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Revision Notes

Manuscript Title: Current status and progress in laparoscopic surgery for gallbladder carcinoma

Manuscript Number: 81882

Dear Editors and Reviewers,

Thank you very much for your professional review work on our manuscript "Current status and progress in laparoscopic surgery for gallbladder carcinoma". There are several problems that need to be addressed in this review. We have made the corresponding revisions of our previous draft according to your nice suggestions and supplemented extra data to make our results convincing. The responses to the reviewers' comments have been answered point-by-point. The detailed corrections are listed below. The reviewers' comments are laid out in ***blod italics*** and the revised contents of the manuscript are given in the red typeface.

The response to comments of Reviewer #1 "***Comprehensive review on the current status of laparoscopic surgery for gallbladder carcinoma. The authors have done well to examine the literature on the safety and feasibility as well as long term oncological outcomes of laparoscopic surgery for gallbladder carcinoma. Title, abstract and background is well written. My only comment on the discussion is as follows: 1. Perhaps the authors can expound more on the benefits and short-term outcomes of laparoscopic surgery as compared to laparotomy for GBC. Is there any data on complication rate, conversion rate, length of stay, time to return of bowel function, pain scores, operative time etc in the comparative studies in the literature? These should be discussed in greater detail***" is as follows.

We have searched the databases again for comparative studies of

laparoscopic and open surgery for GBC and added a paragraph about the short-term outcomes of laparoscopic surgery as compared to laparotomy for GBC in terms of operative time, intraoperative bleeding, time to postoperative activity and diet recovery, drainage tube removal time, lymph node yield, complication rate, length of stay and conversion rate after the first paragraph in the discussion part. No specific data on pain scores or concrete time to return of bowel function was found, but studies have shown minimally invasive surgery can relieve wound-related pain and promote earlier ambulation and gastrointestinal peristalsis compared to open surgery, which is also embodied in the paragraph. We will explore more on these two aspects in our future research. The new second paragraph is as follows: "Recent studies have proven the short-term benefits of laparoscopic surgery compared to laparotomy for GBC. A single-center retrospective study by Dou et al., including 99 patients with T2 and T3 stage GBC who underwent radical resection, showed that compared with open surgery, the laparoscopic group had lower intraoperative bleeding volume (233.91±26.35ml versus 461.25±53.15ml, P<0.01) and shorter postoperative hospital stay (10.32±0.60 days versus 14.74±0.91 days, P<0.01); although it had longer operation time (292.35±14.41min versus 249.02±13.30min, P=0.033)[87]. Lymph node yield (9.39±0.68 versus 8.26±0.52, P=0.208) and incidence of postoperative morbidities, including bile leakage (0.11 versus 0.07, P=0.521), postoperative bleeding (0.05 versus 0.02, P=0.448) and abdominal abscess (0.05 versus 0.07, P=0.738) were similar between the two groups[87]. Another retrospective analysis of 102 patients with GBC reported that the patients who underwent laparoscopic surgery experienced a shorter postoperative activity time (2±1 days versus 4±1 days, P<0.001), eating time (2±1 days versus 4±2 days, P<0.001) and drainage tube removal time (4±3 days versus 6±3 days, P<0.001) compared with those who underwent open surgery[88]. Similarly, according to the 18 studies comparing laparoscopic and open radical cholecystectomy for GBC analyzed by Lv et al., the laparoscopic group had a significantly smaller volume of intraoperative blood loss, a shorter

time of drainage tube extraction and diet recovery, a lower rate of postoperative complications such as pulmonary infection and thrombus formation (which was 10.1% compared with 15.8%) and a shorter length of postoperative hospital stay. The shorter hospital stay is theoretically because of reduced wound-related pain, early-period ambulation and earlier gastrointestinal peristalsis. Operative time, intraoperative gallbladder violation, R0 resection rate, lymph node yield and overall recurrence rate were comparable in the two groups[89]. Predictive factors for conversion to open surgery may include a positive liver margin, massive intraoperative bleeding and an interval between surgeries of more than 60 days, which may cause severe abdominal adhesions[34]. In the prospective study of Cho et al., including 33 patients with early-stage GBC who underwent laparoscopic surgery, three patients with liver invasion noted by diagnostic laparoscopy had their procedure converted to laparotomy, and another conversion occurred owing to bleeding during locoregional laparoscopic lymphadenectomy[24]. A retrospective study showed that 7 out of 30 patients undergoing laparoscopic extended cholecystectomy with bi-segmentectomy in their center required conversion to open surgery due to distortion of anatomical landmarks and suspected involvement of extrahepatic organs that caused technical difficulty[90]. The rate of conversion to open surgery decreases with the improvement of surgical experience and equipment." The supplemented contents are according to reference 87 "*Dou C, Zhang C, Zhang C, Liu J. Propensity Score Analysis of Outcomes Following Laparoscopic or Open Radical Resection for Gallbladder Cancer in T2 and T3 Stages. J Gastrointest Surg 2022; 26 (7): 1416-1424.[PMID:35296956 DOI:10.1007/s11605-022-05288-y]*", reference 88" *Feng J W, Yang X H, Liu C W, Wu B Q, Sun D L, Chen X M, Jiang Y, Qu Z. Comparison of Laparoscopic and Open Approach in Treating Gallbladder Cancer. J Surg Res 2019; 234: 269-276.[PMID:30527484 DOI:10.1016/j.jss.2018.09.025]*", reference 89 "*Lv T R, Yang C, Regmi P, Ma W J, Hu H J, Liu F, Yin C H, Jin Y W, Li F Y. The role of laparoscopic surgery in the surgical management of gallbladder carcinoma: A systematic review and meta-analysis. Asian*

J Surg 2021; 44 (12): 1493-1502.[PMID:33895048 DOI:10.1016/j.asjsur.2021.03.015]", reference 34 "*Vega E A, Sanhueza M, Viñuela E. Minimally Invasive Surgery for Gallbladder Cancer. Surgical Oncology Clinics of North America 2019; 28 (2): 243-253.[PMID:30851826 DOI:10.1016/j.soc.2018.11.001]*", reference 24 "*Cho J Y, Han H S, Yoon Y S, Ahn K S, Kim Y H, Lee K H. Laparoscopic approach for suspected early-stage gallbladder carcinoma. Archives of Surgery 2010; 145 (2): 128-133.[PMID:20157079 DOI:10.1001/archsurg.2009.261]*", and reference 90"*Nag H H, Sachan A, Nekarakanti P K. Laparoscopic versus open extended cholecystectomy with bi-segmentectomy (s4b and s5) in patients with gallbladder cancer. J Minim Access Surg 2021; 17 (1): 21-27.[PMID:31603079 DOI:10.4103/jmas.JMAS_98_19]*".

The response to comments of Reviewer #2 "***This is a wonderfully well written review article on laparoscopic surgery for gallbladder cancer. This reviewer has only one minor question. Page 3 Background lines 5-6: ", the overall survival rate is less than 5%. ..., and the 5-year survival rate is 5%-15%." Which is correct?***" is as follows.

We feel really sorry for the confusing expressions about the survival rate of GBC. In the original manuscript file, "the overall survival rate is less than 5%" is from "Due to the lethality of this tumor, the overall survival of patients with GBC is less than 5% and is strongly associated with the stage of cancer" in the discussion part of "*Open versus laparoscopic surgery in the management of patients with gallbladder cancer: A systematic review and meta-analysis*" by Hayato Nakanishi et al. published in 2022. While "and the 5-year survival rate is 5%-15%" is according to "It is a fatal disease with poor prognosis with over one-third of patients presenting with distant metastasis at time of diagnosis and a median overall survival of six months and a 5-year survival rates ranges from 5% to 15%" in the introduction part of "*Extended liver surgery for gallbladder cancer revisited: Is there a role for hepatopancreatoduodenectomy?*" by Torres et al. published in 2020. We have searched several databases again for the literature

of gallbladder carcinoma published in 2022, and found that most of the publications showed the 5-year survival rate of GBC was less than 5%. Since the survival rate of GBC varies in different time and regions, we think "the 5-year survival rate of GBC is less than 5%" is more accurate in consideration of the publication time and quality of the literature. In response to the reviewer's comments, we have changed the content "Although in digestive system tumors GBC has a relatively low incidence of about 1.2% of all malignant ones, with its extremely high invasiveness, the overall survival rate is less than 5%. The median survival time is 6 months, and the 5-year survival rate is 5%-15%" into "Although GBC has a relatively low incidence of about 1.2% of all malignant tumors of the digestive system, its invasiveness is extremely high. The median survival time is six months, and the 5-year survival rate is less than 5%[4, 5]" according to the reference 4 "*Wu Z, Yu X, Zhang S, He Y, Guo W. The role of PI3K/AKT signaling pathway in gallbladder carcinoma. Am J Transl Res 2022; 14 (7): 4426-4442.[PMID:35958463]*" and reference 5 "*Rakic M, Patrlj L, Kopljar M, Klicek R, Kolovrat M, Loncar B, Busic Z. Gallbladder cancer. Hepatobiliary Surg Nutr 2014; 3 (5): 221-226.[PMID:25392833 DOI:10.3978/j.issn.2304-3881.2014.09.03]*".

On behalf of all the contributing authors, I would like to express our sincere appreciation of your letter and the reviewers' constructive comments concerning our manuscript. These comments are all valuable and helpful for improving the quality of our draft. The manuscript has been carefully revised according to the reviewers' comments, and we hope the correction will meet with approval.

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