

Primary liver transplantation vs liver resection followed by transplantation for transplantable hepatocellular carcinoma: Liver functional quality and tumor characteristics matter

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Fuks *et al* in *Hepatology* offers an approach by which selecting between LR-followed-by-ST and immediate LT might be easier. Here we discuss the results of the aforementioned report in the light of currently available knowledge.

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Abstract

Liver resection (LR) and primary liver transplantation (LT) are two potentially curative treatment modalities for patients with hepatocellular carcinoma (HCC). If an underlying chronic liver disease exists, however, making a decision on which method should be selected is difficult. If a patient has no chronic liver disease, LR may be the preferable option with salvage transplantation (ST) in mind in case of recurrence. Presence of a moderate-to-severe liver failure accompanying HCC usually warrants primary LT. The treatment of patients with HCC and early-stage chronic liver disease remains controversial. The advantages of "LR-followed-by-ST-if-needed" strategy include less complicated index operation, no need for immunosuppression, use of donor livers for other patients in today's organ shortage setting and comparable survival rates. However, primary LT has its own advantages as it also treats underlying chronic liver disease with carcinogenic potential, removes undetected tumor nodules and potentially eliminates need for a ST. An article recently published by

COMMENTARY ON HOT TOPICS

Liver transplantation (LT) remains the most effective treatment modality for patients with hepatocellular carcinoma (HCC) and underlying chronic liver disease provided that the procedure can be justified by a potentially curable tumor stage. In today's Model for End-Stage Liver Disease (MELD) based practice, Milan Criteria (MC) (one lesion < 5 cm or up to three lesions each < 3 cm with the disease confined to the liver) constitute the main parameter by which to predict patients who would benefit most from LT^[1]. While the incidence of HCC is believed to have an increasing trend likely parallel to the increasing number of patients who have had a long lasting course of viral hepatitis infection^[2], global donor organ shortage continues to be the most important issue for patients on wait lists as well as for health care providers in the field. This has led the surgery community to look at liver resec-

tion (LR) as a comparable alternative treatment. Patients could be treated by LR followed by the so-called “salvage transplantation” (ST) in cases of tumor recurrence or hepatic decompensation. This would also help the community and other transplant candidates to gain maximum possible benefit from organs of deceased donors. Indeed, thousands of patients have undergone LR as a result of the adoption of this policy over the last decade, and many of them survived subsequent LT. However, this strategy must be carefully evaluated, as there is no guarantee that every patient with HCC undergoing an initial LR with ST in mind will have recurrent disease within the indications of LT. ST may not be an option if: (1) the recurrence is beyond MC; or (2) the patient has developed contraindications to LT, such as advanced age or medical comorbidities. In addition to these factors, the technical challenges of LT will likely be increased in a patient having undergone previous hepatic resection due to scarring and vascularized adhesions.

Bridge therapy, defined as LR followed by a planned LT, regardless of whether the disease recurs, is another strategy to treat HCC. This approach significantly reduces the chance of progression while awaiting an appropriate organ; the strategy is considered to have become successful if a donor liver is offered by the organ allocation system before the patient drops off of the list due to non-transplantable disease recurrence. However, it has been reported that this approach may be associated with greater technical difficulty during transplantation^[3,4], particularly if the hepatic hilum and the peri-caval area were dissected extensively during the preceding LR. One other downside to use of LR as bridge therapy is that, in the United States for example, resection of HCC removes the opportunity to use that tumor to gain extra MELD points as a “MELD exception”.

For the aforementioned reasons, management of patients with chronic liver disease accompanied by transplantable HCC is an ongoing controversy, leading researchers to seek reliable measures by which to discriminate patients who would benefit from its initial LR from those patients for whom LT should be the first-line treatment.

HOT TOPIC ARTICLE

Fuks *et al.*^[5] recent study published in *Hepatology* in January 2012 may have the potential to provide a new insight into the issue. Looking to clarify this controversy, the authors compared the outcomes of patients ($n = 138$) who underwent LR for transplantable HCC within MC, considering ST in case of recurrence, with those of patients who were primarily listed to undergo LT ($n = 191$). They performed an intent-to-treat based analysis to reveal independent predictors of failure to receive timely ST after initial LT. Out of 138 patients who were supposed to undergo ST in case of recurrence, 26 were excluded because they either underwent LT before recurrence or were diagnosed with a different disease based on final histology. Thus, only 112 patients were planned for ST. Of these,

90 had recurrent disease, of which 30 (33%) did not receive ST because of a recurrence outside the MC. Of remaining 60 patients with recurrence within MC, 21 were not eligible to undergo a major transplant surgery, leaving only 39/90 patients (44%) successfully receiving ST. In the primary LT group, 163 patients underwent LT. After excluding early postoperative deaths and histological diagnoses other than HCC based on explant pathology, this group finally had 146 patients who received a successful LT for HCC. What we can conclude from the results are: (1) One fifth of patients in the initial LR group survived recurrence free. None of those patients required LT for any reason during follow-up; (2) While the median follow-up of whole study population was about 5 years, recurrences (if any) occurred usually much earlier. The median time to recurrence was around 16 mo and was similar in patients regardless of whether they had a recurrent disease within MC or outside MC; (3) The overall 1, 3 and 5-year survival in patients undergoing ST was 94%, 81% and 71%, respectively. The two most frequent reasons for not receiving a ST in within MC group were patient refusal ($n = 10$) and advanced age ($n = 9$); (4) In the group beyond MC, tumor > 5 cm, number of lesions > 3 and major vascular involvement were the most frequent contraindications for a ST, occurring in 8 patients each; (5) Multivariate analysis revealed five factors independently associated with recurrence beyond MC: microscopic vascular invasion, presence of satellite nodules, tumor size > 3 cm, poor tumoral differentiation, and existence of cirrhosis. The authors suggested that presence of ≥ 3 poor prognostic factors should warrant LT before recurrence; (6) ST strategy seemed to save 26 grafts which would otherwise have been used unnecessarily; and (7) However, as a result of this strategy, only 28% of patients included in intention-to-treat analysis and only 39% of patients with recurrence could receive ST, suggesting that primary LT rather than “LR followed by ST if needed” strategy should be the treatment of choice in most of patients with HCC and underlying chronic liver disease.

DISCUSSION

We believe that some important points should be taken into consideration when evaluating the results of this study. As the authors stated in part, a selection bias could not completely be eliminated in this study. All patients in the LR followed by ST group had quite good liver function as determined by having Child-Pugh class A disease and significantly lower mean MELD score (6.5 vs 19.8) compared to those in primary LT group. In addition, none of the patients in the earlier group had portal hypertension or reduced thrombocyte count. Moreover, the proportion of patients with Metavir score of F3 in that group was lower than that in the primary LT group. This data suggests that the severity of underlying liver disease was the main parameter to decide the surgical approach selected to manage patients. This kind of study design may be considered inevitable, however, for comparison

of LT with subsequent ST vs LT, as implemented by Faciuto *et al*^[6] in their retrospective study. Similarly, the average Child-Pugh score and MELD score were lower in the primary LR subsequent ST group than in the primary LT group, though they did not include Child-Pugh class C patients in their analysis. Of 51 patients with HCC undergoing LR as initial treatment, 32 developed recurrence. However, 21 (66%) of those were not eligible to receive ST. Tumor size > 3 cm and high MELD score were shown to be independent risk factors indicating poor survival. There was no difference between the groups in 1- and 4-year overall survival. In a study by Shah *et al*^[7], patients with Child-Pugh class A and B disease and HCC within MC were treated by either initial LR ($n = 121$) or listed for primary LT ($n = 140$). The drop-out rate in the primary LT group was 21.4% (30 patients). There was no information reporting the number of patients who could undergo ST due to recurrence in the LR group. The authors concluded that primary LT yields better overall survival compared to LR if waiting time from listing for LT was < 4 mo. Of note, histological examination of explants in the primary LT group revealed that 46% of patients actually had a disease outside MC. Margarit *et al*^[8] reported that only 6 out of 18 patients with recurrence after LR were able to undergo ST during a 50-mo median follow-up.

Fuks *et al*^[5] included only patients within MC. Despite adoption of these criteria by the United Network for Organ Sharing as well as by the majority of centers outside the United States as an integral part of liver allocation systems, some authors have reported that University of California San Francisco (UCSF) criteria (one tumor < 6.5 cm, maximum of 3 tumors with none > 4.5 cm, and cumulative tumor size < 8 cm) can also be used reliably and could yield a long-term outcome comparable to MC^[9,10]. However, expanding the inclusion criteria beyond the UCSF model resulted in worse survival compared to meeting UCSF criteria^[10,11]. It has to be highlighted that a tumor is likely to result in a drop-out from waiting lists as a waiting list death if it has aggressive histological and genetic features. Perhaps favorable outcomes yielded in patient groups within UCSF criteria result from a relatively good nature of histology despite the tumor size exceeding MC. We don't know what would have happened if Fuks *et al*^[5] had included patients within UCSF criteria in LR and primary LT groups. Similarly, we do not have any information about how many of patients who had a recurrence beyond MC after initial LR ($n = 30$) met the UCSF criteria and what would have been the long-term results if those patients had undergone ST.

Another important point is that the study by Fuks *et al*^[5] did not evaluate if it was possible to throw off an unnecessary LR by proceeding directly to LT in the presence of pejorative factors in patients with early stage chronic liver disease. While preoperative imaging by today's state of the art technology is the mainstay of decision making process when planning the treatment of malignant liver

tumors, there may yet be valuable information obtained from histological evaluation of tissues taken by minimally invasive techniques. The main concern with regard to fine-needle aspiration cytology or core biopsy is that the intervention may cause significant bleeding and tumor seeding. Although much of the evidence is anecdotal, a few reports have suggested that fine needle aspiration cytology or core biopsy be avoided due to tumor seeding risk up to 5%^[12-14]. The risks and benefits of preoperative biopsy may need to be reassessed in the future given newly recognized advantages attributed to histological evaluation. In fact, DuBay *et al*^[15] recently proposed "Toronto Criteria" in which preoperative biopsy is used as a guide when deciding exclusion of patients beyond MC from wait list. They reported that outcomes comparable to those of patients meeting MC could be achieved if histological findings demonstrate well-differentiated carcinoma. Cillo *et al*^[16] reported that tumor differentiation was one of the strongest predictors of biological aggressiveness and therefore recurrence, suggesting that preoperative detection of tumor grade would be of importance in deciding the type of treatment modality. In the study by Fuks *et al*^[5], 30 patients treated with curative-intent LR failed to receive ST due to recurrence outside MC. If this result could have been predicted before LR, those patients likely would have undergone immediate LR. Nonetheless, it has to be stated that the nature of their study was not suitable for such an evaluation.

In light of these data, there should be little argument on treatment of patients with HCC who have no underlying chronic liver disease as well as for those who have severe accompanying cirrhosis. What remains controversial is how to manage the patient with HCC developed on a background of Child Pugh class A disease. In this context, we believe the conclusion drawn in the article by Fuks *et al*^[5] should be paid attention. Primary LT may be a more logical modality as it has the capability of treating the disease while reducing the risk of recurrence by eliminating carcinogenic fibrotic liver tissue as well as the underlying condition. Some oncological parameters and unfavorable histological factors such as tumor size, microscopic invasion of vessels, presence of satellite nodules not detected by preoperative imaging, the real severity of cirrhosis, and differentiation of carcinoma should be taken into account if resection is to be selected as the first-line treatment. If a patient presents with tumor within MC, but histological factors, either by resection or biopsy, suggest recurrence may be more aggressive after LR and may ultimately exclude the option of ST, then LT should be the primary consideration.

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