



## Letter to the Editor

**Comment on experience with LDLT in patients with hepatocellular carcinoma and portal vein tumor thrombosis postdownstaging**


To the Editor;

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and it's the second leading cause of cancer death in East Asia and sub-Saharan African countries [1]. Resection or liver transplantation (LT) provides the best survival in HCCs within Milan criteria, while the ideal treatment for HCCs beyond Milan criteria is downstaging and then proceeding with LT in cases with a satisfactory response. Several procedures which consist of surgical resection with negative margin, transarterial chemoembolization (TACE), transarterial radioembolization (TARE) and radiofrequency ablation have been used for bridging or downstaging for patients with HCC cases prior to LT [2]. Portal vein tumor thrombus (PVTT), which is detected in 10–40% of patients with HCC, was previously considered contraindication for LT, and post-transplant survival rates for patients with PVTT were not satisfactory. However, recent studies showing successful results with TARE in patients with PVTT were published. We would like to share our experience about the effectiveness of LDLT after downstaging (DS) in patients with HCC and PVTT in the light of the recent paper published Soin and colleagues [3]. We also would like to emphasize some of the overlooked points we found in their study, based on the experiences we have gained from about 2750 LT including 415 patients with HCC.

The authors state that they perform liver biopsy to 2% of the patients with HCC [3]. Biopsy is not required for the diagnosis of HCC provided that multidetector computerized tomography (MDCT), magnetic resonance imaging (MRI) and alfa-feto protein (AFP) are evaluated all together. Furthermore, biopsy has no use if LT was being planned. However, protocol biopsy is useful for choosing the optimal management protocol, evaluating the tumor response and for the design of the scientific studies in patients in whom downstaging was planned. Therefore, in our practice we require core biopsy in all patients who are selected for DS if there is no medical contraindication. According to the current literature, risk of the tumor seeding was between 0–19% but recent metanalyses states that the risk is actually below 1% [4,5]. In our high-volume HCC cohort, tumor seeding developed in only one patient.

The authors stated that they are using living liver donors (LLD) with 20% hepatosteatosis or less [3]. In our liver transplant institute, we are using the LLDs evaluation protocol proposed by Lee and

colleagues [6] and we evaluate age, macrosteatosis, remnant future liver volume and body mass index (BMI). The authors stated that they have used grafts with graft to recipient weight ratio (GRWR) 0.6–0.7% in recipients with MELD score less than 19 [3]. In other word, the authors mean that small liver (GRWR < 0.6) can be used in patients in good condition. However, MELD score should not be the only parameter to be evaluated during the decision-making process regarding the use of low GRWR. Macshut and colleagues [7] have shown that donor age, recipient age, Child C, ABO incompatibility and GRWR (<0.6 and 0.6–0.7) were risk factors for small for size syndrome, early graft loss and 1-year mortality of the patients. Our experience is in accord with the data of Maschut and colleagues [7].

The authors have defined the patients included in the study as HCC-cirrhosis [3]. In our opinion, HBV, HCV, alcohol are majority of the causes that may be underlying HCC; however, in significant number of the patients with HCC are diagnosed incidentally and the cirrhotic process did not start in these patients. This can also be seen from the data of the authors because there are patients with MELD score of 6 (lower limit of the range given for MELD score) in all three study groups [3]. A more accurate evaluation would be possible if the authors had provided the Child-Pugh scores of the patients. Another point that should be emphasized in the present study is the fact that the authors have found a causative factor for all the patients with HCC in the present study [3]. Current literature suggests that causes of 5–30% of the patients with HCC could not be determined despite performing adequate laboratory and radiological investigations [8]. The experience of our institute suggests that there is no causative factor in 12.5% of the cases with HCC and 1.5% of the patients with HCC had completely normal non-tumorous liver parenchyma.

The authors have used two different AFP values (100–400 ng/mL) for evaluation of the risk factors for survival of the patients with PVTT [3]. The reason why the authors have chosen to do such an evaluation is not clear. In our opinion, classifying AFP values according to traditional methods has no place in evidence-based medical practice. It is best to calculate an optimal cut-off point using the receiver operator characteristics (ROC) curve analysis to demonstrate the relationship between AFP and recurrence or mortality. Until now, traditional classification has used AFP and HCC relationship and we definitely do not agree with this method. Because this approach causes bias.

Studies in current literature have used different cut-off values for AFP (100–200–300–400–1000) to evaluate the correlation between tumor recurrence, DFS, OS and AFP. However, despite extensive research the role of AFP in patients who receive DS is not determined clearly. One reason for this may be that more than 40% of the patients with HCC have low or normal AFP levels [9,10]. Another important point is lack of information regarding the optimal decrease in AFP levels determining the success of downstaging. Authors have stated that  $\Delta$ AFP of 2000 ng/mL reduced the risk of recurrence by 7.96-fold [3]. Although the importance of AFP

**Abbreviations:** LDLT, living donor liver transplantation; DS, downstaging; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; LT, liver transplantation; MDCT, multidetector computerized tomography; MRI, magnetic resonance imaging; AFP, alfa-feto protein; LLD, living liver donors; GRWR, graft to recipient weight ratio; MELD, model for end stage liver disease; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus.

is a known fact, it is seen that the authors have transplanted patients with or without PVTT having high AFP levels [3]. There is consensus regarding AFP > 1000 ng/mL suggesting vascular invasion or metastatic disease even if it is not determined with radiologic studies. This observation emphasizes the importance of the biologic behavior of the tumor [9,11]. It is known that post-transplant recurrence will be high for these patients if downstaging is not performed. Some studies have found that patients with tumors within Milan criteria with high AFP levels have significantly worse prognosis when compared to patients with tumor outside Milan criteria with low AFP levels [12]. It was shown that when AFP cut-off value of 400 ng/mL is chosen, Milan criteria could be extended without a significant impact on patient survival [12]. Mehta and colleagues [13] have evaluated 407 patients with HCC with a pre-transplant AFP levels > 1000 ng/mL and have shown that during the enlistment period if the AFP levels were down-staged to < 500 or < 100 ng/mL would reduce the recurrence risk by 2.85 and 7.14 folds; respectively. In our opinion, in any patient with HCC and an AFP value > 1000 ng/mL should be scheduled for down-staging regardless of the eligibility for liver transplantation and a transplant should only be performed after the AFP values are reduced below 500 ng/mL.

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### Ethical approval

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### Consent

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### Author contribution

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### Registration of research studies

No.

### Guarantor

No.

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