Liver Transplantation for Hepatocellular Carcinoma: How Far Can We Push the Envelope?

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Hepatocellular carcinoma (HCC) remains one of the most common malignant tumours in Asia. It is the 4th most common cancer in males in Singapore. Due to the prevalence of viral hepatitis, more than 80% of HCC in Asia is associated with cirrhosis. It has an extremely poor prognosis because the tumour is often diagnosed late and is frequently associated with cirrhosis. Without treatment, the average survival time from diagnosis to death is six months. Unlike most other solid organ cancers, where the tumour and its extent determine the treatment and prognosis, in patients with HCC, the management and outcome are greatly influenced by the associated cirrhosis. Not infrequently, death is due to the cirrhosis and its sequelae rather than the tumour[1,2].

Currently, all ablative treatment modalities including percutaneous ethanol injection, radio-frequency therapy and surgical resection are limited to the patients with compensated cirrhosis. Unfortunately, recurrence rates are high after all these therapies. Following surgical resection, recurrence rates have ranged from 47% at three years[3,4] to 100% at five years[5] due to the multifocality of HCC in cirrhosis[5,6]. Only liver transplantation (LT) has the potential to simultaneously cure both the tumour and the underlying cirrhosis.

The early results of LT for HCC were disappointing because of the high rates of perioperative mortality and tumour recurrence. A 75% recurrence rate with a 25% three-year survival was reported from Pittsburgh[7]. The Cincinnati Transplant Tumour Registry reported a disappointing 18% five-year survival rate[8]. It was soon realised that the indications for transplanting the majority of these patients were wrong. Many of the patients with recurrences were transplanted with tumours that were deemed too large to be resected, often without cirrhosis. These tumours were often complicated by vascular invasion and lymph node metastasis. Clearly, these results were not acceptable given the high cost of the procedure and the limited resource of cadaveric donor livers. At the same time, a significant proportion of patients with non-malignant end-stage liver diseases were dying for lack of cadaveric donor livers. In 1989, the Department of Health and Human Services in the United States specifically identified HCC as a contraindication for LT.

It was observed that small incidental HCC in patients transplanted for other end-stage liver diseases were associated with low tumour recurrence rate[7]. This provided the impetus for a number of centres to transplant patients with small (early) HCC and liver decompensation[9-11]. In 1996, Mazzaferro et al[11] reported excellent results when they restricted LT to patients with solitary HCC not exceeding 5 cm in diameter and in others with no more than three tumour nodules, each 3 cm or less in diameter. The four-year overall and recurrence-free survival rates were 85% and 92% respectively. Since then their criteria, referred to as the Milan criteria, has been widely used for selecting candidates with HCC for LT. With these restrictions, the survival rates for transplanting patients with HCC approached that of patients transplanted without malignant disease[10-13].

It has also been observed that the "tumour burden" (number and size) of HCC does not always accurately predict its behaviour. Some small HCC have recurred whereas others with much larger tumours have achieved long-term survival after LT. In a multivariate analysis of 120 patients transplanted with HCC, Jonas et al noted that the only prognostic parameters were vascular invasion and histopathologic grade of differentiation and both these parameters do not always correlate with tumour burden[14]. In autopsy studies, portal vein thrombi have been observed in up to 40% of HCC less than 5 cm in diameter[15]. Clearly, the malignant behaviour of HCC is the result of a complex inter-play of host and tumour factors, the nature of which has not been elucidated[16]. It is not surprising that previous attempts to define the upper limits of "tumour burden" as predictors of recurrence after LT have yielded conflicting results[11,17-19]. Perhaps pre-transplant biopsy of the tumour should be routinely performed, particularly with the development of new diagnostic tools in molecular profiling and genetic analyses[20].

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Recently, there have been a number of reports suggesting that perhaps the Milan criteria might be too stringent. In a series of 70 consecutive patients where tumour size limits were expanded beyond the Milan criteria, Yao et al observed that the survival rates after LT were not adversely affected[19]. In their so called UCSF criteria, patients with solitary HCC up to 6.5 cm and others with up to three tumour nodules, with the largest <4.5 cm and total tumour diameter <8 cm were transplanted. They achieved survival rates of 90% and 75.2% at one and five years respectively. In their series, by expanding the Milan criteria for transplanting patients with HCC, an additional 23% of patients were transplanted with excellent outcome.

In a retrospective analysis of 403 patients with HCC transplanted in Pittsburgh, Fung et al found that if the Milan criteria had been used, 37% of their patients would be denied LT of which almost half did not suffer tumour recurrence[21]. Even if the more liberal UCSF criteria had been used, 32.6% of the patients would have been denied LT for which in 45.3% the tumour did not recur. It is clear that our current criteria for transplanting patients with HCC are from satisfactory. In our zeal of trying to avoid "wasting" a cadaveric donor liver on a patient who may ultimately suffer tumour recurrence, we could be denying a significant proportion of our patients the benefit of a life saving procedure.

The success of LT for patients with HCC complicated with cirrhosis and the lack of a feasible alternative, have resulted in an ever expanding pool of such candidates on the wait list for a cadaveric donor liver. Currently the average waiting period for most blood types in the West is more than a year[19]. Given the rapid progression of HCC and the long waiting period for a suitable donor liver, many initial candidates will become ineligible "drop-outs" for LT[22,23]. As such, patients with HCC have been offered the option of accepting livers from high-risk donors for LT[22]. These are donors with either positive hepatitis B care antibody (HBcAb) or hepatitis C antibody and those with a history of high-risk behaviour for acquiring viral hepatitis or HIV. Even domino or sequential LT have been performed for the patients with HCC by using livers retrieved from patients with familial amyloidotic polyneuropathy[24].

The recent development and clinical application of adult living donor liver transplantation (ALDLT)[25-30], is already having an impact on the management of the patient with HCC. ALDLT has been shown to be a feasible alternative to cadaveric liver transplantation (CLT), with reported donor mortality worldwide of about 0.3%[27,30,31]. A major advantage of ALDLT is an almost negligible waiting time and this is especially important in the management of a rapidly progressive condition such as HCC. Although there has been no controlled trial, data from decision analyses have repeatedly shown there is substantial survival advantage and cost-effectiveness of ALDLT when compared with CLT, especially if the waiting period exceeds six months for the later procedure[32,33]. Currently in the USA, 7.8% of ALDLT is performed for patients with HCC as against 2.7% when CLT is used[34].

A recent survey indicated that patients and their families would be willing to accept far greater risks for the donors with marginal outcomes in the recipients than the transplant team[35]. As ALDLT does not compete for the scarce resource of cadaveric donor livers, which had previously limited the expansion of the criteria for transplanting HCC, it is likely that an increasing number of patients with more advanced HCC will be transplanted. Future selection criteria will be determined by how much risk is acceptable for the donor relative to the benefits to the recipient, by society as a whole and the transplantation community in particular. In addition, since ALDLT can be scheduled, it allows for optimal adjuvant anti-tumour therapy such as trans-arterial chemo-embolisation. This may provide survival advantage for the patients with more advanced HCC who otherwise would not be considered for transplantation.

In conclusion, the indications for transplanting patients diagnosed with HCC are still evolving. Liver transplantation remains the treatment of choice, especially when the tumour is associated with decompensated liver cirrhosis. Previously, due to the scarcity of cadaveric donor livers, only patients with small or early tumours were transplanted. Despite this, a substantial number of patients with HCC "drop-out" because of tumour progression while on the waiting list. In addition, the scarcity of donor livers has also led to some patients with more advanced HCC who could have benefited being denied this life-saving procedure. Recently, the clinical implementation of ALDLT has allowed more timely transplantation of patients with HCC, thus reducing the "drop-out" rate. ALDLT has also allowed expansion of the current criteria for transplanting patients with HCC. Combined with more effective adjuvant anti-tumour therapy, ALDLT has opened up avenues of treatment for patients with advanced HCC and liver decompensation who were previously considered unsuitable for transplantation.

REFERENCES

1. Jonas S, Bechstein WO, Kling N, Guckelberger O, Neuhaus P. Therapy of primary hepatocellular carcinoma. Dtsch Med Wochenschr 1997; 122:617-20.
2. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Tsukamoto T, Hamba H, et al. Clinical significance of prior hepatitis B virus infection in patients with hepatitis C virus-related hepatocellular carcinoma. Cancer 1999; 86:793-8.
3. Fuster J, Garcia-Valdecasas JC, Grande L, Tabet J, Bruix J, Anglada T, et al. Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. Ann Surg 1996; 223:297-302.
4. Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular cancer in Japan. The Liver Cancer study group of Japan. Cancer 1994; 74:2772-80.
5. Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg 1991; 214:114-7.
6. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: A Western experience. World J Surg 1986; 10:311-7.
7. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 1985; 202:401-7.
8. Penn I. Hepatic transplantation in primary and metastatic cancers of the liver. Surgery 1991; 110:726-35.
9. Bismuth H, Chiche I, Adam R, Castaing D Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993; 218:145-51.
10. Romani F, Belli LS, Rondinara SF, De Carlis L, Rimoldi P, Riolo F, Bellati G, et al. The role of transplantation in small hepatocellular carcinoma complicating cirrhosis of the liver. Surg Gynecol Obstet 1994; 178:379-84.
11. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693-9.
12. Llovet JM, Bruix J, Fuster J, Castells AG. Liver transplantation for small hepatocellular carcinoma; the tumour-node-metastases classification does not have prognostic power. Hepatology 1998; 27:1572-7.
13. Figueras J, Jaurrieta E, Valis C, Benasco C, Rafecas A, Xiol X, Fabregat J, et al. Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma: a comparative study. Hepatology 1997; 25:1485-9.
14. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatol 2001; 33:1080-6.
15. Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimossato Y. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. Cancer 1990; 66:2174-9.
16. Kirimlioglu H, Dvorchik I, Rupert K, Finkelstein S, Marsh JW, Iwatsuki S, et al. Hepatocellular carcinoma in native livers from patients treated with orthotopic liver transplantation: Biologic and therapeutic implications. Hepatol 2001; 34:502-10.
17. McPeake JR, O Grady JG, Zaman S, Portmann B, Wight DG, Tan KC, et al. Liver transplantation for primary hepatocellular carcinoma: Tumour size and number determine outcome. J Hepatol 1993; 18:226-34.
18. Herrero IJ, Sangro B, Quiroga J, Pardo F, Herraiz M, Cienfuegos A, et al. Influence of tumour characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. Liver Transpl 2001; 7:631-6.
19. Yao FY, Ferrell L, Bass NM, Watson JJ, Bachetti P, Vernook A, Ascher NL, et al. Liver transplantation for hepatocellular carcinoma: Expansion of tumour size does not adversely impact survival. Hepatology 2001; 33:1394-403.
20. Bonham CA, Subbotin M, Finkelstein S, Marsh W, Dvorchik I. Allelic loss predicts recurrence of hepatocellular carcinoma following liver transplantation. Am J Transplant 2002; (Suppl 3):S459.
21. Fung J, Marsh W. The quandary over liver transplantation for hepatocellular carcinoma: The greater sin? Liver Transpl 2002; 8:775-7.
22. Yao FY, Bass NM, Nikolai B, Davern TJ, Kerlan R, Wu V, et al. Liver transplantation for hepatocellular carcinoma: Analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transpl 2002; 8:873-83.
23. Llovet JM, Fuster J, Bruix J. Intention to treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30:1434-40.
24. Azoulay D, Samuel D, Castaing D, Adam R, Said G, Bismuth H. Domino liver transplants for metabolic disorders: Experience with familial amyloidotic polyneuropathy. J Am Coll Surg 1999; 189:584-93,
25. Lo CM, Fan ST, Liu CL, Wei WI, Lo RJ, Lai CI, et al. Adult-to-adult living donor liver transplantation using extended right lobe grafts. Ann Surg 1997; 226:261-9.
26. Park KM, Lee SG, Lee YJ, Hwang S, Nam CW, Choi KM, et al. Adult-to-adult living donor liver transplantation att he Asia Medical Centre, Seoul, Korea. Transpl Proc 1999; 31:456-8.
27. Todo S, Furukawa H, Jin M, Shimamura T. Living donor liver transplantation in adults: outcome in Japan. Liver Transpl 2000; (Suppl 6):S66-S72.
28. Inomata Y, Uemoto S, Asonuma K, Egawa H, Kiuchi T, Fujita S, et al. Right lobe graft in living donor liver transplantation. Transplantation 2000; 69:258-64.
29. Marcos A, Ham JM, Fisher RA, Olzinski AT, Posner MP. Single-centre analysis of the first 40 adult-to-adult living donor liver transplant using the right lobe. Liver Transpl 2000; 6:296-301.
30. Broelsch CE, Malago M, Testa G, Gamazo CV. Living donor liver transplantation in adults: outcome in Europe. Liver Transpl 2000; 6 (Suppl 2):S64-S65.
31. Renz JF, Roberts JP. Long-term complications of living donor liver transplantation. Liver Transpl 2000; (Suppl 6):S73-S76.
32. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: A life expectancy and cost-effectiveness perspective. Hepatology 2001; 33:1073-9.
33. Cheng SJ, Pratt DS, Freeman RB Jr., Kaplan MM, Wong JB. Living-donor versus cadaveric liver transplantationn for non-resectable small hepatocellular carcinoma and compensated cirrhosis: a decision analysis. Transpl 2001; 861-8.
34. Brown RS Jr., Russo MW, Lai M, Shiffman ML, Richardson MC, Everhart JE, Hoofnagle JH, A survey of liver transplantation from living adult donors in the United States. N Eng J Med 2003; 348:818-25.
35. Cotler SJ, McNutt R, Patil R, Banaad-Omiotek G, Morissey M, Abrams R, et al. Adult living donor liver transplantation: preferences about donation outside the medical community. Liver Transpl 2001; 7:335-40.