POINT-BY-POINT RESPONSES

Dear reviwer 1:

Thank you for your careful and valuable comments. We carefully studied your helpful comments and suggestions, and have revised our manuscript accordingly, they certainly allowed us to improve our paper.

Comment 1: Please spell out the “LVI”.

Response: “LVI” have been defined in the abstract upon first mention. (revised manuscript page 3, paragraph 1, line 1).

Comment 2: Please provide the definition of LVI in the method section.

Response: we have provide the definition of LVI in the method section (revised manuscript page 7, paragraph 1, lines 3-4).

Comment 3: Please provide how to obtain the pathological evidence of cancer.

Response: The pathological evidence of cancer was determined by examination of paraffin sections. All included cases were histopathologically confirmed by an experienced pathologist (revised manuscript page 7, paragraph 1, lines 1-2).

Comment 4: Please provide the number of each preoperative radiologic examination (CT, cUS, MRCP) in the manuscript, and also in the Table1

Response: We have provided the number of each preoperative radiologic examination (CT, cUS, MRCP) in the Table 1.

Comment 5: In follow up section, please provide the definition of recurrence.

Response: we have provide our definition of recurrence in the follow-up section (revised manuscript page 7, paragraph 2, lines 9-12)

Comment 6: Please provide about the neoadjuvant and adjuvant therapy in this cohort.

Response: Whether or not chemotherapy and radiotherapy can benefit HC patients

was controversial. None of the patients received postoperative routine chemotherapy or radiotherapy in our center (revised manuscript page 7, paragraph 2, lines 1-3).

Commnet 7: In the analysis of DFS and OS, resection margin were included. Inclusion criteria of this study was R0 and R1, so positive resection margin indicate R1 resection?

Response: yes, positive resection margin indicate R1 resection. Based on your suggestion, we describe R0 and R1 resection, positive and negative margin in detail (revised manuscript page 7, paragraph 1, lines 12-14).

Commnet 8: Please include the type of surgery in DFS and OS analysis.

Reponse: we divided surgery methods into radical resection with left-sided hepatectomy and radical resection with right-sided hepatectomy, and included the two different methods into DFS and OS analysis (revised manuscript page 9, paragraph 1, lines 7, 12 and table 2).

Comment 9: please discuss about the relationship between LVI and prognosis in patients with cholangiocarcinoma other than Bismuth type IV hilar cholangiocarcinoma.

Response: we have discuss about the relationship between LVI and prognosis in patients with cholangiocarcinoma (revised manuscript page 11, paragraph 2, lines 5-10)

Comment 10: In the limitation, please provide the potential confounding factors to affect the relationship between LVI and the prognosis.

Response: N1 stage and tumor size >30mm may be the potential confounding factors to affect the relationship between LVI and the prognosis (revised manuscript page 13, paragraph 1, lines 1-3)

Dear reviwer 2:

Thank you for your careful and valuable comments. We carefully studied your helpful comments and suggestions, and have revised our manuscript accordingly, they certainly allowed us to improve our paper.

Comment 1: Final determination of BC-IV-CCA was done by what? Imaging findings? Pathology? I doubt if case with BC-IV-CCA which did not necessitate preoperative biliary drainage did exist such frequently (Approx. 30%).

Response: Preoperative BC typing was performed by imaging findings, and preliminary surgical protocols were developed according to the typing results. However, we believe that pathological BC typing is more accurate than radiological BC typing, so final determination of BC-IV-CCA was done by pathology. According to previous reports and our center experience, high bilirubin levels increase postoperative complications, prolong hospital stay, and affect patient prognosis. Our center developed strict preoperative biliary drainage criteria, patients with total bilirubin exceeding 85umol/L have to undergo preoperative biliary drainage.

Comment 2: What modality was most prioritized for judging BC-IV-CCA

Response: Patients clinical features combined preoperative imaging findings, laboratory examination (liver function, tumor marker CA 19-9) may be most prioritized for judging BC-IV-CCA.

Comment 3: what margins was the author's description of margin status? Ductal? Radial? They should be individually assessed.

Response: Based on your suggestion, we found that our definition of the margin condition was not exhaustive, so we gave a detailed explanation in the pathology section (revised manuscript page 7, paragraph 1, lines 4-12).

Comment 4: The author stated that LVI was significantly associated with either tumor size or nodal status. If so, inclusion of these variables together into a single multivariate model was considered inappropriate. If the authors want to emphasize significance of LVI, repeated multivariate analyses alternately including each variable

should be done and must show LVI has the largest hazard ratio compared to those of other variable

Response: we have performed repeated multivariate OS analyses alternately, the results showed that LVI has the largest hazard ratio compared to N1 stage and tumorsize > 30mm. The results are presented in the following table 1-3.

Table 1

variable	HR	95%CI	P value
ALB	0.830	0.546-1.262	0.383
Resection margin	6.353	3.825-10.554	< 0.001
Differentiation	1.293	0.837-1.999	0.247
T stage	1.375	0.369-5.121	0.635
N stage	**2.970**	**1.415-6.234**	**0.004**
AJCC stage	1.102	0.486-2.500	0.816
Portal vein invasion	1.496	0.538-4.164	0.440
Hepatic artery invasion	1.406	0.626-3.159	0.409

Table 2

variable	HR	95%CI	P value
ALB	0.771	0.503-1.183	0.234
Resection margin	7.004	4.187-11.717	< 0.001
Differentiation	1.448	0.930-2.255	0.101
T stage	0.641	0.205-2.006	0.445
AJCC stage	2.373	1.430-3.973	0.001
Portal vein invasion	1.965	0.709-5.444	0.194
Hepatic artery invasion	1.618	0.716-3.655	0.248

LVI	**3.853**	**2.329-6.374**	**< 0.001**

Table 3

variable	HR	95%CI	P value
ALB	0.830	0.546-1.262	0.383
Resection margin	4.902	2.964-8.106	< 0.001
Differentiation	1.182	0.760-1.839	0.457
T stage	0.710	0.223-2.264	0.563
AJCC stage	2.582	1.560-4.275	< 0.001
Portal vein invasion	1.284	0.446-3.629	0.643
Hepatic artery invasion	1.556	0.877-3.577	0.298
Tumorsize	**2.152**	**1.396-3.316**	**0.001**

Comment 5: I don't know why authors emphasized LVI or I think their method to emphasize it is inappropriate. Tumor size or nodal status, either of which is perceivable preoperatively to some extent with radiographic studies. Either seems more useful than LVI for me. The authors should emphasize results of subclass analyses.

Response: Of course, tumor size and nodal status are important for prognosis of type IV HC. But LVI is also an important prognostic factor. In the previous reply, we have mentioned that the HR value of LVI is greater than N1 stage and tumor size. Furthermore, LVI may be present a potential new target for development of anti-cancer strategies. Some studies report that chemotherapy can be beneficial for small node negative breast cancer with positive LVI. As NCCN points out that chemotherapy is beneficial for HC patients with lymph node positive, however, whether chemotherapy can benefit node negative HC with positive LVI need further study. Of course, this hypothesis should be supported with additional studies. That's

why we emphasize the LVI. In the lymph node negative subgroup and tumor size < 30mm subgroup, LVI is still an adverse predictor for OS and DFS.