Liver Transplantation for Hepatocellular Carcinoma: An Asian Perspective

Kenneth S.W. Mak and Kai Chah Tan, Liver Transplant Unit, National University Hospital, Singapore.

Liver transplantation is an established treatment modality for patients with hepatocellular carcinoma (HCC), creating a potential for disease-free, long-term survival. In Asia, due to a severe shortage of donors, resection remains the treatment of choice for patients with HCC and good liver functional reserve. The use of marginal donors, split liver grafts and grafts from living donors are potential solutions that are best performed in experienced liver transplant centres to ensure an optimal outcome. Ethical issues relating to living donor liver transplantation have yet to be fully addressed. The roles of therapies to limit tumour progression during the waiting period, such as transarterial chemoembolization, need to be further investigated in the setting of a prospective trial and their benefits better defined. (Asian J Surg 2002;25(4):271-6)

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the most common tumours in the world with an incidence as high as 30 per 100,000 population in endemic regions. In recent years, the incidence of HCC has been on the rise, due to a variety of factors including the increasing incidence of hepatitis C infection. Despite the many treatment modalities available, HCC continues to be associated with a poor prognosis and has an overall 5-year survival of <5%. Only surgery, be it liver resection or transplantation, offers a chance of long-term, disease-free survival.

LIVER TRANSPLANTATION

Liver transplantation is the most radical form of surgical treatment available for HCC. Not only does it remove the tumour but it also replaces the underlying diseased liver parenchyma. Transplantation removes all the cirrhotic tissue that is at risk for tumour formation and potentially all occult microscopic foci of tumour cells within the diseased liver, which are the main source for tumour recurrence. It also overcomes the limitations of operating in a patient with inadequate liver reserve and, thus, avoids the potential complications of postoperative liver failure.

Liver transplantation was first performed for liver malignancy in the 1960s. In fact, five of the first six liver transplants performed in the United States and two of the first three performed in the United Kingdom, were for patients with primary liver malignancies. Nonetheless, this initial enthusiasm was dampened by poor results. The perioperative mortality was high, in the order of 24% to 70%. Due to poor patient selection, the tumour recurrence rate was also unacceptably high. This resulted in 3-year and 5-year survival rates of 15% to 37% (Table 1). Fewer than 10% of patients were tumour-free for more than 2 years.

The high perioperative mortality and tumour recurrence rates coupled with the high costs and limited supply of donor organs inevitably led to questions regarding the role of liver transplantation for HCC. In Europe, the percentage of liver transplants performed for a malignant indication decreased from
29% between 1983 to 1988, and 10% between 1989 and 1992.\textsuperscript{13}

The early results for transplanting patients with HCC were not uniformly dismal. A good outcome was often noted when patients with "incidental" tumours were transplanted.\textsuperscript{7} The recurrence rate in these patients was lower (0%–13%) compared to patients with HCC diagnosed before transplantation (37%–82%).\textsuperscript{9,14}

In a subgroup of cirrhotic patients with no "adverse" factors, transplantation yielded superior results compared to resection. In a retrospective analysis of 60 patients, Bismuth et al showed that patients with tumours less than 3 cm in diameter, fewer than 3 nodules and without extrahepatic disease had an 83% 3-year survival after transplantation, compared to 18% in the resection group.\textsuperscript{15} When the same centre used the above prognostic criteria to select patients for transplantation, they found that survival results improved (5-year survival rate of 73%) in the entire transplanted patient cohort studied.\textsuperscript{4} Favourable prognostic features have since been identified that yield a better outcome after transplantation.\textsuperscript{14–22} These are summarized in Table 2.

With careful selection using the above prognostic criteria, patients transplanted for HCC have results as favourable as transplantation for non-malignant indications (Table 3).\textsuperscript{4,23,24} Today, liver transplantation is no longer considered an experimental form of treatment but is an established therapeutic modality for HCC.

**Limitations for Transplantation in Patients with HCC in Asia**

Most of the recommendations advocating transplantation as treatment for HCC originated from established liver transplant centres in Europe or the United States. In some of these centres, transplantation has surpassed resection as the treatment of choice in cirrhotic patients with a small HCC and well-preserved liver function.\textsuperscript{24} This approach is supported by intention-to-treat analyses, which suggest that surgical resection and transplantation have at least similar survival rates in patients with no adverse prognostic factors.\textsuperscript{23} Nonetheless, this relies heavily on the premise that there is early availability of donor organ grafts.

The situation in Asia is entirely different from that in the West. Liver transplantation is not available in many Asian countries, as the costs associated with establishing a transplant service and the treatment itself are too high. Even in countries where liver transplantation is available, only limited subsidies are available to support the financially needy patient with a medical indication for transplantation. In Singapore, only a limited number of transplants are subsidized each year by the government. In Japan, no insurance subsidization is available for transplantation in patients with hepatitis B or C viral infection. Because the majority of the patients with HCC in Japan are carriers of viral hepatitis antigens, transplantation is rarely offered as a treatment option.

Although a universal problem, donor liver shortage is particularly acute in Asia for various cultural, religious

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**Table 1. Early results of transplantation for hepatocellular carcinoma**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Operative mortality (%)</th>
<th>Recurrence (%)</th>
<th>1 year (%)</th>
<th>3 years (%)</th>
<th>5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Iwatsuki (Pittsburgh, USA)</td>
<td>1985</td>
<td>37</td>
<td>24 (at 30 days)</td>
<td>43</td>
<td>68</td>
<td>25</td>
<td>-</td>
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<tr>
<td>8</td>
<td>Bismuth (Paris, France)</td>
<td>1987</td>
<td>157</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>O’Grady (King’s College, UK)</td>
<td>1988</td>
<td>19</td>
<td>31 (at 90 days)</td>
<td>65</td>
<td>43</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>Ringe (Hannover, Germany)</td>
<td>1989</td>
<td>79</td>
<td>30</td>
<td>52</td>
<td>38</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Penn (multicentre)</td>
<td>1991</td>
<td>365</td>
<td>-</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>Dalgic (Birmingham, UK)</td>
<td>1994</td>
<td>39</td>
<td>28</td>
<td>46</td>
<td>56</td>
<td>32</td>
<td>26</td>
</tr>
</tbody>
</table>

- = no data.

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**Table 2. Prognostic features for transplantation in patients with hepatocellular carcinoma**

- Small, solitary lesion < 5 cm in diameter
- 3 nodules, each less than 3 cm in diameter
- No vascular or lymphatic invasion
- No extrahepatic disease
LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

and social reasons. In Singapore, of the first nine patients transplanted for HCC over a 5-year period, the median waiting period was 5 months. Two of these patients had a waiting time of 12 months. In a decision analysis model for patients with compensated liver cirrhosis and surgically-resectable HCC, Sarasin et al showed that when the length of the waiting period for a liver graft exceeded an average of 8 months, the survival benefit provided by liver transplantation is overwhelmed by the risk of tumour growth and dissemination.26 This would lead to a potential “drop-out” rate as high as 25% for patients with HCC initially accepted for transplantation. Our experience supports this conclusion, with more than 40% of patients on the waiting list “dropping out” due to worsening of their clinical condition or tumour dissemination. To alleviate the problems associated with donor organ shortage, attempts have been made to use grafts from less traditional sources. As in the West, these include the use of marginal donors, the second graft arising from split liver transplant retrievals and living donors. Nonetheless, it is only living donor liver transplantation (LDLT) that is likely to have a significant impact in alleviating this shortage of donor organs.

Today, LDLT constitutes a significant proportion of the liver transplants performed in Asia. In Hong Kong, Japan, Korea, Taiwan and Singapore, LDLT is offered routinely as a therapeutic option to patients with end-stage liver disease. LDLT constitutes 30% of liver transplants performed in our institution; this includes two of the 16 patients transplanted for HCC. Nonetheless, problems remain in the use of such grafts. Not all potential living donors are suitable and as many as one-third may be rejected due to blood group incompatibility, unsuitable donor liver, as well as high risk to the donor from inadequate liver volume and concomitant medical disease.27 LDLT has real risks and potential complications for the donor. As the minimum graft volume represents 40% of the standard liver volume of the recipient,28 a donor left hepatectomy, right hepatectomy or even an extended right hepatectomy is often required in order to provide sufficient liver function for an adult recipient.28,29 Donor complications have included bleeding, liver dysfunction and failure, biliary complications and even death.27,29–32 Subjecting a healthy donor to such a major operation with potentially disastrous complications has raised ethical concerns.31 It is mandatory that such a strategy should only be undertaken by liver transplant centres highly experienced in both transplant and non-transplant related hepatic surgery. The potential living donor should also be fully counseled concerning the risks involved in the operation.

TREATMENT STRATEGIES FOR HCC IN ASIA IN THE ERA OF LIVER TRANSPLANTATION

In treating patients with HCC, the ideal therapeutic modality is one that provides the lowest immediate mortality and the longest possible tumour-free survival, after considering factors like tumour location and distribution, liver reserve and co-morbid disease.33 Nonetheless, different strategies have been developed in the West and in Asia. The problem of severe donor liver shortage favours the use of resection for patients with easily accessible tumours and good liver synthetic function, in whom the risk of resection is relatively low.20,34 Liver transplantation has no significant role for these patients in Asia, in contrast to that in the West.24,25

Resection is generally safe in patients with good liver synthetic function and no significant portal hypertension. With advances made in surgical techniques, perioperative mortality has decreased significantly from 28% to 0% in the hands of experienced hepatobiliary surgeons.35 Most liver centres report perioperative mortality rates in the

<table>
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<tr>
<th>Ref.</th>
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<th>Survival 1 year (%)</th>
<th>Survival 3 years (%)</th>
<th>Survival 5 years (%)</th>
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</thead>
<tbody>
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<td>45</td>
<td>24 (at 30 days)</td>
<td>43</td>
<td>68</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>23</td>
<td>Bechstein (Berlin, Germany)</td>
<td>1998</td>
<td>52</td>
<td>3.8 (at 2 months)</td>
<td>21</td>
<td>88</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>24</td>
<td>Figueras (Barcelona, Spain)</td>
<td>2000</td>
<td>85</td>
<td>–</td>
<td>–</td>
<td>84</td>
<td>74</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 3. Improved results with strict inclusion criteria when transplanting for hepatocellular carcinoma
order of 5% to 10%.\textsuperscript{3,36} Resection is particularly indicated in patients who present with large tumours and good liver reserve.\textsuperscript{37} With strict inclusion criteria, such patients would not be offered liver transplants, even in the West.

Unfortunately, not more than 20% of patients with HCC are suitable candidates for resection.\textsuperscript{3,38,39} Liver transplantation should then be offered to the patients with “small volume” HCC (< 5 cm in diameter and < 3 nodules in number) complicated by compromised liver reserve. In these instances, only liver transplantation can potentially cure the two disease processes, that of malignancy and cirrhosis. For the remaining patients in whom surgery is contraindicated, a variety of local ablative treatment strategies are available such as transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), cryotherapy, radiofrequency ablation and internal radiation. Palliative combination systemic chemotherapy has been given with mixed results. The treatment strategy adopted at the National University Hospital, Singapore is shown in the Figure.

\textbf{PREVENTING TUMOUR PROGRESSION IN PATIENTS Awaiting Liver Transplantation}

The long waiting period for a suitable donor liver has prompted many centres to offer adjuvant therapy to patients with HCC awaiting a liver transplant. This includes the use of TACE and/or systemic chemotherapy. It is hoped that this may prevent tumour progression in patients enduring the long wait for a liver graft and also decrease the risk of tumour cell spillage during transplantation.\textsuperscript{25,40}

Based on data derived from non-transplanted patients with HCC, TACE has been reported as an effective means of tumour control while awaiting liver transplantation. Various authors have reported TACE to be effective in inducing marked tumour necrosis with only minor adverse sequelae,\textsuperscript{41–43} although there is no evidence of better long-term survival in any randomized, controlled trial to date.\textsuperscript{44–49}

TACE has been shown to offer a survival advantage in a subgroup of patients with tumours more than 3 cm in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Treatment strategy for hepatocellular carcinoma at National University Hospital, Singapore. TACE = transarterial chemoembolization; RF = radio frequency; PEI = percutaneous ethanol injection.}
\end{figure}
size. A 74% disease-free survival rate at 5 years was similar to that of patients with smaller tumours who underwent liver transplantation. This raises the possibility of TACE being used to downstage tumours and, thus, expand the selection criteria for transplantation.

In view of our potentially long waiting period for a suitable donor graft, we routinely offer TACE to our patients with HCC awaiting transplantation. Twelve of our 16 patients with HCC underwent TACE pre-operatively; this was repeated every 3 to 6 months until they received a liver graft. Three patients were not given TACE, as they underwent transplantation soon after being placed on the waiting list, or in the context of a living related transplant. In one patient, HCC was diagnosed incidentally after histological examination of the explanted liver post-transplantation.

Although systemic chemotherapy has been used to complement liver transplantation in some centres, there are few data from prospective controlled trials to support its adoption perioperatively. Some authors have suggested some efficacy in the context of large, high-risk tumours. Nonetheless, these same patients would not fulfill the strict selection criteria generally adopted for transplantation. The use of systemic chemotherapy in this setting is, therefore, considered investigational.

**Summary**

Today, liver transplantation is an established treatment modality for patients with HCC, allowing a potential for disease-free, long-term survival. It complements the therapeutic armamentarium of the hepatobiliary surgeon and has a distinct benefit in the subgroup of patients with small tumour burdens and inadequate liver reserves to tolerate resection.

In Asia, for the patient with HCC and good liver functional reserve, resection remains the treatment of choice, as the severe shortage of donor liver limits the application of transplantation. The use of marginal donors, split liver grafts and grafts from living donors will help alleviate the problem of organ shortage but are best performed in experienced liver transplant centres to ensure the best possible outcomes. Ethical issues related to the use of LDLT for the treatment of adult patients with HCC remain to be addressed. The role of therapies to limit tumour progression during the waiting period needs to be further investigated in the setting of a prospective trial and their benefits better defined.

**References**


