Author's response to reviews

Title: Biliary reconstruction with or without an intraductal removable Stent in Liver Transplantation: A Randomized Controlled Trial An original Diffusion of the surgical methodology

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Version: 2 Date: 22 October 2015

Author's response to reviews: see over
Letter to the editors

Title: Biliary reconstruction with or without an intraductal removable Stent in Liver Transplantation: A Randomized Controlled Trial And original Diffusion of the surgical methodology.

Dear Editors,

Please find a second revised version of our manuscript that has been modified according to the reviewers’ suggestions and the editorial requests. All of the changes are highlighted. We would like to thank the reviewers and the editors for giving us the opportunity to provide a point-by-point response to their comments and queries. All of the questions and comments have been addressed in the revised version of the manuscript.

To reviewer 1

We thank the reviewer for his kind and relevant comments.

- It is not clear from the manuscript how a 2 cm long tube without fixation will remain in position to maintain an adequate anastomosis. This is maybe clarified in the video that is accessible for the study center at randomization, but is not available for the present review.

The tube has to be placed against the papilla, this positioning being part of the technique. Its length can thus be adapted to allow this spontaneous positioning. Indeed, this point is clarified in the video that is accessible in every study center and provided in attached file for the present review.

- The study is less likely to affect the more common multiple intra-hepatic strictures related to ischemia to the graft during the peritransplant period.

Indeed, this technique may not be effective in case of intrahepatic ischemic strictures. We planned a meticulous retrieval of data regarding those cases; they will be discussed afterwards in the final analysis and results.
• A significant shortcoming of the study is the length of follow-up decided to be 6 months after transplantation. The investigators state themselves in the background section of the study “biliary strictures mainly occur later, within 5-8 months, and up to one year in the great majority”. Thus, a follow-up of one year would be more relevant to evaluate outcome in the study groups.

We thank the reviewer for this relevant comment. Biliary strictures mostly occur within the first 3-5 months in the literature. A six months follow up would allow to detect the majority of it and to minimize bias related to concomitant transplantation late complications or loss of follow up. Extending the follow up may add confusing factors that would interfere with the results and complicate the analysis. However, we are looking forward to extend the follow-up period to 1 year. This modification relies on the budget allocated by the French Ministry of Health.

To Reviewer 2

We thank the reviewer for his relevant comments. All of the questions and comments needing changes have been addressed in the revised version of the manuscript.

• I did not find a comment on T-tubes used? Is it an exclusion criterion?

We rather not impose a specific type or brand of T-tube, depending on each center's habits and organization, since it may complicate the diffusion of the study.

• How about the Berlin side-to-side anastomosis?

In our knowledge, none of the surgeons involved in the included centers actually perform this kind of anastomosis. We specified in the whole protocol and the video that the biliary anastomosis should be end-to-end style.

• The definition of biliary leakage is very randomly. Why not use the ISGLS criteria with an increase in serum/drainage bilirubin ratio>3 within 7 days after LT, requirement for drainage for>7d due to biliary leakage, macroscopically bile over wound or drainage distinguishing Type A (not clinically relevant because it vanishes before day 7), type B (intervention) or Type C (reoperation). It is your primary endpoint and this should be based on criteria internationally accepted, used and solid as a rock. Otherwise the definition may be a little wishy washy and very easily to manipulate. Especially, patients with cholestatic disease with initial bilirubin values >30mg/dl will have significantly increased bilirubin in drainage without any clinical relevance!!!!
We thank the reviewer for this relevant comment. Obviously, precise definitions and
standardized criteria are important for primary endpoint evaluation. We modified the
manuscript accordingly.

- **Even biliary stenosis is even more difficult to define. Mostly, endoscopists
describe a stenosis which comes from a diametric discrepancy of donor and recipient.**

We agree with this comment. We defined the event of a biliary stenosis as following:
“a size discrepancy between the two sides of the bile duct anastomosis on specific
imaging (MR cholangiography, ERCP), associated to an upstream bile tract
distention, with a clinical and biological cholestasis, after excluding other cholestasis
causes (rejection, viral reactivation).”

- **What is a clinical and biological cholestasis? Every patient will have elevated
yGT AP or bilirubin in the early postoperative course. Define cut-offs and
trigger indicating that something is wrong and that a cholestasis has to be
considered: e.g. 3-fold elevation from baseline within 2 days. You have to be
precise and maybe redefine your protocol.**

We thank the reviewer for this comment and agree with the need of precision in this
definition. We redefined the protocol accordingly.

- **Please use Charriere and not French, as the angloamericans were unable to
pronounce this beautiful French word ;-)!**

We warmly thank the reviewer for this nice comment and have changed the
manuscript accordingly!