

## POINT-BY-POINT ANSWER TO THE REVIEWERS' COMMENTS AND EDITOR'S SUGGESTIONS

### Reviewer 02832130

1. The key word has been modified according to your suggestion
2. 1/189, 0.53% has been added according to your suggestion
3. The three minor complications (mild pain) have been cited in the text
4. Besides the paper with more cases (REFERENCE 52), there are in literature just two papers dealing with LA of liver mets from NEN: the former is a report of two patient and three tumors treated with MRI-guided LA, the latter is a brief letter reporting the preliminary results of LA in 13 of the 21 patients reported in REFERENCE 52. Both papers are cited in the text (REFERENCES 43 and 44), but in our opinion they are not worthy of comprehensive discussion
5. To our knowledge, there are just two studies in literature dealing with the combination treatment of NEN liver mets with LA and TACE. They are cited (REFERENCES 50 and 51) and discussed in the last ten lines of the section "Ablation techniques"
6. To our knowledge, there are no studies in literature dealing with the value of MRI in evaluating the response to LA of NEN liver mets.

### Reviewer 03270441

1. Our manuscript is an Opinion Review based on the available literature, it is not a clinical or experimental study. The number of papers published in literature on LA of liver mets from NEN is quite limited, and just one study reports a number of patients and procedures high enough to suggest some conclusions (REFERENCE 52): in this study, the authors stated that LA spares the liver parenchyma more than the other liver-directed therapies, and we have limited ourselves to report their statement. However, there in literature many papers reporting that LA of primary and secondary liver and kidney tumors other than NEN is less invasive and more parenchyma sparing than the other ablation techniques (for instance, see references 33, 34, 45, 47, 48, 49 and 50 of our Opinion Review)
2. Likewise, there are no studies in literature dealing with cryoablation or microwave ablation of liver mets from NEN, except for a report of thirteen patients treated with cryoablation (published in 1998 with a median follow up of just 13 months: REFERENCE 41), and a report of one patient treated with microwave ablation (REFERENCE 42). How could we have analyzed the data about cryoablation and microwave? Maybe, before reviewing, the Reviewer should review the literature...
3. The first three words of the title of this Opinion Review are "**Liver-directed therapies**", not "**Ablation therapies**". Therefore, also catheter-based therapies are related with the topic of the manuscript.
4. The Reviewer should pay more attention to his remarks: in no part of our "Conclusions" there is any mention of "sparing the liver parenchyma than any other liver - directed therapy".

### Reviewer 03726743

1. The goal of the Opinion Review has been clarified in the Abstract
2. English language polishing has been made throughout the text, and long paragraphs have been shortened

3. A table has been added, detailing patients and tumors characteristics of the study analyzed in the Opinion Review

**Reviewer 00041957**

1. Yes, LA uses 21 gauge needles, that are quite thinner than RFA electrodes. This characteristic is reported in the text (line 25 of the Section “ABLATION TECHNIQUES”), and has been highlighted by previous reports (REFERENCES 33, 34, 45, 46, 47).
2. Yes, the thin diameter of the needles enables to reach all the liver segments and lesions in at risk location. We treated some HCC in segment I that were refused for RFA or MWA by many experienced interventional oncology centers, because portal vein branches had to be passed through to reach the target (unpublished data). In this regard, there is an interesting report by Chai et al in LA of liver tumors located in the portacaval space (Lasers Surg Med 2019; 51:866-873). This new reference has been added to the manuscript
3. Sorry, but I can not answer to your question. I have no experience with the laparoscopic approach, and to my knowledge there is no study in literature dealing with LA under laparoscopic approach.