

Format for ANSWERING REVIEWERS



October 18, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 22526-review.doc).

Title: Solid, non-skin, post-liver transplant tumors: Key role of lifestyle and immunosuppression management

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer's code:** 02520359

1) In this review, we are expressly interested in de novo cancer after liver transplantation to study the risk factors and pro-oncogenic mechanisms after LT. Recurrence of HCC after LT is a different issue that involves the recurrence risk factors associated with this explanted cancer on the liver such as size, number of nodules and the presence of vascular microembolus and related to the biology of the tumor such as reflected by the rate of alpha fetoprotein before transplantation. However, Vivarelli [Hepatocellular Carcinoma Liver Transplantation for Calcineurin Inhibitors Under Reassessment of Risk Factors for Tumor Recurrence, *Annals of Surgery*, 2008] found in 139 liver transplant patients in a retrospective study a link between the mean serum anticalcineurin (cyclosporin or tacrolimus) over the first three months after the LT and the risk of HCC recurrence suggesting a pro-oncogenic role of anticalcineurins for this cancer. More recently, the same result was found in 210 patients transplanted for HCC [Rodríguez-Perálvarez]. Reduced exposure to calcineurin inhibitors early after-liver transplantation prevents recurrence of hepatocellular carcinoma. *J Hepatol*. 2013 December; 59 (6): 1193-9]. It would be interesting to confirm these data in a prospective study.

2) In Baccarini's cohort, the median time to diagnosis of a solid cancer was 4.2 years after the LT and 5 years in Haagsma and Aberg's cohort. In our cohort of 465 patients [Carenco, Incidence of solid organ cancers after liver transplantation: comparison with regional cancer incidence rates and risk factors, *Liver International*, 2014], the mean time to diagnosis of solid cancers after LT was 6.3 +/- 4.3 (median 6 years). This serious complication therefore arises long after the LT and is a leading cause of long-term death after LT [Adam R, V Karam, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European liver transplant registry (ELTR). *J Hepatol* 2012; 57: 675-688].

(2) **Reviewer's code:** 00036463

1) By "lower level of immunosuppression" we mean "minimum effective level of immunosuppression". Indeed, acute rejection and chronic rejection are less frequent and less severe complications in liver transplantation compared to kidney transplants. The level of immunosuppression used after LT is therefore usually lower than that used after kidney transplantation, but there is no study to our knowledge that directly compared the immunosuppression protocols in these two indications.

2) In Baccarini's cohort, the median time to diagnosis of a solid cancer was 4.2 years after the LT and 5 years in Haagsma and Aberg's cohort. In our cohort of 465 patients [Carenco, Incidence of solid organ cancers after liver transplantation: comparison with regional cancer incidence rates and risk factors, *Liver International*, 2014], the mean time to diagnosis of solid cancers after LT was 6.3 +/- 4.3 years (median 6 years). This serious complication arises long after the LT and is a leading cause of long-term death after LT [Adam R, V Karam, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European liver transplant registry (ELTR). *J Hepatol* 2012; 57: 675-688].

We did not find any more precise data on the mean time to development of solid cancers according to each location after the LT in the literature. The number of solid cancers found in each cohort is too weak to highlight a mean time of occurrence of different cancers and to characterize them "into early versus late development".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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