

Therapeutic options for intermediate-advanced hepatocellular carcinoma

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on the optional therapeutic modalities for intermediate-advanced HCC.

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies, ranking the sixth in the world, with 55% of cases occurring in China. Usually, patients with HCC did not present until the late stage of the disease, thus limiting their therapeutic options. Although surgical resection is a potentially curative modality for HCC, most patients with intermediate-advanced HCC are not suitable candidates. The current therapeutic modalities for intermediate-advanced HCC include: (1) surgical procedures, such as radical resection, palliative resection, intraoperative radiofrequency ablation or cryosurgical ablation, intraoperative hepatic artery and portal vein chemotherapeutic pump placement, two-stage hepatectomy and liver transplantation; (2) interventional treatment, such as transcatheter arterial chemoembolization, portal vein embolization and image-guided locoregional therapies; and (3) molecularly targeted therapies. So far, how to choose the therapeutic modalities remains controversial. Surgeons are faced with the challenge of providing the most appropriate treatment for patients with intermediate-advanced HCC. This review focuses

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer-related death^[1]. Patients at the early stage are those who present with an asymptomatic single HCC with the nodule < 5 cm in diameter or ≤ 3 in number. Patients exceeding these limits, but free of cancer-related symptoms and vascular invasion or extrahepatic spread, are considered at the intermediate stage. The patients with the cancer-related symptoms and vascular invasion or extrahepatic spread are deemed at the advanced stage. HCC is frequently diagnosed at the late stage and has a high mortality rate. Surgical resection is a potentially curative therapy for HCC, however, only 10%-30% of patients with HCC are eligible for curative hepatectomy. Comprehensive therapy for HCC has become the focus of interest in recent years^[2-6]. The current therapeutic modalities

for intermediate-advanced HCC are collected and evaluated as follows.

SURGICAL PROCEDURES

Radical resection is still the first choice for treatment of HCC^[7,8], even at the intermediate or advanced stage^[9,10]. If radical resection is impractical, palliative resection combined with comprehensive therapy can significantly prolong patients' survival time^[11,12]. Intraoperative comprehensive therapy includes radiofrequency ablation, cryosurgical ablation, and hepatic artery and portal vein chemotherapeutic pump placement. Two-stage hepatectomy can improve the survival rate in selected patients with advanced HCC^[13,14]. Liver transplantation has been shown to achieve excellent survival rate in appropriate HCC patients^[15,16].

Radical resection

Radical resection for intermediate-advanced HCC is indicated as follows: (1) single HCC with large or huge tumor nodule, swelling outward, clear border or pseudocapsule, and less than 30% hepatic tissue destroyed measured by computed tomography (CT) or magnetic resonance imaging (MRI) scan, or more than 50% compensatory hepatic hypertrophy; (2) multiple HCC with 3 or fewer nodules localized in one lobe or segment of the liver^[17,18]. It should be pointed out that tumor nodules limited to the liver are not the absolute operative indication. The outcome of radical resection could be affected by multicentric occurrence of HCC, tumor nodule adjacent to major blood vessel or bile duct, and the hepatic insufficiency induced by coexisting cirrhosis^[19].

With the deeper recognition of the pathology of HCC, the rational criteria of negative surgical margin are initially determined as follows: (1) > 2 cm margin free from tumors < 5 cm in diameter; (2) > 1 cm margin free from tumors 5-10 cm; and (3) > 0.5 cm margin free from tumors > 10 cm. More than 90% hepatectomies fulfilling the above-mentioned criteria can achieve negative surgical margin^[20]. Thereby, healthy hepatic tissue should be reserved as much as possible during radical resection so as to enhance the operative security, to facilitate the postoperative recovery and to help with further treatment.

Palliative resection

The indications of palliative resection for intermediate-advanced HCC are: (1) multiple HCC with 3-5 tumor nodules, exceeding half of the liver; (2) multiple HCC with nodules localized in 2-3 adjacent segments or half of the liver, more than 50% compensatory hypertrophy in the tumor-free liver demonstrated by image examinations; (3) central HCC with more than 50% compensatory hypertrophy in the tumor-free liver; (4) hilar lymph node metastasis should be cleared up during hepatectomy; and (5) invaded organs around the liver, such as colon, stomach, diaphragm, right adrenal gland, *etc.*, and single metastatic neoplasm far from the liver (e.g. lung metastasis) should be resected^[17].

Intraoperative radiofrequency ablation

Radiofrequency ablation (RFA) is a technique in which an electromagnetic energy deposition is used to thermally ablate the hepatic tumor tissue^[21]. During RFA treatment, heat energy generated by high-frequency alternating currents targeted at the living tissues causes protein denaturation at a temperature of 60-110°C through ionic vibration, resulting in coagulative necrosis of the target lesion. In addition, RFA treatment stimulates the immune system and provides an easy way to achieve *in vivo* vaccination against tumoral antigens^[22].

RFA is generally indicated for HCC patients who are not candidates for either liver resection or transplantation^[23]. HCC patients are required to have ≤ 5 nodules, each < 3 cm in diameter, no evidence of vascular invasion or extrahepatic spread, 0 score performance status of the Eastern Cooperative Oncology Group (ECOG), and liver cirrhosis in Child-Pugh class A or B. The more versatile radiofrequency probes allow ablation of nodule > 5 cm. When complete resection by major hepatectomy is dangerous because of difficult nodule location, selective use of intraoperative RFA will be helpful^[24]. The integration of intraoperative RFA into resection surgery contributes to complete removal of nodules with adequate margin, diminishes the extent of parenchymal resection, and improves the resectability rate for patients with advanced HCC^[24].

Pretreatment imaging must carefully define the location of tumor nodule with respect to the surrounding structures for RFA in HCC: nodules located on the surface of the liver can be considered; nodules adjacent to the hepatic vessels may be considered because flowing blood usually protects the vascular wall from thermal injury; nodules adjacent to the hepatic hilum represents a relative contraindication due to the risk of thermal injury of the biliary tract; and nodules adjacent to any part of the gastrointestinal tract must be avoided^[25].

Intraoperative cryosurgical ablation

Although RFA has been the most widely utilized ablation modality for HCC, cryosurgical ablation has several advantages (most significantly, the ability to produce larger and more precise zones of ablation) over RFA^[26].

Cryosurgical ablation for HCC patient relies on nonspecific tissue necrosis due to freezing as well as microvascular thrombosis. Argon-helium cryosurgical ablation is able to induce the necrosis of tumor cells through the formation of extracellular and intracellular ice crystals and then cell dehydration due to rapidly freezing (< -140°C) as well as rapidly thawing (20-40°C) the tumor tissues with argon/helium gas. Therefore, argon-helium cryosurgical ablation has become one of the major therapeutic approaches for unresectable intermediate-advanced HCC.

The indications of cryosurgical ablation for HCC patient are: (1) nodules < 5 cm in diameter, ≤ 3 in number; (2) nodule > 5 cm with irregular margin, may be given intraoperative cryosurgical ablation with or without excision of nodule. Intraoperative cryosurgical ablation offers

an effective and safe option for management of advanced HCC^[27]. HCC patients with diffuse infiltrative disease or large bilobar nodules (> 50% of liver volume) are not candidates for cryosurgical ablation because complete ablation of the nodules might induce hepatic failure.

Intraoperative hepatic artery and portal vein chemotherapeutic pump placement

The liver has a dual blood supply from the hepatic artery and the portal venous system. For HCC patients who are not suitable for hepatectomy confirmed by intraoperative exploration, two chemotherapeutic pumps could be implanted subcutaneously into the upper abdominal wall near the incision, with the tip of pump catheter separately inserted into the hepatic artery and portal vein during the operation, followed by postoperative chemotherapy. The advantage of intraoperatively implanted chemotherapeutic pump is the ability to accurately and selectively place into the main trunk or branch of hepatic artery and portal vein. For resectable intermediate-advanced HCC, the postoperative hepatic artery and portal vein dual perfusion chemotherapy *via* chemotherapeutic pumps could prevent tumor recurrence^[28].

Two-stage hepatectomy

Two-stage hepatectomy has been developed as a surgical strategy for extremely difficult patients with intermediate-advanced HCC^[7]. This strategy is applied when it is impossible to resect the tumor in a single procedure. The main principles of this strategy are: huge HCC with the remnant liver volume cannot maintain hepatic function after hepatectomy; central or hilar HCC adjacent to or invaded major blood vessel; and serious cirrhosis with possible hepatic decompensation after hepatectomy.

For unresectable HCC, preoperative intervention with transcatheter arterial chemoembolization (TACE)^[29], portal vein embolization (PVE)^[30,31], or percutaneous RFA could control tumor progression and invasion, downstage tumor status, increase remnant liver volume, and decrease tumor recurrence rate, thus making the two-stage hepatectomy possible. The indication of two-stage hepatectomy is that tumor diameter reduced to 50% of the initial size, and nontumorous liver tissue had significant compensatory hyperplasia. Sequential TACE and PVE could broaden the surgical indication and the safety of major hepatic resection for advanced HCC patient with damaged liver^[32,33].

Non-anatomic local excision of liver cancer or hepatic segmentectomy should be used in the two-stage hepatectomy so as to maximally preserve the normal liver tissue. For the patients with HCC invading the hepatic hilum and inferior vena cava, total hepatic vascular exclusion (HVE) should be prepared to avoid massive hemorrhage during hepatectomy.

Liver transplantation

Liver transplantation is an ideal treatment option, as it simultaneously cures HCC. However, up to date, there are no uniform criteria of liver transplantation for HCC

patients in China. The United Network for Organ Sharing (UNOS) criteria for liver transplantation are usually adopted in the world: single tumor ≤ 5 cm; 2-3 tumors, each ≤ 3 cm; no macrovascular invasion; and no extrahepatic spread to surrounding lymph nodes, lungs, abdominal organs, or bones^[34]. However, if the UNOS criteria are strictly adopted in China, it means that most HCC patients will lose the opportunity of liver transplantation, because more than 100 000 patients die of advanced HCC each year. For this reason, the indication of liver transplantation for advanced HCC should be relatively loose in China. For the patients with unresectable huge or multiple HCC, if no vascular invasion and no extrahepatic spread, liver transplantation is the treatment of choice. Considering the limited organ supply, high cost, and considerable risk, we suggest that only those HCC patients with a high probability of survival benefit should be selected to receive liver transplantation. The shortage of donor livers is the major constraint of liver transplantation.

INTERVENTIONAL TREATMENT

Although surgical resection has been the first choice for treatment of HCC, a simple surgical exploration could accelerate the process of disease and even cause death due to the postoperative complication of patients with unresectable HCC. With advances of medical imaging and improvement of interventional technology, interventional treatment has become an effective approach to inoperable HCC^[35-37]. The common approaches of interventional treatments for inoperable HCC include transcatheter arterial chemoembolization, portal vein embolization, and image-guided locoregional therapies.

Transcatheter arterial chemoembolization

For the treatment of inoperable HCC demonstrated by preoperative image examination, the priority is transcatheter arterial chemoembolization (TACE). The theoretical basis of TACE is the special vascular supply of liver and HCC. Liver derives dual blood supply from portal vein and hepatic artery, the former accounts for 2/3 to 3/4 while the latter for only 1/4 to 1/3. HCC derives 90% blood supply from hepatic artery and only 10% from portal vein. Thus, TACE provides a higher local concentration of chemotherapeutic drugs into tumor compared with intravenous perfusion chemotherapy, and meanwhile, it blocks blood supply of HCC, but only exerts little influence on blood supply of the liver. The consequence is that the major portion of cancer nodule becomes necrotic, while hepatic function remains unchanged or little impaired.

Better patient selection and selective segmental chemoembolization may improve the benefit-risk ratio of TACE^[38]. TACE is indicated in intermediate-advanced HCC even in the setting of portal vein involvement (excluding main portal vein)^[39]. The presence of main portal vein thrombosis, extrahepatic metastasis, Child-Pugh class C liver function, and severe hepatic arterio-portal shunts is considered as contraindications for TACE.

Portal vein embolization

Percutaneous transhepatic portal vein embolization (PVE) is a useful procedure for the preoperative intervention of advanced HCC patients selected for hepatectomy. PVE could increase the volume and function of the future remnant liver through the acceleration of hepatocyte proliferation, and embolize possible hepatic arterio-portal shunts, so as to prevent postoperative liver insufficiency.

For the treatment of intermediate-advanced HCC, the combination of TACE and PVE not only blocks most blood supply of main tumor and satellite lesions, but also increases the local concentration of chemotherapeutic drugs into tumor, so as to more effectively control the tumor growth and decrease tumor recurrence. Contraindications to PVE include distant metastases, uncontrolled coagulopathy, active cholangitis, portal hypertension, and renal failure^[40].

Image-guided locoregional therapies

Ultrasound or CT guided locoregional therapies have a therapeutic effect in advanced HCC patients by means of thermoablative therapy (radiofrequency ablation, microwave coagulation, laser ablation), cryotherapy (argon-helium knife, liquid nitrogen), or chemical therapy (ethanol injection, acetic acid injection) to destroy tumor tissues. To date, the commonly used therapies include percutaneous RFA, microwave coagulation, cryoablation therapy, and ethanol injection, especially with percutaneous RFA as the first choice to inoperable HCC. The roles of different locoregional therapies may change with further development of technology and availability of data from future prospective randomized trials^[38,41-43].

MOLECULARLY TARGETED THERAPIES

Recently, molecularly targeted therapies, including sorafenib, sunitinib, brivanib, cetuximab, erlotinib plus bevacizumab, and lapatinib, have emerged as promising therapeutic approaches for advanced HCC^[44,45]. Sorafenib, as an orally-active multikinase inhibitor targeting both tumor cells and the tumor vasculature, and the first agent to improve the overall survival status for patients with advanced HCC, has been approved for systemic therapy in patients with advanced HCC in Eastern and Western countries^[3,46-48]. Many other molecularly targeted agents of blocking epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and mammalian target of rapamycin (mTOR) are at different stages of clinical development for the treatment of advanced HCC^[49-51].

CONCLUSION

For the treatment of intermediate-advanced HCC, various surgical procedures may produce the definite therapeutic effects. The interventional treatment can also improve the prognosis to a great extent, but so far there is still lack of a special effective approach. In recent years, the model of comprehensive therapies mainly based on surgical

resection has been adopted to further enhance the curative effect, prolong the survival time, and improve the life quality of the patients. According to the indications and advantages of each therapeutic method, combined with the patient's clinical stage, the selection of therapeutic approaches to maximize the efficacy and minimize the adverse effect is very important for designing a more rational therapeutic plan for intermediate-advanced HCC.

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