Editorial

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Surgical treatment of hepatocellular carcinoma

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SUMMARY Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, and cirrhosis is a risk factor for HCC. Resection is indicated for those unilobar tumors without vascular invasion and metastases in the liver and preserved liver function. Small HCC (< 2 cm) without microvascular invasion is associated with a 5-year recurrence rate as high as 50% to 60%, whereas liver transplantation is indicated for those within the Milan criteria (solitary tumor ≤ 5 cm or two or three nodules ≤ 3 cm) who have decompensated cirrhosis. The 1-, 3-, and 5-year survival rates of living donor liver transplantation for HCC are 85%, 75%, and 70%, respectively. This review summarizes the scientific evidence supporting the clinical practice recommendations for patients with HCC, and it discusses surgical treatment of HCC.

Keywords liver transplantation, living donor, hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancers, the sixth most common neoplasm, and the third most common cause of cancer death (*1*). Risk factors for HCC include the hepatitis B and C viruses, alcohol use, and nonalcoholic fatty liver diseases (*2*). Approximately half of HCC cases are diagnosed early (*3*). For early-stage HCC, curative treatment with partial liver resection or liver transplantation remains the mainstay of therapy, and it is discussed in this review.

2. Resection

Partial liver resection is a potentially curative therapeutic option for HCC. Indications for partial resection include unilobar tumors without vascular invasion and metastases in the liver without cirrhosis. The 5 -year survival rate after resection for HCC is 50 % to 68% in experienced centers (*4-7*). Impaired hepatic function and/or significant portal hypertension are related to poor tolerability of resection. Regional lymph node metastases are associated with decreased survival (*8*).

Selection of appropriate candidates for resection is based on the Child-Pugh classification as determined by bilirubin and albumin levels, prothrombin time, the presence of ascites, and encephalopathy (*9*). Child-Pugh class A is a good indication for partial liver resection, whereas Child-Pugh class C is not indicated due to the risk of liver failure after resection. Varices, ascites, and portal hypertensive gastropathy can be surrogate indices of portal hypertension. In East Asia (including Japan), the retention rate of indocyanine green has been used to determine the extent of the liver resection (*10*). Improved surgical techniques and careful patient selection have decreased the mortality rate to nearly 0% and the major complication rate to approximately 3% (*11*).

The future liver remnant – the liver volume estimated to remain after resection– is an important factor for patients undergoing liver resection. The minimum safe amount of remaining liver parenchyma ranges from 20% to 40% of the total (*12*). In preparation for hepatic resection, portal vein embolization (PVE) can be safely and effectively utilized to induce hypertrophy of the remnant liver without causing liver dysfunction (*13*). Combining liver partition and portal vein ligation for staged hepatectomy results in more marked and faster regenerative ability than PVE (*14*) but is associated with high morbidity and mortality.

From an oncological point of view, anatomic resection is recommended when the tumor invades the segmental portal branches or it has satellite lesions. Ultrasound is useful for detection of tumor vessel (*15*) and the lesions missed in preoperative imaging or intraoperatively (*16*). Anatomic resection is associated with better recurrence-free survival than non-anatomic resection (*17*).

Unfortunately, a cure is not always obtained and the 5-year recurrence rate is around 50% to 70% (*18*). Risk factors for recurrence include macro and/or micro vascular invasion, multifocal tumors, and high alpha fetoprotein levels preoperatively (*19,20*). Small HCC

(< 2 cm) without microvascular invasion is associated with a 5-year recurrence rate as high as 50% to 60% (21). Approximately 80% of recurrent lesions are in the liver. Only 15% of recurrent tumors can be resected (*22*). The peak of recurrence is bimodal: the first peak occurs around 1 year after resection and the second, 4 to 5 years after resection (*18*). Late recurrence is reported to represent de novo HCC.

Currently, adjuvant chemotherapy offers no established benefit in preventing recurrence. A randomized clinical trial (*23*) comparing sorafenib versus a placebo after partial hepatectomy or ablation for HCC revealed no statistical inter-group difference in survival. Systemic chemoembolization is also ineffective, whereas retinoids, vitamin K2, transarterial ^{131}I-lipiodol, and interferon have shown promising results, but a real benefit has yet to be established (*24*). A randomized, open-label, phase 3 trial (*25*) noted that adjuvant immunotherapy with autologous cytokine-induced killer cells ($CD3^+/CD56^+$ and $CD3^+/CD56^-$ T cells and $CD3^-/CD56^+$ natural killer cells) increased recurrence-free and overall survival after curative treatment.

3. Liver transplantation

Liver transplantation is indicated when HCC is deemed to be unresectable due to impaired liver function, severe portal hypertension, or tumor location. The tumors should meet the Milan criteria, which include a single tumor ≤ 5 cm or two to three tumors ≤ 3 cm without major vessel invasion or extrahepatic tumor spread based on imaging studies (*26*). The 4-year patient survival rate of patients fulfilling the Milan criteria who undergo liver transplantation is 75%, with a recurrence-free survival rate of 83%.

The Milan criteria have been adopted by the United Network for Organ Sharing (UNOS) as the inclusion criteria for deceased donor liver transplantation. They have also been adopted by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver guidelines, and an international HCC consensus conference (*27-29*). UNOS data indicate a 5-year survival rate of 61% for patients receiving a liver transplantation under the Milan criteria (*30*). UNOS has a "sickest first" approach, which prioritizes candidates whose liver function has been evaluated using the Model for End Stage Liver Disease (MELD) score. UNOS adopted the HCC exception score.

In Japan and other Asian countries, most transplants are living - donor liver transplantations (LDLT). As LDLT is a private issue among patients and their families, indices of tumor status are considered on a case-by-case basis. Accordingly, the expanded Milan criteria (*26*) have been adopted by many transplantation centers performing LDLT, without a significantly higher rate of HCC recurrence.

In Japan, the Japanese Organ Transplantation Act was approved in 1997 and revised in 2006. The number of livers from deceased donors, however, is inadequate for the number of potential recipients. As of the end of 2016, 378 deceased donor liver transplantations were performed. During the same period, 8,825 LDLTs were performed; of these, 1,598 involved patients with HCC. The 1-, 3-, 5-, 10-, 15-, and 20-year survival rates of LDLT for HCC are 85%, 75%, 70%, 62%, 55%, and 54%, respectively.

One study enrolled 965 patients who underwent LDLT for HCC between 1990 and 2005 (*31*). Of those patients, 301 had tumors outside the Milan criteria. New criteria consisting of the tumor number, serum alpha-fetoprotein levels, and a maximal tumor diameter of 5 cm that allowed for enrollment of the maximal number of subjects resulted in a 5-year recurrence rate of less than 10%. Based on the study's results, new criteria for LDLT, *i.e.*, candidates with a tumor ≤ 5 cm in size, tumor number ≤ 5, and alfa-fetoprotein level ≤ 500 ng/mL (the so-called "5-5-500" rule), were established.

Following that study, patients who satisfy the 5-5-500 rule for LDLT or on the list for deceased donor liver transplantation are now covered by Japan's National Heath Insurance. Tumors are diagnosed as HCC based on computed tomography or magnetic resonance images obtained within 1 month of transplantation. Tumors are diagnosed based on dynamic computed tomography, hypodensity on plain computed tomography, and hyperintensity during the arterial phase and hypointensity during the portal phase of contrast-enhanced computed tomography. Local treatment of HCC must be administered at least 3 months before transplantation.

One topic of debate is the indications for liver transplantation when HCC outside the criteria is downstaged to a level within the criteria. The therapeutic modalities for downstaging include locoregional therapies such as transarterial chemoembolization or radioembolization and radiofrequency ablation.

One review reported a > 40% success rate of downstaging (*32*) with a 1-year overall survival rate ranging from 87% to 100, a 4- to 5-year survival rate varying from 90% to 70%, and a recurrence rate of 16%. The utility of downstaging might depend on the selection of patients expected to have a more favorable outcome. Current UNOS policy includes a downstaging protocol to allow patients to obtain HCC MELD exception points if specific criteria are met (*33*).

4. Conclusions

Surgical resection and transplantation remain curative therapeutic options for patients with early-stage HCC, and both result in comparable survival rates for properly selected patients. A successful outcome for transplantation due to HCC is a 5-year survival rate comparable to that for transplantation due to reasons other than HCC.

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