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Whole-course management of interventional treatment in liver cancer patients with portal hypertension

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ABSTRACT

Primary liver cancer often occurs in patients with hepatitis and cirrhosis. Some patients have portal hypertension due to cirrhosis, and present with varying degrees of collateral circulation, splenomegaly and hypersplenism, ascites, and liver dysfunction. It often interferes with the treatment of tumors and affects the disease prognosis. There are internationally recognized guidelines for interventional treatment of liver cancer and portal hypertension which will not be repeated in this paper. This paper focuses on how to treat portal hypertension and intervene with tumors in the treatment of liver cancer to optimize the management of patients with liver cancer and portal hypertension. We propose that the Interventional Management Mode of Liver Cancer with Portal Hypertension can improve the treatment of liver cancer patients with portal hypertension.

1. Horizontal interventional management mode

1.1. Systematized treatments

Systematic interventional treatments are important for the treatment of portal hypertension combined with liver cancer. Historically, the treatment of liver cancer and the treatment of portal hypertension have been considered separately and insufficient weight has been placed on the relevance of the combination of the two. This neglects the importance of the treatment of portal hypertension in the overall case management of liver cancer patients, reduces the efficacy of the treatment of portal hypertension and affects the prognosis and survival of patients with liver cancer. Taking traditional surgical resection of liver cancer as an example, in 2015, Berzigotti et al.,[1] showed through systematic review and meta-analysis that clinically significant portal hypertension (CSPH) significantly increases the risk of 3-year and 5-year mortality and of clinical decompensation after surgery forhepatocellular carcinoma. Similarly, our previous research on transcatheter arterial chemoembolization (TACE)used on mid-stage liver cancer patients with partial portal hypertension and hypersplenism showed a coherent conclusion. With TACE treatment alone, without treating portal hypertension and splenomegaly (due to poor tolerance to chemotherapy and embolization and the relatively long treatment interval), the tumor treatment effect is significantly inferior to partial splenic embolization (PSE) combined with TACE treatment.[2] Therefore, the treatment of portal hypertension is of great significance for the treatment of liver cancer and needs to be interspersed throughout the treatment of liver cancer. Systematic planning and analysis according to different treatment goals and options for different stages of liver cancer are required to integrate portal hypertension treatment into the treatment of liver cancer to improve treatment outcomes.

1.2. Standardized treatment

In standardized treatment, as well as in the treatment of portal hypertension in liver cancer patients, doctors should strictly follow the recommended guidelines for the treatment of portal hypertension, such as the American Association for the Study of Liver Diseases (AASLD) guidelines and the European Baveno consensus. Patients should be well stratified and individualized to manage the risk of portal hypertension, ensuring standardized treatment. It must be noted that transjugular intrahepatic portosystemic shunt (TIPS) was previously considered unsuitable for patients with liver cancer; however, this viewpoint was deemed a misunderstanding of the relevant guidelines. According to the AASLD Practice Guide: The Role of TIPS in the Management of Portal Hypertension, hepatoma, especially if central, is listed as a relative contraindication for TIPS treatment. Secondary prevention variceal bleeding, refractory cirrhotic ascites, and refractory acute bleeding

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varices are indications for TIPS treatment.[3] At the same time, physicians need to adhere to the guidelines more closely. An early TIPS with PTFE-covered stents within 72 h (ideally <24 h) must be considered in patients bleeding from esophageal varices (EV), gastroesophageal varices type 1 (GOV1) and gastroesophageal varices type 2 (GOV2) at high risk of treatment failure (e.g.Child-Pugh class C < 14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy.[4] Therefore, to provide effective treatmentfor patients with liver cancer and portal hypertension, strict consideration of both indications and contraindications must be practiced as part of standard protocol.

1.3. Whole-course treatment

Optimal whole-course treatment requires full interpretation of the significance of the Barcelona Clinic Liver Cancer (BCLC) staging system, portal hypertension treatment and management of the whole process for liver cancer patients with portal hypertension. The BCLC staging system places great emphasis on whether or not to combine portal hypertension treatment, especially in early liver cancer, and whether portal pressure increases directly affect the choice of treatment strategy. According to the BCLC staging system, patients with stage Adisease, who have a combination of portal hypertension or elevated bilirubin, are advised to undergo ablation or transplantation rather than surgical resection.[5] In general, the earlier the stage of the liver cancer, the more active the intervention should be for the portal hypertension. Patients with stage Adisease tend to have better liver function reserve. Therefore, the portal hypertension should be actively treated, and efforts should be made to effectively cooperate with tumor treatment through the treatment of portal hypertension. The treatment goals for patients with stage B disease are palliative care, reducing complications of portal hypertension, and maximizing patient survival. It is important to note that repeated chemotherapy embolization in patients with stage B disease can lead to cirrhosis and increased portal hypertension. In addition to evaluating the efficacy against the tumor, physicians should also fully evaluate patients' portal hypertension and take the necessary precautions. The treatment goals of patients with stage C disease are palliative treatment, reducing complications of portal hypertension and improving the quality of life of patients. The concept of "thrombus-related portal hypertension" was first proposed by us in the academic field because a considerable proportion of stage C disease patients eventually died of portal hypertension complications caused by blockage by a portal vein thrombus, including severe upper gastrointestinal bleeding and intractable ascites and liver failure, rather than extensive metastasis of tumors. It is also closely related to the characteristics of the liver as the organ of digestion and metabolism. Therefore, to reduce complications and improve the quality of life of patients with portal hypertension, we advocate the effective treatment of portal hypertension in stage C disease patients with stable intrahepatic lesions and severe portal hypertension. Further research is needed to determine whether this approach will bring survival benefits to patients. For some patients with stage D disease, especially those with Child-Pugh C grade (Child-Pugh score ≥ 10) caused by intractable ascites, such as small tumors (especially ≤ 3 cm), TIPS treatment can be actively carried out to eliminate or alleviate ascites, so as to present the opportunity to treat tumors. Therefore, the treatment of patients with hepatocellular carcinoma complicated with portal hypertension should make use of not only the relevant guidelines for diagnosis and treatment of hepatocellular carcinoma (such as the BCLC staging system and NCCN guidelines) but also the relevant guidelines for treatment of portal hypertension (such as the AASLD guidelines and Baveno consensus), and strive to achieve full integration and flexible use of the two.

2. Longitudinal intervention management mode

2.1. PSE

PSE occludes part of the spleen through branch embolization of the splenic artery to relieve spleen symptoms, reduce splenic venous return, and reduce portal pressure.[6] For the reduction of blood cells caused by hypersplenism, especially the decrease in platelet count, PSE is minimally invasive and has rapid efficacy.[2] Patients with BCLC stage A disease receiving ablation therapy who have a platelet count of less than 50×10^9/L due to splenomegaly have a higher risk of percutaneous puncture, and PSE can be performed before ablation to improve spleen symptoms and platelet count. Ablation treatment can be performed when the platelets rise above 50×10^9/L. Patients with BCLC stage B disease have difficulty tolerating conventional TACE if the blood count is low due to splenomegaly. PSE may be used first or in combination to reduce the side effects of chemotherapy drugs on blood cells in TACE. Patients with primary liver cancer and splenomegaly have a better tolerance to PSE when combined with TACE, because the treatment interval is relatively shorter, and the tumor treatment effect is better than TACE treatment alone.[2] In addition, PSE relieves upper digestive hemorrhage caused by left portal hypertension.[7] Of course, PSE still has limitations in reducing portal pressure. For patients with ascites and portal vein thrombosis, the risks and potential benefits of PSE should be weighed carefully.

2.2. Percutaneous transhepatic variceal embolization (PTVE) and balloon-occluded retrograde transvenous obliteration (BRTO)

PTVE and BRTO have a definite therapeutic effect on the prevention and treatment of variceal hemorrhage caused by portal hypertension.[8] The procedure of PTVE is relatively simple. The embolization is performed by percutaneous puncture of the intrahepatic portal vein and then the catheter is placed in the varicoseportal vein. PTVE has a rapid hemostasis effect on the upper gastrointestinal hemorrhage caused by portal hypertension and BCLC. The disadvantage is that it cannot reduce the pressure of the portal vein, and other collateral veins may be broken during the procedure. Fissure bleeding, with short- and long-term adverse effects, often requires joint PSE for further efficacy.[9] For larger collateral vessels, the embolization effect is also poor. BRTO has obvious advantages for patients with large gastric and renal shunts and has significant advantages in the treatment and prevention of gastric varices bleeding and refractory hepatic encephalopathy, especially due to the large autologous shunt vein4,10. It is better than PTVE by balloon isolation, embolization, and hemostasis, with better long-term effects. Its shortcomings are increased portal vein pressure after embolization and other symptoms of portal hypertension, such as increased ascites.[11] From the perspective of hemostasis and prevention of bleeding, PTVE and BRTO can reduce complications, improve quality of life, and improve tumor treatment tolerance in BCLC patients with hepatic variceal hemorrhage. The technical requirements of the two, especially the former, are relatively low, and these can be carried out in intervention departments that have a general level of technical expertise.

2.3. TIPS

When the tumor is controllable and not located on the shunt, TIPS can be a good adjuvant for tumor treatment as long as the indications for TIPS treatment are strictly controlled. TIPS treatment can significantly improve the patient's tolerance to tumor treatment. TIPS should be performed as soon as possible, so long as the tumor is at a sufficiently early stage and there are no other contraindications. For patients with stage A BCLC, it is best to strive to effectively coordinate treatment with tumor resection. For patients with stage B BCLC, the treatment goals are palliative care, reducing portal hypertension complications, and maximizing patient survival. For patients with stage C BCLC, if the patient is relatively stable after systemic treatment, TIPS should be selected in the event of subsequent severe variceal hemorrhage, recurrent hemorrhage after endoscopic variceal ligation (EVL) and nonselective beta blocker (NSBB) therapy, or refractory ascites. Brachyseed implantation, insertion of a stent loaded with brachyseed, or brachyseed strand implantation should be considered asappropriate when the patient's condition is stable. Care

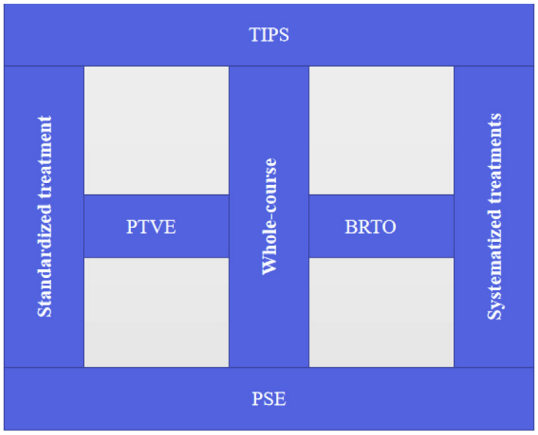

Fig. 1. Interventional management mode of liver cancer with portal hypertension.

must be taken when performing TIPS in patients with stage C BCLC. The technical difficulty caused by occlusion of the portal vein should be fully evaluated. At the same time, there should be full communication between doctors and patients, and the purpose of the operation should be to prevent the failure of endoscopic treatment. At the same time, the liver function of the patient should be fully evaluated, and the incidence of decompensation of liver function caused by the shunt of portal vein tumor thrombus should be reduced by TIPS. For some patients with stage IV BCLC, especially because of refractory ascites, and Child-Pugh grade C (Child-Pugh score ≥ 10 points), such as small tumors (≤ 3 cm), TIPS treatment can be used to eliminate or reduce ascites and maximize the opportunity to treat cancer.

In summary, thehorizontal and longitudinal interventionmanagement mode constructs a complete Interventional Management Mode of Liver Cancer with Portal Hypertension (Fig. 1). On the basis of longitudinal interventionmanagement mode, the treatment methods of different steps in thehorizontal interventional management mode can also be applied in sequence according to specific needs, such as PSE + PTVE, BRTO + TIPS, and PSE + TIPS, which often complement one another. In the final analysis, clinicians need to clarify the complex pathology and pathogenesis of liver cancer complicated with portal hypertension. The treatment of the two cannot be completely divided and independent. Ignoring portal hypertension and performing repeated interventions often leads to cirrhosis and increased portal hypertension. Fatal complications and decompensation of liver function occur, preventing further cancer treatment. Although the treatment of liver cancer with portal hypertension is complicated, the careful, systematic, standardized, full implementation of the Interventional Management Mode of Liver Cancer with Portal Hypertension can simplify treatment and solve problems.

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