

Answering Reviewers

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Title: A comparative study of ROR2 and WNT5a expression in squamous /adenosquamous carcinoma and adenocarcinoma of gallbladder

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Dear Author This manuscript is original. Some parts of introduction and discussion was repeated. This parts should be out of article. Best regards

Answer: Thank you for this observation. The discussion has been rewritten with the redundant parts removed.

Dear authors, This manuscript shows the large number of squamous/adenosquamous carcinoma and adenocarcinoma of gallbladder with ROR2 and WNT5a expression for the first time, These are my comments,

1. The title of the manuscript is "A comparative study of ROR2 and WNT5a expression in squamous/adenosquamous carcinoma and adenocarcinoma of gallbladder" but from the introduction part and even in your results this two type of gallbladder cancer almost have the same prognosis. It might not be encouraged the reader.

Answer: Thank you for your astute observation. Indeed, these two types of tumors are very similar, but previous reports have also suggested that

squamous cancer of the gallbladder shows differences with adenocarcinoma cancer of the gallbladder with an advanced T stage but less common nodal involvement and distant metastasis (Kalayarasan et al., Am J Surg. 2013; 206(3):380-5). Since we also used the TNM stage classification in our experiments to analyze its correlation with ROR2 and WNT5a expression, we believed it necessary to collect and analyze two different cancer samples for this study.

2. The introduction part, what is the true scientific questions of this study. To described the expression levels of ROR2 and Wnt5a in gallbladder cancer for the first time or to compared two different types of gallbladder cancer or to investigate the risk factors of survival of cancer. You should state clearly.

Answer: This is an excellent suggestion. We have rewritten the introduction to focus on whether ROR2 and Wnt5a can be regarded as risk factors of survival for of two different types of gallbladder cancer.

3. There are a large number of results but seem to be redundant and did not correlated to the title and aim of study.

Answer: Thank you for pointing this out. We have revised the manuscript for improved clarity and cohesiveness.

4. The discussion part seemed to be redundant.

Answer: Thank you for this observation. The discussion has been rewritten with the redundant parts removed.

5. The outcome of the study shows just that ROR2 and WNT5a expression associated with aggressive behavior of cancer that may be only little to apply in clinical practice because we all know that the gallbladder cancer has a poor prognosis. Due to the low incidence of gall bladder carcinoma, this type of carcinoma is usually referred to as part of the group, together with

intrahepatic and extrahepatic carcinoma. Regarding the third reference in the paper (2005), newer studies have shown that liver progenitor cells can develop as cholangiocyte and hepatocyte (Moeini et al, Clin Cancer Research, 2015). Gallbladder carcinoma ARE sensitive to chemotherapy, contrary to the author's claim, as stated in ABC-02 Study (Valle et al, New England Journal of Medicine, 2010). Life expectancy with dual chemotherapy regimen is omitted. However, it is 11.7 months (ABC-02 Study).

Answer: Thanks for your comments. First, on the basis of our results, we think that ROR2 and WNT5a expression might be useful as early diagnostic markers of gallbladder cancer. Second, we believe that it also shows a novel insight into molecular signaling transduction in gallbladder cancer and provides molecular targets of gallbladder cancer treatment in future drug screens.