Peer Review File

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Reply to comments and suggestions raised by Reviewer A:

Reviewer: The present study aimed at comparing the short- and long-term outcomes of laparoscopic (LR) and open liver resection (OR) in treatment of perihilar cholangiocarcinoma (pCCA). Forty-five patients in the LR group and 243 in the OR group were analyzed. After inverse probability of treatment weighting (IPTW) and propensity score matching (PSM), the intraoperative blood loss, incidence of surgical site, infections (SSIs), length of stay (LOS), and number of perioperative blood transfusions (PBTs) were significantly lower in the LR group than in the OR group. Only after IPTW was the 30-day mortality rate significantly lower in the LR group than in the OR group. No significant difference in overall survival (OS) or recurrence-free survival (RFS) was observed between the two groups after IPTW or PSM. The authors concluded that LR is safe and feasible for treating pCCA after rigorous patient selection. These patients presented similar long-term but better short-term outcomes than did the OR patients. However, several unclear points should be clarified.

Nevertheless, out of an already rare disease, this study seems to include a subgroup of selected tumors limited in size (since only partially extended hemihepatectomies were performed), and these conclusions need to be generalized cautiously.

Reply: Thank you very much for your professional and detailed comments. These comments will be very helpful in improving the quality of this research, which is very important to us. We have made every effort to explain and clarify all the issues you mentioned, hoping to gain your approval. Thank you again for your comments.

Scientific and methodological accuracy of the paper

Comment 1: In this cohort, authors performed only partially extended right and left hepatectomies (H14’5678 and H12345’8’) without any formal extended right or left, i.e., H145678 and H123458 as described by Nagino et al. Is the reason patient selection for this study? or the reason for performing

only partially extended resections is routine surgery for all pCCA? One should keep in mind the clear oncologic advantages of formally extended hepatectomies already described by Nagino et al. If this is a patient selection, please state that clearly in the methods and discussion. Finally, if this is the case conclusions cannot be generalized to all pCCA and authors should nuance.

Reply 1: Thank you for your comment. We highly respect your viewpoint. A study by Professor Nagino et al. (PMID: 21964888) confirmed the oncological benefits of formal extended right or left hepatectomy (H145678 or H123458) for pCCA. However, oncological benefits were observed after excluding perioperative deaths. The high perioperative mortality risk associated with formal extended right or left hepatectomy should not be overlooked, especially in pCCA patients who are not well prepared for PTCD, have not normalized bilirubin levels, and have not undergone PVE. These patients may not tolerate extensive liver resection. Therefore, there is controversy regarding the suitability of "formal extended right or left hepatectomy" for pCCA patients.

Furthermore, we would like to discuss the definition of "extended right or left hepatectomy". Different surgeons may have different interpretations of this term. In Professor Nagino's article, H45678 or H23458 is described as an extended hemihepatectomy, but in reality, such liver resection should be considered a traditional right trisectionectomy or left trisectionectomy, as described in "The 'New World' Terminology" (the image below is a report on "The 'New World' Terminology").

TABLE 1. Examples of the New Notation for Hepatectomy

	Type of Hepatectomy (Traditional Nomenclature)	New Notation
1	Anatomical resection of S6	H6
2	Nonanatomical resection of S6	H6′
3	Anatomical resection of S5 and S6*	H56
4	Nonanatomical en bloc resection of S5 and S6*	H5′6′
5	Nonanatomical separate resection of S5 and S6*	H5′/6′
6	Anatomical resection of S6 with partial extension to S5 and S7*	H65′7′
7	Nonanatomical separate resection of S6 × 2*	H6′/6′
8	Medial sectionectomy with partial extension to S5	H45′
9	Central bisectionectomy and 1 separate nonanatomical en bloc resection of S2 and S3	H458/2′3′
10	Left lateral sectionectomy and 3 separate nonanatomical resections of S5, S6, and S7	H23/5′/6′/7′
11	Anterior sectionectomy	H58
12	Posterior sectionectomy	H67
13	No. 12 procedure with partial extension to S8 and RHV resection	H678′-RHV
14	Left hemihepatectomy	H234
15	No. 14 procedure and 2 separate nonanatomical resections of S6 and S8†	H234/6′/8′
16	Right hemihepatectomy	H5678
17	No. 16 procedure and 2 separate nonanatomical resections of S2 and S4‡	H5678/2′/4′
18	Left trisectionectomy	H23458
19	Right trisectionectomy	H45678
20	Left hemihepatectomy with combined resection of the caudate lobe and extrahepatic bile duct†	H1234-B
21	No. 20 procedure with partial extension to S58 and MHV resection†	H12345′8′-B-MHV
22	Right hemihepatectomy with combined resection of the caudate lobe and extrahepatic bile duct‡	H15678-B
23	No. 22 procedure with partial extension to S4 and MHV resection‡	H156784′-B-MHV
24	No. 22 procedure with pancreatoduodenectomy	H15678-B-PD
25	Left trisectionectomy with combined resection of the caudate lobe and extrahepatic bile duct†	H123458-B
26	No. 25 procedure with portal vein resection	H123458-B-PV
27	No. 25 procedure with portal vein and hepatic artery resection	H123458-B-PV-HA
28	Right trisectionectomy with combined resection of the caudate lobe and extrahepatic bile duct‡	H145678-B
29	No. 28 procedure with portal vein resection	H145678-B-PV
30	No. 28 procedure with inferior vena cava resection	H145678-B-IVC

B indicates extrahepatic bile duct resection; H, hepatectomy; HA, hepatic artery resection; IVC, inferior vena cava resection; MHV, middle hepatic vein resection; PD, pancreatoduodenectomy; PV, portal vein resection; RHV, right hepatic vein resection; S, Couinaud hepatic segment.

*See Figure 1A.

†See Figure 1B.

‡See Figure 1C.

From our viewpoint, the term "extended hemihepatectomy" should be distinguished from trisectionectomy. For example, an extended left hemihepatectomy should be represented as H2345'8', while H23458 should be considered a left trisectionectomy. When performing an extended

hemihepatectomy, we performed hemihepatectomy + hilar resection, and we did not resect the main hepatic vein. Therefore, for extended hemihepatectomy, we only removed the partial IV segment or the partial V and VIII segments.

The purpose of our approach is to ensure a larger volume of the remaining liver. In China, many patients have poor compliance. Even when surgeons strongly recommend PTCD followed by waiting for TB levels to decrease to a safe range or suggest PVE to ensure surgical safety, patients may not agree. The majority of patients with pCCA are eager to undergo surgery shortly after diagnosis. Especially at our center, many patients who undergo radical surgery for hilar cholangiocarcinoma still have elevated TB levels. If TB levels are not normalized and PVE is not performed, patients usually cannot tolerate trisectionectomy. Therefore, to ensure the safety of the surgery, we chose to perform an extended hemihepatectomy instead of a trisectionectomy. The choice of this surgical approach, as confirmed by the results of this study, greatly ensures patient safety (30-day mortality: LR group, 0.0%; OR group, 4.5%) while providing satisfactory survival benefits (5-year OS rate: LR group, 30.6%; OR group, 26.4%).

Changes in the text: We have clarified the extent of hepatectomy in the context of limitations (see Page 14, Lines 27~30 and Page 15, Line 1).

"(4) All extended hemihepatectomies were either H4'5678 or H2345'8'. Therefore, the results of this study may only be applicable to patients undergoing this type of hepatectomy. If the hepatectomy involved the H45678 (right trisectionectomy) or H23458 (left trisectionectomy) range, further study validation was needed for the conclusions of this study."

Comment 2: Other patient selections biases coming out from this type of studies with a 10-year timespan patient inclusion are time biases. Indeed, surgical techniques have progressed significantly in recent years, and outcomes of OR may be worse than those of LR in recent years. Please discuss.

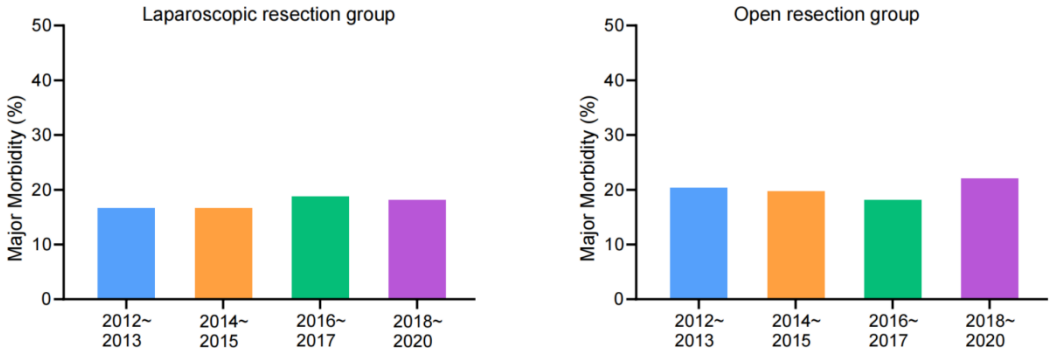
Reply 2: Thank you for your comment. In recent years, due to the development and application of laparoscopic technology, there have been numerous clinical studies assessing laparoscopic and open surgery in various fields. However, because pCCA is not common, to ensure an adequate number of cases, this study chose a wide research interval.

We understand your concerns; therefore, we divided the LR group and OR group into intervals of 2 years and calculated the incidence of major morbidity within each interval. We hope to indirectly

reflect the impact of surgical duration on the surgical learning curve through the incidence of major morbidity. We found that over time, both in the LR group and OR group, the incidence of major morbidities tended to stabilize.

Changes in the text: We attempted to use the incidence of major morbidities as an indirect measure of surgical proficiency. In the "Surgical procedure" section, we described the trend of the incidence of major morbidities over time (see Page 7, Lines 5~9).

"This study used the incidence of major morbidity to reflect the learning curve of the LR and the OR. In both the LR group and the OR group, the incidence of major morbidities remained stable over time, indicating that the surgical learning curve reached a plateau, as shown in Supplemental Material 2.



	2012.01~2013.12	2014.01~2015.12	2016.01~2017.12	2018.01~2020.01
Laparoscopic resection group	**16.7% (1/6)**	**16.7% (2/12)**	**18.8% (3/16)**	**18.2% (2/11)**
Open resection group	**20.4% (11/54)**	**19.7% (13/66)**	**18.2% (10/55)**	**22.1% (15/68)**

Comment 3: Although patient characteristics were more equilibrated after IPTW and PSM, nonobserved differences could persist. This is even more obvious when no deaths (0%) were reported in the LR group vs 4.5% in the OR group. Please discuss.

Reply 3: Thank you for your comment. We noticed this phenomenon during our data analysis. Differences in 30-day mortality were not observed in either the original cohort or the PSM cohort but only in the IPTW cohort. We think that this is a statistically significant difference that can only be observed in a larger sample size. In other words, this is one of the advantages of applying IPTW. Based on the results after IPTW, we can speculate that the wider application of LR in pCCA curative resection may significantly reduce the incidence of 30-day mortality. This could be an advantage of LR.

Changes in the text: We have added a discussion regarding this comment and removed some discussion about PSM and IPTW (see Page 14, Lines 16~19).

"In other words, when the laparoscopic approach is more widely used in curative resection for pCCA, there may be a potential advantage in reducing the incidence of 30-day mortality. Notably, this hypothesis needs further validation in larger cohorts to confirm its potential benefit. ~~After IPTW and PSM, it is possible to draw a similar conclusion that the laparoscopic approach is more favorable for pCCA in terms of short-term outcomes. Therefore, in selected patients with pCCA, LR can be considered to have better short-term outcomes than OR."~~

English language and grammar

Comment 4: English grammar should be revised for minor corrections.

Reply 3: Thank you for your comment. We have made further revisions to improve the English language and grammar and have entrusted a professional language editing service to help us. The attached figure is proof of the language editing. We hope that this language revision will meet your approval. Thank you.

Changes in the text: All revisions for the English language and grammar have been completed. However, due to the extent of the revisions, language editing has not been performed to avoid interfering with other modifications. We sincerely hope for your understanding of this matter.

Reply to comments and suggestions raised by Reviewer B:

Reviewer: This is a single-center study comparing laparoscopic (LR) vs open resection (OR) for PHC between 2012 and 2020.

Although the data are retrospective, the study is well designed to use PSM and IPTW in a fairly large number of patients.

Although long-term outcomes were comparable, short-term outcomes were better in the LR group.

Reply: Thank you very much for your comments. These professional opinions will enhance the quality of this study. We are honored that you have taken the time to review our study. We hope that our response will be met with your approval. Thank you once again.

Comment 1: The choice for LR or OR was obviously based on selection. The LR group included more patients with early-stage tumors. Selection bias inevitably occurred, which was compensated for by

the use of PSM and IPTW in the analysis.

Reply 1: Thank you for your comment. The optimal method for comparing the effectiveness and safety of LR and OR is to conduct a randomized controlled trial (RCT). However, RCTs are often expensive and challenging. In this study, we aimed to collect retrospective data and use propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) to minimize selection bias and simulate two randomized cohorts as closely as possible to two randomized cohorts. Through our data analysis, we found that LR has some advantages in short-term outcomes and laid the theoretical foundation for future prospective cohort studies comparing LR and OR.

Comment 2: How was preoperative biliary drainage (PBD) performed; PTCD as mentioned in the manuscript suggests the percutaneous approach. Was endoscopic biliary drainage not used?

Reply 2: Thank you for your comment. This is an independent study conducted at our center. For patients with an initial diagnosis of pCCA who are scheduled for curative resection, PTCD is usually chosen as the preferred method for preoperative biliary drainage (PBD). The selection of PTCD is mainly based on the following considerations: 1) endoscopic stent placement can only address main bile duct obstruction, while PTCD can target both the left and right bile ducts and their branches; 2) PTCD allows for multiple punctures of different branches; and 3) endoscopic stent placement may cause bile duct edema, which can increase the difficulty and risk of surgery, whereas PTCD usually does not cause bile duct edema.

Furthermore, considering that PTCD is an external drainage method, the patient's bile cannot enter the intestine through the bile duct. However, in our center, we request that patients repeatedly filter the bile drained by PTCD and drink the filtered bile as much as possible. This approach ensures that bile can enter the intestine and exert its function.

Based on the above considerations, our center chooses PTCD rather than endoscopic stent placement as the PBD method.

Changes in the text: To avoid confusion, we have described the method of percutaneous biliary drainage (PBD) in the "Surgical procedure" section (see Page 6, Lines 13~18).

"In patients with severe hyperbilirubinemia (TB > 10 mg/dL) prior to surgery, percutaneous transhepatic cholangial drainage (PTCD) was employed for biliary decompression. For those with moderate but not severe jaundice (TB > 3 mg/dL), the determination to proceed with PTCD

was based on the patient's overall condition and hepatic function. At our center, patients were requested to filter the drained bile repeatedly and ingest it orally to make it pass through the digestive tract."

Comment 3: Although preoperative jaundice occurred in >75% of patients, the rate of pe-operative biliary drainage was 60% and 34.6% in the LR and OR group, respectively (p=0.002). Please explain why PBD was not performed in most of the patients in the OR group. This could have a negative impact on short-term outcomes.

Reply 3: Thank you for your comment. First, we apologize for not explicitly defining jaundice in the "Methods" section. Typically, a total bilirubin (TB) concentration > 54 μmol/L (3 mg/dL) is considered to indicate jaundice, while a TB concentration > 180 μmol/L (10 mg/dL) is considered to indicate severe jaundice. For patients with severe preoperative jaundice, we performed percutaneous transhepatic biliary drainage (PTCD) to reduce TB levels. For patients who experienced preoperative jaundice or severe jaundice, we assessed their general condition and liver function to determine whether PTCD is necessary to lower TB levels. Therefore, in this study, the percentage of patients with preoperative jaundice was greater than 75%, but the proportion of patients who underwent PTCD was lower for the aforementioned reasons.

Second, the rate of PTCD was significantly lower in the open resection (OR) group than in the laparoscopic resection (LR) group. There could be several reasons for this phenomenon. In China, doctors usually recommend PTCD for jaundiced patients to ensure liver function, but patient compliance is not always optimal. After diagnosis, many patients request immediate surgery and are unwilling to undergo drainage while waiting for the operation. Therefore, for patients undergoing open surgery, in our center, we still proceed with the operation without waiting for TB levels to normalize completely. Consequently, in terms of the extent of liver resection, we tend to be more conservative, opting for extended hemihepatectomy rather than trisectionectomy, to maximize the safety of the procedure. As a relatively new technique, laparoscopic surgery requires aggressive preoperative preparation to minimize the burden on the liver.

The lower PTCD rate in the OR group may have a negative impact on short-term outcomes. Although this may have been evident in the original cohort, after propensity score matching (PSM) and inverse probability of treatment weighting (IPTW), there was no significant difference in PTCD

rates between the LR and OR groups. Particularly, after IPTW, the standardized mean difference (SMD) for PTCD was <0.1, indicating that the difference in PTCD rates between the two groups can be considered negligible. Therefore, from a statistical perspective, the difference in short-term outcomes between the two groups is not attributed to the difference in PTCD rates. However, due to your reminder, we believe it is necessary to supplement this information in the discussion section, which specifically addresses the difference in PTCD rates among the different groups in the original cohort.

Changes in the text: We have added an explanation and interpretation in the "Discussion" section regarding the difference in PTCD rates between the two groups and its impact on the outcomes (see Page 12, Lines 29~30 and Page 13, Lines 1~3).

"Additionally, in the original cohort, the rate of PTCD in the LR group was significantly lower than that in the OR group. The reason for this phenomenon was that because LR is a new technique, prompted surgeons tend to perform more aggressive preoperative preparation, thereby reducing the burden on the liver and reducing surgical risk. However, this difference was effectively balanced in the PSM and IPTW cohorts."

Comment 4: There is a discrepancy between the rate of macrovascular invasion (28.9% after PSM) and the rate of vascular resections performed in both groups (11.1% after PSM). A distinction between macrovascular invasion extending to future remnant liver segments would be helpful.

Reply 4: Thank you for your comment. We fully agree with your viewpoint. We performed vascular resection and reconstruction for patients with invasion of the major vasculature to the remaining liver, as described in the "Surgical procedure" section. We included "vascular resection and reconstruction" among the matched variables, which should be considered equivalent to distinguishing between major vascular invasion and major vascular invasion of the remaining liver. We hope this explanation is satisfactory.

Comment 5: The ability to perform complex vascular resections is considered a hurdle when undertaking LR for PHC.

Reply 5: Thank you for your comment. Indeed, as you mentioned, complex vascular resection is a challenge in performing curative resection for pCCA patients, and we fully agree with your viewpoint. Therefore, we wrote a paragraph in the manuscript to discuss the impact of vascular resection and

reconstruction on curative resection for pCCA patients, as described in the fourth-to-last paragraph of the "Discussion" section. In the initial stages of applying LR for pCCA, major vascular invasion was considered a contraindication. However, with advancements in technology, laparoscopic vascular resection and reconstruction have gradually been performed successfully and have gained acceptance. We believe that with the development of laparoscopic techniques and improvements in surgical skills, complex vascular resection and reconstruction can also be performed effectively and gained recognition from our colleagues in the field.

Comment 6: The rate of vascular resections in this series is lower than usually reported in literature. Additionally, hepatic arterial and portal venous resections and reconstructions should be defined. Presumably, all vascular reconstructions in the LR were performed on the portal venous system. The authors need to clarify this point.

Reply 6: Thank you for your comment. The proportion of patients who underwent vascular resection and reconstruction in the LR group was relatively low, but the proportion in the OR group was not significantly different from that in previous studies. Due to the technical complexity of performing vascular resection and reconstruction laparoscopically, patients requiring these vascular surgical procedures tend to be more inclined toward OR in regard to surgical selection. This is a result of patient selection bias. However, in this study, we applied both PSM and IPTW for matching to minimize this bias as much as possible. Additionally, we fully agree with your suggestion to clarify that vascular resection and reconstruction were performed on the portal vein. Yes, in this study, all vascular resection and reconstruction procedures were performed on the portal vein. Furthermore, the surgical process of portal vein resection and reconstruction is illustrated in Figures E and F of Supplemental Material 1.

Changes in the text: We have clarified in the "Surgical procedure" section of the manuscript that vascular resection and reconstruction refer to portal vein resection and reconstruction. We have also correspondingly modified the variable names in Table 1 and Table 2 (see Page 7, Lines 1~2).

"In addition, portal vein resection and reconstruction were performed when the tumor invaded the portal vein (Vp3 or Vp4)."

Comment 7: Please use the ISGL criteria for reporting posthepatectomy liver failure.

Reply 7: Thank you for your comment. We reviewed the cases of all patients and redefined PHLF according to the ISGL criteria. In this study, all patients who met the ISGL criteria also met the "50-50" standard for PHLF. Therefore, this does not affect our results.

Changes in the text: We defined PHLF in the "Short- and long-term outcomes" section and changed the references to support the new definition (see Page 7, Lines 29~30).

"postoperative grade B/C liver failure (as defined by the International Study Group of Liver Surgery)"

Comment 8: Please define positive surgical margins (<1 mm?)

Reply 8: Thank you for your comment. We defined the term "positive surgical margins" in our study.

Changes in the text: We have added the definition of positive surgical margins (see Page 8, Lines 3~4).

"Positive surgical margins were defined as a distance between the surgical margin and the tumor < 1 mm."

Comment 9: Finally, the use of robot-assisted resection for biliary tumors is increasing. How do the authors envisage the laparoscopic approach in the light of the evolution of the robotic approach.

Reply 9: Thank you for your comment. Laparoscopic cholecystectomy was one of the earliest minimally invasive surgical techniques, but the development of minimally invasive treatments for hepatobiliary surgery has been challenging. Hepatobiliary surgery, especially for pCCA, often requires combined major hepatectomy and reconstruction of the bile duct, especially in cases of Bismuth type III pCCA with invasion of the common hepatic duct. In addition, these cases often involve invasion of the right hepatic portal vein, necessitating combined vascular resection and reconstruction, which increases surgical difficulty. Although laparoscopic techniques have advantages such as small incisions, minimal trauma, and a clear surgical field of view, the surgeon is limited by the fixed incision location on the patient's body surface, and the direction of the surgeon's hand movement is opposite to the direction of the instrument's tip movement, creating a "chopstick effect". Therefore, performing precise operations in a confined space using laparoscopic techniques is challenging. However, this is precisely where robotic technology excels. It allows precise and stable suturing and knot tying in narrow spaces, improving the accuracy and safety of surgery, eliminating the "chopstick effect", and helping overcome

surgical challenges in hepatobiliary surgery, facilitating the minimally invasive treatment of hepatobiliary diseases.

Currently, the advantages of the da Vinci robotic system in the field of surgery have become apparent. However, its clinical application is limited due to the high cost of consumables. In addition, the early difficulties faced in the development of robotic technology were mainly due to surgeons' unfamiliarity with the robotic equipment and lack of proper technical training, resulting in a failure to understand its limitations, such as the lack of force feedback in the da Vinci system, which makes it difficult to identify tissue tension during grasping or traction, leading to unnecessary tissue damage. Therefore, when performing da Vinci robotic biliary surgery in the early stages, it is necessary to have a well-coordinated surgical team and an experienced expert provide surgical guidance.

In the future, as our understanding and understanding of the da Vinci robotic system deepen, the indications for minimally invasive hepatobiliary surgery will further expand, and the clinical application of the da Vinci robotic system may significantly increase. Laparoscopic surgery may primarily be used for procedures such as abdominal exploration, tissue biopsy, or simple operations such as left lateral liver resection. We believe that the most beneficial approach for patients is to utilize the advantages of both robotic da Vinci surgery and laparoscopic surgery according to their respective strengths.

In recent years, we have performed robotic surgery for pCCA patients. Now, we are collecting the data, and the results will be reported in another paper.