Review

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Liver transplantation for hepatocellular carcinoma

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Summary **Marked improvement in the prognosis for patients with liver cancer who undergo liver transplantation has been achieved as a result of advances in liver transplantation techniques. Given the current shortage of organs in China, a favorable long-term survival rate might be achieved with rigorous selection of suitable patients and therefore benefit society the most. Further study of the mechanism of cancer recurrence following liver transplantation, continuing to optimize pretreatment strategies prior to liver transplantation, and paying closer attention to the prevention and treatment of cancer recurrence following liver transplantation are important steps to improve the long-term clinical benefit of liver transplantation for patients with hepatocellular carcinoma. Perfecting the techniques of liver transplantation using a marginal donor liver is the main way to solve the current problem of an organ shortage for patients with liver cancer.**

Keywords: Hepatocellular carcinoma (HCC), liver transplantation, organ shortage

1. Introduction

There is a higher prevalence of hepatocellular carcinoma (HCC) in China, which accounts for 50% of the world's cases of liver cancer. HCC is the second most common cause of cancer mortality among all malignant tumors (*1*). HCC is accompanied by cirrhosis and has multiple foci, so fewer than 30% of patients with HCC can undergo surgical resection and the 5-year recurrence rate after surgery is 70% (*2*). Liver transplantation (LT) is surgery to remove a diseased liver and completely eliminates the cause of cancer recurrence, so LT is an effective way to cure liver cancer.

Data from the China Liver Transplant Registry (CLTR) shows that HCC currently accounts for about 50% of all liver transplants each year and that 50% of patients with HCC have advanced liver cancer falling outside the Milan criteria. Rational use of liver transplants cannot be achieved for high recurrence rate after transplant. As the number of patients waiting for LT increases, the problem of a shortage of organs is worsening. There is debate over whether to expand the use of donor resources by using marginal donor livers for LT. This paper discusses eligibility criteria for LT to treat HCC, perioperative prevention of the recurrence of HCC, and expanding the pool of donors for LT to treat HCC.

2. Eligibility criteria for LT

In clinical practice, factors for cancer recurrence after LT are key aspects of the eligibility criteria for LT. Therefore, the criteria for liver transplant recipients have been revised as LT techniques have been developed. Mazzaferro *et al*. proposed the earliest criteria for LT to treat HCC known as the Milan criteria. The 4-year overall survival rate was 85% and the disease-free survival rate after LT was 92% for patients with HCC who were selected in accordance with the Milan criteria (*3*). The Milan criteria were the first criteria for LT and were widely used by most transplant centers. However, the strict limitations of the Milan criteria meant that many patients with HCC falling outside the Milan criteria despite a lack of major vascular invasion or lymph node metastasis were not eligible to undergo LT. The Milan criteria attach greater importance to the size and number of tumors without considering the biological characteristics of HCC. Many transplant centers began to explore broader criteria for LT to treat HCC, leading to development of the Pittsburgh modified TNM criteria, the University of California San Francisco (UCSF)

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criteria, the new Kyoto criteria, the Canadian criterion of total tumor volume, and the up-to-seven criteria.

In 2001, Yao *et al*. at UCSF devised the UCSF criteria. Compared to the Milan criteria, the UCSF criteria reduced the rate of recipient loss and expanded the indications of LT for HCC without significantly increasing the rate of HCC recurrence (*4*). The UCSF criteria have gradually been adopted as the criteria for LT by many transplant centers because they have better reference values compared to the Milan criteria. Data on 2,610 liver transplants for primary HCC at two centers (Tianjin First Central Hospital and Beijing Armed Police Hospital) from January 1999 to December 2011 revealed that the 5-year cumulative survival rate was 77.1% for patients meeting the Milan criteria and 68.9% for those meeting the UCSF criteria (*5*). There was no significant difference in the cumulative survival rate of the two groups. Patients with HCC meeting the UCSF criteria but falling outside the Milan criteria accounted for 25.4% of all recipients, and those patients had a 5-year cumulative survival rate of 58.1%. This figure was greater than 50% but significantly lower than the survival rate for patients meeting the Milan criteria. Therefore, more than 50% of patients falling outside the Milan criteria and the UCSF criteria can undergo LT, representing a significant increase in potential liver transplant recipients (data showed that the number of recipients could be increased by 50% without significantly reducing the long-term survival rate).

Similar to the Milan criteria, the UCSF criteria mainly focus on preoperative imaging studies that may not coincide with actual pathology results. There are limitations on the eligibility criteria for LT to treat HCC depending on the number and size of tumors (*6,7*). One clinical pathological study at the authors' hospital found that the stage of HCC could not be determined accurately in 27% of patients prior to surgery even when sophisticated imaging studies were performed. In addition, these aforementioned criteria do not reflect the history of liver disease, prognostic factors for liver cancer, and other biological characteristics that often lead to marked discrepancies in prognosis. Over the past few years, the "Hangzhou criteria" and the "Fudan criteria" have been proposed in China (*8*). These criteria use the serum levels of alpha-fetoprotein and pathology according to a liver biopsy to evaluate tumors, but these criteria do not reflect the true histological grade due to the heterogeneity of liver cancer. Moreover, a liver biopsy may increase the risk of cancer spreading, so this approach is used by few transplant centers (*9*).

About 50% of Chinese patients with liver cancer have advanced cancer, so expanding eligibility criteria would benefit these patients, but this also means a higher rate of recurrence. Satisfactory survival rates and a quality of life like that with a normal liver transplant could not be achieved for patients with HCC falling outside the Milan criteria, and LT was only considered to be a palliative treatment. In light of the shortage of donor organs, more rigorous selection criteria are needed in order for donor resources to best benefit society.

3. Perioperative treatment

3.1. *Preoperative treatment*

Because of the shortage of organs in China, patients must wait significantly longer for LT. If patients do not receive interventional treatment while they are waiting for a donor, patients with a small tumor, much less those with a larger tumor, may cease to be eligible for surgery. This means that preoperative adjuvant treatment is absolutely necessary. Common treatments include transcatheter arterial chemoembolization (TACE), systemic chemotherapy (UFTM), percutaneous ethanol injection (PEIT), and radio-frequency catheter ablation (RFCA). The most prevalent of these treatments is TACE. A randomized controlled trial (RCT) and meta-analysis (*10*) found that patients with unresectable liver cancer who underwent TACE had a significantly improved 2-year survival rate compared to patients not undergoing that treatment (31-63% *vs*. 27%). However, whether TACE can improve the prognosis of LT is still being debated. In a control study by Decaens *et al*. (*11*), 100 patients with liver cancer underwent TACE prior to surgery and 100 patients underwent LT alone. Preoperative TACE had no effect on the 5-year survival rate (59.4% for TACE *vs*. 59.3% for non-TACE, $p = 0.7$). Treatment in the form of TACE, UFTM, or RFCA to down-stage a tumor prior to LT resulted in no significant difference in the 5-year survival rate for patients undergoing that treatment compared to patients not undergoing that treatment (unpublished data). However, patients who received that treatment can wait substantially longer. Thus, TACE, UFTM, or RFCA is recommended to delay the progression of cancer in light of the shortage of livers.

3.2. *Effects of postoperative therapies on cancer recurrence*

There is no consensus on whether patients undergoing LT for HCC should be treated with chemotherapy or not. Soderdahl *et al*. (*12*) found that epirubicin was ineffective at preventing cancer recurrence after LT. A study by Bernal *et al*. (*13*) also found that chemotherapy with cisplatin and doxorubicin was ineffective. However, a study did report that 25 patients who received chemotherapy combining 5-FU, cisplatin, and doxorubicin had a better 3-year survival rate compared to previous patients (*13*). Immunosuppressors are an important treatment after organ transplantation, so choosing the right immunosuppressors is vital to the prognosis after LT to treat HCC. Rapamycin is a novel macrolide immunosuppressor that is more frequently used in clinical settings as a basic immunosuppressor

because of its dual role of immunosuppression and anti-tumor action. Sorafenib, a new molecularly targeted drug, has an effect on advanced HCC according to a large RCT and its effect on treating the postoperative recurrence of cancer has been noted in studies. Studies on the combined use of rapamycin and sorafenib to prevent cancer recurrence after LT are underway, and initial results have been favorable.

4. Expanding the pool of donors for LT to treat liver cancer

4.1. *Hepatectomy or liver resection and transplantation for liver cancer*

Liver resection and transplantation refers to LT to treat the intrahepatic recurrence of cancer (single lesions smaller than 5 cm, and fewer than 3 lesions smaller than 3 cm) or liver failure following a previous hepatectomy to treat resectable primary HCC (single lesions smaller than 5 cm, and fewer than 3 lesions smaller than 3 cm) along with complimentary liver function. A hepatectomy prior to LT was previously assumed to potentially cure some patients with liver cancer, thus allowing other needier patients to receive donor livers. The progression of liver cirrhosis and not the recurrence of cancer is what leads to LT for certain patients with HCC following a hepatectomy. Forty to 80% of patients with cancer recurrence after hepatectomy can undergo LT (*14*). Thus, LT is considered to be a stopgap measure for patients with cancer recurrence after a hepatectomy. A study has reported that a hepatectomy prior to LT might increase the surgical mortality and the rate of cancer recurrence postoperatively, thus decreasing the survival rate of patients. A study found that the outcomes of LT were not satisfactory if cancer recurred soon after a hepatectomy (*15*). Surgical techniques have improved and data from the CLTR indicated that liver resection and transplantation has a 1-, 3-, and 5- year-survival rate of 73%, 51.77%, and 45.84%, respectively, while LT alone has a 1-, 3-, and 5-year-survival rate of 74.49%, 55.10%, and 48.81%, respectively (*16,17*). As these figures indicate, there was no significant difference in the survival rate as a result of liver resection and transplantation and LT alone. A hepatectomy might control the progression of cancer and allow recipients to wait longer, so it could increase the chances for other patients to receive a donor liver to some extent. A hepatectomy could also rule out patients who are likely to have cancer recur and enhance recipient selection. Accordingly, a hepatectomy prior to LT warrants consideration.

4.2. *Utilization of livers from hepatitis B-positive donors*

China has a massive population with hepatitis B, so most patients with liver cancer are also infected with the hepatitis B virus. Conversely, some donors are unable to donate merely because they are hepatitis B carriers. Therefore, use of livers from hepatitis B-positive donors might possibly relieve the shortage of donors. Livers from hepatitis B-positive donors consist of livers from anti-HBc-positive and HBsAg-positive donors. Livers from anti-HBc-positive donors have been widely utilized in LT thus far, but there is still disagreement about the use of livers from HBsAg-positive donors.

Early on, the use of livers from HBsAg-positive donors was precluded because they led to transplant failure. With the improvement in and maturity of prophylaxis against hepatitis B after transplantation, livers from HBsAg-positive donors have gradually been used by various transplant centers. Studies have found that suitable anti-viral therapy provides satisfactory effectiveness when using livers from hepatitis B-positive donors for LT. Loggi *et al*. (*18*) reported 10 liver transplants using livers from hepatitis B-positive donors and they noted no complications related to hepatitis B after transplantation. The current authors studied 39 liver transplants using livers from hepatitis B-positive donors at this Hospital. Most recipients had liver cirrhosis associated with hepatitis B along with primary liver cancer (with a TNM stage of T4N0M0). The selection criteria for donor livers were a good shape and appearance as well as normal function. In the 39 transplants studied, the 1-, 3-, and 5-year-survival rate was 65%, 38%, and 24%, respectively. All the recipients received adefovir along with entecavir, and no transplant failures were caused by the recurrence of hepatitis B. Thus, the use of potent anti-HBV therapy after transplantation should allow livers from hepatitis B-positive donors with no other risk factors to be used in LT for hepatitis B-positive patients with progressive liver cancer. The risk of using these types of donor livers should be fully explained to patients and their families, and informed consent must be obtained before transplantation.

4.3. *Use of other types of marginal donor livers*

Other types of marginal donor livers consisting of livers from deceased donors, livers from elderly donors, steatotic donor livers, ABO-incompatible donor livers, and donor livers with a long cold ischemia time could be utilized in suitable patients with liver cancer. This would therefore increase the sources of donor livers and shorten the waiting time for transplant patients.

5. Conclusion

Marked improvement in the prognosis for patients with liver cancer who undergo LT has been achieved as a result of advances in LT techniques. Given the current shortage of organs in China, a favorable long-term survival rate might be achieved with rigorous

selection of suitable patients and therefore benefit society the most. Further study of the mechanism of cancer recurrence following LT, continuing to optimize pretreatment strategies prior to LT, and paying closer attention to the prevention and treatment of cancer recurrence following LT are important steps to improve the long-term clinical benefit of LT for patients with HCC. Perfecting the techniques of LT using a marginal donor liver is the main way to solve the current problem of an organ shortage for patients with liver cancer.

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