Date: 12/24/2019.

The Editor,

World Journal of Gastrointestinal Oncology.

Subject: Submission of revised Manuscript Number: 52609

Respected,

We, the authors, like to thank you for giving us the opportunity to submit the revisions for our manuscript. The manuscript has been amended according to your feedback/comments and the reviewer's report. All points raised have been addressed, and the changes made to the manuscript are in red colour. We have also provided below a point to point explanation to the reviewers comments as well as made the corrections in the revised manuscript.

We hope you consider our work for publication.

Thank you.

Corresponding Author.

Reviewer #1: Reviewer's code: 00053659

1. Virarkar et al. reviewed the epithelioid hemangioendotheliomas of the liver (EHL). In my opinion, this is well written review that would be very helpful for any clinician. I have never encountered EHL patient in my 30 years experiences with thousand surgical cases. However, there are several misspellings and the format of the paper does not follow the guidelines. Otherwise, it is interesting.

Reply: Thank you for the comment. We have corrected the misspellings and edited the revised manuscript as per the journal guidelines.

Reviewer #2: Reviewer's code: 00053888

1. This is an interesting review of hepatic epithelial haemangioendothelioma of the liver. This is a very rare tumour that is essentially only seen in major transplant units in the West. The outcome of this disease is interesting and the authors touch on a number of areas including genetics, presentation, imaging, treatment and outcome. This manuscript will be of interest to those involved in the care of these patients but is unlikely to have wide appeal. There are a number of small typographical errors that need addressing and probably too many figures. The authors might consider providing a summary table of the outcomes of various treatments that are in published domain and specifically I am thinking of transplantation.

Reply: Thank you for the comment. We have corrected the typographical errors. The below mentioned tables have been added to the revised manuscript summarizing the outcomes of various treatments.

Table 1. Summaries of medical management studies for EHL.

Study	**Year**	**Country**	**Patients**	**Medical Management**	**Dose**	**Outcome**	**Duration of follow up**
Salech et al. [83]	2010	Chile	1	Thalidomide	300 mg daily	Partial response	109 months
Raphael et al. [84]	2010	United Kingdom	1	Thalidomide	400 mg daily	Stable disease	84 months
Kassam and Mandel [85]	2008	Canada	1	Thalidomide	400 mg twice daily	Progressive disease	Not available

Bolke et al. [86]	2006	Germany	1	Thalidomide	Unknown	Progressive disease/death	Not available
Mascarenhas et al. [51]	2005	United States	1	Thalidomide	Unknown	Partial response	Not available
Soape et al. [62]	2015	United States	1	Thalidomide	200 mg nightly	Progressive disease	12 months

Table 2. Summaries of chemotherapeutics management studies for EHL.

Study	**Year**	**Country**	**Patients**	**Chemotherapy agent**	**Dose**	**Outcome**	**Duration of follow up**
Emad et al. [87]	2019	Egypt	9/28	Propranolol, prednisolone, vincristine, cyclophosphamide.	First line therapy: 0.6 – 1-2 mg/kg/day propranolol and/or 0.5-2 mg/kg/d prednisolone Salvage therapy: 1 million units/m2/week interferon, 1.5 mg/m2/week vincristine	Regression on propranolol, propranolol/prednisolone, propranolol/prednisolone/ vincristine, propranolol/prednisolone/ cyclophosphamide, propranolol/prednisolone/ vincristine/ cyclophosphamide, prednisolone/ interferon (1/2)* Progression on prednisolone/interferon (1/2)*, prednisolone/vincristine/cyclophosphamide, Prednisolone/embolization /cyclophosphamide.	Minimum of 12 months
Kim et al. [88]	2010	Japan	1	Carboplatin, paclitaxel, and bevacizumab	15 mg/kg, every 21 days (bevacizumab)	Progression	Not available

Mizota et al. [89]	2011	Japan	1	Carboplatin, paclitaxel, and bevacizumab	15 mg/kg, every 21 days (bevacizumab)	Progression	3 months
Calabro et al. [79]	2007	Italy	1	Interferon α-2a	Not available	Stable disease	Not available
Kayler et al. [90]	2002	United States	1	Interferon α-2a	3 million units daily	Partial response	4 months
Marsh R et al. [91]	2005	United States	1	Interferon α	3 million units, 5 days/week for 1 year	Complete response	84 months
Galvão et al. [92]	2005	Brazil	1	Interferon alpha 2b	3 million units daily 9 weeks before and 1 week after liver resection	Complete response	36 months
Agulnik et al. [93]	2013	United States	1	Bevacizumab	15 mg/kg, every 21 days	Partial response	Not available
Lau et al. [67]	2015	United States	1	Capecitabine and bevacizumab	Not available	Partial response	6 months
Lakkis et al. [94]	2013	France	2	Cyclophosphamide	50 mg daily continuous	Complete response (1/2) and Partial response (1/2)	6 and 24 months
Sangro et al. [95]	2012	Spain	1	Sorafenib	200 mg every 36 hours	Partial response	6 months

Kobayashi et al. [64]	2016	Japan	1	Sorafenib	400-800 mg twice daily	Partial response	60 months

*On prednisolone/interferon treatment, regression was reported in 1 patient and progression in the other patient.

Table 3. Summary of surgical management studies for EHL.

Study	**Year**	**Country**	**Patients**	**Study Design**	**Surgical management**	**Outcome**	**Duration of follow up**
Bachmann et al. [72]	2003	Switzerland	1	Case report	Selective hepatic artery ligation	Stable, asymptomatic, heart failure signs disappeared	48 months
Bostancı et al. [69]	2014	Turkey	1	Case report	Selective internal radiotherapy	Partial response	12 months
Grotz et al. [96]	2010	United States	11/30	Retrospective	Hepatic resection	A 1-, 3- and 5-year overall survival of 100%, 86% and 86% and a disease free survival of 78%, 62% and 62%, respectively	60 months

Wang et al. [97]	2012	China	17/33	Retrospective	Hepatic resection	No significant difference in overall survival between the 17 patients who underwent liver resection alone 3-year survival rate 74.1 %	1 patient underwent liver transplant and died 12 months post-transplant.

Table 4. Summary of liver transplant studies for EHL.

Study	**Year**	**Country**	**Liver transplant patients**	**Study Design**	**Reason for liver transplant**	**Outcome**
Emamaullee et al. [98]	2010	Canada	5/6 (1 patient did chemotherapy and surgical resection)	Retrospective	EHL (5/5), Recurrence (1/5).	1 patient had recurrence twice after two transplants but 2nd transplant resulted in stable disease. 1 patient had recurrence in less than 6 months post-transplant and passed away less than 1 year post-transplant. 4 patients have stable disease post-transplant.
Nudo et al. [99]	2008	Canada	11/11	Retrospective	EHL	3/11 patients died (2 had recurrence while 1 died due to hepatic artery thrombosis). 4/11 patients had recurrence. 2/5 did surgical resection (both failed and 1/2 patients died at 61 months post-

						resection while other patient did a second transplant and patient is still alive). 1/11 patients did radiotherapy. 1/11 patients assigned pegylated interferon and died 11 months later
Rodriguez et al. [73]	2007	United States	110/110	Retrospective	EHL	1/110 had operative death and 2/110 patients died within 30 days post-transplant. 1-year, 3-year, and 5-year overall survivals were 80%, 68%, and 64%, respectively. 31/110 were 5-year survivors. 38/110 patients died during follow-up. 12/38 patients died of recurrent EHL with distant involvement. 12/110 required re-transplantation including four patients who did a third transplant. For re-transplantation patients: 1-year, 3-year, and 5-year allograft survivals were 70%, 60%, and 55%, respectively
Mosoia et al. [100]	2008	France	6/9	Retrospective	EHL	2/6 had recurrence and died (1 patient had recurrence and died at 56 months while other patient had liver recurrence and died at 6 months).

Lerut et al. [101]	2007	France	59/59	Retrospective	EHL	Early (<3 months) and late (>3 months) post-LT mortality was 1.7% (1 patient) and 22% (14 patients). 14 (23.7%) patients with recurrence after a median time of 49 months (range, 6–98). 9 (15.3%) patients died of recurrence and 5 survived with recurrent disease. Disease-free survival rates at 1, 5, and 10 years post-liver transplant are 90%, 82%, and 64%.
Mehrabi et al. [74]	2006	Germany	128/286	Review	EHL	The most common management has been liver transplantation (44.8% of patients), followed by no treatment (24.8%), chemotherapy or radiotherapy (21%), and liver resection (9.4%). The 1-year and 5-year patient survival rates were 96% and 54.5%, respectively, after liver transplant; 39.3% and 4.5%, respectively, after no treatment, 73.3% and 30%, respectively, after chemotherapy or radiotherapy; and 100% and 75%, respectively, after liver resection.

Jung et al. [75]	2016	Korea	2/8	Retrospective	EHL	One patient died from tumor recurrence at 9 months and the other is alive after 5 years without recurrence.
Cardinal et al. [102]	2009	United States	17/25	Retrospective	EHL	Mean survival of 172 (124-220) months in the liver transplant group
Abdoh et al. [103]	2017	Finland	1	Retrospective	EHL	Recurrence after 1 month and died 1 month later.
Grotz et al. [96]	2010	United States	11/30	Retrospective	EHL	1-, 3- and 5-year overall survival of 91%, 73% and 73% and a disease free survival of 64%, 46% and 46% respectively.

Reviewer #3: Reviewer's code: 03253490

1. Virarkar et al. presented a review of the literature about the Primary epithelioid hemangioendotheliomas (EH) of the liver. The review is very interesting. Some references are repeated a lot (for. Example 77). Please check and revise the manuscript for compliance to this journal's author guidelines. Thank you for giving opportunity to review your manuscript Yours sincerely

Reply: Thank you for the comment. The repeated references have been deleted. We have also edited the revised manuscript as per the journal guidelines.

Reviewer #4: Reviewer's code: 00069105

1. Dear sirs: Your review is adequate, well written and easy to read My major concern is that is a classical review not a systematic review and now this classical reviews are not so influential as systematic review I think that some tables resuming series of cases in the treatment will be very interesting Figures are great

Reply: Thank you for the comment. The below mentioned tables have been added to the revised manuscript summarizing the various treatments.

Table 1. Summaries of medical management studies for EHL.

Study	**Year**	**Country**	**Patients**	**Medical Management**	**Dose**	**Outcome**	**Duration of follow up**
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Galvão et al. [92]	2005	Brazil	1	Interferon alpha 2b	3 million units daily 9 weeks before and 1 week after liver resection	Complete response	36 months
Agulnik et al. (unknown site of disease) [93]	2013	United States	1	Bevacizumab	15 mg/kg, every 21 days	Partial response	Not available
Lau et al. [67]	2015	United States	1	Capecitabine and bevacizumab	Not available	Partial response	6 months
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Nudo et al. [99]	2008	Canada	11/11	Retrospective	EHL	3/11 patients died (2 had recurrence while 1 died due to hepatic artery thrombosis). 4/11 patients had recurrence. 2/5 did surgical resection (both failed and 1/2 patients died at 61 months post-resection while other patient did a second transplant and patient is still alive). 1/11 patients did radiotherapy. 1/11 patients assigned pegylated interferon and died 11 months later
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Abdoh et al. [103]	2017	Finland	1	Retrospective	EHL	Recurrence after 1 month and died 1 month later.

Grotz et al.[96]	2010	United States	11/30	Retrospective	EHL	1-, 3- and 5-year overall survival of 91%, 73% and 73% and a disease free survival of 64%, 46% and 46% respectively.

Reviewer #5: Reviewer's code: 00058381

1. This manuscript deals with hepatic hemangioendothelioma; an overview and illustrative images are provided. Specific comments: The title announces an "update" on this subject; therefore, the passages just conveying textbook knowledge should be shortened or omitted in favor of those really offering an update and current scientific results (or future perspectives). In order to improve the readability of the text, stylistic and linguistic improvement is required; e.g., Abstract: "these tumor is confused with angiosarcoma"; Introduction: "Up to 21% of EH are found in liver, making it the most commonly affected organ (1). Despite the liver, being the most commonly affected organ, primary epithelioid hemangioendotheliomas of the liver (EHL) are rare tumors with an incidence rate of less than 0.1 per 100,000 population (2)"; Section "Chemotherapy": "Bevacizumab is also been considered for medical management of EHL (67, 68)"; etc. Additional comment: Some parts of the reference list are not consistent with the guidelines of the journal.

Reply: Thank you for the comment. We have edited the revised manuscript as per the reviewer comments and are mentioned below. The reference list has been arranged as per the journal guidelines.

1. Abstract: "these tumor is confused with angiosarcoma";

Corrected: this tumor is misdiagnosed with angiosarcoma

2. Introduction: "Up to 21% of EH are found in liver, making it the most commonly affected organ (1).

Corrected: However , the most commonly involved organ is the liver.

3. Despite the liver, being the most commonly affected organ, primary epithelioid hemangioendotheliomas of the liver (EHL) are rare tumors with an incidence rate of less than 0.1 per 100,000 population (2)";

Corrected: Primary epithelioid hemangioendotheliomas of the liver (EHL) are rare tumors with an incidence rate of less than 0.1 per 100,000 population.

4. Section "Chemotherapy": "Bevacizumab is also been considered for medical management of EHL (67, 68)"; etc.

Corrected: Bevacizumab has been utilized for the management of EHL.

Reviewer #6: Reviewer's code: 03656588

Primary epithelioid hemangioendotheliomas of the liver (EHL) are rare tumors. The EHL is confused with angiosarcoma, cholangiocarcinomas (CC), metastatic carcinoma, and hepatocellular carcinoma (HCC) etc . 2) The review briefly introduced the imaging signs(such as B-US, CT, MRI, PET-CT) and therapeutic methods(such as medications, chemotherapy, interventional therapy, surgery). Especially the typical imaging signs of EHL are important clinical reference value.

Reply: Thank you for the comment.