

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 03475479

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-24

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-02-24 09:28

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**Review time:** 1 Day and 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

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

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 05419473

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Postdoctoral Fellow

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-24

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2021-04-08 04:22

**Reviewer performed review:** 2021-04-08 05:30

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

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: 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 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? Introduction -"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 representative 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. -" 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. -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>. -In the US, the term eMELD score is not used. Instead, MELD exception is used as a term. -Overall, nice introduction, but the authors could probably cut it down to 1 or slightly more than 1 page (now almost 2 pages). Hepatocellular carcinoma (HCC) -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. -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-Usó 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, Kimura S, McVey J, Hashimoto K, Yeh H, Miller CM, Markmann JF, Sasaki K, Aucejo FN. Reframing the approach to patients with hepatocellular carcinoma:

Longitudinal assessment with hazard associated with liver transplantation for HCC (HALTHCC) improves ablate and wait strategy. *Hepatology*. 2018 Oct;68(4):1448-1458. doi: 10.1002/hep.29907. PMID: 29604231. 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. -“ 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. Intrahepatic Cholangiocarcinoma (iCC) -“ 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) -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. -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 Hepatic angiosarcoma (HAS) The authors should engage in a discussion on undifferentiated embryonal sarcoma too (maybe 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. Colorectal Liver Metastases (CRLM) 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.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 05533165

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Canada

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-24

**Reviewer chosen by:** Jin-Lei Wang

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

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. 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. 2. Introduction HCC – risk factors for cirrhosis, I would add autoimmune liver disease. I would remove aflatoxin (rare). 3. Page 7 – please provide references for “additional criteria have been published by several groups from Asia”. 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. 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. 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. 7. Secondary liver cancer – I suggest starting with NET then you can have the section on CRLM. 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. 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. 10. Table 1 – for ETC criteria and Asian criteria, what is the 5-yr OS? 11. Table 1 – Kyushu and Samsung criteria, is there no 5-yr OS provided?

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 05458764

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Croatia

**Author's Country/Territory:** Germany

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**Review time:** 9 Days and 14 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

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. 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.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 04091635

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Slovenia

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-24

**Reviewer chosen by:** Jin-Lei Wang

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**Review time:** 12 Days and 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

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. 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. 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. Additional criteria in Asia are mentioned without citation. CRLM It is true that the data from recent prospective studies (SECA and TRANSMET) are the most important. But there are some interesting studies which should be compared to these results. Muelbacher published 2 articles with long-term survivors and described the role of micrometastases and influence on survival. I believe that critical evaluation of the authors could also elucidate the importance of primary tumor in patient selection.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**Manuscript NO:** 64812

**Title:** Liver transplantation in malignant disease

**Reviewer's code:** 05226494

**Position:** Editorial Board

**Academic degree:** MBBS, MD

**Professional title:** Additional Professor

**Reviewer's Country/Territory:** India

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-24

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2021-04-08 08:19

**Reviewer performed review:** 2021-04-27 02:19

**Review time:** 18 Days and 17 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

It's very well written and needs minor revision.