Peer Review File

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Reply to comments and suggestions raised by Reviewer A:

Reviewer: The authors present a well-written work examining Long- and short-term outcomes for resectable gallbladder carcinoma patients treated with curative-intent laparoscopic versus open resection: A multicenter propensity score-matched comparative study. Unfortunately, this manuscript is not accepted as its form. Several major points should be revised.

Reply: We are honored to receive your feedback, and your comments have been highly valuable for improving the article. We greatly appreciate the questions you raised, and we have made revisions accordingly to address the areas that needed significant improvement. We sincerely thank you and look forward to your approval.

Major point

Comment 1: This study examined the short-term and long-term prognosis of laparoscopic surgery and open surgery for gallbladder cancer that was curatively resected according to NCNN guidelines. We perform prognostic analysis using propensity matched analysis. There were no major differences in long-term results between the two groups. In terms of short-term results, laparoscopic surgery has better results than open surgery. Even when compared with past studies, no new findings have been obtained from this study. In addition to that, the significance of performing PSM in this study is unclear.

Reply 1: Thank you for your comment. First, as you mentioned, previous studies have explored the effectiveness of laparoscopic radical surgery for gallbladder cancer (GBC), but most of these studies included only early-stage GBC (T1) patients who underwent laparoscopic cholecystectomy alone. The surgical difficulty and outcomes differ between GBC surgeries that involve only cholecystectomy and those that include liver resection, cholecystectomy, or lymph node dissection as part of radical surgery. The latest NCCN guidelines recommend radical resection in all cases. Therefore, in this study, all laparoscopic radical resections included liver resection, cholecystectomy, and lymph node dissection. This is the first difference between our study and previous studies.
Second, in our view, the significance of medical research lies not only in discovering new perspectives but also in transforming empirical viewpoints into medical evidence through evidence-based medicine. This provides references for disease treatment and serves as a basis for updating disease-related guidelines. Conducting a multicenter randomized controlled trial (RCT) on this subject is challenging due to the incidence rate of gallbladder cancer and the limited promotion of laparoscopic radical surgery for gallbladder cancer. The retrospective LR and OR cohorts collected may have significant confounding factors, as they were obtained through nonrandomized selection. We used propensity score matching (PSM), a statistical method, to control for confounding factors between the two cohorts and to simulate the process of random selection. In simple terms, we used PSM to simulate multicenter RCT studies based on retrospective studies, making the results more persuasive.

Comment 2: AC is essential to prolong the long-term prognosis in patients with GBC from recent study. Please add the following manuscript in this paper. Please clearly describe the regimen of AC in this study.

# Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial


Reply 2: Thank you for your comment. The study you mentioned is indeed relevant to our research. We briefly described these two studies in the revised article. Additionally, in the Methods section, we have listed commonly used AC regimens, including capecitabine, gemcitabine, and gemcitabine plus cisplatin, and we have also presented the proportions of patients who underwent these regimens in the Results section. All AC regimens included in our study are recommended by the NCCN. We have provided additional explanations for the above in the Methods section.

Changes in the text: We have added detailed information about regimens (see Page 10, line 11) and cited “Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT):
a multicenter, open-label, randomized, controlled, phase 3 trial” as advised (see Page 15, line 14).

**Comment 3:** Considering high rate of mortality and malignant potential in GBC, it is important to perform NAC for advanced GBC. It could be completely cured by aggressive surgery including vascular resection and reconstruction; however it is more important to perform AC for patients with advanced GBC. Please add the following paper in this manuscript.

# Surgical outcomes of gallbladder cancer: the OMEGA retrospective, multicenter, international cohort study. Anita Balakrishnan, The Lancet 2023

# Preoperative Systemic Inflammation and Complications Affect Long-term Gallbladder Carcinoma Outcomes Following Surgery with Curative Intent. Tomoyuki Abe 2016 Anticancer Research

**Reply 3:** Thank you for your comment. We greatly appreciate your perspective. With advancements in drug treatment technologies, the treatment of tumors has become increasingly comprehensive, now including neoadjuvant chemotherapy, surgical treatment, and adjuvant chemotherapy. Through personalized comprehensive treatment, the aim is to eliminate tumor cells to the greatest extent possible, thereby improving the prognosis. We have added content about comprehensive treatment to the Discussion.

**Changes in the text:** We have cited “Surgical outcomes of gallbladder cancer: the OMEGA retrospective, multicenter, international cohort study” (see Page 16, line 8) and “Preoperative Systemic Inflammation and Complications Affect Long-term Gallbladder Carcinoma Outcomes Following Surgery with Curative Intent” (see Page 16, line 8) as advised.

**Reply to comments and suggestions raised by Reviewer B:**

**Reviewer:** This is well organized study with PMS methods. I need to have some clarification but otherwise almost ready.

**Reply:** We greatly appreciate your recognition of the strengths of our study, as it serves as an important motivation for our team. The issues you pointed out have allowed us to optimize and supplement certain details of this study. We have responded to and made revisions accordingly.
Comment 1: How was the diagnosis of GB cancer (or suspicion) done before surgery?

Reply 1: Thank you for your comment. The suspicion of gallbladder cancer was based on preoperative imaging examinations, such as enhanced CT and MRI, and tumor markers, such as CEA and CA19-9. The diagnosis of gallbladder cancer was confirmed through postoperative pathological examination.

Changes in the text: We have modified our text as advised (see Page 8, line 20).

Comment 2: How was the adjuvant chemotherapy for study population?

Reply 2: Thank you for your comment. The same question was raised by another reviewer. We have added an explanation of the adjuvant chemotherapy regimen to our article. Since this study is a multicenter retrospective study, we can only list the types of regimens and cannot provide more detailed information. Generally, the dosage and duration of adjuvant chemotherapy were based on the drug package inserts and our clinical experience. Additionally, it should be noted that the AC patients included in this study received AC regimens recommended by the NCCN. We have added relevant explanations to the Methods section. We have also included the proportions of the three most common regimens in the Results section.

Changes in the text: We have added a broad description of the AC regimens (see Page 10, line 11) and listed some of their proportions (see Page 13, line 7).

Comment 3: Where were the sites of recurrence after surgery? Rate of LN recurrence?

Reply 3: Thank you for your comment. In our database, the sites of recurrence of gallbladder cancer are categorized as intrahepatic, extrahepatic, and intrahepatic and extrahepatic recurrence. Generally, extrahepatic recurrence is lymph node metastasis. However, due to the highly invasive metastatic ability of gallbladder cancer, we often find that extrahepatic metastasis in patients undergoing reoperation is actually tumor implantation metastasis rather than lymph node metastasis. Therefore, going from our database, we do not equate extrahepatic metastasis with lymph node metastasis. In this study, the proportion of extrahepatic metastasis was 22.0% (61/277).
Reply to comments and suggestions raised by Reviewer C:

Reviewer: In this multi-center study, the authors aimed to analyze the outcome of laparoscopic resection (LR) of GBC (with curative-intent) and compare it to open resection (OR). The study reported wider application of adjuvant chemotherapy (AC) in LR group, longer operation time, higher number of harvested lymph nodes and a lower overall morbidity rate. An association between AC and patients’ survival was also observed; however, no significant difference in survival was reported between LR and OR groups.

However, several issues that should be addressed as they influence the quality and value of the study:

Reply: We greatly appreciate all of your suggestions. You have provided a comprehensive range of suggestions, which are crucial for improving the quality and value of this study. We will respond to and incorporate each of your suggestions into our revisions.

Comment 1: A total of 626 patients met the inclusion criteria of the study and thus were considered as the primary population. However, the choice of PSM (1:3) to eliminate potential bias between groups led to a huge loss of data in post-matching population. As shown in the included tables (table 2 in specific), the pre- and post-matching P values of most included variables are identical in significance. That raises the question whether the choice of PSM is actually suitable for this specific study. Why did not the authors consider other matching methods such as IPTW in which the data loss can be avoided?

Reply 1: Thank you for your comment. First, we acknowledge your point about whether PSM is truly suitable for this study. If a team wants to investigate the short-term and long-term outcomes of laparoscopic and open resection, the highest level of evidence would be a multicenter randomized controlled trial (RCT). However, conducting a multicenter RCT for a relatively rare condition like gallbladder cancer is challenging. Therefore, we retrospectively collected multicenter data and planned to use statistical methods such as PSM or IPTW to mitigate nonrandom selection bias and simulate a random selection process, thus improving the reliability of the results. This is the rationale behind our choice of PSM.
Second, we fully acknowledge your point that PSM (1:3) can result in significant data loss. However, given the limited adoption of laparoscopic cholecystectomy for gallbladder cancer, the number of cases is already small. Therefore, data loss cannot be avoided if PSM is done.

Third, due to the substantial difference in sample size between the LR group (51 cases) and the OR group (575 cases), IPTW may lead to an increase in estimated variance. This is because the introduction of weights may increase the variability of the observed values, affecting the stability of the results. Additionally, considering the difference in sample size between the two groups in this study, some extreme observations may be assigned larger weights, leading to an excessive influence on the results. This may result in the model being overly sensitive to a small portion of observations, introducing uncertainty. Therefore, considering the significant difference in sample size between the two groups, we chose to use PSM alone to simulate the random selection process.

Comment 2: In the exclusion criteria, the authors mentioned the exclusion of patients with”missing important variables”, the sentence should be rephrased or the definition of “important ” should be provided. The current expression indicates the inclusion of patients with missing data whenconsidered “less important”.

Reply 2: Thank you for your comment. We have rephrased "important variables" as "complete variables". Following your suggestion, this may help readers better understand the source of the data in the article.

Changes in the text: We have modified our text as advised (see Page 8, line 25).

Comment 3: The study considered the cases of LR conversion to OR as part of LR group, yet no explanation or justification of such consideration was provided throughout the study.

Reply 3: Thank you for your comment. The purpose of this study is to compare the outcomes of patients who underwent laparoscopic surgery and open surgery. Conversion from laparoscopic to open surgery is one of the perioperative outcomes of laparoscopic surgery, so we consider patients who underwent conversion from laparoscopic to open surgery to still be part of the laparoscopic group.

Changes in the text: We have provided an explanation in the statistical analysis section of the methods for treating patients who were converted from laparoscopic surgery to open surgery as part of the
laparoscopic group (see Page 10, line 27).

**Comment 4:** The study observed that AC was more common after LR and reported the influence of AC on survival. Considering that adjuvant therapy is currently provided to the majority of cancer patients after surgery, the author should explain why it is more common after LR and how such results are significant to this study.

**Reply 4:** Thank you for your comment. This study found that the LR group had more patients who received AC. This phenomenon may be related to its lower occurrence of complications. Postoperative morbidity could impact the patient's physical condition, leading to a reduced tolerance to AC and a lower usage rate. Performing surgery through a laparoscopic approach could lead to fewer morbidities, allowing more patients to receive AC. This may be a pathway to improving long-term survival by selecting the surgical approach. However, this is only a speculative hypothesis based on the results, which needs to be tested by larger prospective studies.

**Changes in the text:** We have supplemented the Discussion with the reasons for using additional adjuvant chemotherapy after laparoscopic resection, as well as the clinical significance of this result (see Page 15, line 30).

**Comment 5:** In the conclusion section (abstract), the author mentioned a better short-term outcome after LR; however, only one variable of those included in short-term analysis (table 2) showed statistically significant difference. Such a conclusion is hard to be supported by the reported results.

**Reply 5:** Thank you for your comment. We agree with your suggestion. In the short-term outcomes, the only difference observed was a lower overall morbidity rate in the LR group. Therefore, we have modified the Conclusion subsection of the Abstract, replacing the previous statement of better short-term outcomes in the LR group with a lower overall morbidity rate in the LR group.

**Changes in the text:** We have revised the Conclusion of the Abstract (see Page 4, line 25).

**Comment 6:** The aim of the study was to investigate the influence of LR, yet the results indicate that
the real significant influence is actually that of tumor stage and AC application, which is currently considered as a common knowledge or widely anticipated results, as relevant guidelines already addressed such influence.

Reply 6: Thank you for your comment. We acknowledge your viewpoint that the impact of tumor staging and adjuvant chemotherapy on long-term survival is widely accepted. The purpose of this study was to explore the potential advantages of laparoscopic gallbladder cancer resection in intraoperative and postoperative outcomes, as well as to challenge the conventional surgical perspective of limited oncological benefits of laparoscopic gallbladder cancer resection. This study revealed that the LR group led to a greater opportunity for adjuvant chemotherapy, which translated into better long-term survival. Therefore, this study provides valuable references for surgical and adjuvant treatment strategies for resectable gallbladder cancer patients.

Comment 7: The authors alternatively used different terms throughout the study to describe similar concepts, such as RFS and PFS, morbidity and complications. Although those concepts may seem similar, they actually differ in certain aspects. Therefore, it is better to choose the terms most suitable for the study and avoid the mentioned confusion.

Reply 7: Thank you for your comment. The issues regarding these details have been revised based on your corrections. We have made the necessary changes throughout the entire text to use "morbidity" and "PFS" consistently. Thank you very much for your attention to detail.

Changes in the text: We have modified our text as advised throughout the document.

Comment 8: In the discussion section, the author mentioned for the first time the 5-year survival rates. Results should not be introduced in the discussion section, they should be mentioned earlier and then explained or addressed in the discussion.

Reply 8: Thank you for your comment. We have reorganized the writing order according to your suggestions. In the Results section, we have added the 5-year overall survival and progression-free survival rates of patients who received adjuvant chemotherapy and those who did not. We have also offered an explanation for these findings in the Discussion.

Changes in the text: We have modified our text as advised (see Page 13, line 4).
**Comment 9:** Few mistakes in grammars and expressions are present in the study. A further revision and editing of the manuscript should be carried. Based on the previously mentioned issues we reached the conclusion that the manuscript does not meet the standard of publication of this journal and thus we recommend to reject the manuscript in its current form.

**Reply 9:** We greatly appreciate every valuable suggestion and comment you have made regarding this study. We have made modifications and adjustments to the entire manuscript based on your suggestions and comments. Additionally, we have carefully reviewed and revised the content of the manuscript. We hope that the changes we have made to the article meet with your approval. The issues you pointed out, such as consistency in terminology and correspondence between results and conclusions, are not only important for this study but also for our future research work. We will carry the meticulous attitude you have shown toward this manuscript into our future research. Once again, we sincerely thank you for your valuable suggestions and comments on this study.