Liver Cancer

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Review

Liver Transplantation for Hepatocellular Carcinoma

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Key Words
Hepatocellular carcinoma · Liver transplantation · Living donor

Abstract
Hepatitis B is endemic in many regions of Asia, including China, Korea and India. This results in a heavy burden of hepatocellular carcinoma (HCC) because hepatitis B virus is a major risk factor in the development of the disease. In addition, the incidence of hepatitis-C-related HCC is on the rise in the United States. HCC patients with poor liver function reserve are not suitable candidates for resection, and liver transplantation (LT) has emerged as the treatment of choice for small unresectable HCCs. To treat more HCC patients with LT, the standard patient selection criteria have been expanded at a number of centers. Careful and well-considered selection of patients is the key to success in LT for HCC. Although tumor size and tumor number are used to predict whether transplantation is likely to be successful, the weighting that should be attached these two parameters has not been determined. In addition to the size and number of lesions, the morphology of HCC is also predictive of its behavior. Well-circumscribed lesions, in general, are less aggressive than those with poorly defined borders. On the waiting list for LT, HCC patients compete with liver failure patients. It is essential that the criteria used for selecting HCC patients for LT should be easily applicable and fair to other transplant candidates. In the face of the scarcity of deceased-donor livers and the inevitable risks for living liver donors, a predictably low rate of recurrence of HCC after LT is mandatory.

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Introduction

Hepatitis B is endemic in many regions of Asia, including China, Korea and India. Because hepatitis B virus is a major risk factor for hepatocellular carcinoma (HCC), these areas have a high incidence of the disease. In the United States, the incidence of hepatitis-C-related HCC in African Americans and Hispanics is also on the rise [1]. HCC that occurs in livers with advanced cirrhosis cannot be treated with resection, and liver transplantation (LT) has emerged as the treatment of choice for small unresectable HCCs [2, 3]. The classic criteria for selecting HCC patients to undergo LT are the Milan criteria, which have a reliable long-term track record [4].The Milan criteria have been modestly expanded to include patients with slightly larger HCCs as transplant candidates, and such an expansion of criteria did not result in a significantly higher rate of disease recurrence after transplantation [5].

Standard Criteria for Transplantation

LT has been used to treat HCCs that cannot be resected because of extensive dissemination, but with very poor survival outcomes [6]. In the early 1990s, it was found that in the treatment of small HCCs, the survival outcome of LT was better than that of liver resection [7]. It was also realized that HCC patients who had smaller and fewer tumors and no portal vein tumor thrombi had better survival outcomes. As a result, the concept of restrictive criteria on HCC started to emerge. The classic work of Mazzaferro – the Milan criteria – prospectively examined tumor size and number on computed tomography, and became definitive in the selection of HCC patients for LT, with good results [4]. The Milan criteria (one lesion ≤5 cm or two to three lesions ≤3cm) were well accepted but were often considered too restrictive in granting patients the opportunity of LT to treat the otherwise incurable malignancy.

A modest expansion of the Milan criteria was adopted and named the UCSF (University of California, San Francisco) criteria. In this new set of criteria, tumors up to 4.5 cm in size are acceptable and the total tumor diameter of up to three lesions is set at ≤8 cm. The UCSF criteria have been in use since mid-2006 and have had the effect of including more patients as transplant candidates [8]. In a study by Yao et al. [5], the 5-year patient survival rates of living-donor liver transplantation (LDLT) for HCCs within the UCSF criteria and HCCs within the Milan criteria were 65 and 72%, respectively.

The Milan and the UCSF criteria reflect the aggressiveness of HCCs in terms of their size and number. Tumor size correlates positively with tumor grade and with the likelihood of vascular invasion [9, 10]. Although tumor biopsy is also used [11] to determine tumor grade, inaccuracies can occur because of sampling error [12] or intratumoral heterogeneity of tumor cell differentiation [13].

Allocation of Deceased-donor Liver Grafts

Patients with unresectable HCCs often have relatively well preserved liver function, and their Model for End-stage Liver Disease (MELD) scores are often low. Therefore, allocation of deceased-donor liver grafts according to disease severity previously disadvantaged them. To give such HCC patients a fair chance of LT, they are now granted an arbitrary MELD score. The assigned score is meant to equate with the dropout risk of transplant candidates dying from progressive liver failure. However, this measure was found to advantage eligible HCC patients, and therefore the assigned score was lowered from 29 to 24 and then to 22 [14].

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In regions with a scarcity of deceased-donor livers, it is imperative that transplant candidates who are not HCC patients are not disadvantaged. Scores assigned to HCC patients should not be too high, and the accuracy of tumor staging by imaging must be ensured. These measures, together with good long-term patient survival after transplantation, justify the use of precious deceased-donor liver grafts on HCC patients.

Expanded Criteria for Transplantation

In the selection of HCC patients for LT, the University of Tokyo has adopted the 5–5 rule (HCC ≤5 cm and ≤5 in number), and a recurrence-free survival rate of 94% after transplantation was achieved [15]. At Asan Medical Center, patients with HCCs not larger than 5 cm and not more than 6 in number and with no gross vascular invasion are eligible for LT. A 5-year survival rate of 81.6% was achieved [16]. Kyoto University further extended the number of HCCs to 10 with a serum proteins induced by vitamin K absence or antagonist-II (PIVKA-II) level ≤400 mAU/ml. The resulting 5-year survival rate was 86.7% [17]. At Kyushu University, a 5-year survival rate of 82.7% was achieved in patients with HCCs ≤5 cm and serum PIVKA-II levels <300 mAU/ml [18]. In a study involving 49 centers and 653 patients in Japan, patients with HCCs beyond the Milan criteria but with serum α-fetoprotein levels ≤200 ng/ml and serum PIVKA-II levels ≤100 mAU/ml had a disease-free survival rate of 84.3% [19].

Down-staging for Transplantation

Down-staging HCCs to a stage that meets the Milan criteria is certainly an attractive way to render more patients suitable for LT. Transarterial chemoembolization and radiofrequency ablation are the two commonest methods of down-staging.

Yao et al. [20] prospectively studied the mid-term outcome of HCCs that were down-staged by radiofrequency ablation or transarterial chemoembolization to meet the Milan criteria. A minimum observation period of 3 months was required before LT was allowed to take place, and down-staging failed in 18 (29.5%) of the 61 patients. In patients who were transplanted after successful down-staging, a 4-year survival rate of 92.1% was achieved. None of the 35 LT recipients developed recurrence of HCC during a median follow-up period of 25 months. Microvascular invasion was not found in any of the 35 excised livers, but macrovascular invasion was found in one. Six of the 41 patients down-staged were still awaiting transplantation.

In the study by Concejero et al. [21] at a center in Taiwan, patients with HCCs within the Milan criteria were carefully selected to undergo LDLT, and a 5-year survival rate of 90% was achieved. Eight patients were down-staged by transarterial chemoembolization or ethanol injection to meet the Milan criteria, and none of them developed recurrence of HCC. Seven patients had HCCs within the Milan criteria and initially underwent liver resection, but HCC recurred after resection. They therefore underwent salvage LDLT, after which no HCC recurrence was found.

Salvage Transplantation

An intention-to-treat analysis showed that LT for patients with small, resectable HCCs yielded superior survival outcomes than did liver resection [22]. Nevertheless, if deceased-

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donor livers are scarce, patients with small, resectable HCCs are offered liver resection rather than LT, because the use of deceased-donor liver grafts in such cases is hardly justifiable. It has been proposed that patients with HCCs beyond the Milan criteria should be treated with liver resection first and can be salvaged with LT later if they develop recurrent HCC that is within the Milan criteria and is not too aggressive [23]. Salvage LT for recurrent HCC within the Milan criteria carried out at the Asan Medical Center had outcomes comparable with those of primary LT [24]. Recurrence of disease after liver resection for large and multiple HCCs is often extrahepatic and thus contraindicates salvage transplantation. As a result, the Asan Medical Center proposed primary LT for HCC consisting of three or more lesions that meet the criteria for transplantation (number ≤6 and size ≤5 cm) [16, 25].

In contrast, Sala et al. [26] reported acceptable survival outcomes of prophylactic LT for HCC that was likely to recur after resection. In fact, HCC that has a high propensity for spreading requires the most radical treatment, i.e. LT, provided that the malignancy remains intrahepatic [27].

Early detection of HCC recurrence is crucial, as salvage transplantation is inadvisable when recurrence has developed into the late stages. Salvage LT would be precluded in most cases in which the patient does not have a strong desire for a salvage operation or when the relatives of the patient do not show enthusiasm as potential liver donors.

Primary Transplantation Instead of Resection

Failure of liver resection for HCC is often caused by development of new primaries in the remnant liver. The advantage of LT over liver resection is the total hepatectomy, which leaves no premalignant liver tissue behind. Primary LT involves the most radical resection of tumors as well as the liver bed, which is a mass of premalignant tissue. Microvascular invasion by HCC is associated with higher tumor recurrence rates after LT. A multicenter study showed that for patients who underwent LT as treatment for HCC, the chance of tumor recurrence doubled if microvascular invasion was present. However, the percentage of salvage transplantations in the series was not reported.

Microvascular invasion is an important factor for HCC recurrence after resection [28], and so its presence warrants transplantation. However, the overall 5-year survival rate of patients undergoing LT for HCCs within the up-to-7 criteria is greater than 80%, irrespective of microvascular invasion. Thus, this subgroup of patients benefits most from primary LT even if the HCC is resectable [27].

Donor Risk Versus Recipient Benefit

Unless diagnosed at a very early stage, primary cancers of major and vital organs result in high levels or mortality. From this point of view, a 50% post-LT survival rate for patients with HCC should not be considered low. It is certainly high enough for enthusiastic potential living liver donors and for potential recipients who desperately want to live.

Whether a lower recipient survival rate resulting from more liberal expansion of patient selection criteria should be accepted for LDLT in the treatment of HCC is a complex ethical question. To a living donor and the recipient, a lower recipient survival rate may be acceptable; the liver graft can be considered a gift dedicated from one to the other, and the recipient, by accepting the gift, is not depriving other LT candidates of a chance of transplantation. Nonetheless, too low a recipient survival rate could render the liver graft donation futile.

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Table 1. Survival rates at different Asian transplant centers adopting expanded patient selection criteria

Criteria	Tumor size (cm)	Tumor number	Biomarkers	Overall survival
University of Hong Kong [30]	≤6.5 ≤4.5	1 ≤3	Not tested	3-year 78% 5-year 66%
Chang Gung Hospital [21]	≤6.5 ≤4.5	1 ≤3	Not tested	3-year 96% 5-year 90%
Asan Medical Center [16]	≤5	≤6	Not tested	3-year 88% 5-year 82%
University of Tokyo [15]	≤5	≤5	Not tested	3-year 82% 5-year 75%
Kyoto University [31]	≤5	≤10	PIVKA-II ≤400 mAU/ml	5-year 87%
Kyushu University [18]	≤5	No restriction	PIVKA-II <300 mAu/ml	3-year 86% 5-year 83%

A survey showed that patients and their relatives are often willing to accept higher risks and poorer recipient outcomes, whereas the transplant team is not [29]. LDLT could expedite the treatment of HCC [30], but such procedures are often carried out before the HCC can be categorized to identify aggressive and rapidly progressing tumors.

Biological staging of HCCs with α-fetoprotein and PIVKA-II as biomarkers might help to identify aggressive lesions, which indicate poor survival after LDLT. Positron emission tomography using the tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is commonly employed to identify aggressive HCC lesions [31, 32]. In a study, HCCs which were negative for ^{18}F-FDG and slightly beyond the Asan criteria had a recurrence rate of less than 30% [33]. With modest expansions of patient selection criteria, satisfactory 5-year survival rates have been achieved at Asian transplant centers (table 1).

Summary and Conclusion

Careful and well-considered selection of patients is the key to success in LT for HCC. Although tumor size and tumor number are used to predict whether a transplantation would be successful, the weighting carried by these two parameters has not been determined. In addition to size and number, the morphology of HCC is also predictive of its behavior. Well-circumscribed lesions, in general, are less aggressive than those with poorly defined borders [34].

HCC patients on the waiting list for LT compete with liver failure patients. It is essential that the criteria used for selecting HCC patients for LT are easily applicable and fair to other transplant candidates. In Asia, where a large majority of LTs involve LDLT, more flexible criteria can be tested under careful clinical trial settings, and future policies and practice should be guided by the data so generated.

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