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REVIEW

Optimizing Treatment Selection for Early Hepatocellular Carcinoma Based on Tumor Biology, Liver Function, and Patient Status

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Abstract: Early-stage hepatocellular carcinoma (HCC) represents a critical window for curative treatment. However, treatment selection is complicated by significant heterogeneity in tumor biology, liver function, and patient performance status. This review provides a comprehensive overview of current curative-intent strategies for early-stage HCC, including liver transplantation, surgical resection, and local ablative therapies. We emphasize the importance of integrating tumor-specific characteristics-such as microvascular invasion, size, and anatomical location-with liver reserve metrics, including portal hypertension, Child-Pugh classification, and novel indices like albumin-bilirubin and albumin-indocyanine green evaluation grades. Furthermore, we discuss recent advances in non-thermal ablation techniques (eg, high-intensity focused ultrasound and irreversible electroporation), and technical innovations in radiofrequency ablation and cryoablation that are expanding the therapeutic landscape. By combining macro-level functional assessments with micro-level biological indicators, this review advocates for a personalized, evidence-based framework to optimize long-term outcomes in early HCC. The future of HCC management lies in standardizing individualized therapy.

Keywords: early-stage hepatocellular carcinoma, individualized treatment, liver transplantation, resection, local ablation techniques, treatment

Introduction

Globally, liver cancer ranks sixth in incidence and fourth in cancer-related mortality.[1] Hepatocellular carcinoma (HCC) is the predominant histological subtype of primary liver cancers, accounting for approximately 85% of all cases.[1] Surgical resection and liver transplantation (LT) are considered the most effective treatments, particularly for patients with early- to intermediate-stage HCC. However, the availability of liver donors is limited—especially in many Asian countries—and patients with impaired baseline liver function may not be suitable candidates for surgical intervention.[2] Given the heterogeneity of HCC, it is essential to weigh the risks and benefits of different treatment options by considering tumor biology, liver functional reserve, and patient performance status, in order to develop an individualized therapeutic strategy. With the continuous advancement of medical technologies, various novel treatment modalities have been introduced for patients who are not suitable for surgical resection or LT.[3] To support treatment decision-making, more than ten staging systems have been proposed for HCC, among which the Barcelona Clinic Liver Cancer (BCLC) staging system is most widely used. It categorizes HCC into stages 0, A, B, C, and D, and provides corresponding treatment recommendations based on patient performance status, including LT, locoregional therapies, systemic pharmacological treatments, and best supportive care.[4,5] Despite the availability of multiple

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treatment approaches, the overall prognosis for HCC remains suboptimal. In 2017, approximately 819,000 individuals died from liver cancer worldwide, and the 5-year overall survival (OS) rate was around 60%.[6–8] However, with improvements in liver cancer screening-particularly in radiologic imaging-the detection rate of early-stage HCC has significantly increased.[9,10] This underscores the importance of selecting more effective treatments for early HCC, which is critical to improving long-term survival outcomes.

Herein, we summarize the current treatment strategies for early-stage HCC. This review aims to provide clinicians with an evidence-based reference for individualized treatment planning in early-stage HCC, based on a comprehensive assessment of tumor characteristics, liver function, and patient condition.

Liver Transplantation: High Status vs Short Supply

LT is regarded as an optimal therapeutic strategy for liver cancer, as it simultaneously eradicates the tumor and the underlying pathological liver environment. Reported 5-year survival rates exceed 70%.[11,12] Considering the limited availability of transplantable organs, careful patient selection and ensuring equitable organ allocation are critical in LT. According to the Milan criteria, LT is considered ideal for patients with BCLC stage 0/A HCC, clinically significant portal hypertension (CSPH) and no other surgical contraindications.[13] However, even among patients strictly selected based on the Milan criteria, approximately 10% experience tumor recurrence following LT.[14] To optimize both therapeutic outcomes and donor organ utilization, it is essential to identify candidates with more favorable tumor biology and a lower risk of recurrence. Nonetheless, many proposed biomarkers of tumor aggressiveness, such as microvascular invasion (MVI), as well as various radiologic parameters, have limited predictive value due to interpatient variability and insufficient external validation.[15]

Since 2002, the Milan criteria have been used in conjunction with the Model for End-Stage Liver Disease (MELD) score to evaluate and prioritize patients with HCC for LT. The MELD score, originally developed to predict 3-month mortality in patients with cirrhosis, has become a key factor in organ allocation.[3,15] Over the years, several modifications to the organ sharing policies have been introduced to enhance fairness and better identify patients who would derive the greatest benefit from LT. One of the most recent policy changes implemented by the United Network for Organ Sharing (UNOS) established an upper limit of 34 points for MELD exception scores granted to patients with HCC.[15] This change aims to balance access to LT between HCC patients and those without HCC, as excessive prioritization of exception candidates could lead to increased waitlist dropout for non-HCC patients.[15] In addition, patients with unifocal T1 hCC lesions (tumors $\leq$2 cm without vascular invasion or metastasis) are no longer eligible for MELD exception points under the current policy.[16] This decision is based on the rationale that these patients generally have indolent tumor biology, access to alternative local therapies, and a relatively low short-term mortality risk, which makes prioritization less urgent.[16] Another important update in MELD exception policy is the requirement of a minimum 6-month waiting period before awarding exception points. This mandatory observation period helps to select candidates with more favorable tumor biology-specifically, those with a lower risk of recurrence or MVI-thus improving post-transplant prognosis.[17] Notably, studies have indicated that patients with shorter pre-transplant wait times may face a higher risk of recurrence and reduced survival, possibly due to the inclusion of more aggressive tumors that do not reveal their nature during a brief observation window.[17] These revisions collectively reflect an evolving approach in transplant oncology that seeks to integrate tumor biology, treatment responsiveness, and equitable organ distribution in HCC-related LT decisions.[15,16]

To summarize, current UNOS guidelines recommend that before applying for MELD exception points, patients with early-stage HCC (2–3 cm) and single lesions should first undergo locoregional therapy, such as ablation or transarterial chemoembolization. Patients with compensated cirrhosis who demonstrate a complete response to locoregional therapy are not eligible for MELD exception points, whereas those with residual viable tumor may be prioritized. In the event of tumor recurrence after an initial response, patients may still receive MELD exceptions without needing to complete a new six-month waiting period. Additionally, down-staging strategies are permitted in selected patients whose tumors exceed the Milan criteria, provided they demonstrate favorable tumor biology and meet response criteria prior to transplant listing.[15,16,18,19]

In summary, although LT offers the most comprehensive curative potential for early-stage HCC, its application remains limited by organ shortages and evolving selection criteria. Future research should focus on refining biomarkers to better predict post-transplant outcomes and improve equitable organ allocation.

Early HCC: Treatment Choice is Inseparable from Tumor and Patient

The factors determining the prognosis of HCC are complex and heterogeneous. The selection of an appropriate treatment strategy depends not only on tumor-related factors-such as vascular invasion, lesion size, and location-but also on patient-related clinical conditions. These include the presence of portal hypertension (PH), liver functional reserve, extent of cirrhosis, comorbidities, and eligibility for curative procedures such as resection or LT. Approximately 80% of HCC patients have underlying chronic liver disease, which often leads to hepatic dysfunction and PH.[20] While various therapeutic options are available for early-stage HCC, treatment allocation should prioritize not just technical feasibility, but also the anticipated outcomes, balancing oncological control with preservation of liver function and overall patient condition.[21]

Thus, treatment decisions for early-stage HCC must consider not only tumor burden but also patient-specific clinical variables, underscoring the importance of individualized multidisciplinary assessment.

Tumor Characteristics: Microvascular Invasion

As HCC is characterized by abundant and often immature vascular structures, MVI has become a key concern in treatment planning.[22] MVI is widely recognized as a major contributor to tumor recurrence and is considered an independent prognostic factor associated with poorer outcomes, even in patients with small, unifocal HCC.[23,24] A meta-analysis involving of 3033 patients demonstrated that patients in MVI-negative group had significantly better OS compared to those in the MVI-positive group (hazard ratio = 2.39, $P < 0.001$), highlighting the negative impact of MVI on survival outcomes in early-stage unifocal HCC.[24] Contrast-enhanced imaging techniques, including dynamic contrast-enhanced CT and MRI, are widely utilized to evaluate the vascularity of HCC and have been shown to correlate with tumor aggressiveness. In recent years, several studies have explored the use of quantitative imaging biomarkers-such as enhancement patterns, wash-in and wash-out kinetics, and radiomics-based texture features-to predict the presence of MVI preoperatively.[25–28] Considering that MVI cannot be directly confirmed without histopathological examination, researchers have sought to identify surrogate predictors of MVI, including serum biomarkers (eg, α-fetoprotein ≥15 ng/mL, des-γ-carboxy prothrombin ≥100 mAU/mL, and tumor characteristics (eg, size ≥2 cm),[29] multifocality,[30] and imaging features (eg, non-smooth margins, peritumoral enhancement on CT/MRI).[30–32]

HCC often exhibits a tendency to spread along the portal pedicles, leading to segmental tumor deposition and the formation of microthrombi within the portal venous system.[33] Based on this biological behavior, anatomic resection (AR) has been proposed as a surgical approach that enables complete removal of the tumor along with its corresponding portal vein territory, potentially improving oncologic outcomes.[34,35] However, the benefits of AR appear to be most pronounced in tumors of limited size. In a multicenter study involving 5781 patients undergoing hepatectomy, those who received AR demonstrated significantly better survival compared to those undergoing non-anatomic resection (NAR), but the difference was statistically significant only in the subgroup with tumor sizes between 2–5cm.[36] Recent studies have further confirmed that AR may reduce recurrence risk and improve OS in patients with small, solitary HCC lesions (≤ 5 cm).[37,38] In larger tumors, however, factors such as residual liver function may diminish the relative advantage of AR.[39] In contrast, NAR focuses on achieving an adequate margin of non-tumorous liver parenchyma, without regard for segmental anatomy or Glisson's pedicles.[40] Given that the majority of HCC patients have underlying chronic liver disease, preservation of functional liver tissue is critically important. Additionally, studies have shown that microsatellite lesions and vascular thrombi are rare in tumors <2cm, suggesting that MVI is uncommon in very early-stage HCC.[41] Thus, NAR is particularly valuable in cirrhotic patients, as it allows for effective tumor removal while minimizing the loss of healthy liver parenchyma.[42] In clinical practice, AR is generally recommended for patients with single, small (2–5 cm), moderately to poorly differentiated HCC, particularly when AFP >100 μg/L or MVI is suspected. Conversely, NAR may be a more suitable option for patients with small (<3 cm), well-differentiated tumors and advanced liver dysfunction, where preserving liver function is a primary concern.[43]

Overall, MVI remains a major prognostic factor in early HCC, yet reliable non-invasive prediction methods are still under development. Integration of advanced imaging biomarkers and serum indicators holds promise for improving risk stratification.

Tumor Characteristics: Location and Size

Certain tumor locations-such as those adjacent to hollow organs, the diaphragm, major blood vessels, or bile ducts-pose significant challenges in the treatment of HCC.[44] Selecting an appropriate therapeutic approach based on tumor location is crucial to balance treatment efficacy and safety. Given the liver's complex vascular anatomy, perivascular HCC is defined as a tumor with an axial diameter greater than 3 mm and a minimum distance of less than 5 mm from the primary or secondary branches of major hepatic vessels, including the portal vein and hepatic vein.[29,33]

Based on current evidence, for solitary HCC lesions smaller than 3 cm with well-preserved liver function, treatment strategies may vary depending on tumor location: laparoscopic limited resection is preferred for subcapsular tumors. Percutaneous thermal ablation is recommended for deeply located tumors < 2cm, except those adjacent to the Glissonean system. Laparoscopic AR is suitable for deep-seated nodules < 2–3 cm in the left lobe of the liver. Open AR is advised for deep nodules < 2–3 cm in the right lobe, which is technically more complex. Tumors adjacent to Glissonean pedicles should be resected either open or laparoscopically, depending on accessibility and surgical expertise.[45] Regarding treatment outcomes, a meta-analysis involving 5203 patients showed no significant difference between laparoscopic liver resection and open resection in terms of operative time, and 1-, 3-, and 5-year progression-free survival and OS. However, laparoscopic liver resection was associated with reduced surgical trauma and lower complication rates, particularly in patients with small HCC.[46] Therefore, individualized treatment planning should be based on a comprehensive assessment of tumor location, liver function, and anatomical feasibility, while also taking into account the technical expertise available at the treating center.

In conclusion, tumor location and size significantly influence treatment strategy. However, there is a lack of high-quality evidence directly comparing modalities in anatomically complex lesions, highlighting a need for prospective multicenter trials.

Patient-Related Factors: Liver Function and Residual Liver

Many patients with HCC have an underlying background of chronic liver disease. Cirrhosis has been identified as an independent risk factor for the onset and progression of HCC.[47] Patients with chronic liver disease often experience various complications after anesthesia and surgery.[48] In individuals with advanced liver disease, refractory ascites and life-threatening complications may occur even when the surgical resection is limited.[49] Among these complications, postoperative liver failure is particularly concerning, often characterized by elevated prothrombin time-international normalized ratio and hyperbilirubinemia appearing approximately five days after surgery.[50] Given the risks of postoperative complications and multicentric tumor recurrence, treatment planning for patients with HCC and underlying liver disease should carefully consider the functional reserve of the remnant liver and the potential impact of interventions on residual hepatic function.

Liver function assessment plays a crucial role in determining treatment strategy for HCC. Two commonly used approaches include the BCLC staging system and treatment algorithm,[51] and the Japan Society of Hepatology clinical guidelines for HCC.[52] The BCLC system primarily relies on the Child-Pugh classification to evaluate hepatic function, whereas the Japan Society of Hepatology guideline assesses the degree of liver damage, with the indocyanine green retention rate at 15 minutes (ICGR15) being one of its key parameters.[53,54] ICGR15 is widely recognized as a valuable tool for evaluating hepatic functional reserve and predicting postoperative mortality risk.[54,55]

It helps determine the safe resection volume for individual patients based on their underlying liver condition. In patients with HCC undergoing limited liver resection, minimizing the removal of non-tumorous, functional liver parenchyma can reduce operative stress and improve surgical tolerability.[55] Some researchers argue that the ICGR15 is a simple and effective tool for estimating the safe resection volume when the value is below 30–40%. However, its correlation with actual hepatic functional reserve diminishes when the ICGR15 value exceeds this threshold. Therefore, ICGR15 may not be reliable for evaluating liver function in patients with advanced chronic liver disease. In such cases, the Child-Pugh (CP) score is considered a more suitable and comprehensive assessment tool.[56]

It is worth noting that the CP classification, while widely used, has inherent limitations. It is considered a relatively subjective and coarse tool, particularly due to the difficulty in accurately assessing ascites and hepatic encephalopathy. To address these shortcomings, Johnson et al[57] proposed the albumin-bilirubin (ALBI) grading system, an objective liver function assessment method based solely on serum albumin and bilirubin levels. Subsequent studies have shown that the ALBI grade is more accurate than CP grade in predicting postoperative liver failure.[58]

However, from a comprehensive clinical perspective, ALBI grading alone may be insufficient for determining surgical strategy.[59] More recently, researchers have introduced a novel liver function evaluation model focused on long-term survival, known as the albumin-indocyanine green evaluation (ALICE) grade. This system incorporates preoperative serum albumin levels and ICGR15 values, enabling more refined stratification of CP A and B patients into ALICE Grade 3 categories. Additionally, the PH index is integrated into the model to better estimate the preoperative hepatic functional reserve in patients with HCC.[60,61] With advancements in surgical planning, three-dimensional volumetric analysis has emerged as a critical tool for precise preoperative design and evaluation of liver resection. It assists surgeons in accurately defining the extent of resection, especially in patients with marginal liver reserve.[62,63]

Taken together, accurate assessment of liver function and remnant liver volume is essential in HCC treatment planning. While several grading systems exist, standardization and validation across diverse patient populations remain areas for improvement.

Portal Hypertension

PH results from increased intrahepatic vascular resistance, primarily due to impaired hepatic sinusoidal circulation. It commonly occurs as a consequence of chronic liver diseases, particularly cirrhosis.[64] And it is a major contributing factor to various complications of cirrhosis, including ascites, esophageal and gastric varices, hepatorenal syndrome, hypersplenism, and hepatic encephalopathy.[65] PH is defined as a hepatic pressure gradient (between portal venous pressure and inferior vena cava pressure) that exceeds the normal range by at least 5 mmHg. When the hepatic venous pressure gradient ≥10 mmHg, it is referred to as CSPH.[66] A meta-analysis encompassing 11 studies demonstrated that CSPH is associated with increased risks of postoperative hepatic decompensation as well as higher 3- and 5-year mortality rates in patients with HCC, compared to those without CSPH.[67] These findings underscore the importance of a multifactorial evaluation in guiding treatment selection for HCC patients. According to the The American Association for the Study of Liver Diseases (AASLD) guidelines, LR is the preferred treatment option for resectable HCC in cirrhotic patients with preserved hepatic function and no evidence of CSPH.[68] Similarly, the Asia-Pacific Association for the Study of the Liver (APASL) recommends LR as the first-line therapy for patients with CP A cirrhosis, provided that tumor burden and liver function meet the criteria for resection.[69]

Overall, CSPH is a critical determinant of surgical eligibility in cirrhotic patients. Future studies should refine non-invasive tools for evaluating PH and explore its impact on long-term oncological outcomes.

Importance of Local Ablation for Early HCC

As mentioned above, although surgical resection remains a curative option for HCC, fewer than 30% of patients are eligible for surgery due to factors such as advanced disease stage, poor liver function, or comorbidities.[70] Even among patients with early-stage HCC, not all are suitable surgical candidates, and postoperative liver function deterioration remains a clinical concern. Consequently, a range of non-surgical treatment modalities has been developed. Among these, local ablative therapies have emerged as effective alternatives, capable of achieving curative intent in selected patients. Evidence from long-term follow-up studies has shown that, in certain cases, both short- and long-term survival outcomes of ablation are comparable to surgery. Additionally, ablative therapies offer distinct advantages such as minimal invasiveness, lower bleeding risk, and high repeatability.[71,72] Current ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), and cryoablation. RFA utilizes high-frequency alternating current to generate thermal energy that induces coagulative necrosis in tumor tissue.[69] MWA delivers electromagnetic waves through an antenna to directly heat and destroy tumor cells.[73] In contrast, cryoablation works by freezing tissue to cytotoxic temperatures, followed by thawing, to induce cell death.[74] The therapeutic role of local ablation has been well-established through years of clinical application and is endorsed by multiple international guidelines:

AASLD recommends thermal ablation as the first-line treatment for HCC lesions <3 cm, particularly for very early-stage tumors (BCLC 0), with RFA or MWA preferred in suitable candidates.[69] The European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer state that RFA is appropriate for very early HCC (<2 cm) and is the first-line therapy for unresectable BCLC 0-A tumors. Moreover, it may be considered a first-choice option even for resectable tumors (2–3 cm) in favorable locations. MWA is noted to have potential advantages over RFA for larger

lesions (3–5 cm).[75,76] The APASL guidelines recommend local therapy for CP A or B patients with ≤ 3 nodules, each <3 cm. For lesions ≤2 cm in cirrhotic patients, RFA is the preferred first-line treatment, while PEI may be considered when RFA poses safety concerns.[3] The Chinese HCC management guidelines, in a region with a high liver cancer burden, affirm the importance of local ablation in CP A or B patients with a single tumor <5 cm, or multiple tumors (up to 3) <3 cm, without vascular invasion or extrahepatic spread. RFA is emphasized as a widely accepted local therapy in China due to its convenience, safety, and favorable clinical efficacy.[77]

Despite being widely used for early-stage HCC, thermal ablation techniques such as RFA and MWA have inherent limitations. One major concern is the heat-sink effect,[78] where adjacent blood vessels dissipate thermal energy, resulting in incomplete tumor necrosis. In addition, tumors located near critical structures, such as the bile ducts, diaphragm, or gastrointestinal tract, pose a higher risk of thermal injury.[79] Other challenges include incomplete ablation margins, especially for irregularly shaped or subcapsular tumors, and difficulty achieving adequate safety margins in lesions adjacent to major vessels.[80] These limitations have prompted the exploration of alternative non-thermal ablative techniques in selected patient populations.

In summary, local ablative therapies offer effective alternatives for non-surgical candidates with early HCC. Nevertheless, treatment limitations due to heat-sink effects and proximity to critical structures require further technical refinement.

Emerging Non-Thermal Ablation Techniques

High-intensity focused ultrasound (HIFU) is a non-invasive ablative technique with emerging potential in the treatment of early-stage HCC. It delivers focused acoustic energy through intact skin and soft tissues to induce coagulative necrosis at a specific intrahepatic target, without injuring adjacent structures. Its mechanism involves both thermal (>60°C) and mechanical effects, including cavitation and acoustic streaming, leading to immediate tumor cell death and vascular disruption.[81]

The main advantage of HIFU is its completely non-invasive nature, making it particularly suitable for patients who are unfit for surgery or percutaneous ablation due to age, bleeding risk, or comorbidities. Real-time ultrasound or MRI guidance ensures precise targeting and monitoring, while avoiding thermal injury to vital structures. HIFU is repeatable and may be used as an adjunct to transarterial chemoembolization or systemic therapy.[81]

However, several technical limitations remain. Respiratory motion, rib shadowing, and poor acoustic windows (eg, bowel gas or bone) can hinder accurate energy delivery.[82] Furthermore, its availability is limited to specialized centers, and large-scale comparative studies with RFA or MWA are still lacking.[81]

Preliminary clinical trials have shown that HIFU is safe, well-tolerated, and capable of effective ablation in selected patients. A single-center study by Ng et al demonstrated that HIFU achieved an 80% complete ablation rate for small (<3 cm) unresectable HCCs with minimal complications.[83] Ongoing studies are evaluating its role as bridging therapy before LT and as a re-treatment option following incomplete ablation.[84] Future directions include enhanced image guidance, combination with immunotherapy[85] or nanomedicine,[86] and evaluation of long-term efficacy and cost-effectiveness. While early evidence is encouraging, further standardization and head-to-head trials are needed to define its role in the management of early-stage HCC.

Irreversible electroporation (IRE) is a non-thermal ablation modality that has emerged as a promising option for HCC, particularly for tumors located near heat-sensitive structures. IRE induces cell death through the application of high-voltage, short-duration electrical pulses, which create permanent nanopores in the cell membrane, leading to apoptosis while preserving the extracellular matrix and adjacent vital structures.[78] The non-thermal nature of IRE offers significant advantages over conventional thermal ablation, especially for lesions adjacent to major blood vessels, bile ducts, or the diaphragm, where thermal injury is a concern. Additionally, IRE does not suffer from the heat-sink effect, making it more effective for perivascular tumors.[87,88] Despite these advantages, IRE has several limitations. The procedure requires general anesthesia and neuromuscular blockade, and is technically demanding, often requiring real-time imaging for precise multi-electrode placement.[89] Several clinical studies have demonstrated the safety, feasibility, and promising local control rates of IRE in early-stage HCC. In a systematic review, Scheffer et al reported that IRE is well-tolerated and effective in hepatic tumors located in challenging anatomical locations.[90] Similarly, Niessen et al observed favorable

long-term survival outcomes in patients with unresectable liver tumors treated with percutaneous IRE.[91] While not yet a mainstream option, IRE represents an important complementary modality in the local treatment landscape for early-stage HCC, especially in patients unsuitable for thermal ablation.

While HIFU and IRE have shown promising early results, their clinical adoption is limited by technical complexity and insufficient large-scale comparative studies. More robust evidence is needed to define their roles in treatment algorithms.

Technical Innovation and Improvement for Early-Stage HCC Therapy

Cryoablation is a novel local treatment modality for HCC. However, its widespread adoption has been limited by concerns about bleeding risk observed in early clinical experiences.[92,93] With advancements in therapeutic technologies and growing clinical experience, cryoablation has become a safe and effective option for local tumor control, demonstrating OS rates comparable to RFA in patients with tumors < 5 cm. It offers the advantage of creating larger and more precise ablation zones, which may be beneficial in select cases.[94] Moreover, cryoablation has proven to be safe and feasible in treating tumors located in challenging anatomical sites, such as perivascular HCC, or lesions adjacent to the heart or bile ducts.[95–97] However, it is important to note that cryoshock, a rare but potentially life-threatening complication, has been reported in approximately 1% of cases. This is thought to be related to the release of necrotic tumor debris into the circulation during ablation.[98] Additionally, the risk of serious complications increases with larger tumors, making early-stage HCC (BCLC stage 0 or A) more suitable for cryoablation.[99] It should also be noted that most current cryoablation studies involve small sample sizes and limited follow-up durations, and long-term outcomes remain to be validated through larger prospective trials.

Another non-invasive local treatment modality is stereotactic body radiotherapy (SBRT), which was first introduced for liver tumors in the 1990s. Recent evidence suggests that SBRT provides local control comparable to hepatic resection in patients with small HCC (≤2 nodules) or CP A cirrhosis, with the added benefit of being less invasive.[100,101] However, SBRT is technically demanding due to the need for precise tumor localization, strict radiation dosing, and control of respiratory motion, which may limit its routine clinical use.[102] In summary, this review highlights recent advances in the therapeutic efficacy and complication profiles of various treatment modalities for early-stage HCC, as outlined in Table 1.

Among recent technical advancements in local therapies, RFA continues to play a prominent role. Due to the high recurrence rate of HCC, many patients require multiple sessions of ablation during the course of treatment. To address the limitations of conventional monopolar RFA-such as insufficient ablation volume-multibipolar RFA has been developed, offering a larger and more uniform zone of coagulative necrosis. This technique frequently incorporates the "no-touch" approach.[109] The no-touch technique involves placing electrodes outside the tumor, without direct puncture of the lesion itself, in accordance with the tumor-free principle. This approach minimizes the risk of tumor seeding and local recurrence. Several studies have reported that no-touch multibipolar RFA achieves higher local control rates and improved technical success compared to conventional RFA.[110] However, the no-touch method is technically more demanding, as it requires the precise placement of multiple electrodes in a geometrically ideal configuration surrounding the tumor to create an adequate safety margin. Therefore, achieving optimal outcomes with this technique depends heavily on the surgeon's experience and technical proficiency.[110,111]

Overall, technical innovations such as no-touch RFA and image-guided cryoablation are expanding therapeutic options in early HCC. However, their long-term outcomes and cost-effectiveness remain to be validated through larger trials.

The management of early-stage HCC presents a complex clinical challenge, requiring the integration of tumor biology, liver function, anatomical considerations, and patient performance status. While curative options such as liver transplantation, anatomic resection, and local ablation are widely accepted, treatment selection remains highly individualized and often institution-dependent.

Immunotherapy in Early-Stage HCC: Emerging Role and Perspectives

Recent advances in systemic therapies-particularly immune checkpoint inhibitors (ICIs)-have significantly improved outcomes in advanced HCC. While immunotherapy is currently not standard for early-stage disease, its potential role is being actively explored in combination with curative treatments. For instance, several ongoing clinical trials are

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Table 1 Advantages of Different Treatment Methods for Early HCC in Recent years

Study	Year	Country	Study Period	Study Design	No. of Patients	Prognosis	VS	Safety
Tamai H, et al[103]	2021	Japan	From January 2016 to March 2020	Pro	513 patients with 630 hCC (≤3cm): RFA (n=174, 214 hCC) MTA (n=339, 416 hCC)	OS with 3 years: 77% vs 95% P=0.029	RFA vs MTA	14% vs 8%, P<0.05
Imai K, et al[90]	2018	Japan	From 2000 to 2015	Pro	308 patients (≤3 cm): SR (n=149) RFA (n=159)	OS with 3 years: 91.0% vs 90.7% OS with 5 years: 86.7% vs 73.3%	SR vs RFA	–
Lee S, et al[104]	2018	Korea	From January 2006 to December 2010	Pro	283 patients (≤3 cm, BCLC 0 or A): SR (n=182) RFA (n=101)	OS with 5 years:93.5% vs 82.3% P<0.001 OS with 10 years: 91.9% vs 74.1% P<0.001	SR vs RFA	–
Uhlig J, et al[105]	2019	USA	From 2004 to 2015	Pro	18296 patients: SR (n = 10085) RFA (n = 8211)	OS with 5 years: 39.4% vs 37.3% P=0.07 (severe hepatic fibrosis/cirrhosis) OS with 5 years: 52.3% vs 49.7% P=0.78 (tumor< 1.5cm)	SR vs RFA	30-/90-day mortality:4.6%/8% vs 0% P<0.001
An C, et al[106]	2021	China	From October 2012 to December 2018	Pro	144 patients (≤3 cm, proximity to hepatic and portal veins): RFA (n=70) MWV (n=74)	OS with 5 years: 77.7% vs 74.6% P=0.600 DFS with 5 years: 24.7% vs 40.4% P=0.570 LTP with 5 years: 24.3% vs 8.4% P=0.030	RFA vs MWV	–
Cha SY, et al[107]	2020	Korea	From January 2015 to April 2018	Pro	111 patients (perivascular HCC): Cryoablation (n=61) RFA (n=50)	Local tumor progression (LTP) with 1 years: 8.3% vs 8.7% P>0.05 LTP with 3 years: 17.3% vs 26.1% P>0.05	Cryoablation vs RFA	Vascular thrombosis: 9.8% vs 6.0%, P=0.493 Hepatic infarction: 3.3% vs 12.0%, P=0.137
Ogiso S, et al[108]	2021	Japan	From 2005 to 2016	Pro	221 patients: Laparoscopic liver resection (LLR) (n=85) RFA (n=136)	OS and DFS were similar Recurrence-free survival rates with 3 years: 49.2% vs 22.1% local recurrence-free survival rates with 3 years: 94.9% vs 63.6%	LLR vs RFA	LLR had higher incidence of blood transfusions, complications, and longer hospital stay

investigating adjuvant or neoadjuvant immunotherapy following surgical resection or ablation, aiming to reduce recurrence risk by targeting residual micrometastatic disease.[112]

Preliminary studies suggest that ICIs, such as nivolumab and atezolizumab plus bevacizumab, may help modulate the tumor microenvironment and enhance long-term immune surveillance even in early-stage settings.[113] However, concerns remain regarding immune-related adverse events and the optimal timing and duration of treatment. Further evidence from prospective trials is needed before routine adoption in early-stage HCC.

Discussion

A major limitation in current practice is the lack of reliable preoperative predictors for tumor behavior, particularly MVI, which strongly influences recurrence and survival outcomes. Although several radiological and serological indicators have been proposed, none have been universally adopted, highlighting a need for more validated and accessible predictive tools.

In terms of liver function evaluation, while the CP classification remains the most widely used, newer scoring systems such as ALBI and ALICE offer greater objectivity and granularity. However, their application in routine practice remains inconsistent, and further validation is needed across diverse patient populations.

Technological advancements in ablative therapies, including no-touch RFA, cryoablation, IRE, and HIFU, have expanded treatment options for patients who are ineligible for surgery. Nonetheless, most evidence for these novel approaches comes from single-center studies with limited follow-up, and large-scale, multicenter randomized trials are lacking.

Finally, the growing emphasis on personalized medicine calls for treatment frameworks that go beyond staging systems alone. Future strategies should incorporate genetic profiling, tumor microenvironment analysis, and dynamic liver function assessment to better stratify patients and guide therapy.

Conclusion

The management of early-stage HCC requires a strategic balance between oncologic efficacy and liver function preservation. Treatment selection should be individualized, based on an integrated assessment of tumor biology, anatomical features, liver functional reserve, and patient performance status.

LT remains the most comprehensive curative option, but its availability is limited. Surgical resection, particularly AR guided by tumor location and vascular involvement, is appropriate for patients with favorable liver function. Local ablative therapies-especially advanced approaches such as no-touch RFA, HIFU, and IRE-offer promising alternatives for non-surgical candidates, particularly in technically challenging tumors or patients with cirrhosis.

By aligning macroscopic factors (eg, liver function, PH) with microscopic determinants (eg, MVI, tumor differentiation), clinicians can adopt a personalized, evidence-based treatment algorithm. Future efforts should focus on refining predictive models and incorporating novel technologies to enhance precision and long-term survival outcomes in early-stage HCC.

Future Outlook

Currently, patients with HCC face significant challenges, including insidious onset, high recurrence rates, and early metastatic potential. In cases of early-stage HCC, timely access to standardized treatment is closely associated with improved survival and prognosis. For clinicians, the concept of "standardization" is particularly critical in optimizing therapeutic outcomes. While adherence to established treatment guidelines is essential, it must be complemented by individualized assessment, taking into account each patient's clinical profile. A comprehensive evaluation-ranging from macroscopic parameters such as liver function and portal pressure, to microscopic factors such as the tumor microenvironment and vascular supply-can provide a more precise understanding of disease biology and guide therapy selection. The integration of both macro- and micro-level perspectives offers new clinical insights and potential therapeutic targets, paving the way for more personalized and effective strategies in the management of early-stage HCC.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ALBI, albumin-bilirubin; ALICE, albumin-indocyanine green evaluation; AR, anatomic resection; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; JH, Japan Society of Hepatology; LT, liver transplantation; MELD, Model for End-stage Liver Disease; MVI, microvascular invasion; MWA, microwave ablation; NAR, non-anatomic resection; OS, overall survival; PH, portal hypertension; RFA, radiofrequency ablation; UNOS, United Network for Organ Sharing.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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