Answering reviewers

Reviewer comment:

In order for the title to reflect the objective of the study, "with and without sorafenib" should be included after "Transarterial Radioembolization"

Reply: Disease Control and Failure Patterns of Unresectable Hepatocellular Carcinoma Following Transarterial Radioembolization with Yttrium-90 Microspheres and with/without sorafenib

Reviewer comment: The abstract is excessively long (more than 500 words)

Reply: **Revised the abstract to make it shorter.**

Reviewer comment: The authors state that "disease progression among TARE-sorafenib procedures was commonly extrahepatic". But this statement is misleading, because the most common location for this strategy was intrahepatic (38%), followed by intra + extrahepatic + extrahepatic only (32%). Therefore, the correct statement is that extrahepatic progression was more common in this strategy (32%) than in TARE alone (13%). This should also be corrected throughout the manuscript.

Reply: Dominant failure patterns were intrahepatic for both *TARE_alone* (44.5%) and *TARE_sorafenib* (38.4%). Extrahepatic progression was more common in *TARE_sorafenib* (32%) and *TARE_no_sorafenib* (40%) than in *TARE_alone* (12.7%).

Reviewer comment: The authors state that "disease progression among TARE-sorafenib procedures was commonly extrahepatic". But this statement is misleading, because the most common location for this strategy was intrahepatic (38%), followed by intra + extrahepatic + extrahepatic only (32%). Therefore, the correct statement is that extrahepatic progression was more common in this strategy (32%) than in TARE alone (13%). This should also be corrected throughout the manuscript.

Reply: TARE with/without sorafenib according to individuals' disease burden provided DCR ~70% with intrahepatic progression as dominant failure pattern. Extrahepatic progression was more common in procedures with initially high disease burden.

Reviewer comment: The authors state that "disease progression among TARE-sorafenib procedures was commonly extrahepatic". But this statement is misleading, because the most common location for this strategy was intrahepatic (38%), followed by intra + extrahepatic + extrahepatic only (32%). Therefore, the correct statement is that extrahepatic progression was more common in this strategy (32%) than in TARE alone (13%). This should also be corrected throughout the manuscript.

Reply: Between these 2 subgroups, incidence of intrahepatic progression was comparable (~40%) but extrahepatic progression was much less common with TARE alone (12.7% vs 32%).

Reviewer comment:I consider that the number of patients in whom the post-treatment study was carried out exclusively within the first month after RE, should be clarified. As it is an excessively short time, it is not possible to detect any tumor response to treatment. Only in the event that during that time evident progression of the disease has been detected, the patient should be included in the analysis.

Reply: **Mentioned this issue as study limitation in the discussion.**

Reviewer comment: The authors state that "disease progression among TARE-sorafenib procedures was commonly extrahepatic". But this statement is misleading, because the most common location for this strategy was intrahepatic (38%), followed by intra + extrahepatic + extrahepatic only (32%). Therefore, the correct statement is that extrahepatic progression was more common in this strategy (32%) than in TARE alone (13%). This should also be corrected throughout the manuscript.

Reply: The most common site of first disease progression was intrahepatic area for both *TARE_alone* (44.5%) and *TARE_sorafenib* procedures (38.4%). Extrahepatic progression (including both extrahepatic only and intrahepatic with extrahepatic) contributed to more than 30% cases in *TARE_sorafenib* (32%) and *TARE_no_sorafenib* (40%) subgroups, much higher than *TARE_alone* (12.7%) subgroup.

Reviewer comment: In the Discussion section, when the authors refer to the changes in the DCR between TARE alone and TARE-sorafenib, they refer to percentage points (arithmetic difference of

two percentages): 6.3% and 12%, respectively. The decrease in DCR would actually be 7.3% (from 85.7 to 79.4%) and 21.43% (from 56 to 44%)

Reply: It is noteworthy that in subgroups without sorafenib, *TARE_alone* and *TARE_no_sorafenib*, decrease of DCRs of treated area and intrahepatic area were 6.3 percentage points (from 85.7 to 79.4%) and 12 percentage points (from 56 to 44%), respectively. In the meantime, decrease of DCR of *TARE_sorafenib* was only 3.7 percentage points (from 87.7 to 84%).

Reviewer comment: I would encourage the authors to include the absorbed doses per tumor for a more accurate analysis of the factors that predict the response to treatment in both strategies. As the authors themselves state, there is increasing evidence (some of them presented in the last month for glass spheres) of the importance that dosimetry has in the outcome of patients with HCC treated by RE.

Reply: Therefore, aggressive TARE based on advanced and personalized dosimetry with radiation dose to tumor exceeding tumoricidal threshold, around 200 Gy as claimed by several studies, might increase response of treated area[29-31]. We acknowledge that tumor specific dose estimates may further stratify tumor response status, but the retrospective calculation of tumor doses are beyond the scope of this work.

Reviewer comment: I consider that the number of patients in whom the post-treatment study was carried out exclusively within the first month after RE, should be clarified. As it is an excessively short time, it is not possible to detect any tumor response to treatment. Only in the event that during that time evident progression of the disease has been detected, the patient should be included in the analysis.

Reply: Furthermore, all of 3 post-treatment imaging studies done within the first month after TARE showed rapid disease progression, either in treated area (*TARE_sorafenib n* = 1) or extrahepatic area (*TARE_no_sorafenib n* = 2).

Reviewer comment: The authors state that "disease progression among TARE-sorafenib procedures was commonly extrahepatic". But this statement is misleading, because the most common location for

this strategy was intrahepatic (38%), followed by intra + extrahepatic + extrahepatic only (32%). Therefore, the correct statement is that extrahepatic progression was more common in this strategy (32%) than in TARE alone (13%). This should also be corrected throughout the manuscript.

Reply: *TARE_alone* for procedures with IHT ≤ 50% and absence of ADFs and *TARE_sorafenib* for procedures with IHD > 50% and/or presence of ADFs could provide acceptable disease control of ~70% in unresectable HCC patients. Intrahepatic progression was the most common failure pattern in both subgroups but extrahepatic progression was far more common in *TARE_sorafenib*. Strategies that improve intrahepatic control for liver-only disease (dosimetry-based TARE) and extrahepatic control for metastatic disease (additional systemic therapy) could improve TARE outcome for HCC patients.

Science editor: Issues raised: I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text.

Reply: Article highlights sees below:

This study describes the disease control and failure patterns of unresectable hepatocellular carcinoma (HCC) patients who underwent trans-arterial radioembolization (TARE) with yttrium-90 (Y-90) microspheres with/without sorafenib according to individuals' disease burden, i.e., intrahepatic tumor (IHT) and adverse disease features (ADFs), consisting of macrovascular invasion, extrahepatic disease (EHD) and infiltrative/ill-defined HCC. The key findings were that TARE alone for procedures with IHT ≤ 50% and absence of ADFs and TARE with sorafenib for procedures with IHD > 50% and/or presence of ADFs could provide acceptable disease control rate (~70%). Intrahepatic progression was dominant failure pattern in both treatment subgroups (~40%). Extrahepatic progression was far more common in procedures with higher disease burden, i.e., IHD > 50% and/or presence of ADFs and pre-existing EHD. Therefore, strategies that improve intrahepatic control for liver-only disease (dosimetry-based TARE) and extrahepatic control for metastatic disease (additional systemic therapy) could improve TARE outcome for HCC patients.

Science editor: References: A total of 35 references are cited, including 4 references published in the last 3 years; Self-cited references: There are 2 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e., those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

Reply: **Number of self-cited reference is 2 of 35, less than 10% and they were reasonable.**

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