Author's response to reviews

Title: Overexpression of Cystatin SN positively affects survival of patients with surgically resected esophageal squamous cell carcinoma

Authors:

You-Fang Chen M.D. (chenyf@sysucc.org.cn)
Gang Ma M.D. (magang@sysucc.org.cn)
Xun Cao M.D. (mr.caoxun@gmail.com)
Rong-Zhen Luo M.D. (luorzh@sysucc.org.cn)
Li-Ru He M.D. (helir@sysucc.org.cn)
Jie-Hua He M.D. (hejh@sysucc.org.cn)
Zhi-Liang Huang M.D. (huangzhl@sysucc.org.cn)
Mu-Sheng Zeng Ph.D. (zengmsh@sysucc.org.cn)
Zhe-Sheng Wen M.D. (wenzhsh@sysucc.org.cn)

Version: 3 Date: 10 April 2013

Author's response to reviews: see over
RE: Manuscript No.: 3788719048863275
Title: Overexpression of Cystatin SN positively affects survival of patients with surgically resectable esophageal squamous cell carcinoma

Dear Editors:
Thank you for reviewing the above-referenced manuscript submitted earlier to your office. I would like to take this chance to express our appreciation to you and colleagues.

In accord with the Editor and Reviewer’s comments and suggestions, the manuscript has been revised extensively, and some data has been added into the “Results” and the “Discussion” sections accordingly in our revised manuscript. All changes have been highlighted and underlined with red ink. We feel that the revised manuscript has been strengthened by both the Editor and Reviewer’s comments and suggestions and we are very appreciative of their time and effort. A point-by-point response to the comments and suggestions has been prepared and follows this cover letter.

In addition, the format of our manuscript has been properly prepared and corresponds with BMC Surgery style.

If there are any questions or problems for our re-submission, please feel free to contact me.

Sincerely yours,
Zhe-Sheng Wen, M.D.,
Department of Thoracic Oncology,
Cancer Centre, Sun Yat-Sen University,
No. 651, Dongfeng Road East, 510060 Guangzhou, China
Tel: 86-20-87343314
Fax: 86-20-87343615
E-mail: wenzhsh@sysucc.org.cn
Response to comments of the Reviewers

Reviewer: Professor ISMAIL SERT

Response to comments

Q 1-3. Many thanks for Comments! We feel that our revised manuscript have been strengthened by the Reviewer’s comments. The subject is well defined. As well as, the title and the abstract accurately convey our results and conclusions.

Q4. The Reviewer is right! We agree that it is necessary to confirm our results by RT-PCR. Our future studies will focus on the expressive level of Cystatin SN in RT-PCR and its correlations with the expression levels of upstream and downstream effectors. In accord with Reviewer’s comments, we have described this limitation of our study in the “Discussion” Section. (See the 8th to 11th line of page 15 in the revised manuscript).

Q5. The Reviewer is right! Surgical margin statuses are very important for esophageal malignances. We agree that it is necessary to describe the surgical margin status in the present study. In our study, the patients who underwent complete surgical resection (R0) were eligible for our study. We have added it into the “Methods” section of our revised manuscript. (See the 20th to 22th line of page 6 in the revised manuscript).

Q6. Many thanks for suggestions! In our study, we revealed the reverse effect of Cystatin SN in esophageal carcinoma. As the Reviewer mentioned, some previous indicated that Cystatin SN serve as an oncogene in gastric and colorectal cancer, which contradicts our findings. We believe that can be explained by two particular factors. Firstly, histology differences such as squamous cell carcinoma and adenocarcinoma might explain the observed phenomena. Secondly, the heterogeneity of biomarkers might also result in the discrepancies in the findings between the previous literatures and our study. These results are similar to those of a number of previous reports. Cystatin C is a nonglycosylated 13 kDa basic protein, consisting of 120 amino acids. It belongs to the cystatin superfamily of cysteine proteinase inhibitors. Strojan et al.[1] demonstrated significantly longer survival in squamous cell carcinoma of the head and neck patients with high Cystatin C than in those with low Cystatin C. However, in colorectal cancer [2], the patients with high levels of Cystatin C exhibited a significantly higher risk of death than those with lower levels. Alterations in secretion may result in higher extracellular and lower intracellular levels of Cystatin C and, therefore, the reverse correlation of Cystatin C with patients’ survival is to be expected. On the other hand, one has to be aware that cysteine proteases and consequently their inhibitors are also involved in biological processes other than tissue remodeling during the progression of primary tumors, such as the regulation of inflammatory and immune responses[3] or apoptosis[4], so that different level of Cystatin C may lead to various clinical outcomes. (See the 7th to 22th line of
Q7. It is true that there were some grammatical errors in the manuscript. We have checked our manuscript carefully, and corrected all the grammatical errors. Many thanks for corrections!

Q8. Many thanks for suggestions! 79 patients received systemic chemotherapy. The median overall survival (OS) was 66 months. The 5-years survival was 53.8%. We have added the results in the “Results” section in our revised manuscript. (See the 5th to 6th line of page 10 in the revised manuscript)

Reviewer: Professor REKHA KUMAR

Response to comments

Q1. Excluding the patients who had KPS<70 or/and refused chemotherapy, 79 patients have completed systemic adjuvant chemotherapy (cisplatin-based combinations) after curative-intent surgery. (See the 3rd to 6th line of page 10 in the revised manuscript)

Q2. Studies have indicated that proteases are involved in both primary and metastatic tumor growth. (See the 4th to 5th line of page 12 in the revised manuscript)

Q3. Those observations indicate that the expression of Cystatin SN in different cancers may be tissue–specific. (See the 14th to 16th line of page 12 in the revised manuscript)

Q4. We failed to show any significant correlations between Cystatin SN expression and patients clinicopathological parameters. In contrast, some studies revealed that overexpression of Cystatin SN correlated with descending pathological TNM stage for gastric and colorectal cancer. (See the 16th to 19th line of page 12 in the revised manuscript)

Q5. Our results suggested that Cystatin SN in ESCC maybe play a significant role in the early stage of carcinogenesis. (See the 4th to 4th line of page 14 in the revised manuscript)

Q6. Consistent with the findings reported by the previous studies, we also suggested some factors, including age, gender, tumor location, surgery and pT status, were not the independently significant predictive factors for ESCC survival. (See the 19th to 22th line of page 14 in the revised manuscript)
Q7. Compared with the patients with low expressive level of Cystatin SN, high expressive patients have more favourable survivals. (See the 18th to 20th line of page 15 in the revised manuscript)

Q8. The Reviewer is right! We agree that it is necessary to confirm our results by RT-PCR. Our future studies will focus on the expressive level of Cystain SN in RT-PCR and its correlations with the expression levels of upstream and downstream effectors. In accord with Reviewer’s comments, we have described this limitation of our study in the “Discussion” Section. (See the 8th to 11th line of page 15 in the revised manuscript).

References