

September 28, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 1168-review.doc).

**Title:** Prognostic Factors in Resectable Cholangiocarcinoma Patients: CEA, Lymph Node, Surgical Margin, and Chemotherapy

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**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**ESPS Manuscript NO:** 1168

The authors thank you the Reviewers for the critique of our manuscript, and appreciate the general expressions of interest in the data. We have paid attention to all Reviewers' comments point-by-point in the letter below, and made the corresponding changes in the revised manuscript. We feel that the manuscript has been improved by virtue of these changes and have led to a clearer presentation of the data.

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

#1 Since receiving adjuvant chemotherapy, which as mentioned by the authors is a controversial issue in resectable cholangiocarcinoma, seems to be a good prognostic factor and the number de treated patients was 133 an effort to distinguish between different pharmacological treatments would be highly interesting. The authors indicated that combination of fluorouracil and mitomycin C was the most administered regimen. It would be interesting to know whether the prognostic value of adjuvant chemotherapy would be increased if only patients treated with this regimen were considered.

RESPONSE: We thank the reviewer for this feedback. We have added this result to our manuscript. The results showed the combination between fluorouracil and mitomycin C was not superior to other regimen (median survival time was 17.3 months (95%CI: 12.8, 21.7) vs. 22.3 months (95%CI: 20.3, 24.3), respectively;  $P = 0.20$ ).

#2 In addition to the Kaplan-Meier survival curve for the general population, it would be nice to see the comparisons for the curves corresponding to the four situation with prognostic value shown in Table 4, i.e., Serum CEA (<2.5 vs.  $\geq 2.5$  ng/mL), lymph node metastasis (yes vs. no), receiving adjuvant chemotherapy (yes vs. no) and surgical margin (negative vs. positive).

RESPONSE: We agree. We have added figure 2 in our manuscript as your suggestion.

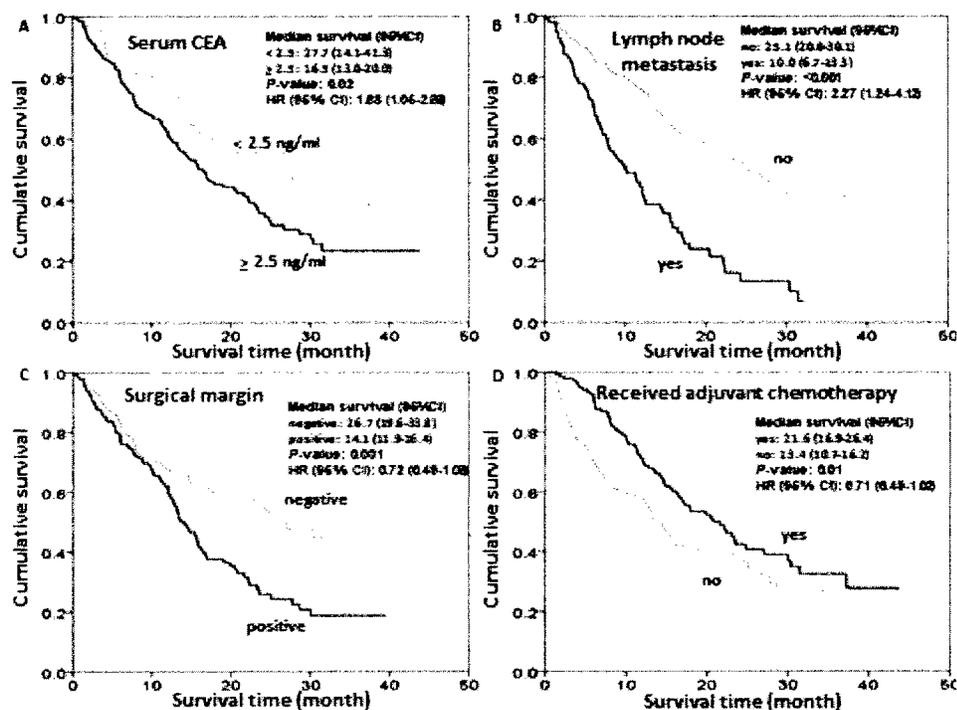


Figure 2 Kaplan-Meier survival curve showed significant difference in survival rate regarding prognostic factors. A: serum CEA level  $\geq 2.5$  ng/mL at presentation; B: lymph node metastasis; C: surgical margin; D: receiving adjuvant chemotherapy.

#3 Since part of the originality of the present study is based on differences regarding the etiology of cholangiocarcinoma in the studied population it would be advisable to include this information (e.g., *Opisthorchis viverrini* infestation) in the univariate and multivariate analyses.

RESPONSE: The reviewer brings up an excellent point. Unfortunately, this study did not directly evaluate the infection of parasitic infection in this population by standard technique i.e. serum ELISA, stool examination for parasite. However, we found *Opisthorchis viverrini* larva in pathological reports from three patients. All of these patients did not receive adjuvant chemotherapy. The survival times of these patients were 3.4, 4.26, and 16.23 months, respectively. Due to limited definite evidence of the parasitic infection, we could not compare median survival time of cholangiocarcinoma patients with parasitic infection and other etiology.

#4 Since the authors have the data, it would be also interesting to carry out the analysis of patients treated with adjuvant chemotherapy regarding their response, for instance as changes in CEA levels.

RESPONSE: We appreciate the attention to this point. We defined CEA response as the post treatment serum CEA level decreased more than 25% from baseline (1). The patients who had post treatment serum CEA level were 136 cases. 44 cases (32.4%) of these patients were CEA response cases. Furthermore, we found that the median survival time of CEA response was not significantly difference when compare with non-responder (median survival time was 24.8 months (95%CI 17.6, 32.1) vs. 23.1 months (95%CI: 21.1, 25.0), respectively;  $P = 0.98$ )

#5 Discussion Line 1: The sentence is incomplete. It seems that "BMI" is missing.

RESPONSE: Thank you for your suggestion. We have corrected the manuscript.

3 References and typesetting were corrected

Thus, all comments have been addressed and the corresponding revisions incorporated into the revised manuscript. The authors thank the reviewers for their comments which have led to an improved manuscript and a better presentation of the data. We now hope that our paper in its revised version can be found acceptable for publication in *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

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