Format for ANSWERING REVIEWERS

March 13, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 33394-review.doc).

Title: Laparoscopic approach to suspected T1 and T2 gallbladder carcinoma

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Name of Journal: *World Journal of Gastroenterology*

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RESPONSE TO REVIEWER (No.01560494)

We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us significantly improve the paper.

Comments

Laparoscopic approach IS unfit for T2 gallbladder cancer according to NCCN guide.

Response: We thank the Reviewer for this pertinent comment. Of course, it is not standard yet to perform laparoscopic radical cholecystectomy including regional lymphadenectomy and gallbladder bed resection for T2 gallbladder carcinoma. However, laparoscopic radical cholecystectomy can be performed safely with the benefit of laparoscopic view, and it can be an option of the treatment for T2 gallbladder carcinoma in well-selected patients. In our institute, we employ open radical cholecystectomy when extrahepatic bile duct resection is required in order to obtain negative margins or perform thorough lymph nodes resection. The main point of this study is not only laparoscopic radical resection for T2 gallbladder carcinoma but laparoscopic approach for the

management of the gallbladder lesions difficult to differentiate from gallbladder carcinoma.

We wish to thank the Reviewer again for his or her valuable comments.

RESPONSE TO REVIEWER No.03665440

We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us significantly improve the paper.

Comments

Thank you for the opportunity to review this manuscript. This is a retrospective but interesting study aiming to evaluate laparoscopic surgery for "suspected" T1 and T2 gallbladder cancer. Wide spread of the laparoscopic approach has been hampered by the risk of tumor dissemination as well as by the difficulties in preoperative (and operative) diagnosis for malignancy and staging, as described by the authors. Their operative outcomes shown in the manuscript, with a precise algorithm for surgical management, are likely to be acceptable. It is assumed that the laparoscopic procedures have been performed by skilled endoscopic surgeons. In addition, I agree the point that the laparoscopic surgery potentially has an advantage of precise view for lymph node dissection over open surgery. However, their definitive conclusions appear not to match the results. "LCWL and LCGB" can safely be performed with a well-planned strategy and skilled surgeons, but the issue of "minimally invasive procedures" has not been addressed in this study. Furthermore, the presented data of RFS as "long-term results" in comparison with open surgery seems not appropriate for publication, which may cause misunderstanding. I cannot find any data for baseline characteristics of the open group or comparison of background factors for lap vs open in this report. #1 The data of RFS in comparison with open surgery is presented in Figure 5. There would be a potential bias with a substantial difference in follow-up period. If the authors would like to present the data, baseline characteristics of the open group and

comparison of background factors for lap vs open should be analyzed. In addition, a limitation to interpret the figure should be added. Otherwise, the data and description for the RFS in lap vs open could be omitted, if the figure seemed misleading. #2 The conclusions of the paper should be reconsidered, since less invasiveness of the laparoscopic procedure has not been estimated in this study. #3 "Whole-layer cholecystectomy" or "the whole-layer gallbladder wall" should be explained briefly, according to some references (e.g. Honda, G. J Hepatobiliary Pancreat Sci 23(9): E14-9; 2016, Sugioka, A. J Hepatobiliary Pancreat Sci 24(1): 17-23; 2017) #4 In the first paragraph of Discussion, the authors mentioned that "laparoscopic radical resection for GBC has rarely been reported". There are several studies regarding the theme as referred by the authors. Thus, the word "rarely" is inappropriate. I would like to know the distinguishing or important points of the current report in relation to results of the preceding relevant studies. #5 In the 4th para of Discussion, the term "overwhelmingly" seems too exaggerated. #6 General information about diagnosis and surgery for gallbladder carcinoma can be shortened with appropriate indication of the references. #7 An additional comment would be needed as to whether the D2 dissection can be completed without EBR. #8 In "Laparoscopic gallbladder bed resection" of the Methods section, the sentence "the positions of trocars are similar to those for laparoscopic gastrectomy" seems not necessary.

#1 The data of RFS in comparison with open surgery is presented in Figure 5. There would be a potential bias with a substantial difference in follow-up period. If the authors would like to present the data, baseline characteristics of the open group and comparison of background factors for lap vs open should be analyzed. In addition, a limitation to interpret the figure should be added. Otherwise, the data and description for the RFS in lap vs open could be omitted, if the figure seemed misleading.

Response : We thank the Reviewer for this pertinent comment. Selection bias exists between laparoscopic surgery and open surgery indeed. When extrahepatic bile duct resection was required due to cancer invasion to the common bile duct or positive lymph node metastasis, we selected the open radical resection. Furthermore, some cases were diagnosed with gallbladder carcinoma after the conventional laparoscopic cholecystectomy, and they

underwent additional open surgery. The Review's comments were accurate, and it was inappropriate to compare laparoscopic and open surgery. We decided to omit the comparison of RFS in this study. The follow-up period after the laparoscopic approach was short, but RFS of our laparoscopic approach was relatively good and acceptable, we think.

#2 The conclusions of the paper should be reconsidered, since less invasiveness of the laparoscopic procedure has not been estimated in this study.

Response: In our laparoscopic procedure, the intraoperative blood loss was very low, and no severe complications were encountered. The length of the postoperative hospital stay was also relatively short. Therefore we thought that our laparosocpic approach was less invasive. However, we have not conducted comparative studies of laparoscopic surgery and open surgery on the perioperative oucomes because there was a certain selection bias. As the Reviewer pointed out, the conclusion that the laparoscopic procedure was less invasive is not proper. We deleted the statement of less invasiveness and corrected the conclusion.

#3 "Whole-layer cholecystectomy" or "the whole-layer gallbladder wall" should be explained briefly, according to some references (e.g. Honda, G. J Hepatobiliary Pancreat Sci 23(9): E14-9; 2016, Sugioka, A. J Hepatobiliary Pancreat Sci 24(1): 17-23; 2017)

Response: We added the explanation about whole-layer cholecystectomy by reference to the literature describing the surgical anatomy of the gallbladder wall in detail.

#4 In the first paragraph of Discussion, the authors mentioned that "laparoscopic radical resection for GBC has rarely been reported". There are several studies regarding the theme as referred by the authors. Thus, the word "rarely" is inappropriate. I would like to know the distinguishing or important points of the current report in relation to results of the preceding relevant studies.

Response: As the reviewer suggests, we modified the description that

"laparoscopic radical resection for GBC has rarely been reported" to "Several studies on laparoscopic radical resection for GBC have been reported". The main point of this study is not only laparoscopic radical resection for T2 gallbladder carcinoma but also laparoscopic approach for the management of the gallbladder lesions difficult to differentiate from GBC. There have been no reports on effective laparoscopic approaches to the lesions suspected of GBC. We believe that our laparoscopic approach is feasible for the management of suspected T1 and T2.

#5 In the 4th para of Discussion, the term "overwhelmingly" seems too exaggerated.

Response: We changed the term "overwhelmingly" to "much".

#6 General information about diagnosis and surgery for gallbladder carcinoma can be shortened with appropriate indication of the references.

Response: The description of diagnosis and surgery for gallbladder carcinoma was partially omitted and shortened.

#7 An additional comment would be needed as to whether the D2 dissection can be completed without EBR.

Response: Whether the D2 lymph node dissection without EBR is sufficient is a difficult problem. We think that clinically sufficient lymph node dissection around the common bile duct and preservation of pericholedochal small vessels to prevent biliary ischemia are possible with the laparoscopic magnified view. However, the lymphatic infiltration around the bile duct is a main pathway for tumor spread. Therefore, when positive lymph node metastasis or advanced microscopic neurovascular invasion is suspected, we now perform thorough regional lymphadenectomy with EBR by laparotomy, not by laparoscopic surgery. We added the description about the D2 lymphadenectomy without EBR.

#8 In "Laparoscopic gallbladder bed resection" of the Methods section, the sentence "the positions of trocars are similar to those for laparoscopic

gastrectomy" seems not necessary.

Response: We deleted the sentence "the positions of trocars are similar to those for laparoscopic gastrectomy".

We wish to thank the Reviewer again for his or her valuable comments.

RESPONSE TO REVIEWER No.00919923

We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us significantly improve the paper.

Comments

This is a well written meaningful paper on laparoscopic approach for early GB cancer. In addition, authors achieved good results in laparoscopic treatment for T1 and T2 GB cancer and showed instructive information from their experiences.

Response：We thank the Reviewer for this pertinent comment. We revised our manuscript with reference to all reviewers' commens. We would like to send our most sincere thanks for the reviewers.

We wish to thank the Reviewer again for his or her valuable comments.

Sincerely yours.

Yusuke Ome
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