

# Changes in and challenges regarding the surgical treatment of hepatocellular carcinoma in China

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**SUMMARY** Hepatocellular carcinoma (HCC) is a common malignant tumor with a high morbidity and mortality in China and elsewhere in the world. Due to its tumor heterogeneity and distant metastasis, patients with HCC often have a poor prognosis. A surgical treatment such as a radical hepatectomy is still the treatment of choice for patients with HCC in current clinical practice. However, the high rate of recurrence and rate of metastasis after surgery diminishes the survival of and prognosis for these patients. In an era of targeted therapy and immunotherapy, the surgical treatment of HCC must change. This review focuses on the definition, feasibility, and criteria with which to evaluate neoadjuvant therapy for HCC in order to provide a new perspective on surgical treatment of HCC.

**Keywords** hepatocellular carcinoma, surgical treatment, neoadjuvant therapy

## 1. Introduction

China has the most patients with hepatocellular carcinoma (HCC), and it accounts for nearly half of the world's patients with HCC (1). HCC is the second most prevalent malignancy in China, and 300,000 to 400,000 Chinese die from it every year (2). A survey of the current status of HCC treatment in China indicated that most patients with HCC have cancer in an intermediate or advanced stage when diagnosed, precluding the chance for surgery (3). Although the 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" has expanded the indications for surgical resection from stage Ia to stage IIIa according to Chinese Liver Cancer staging (CNLC) (4), the postoperative rate of recurrence has increased, and the effectiveness of treatment still needs to be improved.

Over the past few years, targeted therapies and immunotherapies for HCC have continued to emerge, offering hope for the non-surgical treatment of HCC. This review describes the history of the development of HCC surgery, the use of neoadjuvant therapy, and surgical treatment of advanced HCC in order to provide some insight to devise strategies for surgical treatment of HCC and to update guidelines.

## 2. Overview of the development of HCC surgery in China

Before the 1950s, hepatectomies were seldom reported

in China. Since the 1950s, Chinese surgeons have gradually performed regular extensive liver resection after bile duct exploration (5). However, the patients who underwent surgery at that time all had advanced HCC, the surgical procedure was complicated and time-consuming, and the postoperative mortality rate was as high as 30% (6). As surgical techniques continued to improve after the early 1960s, procedures such as a hepatectomy, a hemihepatectomy, and a regular hepatectomy began to be widely performed. In the 1970s, local resection of small HCC was proposed as a treatment model, and alpha-fetoprotein was measured. At the same time, the concept of "subclinical HCC" appeared, gradually leading to clinical orthotopic liver transplantation. After the 1980s, a regular hepatectomy was mainly performed, and surgical restrictions on the liver were lifted (6). In the 1990s, resection of giant HCC and laparoscopic liver resection were developed, and PVTT and bile duct tumor thrombus removal have been successful (7). The first living donor liver transplantation in China was completed (8). As modern liver surgery has rapidly developed since the beginning of the 21st century, many difficult liver surgeries can be completed laparoscopically or with robot assistance. New assistive technologies for liver surgery also continue to emerge, such as preoperative assessment of liver reserve function, preoperative three-dimensional imaging, intraoperative ultrasound, indocyanine green fluorescence imaging, laparoscopy and robotics, combined liver segmentation, and staged liver resection with portal vein ligation; these

technologies have improved the efficiency and accuracy of surgery (9). As surgical procedures and preoperative assistive technologies have continued to improve, the mortality rate for liver resection has dropped to less than 1% (6). However, the high rate of recurrence of HCC still limits the prospects of surgical treatment of HCC.

### 3. The concepts of down-staging therapy, conversion therapy, and neoadjuvant therapy

Down-staging therapy refers to converting a tumor in a later stage that was originally inoperable into one that is operable and in an earlier stage through systemic or local treatment. Conversion therapy refers to converting a tumor that was originally inoperable into one that can be resected using systemic or local treatment. However, conversion therapy is not the same as down-staging therapy. As an example, a tumor thrombus in the portal vein or superior mesenteric vein falls under BCLC stage C, which is not suitable for surgical resection. Conversion therapy is used to limit the tumor thrombus to the portal vein so that surgery can be performed. The tumor thrombus still falls under BCLC stage C and has not been down-staged, but it has been converted for resection. Therefore, conversion therapy can be regarded as a form of down-staging therapy. Neoadjuvant therapy refers to a tumor that can be surgically resected but it may have a high risk of recurring postoperatively. Therefore, local or systemic treatment is used for a period of time before surgery.

### 4. The focus of the use of neoadjuvant therapy in HCC

At present, research on neoadjuvant therapy for HCC has just started. Data from a clinical trial database indicate that as of October 2020, there are only 24 promising projects related to neoadjuvant therapy for HCC around the world. Only 15 of those projects are related to targeted immunotherapy, and neoadjuvant therapy for HCC in conjunction with surgery has not received sufficient attention (Table 1).

#### 4.1. The necessity and feasibility of neoadjuvant therapy for patients with HCC

According to the 2019 version of "Guidelines for the Diagnosis and Treatment Standards" (4), the indications for resection of HCC in China range from stage Ia to IIIa, which correspond to stage A, B, and part of C according to BCLC staging. HCC itself has a high rate of postoperative recurrence and expanded surgical indications involve more risk factors for recurrence including multiple tumors and vascular invasion, so the risk of recurrence increases further. Research on other types of cancer, such as colorectal cancer, has indicated that tumor micrometastasis occurs much earlier than

**Table 1. Global studies related to neoadjuvant therapy for HCC (35 projects)**

Status of research	Number
Hepatocellular carcinoma & neoadjuvants	35
Discontinued project	2
Non-neo-adjuvant treatment	9
Promising neoadjuvant therapies for HCC	24
Chemotherapy	1
Sorafenib	2
Radiotherapy	2
HAIC/TAI/TACE-TAI	6
Immunity therapy	6
Combined therapy based on immunotherapy	7
Phase III study or more than 150 subjects	9
Research from China	15

Data as of: November 18, 2020, source: <https://www.clinicaltrials.gov/>

expected. Metastatic seeding usually occurs several years before diagnosis or surgery. At the current point in time, tumor metastasis cannot be detected clinically (10).

In the event of early metastasis, an advantage of neoadjuvant therapy is that patients can receive multidisciplinary and systemic treatment earlier, micrometastasis can be controlled, the tumor burden can be reduced before surgery, the rate of R0 resection can be increased, recurrence can be delayed, and survival time can be prolonged (11-13). Patients with disease progression within 2 to 3 months are considered to benefit little from surgery. At the current point in time, neoadjuvant therapy can be used as a form of screening to avoid unnecessary surgical trauma to those patients (14). Neoadjuvant therapy has yielded favorable results in the treatment of various forms of cancer such as breast cancer (15), bladder cancer (16), colorectal cancer (17), and melanoma (18). Immunotherapy drugs have unique advantages in neoadjuvant therapy. Tumor-specific CD8+ T cells that are revitalized by immunotherapy will be activated, kill tumor cells, and circulate in the blood again. After the primary tumor is removed, the tumor-specific CD8+ T cells in the circulatory system and the T cells present at a metastatic focus can serve as a stable tumor-specific CD8+ T cell bank (11).

#### 4.2. Indications for neoadjuvant therapy in patients with HCC

Wei *et al.* (19). compared the survival of patients with PVTT III HCC who received neoadjuvant radiotherapy and surgical resection with those who only received surgical resection. The neoadjuvant radiotherapy group had a longer long-term overall survival and disease-free survival than did the group receiving surgery alone. Neoadjuvant radiotherapy can reduce the risk of HCC recurring and death due to PVTT, and patients with large HCC can also benefit from preoperative TACE. Li *et al.* (20). retrospectively analyzed patients who underwent radical resection of massive HCC without large vessel

invasion in a multi-center database from 2004 to 2014, and they found that patients who received TACE before surgery had a lower mortality rate (67.9% vs. 81.0%) and rate of recurrence (76.2% vs. 85.7%) than did patients who did not receive TACE ( $P = 0.052$  and  $0.116$ ). Patients receiving TACE before surgery had a median overall survival time of 32.8 months and a disease-free survival time of 12.9 months, which were better than the median overall survival time of 18.1 months and the disease-free survival time of 4.1 months for patients not receiving TACE ( $P = 0.023$  and  $0.009$ ). TACE before surgery was an independent predictor of overall survival. Therefore, neoadjuvant therapy is crucial for patients with HCC with PVTT, giant liver tumors, and multiple liver tumors, and especially for patients who undergo resection in line with the expanded surgical indications according to BCLC staging in the 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer." Those patients all have a high risk of postoperative recurrence. Thus, rationally determining when to use neoadjuvant therapy is crucial. Establishing objective indicators with which to evaluate the efficacy of these therapies is vital.

#### 4.3. Objective indicators with which to screen and evaluate neoadjuvant therapy

The objective response rate (ORR) refers to the ratio of patients with complete or partial remission of tumors as a result of treatment. This is an important indicator that is used to evaluate the efficacy of neoadjuvant therapy. Only therapies with a higher ORR are ideal neoadjuvant therapies. The current ORR benefit of single-drug therapy is limited, and combination therapy may have a higher ORR. Results of a phase Ib clinical study of lenvatinib combined with nivolumab in the treatment of patients with unresectable HCC were announced at the 2020 American Society of Clinical Oncology (ASCO) Gastrointestinal Tumor Symposium, and the study noted an ORR of 54.2%. Data from a phase Ib study of drug K combined with lenvatinib in the treatment of advanced HCC at the European Society for Medical Oncology (ESMO) conference in 2019 indicated that the ORR after the combination was 40.3%. Qin *et al.* (21) found that carrelizumab combined with apatinib resulted in

an ORR of 44.4%. In 2019, the Fifth European Society of Medical Oncology Asian Annual Meeting reported that atezolizumab combined with bevacizumab to treat patients with unresectable HCC who had not received systemic treatment before resulted in an ORR of 27.0%. Xu *et al.* (22) found that carrelizumab combined with the FOLFOX4 regimen resulted in an ORR of 26.5% (Figure 1).

The disease control rate (DCR) refers to the proportion of patients whose cancer has completely remitted, partially remitted, or which remains the same (stable) for a certain period because neoadjuvant therapy can be used to treat a surgically resectable tumor. If the DCR is low, many patients will have disease progression during treatment and tumors that could be surgically resected will become inoperable. This will have a great negative effect not only on the patient but also on the doctor. Studies have indicated that a combination of medications results in a higher DCR than does a single medication (23). The REFLECT study compared the effects of lenvatinib and sorafenib as first-line treatments for unresectable advanced HCC, and it found that the DCR was 73.8% in patients receiving both drugs and 50% in those receiving sorafenib alone. A study announced at the 2019 ASCO annual meeting indicated that treatment of HCC with pabrizumab alone had a DCR of 62.2%. The Phase 1 and Phase 2 CheckMate-040 clinical study, which was announced at the same conference announced, found that nivolumab combined with ipilimumab for the treatment of HCC had a DCR of 54%. At the ESMO conference held in Barcelona, Spain in 2019, Lee *et al.* announced that the PD-L1 inhibitor atezolizumab combined with bevacizumab in the treatment of advanced HCC had a DCR of 72%. At the 2019 Annual Meeting of the American Association for Cancer Research, a study of the safety and efficacy of pembrolizumab combined with lenvatinib in the treatment of unresectable HCC indicated that the combination of drugs had a DCR of 93.3%. A study of lenvatinib combined with nivolumab in the first-line treatment of unresectable stage Ib HCC was announced at the ASCO Gastrointestinal Tumor Symposium held in 2020, and it found that the combination of drugs had a DCR as high as 96.7%. As is evident, a combination of medications has a significant advantage in terms of the

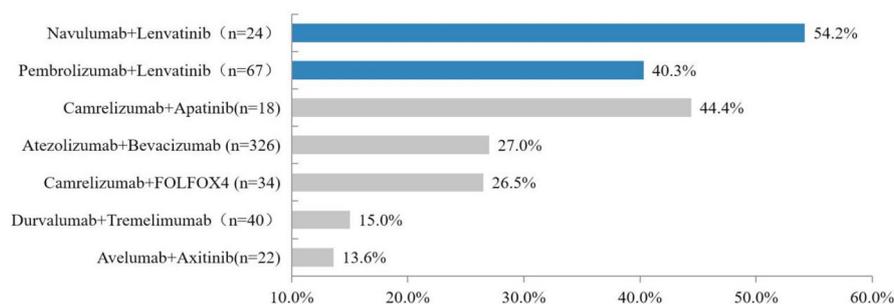


Figure 1. The ORR for several first-line combined immunotherapies for advanced HCC.

DCR compared to a single medication.

Progression-free survival (PFS) refers to the time from the beginning of treatment to tumor progression. This indicator can determine the course of neoadjuvant therapy to a certain extent. At present, the shortest PFS for single-agent therapy to treat advanced HCC is 2.8 months (sorafenib) (24) and the longest is 7.4 months (lenvatinib) (25). The shortest PFS for combination therapy is 5.6 months (atezolizumab combined with bevacizumab) (26) and the longest is 9.3 months (pembrolizumab combined with lenvatinib) (27). If the current duration of neoadjuvant therapy for advanced HCC is kept to 4 to 6 cycles (2 to 3 months), then it is within the PFS for most forms of treatment.

Liver-related adverse reactions that are grade III or worse should serve as an important indicator with which to evaluate the safety of neoadjuvant therapy. The ideal neoadjuvant therapy should try to ensure minimal impact on liver function and avoid postoperative liver failure in order to ensure that patients can successfully and safely undergo liver resection after neoadjuvant therapy. At present, the rate of all liver-related adverse reactions to neoadjuvant therapy that are grade III or worse is  $\leq 10\%$  for targeted monotherapies or immunotherapies. The rate of adverse reactions to pembrolizumab combined with lenvatinib is about 10.4%, and that for nivolumab combined with lenvatinib is about 10%. Therefore, whether targeted therapy or immunotherapy should be used as a preoperative neoadjuvant therapy should ideally be based on how safe it is to the liver.

#### 4.4. Neoadjuvant treatment plan

At present, most guidelines for neoadjuvant therapy do not have recommended regimens or protocols. Only the 2020 edition of CSCO's "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" recommend neoadjuvant radiotherapy for patients with a tumor thrombus in the portal vein trunk or branch (28). TACE has yet to be accepted as a neoadjuvant therapy because of its low effectiveness and related liver toxicity. As targeted therapies and immunotherapies are developed, they will need to be screened to determine if they qualify as an ideal neoadjuvant therapy in terms of ORR, DCR, PFS, or the incidence of liver-related adverse reactions. Neoadjuvant therapies offer great promise for the future.

### 5. Clinical significance of surgical treatment for patients with CNLC stage IIIb HCC

The 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" specified that patients with stage IIIb cancer mainly receive systemic treatment (sorafenib, lenvatinib, FOLFOX4, and regorafenib), TACE, or radiotherapy. Surgical treatment was not an option. As systemic therapy is further used to treat patients with advanced HCC, in the current authors'

clinical experience several patients with stage IIIb HCC who have undergone combined treatment have become eligible to undergo surgical resection. Postoperative pathological examinations have indicated that the main body of the tumor was partially or completely necrotic, suggesting that some stage IIIb tumors can be surgically removed after systemic treatment, but there is still a lack of indicators with which to objectively evaluate whether patients with stage IIIb HCC can undergo surgical treatment.

No evidence of disease (NED) refers to the fact that no evidence of residual tumor is found after a tumor is treated using existing methods of testing. This means that a tumor is no longer present in a patient. NED is a static concept. It only indicates that tumor cells cannot be detected at the time of testing. False negative results due to insufficient sensitivity of the method of testing cannot be ruled out. If, however, NED continues for a sufficient amount of time, then a radical cure is deemed to have been achieved. In 2016, ESMO's guidelines for metastatic colorectal cancer listed NED as a treatment target. However, current Chinese and Western guidelines and expert consensus opinions on treatment of primary HCC have not mentioned the concept of NED, and no studies have reported on both primary HCC and NED.

As systemic treatments develop, the goal of surgical treatment of primary HCC is no longer limited to radical resection. Patients with stage IIIb HCC can become eligible for surgical resection after systemic treatment and NED is achieved. Therefore, the concept of NED could be applied to treatment of HCC to objectively evaluate whether patients with stage IIIb HCC can undergo surgery. As the effectiveness of systemic treatment continues to improve, the proportion of patients with HCC in whom NED is achieved will also increase substantially, and NED will be an important goal for the surgical treatment of HCC in the future. Therefore, guidelines are not static. With an effective evaluation system in place, some patients with stage IIIb HCC could receive surgical treatment, and the indications for surgical treatment of HCC in the Chinese guidelines should be further expanded.

### 6. Problems and challenges

Surgical treatment is still the main treatment for patients with resectable HCC. That said, researchers are increasingly exploring multimodal therapies to reduce the rate of recurrence and increase the proportion of patients who are eligible for surgery. However, the role of neoadjuvant therapy in treating HCC still needs to be studied further due to the lack of high-level evidence in the literature. Therefore, future research on neoadjuvant therapy should obtain more data by paying more attention to the standardization of endpoints and trial design and by identifying biomarkers

of therapeutic response and mechanisms of resistance. As neoadjuvant therapy continues to develop thanks to advances in immunotherapy and targeted therapy, randomized controlled trials of large samples will need to be conducted to determine the best combination and sequence of multimodal therapies.

## 7. Conclusion

The probability of postoperative recurrence has increased as surgical indications for HCC have expanded, and postoperative adjuvant therapy has become a topic of interest. The use of neoadjuvant therapy to treat HCC has just started. It is theoretically feasible and requires more practical experience. At the same time, the current era of targeted therapy and immunotherapy has made that therapy more feasible. Neoadjuvant therapy will definitely become a new area of interest in the treatment of resectable HCC with a high risk of recurrence. With effective systemic treatment, extrahepatic metastasis will no longer be a contraindication for surgery. Therefore, surgical treatment needs to be gradually expanded to include advanced HCC, and medical treatment using neoadjuvant therapy needs to be provided in the early stages of HCC. In addition, knowledge about treating HCC needs to be standardized so that new treatment strategies and protocols can be developed.

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