of cancer-related death by 2030.[2] Most HCC patients suffer from a concomitant chronic liver disease, most commonly hepatitis B and C, in addition to the rising global epidemic of metabolic associated liver disease, mainly due to obesity and diabetes.[3] Surgical therapies are considered curative; however, they are applicable to the minority (20–30%) of patients only. Most patients experience a high rate of disease recurrence, up to 50% after 2 years and 70% after 5 years from surgery.[4] Furthermore, unresectable patients receive systemic and local therapies, which are generally considered palliative and offer only modest improvement in survival outcomes.

Therefore, multidisciplinary management, involving relevant specialties to managing HCC and underlying CLD, such as medical, surgical, and radiation oncology; gastroenterology and hepatology; pathology; nuclear medicine; radiology and interventional radiology, is urgently needed. Medical research must address the inflection points that can improve patient outcomes, such as development of perioperative therapies in surgical patients to lower recurrence rate and improving outcomes of systemic and local therapies in nonsurgical patients. Personalized therapeutic approaches to HCC are also necessary, given the heterogeneity of HCC in early and late stages of the disease spectrum and the variety of HCC risk factors.

This article will introduce a clinically oriented algorithm for multidisciplinary management of HCC patients in routine practice and will outline opportunities to integrate personalized medical research approaches that are both feasible and applicable to low- and high-income countries and resource settings. This is very timely given the rising incidence and mortality of HCC and the challenges facing access to healthcare and medical research at all local, national, and global levels.

Clinical Presentation of HCC

The clinical challenge of early detection of HCC can be summarized in four main reasons: 1) underutilization of HCC screening algorithms in potential candidates, such as patients with established cirrhosis and chronic liver disease outlined in several society guidelines; 2) decreased sensitivity of standard screening tools, such as liver ultrasound, due to their limitation in obese patients in detecting small lesions and dependency on operator efficiency; 3) lack of awareness about patients at risk for chronic liver disease and cirrhosis, such as obesity, diabetes, and metabolic syndrome, which could trigger careful history and physical exam and basic liver imaging such as ultrasound to diagnose cirrhosis; and 4) reduced

Received: 13 March 2025
Accepted: 14 March 2025
Published: 28 March 2025

density of parenchymal innervation of sympathetic and parasympathetic nerve fibers caused by regenerating nodules in cirrhotic liver can lead to delay in HCC presenting symptoms, including pain, until tumors are large enough to cause pressure effects and/or capsule and nearby organ invasion. Therefore, the majority of patients are usually diagnosed at an advanced stage not amenable for curative options such as resection or transplant or ablation.

Clinical Management of HCC

The Overarching Question: Do You Know Your Patient?

Taking care of cancer patients is a privilege that should never be taken for granted. Given the overwhelming volume of patients in a clinical setting, treatment teams can become desensitized and overlook the necessity of patient-centered and personalized approaches to treating patients at the basic human level. For patients their clinical appointment can be a highlight of the day, and at times throughout their cancer treatment spectrum could literally mean the difference between life and death. Therefore, getting to know your patient at a personal level from day one is critical to developing this long-term relationship. This includes learning about a patient's personal values and their understanding of their cancer type, current cancer stage, and cancer trajectory in both best- and worst-case scenarios. This is paramount to building your relationship with your patient and creating mutual understanding from the outset. This also helps the treating team present therapeutic options and explain benefit-to-risk ratio in a personalized manner that is relevant to their patient's specific case based on their personal belief, values, socioeconomic support, and family relationships. I personally apply what I call "medical timeout", starting with some basic questions to my patient such as: Tell me more about yourself, I want to get to know who you are better. Do you prefer I talk with you alone or with your accompanying personnel today? And in select cases where patients present with advanced uncurable disease, I also pose a statement before I pause: "I have seen the full spectrum and I have seen patients do much better than expected. However, in a lot of cases, this cancer will eventually take your life. Tell me what I should know now to help me help you if there comes a time when you communicate with me".

The point here is: getting to know your patient and setting their goals of care and their expectations at time of diagnosis and at every turning point of their cancer stage is not only a necessity to streamline their care but it is also a basic human right. It is part of their access to medical research at a personal level, based on your explanation of their expected trajectory, as reflected in prior research findings relevant to their specific disease stage and their selected therapy [see Figures 1 and 2]. It is the clinical team's responsibility to present these medical research findings to their patients.

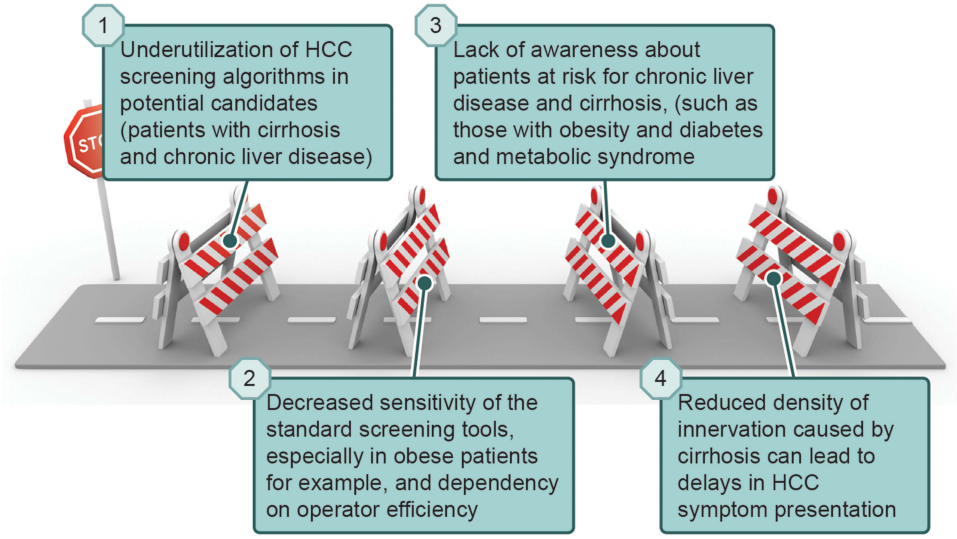

Figure 1 Barriers to effective screening strategy and early diagnosis of hepatocellular carcinoma.
Abbreviation: HCC, hepatocellular carcinoma.

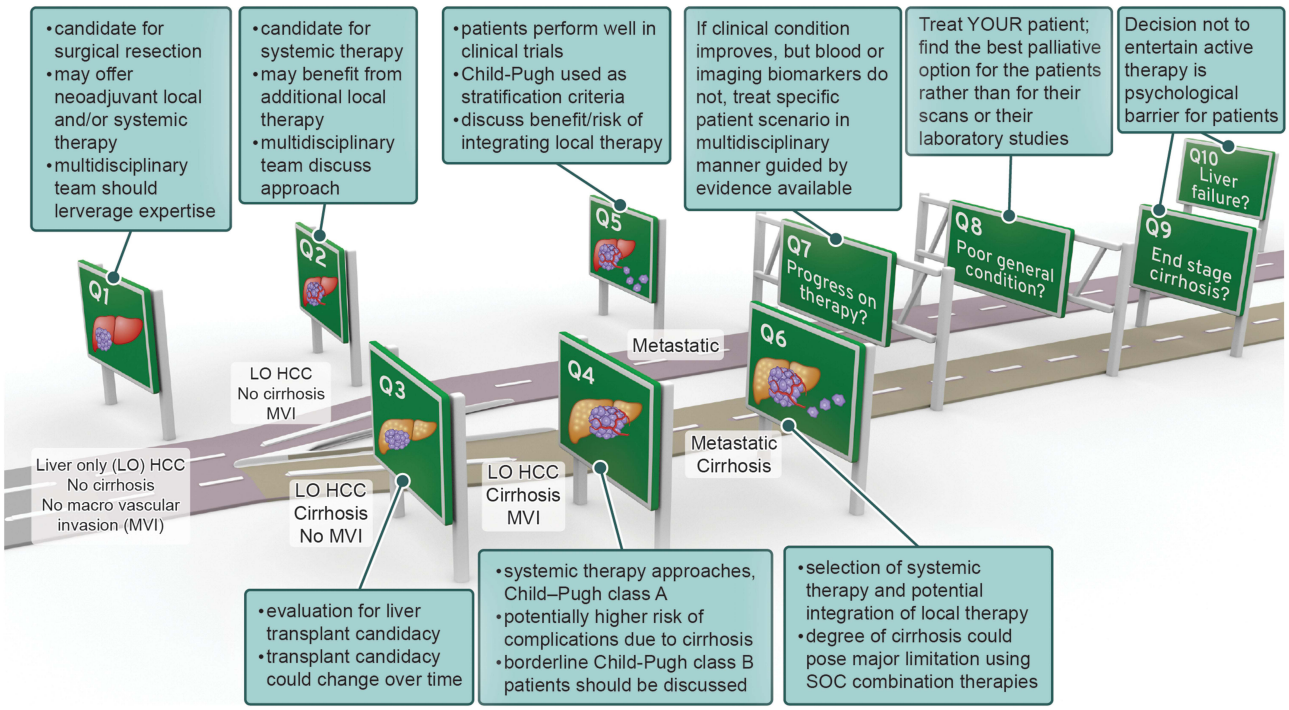

Figure 2 Practical integration of research strategies into hepatocellular carcinoma management based on tumor stage, clinical condition, and hepatic reserve assessment.
Abbreviations: Q, question; LO, liver only; MVI, macro vascular invasion; SOC, standard of care.

Question 1: Does Your Patient Have Liver-Only HCC with No Cirrhosis, or Major Vascular Invasion on Imaging?

This category represents a localized hepatocellular carcinoma setting with good hepatic reserve and therefore surgical resection evaluation is warranted. In general, it is very likely to be able to resect unilobar HCC tumors; however, risk of recurrence is high in the case of multinodular tumors. Therefore, surgical candidacy is subject to the expertise of the surgical team and the depth of the team's multidisciplinary experience, given that neoadjuvant local and/or systemic therapy may offer an opportunity to downsize tumors and enable safe resection in select cases. Additionally, practice guidelines differ at the global level, especially in Asian countries where surgical options could be extended to select cases of major vascular invasion of small portal vein branches, such as segmental involvement. This is related to high expertise managing HCC in select countries with high incidence of HCC, such as China and Japan. Notably, a large number of perioperative clinical trial approaches and retrospective studies point to select groups of patients who may benefit from neoadjuvant and/or adjuvant approaches and high-risk surgical situations. However, to date, the level of evidence did not rise up to high level emerging from randomized Phase 3 trials, to justify adopting these strategies into routine practice and management guidelines. Therefore, multidisciplinary teams responsible for managing liver cancer patients should present a personalized plan based on local expertise and based on multidisciplinary review of available evidence and medical research literature that could support perioperative intervention in select potentially resectable cases. It is critically important to involve your patient in this discussion to examine the multidisciplinary consensus and the benefit-risk ratio and to confirm that they align with the patient's goals of care.

Question 2: Does Your Patient Have Liver-Only HCC with No Cirrhosis but with Major Vascular Invasion or Infiltrative Tumor on Imaging?

In general, patients with major vascular invasion or infiltrative tumor on imaging are candidates for systemic therapy approaches based on their advanced disease setting. However, multidisciplinary discussion could greatly benefit this category, especially in case of low-volume tumor load or very focal vascular invasion, which may benefit from additional

https://doi.org/10.2147/JHC.S523470

local therapy approaches in select cases based on expert team consensus. There is also a growing level of evidence to support combining local and systemic therapies in advanced HCC. However, multidisciplinary discussion of every case is critical to the application of these approaches which are not yet considered routine standard of care practice. Sequential therapy is also required in select cases to ensure tolerance to the selected systemic therapy approach before embarking on adding local therapy in select cases. Patients' involvement in decision making is critical to evaluating the benefit risk ratio and it is important to present available medical research data to the patient, using multidisciplinary discussion and consensus regarding the patient's specific case. However, a balanced and cautious educational approach showed be deployed to avoid overwhelming patients and their families. It should also be tailored to their needs and their interest in research in general and not limited to their specific demographics to ensure equity in presenting research opportunities to them and their decision makers.

Question 3: Does Your Patient Have Liver-Only HCC with Cirrhosis but No Major Vascular Invasion on Imaging?

Evaluation for liver transplant candidacy is a standard approach in patients with cirrhosis and liver-only disease with no major vascular invasion or metastasis. However, given the differences in tumor parameters and other prognostic factors – such as tumor markers and, in some centers, PET scan imaging to evaluate candidacy for liver transplant – specific cases should be discussed in a multidisciplinary manner even if the case does not fit institutional and local guidelines for liver transplant at time of presentation, given the institutional and regional differences of specific transplant criteria and waitlist imposed on patients and physicians. This is also because evolving medical research suggested that downsizing tumors that were not within transplant criteria at baseline, by applying local and/or systemic therapies can lead to tumor stage improvement and can change the tumor biology as manifested by improvement of tumor parameters on imaging and tumor markers from blood testing. Therefore, in select cases, transplant candidacy could change over time. Multidisciplinary management across the spectrum of the disease is necessary to rule out the use of local and systemic therapy and teams should regularly reexamine transplant candidacy in select patients, given that it is a curative option for HCC that is concomitant with cirrhosis. This is another critically important setting where discussion of medical research for the outpatient is paramount to their understanding of the benefits risk ratio of proceeding with liver transplant, which is a life-changing experience for most patients.

Question 4: Does Your Patient Have Liver-Only HCC with Cirrhosis and Major Vascular Invasion or Infiltrative Tumor on Imaging?

Patients with HCC associated with cirrhosis and major vascular invasion, or infiltrative tumors generally qualify for systemic therapy approaches; however, these patients remain at risk for increased complications due to their cirrhosis, depending on how advanced it is and the status of their hepatic reserve and liver function status. The standard hepatic reserve assessment tool is the Child–Pugh classification, developed in 1973 to assess postoperative mortality in patients with cirrhosis who are undergoing major abdominal surgery. Thus, this classification tool was not developed specifically for HCC patients, yet over time became the standard tool to assess hepatic reserve in HCC patients. Notably, the standard patient population for active systemic therapy based on landmark clinical trials became Child–Pugh class A, which became a standard population for testing new drugs in large, randomized studies. However, evolving evidence from retrospective and prospective clinical trials suggests the safety and efficacy of systemic therapies in select patient population defined as early Child-Pugh class B. Further research – including large, randomized studies – into the use of systemic therapies in this population is warranted, as this could eventually change standard of care for determining eligibility of enrollment in a clinical trial and for determining appropriate treatment approaches in routine clinical practice. This is another opportunity to grant access to participation in medical research to your patient with borderline Child-Pugh classification B. This option should be = discussed in clinic, with multidisciplinary discussion of the safety of the specific therapy and a plan for close monitoring of patients in this category under active treatment. Your patient's understanding of the medical research available for their specific case in addition to benefit risk ratio is critical to decision making and the establishment of goals of care.

Question 5: Does Your Patient Have Metastatic Disease with No Cirrhosis?

Patients with metastatic HCC and no cirrhosis and who have excellent hepatic reserve and performance status represent a unique patient population that consistently performs well in clinical trials. The degree of the hepatic reserve, defined using the Child-Pugh classification, and the performance status grade are used as standard stratification criteria for randomized trials. Furthermore, depending on the load of their metastatic disease, multidisciplinary management of this category of patients calls for discussing the benefit risk ratio of integrating local therapy approaches to patients with low-volume metastatic disease, especially in cases where palliative local therapy is warranted for symptom control or for organ preservation.

Question 6: Does Your Patient Have Metastatic Disease with Cirrhosis?

In patients with metastatic HCC and cirrhosis, the determining factor for the selection of systemic therapy and the potential integration of local therapy approaches is more complicated. This is because the degree of cirrhosis could pose a major limitation in this category of patients. For patients with advanced cirrhosis with high score Child-Pugh B class, it is even more risky to entertain certain approved standard of care combination systemic therapies, let alone integrating local therapies into their systemic management strategies. However, even in patients with an advanced stage of cirrhosis, there is always room for palliative local therapy approaches for symptom control and organ preservation such as low-dose radiotherapy or selective and highly focused ablative therapies to painful metastasis or bony or vertebral metastasis, to give a few examples. This is a major example of the importance of your patient's access to medical research through presenting available data for their specific case scenario and the benefit risk ratio based on multidisciplinary discussion and available resources and specific expertise at your institution.

Question 7: What is the Pattern of Your Patient's Progression on Current Local or Systemic Therapy?

One of the very practical areas across the spectrum of HCC patients' management is to know how to assess and or define their response to local and systemic therapies. The binary choice that relies on imaging findings and tumor markers alone usually fails to define the clinical meaningfulness of any treatment outcome. I strongly believe that response to therapy should rely on a composite score that gives the highest weight to the clinical condition of your specific patient. We all have encountered this scenario in which patient's clinical condition has clearly and unequivocally improved since starting the specific local or systemic therapy, even though the imaging and/or tumor marker findings are indicating mixed response or frank disease progression. In these specific situations, it is imperative to treat your own specific patient in a multidisciplinary manner guided by evolving evidence-based medicine available from medical releases and literature that can explain the discrepancy in your specific patient's situation. An example of this discrepancy is what has been reported as pseudo-progression in the case of immunotherapy. However, more importantly, even with a lack of obvious explanation for the discrepancy, multidisciplinary efforts should be maximized to review of the pattern and the magnitude of the discrepancy based on the imaging and or tumor markers and integrate carefully selected local and/or systemic therapy approaches if warranted by multidisciplinary discussion and supported by medical research. A stark example is the clinical improvement of the patient after specific therapy that is challenged by a new small tumor, that defines clear progression by standard tumor assessment criteria. An appropriate multidisciplinary management in this scenario could lead to adding localized appropriate therapy to the new tumor and performing "Short-term" restaging evaluation and maintaining patient on the same systemic therapy that led to clinical improvement in this patient specific case. This practical approach, what has been known as "Short-term" follow-up, is very helpful in a lot of situations where the magnitude of the progression based on imaging and/or tumor markers is not alarming. Collectively, this is a very delicate and unique situation across the spectrum of patient management that warrants careful examination before deciding on changing a therapeutic approach that has been well-tolerated and led to clinical improvement. Your patients' access to medical research regarding their situation through presenting available data from literature and explaining your multidisciplinary team discussions is very critical to their understanding of this unique situation and their level of comfort about the final decision, which in most cases would be aligning with their goals of care and personal values, especially in case of metastatic disease when the goals of care are palliative and focused on improving quality of life to patients and their families.

Question 8: Does Your Patient Have Poor General Condition with Advanced Performance Status Due to Disease Burden That is Beyond Liver Transplant Criteria in Select Cases?

One of the major areas of medical research in general and cancer research in particular, is focusing on the overall picture of your patient's clinical condition and performance status, which at times present a major discrepancy between results of imaging studies and laboratory evaluation. I believe you can present this concept to your patient in the following statement: "I am trying to find the best treatment option for you as a person rather than for your scans and laboratory studies". Patients really appreciate when we approach them at a personal level and address their specific clinical scenario and present medical research to them in this context, working together to determine the best option for their unique case in light of their own goals of care. Mounting evidence about poor outcomes for HCC, including worsening survival, is available from medical research in patients with poor overall general condition and advanced performance status. This is reflected in excluding patients with poor performance status from clinical trial enrollment and in different medical societies' management guidelines that advise against active treatment of patients under this category. There are very few exceptions to this general rule – such as a potential candidate for liver transplant presenting with poor overall condition because of their active liver failure while their small tumor load does not exclude them from liver transplant when they meet standard criteria. Therefore, multidisciplinary management remains necessary for this category of patients. Even more importantly, patient's access to medical research conducted for this category is critical their decision making and establishment of goals of care, given that it represents a critical decision point to decide on whether to actively treat or not. This is what is known medically as "a go-no-go decision" about therapy, which means a life and death decision in this situation.

End-Stage Disease Questions: Question 9: Does Your Patient Have End-Stage Cirrhosis That is Beyond Liver Transplant Criteria in Select Cases? and Question 10: Does Your Patient Have End-Stage Liver Failure Due to High Tumor Burden?

These two categories that define "end-stage HCC" represent a major challenge to medical teams and even more so for patients suffering from end-stage liver cirrhosis defined as Child-Pugh C class who are not candidates for liver transplantation or patients suffering from liver failure due to high tumor burden. This is because it represents a psychological barrier to patients, in particular for being told that active therapy will only shorten the lifespan based on evidence from medical research that established this criterion as an exclusion from clinical trials entry and from active therapy in routine practice. Specifically, this concept is very hard to digest for patients who are reasonably doing well and are active and independent. It is a unique situation where patient-physician interaction and the circle of trust between patients and their families and their treating team could facilitate the discussion and understanding of medical research in this area, saving patients and their families from seeking second and third opinions during the last phase of the disease and in an end-of-life situation when we should maximize the quality of life and encourage patients to spend this valuable time with their beloved ones. I believe that the decision not to entertain active therapy is as important, if not more important, than the decision about specific therapy selection for those who can handle it.

Conclusion

Access to medical research is truly a basic human right which should be protected and implemented across all stages of the HCC disease spectrum. Research opportunities in the context of HCC management is summarized in HCC treatment allocation algorithm-7 scenarios (HCC-TAA-7); see 7 scenarios in Table 1. Joint effort between all stakeholders is a must, starting from patients and their families, caregivers, and advocates and including healthcare workers and the local health system stakeholders and joined by local policy makers to guide healthcare policies and the allocation of resources. Major efforts towards facilitating access to medical research should be streamlined and not limited to enrollment in clinical trials or research projects, but also expanded to patient education about available medical research that is relevant to their specific situation to guide their therapy decisions and align with their goals of care. Patients and their advocates must be represented on committees related to crafting or revising healthcare policies and also other activities at societies levels or governmental

Table 1 Hepatocellular Carcinoma Treatment Allocation Algorithm-7 scenarios (HCC-TAA-7)

Hallmarks	→	Surgical Evaluation	→	Research Opportunities and Endpoints
Scenario 1: Resectable Liver-only HCC without major vascular invasion, advanced cirrhosis or portal HTN				
• Unilobar HCC and deemed resectable per institutional guidelines • Compensated liver functions: Child-Pugh A • Platelets >100,000 and no significant portal hypertension (minimal or no varices)	→	• Pre-operative assessment by multidisciplinary teams, including surgical, medical, and radiation oncology, and Gastroenterology/hepatology teams • Multidisciplinary/Tumor board discussion	→	• Neoadjuvant therapies followed by surgery: endpoints to include major pathologic response (percentage of tumor necrosis at time of surgery) rate assessment • Adjuvant therapies after surgery: endpoints to include molecular (eg ctDNA) and imaging recurrence • Peri-operative serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature.
Hallmarks	**→**	**Local Therapy Evaluation**	**→**	**Research Opportunities and Endpoints**
Scenario 2: Unresectable liver-only HCC without major vascular invasion, or advanced cirrhosis or portal HTN				
• Multifocal, bilobar HCC and deemed unresectable per institutional guidelines • Compensated liver functions: Child-Pugh A • Platelets >100,000, and no significant portal hypertension (minimal or no varices)	→	• Pre-procedure assessment by multidisciplinary teams, including surgical, medical, and radiation oncology, and Gastroenterology/hepatology teams • Multidisciplinary/Tumor board discussion to select options: 1. Ablation procedures if ≤3 lesion and ≤ 3 cm each. 2. Intra-arterial therapies such as trans-arterial chemo-embolization (TACE) or radiotherapy with Yttrium-90 (Y-90) or external beam radiation (XRT) if size is 3-7 cm. 3. Radiotherapy (Y-90 or XRT) if single mass > 7 cm 4. Yttrium-90 if multifocal or bilobar tumors.	→	• Neoadjuvant therapies to downsize tumors and enable surgery: endpoints to include rate of surgical conversion. • Clinical trials to assess strategies of combined local therapies or combined local plus systemic therapies in a single-arm or randomized studies design to include response rate and survival endpoints • Peri-procedures serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature.
Scenario 3: Unresectable, transplantable liver-only HCC without major vascular invasion but with advanced cirrhosis or portal HTN				
• Meets transplant criteria per current regulatory, societies, and institutional guidelines • Compensated liver functions (Child-Pugh A) • If Decompensated liver functions (Child-Pugh B) or significant portal hypertension (esophageal/gastric varices) → need gastroenterology and hepatology evaluation and practice caution and multidisciplinary assessment before applying with local and systemic therapies. • If main portal vein thrombosis (bland or tumor thrombus) → need gastroenterology and hepatology evaluation to practice caution and apply multidisciplinary assessment before applying systemic therapies and to assess benefit:risk ratio of anticoagulation in case of bland thrombosis, given the risk of bleeding in case of large varices that are at risk for bleeding.	→	• Pre-transplant assessment to confirm transplant candidacy and bridging therapy by multidisciplinary teams, including surgical, medical, and radiation oncology, and Gastroenterology/hepatology teams • Multidisciplinary/Tumor board discussion to select options: • Ablation procedures if ≤3 lesion and ≤ 3 cm each • Intra-arterial therapies such as trans-arterial chemo-embolization (TACE) or radiotherapy with Yttrium-90 (Y-90) or external beam radiation (XRT) if size is 3-7 cm. • Yttrium-90 if multifocal or bilobar tumors.	→	• Bridging therapies clinical trials to assess strategies of combined local therapies or combined local plus systemic therapies in a single-arm or randomized studies design to include response rate and rate of drop out from transplant list • Peri-procedures and peri-transplant serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature.
Scenario 4: Unresectable, transplantable liver-only HCC without major vascular invasion but with advanced cirrhosis/portal HTN				
• Compensated liver functions (Child-Pugh A) • If Decompensated liver functions (Child-Pugh B) or significant portal hypertension (esophageal/gastric varices) → need gastroenterology and hepatology evaluation and practice caution and multidisciplinary assessment before applying with local and systemic therapies • If main portal vein thrombosis (bland or tumor thrombus) → need gastroenterology and hepatology evaluation to practice caution and apply multidisciplinary assessment before applying systemic therapies and to assess benefit:risk ratio of anticoagulation in case of bland thrombosis, given the risk of bleeding in case of large varices that are at risk for bleeding.	→	• Discuss local therapy candidacy by multidisciplinary teams, including surgical, medical, radiation oncology, and GI/hepatology teams • Multidisciplinary/Tumor board teams to discuss benefit:risk ratio for different systemic therapies options, ONLY if deemed safe per multidisciplinary discussions: • Multidisciplinary/Tumor board teams to discuss benefit:risk ratio for different local therapies options, ONLY if deemed safe per multidisciplinary discussions: • Ablation procedures if ≤3 lesion and ≤ 3 cm each • Selective intra-arterial therapies such as trans-arterial chemo-embolization (TACE) or radiotherapy with Yttrium-90 (Y-90) or external beam radiation (XRT) if size is 3-7 cm. • Selective Yttrium-90 if single large tumor > 7 m, or multifocal or bilobar tumors.	→	• Neoadjuvant therapies to downsize tumors and enable transplant: endpoints include rate of transplant conversion. • Bridging therapies clinical trials to assess strategies of combined local therapies or combined local plus systemic therapies in a single-arm or randomized studies design to include response rate and survival endpoints • Peri-procedures and peri-systemic therapies serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature.

(*Continued*)

https://doi.org/10.2147/JHC.S523470

Table 1 (Continued).

Hallmarks	→	Systemic Therapy Evaluation	→	Research Opportunities and Endpoints
Scenario 5: Advanced HCC with major vascular invasion and/or metastatic disease without advanced cirrhosis or portal HTN				
• Compensated liver functions (Child-Pugh A) • Platelets >100,000, no significant portal hypertension (minimal or no varices) • If main portal vein thrombosis (bland or tumor thrombus) à need gastroenterology and hepatology evaluation to practice caution and apply multidisciplinary assessment before applying systemic therapies and to assess benefit:risk ratio of anticoagulation in case of bland thrombosis, given the risk of bleeding in case of large varices that are at risk for bleeding.	→	• Pre-therapy assessment by multidisciplinary teams, including medical and radiation oncology, and GI/hepatology teams • Multidisciplinary/Tumor board discussion to select options: 1. Approved immunotherapy regimens if no contraindications (eg autoimmune disease) 2. Approved anti-angiogenesis regimens if no contraindications (eg uncontrolled HTN) 3. Practice caution when combining local therapy approaches for palliative purposes (eg pain control or prevention of further progression of portal vein tumor thrombus) 4. Combined local therapies in case of oligo-progression if clinical condition is stable, especially if further systemic therapies are limited.	→	• Clinical trials to assess strategies of combined new systemic therapy approaches or combined systemic plus local therapies in a single-arm or randomized studies design to include response rate and survival endpoints • Serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature. • Liver-directed therapies combined with systemic therapy randomized to systemic therapy alone to assess the value/survival advantage of local therapies in delaying liver tumors progression and liver failure.
Scenario 6: Advanced HCC with major vascular invasion and/or metastatic disease without advanced cirrhosis or portal HTN				
• Compensated liver functions (Child-Pugh A) • If Decompensated liver functions (Child-Pugh B) or significant portal hypertension (esophageal/gastric varices) → need gastroenterology and hepatology evaluation and practice caution and multidisciplinary assessment before applying systemic therapies • If main portal vein thrombosis (bland or tumor thrombus) à need gastroenterology and hepatology evaluation to practice caution and apply multidisciplinary assessment before applying systemic therapies and to assess benefit:risk ratio of anticoagulation in case of bland thrombosis, given the risk of bleeding in case of large varices that are at risk for bleeding. This is particularly true in case of low platelets count <50,000 due to hypersplenism.	→	• Pre-therapy assessment by multidisciplinary teams, including medical and radiation oncology, and GI/hepatology teams • Multidisciplinary/Tumor board discussion to select options: 1. Approved immunotherapy regimens if no contraindications (eg autoimmune disease) 2. Approved anti-angiogenesis regimens if no contraindications (eg uncontrolled HTN, or bleeding varices or high-risk varices such as varices red whale signs) 3. Practice caution when combining local therapy approaches for palliative purposes (eg pain control or prevention of further progression of portal vein tumor thrombus) 4. Combined local therapies in case of oligo-progression if clinical condition is stable, especially if further systemic therapies are limited.	→	• Clinical trials to assess strategies of combined new systemic therapy approaches or combined systemic plus local therapies in a single-arm or randomized studies design to include response rate and survival endpoints • serial tissue, blood, imaging and stool sampling research for biomarkers studies: eg immune and molecular profiling and microbiome signature. • Liver-directed therapies combined with systemic therapy randomized to systemic therapy alone to assess the value/survival advantage of local therapies in delaying liver tumors progression and liver failure. • Clinical trials designed for Child-Pugh B patients to closely monitor liver function status and assess safety.
Hallmarks	→	**If Not Candidate for Transplant**	→	**Research Opportunities and Endpoints**
Scenario 7: Any HCC stage with Child-Pugh C stage and or poor performance status >2 Assess Transplant Candidacy if meets criteria				
• Assessment by multidisciplinary teams, including surgical and medical oncology, and gastroenterology/hepatology teams	→	• Comfort care measures only. Avoid systemic and local therapies. • Assessment by multidisciplinary teams, including medical oncology, and Gastroenterology/hepatology teams to optimize medical management, including cirrhosis and portal hypertension complications. • Consult social work and case management teams to optimize home health, family support, and transition to home hospice care.	→	• Clinical trials to assess the value of strategies of palliative and comfort care measures in improving quality of life and prolonging survival. • Clinical trials to assess the value of integrative medicine and natural medicine approaches in improving quality of life and prolonging survival.

Abbreviations: HCC, hepatocellular carcnoma; HTN, hypertension; ctDNA, circulating tumor DNA; TACE, trans-arterial chemo-embolization; Y90, yttrium-90; XRT, external beam radiation.

healthcare entities that are related to access to medical research and patient confidentiality and research grants announcements and resource allocation. This concept will afford patients a fair and informed access to active medical research and should be rewarded through healthcare policies and insurance payment plans to allow and incentivize patients' active research participation by treating medical teams and documentation of the discussions and the outcome to help patients and their families and provide them with a major resource to enable them to make their own decisions based on their understanding of their current medical condition, disease stage, and available medical research data relevant to their specific case and available options of active and open clinical trials and research projects. This should also be aligned with patient's own values and goals of care and guided by available local resources and specific medical teams' expertise to ensure relevance to your specific population and sustainability for the healthcare resources and should be implemented in local management guidelines and

hospital systems treatment algorithms to ensure standardization of patients' management as guided by multidisciplinary care and available resources and local patient population values.

Therefore, integrating specific institution-wide research initiatives into all operations, including clinical and business, is the best road to supporting research infrastructure and enhancing patients' access to research which should be considered a 24/7 task. It is important to realize that inter- and intra-institutional collaboration is about compromising, but without compromising your own patients' values, which is critical to embarking on consortia and alliances for large scale initiatives. Importantly, building a "Conscious Business" model that focuses on your own specific patient population and their medical issues and their medical research needs with the help of diverse workforce and stakeholders is a winning strategy. However, adopting a collaborative "Conscious Business" model must be supported by a collaborative institutional and team culture and servant leadership. Engagement of diverse stakeholders in this setting becomes a must; including patients and their advocates, community leaders and legislators, pharmaceutical alliances, business partners, medical and health sciences schools' integration to train the next generation of healthcare workers, non-profit organizations, medical societies and foundations to eventually create a values-based culture. Eventually, this will lead to capacity building that is tailored to your patient population and workforce and local resources priorities, which will help provide a "personalized" approach to your patients' access to medical research. Thus, designing future projects to integrate access to medical research into patients' management across the spectrum of their disease should be customized based on your patient population needs and institution's strengths and requires collaboration to address disparity in healthcare/trials access.

Funding

This work was supported by the National Institutes of Health/National Cancer Institute under award numbers P50 CA217674 (The MD Anderson Cancer Center Specialized Program of Research Excellence [SPORE] in Hepatocellular Carcinoma Grant) and editorial and images generating assistance by Rachel A Davidowitz, PhD, Senior Scientific Illustrator).

Disclosure

Dr. Ahmed Omar Kaseb received research support from Genentech, BMS, Merck, Eisai, Exelixis, AdaptImmune and Tvardi and has been on the advisory board/has received honoraria from/been a consultant for: Genentech, BMS, Merck, Eisai, Exelixis. The author reports no other conflicts of interest in this work.

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