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Recent Advances, Future Directions and Clinical Outcomes of Hepatectomy in Hepatocellular Carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) represents the predominant and most fatal malignancy globally. The primary therapeutic approach for HCC is Hepatectomy, which presents a potential for curative outcomes. This analysis aims to offer an exhaustive examination of the clinical repercussions linked to liver resection or Hepatectomy in HCC, underscore recent advancements in surgical methodologies, and deliberate on future pathways to enhance treatment efficacy in this domain. **Methods:** A thorough exploration of the literature was carried out across prominent databases, including Google Scholar, PubMed, ScienceDirect, and Cochrane Library. Research articles were chosen based on their pertinence to the outcomes of Hepatectomy in HCC, advancements in surgical techniques, and forthcoming therapeutic schemes to scrutinize the short- and long-term clinical consequences and the variables influencing these outcomes. **Results:** Hepatectomy for HCC manifests notable diversity in clinical outcomes, impacted by the nature of the tumor, characteristics of the patient cohort, and proficiency of the surgical team. Short-term results, like perioperative morbidity and mortality rates, have demonstrated enhancements in tandem with refinements in preoperative evaluations and intraoperative management. The duration of outcomes, encompassing overall survival and disease-free survival, displayed significant associations with extended resections, tumor characteristics, and postoperative assessments. Recent progressions in Hepatectomy have played a role in diminishing perioperative complications and expediting the recovery process. Furthermore, the amalgamation of adjuvant and neoadjuvant therapies, alongside the emergence of pharmaceutical modalities, can elevate survival rates and enhance the quality of life for individuals with HCC. **Conclusion:** Hepatectomy emerges as a pivotal intervention for HCC, yielding progressively superior outcomes owing to technological advancements and enhanced perioperative care. Prospective investigations will refine surgical techniques, optimize adjuvant therapies, and formulate robust predictive frameworks for diverse therapeutic modalities. This comprehensive assessment accentuates the significance of sustained innovation and interdisciplinary cooperation to elevate the standard of care for HCC patients. Moreover, continuous investigation into adjuvant and neoadjuvant treatments, such as immunotherapy and targeted therapies, is imperative for enhancing long-term prognoses.

Keywords: *Hepatocellular carcinoma, Hepatectomy, Clinical outcomes, Surgical techniques, Minimally invasive surgery, Adjuvant therapy.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Its incidence is increasing in specific Western populations, significantly contributing to the global cancer burden. Liver cancer is the second leading cause of cancer-related deaths in both Brazil and the United States, according to a recent epidemiological study.[1] Liver disease is prevalent in many Asian countries, including Korea, where liver cancer is a significant cause of cancer-related mortality, ranking third in the nation.[2,3] While surgical resection remains the preferred and curative treatment for hepatocellular carcinoma (HCC), various other therapeutic options are available, including radiofrequency ablation, transarterial chemoembolization (TACE), and external radiation. Laparoscopic liver resection is increasingly recognized as a viable option for liver surgery.[4,5] Historically, open hepatectomy was the standard approach for liver cancer, including HCC. However, recent technological advancements have made laparoscopic hepatectomy a viable alternative.[6,7] Geographically prevalence and incidence of HCC reveal that in 2020 Thailand, Vietnam, and Cambodia experienced notably high hepatocellular carcinoma incidence and mortality rates, ranging from 22 to 24 cases per 100,000 people (Table 1). While Mongolia had the highest rate, China reported an overall number of HCC cases, followed by Japan, Thailand, and Vietnam.[8] According to GLOBOCAN 2020, countries such as Iran, Afghanistan, Qatar, Azerbaijan, Iraq, and Nepal, which historically had low rates of hepatocellular carcinoma (HCC), have seen a dramatic surge in cases over the past two years.[9] The United States has seen a threefold increase in hepatocellular carcinoma (HCC) cases over the past four decades, primarily attributed to the aging population with chronic hepatitis C. Experts predict a staggering 22 million cases of HCC in the country within the next twenty years.[10] Japan has experienced a dramatic decline in hepatocellular carcinoma (HCC) cases, mainly due to a significant reduction in hepatitis C virus infections.

Similarly, China's HCC incidence is decreasing due to increased hepatitis B vaccination rates.[11] South Korea saw a substantial decline in the age-adjusted rate of liver cancer between 1999 and 2019, decreasing from 28.9 to 16.1 and further to 11.5 in 2020 per 100,000 people.[10] The Western Pacific region had the highest number of new liver cancer cases, deaths, and lost healthy life years in 2019. However, the United States saw the most significant increase in these figures between 2010 and 2019, with a 41% rise in new cases, a 42% increase in deaths, and a 36% increase in DALYs.[12]

Incidence and mortality of HCC data adapted by GLOBOCAN 2024. Hepatocellular carcinoma (HCC) rates have been climbing globally for the past two decades, and this trend is expected to continue in some countries, including the United States, until at least 2030.[13] Etiological factors include hepatitis B, hepatitis C, alcoholic liver diseases, and non-alcoholic liver/fatty liver diseases. These are the factors that are primarily responsible for hepatocellular carcinoma. More than 70% of cases of HCC are associated with chronic hepatitis B and C virus.[14]

Table 1: Incidence & mortality of HCC by country division[8]

Country	Incidence		Mortality	
	Case	ASR (%)	Case	ASR (%)
China	410,038	18.2%	391,152	17.2%
Japan	45,663	10.4%	28,155	4.8%
Thailand	27,394	22.6%	26,704	21.9%
Vietnam	26,418	23.0%	25,272	21.9%
Indonesia	21,392	7.9%	20,920	7.7%
Republic of Korea	14,788	14.3%	11,158	9.9%
Philippines	10,594	11.4%	9,953	10.8%
North Korea	5,607	15.5%	5,228	14.4%
Myanmar	5,466	10.0%	5,281	9.7%
Cambodia	3,142	24.3%	2,946	22.9%
Mongolia	2,236	85.6%	2,060	80.6%
Lao	1,272	24.4%	1,192	22.9%
United States	42,284	6.9%	31,078	4.7%

Hepatectomy is a procedure where we remove all or a part of the liver using traditional (open surgery) or minimally invasive technique (laparoscopic surgery). Hepatectomy is also known as liver resection. Some types of hepatectomy include partial hepatectomy, left hepatectomy, right hepatectomy, right lobectomy, or extended left hepatectomy. Hepatectomies are usually performed to treat hepatic neoplasms, which can be benign or malignant. Hepatectomy is a procedure that can be a treatment option for HCC patients. EASL-EORTC guidelines recommend hepatectomy in Barcelona Clinic Liver Cancer (BCLC) stage 0 or A and normal bilirubin and portal blood pressure. Hepatectomy can be safe and effective for tumors at least 10 cm in diameter.[15] We found four adverse predictors of survival liver cirrhosis: multiple intrahepatic metastases (≥4), poor histological grade, and significant portal vein invasion.[15] Our findings suggest that patients with huge HCC accompanied by two or more adverse predictors are not appropriate candidates for direct hepatic resection.[15]

By reviewing the results of hepatectomy for hepatocellular carcinoma, we can identify opportunities to enhance patient survival and minimize complications, which include preoperative factors (such as COUNT score, MELD score, tumor diameter, and hospital stay), Surgical techniques, comorbidities, micrometastases, etc. This review analyzes the clinical outcomes of hepatectomy, highlighting recent advancements in surgical techniques and discussing future directions for improving patient care.

1. Short Term Outcomes

We have reviewed articles on the outcomes of hepatectomy in HCC patients. Galun *et al*. analyzed 229 patients with HCC who underwent hepatectomy, where we have two groups, G1 (having 151 patients <70 Years) and G2 (having 78 patients >70 Years). Liver cirrhosis was present in most patients, 59.6% of G1 and 50% of G2. The mean overall morbidity rate of 229 patients was 31.1% in G1 and 46.2% in G2. We have found that patients aged more than 70 Years have a higher morbidity rate than younger patients. The overall morbidity rate in this study is only 38.70% in 229 patients. According to this study, the overall mortality rate was 2.6% in G1 and 6.4% in G2 within 30 days of surgery.[16] Wei *et al*. studied 155 patients who underwent hepatectomy for HCC; 126 underwent right and 29 underwent left extended hepatectomy. We have experienced an overall 55.5% morbidity rate (n=86). The morbidity rates (in 86 patients) of patients with normal liver, Chronic hepatitis, and cirrhosis were 53.6% (15 of 28), 56.2% (41 of 73), and 55.6% (30 of 54), respectively. Postoperative complications were noted in 43 patients, commonly ascites and pleural effusion, which need only conservative treatments. The overall mortality rate was 8.4% (13 of 155), with most deaths occurring in 30 days due to bleeding, infections, and liver failure.[17] Lee *et al*. conducted a total of 3386 patients with HCC who underwent hepatectomy within the duration of 39.3 months. Among 3386 patients, a total of 1957 had detailed records of their postoperative complications, which were analyzed. Among them, 1250 patients were uneventful or experienced only grade 1 complications during the postoperative period. Grade II complications occurred in 491 patients and could be treated with pharmacological therapy. The overall 30-day mortality rate was 1.8%.[18] Harimoto *et al*. discovered outcomes of laparoscopic vs open hepatectomy, revealing some outcomes that favor laparoscopic hepatectomy. The short-term outcomes are: (1) Significantly less blood loss was observed, (2) Postoperative complications were experienced fewer, (3) Patients with laparoscopic surgery had shorter stays at the hospital, (4) There were no hospital deaths in laparoscopic hepatectomy group, and (5) Recovery was faster than open hepatectomy.[19]

Sanyal *et al*. performed a study on 200 patients over. The median age was 64 years. One hundred eighty-one patients were aged less than 80 at the time of resection, and 19 were aged over 80 years. According to this study, complications after hepatectomy were almost similar between both age groups, primarily due to respiratory and infectious diseases. The overall percentage of morbidity was 21.4%. The mortality was significantly higher in the age group less than 80 years within 30 days of surgery, and the reason was sepsis or multi-organ failure.[20] Hepatectomy, in the case of HCC, is a safe procedure where the mortality rate is around 2% in 30 days (in-hospital) and a 90-day mortality rate is 5%. That is due to advancements in surgical techniques and improved patient selection.[21] In another study, they had 18 patients with a median age of 65.5 years (range 55-77) 17 were male, and one was female. The overall morbidity rate was 77.8%, where four patients had complaints of pneumonia, three patients had complaints of myocardial infarction, heart failure, or acute pulmonary edema, two patients had intra-abdominal abscess, and two patients had acute kidney injury. The mortality rate of 30 days after surgery was 0% in this study.[22] The average duration of hospitalization for short-term outcomes of hepatectomy in HCC patients was taken 30 days after surgery. The factors affecting the stay at the hospital were morbidities like plural effusion mostly, cardiac morbidities, and kidney morbidities.

2. Long-term outcomes

In a study, the patients were divided into three groups based on tumor size. The follow-up period was 20 months. The 5-year overall survival rate was 56% for the entire cohort study. A clear correlation between tumor size and overall survival rate was observed. Patients with small HCC <5cm had the best 5-year OS, 88.6%. Patients with large HCC 5-10cm had a significantly lower 5-year OS of 51.6%. Patients with huge HCC >10cm had the lowest 5-year OS at 41.1%. In this study, we have noted that the disease-free survival rate for the entire cohort study was 46.3%.[23] A study was performed in 1999 where 211 patients underwent 153 primary and 58 minor hepatectomies. The study aimed to study disease-free and overall cumulative survival rates of patients who underwent hepatectomies with HCC. The median overall survival rate for the patients with HCC was 35 months. The 1, 3, and 5-year disease-free survival rates were 60%, 38% and 27% respectively. The five-year survival rate of patients undergoing hepatectomy for HCC has improved from 12% to 20% in earlier years to 35% to 50% in recent years.[24]

A meta-analysis was performed in 2022, and they screened about 6983 articles, removed 2337, and included the remaining 4646 in the meta-analysis. The study analyzed data from over 82,000 patients with HCC who underwent curative surgical resection. The summarized long-term outcomes are as follows: 1-year overall survival was excellent, and around 89% across all regions. The 5-year OS was 56%, indicating significant room for improvement in long-term survival. The 1-year recurrence-free survival rate was around 71%, suggesting the Importance of patient selection and post-surgical treatments. The 5-year recurrence-free survival rate was only 35%, highlighting a high recurrence rate as a significant challenge.[25] A study was performed in 2020 where 200 patients underwent hepatectomy; 181 patients were <80 years of age, and 19 were >80 years of age. The long-term outcomes, according to this study, reveal patients aged less than 80 years had a 41.8% survival rate, while patients more than 80 years of age had a survival rate of 37.24%. There was no significant difference in survival between the two groups (p=0.53). Kaplan-Meier curves suggest patients over 80 may have a better survival rate at 1 and 3 years, but this evens out the younger by year 5.[20]

A study was performed with over 6785 patients with HCC who underwent hepatic resection where we have noted the long-term outcomes: expected survival rates for one year is 85%, three years is 64%, 5-year is 45%, and 10-year is 21%. Up to 80% of experience recurrence within five years. The treatment for recurrence in this study given was aggressive surgical approaches in those patients with limited recurrence in the liver, Multimodality therapy including transarterial chemoembolization, percutaneous ablations, and surgery can offer a 20% overall 5-year survival rate for recurrent HCC.[21]

3. Factors Influencing Outcomes

Patients with underlying liver conditions are considered a high-risk cohort for significant hepatic resection of hepatocellular carcinoma (HCC). Recent reports have highlighted that the morbidity and mortality rates for individuals with severe fibrosis (cirrhosis) who undergo liver resection range between 20–70% and 8–32%, respectively.[26] The potential risks associated with postoperative morbidity and mortality are concerning for both patients and healthcare providers. Complications or fatalities following the procedure led to prolonged hospital stays and increased healthcare expenses. Hence, it is imperative to identify the predictors of postoperative morbidity and mortality after primary HCC resection, particularly in patients with underlying liver conditions.[17] The morbidity rate post-surgery may vary based on the criteria used to define postoperative complications. However, the overall morbidity rate of 37.0% in the current study aligns with findings from previous research. Studies have identified pleural effusion as the most common postoperative complication, followed by hepatic abscess, hepatic dysfunction, ascites, hemoperitoneum, and biliary fistula.

Conversely, it was reported ascites, pleural effusion, wound infection, bile leakage, intraperitoneal abscess, liver failure, encephalopathy, hemorrhage, and gastrointestinal bleeding as prevalent complications. The observed postoperative morbidities in the study are consistent with those reported in earlier research. Factors such as preoperative serum aspartate aminotransferase levels, comorbidities, perioperative blood transfusions, Child-Pugh classification, indocyanine green retention test results, type of surgery, and intraoperative blood loss have been identified as risk factors for hospital mortality in HCC patients undergoing hepatic resection.[27] It revealed that portal hypertension, Child B classification, and preoperative platelet count below 100×10^9/L are risk factors for perioperative mortality in HCC patients with underlying liver conditions following primary hepatic resection.[28] These factors are independent of the surgical procedures but are contingent on the patient's preoperative liver function status. Practical preoperative assessment of hepatic function status and residual liver volume is crucial for reducing hospital mortality after primary hepatic resection in HCC patients with underlying liver conditions.[29] This approach helps prevent postoperative hepatic failure, a primary cause of hospital mortality, as evidenced in this study.

Additionally, the Child-Pugh classification remains the preferred method for assessing liver function preoperatively in HCC patients with underlying liver conditions.[30] At our hepatobiliary surgical center, individuals classified as Child Care are strictly excluded from undergoing hepatic resection for HCC. For patients classified as Child B, factors such as portal hypertension, surgical complexity, and potential prognosis improvement post-surgery are carefully considered before proceeding with major hepatic resections for HCC. Re-resection remains the preferred treatment for recurrent tumors following the initial surgical excision of HCC, a strategy supported by numerous retrospective studies.[31]

It was discovered in 1996 that the preoperative platelet count was correlated with postoperative hepatic dysfunction following the surgical resection of HCC in cirrhotic patients, albeit not in an independent manner. It illustrated that preoperative platelet counts of less than 100×10^9 /L and the necessity for blood transfusion were autonomous predictors of postoperative complications in contemporary practice. Recent animal experiments have brought to light the significant role of platelets in liver regeneration after hepatectomy. In 2009, it disclosed that preoperative platelet counts below 100×10^9 /L were a distinct risk factor for a substantial volume of ascites post-hepatic resection. It is postulated that the preoperative platelet count might mirror the extent of liver injury (fibrosis or cirrhosis) in patients with underlying liver conditions, whereby a low platelet count emerged as a risk element for postoperative morbidity and hospital mortality in the ongoing investigation. Nonetheless, further explorations are imperative.[32]

There are various treatment modalities presently accessible for individuals with HCC. Treatment strategies should be personalized based on the disease stage, liver function, and the patient's performance status.[33] Curative treatments should be proposed for suitable candidates, encompassing ablation (surgical or percutaneous) for diminutive tumors generally <2 cm, liver resection, and orthotopic liver transplantation (OLT).[34] Regrettably, a notable percentage of patients, ranging from 30% to 66%, do not undergo any treatment throughout their illness trajectory, predominantly due to inadequate referral to the appropriate specialist or care team.[35] Furthermore, the treatment approach is frequently influenced by the treating provider's preference, which varies by specialty and may only sometimes be grounded on evidence leading to substantial variances among treated patients.[36]

Consequently, prevailing recommendations advocate for the multidisciplinary assessment of all patients, with recent research demonstrating enhanced care processes and overall superior outcomes with the implementation of this protocol.[37] The scope of liver resection for HCC has progressively broadened over the past decade. Typically, liver resection should be deliberated for patients with nonmetastatic disease and normal underlying liver function or with compensated cirrhosis and devoid of portal hypertension indications.[38] Patients with acknowledged liver ailments should undergo liver function appraisal using an established system. Standard procedure involves categorizing patients based on the CTP criteria, with only those falling under CTP class A deemed suitable for extensive resection.[39] Another metric is the Model for End-Stage Liver Disease (MELD) score, with a threshold of <10 points serving as the safety limit for liver resection.[40]

Recent studies have underscored the incremental discriminatory capacity of the Albumin-Bilirubin (ALBI) score even within the CTP A bracket, notwithstanding the unexplored role in enhancing patient selection.[41] Evaluation of portal hypertension is conducted through clinical parameters (e.g., ascites, abdominal varices, history of upper gastrointestinal variceal bleeding) and indirect laboratory (e.g., thrombocytopenia) and imaging (e.g., splenomegaly, recanalized umbilical vein, gastric/esophageal varices) proxies.[42] In some instances, patients may present with conflicting findings, warranting the measurement of the direct hepatic vein–portal vein gradient to rule out portal hypertension (<10 mm Hg) before proceeding with liver resection.[43] Among patients meeting the specified criteria, the role of resection should consider other potentially curative competing strategies (i.e., ablation and OLT) and the corresponding outcomes based on an intention-to-treat analysis. Several randomized controlled trials16-18 and a minimum of 3 meta-analyses 19-21 have investigated the comparative effectiveness of liver resection versus ablation for early-stage disease.[44] The trials differed in their selection criteria, including solitary lesions <5 cm,16, and the other having characteristics similar to those outlined for the Milan criteria.[45] Each trial had significant methodological limitations that restricted the interpretation of the findings. Nevertheless, one trial and all meta-analyses concluded that percutaneous radiofrequency ablation (RFA) was inferior to liver resection in terms of overall survival and recurrence-free survival, with RFA offering the advantage of being a less invasive approach associated with fewer complications and shorter hospital stays.[46] A synthesis of results from 25 non-randomized trials analyzed in the Cochrane meta-analysis revealed comparable long-term outcomes for patients with very early-stage tumors (<2 cm) when comparing both strategies.[47] Based on this evidence, our team favors liver resection for small HCC. Nonetheless, in cases where a patient presents with a small tumor (<2 cm) and borderline liver function, or with a high burden of comorbidities, and when the tumor is located in a deep part of the liver (necessitating a major liver resection), ablation represents a suitable treatment option.[48] An important aspect to consider regarding outcomes following percutaneous ablation is the inherent limitation of this method in treating lesions in unfavorable locations. For instance, those close to hollow organs are positioned high in the dome near the diaphragm or proximity to major vessels or hilar structures. In such scenarios, a more suitable approach may involve surgical (laparoscopic or open) ablation or even liver resection despite it being a more extensive procedure.[49] When contemplating liver resection for lesions >2 cm, the potential role of OLT should also be evaluated. Orthotopic liver transplantation has been established as the preferred treatment for patients meeting the Milan criteria (1 tumor ≤5 cm or up to 3 tumors none >3 cm).[50] Long-term outcomes in line with these criteria are comparable to those of patients undergoing OLT for non-malignant conditions, with a 5-year overall survival rate of 65% to 78%,22,23 advocating for the allocation of deceased donor livers to this population, irrespective of organ scarcity.[51] Moreover, some groups have introduced "expanded" criteria, the University of California, San Francisco (UCSF) criteria being the most extensively studied expansion, where OLT is considered for individuals with a single tumor up to 6.5 cm or up to 3 tumors with the largest being 4.5 cm and a combined diameter of the three tumors not exceeding 8 cm. The 5-year overall survival rate using these criteria was reported as 75% in the initial study, although these findings have not been universally replicated.[52] Liver resection has undergone significant advancements in recent decades, rendering it a safe procedure when conducted within appropriate parameters and with careful patient selection.[53] Cirrhosis is recognized as an important risk factor for increased postoperative complications, such as bile leakage, post-hepatectomy liver failure (PHLF), and mortality.[54]

In the context of treating hepatocellular carcinoma (HCC) through hepatectomy, evaluating the baseline liver function is crucial; the resection should adhere not only to general oncologic principles (achieving complete R0 resection) but also prioritize optimizing recovery, reducing postoperative complications, and preserving sufficient liver function.[55] Various approaches have been investigated to inform liver resection strategies for this patient population and enhance long-term outcomes.[56] Furthermore, apart from established tools that categorize patients based on baseline liver function and aid in patient selection for resection (as previously mentioned), the recovery and maintenance of adequate liver function postoperatively for those undergoing hepatectomy are also influenced by the extent of liver resection, specifically the volume of the remaining liver (known as the future liver remnant [FLR]) and its functionality.[57] Functional assessments like the indocyanine green retention rate at 15 minutes, predominantly utilized in Asia, assist in determining the extent of liver resection that can be tolerated.[58]

Conversely, in North America and Europe, which align with our practice, the FLR volume in patients already earmarked for resection (and thus possessing preserved liver function/compensated cirrhosis) is utilized to gauge the feasible extent of resection.[59] For individuals with compensated cirrhosis and no portal hypertension, an FLR ratio of 40% is considered optimal and has been identified as the safe threshold for resection in this cohort.[60] Studies examining the proportional contribution of different liver segments to the total liver volume have indicated that the right lobe accounts for 65% to 67% of the total liver volume. Thus, following a right hepatectomy, the expected FLR ratio would fall below the 40% threshold.[61]

A method to facilitate secure major liver resection in patients who would otherwise have an FLR below 40% involves the systematic utilization of preoperative portal vein embolization (PVE). The safety and feasibility of portal vein embolization have been firmly established. Typically performed percutaneously, PVE involves embolizing the portal vein branch on the same side as the tumor-bearing liver. This process triggers regeneration and hypertrophy of the opposite lobe within 4 to 8 weeks post-PVE. The success rate of PVE varies depending on the indication, tumor histology, baseline liver function, and initial FLR ratio but averages around 85%. Investigations have demonstrated that the overall outcomes post major hepatectomy after PVE, both in the general populace and specifically in patients with HCC, are comparable to those achieved with liver resection lacking PVE but with adequate baseline FLR, thus affirming the advantages of PVE as a means to broaden the pool of resection-eligible patients.[62]

4. Comparison with Other Treatments

liver resection yielded superior overall survival (OS) outcomes compared to radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) in patients with multiple small hepatocellular carcinomas (HCCs).[63] Given the demographic advantage of the resection group, propensity score (PS) matching was utilized to achieve baseline feature equilibrium. Following matching, the OS discrepancy did not reach statistical significance.[64] Nevertheless, concerning recurrence-free survival (RFS), the resection cohort consistently demonstrated enhanced RFS compared to the RFA or TACE group in both pre and post-SP matching. While statistical significance was lacking before and after PS matching, notable major complications occurred more frequently in the resection group than in the RFA or TACE groups.[65] Multiple meta-analyses and randomized controlled trials (RCTs) have compared outcomes in multiple HCCs meeting Milan criteria between resection and RFA.

Specific RCTs and meta-analyses have favored resection over RFA concerning survival and recurrence, albeit on populations with a considerable proportion of single tumors, tumors larger than 3 cm, or unknown ALBI grade.[66] Other RCTs and meta-analyses have shown no significant OS disparity between RFA and resection groups despite a lower RFS associated with RFA.[67] Studies comparing resection to TACE have reported more favorable survival outcomes with resection. The study focuses on multiple HCCs within Milan criteria characterized by small but multiple tumors (2–3 nodules, ≤3 cm). Analysis revealed no statistically significant OS difference among the three groups, while RFS favored the resection group over the RFA or TACE group.[68] Findings suggest that RFA and TACE may be inadequate treatments, justifying resection as the primary approach for small but multiple HCCs. Concerns regarding de-novo recurrence and hidden intrahepatic metastasis have historically deterred liver resection in patients with various HCCs, with estimated rates exceeding 70% at five years, higher than single HCC rates. Despite observing a high recurrence rate in the resection group, it remained lower than in the RFA or TACE groups.[69] The benefit of hepatic resection lies in excising visible tumors and potential microscopic tumor tissues with adequate margins, potentially explaining the superior RFS in the resection recipients. Another consideration is the risk of reduced future liver volume post-resection affecting liver function, with hepatic failures leading to liver transplantation being rare but exclusive to the resection group in this study. Given the higher complication rate in the resection group, careful monitoring is essential, as nearly all resection patients exhibited ALBI grade 1, indicating meticulous selection of individuals with preserved liver function.[70]

Previous meta-analyses have compared the effectiveness of Radiofrequency Ablation (RFA) versus Hepatic Resection (HR) in the treatment of small Hepatocellular carcinoma (HCCs); however, there needs to be more consistency in the results. It was discovered that HR showed superiority over RFA in treating HCC patients, especially for tumors measuring less than 3 cm. For tumors larger than or equal to 3 cm, HR did not show a significant difference in survival compared to RFA. On the contrary, Xu *et al*. demonstrated that HR led to significantly better survival outcomes than RFA for HCC tumors larger than 3 cm.[49] Cucchetti *et al*. recently conducted a systematic review suggesting that RFA should be offered for very small HCCs (less than 2 cm) due to the likelihood of achieving complete necrosis in such cases. For larger tumors, specifically those over 2 cm and notably if exceeding 3 cm, surgical resection is the preferred option. These findings align with the research.[51]

Moreover, meta-analysis had several enhancements: firstly, many studies were included. Notably, eight recent studies were published post-2012, thereby enhancing the statistical robustness of the analysis; secondly, the literature search was expanded to non-English publications, resulting in the identification of seven additional studies in Chinese and Korean that were not covered in prior reviews; thirdly, the inclusion of over 16,000 patients from six different countries provided broader and more meaningful results.[71] Traditionally, patients with vascular invasion are classified as BCLC stage C with advanced cancer. Systemic therapy is recommended for managing HCC cases linked to macrovascular invasion. Much of our current knowledge regarding the effectiveness of surgical interventions in advanced HCC is derived from small retrospective studies conducted in Asia and Europe.[72] Results are in line with those of smaller studies conducted outside the United States. The first reported instance of liver resection for HCC in patients with portal vein invasion dates back to 1990. After this, numerous small-scale studies have reported on the use of surgery in patients with vascular invasion, although comparative data with standard treatments are lacking in most cases.[73] In a nationwide multicenter analysis in Japan, demonstrated that liver resection was associated with improved survival in individuals with portal vein tumor thrombosis limited to the first-order or peripheral branch, showing a median survival time of 1.77 years longer than the nonsurgical group.

Furthermore, they reported an improvement in median survival time of 2.89 years in individuals with hepatic vein tumor invasion compared to the non-resection group. Hepatic resection led to a 5-year overall survival rate of 11.1%, contrasting with 0.5% for those who underwent Transarterial Chemoembolization (TACE). Various studies conducted in Asian and European nations have highlighted the survival advantages associated with aggressive surgical resection, particularly in cases of vascular invasion restricted to segmental branches or the right/left portal/hepatic vein, without involvement of the central portal vein.

While there is an absence of a comprehensive cohort study examining the efficacy of surgical resection for hepatocellular carcinoma (HCC) with vascular invasion in the United States, a retrospective multicenter study amalgamated data from various prestigious institutions such as the University of Texas M. D. Anderson Cancer Center (Houston, TX, USA), Mayo Clinic (Rochester, MN, USA), Beaujon Hospital (Paris, France), Kyoto University Graduate School of Medicine (Kyoto, Japan), and Queen Mary Hospital (Hong Kong, China). This study disclosed the clinical outcomes of 102 patients diagnosed with HCC and vascular invasion who underwent surgical resection between 1984 and 1999. The research findings indicated a median survival period of 11 months, with liver fibrosis severity emerging as the sole independent prognostic determinant. Nonetheless, it is crucial to note that this study lacked a control group that received systemic treatment, and the patients encompassed in this analysis underwent surgical resection two to three decades in the past.

5. Recent Advances in techniques and technologies with their Future Directions

5.1 Three-Dimensional Visualization Technology (3DVT)

3D visualization technology (3DVT), a critical method in the management of intricate liver conditions, constructs three-dimensional depictions of human body data derived from computed tomography (CT) or magnetic resonance imaging (MRI) on a computer. The procedure encompasses data collection, image manipulation, three-dimensional rebuilding, image alignment, fusion, and visualization analysis. Fusion imaging, notably the amalgamation of MRI and CT venous phases, allows for precise three-dimensional (3D) construction, aiding in delineating the form and spatial arrangement of structures like the biliary tract, blood vessels, or tumors.[74] This capacity accelerates the precise isolation of target structures and furnishes clinical decision-making support for preoperative diagnosis, surgical strategizing, and approach selection. 3D visualization in liver cancer medicine involves evaluations of hepatic lesions, analysis of the biliary system, identification of hepatic artery and vein anomalies, and assessments of portal vein anatomy. This technology facilitates tailored liver segmentation, volume computations for surgical guidance, and a more distinct determination of lesion attributes and their association with intrahepatic vasculature.[75,76,77]

The characterization of complex liver cancer remains disputable, frequently encompassing central HCC impacting the hepatic hilum, alterations in major intrahepatic vessels such as the hepatic artery, portal vein, and hepatic vein, severe vascular distortions induced by the tumor, malignancies involving inferior vena cava or right atrial thrombosis, and substantial benign or malignant tumors necessitating extensive excision. In scenarios like these, especially those mandating extended resection, 3D visualization technology is a pivotal instrument for surgeons. This technique facilitates the imaging and exploration of intricate anatomical interrelations among intrahepatic structures and tumors, aiding in meticulous preoperative evaluations and surgical strategizing. The classification system grounded on 3D visualization proposed by Fang *et al*. provides decision-making assistance concerning selecting diverse surgical approaches for centrally positioned HCC treatment, thereby contributing to achieving anatomical, functional, and curative resections.[78] Recent research has verified that 3DVT significantly enhances postoperative outcomes for complex liver cancer, leading to reduced hospitalization durations, decreased complication rates, lower mortality, and hastened liver function rec.[78,79] Additionally, 3DVT technology has refined the accuracy of resectability assessments, empowering surgical oncologists to plan more precise liver resections and execute surgeries with increased confidence based on the previously detailed comprehension of anatomy.[80]

5.2 3D Printing Technology

After obtaining three-dimensional outcomes through 3DVT technology, a bespoke, palpable model of a patient's liver can be produced utilizing a 3D printer. The application of 3D printing technology can benefit the treatment and management strategies for HCC in various ways. Primarily, the technology streamlines the creation of customized anatomical liver models derived from patient-specific CT or MRI scans, which aid clinicians in formulating preoperative strategies and play a crucial role in medical education and training. Moreover, this technology substantially enhances the understanding of healthcare professionals and patients by furnishing a detailed representation of anatomical positioning, volumetric dimensions, and proximity of tumors to vascular structures, thereby enabling the refinement of surgical intervention strategies.[81,82,83]

For patients, this results in a more explicit comprehension of their diagnosis and the anticipated treatment course. Within the realm of surgical practice simulations, using 3D-printed models incorporating self-repairing materials facilitates iterative resections, permitting the enhancement of surgical pathways, thereby boosting operative safety and effectiveness.[84] The extensive acceptance of 3D printing in medical instruction and surgical preparation has played a pivotal role in progressing our knowledge of the hepatic structure and enhancing clinical cognitive capacities. Despite numerous investigations and case studies highlighting the usefulness of 3D printed models in preoperative and postoperative decision-making, comprehensive, evidence-based research in this domain needs to be revised. Consequently, further investigations are imperative to thoroughly assess the clinical implications of these models in the context of HCC surgical care.

5.3 Artificial Intelligence (AI)-Based Radiological Imaging

The swift progress of AI has led to notable advancements in medical image analysis through data analysis technology, leading to the emergence of a new field known as radio mics. Developments in liver surgery have emphasized the crucial need for precise preoperative Evaluation of liver function to avert post-hepatectomy liver failure (PHLF), a primary source of morbidity and mortality. A recent study introduced a novel AI application for determining secure resection volumes based on patients' liver function undergoing major hepatectomy. The AI approach exhibited a predictive accuracy for secure resection volumes of 68.8%, surpassing traditional models (45.77%–48.22%).[85] Furthermore, the method notably reduced the mean absolute error in under-predicted volumes, leading to a more precise estimation of secure resection boundaries. These findings underscore the potential of integrating AI into surgical strategizing for liver resections, aiming to diminish the risk of PHLF and enhance clinical results. Practical and viable radio mics models combining MRI radio mics signature with preoperative clinical risk elements have been devised to foresee 5-year survival in patients with operable HCC.[86] This research method, utilizing high-capacity extraction of feature data from radiographic images, holds promise for creating models that predict lesion characteristics and prognosis in a non-invasive manner.

5.4 Minimally Invasive Laparoscopic Hepatectomy (LH) for HCC

LH was initially conducted in individuals with benign growths in the early 1990s.[87,88] With advancements in surgical methodologies, LH has been progressively embraced for HCC with improved safety and comparable long-term outcomes to open hepatectomy.[89,90] Nonetheless, challenging situations, such as tumors situated in posterosuperior segments, large and recurrent tumors, and liver cirrhosis, continue to present potential risk factors for intraoperative and postoperative complications. Alternative approaches like indocyanine green (ICG)-guided LH and robot-assisted laparoscopic hepatectomy (RALH) have been devised and implemented to surmount the constraints of minimally invasive LH.

ICG has been utilized as a navigational tool in real-time during hepatobiliary surgery to aid surgeons in assessing lesion size, location, and the presence of micro-metastasis.[91] It offers an alternative method for intraoperative staining of HCC, which may not be visible on preoperative MRI or intraoperative ultrasound.[92] The consensus guidelines propose two strategies for ICG-guided anatomical hepatectomy: positive and negative staining.[93,94,95] NIR-II (1000–1700 nm) fluorescence, as opposed to NIR-I (400–900 nm), provides enhanced tissue penetration and detection capabilities for micro-metastasis and residual disease.[96] A meta-analysis of 11 retrospective cohort studies involving 959 patients indicated that ICG-guided anatomical hepatectomy led to a higher R0 resection rate and a reduced need for intraoperative blood transfusion compared to conventional LH.[97] While ICG fluorescence imaging can identify tumor locations and microscopic lesions, it is less effective at detecting deeper tumors and distinguishing nodular regenerative hyperplasia from HCC-related tumors in severe cirrhosis.[98,99] Hence, enhancing the specificity of ICG fluorescence imaging remains a crucial challenge for the future.

RALH is a favored technique due to its high-resolution 3D images, tremor-free flexible robotic arms, and capabilities for deep manipulation during anastomosis and precise tumor resection near vital vessels. It excels in complex surgical procedures, overcoming LH limitations.[100] The integration of a 5th-generation Mobile Communication Technology (5G)-based robotic system allows remote robotic surgery, eliminating geographical constraints in healthcare delivery. Some studies suggest RALH improves bleeding control and quicker postoperative recovery than open surgery.[101] However, a recent systematic review found no significant disparities in surgical and oncological outcomes between LH and RALH.[102] Challenges such as high costs and limited experience in many hospitals hinder the widespread adoption of RALH.

ALPPS, a procedure in regenerative liver surgery, addresses the challenges associated with extensive hepatectomy and the risk of postoperative liver failure. It is considered for patients requiring significant liver resection due to liver cancer.[103] ALPPS offers a swifter second-stage procedure compared to conventional two-stage hepatectomy. When compared to portal vein embolization (PVE), ALPPS significantly increases the future liver remnant (FLR) within four weeks and enhances the tumor resection rate for HCC patients by over 90%.[104,86] A meta-analysis involving 2075 patients demonstrated the superiority of ALPPS in terms of FLR and time to hepatectomy over PVE, two-stage hepatectomy (TSH), and portal vein ligation (PVL).[105] Recent research indicates that ALPPS may improve overall survival (OS) and disease-free survival (DFS) in patients with unresectable HCC, potentially halting tumor progression before the second surgery.[105,106] ALPPS, as a promising approach, aims to enhance resectability and safety for inoperable tumors. Nevertheless, data from Eastern Hepatobiliary Surgery Hospital revealed a notably higher incidence of major postoperative complications in HBV-related HCC patients undergoing ALPPS compared to those in the TACE+PVE cohort (54.1% vs 20%, P = 0.007).[106] Various modified ALPPS techniques, such as laparoscopic and robot-assisted ALPPS, ALTPS, RALPP, and simultaneous portal and hepatic vein embolization, have been developed to enhance safety and minimize invasiveness.[107,108,109,110,111] These techniques aim to avert liver splitting, decrease surgical aggressiveness, and mitigate postoperative complications linked to parenchymal separation. A meta-analysis comparing partial and complete ALPPS procedures demonstrated similar outcomes regarding FLR hypertrophy and inter-stage duration, with significantly fewer postoperative complications and lower mortality rates in the partial ALPPS group.[112] When patients fail to achieve adequate FLR hypertrophy post-initial ALPPS stage, a salvage TAE procedure known as TAE-salvaged ALPPS obstructs tumors' primary arterial blood supply while enhancing resectability.[113] Hence, the decision to utilize ALPPS should be tailored to each patient's specific characteristics, including age, degree of liver cirrhosis, tumor characteristics, and the extent of liver resection required.

5.5 Liver Transplantation

Since the pioneering work of Starzl *et al*. in 1967, it has evolved into a crucial life-saving treatment and a proven intervention for patients with end-stage liver disease.[114] Despite stringent selection criteria, HCC remains a significant indication for liver transplantation, particularly in Asia, offering improved survival prospects to patients. Organ scarcity poses a substantial obstacle to liver transplantation as a therapeutic option for HCC. In recent years, various innovative surgical techniques have emerged, leading to advancement in liver preservation methods.[115] Living donor liver transplantation (LDLT) involves the extraction of a portion of the liver from a living donor for transplantation into a recipient. The recent advancements in LDLT are characterized by continuous improvements in surgical techniques to enhance donor and recipient.[116] These advancements include exploring minimally invasive methods like laparoscopic donor hepatectomy to decrease donor morbidity. Ensuring donor safety is a top priority, with ongoing efforts to enhance evaluation processes and safety protocols. LDLT has demonstrated efficacy in treating HCC patients with comorbidities such as methylmalonic acidemia and combined hepatocellular-cholangiocarcinoma.[117,118] Efforts to expand the donor pool involve investigating extended criteria, which may include older donors or individuals with specific conditions after thorough evaluation.[119] Successful liver transplantations in China, known as "wasted liver transplantation," involve extracting a healthy liver segment from patients with benign liver tumors for transplantation into recipients.

Additionally, a liver lobe that would otherwise be discarded was effectively utilized in a hybrid-dual-graft liver transplantation for HCC.[120] In the future, experienced centers may consider this surgical technique for emergent LT in patients with fulminant liver failure or those undergoing LDLT with a small-for-size graft. Domino liver transplantation (DLT) entails transplanting a liver from a donor with a metabolic disorder into a recipient, allowing the donor liver to assume the recipient's liver functions. Ongoing research and advancements aim to enhance transplantation outcomes for HCC, although efficiency metrics can vary among transplant centers.[121] Normothermic oxygenated perfusion and ischemia-free liver transplantation (IFLT) are cutting-edge preservation techniques in liver transplantation. Normothermic oxygenated perfusion involves temporarily restoring blood flow post-death declaration using arterial and venous cannula, reducing ischemia-reperfusion injury.[116] Advancements in HCC transplantation include refining immunomodulation strategies. Despite transplant patients typically being ineligible for immune checkpoint inhibitor therapy due to graft rejection concerns, recurrent HCC patients lacking programmed cell death 1 ligand 1 (PD-L1) expression in their grafts underwent anti-programmed cell death 1 (PD1) therapy without experiencing graft-related adverse events underscoring the potential of PD-L1 expression as a marker for organ rejection following anti-PD1 immunotherapy in transplant recipients. These findings suggest that the absence of graft PD-L1 expression serves as a biomarker indicating the safety of anti-PD1 therapy in liver transplant patients with recurrent tumors.[122]

5.6 Conversion Therapy

It involves the transformation of initially unresectable liver cancer into resectable liver cancer using proven, effective local or systemic treatments.[123,124,125] Within the realm of conversion therapy for HCC, there are primarily two approaches: one targeting oncologically unresectable patients with poor prognosis post-surgery and the other focusing on technically unresectable patients.

Converting unresectable HCC typically involves local, systemic therapy or a combination.[124 134] The effectiveness of TACE in conversion therapy is widely acknowledged,[126] while recent research indicates the promising potential of hepatic arterial infusion chemotherapy (HAIC) in this context. In contrast to sorafenib, the utilization of HAIC alone or in conjunction with sorafenib among patients with unresectable HCC has led to surgical resection, tumor downstaging, and improved prognosis.[127,128] The significant efficacy of immunotherapy combined with targeted therapy in HCC has sparked interest in its application within conversion therapy. An earlier study involving 101 individuals with unresectable HCC highlighted that a therapeutic approach combining tyrosine kinase inhibitor (TKI)/anti-PD-1 antibodies achieved an R0 resection rate of 23.8% (24/101), with 41.7% (10/124) experiencing a pathologic complete response (pCR). The 1-year recurrence-free survival (RFS) and OS rates post-hepatectomy stood at 75% and 95.8%, respectively. Long-term monitoring revealed that undergoing hepatectomy emerged as an independent predictor of favorable OS.[129] In a phase II trial among patients with HCC featuring macrovascular invasion, the application of Lenvatinib with an anti-PD-1 agent for conversion therapy yielded a conversion rate of 55.4%.[130] While combining immunotherapy and targeted therapy has showcased promising results in HCC conversion therapy, further investigations into predictive biomarkers are crucial for guiding clinicians in selecting optimal systemic treatment options for unresectable patients and tailoring conversion therapy accordingly. The amalgamation of local therapy and immunotherapy positively impacts conversion therapy. The single-arm phase 2 study, START-FIT, enrolled 33 patients with locally advanced HCC who underwent TACE, stereotactic body radiotherapy (SBRT), and Avelumab treatment, resulting in 55% (18/33) achieving curative treatment. Numerous clinical trials have substantiated the efficacy of combining TACE and Lenvatinib with anti-PD-1 antibodies as a translational therapy. Based on a prospective investigation, this triple therapy achieved an objective response rate (ORR) of 76.4% and a disease control rate (DCR) of 85.5% (as per the modified response evaluation criteria in solid tumors, mRECIST), with a successful conversion rate of 52.7%.[131] A retrospective analysis demonstrated 1- and 2-year OS rates of 97.1% and 94.4%, respectively, for this triple therapy employed in the conversion therapy setting.[132] These outcomes underscore how the synergistic effects of local therapy, immunotherapy, and targeted therapy can yield enhanced clinical advantages for individuals with unresectable HCC undergoing conversion therapy.

5.7 Adjuvant Therapies

Owing to the absence of standardized adjuvant therapy post-surgery for hepatocellular carcinoma (HCC) on a global scale, the treatment approaches for HCC that typically encompass local, systemic, or a combination of both remain advisable for HCC patients at high risk of recurrence following radical resection.[133] Notably, two local therapies, Transarterial Chemoembolization

(TACE) and Hepatic Arterial Infusion Chemotherapy (HAIC), have demonstrated significant enhancements in Overall Survival (OS) and Disease-Free Survival (DFS) among HCC patients with microvascular invasion (MVI).[134,135] Evidence from a phase III multicenter randomized controlled trial revealed that the DFS for patients receiving adjuvant HAIC was 20.3 months compared to 10 months in the control group (P = 0.001), with recurrence rates of 40.1% and 55.7%, respectively.[134] Moreover, strides have been taken to lessen treatment outcomes by integrating local and systemic therapies. Several clinical trials propose combining postoperative TACE with Tyrosine Kinase Inhibitors (TKIs) as adjuvant therapy that confers clinical advantages. For instance, the amalgamation of TACE treatment with sorafenib resulted in a substantial extension of OS (30.4 months vs. 22.5 months) and Recurrence-Free Survival (RFS) (16.8 months vs. 12.6 months) in HCC patients with portal vein tumor thrombus.[136,137]

The advent of immunotherapy regimens has ushered in notable achievements in adjuvant immunotherapy alone and in conjunction with targeted therapy for HCC. In a global phase III open-label trial named IMbrave050, 668 patients with high-risk HCC post-surgery or ablation were enrolled to receive adjuvant treatment with atezolizumab combined with bevacizumab or to undergo active surveillance. High risk of recurrence following resection was delineated as 1) tumor number ≤3, most significant tumor >5 cm or poor differentiation; 2) tumor number ≤3, most giant tumor ≤5 cm with vascular invasion or poor differentiation; 3) tumor number >4, most giant tumor ≤5 cm or poor differentiation; whereas for ablation: 1) single tumor >2 cm but ≤5 cm; 2) tumor number ≤4 and diameter ≤5 cm. Participants were randomly assigned to receive atezolizumab plus bevacizumab or partake in active surveillance in a 1:1 ratio. At the time of analysis, 33% (110/334) of patients in the combination therapy arm experienced recurrence or mortality, in contrast to 40% (133/334) in the active surveillance group. The combined treatment of atezolizumab and bevacizumab significantly enhanced Recurrence-Free Survival (RFS) as evaluated by an independent review facility (IRF) compared to active surveillance, with median RFS not reached in either group and a 28% reduction in the risk of recurrence or death (HR = 0.72, P = 0.012).[138] A phase II clinical investigation demonstrated that adjuvant therapy combining tislelizumab with interferon (IFN) -α elevated the 1-year RFS rate among HCC patients with MVI.[139] The remarkable efficacy of adjuvant immunotherapy may be attributed to the necrosis of residual microsatellite lesions in the liver induced by immunotherapy after surgery.[140] Single-cell transcriptome sequencing unveiled heightened immune evasion traits of malignant tumor cells in early-stage recurrent HCC. Immune Checkpoint Inhibitors (ICIs) could alleviate immune suppression and enhance the tumor immune microenvironment, diminishing postoperative recurrence rate and improving patient survival.[140,141]

5.8 Neoadjuvant Therapies

The utilization of neoadjuvant therapy, especially neoadjuvant immunotherapy, presents various benefits when compared to adjuvant treatment. Neoadjuvant immunotherapy, for instance, can augment the systemic immune response against tumor antigens, thereby eradicating early micro-metastatic lesions that could act as sites for postoperative recurrence. Furthermore, immunotherapy in scenarios where the primary tumor is present can capitalize on the elevated levels of tumor antigens in the body to enhance antitumor immunity and immune memory function.[142,143]

Encouraging initial findings have been achieved by applying neoadjuvant treatment for HCC utilizing immunotherapy. Different treatment modalities explored thus far include immune monotherapy, immunotherapy in combination with targeted therapy, or local therapy. In a cohort of 15 patients with locally advanced HCC who underwent treatment with cabozantinib and nivolumab, 12 patients underwent R0 resection, and 5 exhibited a primary pathological response (MPR). This observed clinical benefit is believed to be linked to modifying the tumor immune microenvironment in response to neoadjuvant targets and immunotherapy.[144] The effectiveness of toripalimab, either alone or combined with lenvatinib as a neoadjuvant regimen, was validated in a Phase II trial. Of the 16 patients who underwent surgery, one displayed no visible lesions post-neoadjuvant therapy, and three achieved MPR.[145] A prospective, multicenter, randomized controlled study compared the safety and efficacy of perioperative treatment involving camrelizumab plus apatinib to direct surgical resection for resectable HCC at intermediate-high risk of recurrence. The neoadjuvant treatment group in the Phase II study exhibited an MPR rate of 46.2% (24/52), leading to the successful completion of participant recruitment for the Phase III randomized controlled study.[146] In a survey conducted by Marron *et al.*, 7 out of 20 patients treated with neoadjuvant cemiplimab monotherapy demonstrated >50% tumor necrosis, with three patients achieving complete tumor necrosis.[147] According to RECIST 1.1 criteria, three of the 20 patients displayed partial responses, while stable disease was maintained in the remaining patients. Neoadjuvant local treatments for HCC primarily encompass TACE, HAIC, and radiotherapy. Prior studies have indicated that TACE local therapy alone as a neoadjuvant approach for HCC did not yield significant enhancements in patients' 5-year DFS rate or 5-year OS rates.[148] A multicenter, prospective, randomized controlled clinical trial illustrated that HAIC as a neoadjuvant treatment strategy for patients with resectable BCLC stage A/B HCC beyond Milan criteria achieved an ORR of 63.6% and a disease control rate (DCR) of 96%. The neoadjuvant treatment group exhibited notably improved RFS and OS compared to the control group.[149] Combining neoadjuvant immunotherapy with local therapy has also proven successful in enhancing prognosis. Two earlier studies confirmed the efficacy of tislelizumab when combined with TACE or stereotactic body radiotherapy in the neoadjuvant treatment of HCC.[150,151]

CONCLUSION

The advancement in hepatocellular carcinoma (HCC) liver surgery is currently progressing towards a minimally invasive and precise procedure. Hepatectomy emerges as a pivotal intervention for HCC, yielding progressively superior outcomes owing to technological advancements and enhanced perioperative care. Prospective investigations will refine surgical techniques, optimize adjuvant therapies, and formulate robust predictive frameworks for diverse therapeutic modalities. This comprehensive assessment accentuates the significance of sustained innovation and interdisciplinary cooperation to elevate the standard of care for HCC patients. Moreover, continuous investigation into adjuvant and neoadjuvant treatments, such as immunotherapy and targeted therapies, is imperative for enhancing long-term prognoses. Artificial intelligence (AI) plays a crucial role in diagnosing, treating, and managing HCC. Continuous AI development is expected to enable enhanced visualization techniques and surgical strategies, benefiting both surgical oncologists and patients by improving anatomical recognition and expediting surgical processes. Despite its numerous advantages, AI also presents certain limitations. For example, AI algorithms depend on extensive datasets for training, and insufficient or unreliable data can compromise the accuracy of the AI system. Therefore, obtaining a substantial amount of high-quality, unbiased data is imperative for the future advancement of AI in the medical field. The emergence and progression of new technologies like Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) have revolutionized the surgical treatment of liver cancer, particularly for HCC patients with inadequate Future Liver Remnant (FLR), significantly enhancing their survival chances. Systemic therapy, combined with local treatments, has demonstrated distinct advantages in managing HCC surgical treatment. By exploring novel clinical trials and updating perioperative treatment approaches, the treatment landscape of HCC may undergo a significant transformation in the future, especially within surgical management. The application of perioperative treatment in suitable HCC patient populations remains a pressing concern that requires attention. Therefore, identifying effective and user-friendly efficacy prediction biomarkers or radionics features is essential to facilitate personalized and precise perioperative therapy for HCC.

While surgical resection continues to be a vital treatment option for HCC patients, incorporating neoadjuvant and adjuvant treatment strategies has been considered to expand the pool of eligible surgical candidates and enhance long-term outcomes. The IMbrave 050 trial has addressed this critical unmet need and showcased the advantages of increased recurrence-free survival in patients who underwent atezolizumab combined with bevacizumab adjuvant therapy and were at high risk of recurrence post-resection or local ablation. Concurrently, investigations evaluating neoadjuvant Immune Checkpoint Inhibitors (ICIs) alone or in conjunction with resectable HCC patients have also demonstrated positive therapeutic outcomes. With the remarkable advancements in local and systemic therapies, including the progress in immunotherapy, future research will be essential to determine the optimal components for multimodal therapy. Notably, neoadjuvant and adjuvant therapy will significantly modify the role of surgical benefits in the treatment of HCC.

In conclusion, the collective progress in areas such as AI, extensive data analysis, technological innovations, treatment paradigms, and clinical trials in recent years should effectively steer the clinical approach to HCC surgery, ultimately leading to outstanding disease-free survival outcomes for patients with HCC. Moreover, continuous investigation into adjuvant and neoadjuvant treatments, such as immunotherapy and targeted therapies, is imperative for enhancing long-term prognoses.

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