



## Pre-retrieval reperfusion decreases cancer recurrence after rat ischemic liver graft transplantation

### To the Editor:

We read with great interest the article "Pre-retrieval reperfusion decreases cancer recurrence after rat ischemic liver graft transplantation" [1]. This elegant study assessed the impact of ischemic liver graft on the risk of cancer recurrence utilizing a rat liver transplantation model. Oldani *et al.* [1] demonstrated that ischemia/reperfusion lesions lead to an increased risk of post-transplant hepatocellular carcinoma (HCC) recurrence and growth, which can be reversed by graft reperfusion prior to retrieval. However, in this study, they clamped the vena porta and infra-hepatic vena cava during 10 or 30 min prior to flushing and retrieving the liver to simulate the ischemic donors, and the liver was reperfused for two hours after all clamps were removed at the end of the clamping to simulate ischemic/reperfused donors. Apparently, the quality of blood reperfused in this transplantation model is better than the perfusion solution used during normothermic extracorporeal membrane oxygenation (NECMO) after circulatory death in clinical situations to some extent [2]. Thus, we wonder if the risks of post-transplant cancer recurrence can be reduced by graft reperfusion with "perfusion solution" used in clinical prior to retrieval?

In addition in a further study, it is necessary to estimate the combined feasibility and availability of pre-retrieval reperfusion with different NECMO time with the aim to reduce the risk of cancer recurrence and to repair and resuscitate the liver grafts from donation after cardiac death (DCD) donors. This may help

to increase the yield of transplantable livers from this source for HCC candidates awaiting liver transplantation.

### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

### References

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- [2] Fondevila C, Hessheimer AJ, Flores E, et al. Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012;12:162–170.

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## Reply to: "Pre-retrieval reperfusion decreases cancer recurrence after rat ischemic liver graft transplantation"

### To the Editor:

We thank Drs Cheng and Lv [1] for their interest in our work suggesting an increased rate of hepatocellular carcinoma (HCC) recurrence/growth after transplantation of ischemic liver grafts, and the protective effect of *in situ* graft reperfusion prior to retrieval [2].

Our rat transplantation model only approximates clinical reality. It used liver grafts undergoing 10 or 30 min of ischemia prior to retrieval (clamping the porta hepatis and the infra-hepatic vena cava in the donor). HCC cells were injected intra-portal, and liver HCC volumes were repeatedly assessed by magnetic

resonance imaging. A two-hour donor liver reperfusion prior to retrieval was reversing the effects of ischemia/reperfusion and was associated to lower rates of post-transplant HCC growth.

Normothermic extracorporeal membrane oxygenation (NECMO) is the closest clinical procedure to reproduce the studied model, as it allows restoring the perfusion of the donor organs in case of donation after cardiac death (DCD). Apart from being primed with a perfusion solution, NECMO uses the donor's own blood, with a maintained pH between 7.0 and 7.4 [3]. However, it is currently unknown whether NECMO can also have a protective impact on post-transplant HCC recurrence/growth, and this

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field deserves further assessment. Similarly, *ex situ* machine perfusion, either normothermic, hypothermic or sub-normothermic has confirmed protective effects on liver ischemia/reperfusion lesions, but its impact on cancer has never been tested [4–8].

The minimal required time of liver graft reperfusion for preventing HCC growth is currently unknown. The used two-hour reperfusion matches international reports with NECMO or *ex situ* machine perfusion ranging between one and four hours [3,7,8]. It is also in agreement with the need for a minimal two-hour graft normothermic machine reperfusion in order to restore the function of ischemic rat livers [4].

Overall, ischemia/reperfusion may be an added factor altering post-transplant cancer recurrence. This link is likely weaker than the one between pre-transplant HCC characteristics and recurrence, but it deserves further exploration both to better understand the underlying mechanisms and the ways to prevent it.

**Conflict of interest**

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

**References**

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(on behalf of the authors of [2])



## Incidence of anti-HLA donor specific antibodies in liver-transplant patients given mTOR inhibitors without calcineurin inhibitors

To the Editor:

After liver transplantation (LT), immunosuppression with mammalian target-of-rapamycin (mTOR) inhibitors without calcineurin inhibitors (CNIs) is used to preserve kidney function [1], and because of its anti-neoplastic effect, particularly for patients who have a history of hepatocellular carcinoma [2]. However, in kidney-transplant patients, this immunosuppressive strategy has been associated with an increased risk of developing donor-specific antibodies (DSAs) [3]. After a LT, although the impact of the occurrence of *de novo* DSAs on short- and long-term outcomes is still controversial [4], *de novo* DSAs are associated with an increased risk of antibody-mediated rejection [5], chronic rejection [6–8], and anastomotic biliary stricture [9]. However, because the incidence of *de novo* DSAs using the Luminex assay in liver-transplant patients receiving mTOR inhibitor-based

immunosuppression is unknown, this was the aim of this retrospective study.

Between 2008 and 2013, 394 liver-transplant patients were followed-up in our institution. Of these, 61 patients were receiving an mTOR inhibitor (6.5%). Five of the 61 patients were excluded from the study: four because they had not undergone anti-HLA screening after conversion to mTOR inhibitors, and one patient because he received both CNIs and mTOR inhibitors. Hence, 56 liver-transplant patients, converted from CNIs to mTOR inhibitors, were included in this study (Table 1). Twelve patients had undergone an abrupt conversion from CNIs to sirolimus and 44 patients had undergone progressive conversion to everolimus. The target trough (C<sub>0</sub>) levels for sirolimus and everolimus were 6–10 ng/ml. The median time between conversion to mTOR inhibitors and the last follow-up was 28 (range: 2–102) months.

Letters to the Editor