Dear editor of World Journal of Gastroenterology

Thank you for forwarding the editor's and reviewers' comments on our manuscript No 33402. We appreciate their insightful comments and believe that they have improved the quality of our paper. We have carefully considered the valuable comments and made great efforts to improve the manuscript accordingly. The following attachment comprises point by point replies to the reviewers' specific comments (The modifications in the manuscript are underlined in Red Bold). We hope that the revised version of our manuscript meets your requirements for publication.

Sincerely,

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Editor's comment

Thank you for your advice of the format. We have corrected your point. However, We do not know how to write the contents of the Comments; peer-review. Please, advise us for how to write category of peer-review.

The affiliation of first author, Jang Han Jung, has changed. We have amended our paper.

01560494 reviewer's comments

CCRT may not allow tumor downstaging and improve tumor resectability in locally advanced perihilar cholangiocarcinoma.

Reply: Thank you for your feedback on effect of downstaging of the NACCRT. However, the role of neoadjuvant treatment in Klatskin tumor has not yet been established. It is logical to compare the APCT of the pre-NACCRT with that of the post-NACCRT to confirm the effect of downstaging of the NACCRT. Although we were not included in the submitted paper, 4 of 12 NACCRT group underwent downstaging due to downgrade of T stage. However, since this is a study to see the difference between the NACCRT group and the non-NACCRT group, the results of the analysis comparing the initial clinical stage and postoperative pathologic stage were entered in the submitted paper. In conclusion, the downstaging effect of NACCRT from our study cannot be determined, but the analysis of our study may be useful for downstaging. We added the stage change through CT scan before and after NACCRT.

00069774 reviewer's comments

1. What is the CA-19-9 value of the neoadjuvant group before neoadjuvant treatment? Is it decreased after the neoadjuvant and will it affect the multivariate analysis for searching of predicting variables?

Reply: Thank you for your question about CA19-9. In our study, CA19-9 is considered as an independent risk factor for DFS, as CA19-9 was described as a risk factor for predicting recurrence after curative resection of biliary tract cancer (Chung MJ, et al. Preoperative serum CA 19-9 level as a predictive factor for recurrence after curative resection in biliary tract cancer. *Annals of surgical oncology* 2011; 18(6): 1651-1656.). But thanks to your question, we are able to identify a major error in our analysis. The CA19-9 in the neoadjuvant group was analyzed by biliary

decompression and neoadjuvant therapy after CA19-9, which was the closest to the date of surgery, considering the tendency of CA19-9 to be elevated when bilirubin was high. However, CA19-9 in the non-neoadjuvant group was used for the analysis of the values identified at diagnosis before biliary decompression was performed. Then, both groups are newly analyzed with CA19-9, which was measured at the time of diagnosis. The initial bilirubin levels are also analyzed by multivariate analysis using the Cox proportional hazard model. Nevertheless, CA19-9 is analyzed as an independent risk factor for DFS (HR(95% CI), 1.01(>1.00-1.01); p value<0.01). Of course, CA19-9 before and after neoadjuvant therapy are decreased from 181.80(27.075, 1452.500) to 57.85 (21.225, 410.250). In addition, Thank you for pointing out the incorrect analysis of CA19-9.

2. There are so many chemotherapy regimens for neoadjuvant. How many courses of the treatment in the neoadjuvant

Reply: Thank you for pointing out the NACCRT regimen that we should have filled in the method section.

Neoadjuvant concurrent chemoradiotherapy regimen

In this study, 12 patients received NACCRT. Of 12 patients, 5 patients received 5-fluorouracil (5-FU; 450mg/m^2 per day, D1-4) and leucovorin (20mg/m^2 per day, D1-4) with external beam radiotherapy (1.8Gy per day to a total dose of 50.4 Gy or 45 Gy). They received an average of 3.2 cycles of 5-FU/leucovorin. Of 12 patients, 5 patients received gemcitabine (1000mg/m2 per day, D1, 8, 15, 22) with external beam radiotherapy (1.8Gy per day to a total dose of 50.4 Gy or 45 Gy). They received an average of 1.6 cycles of gemcitaine. Of 12 patients, 1 patient received gemcitabine (1000mg/m2 on D1, 8, 15, 22) and cisplatin (70mg/m2 on D1) with external beam radiotherapy (1.8Gy per day to a total dose of 50.4 Gy). He received one cycle of gemcitabine/cisplatin. Of 12 patients, 1 pateint received Tegfur/Uracil (UFT; daily) with external beam radiotherapy (1.8Gy per day to a total dose of 45 Gy).

We added the contents of the regimen used in the NACCRT in Method category.

3. In discussion described 2 out of 12 patients in neoadjuvant group achieved a complete response, why this is not consistent with Table 2 in Result section.

Reply: The response in Table 2 is the response of follow-up image after NACCRT.

Two patients who did not have remnant cancer cells in the tissue obtained from surgery showed partial response and stable disease response in the post-NACCRT image study, respectively. The follow-up image, which is usually performed and evaluated not only by the patients in this study but also by the usual CCRT, is performed one month after the completion of CCRT. In two cases, it appears that inflammation after CCRT was not evaluated as a complete response because it appeared to be mass in the follow-up image. We accepted the reviewer's opinion and added contents to Table 2 and Discussion.

00069105 reviewer's comments

The main problem is that you compare two groups 12 pt (chemort neoadjuvant) vs 45 nochemeort). The groups are not statistically comparable: age, stage,... and regimens of chemotherapy are different between 12. so results have to be taken with caution The results are better for neoadjuvant group but due to small number of patients are not stastistically significative. A propensity match score or case control study is needed.

Reply: Thank you for pointing out the shortcomings of the study. As you pointed out, we think it is the shortest part of this study that we have compared too few study groups with insufficiently matched control groups. However, we believe that an important part of this study is the definition of stage of Klatskin tumor that should undergo NACCRT. As described in the method section of the submitted paper, we find a stage that was involved in the main vessel located in the perihilum without distant metastasis, and was defined through Bismuth classification and TNM stage. In other words, the control group corresponding to the NACCRT group's Bismuth classification and TNM stage was selected in the non-NACCRT patients. For a more statistically significant comparison, we also consider the propensity match score. However, the number of study groups and control groups is small and limited. To compare only the use of neoadjuvant therapies, controlling the two groups under similar conditions is expected to reduce the number of subjects to be compared. It is difficult to conclude that this is a representative neoadjuvant therapy effect, but it may be helpful in determining the role of neoadjuvant therapy in some patients who have Klatskin tumor with bismuth classification III, IV and TNM stage III, IV. We modified the downstaging role of NACCRT from the analysis results to a milder expression.

Minor concerns: Methodology. No preoperative histology of neoadjuvant group? As

you know 10-15% of Klatskin tumors diagnosed are not real Klatskin tumors. (IgG4 cholangitis and so on) We need to know if you have taken a bipsy or citology of these cases

Reply: Thank you for pointing out the biopsy results at diagnosis that we should have filled in the method section. Of the 57 patients, 31 underwent biopsy at the time of diagnosis and 26 did not undergo biopsy. Among the 31 patients who underwent biopsy, 13 were diagnosed as adenocarcinoma and the remaining 18 were suspected of cancer. In analysis of the tissues obtained from the operation, 55 patients were adenocarcinoma. Of 57 patients, 2 patients with no remnant cancer cell were adenocarcinoma in the biopsy performed at the time of diagnosis. In result, all of the 57 patients were adenocarcinoma, which was confirmed by biopsy performed at diagnosis or surgery. We added the contents written above in the Method.

CA19-9 is a very importanta data in your analysis as you now there is a relationship between bilirrubin levels and CA19-9 have you studied this possible interference Any dat about surgica morbidity or mortality and how affect the results

Reply: Thank you for your interest in initial CA19-9 identified as an important factor in our study. Considering that elevated levels of bilirubin may affect the level of CA19-9, we also include initial bilirubin levels as a factor to consider in multivariate analysis with Cox proportional hazard model. Nevertheless, CA19-9 is analyzed as an independent risk factor for DFS (HR(95% CI), 1.01(>1.00-1.01); p value<0.01). In addition, CA19-9 was divided into 300 bases, and bilirubin was divided into 3 bases. We analyzed the effect of each on DFS and OS through Cox proportional hazard model. R0 resection and CA19-9 were additionally identified as factors affecting the OS. On the other hand, the influence of MVI, which was analyzed in the previous data, was not shown as an independent factor. R0 resction is a well-known predicting variable in other studies. There are also previous studies that hyperbilirubin increase perioperative morbidity. However, there was no correlation between perioperative complications and high-level CA19-9 among the 57 patients analyzed in this study. We added the contents written above in the Discussion.

No data about if every patient in non neoadjuvant was given chemort (when? which?)

Reply: We do not describe about adjuvant therapy in detail because it is thought to be the role of neoadjuvant therapy. Of the non-neoadjuvant group, 19 patients

received chemotherapy, 5 patients received radiotherapy and 3 patients received concurrent chemoradiotherapy after surgery for adjuvant therapy. Adjuvant therapy was performed with lymph node metastasis or margin-positive resection. Of the regimens for adjuvant therapy, 6 patients received Fluorouracil/Cisplatin, 3 patients received Gemcitabine/Cisplatin, 3 patients received Gemcitabine, 2 patients received UFT, 1 patient received Tegafur (TS-1)/cisplatin, 1 patient received Tegfur/uracil (UFT)/Cisplatin, 1 patient received Fluorouracil/Carboplatin and 1 patient received Fluorouracil/Leucovorin/Oxaliplatin (FOLFOX). We added the contents in the Discussion.

References are a little bit old and very few. 7/12 are older than 2011.

Reply: There were not many references related to neoadjuvant therapy for biliary tract cancer, and old references were considered necessary. Also, we added 20 references.