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Reviewer Suggestions:

Salvage Locoregional Therapies for Recurrent Hepatocellular Carcinoma

Reviewer #1:

"Dear Authors, thank you very much for your great effort in writing this review article. The review article is written very carefully."

RESPONSE: Thank you for your time and your review.

"I would appreciate if you include the studies that discuss management of recurrent HCC and not primary HCC. In certain modalities, you merged between studies dealing with primary HCC and studies for R-HCC"

."

RESPONSE: Thank you for your concise and accurate review of this work. We agree that improving the focus by adding more content specific to R-HCC is warranted, and we have revised the manuscript to reflect this. Therefore, throughout the manuscript we minimized or removed sentences which referenced primary HCC. We only included sections mentioning studies discussing the management of primary HCC to introduce a modality or in limited cases where data for R-HCC was scarce. We also reorganized several sections to separate a specific section that focuses on strictly data pertaining to R-HCC. The following are examples of data specific to R-HCC added within the manuscript:

Section: Transarterial chemoembolization

"Overall 1 and 3 year survival rates for TACE for R-HCC are reportedly 28-82% and 32-43.9%, respectively[50,53]. Meta-analysis have reported 5-year survival rates for TACE to be 15.5%[54]. Poorer outcomes and prognosis in patients treated with TACE for R-HCC are multiple sessions, tumor size >5cm and ≥2 lesions[50].

Section: Transarterial radioembolization

A retrospective investigation of 41 patients reported time to progression of 11.3 months and overall survival of 22.1 months patients receiving TARE after prior resection.[68]. Due to the advantages of TARE listed above, it has been advocated for advanced, unresectable disease [33,69]. More data is needed to determine efficacy and optimal patient-selection strategies of radioembolization in the context of R-HCC. "

Section: Multimodal Locoregional Therapy Approaches

"To date, few investigations have sought to determine the efficacy of multimodal therapy as a salvage treatment approach in unresectable disease or in instances of R-HCC. For the treatment of larger R-HCC tumors (≦7cm), TACE followed by RFA can reveal additional satellite lesions and have a greater 1-, 3-, 4- year survival rates (92.6%, 66.6%, 61.8%) than RFA alone (85.3%, 59%, 45%) [92,93]" and "Yang et al. published a retrospective investigation of 103 patients with R-HCC treated with either RFA, TACE, or combination therapy of RFA and TACE. Intrahepatic rates of recurrence were lower in the combination group (20.7%) compared to TACE (57.1%) and the RFA group (43.2%). 1-, 3- and 5-year survival rates were also greater in the combination group (88.5%, 64.6%, 44.3%) compared to the TACE alone group(65.8%, 38.9%, 19.5%)[97]."

Reviewer #2:

"Well written review with comprehensive discussion."

RESPONSE: Thank you for your thorough review.

"In "Immuno-locoregional combination therapy" section, the authors discussed immunotherapies for HCC and pointed this direction. However, I think the authors should discuss hyperprogression induced by immunotherapies, as it is crucial in clinical practice."

RESPONSE: We agree that hyperprogressive disease is a crucial consideration when choosing to utilize immunotherapies, especially in the context of clinical management of recurrent HCC or as a salvage treatment option approach. Therefore, within the Immune-Locoregional Combination Therapy, we included the following text:

"It should be noted, adverse events with immuno-checkpoint blockers, such as hyperprogressive disease, have been reported and pose a unique challenge influencing clinical judgment to utilize these agents. Hyperprogressive disease is characterized by a rapid increase in tumor burden and subsequent clinical deterioration in patients treated with immunotherapy agents.