

Chinese expert consensus on the overall management of liver function in conversion therapy for liver cancer (2022 edition)

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Introduction

Primary liver cancer is a significant health issue in China, where it ranks fourth in morbidity and second in mortality among all malignant tumors.^[1-4] The 5-year overall survival rate of Chinese patients with liver cancer from 2012 to 2015 was only 12.2% for males and 13.1% for females.^[5] Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancers.^[6] Furthermore, most liver cancers are unresectable at diagnosis. To combat this, conversion therapy is used, which involves systematic treatments like anti-angiogenic drugs or molecular targeted therapy combined with immunotherapies, as well as locoregional treatments such as transcatheter arterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), ablation therapy, and radiation therapy. The goal is to eliminate unresectable status and increase the chances of surgery. The reported 5-year survival rate after salvage surgery following tumor downstaging varied from 24.9–57%.^[7] However, some patients with advanced-stage liver

cancer still cannot tolerate conversion therapy due to poor baseline liver function or liver damage caused by treatment-related adverse reactions, leading to treatment discontinuation or life-threatening sequelae.^[8] Moreover, there are no all-inclusive guidelines on evaluating and managing liver function throughout the treatment process. To address this issue, the Liver Tumor Branch of the China International Exchange and Promotive Association for Medical and Healthcare (CPAM), in collaboration with experts in the field of hepatobiliary surgery, intervention, hepatology, and oncology, has developed the “Chinese expert consensus on comprehensive liver function management during liver cancer conversion therapy (2022 edition).” A flowchart for the overall management of liver function during conversion therapy for liver cancer is shown in Supplementary Figure 1, <http://links.lww.com/CM9/B835>.

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Recommendation Strength Standard and Level of Evidence

The recommendations in this consensus refer to the evidence level following the criteria listed in the Chinese Society of Clinical Oncology (CSCO) [Supplementary Table 1, <http://links.lww.com/CM9/B835>].

Target Audience

Clinicians specializing in hepatobiliary surgery, intervention, hepatology, and oncology in China are the target audience of this consensus.

Recommendations for Liver Function Assessment in HCC Patients

Before the conversion therapy

1. The diagnosis and treatment based on etiology should be conducted before the surgery for liver cancer. Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection require anti-viral medications. Those with alcoholic liver disease are necessary to completely abstain from drinking. Patients with non-alcoholic fatty liver disease (NAFLD) should manage their weight and control blood glucose levels if they have diabetes. (Grade I)
2. Patients with liver cancer should undergo general health condition assessment before surgery, and nutritional risk screening 2002 (NRS 2002) is recommended for hospitalized patients. If a patient is at nutritional risk, using tools such as patient-generated subjective nutrition assessment (PG-SGA) to assess for malnutrition is recommended. If malnutrition is detected, developing an intervention plan and providing appropriate nutritional support to the patient is essential. (Grade I)
3. Hepatectomy may be recommended for patients with compensating cirrhosis without significant portal hypertension. And for patients with unresectable disease, alternative options such as TACE, HAIC, radiotherapy, targeted agents, and immune checkpoint inhibitors may be considered. Prognostic prediction should assess blood platelets (PLTs), which should be evaluated alongside gastroscopy before surgery for a comprehensive assessment. (Grade I)
4. Multiple laboratory examinations are recommended before hepatectomy, including liver function tests: glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), total bilirubin (TBIL), albumin (ALB), prealbumin (PA), and choline esterase (CHE); complete blood count: white blood count (WBC), hemoglobin (Hb), PLT, neutrophil percentage (N%), and lymphocyte percentage (L%); and coagulation test: prothrombin time (PT), prothrombin activity (PTA), and international normalized ratio (INR). Assessing these parameters provides a

comprehensive understanding of the liver's functional status. (Grade I)

5. Evaluating liver reserve function before liver surgery is crucial. This can be done using tools such as the indocyanine green retention test at 15 min (ICG-R15), Child-Pugh score, and future liver remnant (FLR). Having Child-Pugh class A and/or ICG-R15 <20% is necessary to perform hepatectomy. For patients with cirrhosis, severe fatty liver, and chemotherapy-related liver injury, FLR should account for more than 40% of standard liver volume (SLV), while higher than 30% is acceptable for patients without cirrhosis. (Grade I)

During liver cancer conversion therapy

1. The mechanisms underlying liver injury vary according to the type of interventional therapy. When undergoing conversion therapy for liver cancer, it is recommended to continuously monitor liver function and administer appropriate liver protection medication based on specific interventional measures and treatment intervals. The goal is maintaining liver function below 7 points of Child-Pugh Class B. (Grade II)
2. It is important to note that radiation-induced liver injury can have delayed and prolonged effects. Therefore, having a Child-Pugh score below 7 of Class B is essential before considering radiotherapy. In addition, continuous monitoring and evaluation of liver function is crucial during and after treatment for up to three months. Appropriate administration of liver protective drugs is also imperative. A critical step for avoiding radiation-induced liver injury is to create a radiotherapy plan that prioritizes the protection of healthy liver tissue. (Grade II)
3. Taking immune checkpoint inhibitors or targeted therapies may pose a risk of liver injury. Patients should have a Child-Pugh score below 7 to be eligible for these drugs. It is recommended to regularly evaluate liver function during treatment with immune checkpoint inhibitors every three weeks and every three months for targeted therapies. (Grade II)
4. FLR deficiency is one of the critical factors for postoperative liver failure. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) can be used to increase FLR in patients with FLR/SLV below 30% (normal liver) or below 40% (with chronic liver disease and liver injury), under 65 years old with a good general condition, normal liver function (Child-Pugh A, ICG-R15 <10%), well-tolerated surgery, and without severe cirrhosis, severe fatty liver, severe portal hypertension. (Grade I)
5. Liver function can be affected differently depending on the specific conversion therapy used.

Therefore, it is crucial to consistently evaluate the liver function, renal function, and coagulation test. Taking proactive measures in the event of abnormal liver function is recommended by seeking medication that can effectively protect the liver. (Grade I)

Hepatoprotective and choleric agents can effectively treat liver injury. In cases of hepatocellular injury indicated by GPT or GOT elevation, it is recommended to take hepatic protectors such as glycyrrhizic acid preparations, polyene phosphatidylcholine, glutathione, and silymarin for 1–2 weeks. For cholestasis, which is characterized by the elevation of TBIL, direct bilirubin (DBIL), γ -glutamyl transpeptidase (γ -GT), or ALP, choleric agents are recommended for 4–5 weeks. S-adenosylmethionine (SAME), as a methyl donor (transmethylation) and a precursor of physiological thiol compounds (such as cysteine, taurine, glutathione, and coenzyme A), can prevent and treat cholestasis in conversion therapy and surgery for liver cancer. And SAME is available in both injections and tablets for sequential inpatient and outpatient treatment. Ursodeoxycholic acid increases bile acid flow and promotes the secretion of bile acids by replacing the hydrophobic bile acid from the bile, which affects primary biliary cholangitis (PBC), but with fewer studies in liver cancer.

After the successful conversion therapy and hepatectomy

1. It is essential to regularly monitor parameters such as GPT, GOT, ALP, γ -GT, ALB, PA, and CHE post-hepatectomy. These should be evaluated with TBIL, PTA, and PLT to assess liver function. Evaluation systems like the model for end-stage liver disease (MELD) and 50–50 criteria can also be used for the regular liver function assessment post-hepatectomy. (Grade I)
2. Continuously nutritional assessment after surgery is required. Adequate nutrition support and appropriate treatment with hepatic-protective medication help enhance the recovery of liver function post-hepatectomy. (Grade II)

Physical exercise for rehabilitation

Physical exercise benefits the patients for their physical and psychological health. The recommended form of exercise is mainly aerobic exercise, alongside others. The overall intensity can gradually increase based on the patient's physical potential. (Grade I)

Conclusion

With recent advances in treatments, patients with unresectable liver cancer can now have the opportunity to achieve adequate tumor downstaging. Traditional Chinese medicine also plays an essential role as part of combination therapy in managing patients with HCC.^[9–11] Liver function management is crucial for patients

receiving conversion therapy, and further research, especially large-sample prospective randomized controlled trials, is needed to determine how to increase therapy opportunities in patients with liver cancer.

Conflicts of interest

None.

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