

Title: Significance of 125I Radioactive Seed Implantation on Growth Differentiation Factor and Programmed Death Receptor-1 during Treatment of Oral Cancer

Dear editor,

Thank you for your letter with regard to our manuscript. We greatly appreciate for your time in editing our manuscript and the valuable comments and suggestions from reviewers. Accordingly, The changes have been highlighted in the revised version. The point-by-point answers to the comments are listed as below. We would like to re-submit this revised manuscript to *World Journal of Clinical Cases* and hope it is acceptable for publication in the journal.

Thank you once again for considering the publication of our manuscript. Should there be any questions, please do not hesitate to contact us.

Yours sincerely,

Jia-Bin Li

Reviewer #1: The authors of the submitted manuscript intend to investigate the use of 125I radioactive seed implantation on growth differentiation factor and programmed death receptor-1 during treatment of oal cancer with potential clinical usage. The following points need further consideration. 1. To my knowledge, the use of the use of 125I radioactive seed implantation on oral cancer treatement would not be the mainstream of the choice of treament modalities. Please discuss the rationale of the selection of this modalitiy in oral cancer treatment more deeply. Only one related citation has been found in the introduction section, it, to my opinion, needs more deeply literature review since it is the human study. 2. The complications during and after treatments need to be presented clearly as one of the treatment outcomes.

Reply: Thank you for your valuable comments. We have revised the manuscript accordingly. With regard to Point 1, we have revised the introduction of ¹²⁵I radioactive seeds in the part of Introduction and added the relevant research on the treatment of oral cancer, so as to improve and perfect the background information. As for Point 2, we have compared the total adverse reactions of patients in the two groups from the beginning of treatment to the full recovery and discharge.

Reviewer #2: Authors used radioactive iodine seed implants to compete with surgery and study its

effects on the expression of growth differentiation factor (GDF11) and programmed death receptor-1 (PD-1) in the serum during treatment of oral cancer (OC). They showed the recurrence rate of the research group was better than those of the controls but no significant difference in the survival. There was difference in GDF11 and PD-1 expression at 4 weeks after treatment. In ROC curve analysis, GDF11 and PD-1 had a good predictive value for efficacy and recurrence. Overall, this is an interesting study. There are a few questions which authors need to address. 1. Tumor stage has a significant effect on survival, recurrence and other parameters. Please compare these parameters at the same stage between these two groups. 2. Because there was no difference in survival, I care more about whether patients receiving the implants enjoyed a better life quality than those receiving surgery? 3. Please elaborate on the cause of mortality and complications in the treatment period for these two groups of patients.

Reply: Thank you for your valuable comments. We have revised the manuscript accordingly. With regard to Point 1, we have compared the survival and recurrence of prognosis between patients in the two groups. There was no difference in 3-year mortality between the two groups, but the recurrence rate was lower in the research group. As for Point 2, we failed to investigate the quality of life of patients in this study, which was our limitation. We have proposed the future experimental plan for this point in the Discussion. In view of Point 3, we have proposed that the difference of recurrence rate between the two groups may be due to the fact that ^{125}I radioactive seed implantation can kill tumor focus and tumor cells more comprehensively and completely than traditional radical surgery. For some tumor focus with complex structure and tissue, the limitation of surgical resection is more significant, so the recurrence rate may be higher. However, no difference in prognosis of death maybe because the application of ^{125}I radioactive seeds in the treatment of oral cancer is not comprehensive at present, and there are still improvements in dose, time, or manual operation, and it may also be due to the short follow-up time.