

## **Answering reviewers**

### **Reviewer No. 03015689**

We thank him/her for appreciation in readability of the ms, it was one of our goals.

Point 1) he/she found like the other referee N.... a lack of hierarchy in the sector concerning the biology of HCC and its treatment. We tried to amend these bias of the ms giving a more precise address and expressing what is our opinion. Especially in the section dealing with treatment we enlarged so much adding almost new 50 references that give the reader the most update opinion in this.

Point 2) We are in favor of performing biopsy of cancer as, at least in many Countries, is compulsory by law that you inform patients on his/her exact diagnosis and treatment. If this information ( and images do not give you this certainty) is lacking they can denounce doctor to send him/her to jail. Italy is unique in this sense, judge can jail doctor for malpractice (the lack of correct information is already malpractice) that is a quite undefined situation (in any case, you have to pay a lawyer to defend your self). Reimburse as happens in other Countries once the doctor has been proved wrong comes later in Italy. In addition, images although very useful, do not give ever the certainty of the presence of HCC and now to know the biology and markers of HCC is becoming more important than before. However, we changed sentences on the manuscript making this issue more soft and saying what the international literature agrees.

Point 3) We briefly discussed the papers on LT that are using different criteria than the criteria of Milan. We think that the ms has been improved by that. Thank you.

### **Reviewer No. 00007076**

Point 1): This referee asks for more information on the biology of HCC and we agree with this opinion in case the ms should deal with cancerogenesis or the biology of HCC. However, this is a general review on HCC written for those who want to approach the clinical aspects of HCC, i.e. what is, what the risk factors, what is known on mechanisms that to lead to it, how we stage it and treat it. We report several references for those who are interested to go inside the disease and its mechanism but we remain clinicians.

Point 2) Cancer stem cells are very interesting from the point of view of a researcher on this topic but practical consequences are still lacking. There is controversy on what they are, what they come from and what they can be used for. That means that to review this topic we require a different approach and several pages dedicated to this. It is not the goal of one general review that addresses clinic practice in approaching to HCC than speculation on how it could be.

### **Reviewer No. 03016694**

Point 1) We agree with the referee that the ms could be much improved by discussing all what he/she is suggesting. However, that could mean to write an other review, almost

each of what the referee is suggesting could be worth for a review (i.e. timing and prognostic indexes for LT or the issue on living donor that implies ethical discussion, and so more). We made brief references to all these very important issues that are competence of who is already an expert on this field and not for who is approaching the topic.) Point 2 ) all abbreviations were explained , thank you.

**Reviewer No. 00504156**

We thank the referee for his/her kind appreciation.

Yours sincerely

Prof. Roberto Mazzanti, M.D., Ph.D.

Full Professor of Medicine,

Full Professor of Medical Oncology