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Editorial Board of
World Journal of Clinical Oncology

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Submission of the revised manuscript entitled: "Liver transplantation in malignant disease" (manuscript NO: 64812; ID 02543955) to World Journal of Clinical Oncology

Dear Editorial Board,

please find attached the revised version of our manuscript entitled "*Liver transplantation in malignant disease*" (manuscript NO 64812) to be published in *World Journal of Clinical Oncology* **(ID 02543955)**

We would like to thank all 6 referees for their efforts. Based on their comments we now provide the revised manuscript. All changes in the manuscript are marked with "track-changes". We believe that our work has significantly improved by the reviewers' comments. A point-by-point revision is provided below.

No portion of the contents of the manuscript or any similar paper have been published in any other primary scientific journal or are currently under review elsewhere.

All authors contributed to the work and agree to the content of the paper.

We appreciate your time in handling and reviewing our manuscript and look forward to your response.

Yours sincerely,

Sven A. Lang, MD

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Point-by-point revision

Reviewer 1:

It's very well written and needs minor revision.

Answer:

Thank you for this positive evaluation.

Annotation 1, page 6:

Reviewer:

"Is the author suggesting that LDLT is the option for those having malignancy and not getting a donor graft due to well preserved status of the patient with *HCC"*

Answer:

Thank you for this comment. In fact, we suggest that LDLT can be an option for patients with prolonged waiting time on the list. To clarify this we have rephrased the sentence:

"The increased use of living donor liver transplantation (LDLT) to overcome the problem of prolonged waiting time and organ shortage is an option but not the solution for the problem of timing in transplant oncology even though LDLT has become a standard in various regions worldwide"

Annotation 2, page 7:

Reviewer:

"Pls cite reference"

Answer:

We have now included to references emphasizing the problem of drop-out on the waiting list.

Annotations 3 and 4, page 8:

Reviewer:

"The study has come from Eastern countried where living donation is performed is correct, where they didnt have to depend on organ allocation ; however the pts had advanced malignancy despite no delay due to waiting times... hence the message being given can be better worded."

Reviewer:

"Can be better worded to state the disadvantages faced in following liberal criteria. That patient liver transplant "delays caused by waitlist ultimately goes beyond expanded criteria" or inability to obtain graft in the west in these situations as patient is considered beyond transplant or not given MELD exception points if he is beyond UCSF or with PVT."

Answer:

Thank you for these comments. We apologize the misunderstanding. We have removed both sentences regarding the differences between East and West. Instead, we have now included the following statements:

"These are undoubtedly impressive results in patients with advanced malignancies. However, since the criteria for organ allocation regarding liver transplantation in HCC are much more restrictive in many areas of the world, these results are hardly transferable particularly to Western countries."

We hope that the reviewer can accept this.

Annotations 5, page 10:

Reviewer:

"Is the Diagnosis of HCC-CC sometimes suspected intraoperatively and creating a delimma ; would the authors like to comment on that situation"

Answer:

Thank you for this comment. Usually the suspicious areas inside the liver are of course are not visible intraoperatively. If the diagnosis of HCC-CC is suspected upon preoperative imaging, a biopsy and intense work-up are of course mandatory prior to listing for liver transplantation. However, in the rare case that the diagnosis of combined HCC-CC is suspected intraoperatively and biopsy is taken, it is usually hard for the pathologist to make a sure diagnosis of HCC-CC upon frozen section. We have emphasized this by rephrasing the sentence to:

"Due to difficulties in preoperative imaging, the diagnosis of combined HCC-CC is usually made in the postoperative pathological report and even if suspected intraoperatively, confirmation of combined HCC-CC is often difficult in frozen section."

We hope that the reviewer can accept this.

Reviewer 2:

The article covers a broad field of indications for liver transplantation in malignant diseases. As a review is a very good article, balanced and with extensive overview of the literature. The key problem that is addressed in the article is that liver transplantation is almost the best choice in numerous malignancies, but the question of availability of the organs is the major problem. Conclusions appropriately summarize the data.

Answer:

Thank you for this positive evaluation.

1. Reviewer:

"The only feeling that I have is that in some indications (for example in FLC), a clear message what is today golden standard and what will be in the near future is not conveyed by the authors."

Answer:

Thank you for this suggestion. We have included a statement on the current role of liver transplantation in FLC:

"Nonetheless, given the acceptable outcome published in the aforementioned reports, liver transplantation seems to be a treatment option in selected patients with FLC who are not applicable for liver resection."

We hope that the reviewer can accept this.

2. Reviewer:

"I also have some specific remarks regarding: HCC When talking about waiting lists in the west some description of bridging methods and its influence on dropout should be mentioned."

Answer:

We have included a paragraph regarding bridging methods and drop-outs into the HCC section. Moreover, we have now mentioned downstaging in the same section in the revised manuscript. We hope that this is sufficient for the reviewer.

3. Reviewer:

"Additional criteria in Asia are mentioned without citation."

Answer:

We have rephrased the corresponding sentence:

"*Additional criteria have been published by several groups from all over the world."* In addition, we have included 7 citations at the end of this sentence.

4. Reviewer:

"Muelbacher published 2 articles with long-term survivors and described the role of micrometastases and influence on survival."

Answer:

Thank you for this comment. The publication regarding the first experiences with liver transplantation for CRLM by Mühlbacher et al. (Transplant Proc. 1991 Feb;23(1 Pt 2):1567-8.) is already included in the introduction of the section about "Secondary Liver cancer" on page 18. Nonetheless, we now introduced an additional more precise sentence in the "Colorectal liver metastases" section:

"*The group from Vienna was among the first who reported long-term results regarding liver transplantation for CRLM. Twenty-five patients underwent transplantation and 5-year OS was reported only 12% [137].*"

Moreover, we have now included the manuscript by Kappel et al. from the Vienna group regarding the role of micrometastases in CRLM section:

"*Kappel et al. found the detection of micrometastases in lymph nodes of the primary tumor to be associated with impaired survival after liver transplantation for CRLM [157].*"

5. Reviewer:

"I believe that critical evaluation of the authors could also elucidate the importance of primary tumuor in patient selection."

Answer:

Thank you for this important comment. We have expanded the section about patient selection in CRLM:

"*In addition, the primary tumor seems to be of particular importance for patient selection. Right-sided tumor location, BRAF mutation and signet ring cell carcinoma are associated with poor outcome similar to the data from liver resection [158-161]. Furthermore, lymph node status of the primary seems to have some relevance although this is not an independent prognostic factor [159, 160].*"

We think that this is an important message and again would like to thank the reviewer for this suggestion.

Reviewer 3:

A manuscript of the review entitled "Liver transplantation in malignant disease" by Sven Arke Lang et al. addresses the most recent findings of primary and secondary liver cancer and liver transplantation. The manuscript is very well written and easy to read. All data is relevant, and suggestions on managing patients with malignant disease referred to liver transplantation are clear and consistent with the evidence presented.

Answer:
Thank you for this positive evaluation.

1. **Reviewer:**
"Considering hepatocellular carcinoma is the most indication for liver transplantation among malignant liver disease, adding the role of locoregional therapy as neoadjuvant therapy in liver transplantation and downstaging within Milan criteria would be advisable."
Answer:
Thank you for this suggestion. We have included two paragraphs regarding the role of locoregional therapy and downstaging to within Milan in the HCC section. We think that this substantially improves the manuscript and thank the reviewer for this comment.

Reviewer 4:

Review of manuscript ID: 64812 Title: Liver transplantation in malignant disease Summary: In this review, Lang SA et al. discuss liver transplantation for primary liver tumors and for metastases to liver. They discuss recent studies and report outcomes in these patients. Comments to the authors:

1. Reviewer:
"1. Organization – I suggest breaking down sections further. You can add: Criteria for transplant (for FLC you can say no criteria exist) including exception MELD points and then a section on Outcome following transplant, including recurrence rates."
Answer:
Our manuscript contains the most frequent indications for liver transplantation regarding primary and secondary liver cancer that have been reported so far. For some indication such as HCC, a huge amount of literature is available with regard to selection criteria, outcome, recurrence but also regarding bridging and downstaging prior to transplant while for other indication e.g. FLC no data exists. Moreover, data on bridging and down-staging in HCC is requested by other reviewers (Reviewer 2, 3). If we would reorganize the manuscript according to the reviewer's suggestion, we would have multiple sections with long paragraphs in HCC while other tumor entities would only have very little sections with almost no content. We thinks that a running text is more convenient for the reader. We hope that the reviewer can follow our arguments and accept them.

2. Reviewer:
"2. Introduction HCC – risk factors for cirrhosis, I would add autoimmune liver disease. I would remove aflatoxin (rare)."
Answer:
We thank the reviewer for this comment. We have now removed aflatoxin and included autoimmune disease.

3. Reviewer:
"3. Page 7 – please provide references for "additional criteria have been published by several groups from Asia"."
Answer:

We have rephrased the corresponding sentence:
"*Additional criteria have been published by several groups from all over the world.*" In addition, we have included 7 citations at the end of this sentence. (see also Reviewer 2, 3rd question)

4. Reviewer:

"4. Downstaging – can you add a section discussing this? With new immune-checkpoint inhibitors there is good response and many patients can become eligible for liver transplant."

Answer:

Thank you for this suggestion. We have included a section on this very interesting topic in the HCC section:
"*Finally, novel systemic treatment options based on the use of immune-checkpoint inhibitors have recently been approved for HCC treatment in advanced stages [56, 57]. However, there is almost no literature available regarding their use in neoadjuvant setting before liver transplantation. A major concern when using these drugs in the transplant setting is the risk of organ rejection and death due to hyperactivation of the immune system [57]. Experience so far is limited to case reports. Schwacha-Eipper et al. recently published a case of successful liver transplantation after neoadjuvant use of nivolumab while 2 other case reports indicate fatal hepatic necrosis following immune-checkpoint inhibitor based therapy prior to transplantation [58-60]. Hence, the exact role and handling of these novel agents in neoadjuvant strategies before liver transplantation remains to be elucidated [57].*"
We hope that the reviewer can accept this.

5. Reviewer:

"5. Page 8 – I still think use of sirolimus in patients transplanted for HCC is controversial. Many feel the primary outcome of SiLVER study was not met. Need to add: side effect profile of sirolimus needs to be considered in the decision making process."

Answer:

Thank you for this comment. We have addressed this now in the HCC section:
"*However, when using mTOR inhibitors for immunosuppression, the side effect profile has to be balanced with higher rates of proteinuria, peripheral edema, and incisional hernia on the one hand and preserved renal function on the other hand [64].*"
We hope that this is sufficient for the reviewer.

6. Reviewer:

"6. I don't think you should group FLC with HAS. In the former case, LT is an option in select cases whereas HAS is a contraindication to transplant."

Answer:

We have included HAS into the review become some data is available regarding liver transplantation. It is now considered to be a contraindication based on this data. HAS is grouped as primary liver tumor but not specifically together with FLC. To keep the review well-arranged and easy to read, we would like to keep it in this section. We hope that the reviewer can accept this.

7. Reviewer:

7. Secondary liver cancer – I suggest starting with NET then you can have the section on CRLM.

Answer:
We have changed the organization of the manuscript according to the reviewer's suggestion. Secondary liver cancer now starts with NECLM.

8. Reviewer:
"8. CRLM section – "The current mainstay for treatment of CRLM is surgical resection and if possible," DELETE the word and. End with semicolon after possible."
Answer:
Thank you for this comment. We have changed the corresponding sentence according to the reviewers suggestions.

9. Reviewer:
"9. NET section – "makes is difficult to define the optimal place and timing for liver transplantation in the therapy algorithm of NECLM" CHANGE is to IT."
Answer:
Thank you for this comment. We have changed the corresponding sentence according to the reviewers suggestions.

10. Reviewer:
"10. Table 1 – for ETC criteria and Asian criteria, what is the 5-yr OS?"
Answer:
We are sorry for this mistake. The 5-yr OS for ETC and Asan are now included.

11. Reviewer:
"11. Table 1 – Kyushu and Samsung criteria, is there no 5-yr OS provided?"
Answer:
We are sorry for this. 5-yr OS for Kyushu is now included. To the best of our knowledge, Samsung criteria only provide 5-yr RFS.

Reviewer 5:

The authors present an interesting overview of the use of liver transplant for malignancy. Overall an interesting manuscript that covers a great deal of information in the field in-depth that will contribute significantly to the currently available literature. I have some comments for the authors:

1. Reviewer:
"General: The authors claim that a native English speaker has read and approved this manuscript. There are certain instances that warrant correction, so I would like to advise the authors to ask for another native English speaker of theirs to help them with certain grammar/syntax issues:
eg. 1. "Liver transplantation for malignant disease has become a part of transplant oncology and gains increasing attention"
eg. 2 "Increasing data supports the use of liver transplantation for perihilar cholangiocarcinoma"
eg. 3 "With respect to secondary liver tumors, increasing data support the use of liver transplantation for colorectal liver metastases" etc"
Answer:

We went through the manuscript and corrected certain passages. In addition, another native English speaker was asked to go through the manuscript as suggested by the reviewer.

2. Reviewer:

"Abstract: What do the authors mean by "although the optimal patient selection is still under debate"? Maybe they should consider rephrasing this sentence to reflect better the fact that several criteria have been developed and there is still ongoing research on that?"

Answer:

Thank you for this suggestion. We have rephrased this part:

"*Following the implementation of the Milan criteria, hepatocellular carcinoma (HCC) was the first, generally accepted indication for transplantation in patients with cancer. Subsequently, more liberal criteria for HCC have been developed and research on this topic is still ongoing.*"

Hopefully the reviewer can accept this.

3. Reviewer:

"-"As a result, 1-year overall survival (OS) after liver transplantation has been reported around 80% and 5-year OS to be around 70%" This percentage for 1-year is incorrect. Survival is way higher especially in the US (of course not necessary to cite this publication but the authors should find more respesentative publications to cite): Kwong AJ, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Booker SE, Cafarella M, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2019 Annual Data Report: Liver. Am J Transplant. 2021 Feb;21 Suppl 2:208-315. doi: 10.1111/ajt.16494. PMID: 33595192."

Answer:

We are sorry for this mistake. It is now changed in the manuscript as follows:

"*As a result, 1-year overall survival (OS) rates after liver transplantation nowadays range between 80% and more than 90% while 5-year OS has been reported to be around 70% [1-3]."*

In addition, we have included the reference suggested by the reviewer but also another one from ELTR indicating a slightly lower 1-year OS than in the US. We hope that the reviewer can accept this.

4. Reviewer:

"-" although the first successful liver transplantation in 1967 was performed in a patient suffering from hepatoblastoma [3]" Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ, Jr., Porter KA. Orthotopic homotransplantation of the human liver. Ann Surg. 1968; 168: 392-415 [PMID: 4877589 DOI: 10.1097/00000658-196809000-00009] This is incorrect. The first LT was for biliary atresia: STARZL TE, MARCHIORO TL, VONKAULLA KN, HERMANN G, BRITTAIN RS, WADDELL WR. HOMOTRANSPLANTATION OF THE LIVER IN HUMANS. Surg Gynecol Obstet. 1963 Dec;117:659-76. PMID: 14100514; PMCID: PMC2634660."

Answer:

We apologize for this mistake. We have now removed this statement from the manuscript.

5. Reviewer:

"-Regarding immunosuppression, the authors should refer to the SILVER trial data in their introduction (although they do so later in the manuscript): Geissler EK, Schnitzbauer AA, Zülke

C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation 2016;100:116–25. https://doi.org/10.1097/TP.0000000000000965."

Answer:

The publication is now cited in the introduction. We did not refer to the Silver data in this section to avoid double mentioning since it's discussed in the HCC section.

7. Reviewer:

"-In the US, the term eMELD score is not used. Instead, MELD exception is used as a term."

Answer:

Thank you for this comment. We have changed this. However, we have to assume that there might be readers from outside the US, so eMELD is still mentioned in this section.

8. Reviewer:

"-Overall, nice introduction, but the authors could probably cut it down to 1 or slightly more than 1 page (now almost 2 pages)."

Answer:

Thank you for this comment. We have cut down the introduction from 2 pages to 1 ½ pages. We hope that this is sufficient for the reviewer.

9. Reviewer:

"-I am not sure it is appropriate to say: "Nonetheless, liver transplantation is regarded to be the best treatment option for HCC since it cures both, the tumor and the underlying liver disease." What if there is only a single small HCC without cirrhotic background? Why would LT be better in that setting? Maybe rephrasing is warranted towards HCC in the context of underlying liver disease and probably some mention to the concept of the field effect would be interesting."

Answer:

Thank you for this advice. We have rephrased this sentence now:

"*Nonetheless, liver transplantation is regarded to be the best treatment option for HCC in cirrhotic livers since it cures both, the tumor and the underlying liver disease.*"

10. Reviewer:

"-Regarding HCC criteria, the authors should also mention the HALT-HCC score and the LiTES-HCC score: Sasaki K, Firl DJ, Hashimoto K, Fujiki M, Diago-Uso T, Quintini C, Eghtesad B, Fung JJ, Aucejo FN, Miller CM. Development and validation of the HALT-HCC score to predict mortality in liver transplant recipients with hepatocellular carcinoma: a retrospective cohort analysis. Lancet Gastroenterol Hepatol. 2017 Aug;2(8):595-603. doi: 10.1016/S2468-1253(17)30106-1. Epub 2017 May 22. PMID: 28546007. Firl DJ, Sasaki K, Agopian VG, Gorgen A, Kimura S, Dumronggittigule W, McVey JC, Iesari S, Mennini G, Vitale A, Finkenstedt A, Onali S, Hoppe-Lotichius M, Vennarecci G, Manzia TM, Nicolini D, Avolio AW, Agnes S, Vivarelli M, Tisone G, Ettorre GM, Otto G, Tsochatzis E, Rossi M, Viveiros A, Cillo U, Markmann JF, Ikegami T, Kaido T, Lai Q, Sapisochin G, Lerut J; European Hepatocellular Cancer Liver Transplant Study Group, Aucejo FN. Charting the Path Forward for Risk Prediction in Liver Transplant for Hepatocellular Carcinoma: International Validation of HALTHCC Among 4,089 Patients. Hepatology. 2020 Feb;71(2):569-582. doi: 10.1002/hep.30838. Epub 2019 Aug 19. PMID: 31243778. Goldberg D, Mantero A, Newcomb

C, Delgado C, Forde KA, Kaplan DE, John B, Nuchovich N, Dominguez B, Emanuel E, Reese PP. Predicting survival after liver transplantation in patients with hepatocellular carcinoma using the LiTES-HCC score. J Hepatol. 2021 Jan 13:S0168-8278(21)00004-0. doi: 10.1016/j.jhep.2020.12.021. Epub ahead of print. PMID: 33453328."

Answer:

The HALT- and LiTES score are now included in the manuscript in the HCC section:

"*To overcome the problem of binary decision systems, continuous risk scores were subsequently developed. Particularly, Sasaki et al. described the HALT-HCC score (Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma) that includes the tumor burden score, AFP and MELD-Na after initial evaluation of 8 variables [47]. This score was validated and recalibrated by an international study group using data from more than 4000 patients [48]. After recalibration, HALT-HCC increased in its prognostic utility regarding RFS and OS. Finally, Goldberg et al. recently published the LiTES-HCC score (Liver Transplant Expected Survival HCC) that emphasizes the issue that the majority of deaths after transplantation for HCC are not related to HCC recurrence. In addition, the etiology of liver disease is adjusted to the U.S. population (e.g. the fraction of patients with NASH is higher). 11 variables were included and 4 group based on the LiTES-HCC score were defined. Survival analysis showed a 1-year OS of 97% in the best group vs. 90.2% in worst group that was more pronounced with longer follow-up (5-year OS 86.3% vs. 67%; 10-year OS 72.7% vs. 47.7%) [49]. These data have the potential to change the current practice in prioritization of patients with HCC.*"

Moreover, the suggested literature is now cited.

11. Reviewer:

"-" Finally, the use of mTOR inhibitors as part of the immunosuppressive regime seems to be beneficial in HCC." This seems like the authors express their opinion. They should stick more to the actual data (eg Silver trial) and use citations for everything."

Answer:

The sentence is part of the last paragraph in the HCC section which somehow summarizes the data provided above. Nonetheless, we have rephrased this part now:

"*Finally, the optimal immunosuppression after liver transplantation for HCC is still a matter of ongoing research.*"

We hope that this is sufficient for the reviewer.

12. Reviewer:

"-" In most centers, iCC is considered to be a contraindication for liver transplantation due to poor results with regard to OS and RFS [61, 62]." The authors should use more recent citations for this sentence. Perihilar Cholangiocarcinoma (pCC) "

Answer:

Indeed more recent data on iCC regarding liver transplantation are not excluding iCC from liver transplantation per se. Therefore, we have rephrased the sentence to emphasize this issue:

"*iCC is considered to be a contraindication for liver transplantation due to poor results with regard to OS and RFS based on reports from historical data [85, 86].*"

13. Reviewer:

"-As the authors engage into a waitlist discussion, they should discuss the findings of a recent comparative HCC vs pCC study: *Ziogas IA, Hickman LA, Matsuoka LK, Izzy M, Montenovo MI, Rega SA, Feurer ID, Alexopoulos SP. Comparison of Wait-List Mortality Between Cholangiocarcinoma and Hepatocellular Carcinoma Liver Transplant Candidates. Liver Transpl. 2020 Sep;26(9):1112-1120. doi: 10.1002/lt.25807. Epub 2020 Jul 21. PMID: 32475062.* "

Answer:

Thank you for this suggestion. We have included the citation now into the following sentence: "*Nonetheless, prioritization is currently performed similar to HCC which in turn leads to higher waitlist drop-out in patients with pCC [111]. Hence, refinement of the current practice is warranted.*"

14. Reviewer:

"-Since the authors engage into the use of vascular grafts for LT in pCC, they should also refer to another recent study that described the US experience based on center volume and how the use of vascular grafts that may differ by center, may influence long-term survival: *Ziogas, Ioannis A. MD1; Rauf, Muhammad A. MD1; Matsuoka, Lea K. MD, FACS1; Izzy, Manhal MD2; Rega, Scott A. MS3; Feurer, Irene D. PhD4; Alexopoulos, Sophoclis P. MD, FACS1 Liver Transplantation for Cholangiocarcinoma: Charting a Path With Lessons Learned From Center Experience, Transplantation Direct: April 2021 - Volume 7 - Issue 4 - p e686 doi: 10.1097/TXD.0000000000001133* "

Answer:

Thank you for this suggestion. However, the issue of vascular graft for LT in pCC is not included in our manuscript. We only refer to the statement of the ILTS. Hence, we decided not to include the suggested study. We hope that the reviewer can accept this.

15. Reviewer:

"The authors should engage in a discussion on undifferentiated embryonal sarcoma too (maybe a a separate entity would be better). Relevant literature provided below: Techavichit P, Masand PM, Himes RW, Abbas R, Goss JA, Vasudevan SA, et al. Undifferentiated embryonal sarcoma of the liver (UESL): A single-center experience and review of the literature. J Pediatr Hematol Oncol 2016, 38, 261–8. DOI: 10.1097/MPH.0000000000000529. Babu BI, Bigam DL, Gilmour SM, Dajani KZ, Shapiro AMJ, Kneteman NM. Liver Transplantation in Locally Unresectable, Undifferentiated Embryonal Cell Sarcoma. Transplant Direct 2021, 7, e654. DOI: 10.1097/txd.0000000000001106. Walther A, Geller J, Coots A, Towbin A, Nathan J, Alonso M, et al. Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. Liver Transpl 2014, 20, 191–9. DOI: 10.1002/lt.23773. Dhanasekaran R, Hemming A, Salazar E, Cabrera R. Rare case of adult undifferentiated (embryonal) sarcoma of the liver treated with liver transplantation: excellent long-term survival. Case Reports Hepatol 2012, 2012, 519741. DOI: 10.1155/2012/519741."

Answer:

We thank the reviewer for this suggestion. In general, our manuscript aims to summarize liver transplantation in malignant disease in adults. Therefore, other indication in children e.g. hepatoblastoma is also not included. However, a few case reports exist on liver transplantation for UESL in adults. Therefore, we decided to include a separate section on this tumor entity:

"***Undifferentiated embryonal sarcoma of the liver (UESL)***

UES is a very rare indication for liver transplantation. The tumor was first described by Stocker and Ishak in 1978 [131]. In fact, UESL in mainly diagnosed in children between the ages of 6 and 10 years and it accounts for 1-4% of all solid tumor in the childhood [132, 133]. Surgical resection with or without chemotherapy is currently recommended for therapy of this tumor [133, 134]. Very recently, Babu et al. summarized the experiences with liver transplantation for UESL. Only 28 cases we reported, among them only 4 patients being 18 years of age or older [135]. Notably, the oldest patients was described by Dhanasekaran et al. in 2012. This patient underwent liver transplantation in 2002. Although retransplantation due to ductopenic rejection was necessary, he was tumor free for more than 10 years following the second transplantation [136]. In summary, although very rare, the option of liver transplantation for UESL should be kept in mind even in adults when liver resection is not possible."

We hope that this is sufficient for the reviewer.

16. Reviewer:

"This reference is very recent and that's why I suppose the authors did not cite it, but I think it is important to discuss the survival benefit of transplant over resection based on these findings: Dueland S, Yaqub S, Syversveen T, Carling U, Hagness M, Brudvik KW, Line PD. Survival Outcomes After Portal Vein Embolization and Liver Resection Compared With Liver Transplant for Patients With Extensive Colorectal Cancer Liver Metastases. JAMA Surg. 2021 Mar 31. doi: 10.1001/jamasurg.2021.0267. Epub ahead of print. PMID: 33787838."

Answer:

We thank the reviewer for this suggestion. Indeed, our manuscript was submitted in February while the mentioned manuscript was published in April. Therefore, it was not included in our initial version. However, due to the particular importance we have now included the manuscript and discuss the results in the CRLM section as follwos:

"*Remarkably, the group from Oslo recently published data comparing the results after PVE and subsequent liver resection with those of liver transplantation for CRLM [159]. Analysis of the subgroup of patients with high tumor load (determined by number of metastases (>9) and tumor burden score) showed a survival advantage for patients who underwent liver transplantation (median survival 40.5 months upon liver transplantation vs. 19.2 months upon PVE and resection). Of course, these impressive results have to be confirmed but nonetheless harbor the potential to change the current management or CRLM.*"

Reviewer 6:

Reviewer: Authors reviewed liver transplantation for malignant liver diseases. The manuscript was well-addressed and well-written.

Answer:

We thank the reviewer for this evaluation of our manuscript.

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On behalf of all the coauthors I would like to thank the reviewer for the educational and constructive comments that have led to a significant improvement of the manuscript.

Prof. Dr. med. Sven A. Lang