Manuscript NO: 42426

Title: Is the evaluation of regression change in lymph nodes necessary for predicting the outcome of gastric adenocarcinoma after neoadjuvant chemotherapy?

Dear editors

Thanks to the reviewers for the constructive comments and suggestions on our manuscript. We revised the manuscript carefully and changes were highlighted in the revision. We made a point-to-point response as follows.

Reviewer's comments to authors#1:

This is an important study comparing the regression change in lymph node of gastric adenocarcinoma. The conclusion in which the outcome of the patients with residual tumors is worse compared to the patients with no residual tumors may be revised to include some descriptions about the regression change and metastasis.

Response: Thank you very much for your suggestion. We have added the prognostic significance of LN regression change to the conclusion (Conclusion section, line 10, page 14).

Reviewer's comments to authors#2:

Title: Is the evaluation of regression change in lymph nodes necessary for predicting the outcome of gastric adenocarcinoma after neoadjuvant chemotherapy?

The authors evaluate the clinical significance of the regression change in lymph

nodes of the patients with gastric adenocarcinoma after neoadjuvant chemotherapy. This manuscript is very interesting. However, I feel there are some problems in this article.

(1) Author should indicate the status that this research received consent from the Ethics Committee of the Hospital.

Response: Thanks for the suggestion. We have added the approval by the Ethics Committee of the Hospital to the content (Declarations section, line 2, page 15).

(2) Author should indicate the information such as Stage, T, N et al. before neoadjuvant chemotherapy.

Response: Thanks for the suggestion. In this study, there were 153 cases of T4 stage, 18 cases of T3 stage and 21 cases of uncertain T staging before neoadjuvant chemotherapy. There were 117 cases of N+ stage, 14 cases of N0 stage and 61 cases of uncertain N staging before neoadjuvant chemotherapy (Materials and methods section, line 14, page 6).

(3) Author should indicate the contents of neoadjuvant chemotherapy in this study.

Response: Thanks for the suggestion. Because of retrospective study, the therapy strategies were not uniform. We obtained the therapy information from the medical records. The drugs most used for treatment included oxaliplatin, cisplatin, docetaxel, 5-fluorouracil and Tegafur Gimeracil Oteracil Potassium Capsule (Materials and methods section, line 17, page 6).

(4) Author should indicate the regression change in LNs more detail in Introduction.

Response: Thanks for the comment. We added this part correspondingly. The histopathological changes of LN regression were shown in Fig 1. The histopathological evidence of regression change in LNs was defined as the presence of fibrosis, aggregation of foamy hitocytes or accumulation of mucin pools in LN peranchyma (Materials and methods section, line 21, page 7)

(5) Author indicated that the regression change in LNs is the worse prognostic factor in the patients with breast, esophageal or rectal cancer. However, the regression change in LNs does not affect the outcome in this study. Author should discuss the reason of this discrepancy.

Response: Thanks for the comment about this problem. It was reported that the regression change in LNs was the worse prognostic factor in the patients with breast, esophageal or rectal cancer [1-3]. However, the regression change in LNs does not affect the outcome in this study. The reasons of this discrepancy may be different grouping methods used as well as different LN metastasis rates, different sensitivities to neoadjuvant therapy and different prognosis among different tumors. In the study of rectal carcinoma, there were 80% patients had N0 disease [2], while there were 57.5% had N0 disease in the study of esophageal carcinoma [3]. However, in our study, only 28% patients had no LNs metastasis. In addition, 66.2% patients had N1 disease and 16.9% patients had N2 disease in the study of breast carcinoma [1]. While

in our study, only 15.6% patients had N1 disease and 53.7% patients had N2 or N3 disease, indicating a worse N stage of GAC patients and a subsequent poor prognosis. Moreover, in our previous study, no significant regression of primary tumor was shown in most of the GAC patients, indicating less sensitive to neoadjuvant chemotherapy [4]. These aspects may affect the significance of LN regression in the survival analysis in GAC patients (Discussion section, line 3 and line 20, page 13) .

(6) Author should discuss the mechanism of the regression change after neoadjuvant chemotherapy.

Response: Thanks for the comment. The therapeutic response in either primary tumor or LN metastasis may be similar to the process of normal tissue injury, clearance and repair. It has been shown that some histological changes (eg. foamy histiocytes, marked fibrosis, and acellular mucin pools) appeared more frequently in resected primary tumor, and some histological changes (eg. foamy histiocytes, nodular fibrosis, and hyalinosis) appeared more frequently in LNs from GAC patients received neoadjuvant chemotherapy, compared to those who treated with surgery alone. Among them, nodular fibrosis and hyalinosis in LNs were found exclusively in the neoadjuvant chemotherapy group. The foamy histiocytes are believed to be particularly active in the clearance of apoptotic cells. Their presence in the patients treated with chemotherapy could be an indication of apoptotic tumor cells induced by the chemotherapeutic agent [5]. The acellular mucin pools were produced from tumor cells which were significantly reduced or possibly completely eliminated by

preoperative chemotherapeutic agent [6]. Stromal fibrosis can be seen in the metastatic lymph nodes of breast, gastrointestinal tract and panceatic carcinomas. The fibrosis may be a result of collagen formation [7] (Discussion section, line 2, page 11) .

(7) Author should correct the typographical errors.

Response: Thanks for the comment. We have checked the article and corrected the errors.

Thanks again for the constructive comments and suggestions on this paper and the attention on our study. We appreciate very much.

Best wishes for all the editors and reviewers.

References

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