

Format for ANSWERING REVIEWERS

October 04, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: REVIEW 13177 4.10.2014.doc) entitled: **Current Treatment of hepatocellular carcinoma-steps forward but still a long way to go.** Authored by: Liat Mlynarsky, Yoram Menachem and Oren Shibolet.

We thank you for the opportunity to submit our revised manuscript. The manuscript has been corrected according to the reviewers' comments. All the corrections in the review were underlined. Attached is a point-by point reply to the reviewers.

Reviewer 02527635

Comment: This review manuscript focus on the current treatment strategies in hepatocellular carcinoma. It is throughout review the diagnosis, HCC staging and possible treatment modality for HCC such as liver transplantation, loco-ablative therapies and systemic therapies. Publication was recommended after minor revision which was indicated by file attachment.

Reply: We thank the reviewer for the comments all the minor revisions were corrected

Reviewer 02936324

Comment: 1. Your material is properly prepared. 2. It is noted that your manuscript needs careful editing by someone with expertise in technical English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader. 3. The manuscript is lack of innovation, lack of your own point of view, and no prominence to emphasis. 4. Radiotherapy of hepatocellular carcinoma is becoming more and more important. TACE and radiotherapy is the standard of care for patients with non-surgical HCC, but no Mention of radiotherapy in the manuscript

Reply: 1. We thank the reviewer for the concise remarks. 2. The article was fully edited by an expert in technical English to comply with the reviewer's request. 3. In accordance with the reviewer's suggestion, a paragraph was added in the summary section stating our own point of view on treatment of HCC and treatment algorithm used in our institute. 4. We thank the reviewer for pointing out our oversight regarding radiotherapy. Although this modality is not recommended by EASL and AASLD for the treatment of HCC because of insufficient data, a paragraph describing recent advances in this field concerning HCC was added.

Reviewer 2445638:

Comment: Mlynarsky et al. have written a very interesting and pertinent review covering treatment strategies for patients with hepatocellular carcinoma. They discuss tumor staging methods, resection, several types of tumor ablation, and several systemic therapy

trials and their outcomes. The strength of the article is in the good command of knowledge of the subject area that the authors clearly have. The material is also well presented and written with regard to grammar and language. One adjustment in sectional organization, correction of a couple of typographical errors, and expansion by way of a sentence or two of the conclusion to cover the author's opinion on the way clinicians and researchers should go is suggested. Overall classification: very good to excellent. Grading scale: B, see specific suggestions. Specific suggestions: Page 1, line 10. Should read "Hepatitis C Virus (HCV)" then include HCV in abbreviations. Page 1, line 11. Should read "non-alcoholic steatohepatitis (NASH)" then include NASH in abbreviations. Page 4, line 4. Should read "performed" not "preformed". Page 11, line 22. "." Remove extra period It would be helpful to see a simple Figure showing the treatment pathway. One presumably considers tumor ablation before liver transplant, yet the transplant section is placed before the loco-ablative therapies. Either change that around or, probably better, create a simple flow diagram to show what the current decision process is. The review even in the title reflects frustration in treating the disease with appropriate humility, but it would be optimum to point in a future direction- we may have a long way to go but not aimlessly.

Reply: We thank the reviewer for all the comments. All the typographical errors were corrected. As for the order of the paragraphs, we first described the potentially curative therapies and later palliative locoablative therapies. Our common practice relay on the BCLC algorithm and the EASL guidelines we refered the readers to a flow chart presented there. We believe that adding this figure is redundant and will make the manuscript cumbersome. Finally, we fully agree with the reviewer comment concerning the title and have revised it to be more optimistic. In accordance with the comments by this and the second reviewer a paragraph stating our own opinion was added in the summary section.

Reviewer 00054993:

Comment: This is a concise overview of current treatment strategies in HCC with a critical outlook, helpful for physicians, who take responsibility in making clinical decision for and with patients suffering from the disease. Some minor remarks: How was the completeness of the literature search ascertained? What search criteria and data bases were used? As 85% of HCCs are attributed to chronic HBV and HCV infection and fortunately about 75% of patients survive 5 years after liver transplantation, with tumor recurrence in less than 10%, the authors should include in their review the role of viral re-infection, especially with HCV and address the question of (prophylactic) antiviral treatment after transplantation. The statement in the final paragraph, chapter Systemic therapies on page 11 regarding combined treatment of TACE and sorafenib should be referenced

Reply: We would like to thank the reviewer for the three major comments. The literature search included PubMed, MEDLINE, and Cochrane databases using major key words (Hepatocellular carcinoma, hepatoma, resection, liver transplantation, radiofrequency ablation, transarterial chemoembolization, Drug-eluting beads, sorafenib etc.). Since this is not a systematic review and according to the format of the journal there is no methods section in review articles, therefore there is no appropriate place to state the literature search criteria. A paragraph regarding post transplant anti-viral treatment as an anti-tumor prophylaxis was added. Finally, the missing reference mentioned was added.

References and typesetting were corrected

We hope that the manuscript will be accepted for publication in the *World Journal of Hepatology*.

Sincerely yours,

Oren Shibolet MD

Director of the Liver Unit, Department of Gastroenterology

Tel-Aviv Sourasky Medical Center and Tel-Aviv University

6 Weizman St. Tel-Aviv 64239, Israel. orens@tasmc.health.gov.il

Office: +972-3-6973984

Fax: +972-3-6966286