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Dear Editor,

**Title:** Risk factors of lymphatic metastasis complement poor radiological detection in gallbladder cancer

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

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

The questions from reviewer 1 and our revisions are as follows:

I. Survival analysis of patients with different number of positive lymph nodes (1-2 positive nodes vs 3 or more positive nodes).

We added this part in "Discussion" and a Kaplan-meier chart as Fig S1. Survival analysis shows that postoperative survival of patients in the two groups is statistically different ( $P < 0.05$ , Fig S1). Introduction of several literatures discussing the prognostic value of number of positive nodes were also added.

II. The most updated knowledge of radiological staging of LM and surgical treatment of GBC.

This part was added in "Introduction". We gave the result of MR and PET, suggesting that the poor detection of LM by CT could not easily be overcome by using other radiological method. Standardization of lymphadenectomy, as far as we can see, is one of the most important topics of GBC surgery today. And we use the data from a large database (SEER) to support our point.

The questions from reviewer 2 and our revisions are as follows:

I. Reason of unsatisfactory radiological detection for LM of GB cancer.

We analyzed this topic in "Discussion". The major reason is that large percentage of positive lymph nodes share great similarity with normal nodes in appearance, and the presently used criteria as heterogeneous enhancement and diameter larger than 10mm were not present in all positive lymph nodes. This conclusion was supported by studies of Ohanti et al (Reference 9) and Morimoto et al (Reference 19), which directly compared pathological features of positive lymph nodes with radiological presentations. We added explanation of the reasoning of this phenomenon in details in "Discussion"

II. The size of metastatic lymph nodes and radiological detection

We analyzed this topic in "Discussion". Based on the most frequently used radiological criteria, diameter small than 10 mm means free of LM. However, based on our study, this standard is unsatisfactory for effective detection of most patients with LM. In other words, positive lymph nodes could quite resemble normal nodes in macroscopical appearance.

For prognosis, based on our study, the incomplete lymphadenectomy as the "berry picking" manner is potentially harmful for postoperative survival, since it only resect enlarged lymph nodes, and at the same time nearly 70% of patients with LM had normal-sized positive lymph nodes.

III. Correlation between histological type, age, and LM.

Related data has been added in Table S1 and S2, and explained in "Discussion". There was no statistical significance found in the relation between differentiated type and age or LM ( $P > 0.05$ , Table S1 and S2). However,

there was a tendency that patient with poorly differentiated type tend to have LM. (P=0.250).

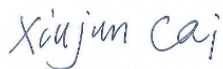
#### IV. Features of metastatic lymph nodes which were not detected by CT.

We reviewed the pathological reports of 22 patients with LM but failed to be detected by CT, none of them were reported to have enlarged positive lymph node ( $>1\text{cm}$ ), however, in 10 patients with LM detected by CT. all of them had at least 1 positive lymph node with diameter larger than 1.0 cm.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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