# Scientific Hepatectomy for Hepatocellular Carcinoma*

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**[Abstract]** With advances in imaging technology and surgical instruments, hepatectomy can be perfectly performed with technical precision for hepatocellular carcinoma (HCC). However, the 5-year tumor recurrence rates remain greater than 70%. Thus, the strategy for hepatectomy needs to be reappraised based on insights of scientific advances. Scientific evidence has suggested that the main causes of recurrence after hepatectomy for HCC are mainly related to underlying cirrhosis and the vascular spread of tumor cells that basically cannot be eradicated by hepatectomy. Liver transplantation and systemic therapy could be the solution to prevent postoperative recurrence in this regard. Therefore, determining the severity of liver cirrhosis for choosing the appropriate surgical modality, such as liver transplantation or hepatectomy, for HCC and integrating newly emerging immune-related adjuvant and/or neoadjuvant therapy into the strategy of hepatectomy for HCC have become new aspects of exploration to optimize the strategy of hepatectomy. In this new area, hepatectomy for HCC has evolved from a pure technical concept emphasizing anatomic resection into a scientific concept embracing technical considerations and scientific advances in underlying liver cirrhosis, vascular invasion, and systemic therapy. By introducing the concept of scientific hepatectomy, the indications, timing, and surgical techniques of hepatectomy will be further scientifically optimized for individual patients, and recurrence rates will be decreased and long-term survival will be further prolonged.
**Key words:** hepatocellular carcinoma; scientific hepatectomy; liver cirrhosis; vascular invasion; immunotherapy

Hepatocellular carcinoma (HCC) is one of the most common malignancies and ranks as the fourth leading cause of cancer-related death in the world[1]. Curative treatment for HCC includes hepatectomy, liver transplantation, and local ablation. Since liver transplantation can eliminate both tumors and the cirrhotic liver, it has been considered the best option for patients with both cirrhosis and early-stage HCC. However, liver transplantation is unlikely to be recommended for all HCC patients due to late stages of disease, high costs, and lack of donors. Ablation is largely limited by both the tumor size and location[2]. Therefore, hepatectomy remains the mainstay of curative treatment for HCC. However, there is a long-lasting debate on hepatectomy approaches between anatomic resection (AR) and nonanatomic resection (NAR) or parenchyma-preserving hepatectomy. Because most HCC patients have varying degrees of cirrhosis, NAR or parenchyma-preserving hepatectomy is commonly performed in cirrhotic patients to ensure the safety of hepatectomy. However, NAR or parenchyma-preserving hepatectomy has not been officially recognized as a standard procedure for HCC because no official nomenclature for this procedure has been available. As a scientific definition of the severity of cirrhosis is lacking in current surgical practice, the choice of hepatectomy approaches, either AR or parenchyma-preserving hepatectomy, is made solely based on the surgeon's personal judgment of the severity of cirrhosis, which inevitably causes much puzzlement and misunderstanding regarding surgical outcomes resulting from the different cirrhotic backgrounds and hepatectomy approaches. Therefore, scientifically staging the cirrhotic severity in the liver could help to clarify the confusion regarding when AR or parenchyma-preserving hepatectomy is indicated.

Significant improvements from technical perspectives have been witnessed in recent years; however,

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long-term survival after hepatectomy has still not been significantly improved, with 5-year recurrence rates greater than 70%[3–5]. Scientific studies have suggested that HCC recurrence after hepatectomy is correlated with two leading causes: multicentric occurrence (MO) and intrahepatic metastasis (IM). MO is primarily associated with chronic hepatitis B or C virus-related cirrhosis, whereas IM is associated with tumor cell spread through vascular invasion (fig. 1)[6–8]. Evidently, neither MO nor IM can be cured by any technically precise hepatectomy because the systemic nature of MO and IM needs to be addressed with systemic approaches.

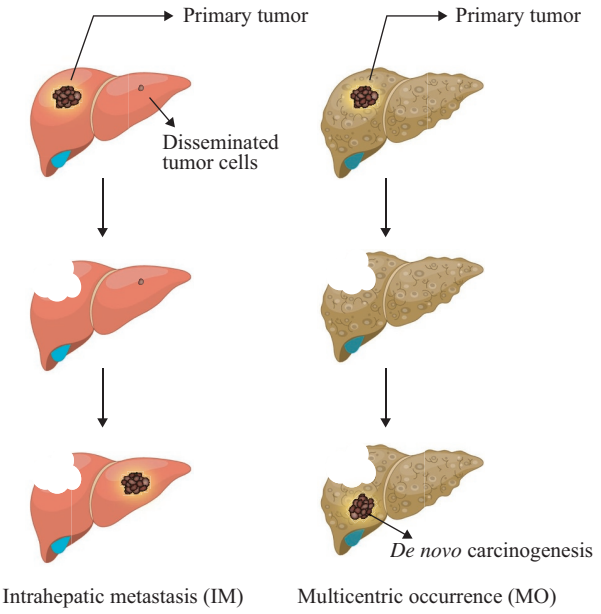


**Fig. 1** Two leading causes of tumor recurrence after curative hepatectomy for HCC patients
After curative hepatectomy of primary tumors, there are two leading causes of intrahepatic recurrence of HCC. Intrahepatic metastasis (IM) is the development of HCC foci from tumor cells that have spread into the remnant liver via vascular invasion before curative hepatectomy. Multicentric occurrence (MO) is the development of new HCC foci in the residual liver due to liver cirrhosis

Currently, immunotherapeutic approaches to treat HCC have made significant progress. The combination of anti-programmed death receptor 1 (PD-1) immunotherapy with tyrosine kinase inhibitors (TKIs) has achieved unprecedented clinical outcomes in the treatment of some advanced HCCs[9]. Some initial unresectable HCCs were converted into resectable HCCs with combined immunotherapy and, in rare cases, even resulted in cure[10, 11]. Mounting evidence has indicated that immunotherapy combined with systemic therapy has played a more effective role in prolonging the survival of patients with unresectable HCC. Therefore, it is time to reappraise the hepatectomy strategy from scientific perspectives regarding the indications, timing, and technical approaches of hepatectomy. We believe that the hepatectomy strategy for HCC has evolved from a purely technical concept emphasizing AR into a scientifically oriented strategy.

## 1 THE SEVERITY OF CIRRHOSIS NEEDS TO BE SCIENTIFICALLY STAGED FOR HEPATECTOMY

### 1.1 Cirrhotic Severity Determines the Safety of Hepatectomy

Cirrhosis is histologically defined as a diffuse state in which the normal lobular architecture is replaced by abnormal nodules and fibrous septa[12]. The architectural distortion results in increased resistance to portal blood flow and leads to portal hypertension. Cirrhosis can be functionally staged as compensated or decompensated[13, 14]. This staging is purely based on clinical symptoms and liver function but does not represent the severity of histological changes. In current surgical practice, surgeons mainly focus on the evaluation of liver functional reserve and the volume of the remnant liver; cirrhosis is only evaluated as “present”’ or “absent” or as to whether it is associated with portal hypertension. Histological staging of the severity of cirrhosis has never come to attention. In patients with Child-Pugh grade A liver function or the indocyanine green retention rate at 15 min in the normal range, the severity of cirrhosis can vary greatly in individuals[15, 16]. Extensive replacement of hepatic lobules by pseudolobules as well as increased fibrosis in the cirrhotic liver will significantly decrease the functional units of the liver and cause an increased risk of posthepatectomy liver failure (PHLF). Our previous study demonstrated that the incidence of PHLF was 38.1% in HCC patients with Child-Pugh grade A liver function and moderate cirrhosis undergoing hepatectomy of three or more liver segments and 63.2% in those with severe cirrhosis undergoing hepatectomy of two or more liver segments[17]. Therefore, preoperative evaluation of the histological severity of cirrhosis is vital for the safety of hepatectomy. Previous studies have indicated that the histological severity of cirrhosis is correlated with the grade of portal hypertension determined by hepatic venous pressure gradient (HVPG) measurement[18]. An HVPG of 10 mmHg or more has been demonstrated to be predictive of postoperative liver dysfunction or poor long-term survival[19]. However, preoperative HVPG measurement has not been commonly adopted for determining surgical strategies because of its invasive nature. The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases guidelines do not recommend hepatectomy for HCC patients with portal hypertension[20]. Meanwhile, several studies

have shown that hepatectomy for HCC patients with portal hypertension is associated with high incidences of PHLF and poor surgical outcomes[19, 21, 22]. In contrast, some studies have suggested that portal hypertension is not regarded as an absolute contraindication to hepatectomy[23–25]. This discrepancy is partially attributed to the ignorance of cirrhotic severity itself. Histological alterations in cirrhosis can result in decreased hepatic lobule function and increased transhepatic perfusion resistance leading to portal hypertension. However, the symptoms of portal hypertension can be significantly affected by the collateral portacaval shunting status in different individuals. Therefore, the symptoms of portal hypertension do not exactly reflect the severity of cirrhosis. Our previous study demonstrated that the histological severity of cirrhosis is a key factor affecting the surgical outcomes of patients with both HCC and portal hypertension, suggesting that the histological severity of cirrhosis is an independent factor influencing surgical outcomes[26]. Our team previously proposed noninvasive cirrhotic severity scoring[27] and direct liver stiffness measurement[16] to evaluate the histological severity of cirrhosis in HCC patients. A multicenter prospective study was carried out, and their effectiveness was validated for staging cirrhotic severity (unpublished data). It is hoped that a clinical staging system for the severity of cirrhosis can be established to improve the safety of hepatectomy.

**1.2 Cirrhotic Severity Affects the Long-term Outcomes of Hepatectomy**

Cirrhosis is regarded as the last stage of fibrosis[28–30], but the severity of cirrhosis varies significantly in different individuals. The Laennec staging system, a modification of the METAVIR system, was first proposed in 2000 for staging the histological severity of cirrhosis[31]. According to the Laennec staging system, cirrhosis is graded into 4A, 4B, and 4C stages, representing mild, moderate, and severe cirrhosis, respectively. This system has been employed to evaluate the progression of fibrosis or cirrhosis over the course of antiviral treatment for hepatitis by analyzing biopsy samples[32]. Nevertheless, evaluation of abnormal nodules and fibrous septa from tiny thin liver samples obtained by biopsy is unreliable. Digital image analysis, which can quantitatively assess fibrosis and calculate the proportion of collagen in the liver, is a newly developed method of objectively calculating the collagen proportionate area (CPA)[33]. Our previous study demonstrated that in HCC patients with Child-Pugh grade A liver function, the CPA values of their liver specimens obtained by liver resection were significantly varied and ranged from 1.6% to 42.8%, which suggests that there are great variations in the histological severity of cirrhosis, but their liver function exhibits no difference[34].

The development of HCC is closely correlated with underlying liver diseases (such as hepatitis B or C virus-related liver cirrhosis), especially in Asia. The annual incidence of HCC arising from established liver cirrhosis has been reported to range between 2.5% and 6.6%[35–37]. Kim *et al*[38] have reported that the cumulative incidence rates of HCC significantly increase with the increment of cirrhotic severity histologically staged by the Laennec staging system. The 3-year cumulative incidence rates of HCC in patients with no, mild, moderate, or severe cirrhosis were 4.3%, 6.3%, 17.1%, and 16.1%, respectively. Using transient elastography, Jung *et al*[39] found that when patients were stratified into 5 groups based on the liver stiffness measured by FibroScan (≤8 kPa, 8.1–13 kPa, 13.1–18 kPa, 18.1–23 kPa, and >23 kPa), the 3-year cumulative incidence rates of HCC were 1.58%, 6.58%, 8.77%, 19.07%, and 24.76%, respectively.

In recent years, mounting evidence has revealed that cirrhosis is a significant factor in decreasing the long-term survival of patients after hepatectomy[40–42]. However, these studies simply regarded cirrhosis as a one-stage condition and ignored the differences in the severity of cirrhosis. In 2011, our team demonstrated for the first time that cirrhotic severity significantly influenced the long-term outcomes of hepatectomy in patients with HCC. The 3-year overall survival rates of HCC patients with mild, moderate, and severe cirrhosis after hepatectomy were 74.3%, 48.1%, and 26.7%, respectively; in addition, the overall survival rates were significantly worse in patients with severe cirrhosis than in those with mild cirrhosis[43]. Subsequently, Kim *et al*[44] reported that the histological severity of cirrhosis is adversely associated with the prognosis of HCC patients after hepatectomy. The 3-year cumulative recurrence rates in patients with no, mild, moderate, or severe cirrhosis were 21.8%, 42.9%, 68.5%, and 86.7%, respectively. Our recent study, which included a large sample size and a long follow-up period, further demonstrated that the histological severity of cirrhosis significantly affects surgical outcomes in HCC patients undergoing curative hepatectomy. The 5-year recurrence-free survival and overall survival rates of HCC patients with no, mild, moderate, or severe cirrhosis after hepatectomy were 36.8% and 64.5%, 34.8% and 60.4%, 17.3% and 43.4%, and 6.1% and 20.1%, respectively[45]. Studies that assessed the prognostic significance of cirrhosis status for long-term outcomes after hepatectomy are summarized in table 1.

According to the Barcelona Clinic Liver Cancer staging system, liver transplantation or hepatectomy is recommended as the first-line treatment for patients with early-stage HCC[46]. However, contradictory outcomes between liver transplantation and hepatectomy have been reported. Adam *et al*[47] reported that for a single

**Table 1 Long-term outcomes of hepatectomy in recent studies with comparative analysis of the cirrhosis status**

| Author | Cirrhosis status | *n* | Overall survival, % | | | *P*-value |
|---|---|---|---|---|---|---|
| | | | 1-year | 3-year | 5-year | |
| Taura *et al*[92] | No cirrhosis | 127 | – | – | 81 | <0.001 |
| | Child-Pugh class A cirrhosis | 129 | – | – | 54 | |
| | Child-Pugh class B cirrhosis | 37 | – | – | 28 | |
| Huang *et al*[43] | Mild cirrhosis | 29 | 85.7 | 74.3 | – | 0.001 |
| | Moderate cirrhosis | 29 | 81.5 | 48.1 | – | |
| | Severe cirrhosis | 19 | 60.0 | 26.7 | – | |
| Wang *et al*[93] | Fibrosis (Ishak stage 1–5) | 135 | – | – | 73 | 0.01 |
| | Cirrhosis (Ishak stage 6) | 54 | – | – | 50 | |
| Kim *et al*[44] | No/moderate cirrhosis | 82 | 95.1 | 91.4 | – | 0.007 |
| | Severe cirrhosis | 10 | 80 | 70 | – | |
| Sasaki *et al*[94] | Normal liver | 64 | – | 85.7 | 75.4 | 0.04 |
| | Liver cirrhosis | 64 | – | 74.9 | 59.1 | |
| Lee *et al*[95] | Without cirrhosis | 387 | 96.1 | 89.9 | 86.6 | <0.001 |
| | With cirrhosis | 262 | 94.5 | 86.9 | 78.5 | |
| Dong *et al*[26] | Mild-moderate cirrhosis (with portal hypertension) | 272 | 81.2 | 53.1 | 39.9 | <0.001 |
| | Severe cirrhosis (with portal hypertension) | 102 | 57.8 | 34.5 | 16.9 | |
| Zhang *et al*[96] | No/mild cirrhosis (without portal hypertension) | 68 | 98.5 | 88.1 | 80.0 | 0.001 |
| | Moderate/severe cirrhosis (without portal hypertension) | 98 | 98.0 | 69.2 | 54.7 | |
| Liang *et al*[45] | No cirrhosis | 220 | 86.0 | 70.5 | 64.5 | <0.001 |
| | Mild cirrhosis | 575 | 84.9 | 70.1 | 60.4 | |
| | Moderate cirrhosis | 597 | 79.1 | 56.7 | 43.4 | |
| | Severe cirrhosis | 132 | 59.9 | 37.9 | 20.1 | |

HCC measuring 5 cm or smaller in a cirrhotic liver, the 5-year overall survival and recurrence-free survival rates after liver transplantation were better than those after hepatectomy (75% and 72% *vs*. 52% and 20%, $P<0.05$). However, Krenzien *et al*[48] reported that the outcomes in HCC patients with cirrhosis undergoing hepatectomy in recent years have improved due to advances in liver surgery. The overall survival was comparable between liver transplantation and hepatectomy for HCC within the Milan criteria in the more recent period of 2005–2011 (5-year overall survival rates: 73% *vs*. 61%, $P=0.07$). Furthermore, Koniaris *et al*[49] compared the long-term outcomes of HCC patients treated with either hepatectomy or liver transplantation using the intent-to-treat analysis and found that the 5-year overall survival rates were not significantly different between hepatectomy and liver transplantation for HCC patients who fulfilled the liver transplantation criteria (53.0% *vs*. 52.0%, $P>0.05$); but for patients with model end-stage liver disease scores less than 10, the 5-year overall survival rates were better after hepatectomy than after liver transplantation. These conflicting results might result from the lack of knowledge of the histological severity of cirrhosis in these studies. In 2015, our team retrospectively analyzed and compared the long-term outcomes of HCC patients with a solitary tumor measuring ≤5 cm after either hepatectomy or liver transplantation[50]. The patients with Child-Pugh grade A liver function who underwent hepatectomy were stratified by the histological severity of cirrhosis according to the Laennec staging system. The results demonstrated that for patients with no or mild cirrhosis, the 5-year recurrence-free survival and disease-specific survival rates did not differ significantly between hepatectomy and liver transplantation. However, patients with moderate or severe cirrhosis after hepatectomy had worse 5-year recurrence-free survival and disease-specific survival rates than those after liver transplantation. Our data demonstrated that the severity of cirrhosis significantly affects the long-term survival of patients who underwent hepatectomy; and for patients with severe cirrhosis, liver transplantation would be a better choice, although hepatectomy is also feasible.

Cirrhotic severity plays a key role when evaluating both the safety and long-term outcomes of HCC patients who underwent hepatectomy. Scientifically staging the severity of cirrhosis in different individuals is of paramount importance for individualizing surgical strategies for HCC patients.

## 2 VASCULAR INVASION NEEDS TO BE SCIENTIFICALLY RECOGNIZED FOR HEPATECTOMY

### 2.1 Systemic Nature of Vascular Invasion

A hallmark of HCC is angiogenesis, which means

that the tumor can induce new vessel formation for growth[51]. Vascular invasion is a typical feature of HCC, and it usually involves either the portal vein or hepatic vein branches, leading to intrahepatic recurrence or distant metastases[52, 53]. Vascular invasion is believed to represent the systemic nature of HCC, and surgical approaches such as hepatectomy or liver transplantation have very limited efficacy, even in patients with microvascular invasion (MVI). MVI is defined as tumor cells invading a portal vein, hepatic vein, or a large capsular vessel of the surrounding hepatic tissues visible only by microscopy[54]. Previous studies have indicated that the incidence of MVI in HCC patients ranges from 15% to 74.4%[55–57]. A meta-analysis analyzing 1501 HCC patients who underwent hepatectomy revealed that MVI significantly decreased the 3- and 5-year disease-free survival rates[56]. Moreover, Wang and colleagues have reported that HCC patients with TNM stage Ⅱ disease and MVI had similar prognosis compared with those with TNM stage Ⅲ disease and without MVI, demonstrating that MVI is a more significant factor influencing tumor recurrence and long-term survival[58]. Several subsequent studies also revealed that HCC patients with MVI, even those with solitary tumors measuring ≤2 cm, had lower recurrence-free survival and overall survival rates[59, 60]. In addition, extensive hepatectomy was unable to solve the problem caused by vascular invasion. Poon *et al*[61] demonstrated that more than 70% of HCC patients with cirrhosis experienced tumor recurrence after hepatectomy, but there was no significant difference between the wide-margin group and the narrow-margin group. Most of the recurrent tumors occurred in a distal segment or multiple segments associated with vascular spread. Furthermore, Moon's study indicated that the 5-year overall survival rate of patients with MVI who received a liver transplantation was only 49%, compared to 100% for patients without MVI[62]. These studies suggest that hepatectomy, even extensive hepatectomy or liver transplantation, has a limited capacity to eradicate the tumor recurrence caused by vascular invasion due to its systemic nature.

**2.2 AR Is Not a Solution for Vascular Invasion**

Over the past few decades, there has been debate about the superiority of AR compared to NAR for providing a better surgical prognosis. Since the functional anatomy of the liver was first successfully described, AR has been regarded as the best approach for hepatectomy. The Brisbane nomenclature of hepatectomy based on Couinaud's segmental anatomy was proposed in 2000 and then adopted by the International Hepato-Pancreato-Biliary Association[63]. As HCC is commonly accompanied by underlying liver cirrhosis, hepatectomy usually must be performed in a parenchyma-preserving manner to prevent PHLF. However, the current Brisbane nomenclature system does not address the nomenclature issues when parenchyma-preserving hepatectomy is performed, and a large amount of inaccurate documentation for hepatectomy has inevitably led to conflicting results in clinical studies. Some authors have suggested that the nomenclature of parenchyma-preserving hepatectomy should be proposed to address this issue[64]. To preserve the liver parenchyma and ensure safety in cirrhotic patients, Makuuchi *et al*[65] proposed anatomic subsegmentectomy of a combination of contiguous territories of the "3rd-order" subsegmental portal venous branches smaller than one Couinaud's segment. NAR is defined as the removal of the tumor with an adequate margin, irrespective of the segments. Some studies have indicated that AR yields better long-term outcomes than NAR after hepatectomy[66–68]. Two recent meta-analyses revealed that AR seemed to offer better surgical outcomes than NAR in HCC patients who underwent hepatectomy, especially for those without cirrhosis and small solitary tumors[69, 70]. However, other studies showed different results. In 2008, a Japanese nationwide survey revealed that no significant difference was observed in the overall survival after hepatectomy for solitary HCC between the AR and NAR groups, although the recurrence rates in the AR group were significantly lower in HCC patients with a tumor diameter of 2–5 cm than in those in the NAR group[71]. A recent study from the University of Tokyo indicated that the AR group showed better disease-free survival than the NAR group, whereas no significant difference was observed in the overall survival. It should be noted that patients who underwent NAR commonly had a higher incidence of severe cirrhosis than those who underwent AR in this study[72]. Whether some tumors were de-novo lesions caused by underlying cirrhosis in the NAR group that erected a false benefit of AR over NAR in disease-free survival remains unknown. Furthermore, a double-blinded prospective randomized trial was conducted by Feng *et al*[73], revealing that the long-term survival outcomes were not significantly different between the AR and NAR groups. In addition, the effects and benefits of AR for HCC with MVI remain controversial. Some studies indicated that AR significantly decreased tumor recurrence after hepatectomy, whereas the overall survival rates were similar between the two groups[74, 75]. Furthermore, other studies failed to demonstrate these benefits when performing AR. A multi-institutional study from Japan assessed the value of AR for HCC with MVI, and the results of a propensity score-matched analysis revealed no significant differences in the long-term outcomes between the AR and NAR groups[76]. Dahiya *et al*[77] demonstrated that the tumor biological characteristics and the severity of cirrhosis were important factors affecting the prognosis of HCC patients after hepatectomy, rather than the type of

resection. A summary of recent studies comparing both the recurrence and survival according to the surgical type (AR or NAR) for HCC patients with MVI is displayed in table 2.

Collectively, for HCC patients with vascular invasion, surgical approaches have limited efficacy because of the systemic nature of vascular invasion. From a technical perspective, AR is an ideal approach for HCC in patients without cirrhosis or with mild cirrhosis, but it is not suitable for those with severe cirrhosis. Therefore, scientifically staging cirrhosis is vital for standardizing a surgical decision for either AR or parenchyma-preserving hepatectomy. Accumulating evidence indicates that AR is not superior to NAR in achieving long-term survival, and surgeons should avoid pursuing AR for better surgical outcomes. In severely cirrhotic patients, parenchyma-preserving hepatectomy should also be considered as a reasonable choice.

## 3 ADVANCES IN SYSTEMIC THERAPY URGE A SCIENTIFIC REAPPRAISAL OF HEPATECTOMY

### 3.1 New Conversion Therapy Is Altering the Indications and Timing of Hepatectomy

For a long time, hepatectomy has only been indicated for a small proportion of patients who are diagnosed with early-stage HCC. For the majority of HCC patients with large HCCs, locally advanced disease, or metastatic disease, how to convert unresectable HCC into resectable HCC has been a longstanding quest for decades. Transarterial chemoembolization might convert unresectable tumors to resectable tumors in only 7%–18% of patients[78, 79]. The rapid development of immunotherapy and molecular targeted therapy has made profound advances in the conversion strategy for HCC. For example, clinical data for systemic therapy in the first-line setting for unresectable HCC show that lenvatinib has a higher objective response rate (ORR) than sorafenib[80, 81]. When molecular targeted therapy is combined with immunotherapy, such as lenvatinib combined with pembrolizumab, bevacizumab combined with atezolizumab, bevacizumab analogs combined with sintilimab, or apatinib combined with camrelizumab, ORRs greater than 20% are observed in the treatment of unresectable HCC[81–83]. In addition, Zhang *et al*[84] reported 35 patients with stage IIIa HCC treated with PD-1 inhibitors combined with TKIs, and the conversion rate was 42.4%. Clinical data for systemic therapy combining targeted and immunotherapy in patients with advanced HCC are summarized in table 3. We believe that the scientific advances in systemic therapy for HCC are profoundly affecting the indications and timing of hepatectomy for HCC.

**Table 2 Comparative studies of survival following anatomic resection *vs*. nonanatomic resection in hepatocellular carcinoma patients with microvascular invasion**

| Author | Resection type | *n* | 5-year DFS (%) | *P*-value | 5-year OS (%) | *P*-value |
|---|---|---|---|---|---|---|
| Yamashita *et al*[97] | AR | 13 | 47 | 0.92 | 88 | 0.84 |
| | NAR | 30 | 23 | | 65 | |
| Matsumoto *et al*[98] | AR | 74 | 33.8 | 0.001 | 46.1 | 0.002 |
| | NAR | 23 | 0 | | 16.3 | |
| Zhao *et al*[74] | AR | 45 | 39 | 0.016 | 52 | 0.277 |
| | NAR | 47 | 20 | | 42 | |
| Zhong *et al*[75] | AR | 100 | 42 | 0.039 | 51.5 | 0.301 |
| | NAR | 170 | 26.4 | | 42.4 | |
| Hidaka *et al*[76] | AR | 86 | 37 | ns | 64.5 | ns |
| | NAR | 86 | 42.2 | | 65.3 | |

AR: anatomic resection; NAR: nonanatomic resection; DFS: disease-free survival; OS: overall survival; ns: not significant

**Table 3 Clinical trials of targeted therapy combined with immunotherapy in patients with advanced hepatocellular carcinoma**

| Therapeutic drug | Study name/design | *n* | ORR, % | OS, months | PFS, months | Recommended as |
|---|---|---|---|---|---|---|
| Lenvatinib+Nivolumab | Phase Ib, single arm | 30 | 54.2 | – | 7.39 | First line |
| Lenvatinib+Pembrolizumab | Phase Ib, single arm | 100 | 36 | 22.0 | 8.6 | First line |
| Apatinib+Camrelizumab | Phase Ⅱ, single arm | 70 | 34 | 20.3 | 5.7 | First line |
| Regorafenib+Pembrolizumab | Phase Ib, single arm | 35 | 29 | – | – | First line |
| Cabozantinib+Nivolumab | CheckMate 040: phase Ⅰ/Ⅱ, nonrandomized | 36 | 19 | 21.5 | 5.4 | First line/ Second line |
| Anlotinib+Penpulimab | Phase Ib/Ⅱ, single arm | 31 | 24 | NE | – | First line |
| Bevacizumab+Sintilimab | ORIENT-32: phase Ⅱ/Ⅲ, randomized | 380 | 21 | NR | 4.6 | First line |
| Bevacizumab+Toripalimab | CT34: phase Ⅱ, multi-center, single arm | 54 | 31.5 | NR | 9.9 | First line |
| Bevacizumab+Atezolizumab | IMbrave150: phase Ⅲ, randomized | 336 | 30 | 19.2 | 6.9 | First line |

ORR: objective response rate; OS: overall survival; PFS: progression-free survival

### 3.2 Adjuvant Therapy Tends to Favor Parenchyma-preserving Hepatectomy

Advances in systemic therapy with TKIs and immune checkpoint inhibitors should also bring promising opportunities in the prevention of postoperative recurrence. Huang and colleagues revealed that sorafenib significantly reduced recurrence and prolonged survival rates in HCC patients with MVI after curative hepatectomy[85]. However, a randomized controlled trial (STORM trial) failed to support the notion that sorafenib could serve as an adjuvant drug for HCC patients after curative hepatectomy[86]. The CheckMate-9DX study is currently investigating whether nivolumab, compared with placebo, will decrease recurrence in HCC patients with a high risk of recurrence after hepatic resection or ablation. Furthermore, the Imbrave 050 trial is ongoing to compare atezolizumab plus bevacizumab with active surveillance in HCC patients at a high risk of recurrence after curative treatment.

In this new era, when systemic therapy has become the main approach for HCC, the liver parenchyma-preserving approach is significantly important for patients sustaining adjuvant therapy when undergoing hepatectomy for HCC. As adjuvant therapy is usually associated with severe side effects, it requires sufficient liver function support, especially in cirrhotic patients whose capacity for liver regeneration is largely decreased. However, the liver is uniquely characterized by its ability to regenerate itself in response to injury. After hepatectomy, liver regeneration is initiated by the proliferation of all of the existing mature cellular populations composing the intact organ, and it involves numerous and sequential changes in gene expression[87,88]. However, experimental models have shown that the regenerative capacity of the liver is inhibited by the presence of cirrhosis[89]. The results from human studies also have revealed that cirrhotic livers have an inferior regenerative capacity. For example, Nagasue and colleagues found that the regenerative capacity of livers with cirrhosis or hepatitis was substantially less than that of normal liver[90]. Yamanaka *et al*[91] also reported that cirrhotic livers generally show poor restoration of the liver volume and liver function. Therefore, preserving the liver parenchyma is important for HCC patients with cirrhosis, especially for severely cirrhotic patients with a limited regenerative capacity.

## 4 CONCLUSION

Technically precise hepatectomy for HCC, such as AR, has been advocated for years; however, posthepatectomy recurrence rates remain high. Scientific evidence suggests that the main causes of recurrence are related to underlying cirrhosis and vascular spread of tumor cells. The strategy of hepatectomy needs to be reappraised based on this scientific evidence. The histological severity of cirrhosis significantly affects the safety and long-term outcomes of hepatectomy and needs to be scientifically staged to individualize surgical approaches for HCC patients. Vascular invasion represents the systemic signature of HCC, and it cannot be eradicated by hepatectomy. However, new advances in systemic therapy have brought significant opportunities for further optimizing hepatectomy strategies for HCC. In this new era, hepatectomy for HCC has evolved from a technical concept emphasizing AR into a scientifically oriented strategy that considers all scientific advances affecting hepatectomy strategies, such as underlying liver cirrhosis, vascular invasion, systemic therapy, and liver parenchyma-preserving techniques, for the best clinical outcomes. By introducing the concept of scientific hepatectomy (fig. 2), the indications, timing, and surgical techniques of hepatectomy will be further optimized for individual patients, and the long-term survival of HCC patients will be further improved.

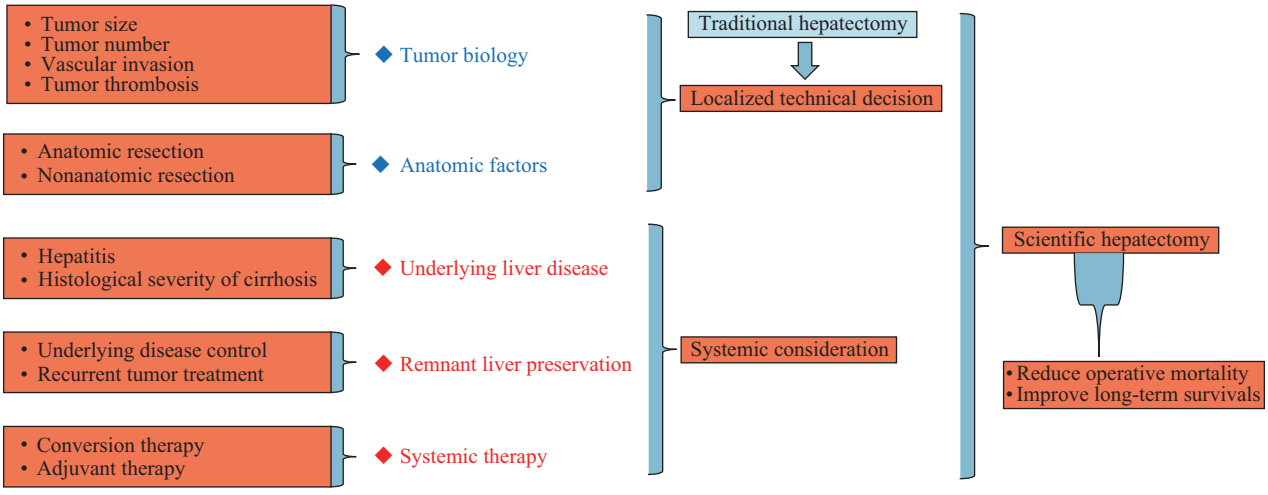


**Fig. 2** Schematic diagram of scientific hepatectomy

**Conflict of Interest Statement**

The authors declare that they have no conflicts of interest.

Author Xiao-ping CHEN is a member of the Editorial Board for Current Medical Science. The paper was handled by other editors and has undergone rigorous peer review process. Author Xiao-ping CHEN was not involved in the journal's review of, or decisions related to, this manuscript.

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