Answering Reviewers

Reviewer 1

Reviewer Name: Anonymous

Review Date: 2018-04-10 20:02

Specific Comments To Authors: This is a useful retrospective review of an extensive cohort of lymph node-negative gallbladder carcinoma patients from SEER, attempting to inform on required lymph node number to be dissected for optimal survival results. I have the following major comments: - It is not clear if there is any clinical value on identifying the optimal number of lymph nodes to be procured for each stage separately as the staging is pathologic for clinically (radiologically) negative lymph node cases. That means that stage is defined post-operatively. As a result the recommendation for patients with IIIA disease (worst case scenario for node negative disease) would be the one for stages I and II too. This is depicted in the guideline. Separating the stages is only going to create confusion from a clinical point of view. Moreover, and equally important for the value of the report, results provided do not exclude the possibility that the next number of lymph nodes (i.e. 4 for stage I, 6 for stage II and 7 for stage IIIA) could not have additional benefit. It is not clear whether the authors performed these comparisons and why they do not report the findings. - The x-tile tool is used for finding an optimal cut-off for prognostic markers by identifying the cut-off of a marker that gives an optimal discrimination of the above or below group but it is not appropriate for a question such as the one the authors have at hand where comparisons should be continued till no survival

difference is found between the two groups. Given the two above points the report should be rewritten and the major conclusion should be that at least 6 nodes are needed (or more if additional comparisons show that) which is also consistent with the current recommendations. Some additional comments: - In methods line 5: it should be one or more LN examined. - In line 7 of methods the exclusion of unknown cause of death could introduce bias. I am not sure that this is advisable in a disease that has more than 90% mortality at 5 years. - In line 8 of methods it should be explained what these codes are. - A discussion should also be included on how the staging of patients was performed in the database. Had all patients had CT scans? Was PET used in any? - In the statistical analysis it should be mentioned if all the parameters considered in the multivariate analysis were significant in univariate analysis. In addition, chemotherapy treatment should be considered as a parameter.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Ans: Thanks for reviewing our paper very much.

1. The major conclusion and the related content throughout the article have been corrected as advised in the review. See the manuscript.
2. Methods line 5: it has been corrected.
3. Methods line 7: actually, after cases were excluded according to other exclusion criteria, all the rest of patients had known cause of death. We added the criterion only for rigorous logic. If the reviewer still thinks that it will introduce bias, we

will delete it. Thanks very much!

4. Methods line 8: adequate information has been added to explain the codes.
5. The staging of patients in the database was based on pathologic histology, rather than radiography. So we did not provide any information about radiography in the discussion. Actually the SEER database does not provide any information about radiography or chemotherapy treatment. We are sorry for that.
6. In the statistical analysis: we have made modification as advised.

Reviewer 2

Reviewer Name: Anonymous

Review Date: 2018-03-30 15:17

Specific Comments To Authors: Focus on the harvested LN number for N0 GB cancer is nice. This paper involves new knowledge, and their insight is so informative for journal readers. Especially, cut-off levels of examined LN number in each stage is excellent. Some GB cancer in stage II or III, tumor may be extended not only LN metastasis but also direct nerve invasion. Hence, intentional nerve dissection may be required in these stages. This point is still controversial, and surgical guideline should be developed for not only LN dissection but also nerve dissection. This point should be mentioned in the Discussion section.

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Ans: Thanks for reviewing our paper very much. Information about nerve dissection has been added in the discussion.