

**Reviewer #1:**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade D (Rejection)

**Conclusion:** Major revision

**Specific Comments to Authors:** In this research, the authors aimed at assessing (and at comparing with each other) the long term outcomes (disease free survival (DFS) and Overall survival (OS)) of 4 different therapeutic strategies (TACE, RFA, repeated hepatectomy (RH) and liver transplantation (LT)) for patients affected by recurrent HCC (rHCC) following HCC resection, performing a network metanalysis of previously published studies on this issue. They identified 30 relevant studies and assembled patients data according to the therapeutic strategy used to treat rHCC. Long term outcomes in different treatment group were assessed and compared with other groups using different statistical methodologies. Despite the manuscript regards an interesting topic (rHCC following HCC resection is unfortunately very common and guidelines regarding the selection of the best management of rHCC may be not always able to guide the clinical practice), and as such may be of interest for clinicians involved in the treatment of HCC, many comments are due.

**Major comments:**

1. **the manuscript is** badly written: the English writing level is very low, there are grammar, orthographical, semantic mistakes. **Many sentences lack a subject or a verb. In the discussion, the sentences are not linked with each other. All of this makes the manuscript really difficult to read and understand. I strongly recommend a deep review from an English mother tongue scientific editor.**

**Answer:** A stringent reviewer is good in some situations but not always. I always remember that duty of a reviewer is to assist author how to improve his/her own manuscript to match the requirements of the journal instead of taunt. English is not my mother language but I know my English writing ability. We had completed the English revision with a certificate. We expect to fit the requirements which were reasonable for a high quality journal.

2. **The differences in OS and DFS among different treatment strategies is related to characteristics of tumor and patients in each treatment arm: this aspect may limit the comparability of different arms, determining a selection bias, and should be highlighted in the paper discussion.**

**Answer:** Of course, the results of OS and DFS of different arms were depending on the patients' characteristics and tumor natures, but not enrolled in this meta-analysis study today. Concerning this issue was discussed in the 2<sup>nd</sup> paragraph. In addition, patient or their family will decide to select the re-treatment methods sometimes and against the advice from doctor. Publication bias (by Egger's regression test) and heterogeneity ( $I^2$  values by Q test) of different arms were showed in the part of results. Therefore, random-effect model was used for analysis and try to overcome the bias from each arm. Usually, this evidence will limit the value of a study with meta-analysis. We will highlight the study results and discussed in the last 2<sup>nd</sup> paragraph of discussion.

@Minor comments:

3. The flow chart of the search strategy and selection of the manuscripts included in the current analysis should be shown.

**Answer:** The flow chart of the search strategy was usually found the meta-analysis articles, but not for all. This search strategy had been mentioned in detail in the part of methods and results instead of flow chart. We deleted flow chart which occupy a large space without scientific value. Because too many figures obtained from meta-analysis study, and these figures were more valuable than flow chart. Therefore, please accept our preparation and we can put it back if reviewer insist.

4. I suggest the authors to report in table 2 the median number of rHCC.

**Answer:** The title of table 2 was predictive p-score in each methods for rHCC. I can't catch the mean of "median number of rHCC". In the table 2, p-score (**not p value**) represented the superiority and p-score=1 will be the best in comparison.

Reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The article needs to be improved upon. The following are the suggestions:

1. Minor: Language, abbreviations and grammar need correction throughout the manuscript

**Answer:** Thanks for your kindness and suggestion. We had completed the English revision with a certificate and we expect to fit the journal requirements.

2. Major:

a. The results need better depiction and summarized along with tables and figures

**Answer:** We had depicted their results in each section, table and figure as shown in the revised text.

b. The following maybe discussed:

i. Wang HL[57], Mo DC, Zhong JH, et al. Systematic review of treatment strategy for recurrent hepatocellular carcinoma: Salvage liver transplantation or curative locoregional therapy. *Medicine (Baltimore)*. 2019;98(8):e14498. in the code ref 57

ii. Simone Famularo et al, Curative versus palliative treatments for recurrent hepatocellular carcinoma: a multicentric weighted comparison, *HPB*, Volume 23, Issue 6, 2021, Pages 889-898, in the code ref 58.

iii. Kostakis ID et al. Comparison Between Salvage Liver Transplantation and Repeat Liver Resection for Recurrent Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *Transplant Proc*. 2019 Mar;51(2):433-436. in the code ref 56

iv. Zhang X, Li C, Wen T, Peng W, Yan L, Yang J. Outcomes of Salvage Liver Transplantation and Re-resection/Radiofrequency Ablation for Intrahepatic Recurrent Hepatocellular Carcinoma: A New Surgical Strategy Based on Recurrence Pattern. *Dig Dis Sci*. 2018 Feb;63(2):502-514. doi: 10.1007/s10620-017-4861-y. Epub 2017 Dec 14. PMID: 29238896. in the code ref 70

**Answer:** Thank the suggestion of these 4 articles which we had read 3 articles during literature search strategy, were worth adding in discussion in this manuscript as coding ref. 56, 57, 58, and 70..

Reviewer #3:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The research aimed to compare the familiar curative treatments including repeated hepatectomy, radiofrequency ablation, trans-arterial

chemo-embolization, and liver transplantation for the patients of rHCC after primary hepatectomy by network meta-analysis. It provided a prominent decision to make the most suitable re-treatment method for the patients of rHCC and attracted lots of readers including clinical doctors.

@The theme and idea are clear, but some meanings are repeated and ambiguous, and need to be revised.

1. In the section “Introduction”, the ranking of leading cause of death was the 2nd in male and 4th in female among all cancers in year of 2019 in Taiwan. Liver cancer is not mentioned.

**Answer: Ref.1.**Health Promotion Administration Ministry of Health and Welfare T, 2021. Cancer Registry Annual Report, 2019, Taiwan.

file:///C:/Users/ed112739/AppData/Local/Temp/MicrosoftEdgeDownloads/.....The ed112739 is my personal hospital ID for informatic safety in our library. Therefore, I had corrected it and changes into a new one for others persons before entering as following.

New; <https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=14913>, Accessed 21 Jun 2022.

The data were obtained and proved as the following 2 Tables.(in Chinese. Sorry.)

男性 10 大癌症死亡率（每 10 萬人口），民國 108 年 <u>Male 2019</u>					
順位	ICD-10	原發部位	個案數 (人)	粗死亡率	年齡標準化 死亡率 <sup>2a</sup>
1	C33-C34	肺、支氣管及氣管	6,190	52.88	26.51
2	C22	肝及肝內膽管	5,363	45.82	24.24
3	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	3,661	31.28	15.51
4	C00-C14 <sup>3</sup>	口腔、咽喉及下咽	3,154	26.95	15.73
5	C15	食道	1,841	15.73	9.03
6	C16	胃	1,436	12.27	5.97
7	C61	攝護腺(前列腺)	1,538	13.14	5.42
8	C25	胰	1,360	11.62	6.02
9	C82-C85	非何杰金氏淋巴瘤	735	6.28	3.20
10	C91-C95	白血病	653	5.58	3.27
	C00-C97	全癌症	30,543	260.94	135.99
					156.86

註： 1. 自 96 年癌症登記報告起，惡性淋巴瘤從各部位獨立出來計算發生率，並納入排名。惡性淋巴瘤：ICD-O-3 M-CODE 請見 p.496 附錄五。  
2. 年齡標準化率<sup>2a</sup>係使用 1976 年世界標準人口為標準人口。年齡標準化率<sup>2b</sup>係使用 2000 年世界標準人口為標準人口。

女性 10 大癌症死亡率（每 10 萬人口），民國 108 年 Female 2019

順位	ICD-10	原發部位	個案數 (人)	粗死亡率	年齡標準化 死亡率 <sup>2a</sup>	年齡標準化 死亡率 <sup>2b</sup>
1	C33-C34	肺、支氣管及氣管	3,511	29.51	12.81	15.04
2	C50	女性乳房	2,633	22.13	11.77	12.98
3	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	2,775	23.32	9.76	11.56
4	C22	肝及肝內膽管	2,518	21.16	8.50	10.29
5	C25	胰	1,137	9.56	4.14	4.87
6	C16	胃	943	7.93	3.36	3.98
7	C56,C57.0-C57.4	卵巢、輸卵管及寬韌帶	683	5.74	3.11	3.42
8	C53	子宮頸	674	5.66	2.83	3.20
9	C82-C85	非何杰金氏淋巴瘤	540	4.54	1.93	2.29
10	C91-C95	白血病	470	3.95	2.00	2.27
	C00-C97	全癌症	19,689	165.48	75.14	87.18

註：1. 自 96 年癌症登記報告起，惡性淋巴瘤從各部位獨立出來計算發生率，並納入排名。惡性淋巴瘤：ICD-O-3 M-CODE 請見 p.496 附錄五。  
2. 年齡標準化率<sup>2a</sup>係使用 1976 年世界標準人口為標準人口。年齡標準化率<sup>2b</sup>係使用 2000 年世界標準人口為標準人口。  
3. 原發部：組織形態之分類碼第 5 碼（性腺碼）為 2；結腸、直腸、乙狀結腸連結部及肛門原發部包含 High grade dysplasia。

- Therapeutic options for primary HCC are clearly depending on specified staging and the international guidelines for following. However, there is still debate on the issue of re-treatment strategies for rHCC. The content and meaning are repeated in the second and third paragraphs of the section "Introduction".

**Answer:** Thanks, and corrected it already

Part 3, in the results. Outcomes of OS-3y and 5y of RH compared with others disclosed 1.64(0.56-4.66) and 1.05(0.43-2.56) superior to LT, RFA, and TACE respectively in the figure 3-E & 3-F. RH had a superior in the cumulative OS-3y and 5y based on this analysis. It is not clear and ambiguous.

- Answer:** We had completed re-writing.

## 2 Editorial Office's comments

- Science Editor:** The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade C (A great deal of language polishing)

Scientific Quality: Grade C (Good)

- Company Editor-in-Chief:** I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve

an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.