

Format for ANSWERING REVIEWERS

November 3, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14292-review.doc).



Title: Cutaneous metastasis of cholangiocarcinoma

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Name of Journal: *World Journal of Gastroenterology*

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On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript. We have studied reviewers' comments carefully and tried our best to revise our manuscript according to the comments.

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

(1) Response to reviewer 00048892

Major Query 1: Your English should be more brushed up.

Response to Major Query 1: We have sought to make use of a copyediting service provided by professional English language editing companies.

Major Query 2: Write down which decimal places are not consistent throughout the manuscript.

Response to Major Query 2: We have changed all percentages to first decimal place including tables and made them consistent throughout the manuscript.

Major Query 3: Since there only 30 cases, how about listing up all cases for clinical features and make a table. Did patients receive chemotherapy? Treatments would affect survival.

Response to Major Query 3: When the cutaneous metastasis (or metastases) occurred, 8/24 underwent surgery including periodic cauterization to the skin lesion while 16/24 didn't. Chemotherapy was carried out in 8/23 patients while 15/23 patients didn't take chemotherapy. Only

4/23 patients received local radiotherapy to the skin metastasis while 19/23 didn't. However, the response to chemotherapy or radiotherapy was poor. We supplemented the treatment data in the results part. Table 1 has demonstrated all the important clinical features of these patients with cutaneous metastasis of cholangiocarcinoma. If we list up these 30 patients for clinical features, it seems a little repetitive.

Additionally, we have corrected all the grammatical, formatted errors and made it clearer according to Minor comments by reviewer 00048892.

Revised portion are marked in highlighted yellow in the manuscript.

(2) Response to reviewer 02461732

Minor Query 1: Because the authors have used published cases, it is difficult to know if these cases are typical or suffer from reporting bias. The authors should note the limitation that only published cases could be included and characteristics of unpublished cases (sex ratio, OSCM, site of metastasis) may not be representative. Additionally, I suggest the authors change the abstract 'Aim' sentence to include "of published cases" at the end.

Response to Minor Query 1: We have changed the abstract 'Aim' sentence to include "of published cases" at the end and mentioned the limitation that only published cases could be included in the discussion part.

Minor Query 2: The authors note the potentially unexpected observation that patients with a single skin met had a shorter survival than those with multiple mets. This may be explained by the need for percutaneous biliary drainage. How many of the patients with a single met had a lesion at the drainage site? Of the patients with a distant skin metastasis, how many had multiple mets and how many had a metastasis-free PBD? It is possible that the patients with more advanced primary tumors were more likely to have PBD and thus more likely to have a single skin met.

Response to Minor Query 2: The review's analysis is reasonable. We analyzed the data and found that among 18 patients with a single cutaneous metastasis, 12 cases (66.7%) had a lesion at the drainage site. Patients who required PTBD usually had more advanced primary tumors and thus more likely to have a single skin metastasis. The status of more advanced primary tumors usually determined a shorter overall survival. We supplemented this interpretation in the discussion part. Among 15 patients with a distant skin metastasis, 9 cases (60%) had multiple metastases.

Minor Query 3: It would be helpful to include figure legends.

Response to Minor Query 3: We supplemented figure legends.

Revised portion are marked in highlighted blue in the manuscript.

(3) Response to reviewer 02542039

Major Query 1: The main prognosis of cholangiocarcinoma is still relied on the tumor staging, although all the cases should be called as distant metastasis, the authors should display the staging of the tumor at local site in term of tumor size, regional lymph node involvement, etc.

Response to Major Query 1: We reviewed all the data of these 30 patients again. When cutaneous metastasis occurred, 12/13 patients had concurrent metastasis of other sites such as bone, lung, brain, lymph nodes. 17 cases didn't provide the description of concurrent metastasis of other sites. We supplemented these data in the result part.

Major Query 2: There are many appearance of skin findings of this metastatic tumor. Have the authors tried to characterize those? Would it be meaningful to compare the size of metastasis and the overall survival? Perhaps some example of figures would be helpful for the readers since this is a very rare entity.

Response to Major Query 2: The cutaneous metastases presented as nodules, papules, erythema and lesions with or without ulcer sized between 0.3cm to 4 cm. Figure 1 A and B demonstrated the metastatic nodule and erythema in the scalp and along the drainage tube respectively. We supplemented these data in the result part and Figure 1 A and B.

The size of skin metastasis had no association with overall survival. We added this analysis in the result part.

Major Query 3: Where those single metastases located? At the PTBD site or distant area? This is helpful to figure why this became significant. The authors should try to explain with a hypothesis.

Response to Major Query 3: Among 18 patients with a single cutaneous metastasis, 12 cases (66.7%) had a lesion at the drainage site. Patients who required PTBD usually had more advanced primary tumors and thus more likely to have a single skin metastasis. The status of more advanced primary tumors usually determined a shorter overall survival partly interpreting this unexpected observation that patients with a single skin metastasis had a shorter survival than those with multiple metastases. We supplemented this interpretation in the discussion part (Page 10, line 3-10).

Major Query 4: Any palliative chemotherapies or radiation treatments were given to any of these patients? Since the overall survival might be altered because of this factor.

Response to Major Query 4: When the cutaneous metastasis (or metastases) occurred, 8/24 underwent surgery including periodic cauterization to the skin lesion while 16/24 didn't. Chemotherapy was carried out in 8/23 patients while 15/23 patients didn't take chemotherapy. Only

4/23 patients received local radiotherapy to the skin metastasis while 19/23 didn't. However, the response to chemotherapy or radiotherapy was poor. We supplemented the treatment data in the results part (Page7, line 31; Page 8, line 1-5).

Revised portion are marked in highlighted grey in the manuscript.

(4) Response to reviewer 02545518

Minor Query 1: Median but not mean of the Age in Table 1 and Results, has to be calculated, because the cases are almost 30 and because authors use Range of Age.

Response to Minor Query 1: We have corrected the mean age to median age in Table 1 and Results.

Minor Query 2: Authors mention that skin metastasis in 50% of the cases was in the drainage region namely previous percutaneous biliary drainage or catheterization site. It would be useful to mention that hepatocellular carcinoma (HCC) has also been related to cutaneous metastasis in the site of biopsy.

Response to Minor Query 2: We mentioned that HCC has also been related to cutaneous metastasis in the site of biopsy in the discussion part.

Revised portion are marked in highlighted pink in the manuscript.

(5) Response to reviewer 00743117

Major Query 1: The way of case collecting could not be validated. Authors included cases of drainage catheter tract recurrence. While they found 15 cases in their survey, Takahashi et al. from Nagoya group had already reported their institutional 23 consecutive cases of this type recurrence (Br J Surg 2010;97:1860-6). Similarly, other authors of high-volume center have experienced not a few cases of drainage catheter tract recurrence, and I do not think that the authors caught up with all the cases. Collecting only cases reported as a rare case report could never represent the real entity of the cutaneous metastasis of cholangiocarcinoma. Consequently, I am afraid that the results of the present review may not help the clinical practice for the advanced cholangiocarcinoma.

Response to Major Query 1: Cutaneous metastasis originated from cholangiocarcinoma is rarely encountered in clinical practice. To date, no comprehensive analysis of such an entity has been reported. Aiming to get a full understanding, we can only rely on scattered case reports or series with disease course description. Takahashi et al. from Nagoya group had already reported their institutional 23 consecutive cases of drainage catheter tract recurrence. However, they didn't provide detailed description of disease course. Thus, we cannot enroll these cases for analyses. At the same time, there are cases with distant cutaneous metastasis of cholangiocarcinoma not reported.

Major Query 2: Authors mentioned that the incidence of scalp metastasis was most frequent in skin metastasis and that bile duct cancer should be suspected when one noticed scalp nodules. I think that skin metastases from breast cancer, lung cancer, and gastric cancer are far more frequent than those from cholangiocarcinoma, and that those presented initially with skin metastasis should be screened for any possible primary diseases including cholangiocarcinoma.

Response to Major Query 2: The review's comment is reasonable. Skin metastases from breast cancer, lung cancer, and gastric cancer are far more frequent than those from cholangiocarcinoma. We revised the statement to "bile duct examination should be performed for cutaneous metastasis of unknown origin"(Page 9, line 7-8).

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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