

Dear Editor in Chief and Editorial Office,

We are thankful for giving us the opportunity to submit a revised version of our manuscript, entitled “Higher volume growth-rate is associated with development of worrisome features in patients with Branch Duct-Intraductal Papillary Mucinous Neoplasms” to your journal “World Journal of Clinical Cases”. We appreciate the comments and suggestions that the Reviewers provided, and we thoroughly considered each point raised. We amended the manuscript as suggested and we think that the Reviewers’ feedback has deeply improved the quality of our work.

We hope that we are meeting all your requests with this revision, and we are fully available to edit again the paper in case you consider it necessary.

Sincerely,

Prof. Andrea Galli (on behalf of all co-Authors)

## **REVIEWERS’ COMMENTS TO AUTHORS:**

### **Reviewer 1:**

- *Comment:* Branch duct type intraductal papillary mucinous neoplasms(BD-IPMNs) is difficult to assess whether it is benign or has malignant potential. Therefore, Fukuoka guidelines and a nomogram predicting the individual risk of malignancy(JY Jang et al. Ann Surg 266(6):1062) for this difficult issue were proposed. Criticisms: 1. Ten of 98 patients developed worrisome features from non-worrisome features for a median follow-up duration of 40.5 months. No patient has high-risk stigmata. The median diameter of the cyst was 19 (11.25-21.25). Then what kinds of findings were included the worrisome features for each patient after 40.5 months follow-up. There are no findings in table 2. belonging to worrisome features that authors proposed in the materials and methods.

- *Reply:* Thank you for your contribution, we kindly appreciate it. Table 2 reports the baseline and demographic characteristics of both the patients who developed a worrisome feature and the patients who did

not. The specific worrisome feature developed at the end of the follow-up by each patient of the “worrisome features” group is stated in the Results section of the manuscript.

- *Comment:* 2. What is the volume measuring equation? Authors used sagittal (antero-posterior) x transversal (latero-lateral) x coronal (cranio-caudal). This is a rough volume. Comment about is to be added in the discussion.

- *Reply:* Thank you for your comment. I’m afraid we have not been sufficiently clear in the Methods section. Volume has been measured by manual segmentation. The section of the manuscript in which the procedure was described has now been amended and clarified.

- *Comment:* 3. Regarding table 5& 6: Baseline cyst size and final cyst size, both were classified to non-worrisome features(88) and worrisome features(10). As authors described and I mentioned in criticism 1, the authors used 98 patients for this study, who have non-worrisome features. What is the timeline of the baseline and final?

- *Reply:* In our study, we retrospectively included 98 patients with at least two contrast-enhanced MRI studies or CT scans (with a 12-month minimum follow-up time), and who did not have any worrisome features or high-risk stigmata at the beginning of their follow-up. We excluded all those patients who have worrisome features or high-risk stigmata, and those who had unsatisfactory or incomplete follow-up data. After a median follow-up time of 40.5 months, 10 people developed worrisome features, while 88 did not. In Table 5 and 6 we reported baseline and final cyst size of patients from each of these two groups (patients without worrisome features at the end of follow-up / patients with worrisome features at the end of follow-up).

- *Comment:* 4. Practically, just measuring the longest diameter can be used easily rather than the calculation of the volume. What is the comparative analysis between the increase of the longest diameter and the volume increase for prediction going to worrisome feature?

- *Reply:* Thank you for your comment. Of course, to measure a single diameter is easier than to measure the volume of a cyst. However, in our study, we demonstrated that volume correlates with the development of

worrisome features as well as diameters. Moreover, we found that volume was superior to diameter in the first year of follow-up to predict the development of worrisome features. We are proposing the volume as a new tool to increase the ability of clinicians in early identification of patients at risk of malignancy.

**Reviewer 2:**

- *Comment:* The study identified volume growth rate is associated with development of worrisome features in patients with Branch Duct-Intraductal Papillary Mucinous Neoplasms. However, several major concerns limit the quality of the study. 1. The cyst volume measurement is the same thing as diameter measurement. In addition, 3 baseline cyst diameters should be measured to determine the cyst volume, the inter-observer variability will be greater than cyst diameter measure alone.

- *Reply:* Thank you very much for your comment. As stated above, volume has been measured by manual segmentation, and it has not been calculated using diameters. Diameters have been measured in order to compare diameter growth rate to volume growth rate. The section of the manuscript in which the procedure was described has now been amended and clarified.

- *Comment:* 2. Inter-observer agreement should be analyzed between different radiologists.

- *Reply:* Thank you for your comment. That is now described in the Methods section of the manuscript.

- *Comment:* 3. The diameter growth rate is a risk factor for BD-IPMN. The cysts that have higher growth rate is potentially more aggressive than other cysts. Therefore, the relationship between diameter growth and high risk feature has no significance.

- *Reply:* In our cohort, we confirmed that a higher cyst diameter growth rate is linked to malignancy risk. More precisely, patients who developed worrisome features had a higher cyst diameter growth rate than patients who did not. However, in our cohort diameter growth rate couldn't predict the development of worrisome features in the first year of follow-up. Our data show that, in contrast to diameter growth rate, volume growth rate could be able to predict the development of worrisome features after a year of follow-up-

- *Comment*: 4. The follow up time is not sufficient as BD-IPMN develop very slow.

- *Reply*: Thank you, this is a very good point. We believe that small increases in diameter can result in bigger volume variations, so that a shorter follow-up could be justified, in our opinion. Indeed, the first-year volume was superior to diameter growth in predicting the development of worrisome features in our cohort. We are now conducting a prospective extension of our study in order to corroborate the strongness of our results. This is now stated in the Discussion section of our manuscript.