

Peer Review File

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Review comments

Reviewer A

Comment 1:

Nice literature review for the options of locoregional therapies in multifocal HCC.

Reply 1:

Thank you for the kind words! We are glad that you enjoyed our manuscript.

Reviewer B

Interesting and well comprehensive review on a cutting-edge topic. My comments:

Comment 1:

The authors should provide a reproducible search string in the Material and Methods section of the manuscript.

Reply 1:

This has now been included in the required methods table (Table 1) (see page 16, line 2).

Comment 2:

I would replace ref 14 with a more recent and update meta-analysis of only RCTs (so with stronger level of evidence): PMID: 33339274

Reply 2: This has now been addressed. The prior reference was removed and the new reference, with its associated survival and complication data, was included. We appreciate the more up-to-date reference, thank you!(see page 5, lines 34-40).

Comment 3:

The authors should comment also other percutaneous loco-regional treatments such as cryoablation and laser ablation

Reply 3: Cryoablation (CA) and laser thermal ablation (LTA) have now been touched upon in the manuscript. These were initially left out of the analysis as there is limited recent clinical data available on these techniques. From the data available, these techniques appear non-inferior to RFA/MWA, but have their own unique challenges. (see page 6, lines 1-18).

Comment 4:

When commenting the role of TACE the authors should comment also the proposed biomarkers for treatment prognosis (ALBI, ART score....) and the prognostic effect of hypertransaminasemia in patients treated with TACE (cite the recent original article PMID: 34683182)

Reply 4:

Regarding ALBI, we have referenced both this grading system's initial discovery article as well as its direct application in the multinodular post-TACE setting with grade migration. Next, with respect to ART, the manuscript as it currently stands should adequately address ART (with the caveat that it seems to be inadequate in predicting OS across multiple patient populations). Finally, the reference using transient hypertransaminasemia as a positive prognostic marker indicating tumoral cytolysis following superselective cTACE was included as recommended. (see page 9, lines 25-43 and page 10, lines 1-20).

Comment 5:

The authors should comment the potential role of combo therapy between TARE and sorafenib

Reply 5:

This has now been addressed in the combination therapy section directly through the SORAMIC trial (which included combination SIRT + sorafenib treatments) as well as indirectly through the SARAH trial (which looked at SIRT versus sorafenib only). The subanalyses in the SORAMIC trial could be of particular interest (see page 13, lines 24-36).

Comment 6:

Do the authors think there is a role for systemic therapies in these patients? For example, after multiple ineffective TACE sessions.....

Reply 6:

Absolutely! We have now expounded upon the role of sorafenib in the setting of refractory TACE. Carefully adding sorafenib in these patients can increase OS, but also buy patients more time between TACE sessions (see page 10, lines 21-31).