

## Round-1

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

**Manuscript NO:** 65399

**Manuscript Type:** REVIEW

**Title:** GALLBLADDER CANCER – HISTORICAL TREATMENT AND NEW MANAGEMENT OPTIONS

**Authors:** Kenji Okumura, Shekhar Gogna, Mahir Gachabayov, Daniel Moritz Felsenreich, Matthew McGuirk, Aram Rojas, Luis Quintero, Ramanathan Seshadri, Katie Gu, Xiang Da Dong

Dear Editor,

Please find enclosed the resubmitted revised manuscript for the review titled; GALLBLADDER CANCER – HISTORICAL TREATMENT AND NEW MANAGEMENT OPTIONS; Manuscript NO: 65399.

We have read thoroughly all the reviewer comments with the constructive criticism which I do respect for the perfection of the manuscript.

We have taken all comments into consideration and we answered the questions and revised the text accordingly (all changes are highlighted in bold).

We are herewith attaching the revised manuscript and the point to point replies to the reviewers. We always do appreciate very much your support.

With my best regards,

Sincerely,

Kenji Okumura

Reply to reviewers:

Reviewer #1:

Specific Comments to Authors: In this review, the authors examined “the causes of gallbladder cancer along with new innovative treatments in the management of gallbladder cancer”. Even the review is quite comprehensive and could be useful for clinicians and general readers, it lacks of novelty and might not sufficiently contribute to the research fields. To improve the review, the authors may need to consider these issues. - The pathogenesis, pathophysiology, and molecular mechanisms of the

carcinogenesis of gallbladder cancer should be provided, rather than giving the list of risk factors. The development of the treatments as well as the preventions that corresponding to the mechanisms of carcinogenesis and progression should be addressed. If it is unknown or the data are insufficient, then it also needs to explain. - The authors should discuss more about the advancement of diagnosis and treatments, and suggest the future direction of research to improve such issues of gallbladder cancer. The whole review is summarized the data of findings in the past but the critical analysis and synthesis are lacking. - The tumor markers mentioned in the review are not specific to only gallbladder cancer, but could also be increased in other cancers. The authors should make clear how these markers could be useful for the diagnosis or prognosis of gallbladder cancer. For example, in Line 164, the diagnostic algorithm is referred, but the details of the algorithm are not given. - As the title indicates "New treatment options", it would be better to include all available options, both medical and surgical, with adequately address the discussion of pros and cons of each. In the present version, there are only surgical options provided. - The abbreviation should be consistent, e.g., for cholangiocarcinoma, there are CAC and CCA, and sometimes the full word is spelled out. - There are some typos need to be corrected.

**Answer:**

**We like to thank the reviewer for a thorough review of this manuscript. The pathogenesis, pathophysiology and molecular mechanisms of the carcinogenesis of gallbladder cancer was not reviewed in depth with this manuscript since it was not the focus of this review. The risk factors were listed as this is a clinical review on the management of gallbladder cancer.**

**With the current revision, we have expanded previous non-surgical options and included additional options with respect to management of gallbladder cancer. We also updated all the abbreviations as indicated by the reviewer.**

**Reviewer #2:**

Specific Comments to Authors: In this review article "GALLBLADDER CANCER – HISTORICAL TREATMENT AND NEW MANAGEMENT OPTIONS", authors aimed to examine the causes of gallbladder cancer along with new innovative treatments in the management of gallbladder cancer, and they have also examined various genetic predispositions for gallbladder ca. Authors have tried to cover too many aspects of GBC in one review article- needs to be shortened for clear messages. This article does not add to current understanding on this subject. Many aspects have not been covered adequately: 1. minimally invasive approach for radical cholecystectomy (Han HS, Laparoscopic Surgery for Gallbladder Cancer: An Expert Consensus Statement. Dig Surg. 2019, Vega EA. Comparison of oncological outcomes after open and laparoscopic re-resection of incidental gallbladder cancer. Br J Surg. 2020) 2. Staging laparoscopy: Agarwal AK. The role of staging laparoscopy in primary gall bladder cancer--an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer. Ann Surg. 2013 Aug 3. Robotic surgery: Goel M. Robotic surgery for gallbladder cancer: Operative technique and early outcomes. J Surg Oncol. 2019 4. Current status of PET scan in staging (Goel S, . 18-FDG PET-CT should be included in preoperative staging of gall bladder cancer. Eur J Surg Oncol. 2020 ) 5.

Role of chemotherapy +/- RT in neoadjuvant and adjuvant setting has not been discussed adequately. (Chaudhari VA, Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications. HPB (Oxford). 2018) 6. Initial part of review - epidemiology/clinical presentation can be shortened. 7. There are duplication of the content at places e.g. management of incidental GBC. 8. How augmented reality is beneficial specifically for GBC. 9. Please discuss Chemotherapy and recent advances separately for better understanding.

**Answer:**

**We like to thank the reviewer on these critical comments. We have expanded the sections on minimally invasive approaches to gallbladder cancer including laparoscopy and robotic surgery. Several sections on advances in management of gallbladder cancer has been updated as well. The new information, including additional references were added to the revised manuscript.**

Reviewer #3:

Specific Comments to Authors: it is well written review article thank you

**Answer:**

**We like to thank the reviewer on their comments and critical review.**

Reviewer #4:

Specific Comments to Authors: The article does not report new concepts about gallbladder cancer.

**Answer:**

**We agree with the reviewer on their comments. However, the purpose of this manuscript was a narrative review. Therefore, this manuscript does not contain new information as indicated by the reviewer.**

#### 4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

**Answer: the revised manuscript has been reviewed and corrected for any issues related to grammar or language.**

## 5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly. Now we list the abbreviations rules as follows.

- (1) Title: Please spell out any abbreviation in the title. Abbreviations are not permitted.
- (2) Running title: Please shorten the running title to no more than 6 words. Abbreviations are permitted.
- (3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).
- (4) Key words: Abbreviations must be defined upon first appearance in the Key words.
- (5) Core tip: Abbreviations must be defined upon first appearance in the Core tip. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)
- (6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)
- (7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Examples: Example 1: Hepatocellular carcinoma (HCC).  
Example 2: Helicobacter pylori (H. pylori)
- (8) Figures: Please verify the abbreviations used in figures and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.
- (9) Tables: Please verify the abbreviations used in tables and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

### **Answer:**

**The revised manuscript was formatted to adhere to the above guidelines.**

## 6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

- (1) Science editor: 1 Scientific quality: The manuscript describes a Review of the Gallbladder cancer. The topic is within the scope of the WJGO. (1) Classification: Grade B, B, C and D; (2) Summary of the Peer-Review Report: The authors should discuss more about the advancement of diagnosis and treatments. Many aspects should be covered adequately. The questions raised by the reviewers should be answered; (3) Format: There are 5 tables and 5 figures; (4) References: A total of 102 references are

cited, including 18 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference; and (6) References recommendations (kindly remind): The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B. The authors are native English speakers. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJGO.

**Answer:**

**In response to the above comments, the revised manuscript has been corrected with respect to the reviewers' comments and inputs. Specifically, the advancement of diagnosis and treatments were expanded in the revised manuscript.**

The references were updated with DOI numbers added to the revised manuscript.

(2) 5 Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; (4) Uniform presentation should be used for figures showing the same or similar contents (using lettered panels); for example: "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ..."; and (5) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

**Answer:**

**(1) The "Author Contributions" section has been added to the revised manuscript.**

**(2) The pictures provided are the original artworks of Dr. Lala Orujova. She has been credited in the acknowledgement section for her work. The authors are providing the best quality images available for those images.**

**With the revised manuscript, the figures have now been arranged using a powerpoint format as requested by the editors.**

**(3) PMID and DOI numbers have now been added to the revised references.**

**(4) Uniform presentation is added to the revised manuscript.**

**(5) Figure 4 is reprinted with permission.**

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

**Answer:**

**We like to thank the editors for their efforts.**

### **Round-2**

Dear Editor,

Please find enclosed the new revised manuscript entitled "Gallbladder Cancer – Historical treatment and new management options".

- This reviewer failed to see the highlighted revision, although it was mentioned that the revised text has been highlighted in bold. Thus, it is hard to compare and decide if the authors have adequately addressed the points of concerns of the reviewers. - Even the authors explained that this is a clinical narrative review, the critical synthesis of knowledge from the previous reports together with the perspective/suggestion for a research on the same topic is also important for a review article in scientific journal. Otherwise, it rarely adds up any information to the current understanding of the field.

**Answer:**

**We have read all the reviewers' comments along with the most recent reviewer's comments. We do appreciate the reviewers' efforts in pointing out the areas for improvement. We have made significant changes to the manuscript taking into consideration the comments made by the reviewers.**

**In particular, the sections on newer developments in management of gallbladder cancer including chemotherapy, immunotherapy, and advances in surgical management were revised. All major changes in the new manuscript are highlighted in yellow in the new manuscript. We hope the changes are sufficient with respect to the comments raised by the reviewers.**

We look forward to your positive response.

With my best regards,

Sincerely,

Kenji Okumura and Xiang Da Dong