

Peer Review File

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Reviewer Comments

This manuscript presents the value of contrast-enhanced ultrasound (CEUS) to evaluate the response to neoadjuvant chemotherapy.

Strength:

A. The study is well-designed

B. The results may be applicable to clinical practice.

Reply: Thank you very much for your very positive comments.

Weakness:

A. There were relatively small number of cases.

Response: Thank you for your comment. We have modified our text at the part of limitation as advised (**see Page11 Line 276-280**): the sample size in this exploratory study was relatively small. In the luminal A subgroup, a relatively small number of patients were enrolled (20/143, 13.9%), and these patients were considered to be less sensitive to and would benefit less from NAC therapy. Further studies are required to assess stratified subgroups with larger sample sizes, which could provide sufficient statistical power to address the impact of breast cancer subtype on CEUS parameters

B. Qualitative features of CEUS are not evaluated.

Response: We thank for the comment. The qualitative features of CEUS is important for the differentiation of breast lesions. However, it was reported that qualitative features (i.e., homogeneous or heterogeneous enhancement; presence or absence of bold perfusion defects; presence or absence of the crab claw-like pattern) on CEUS were not significant predictors of response to NAC at early time point (1). We will incorporate the qualitative features of CUES in the further studies to investigate the potential value of qualitative and quantitative features of CUES in evaluating the response to NAC.

C. Manuscripts must be edited according to the author's instructions.

: Abbreviations needs to be explained the first time they are used.

: Inequality marks are missing, e.g. P value

: There are English grammatical errors.

Response: Thank you for your pointing out the errors. We have scrutinized the manuscript, and made according revisions including typos, grammatical errors based on the advised suggestion.

Introduction

-Page 2, line 61: Describe the limitation of MRI to assess the response to neoadjuvant

chemotherapy in terms of interobserver variability, lesion type (mass or non-mass enhancement), and so on.

Response: Thank you for your important suggestion. We have added the limitations of MRI to assess the response to NAC (see **Page2 Line 62-66**): Studies have reported the high interobserver variability of MRI for response patterns and tumor diameter in evaluating NAC responses . Moreover, a definite standard for drawing region of interest (ROI) of non-mass enhancement lesion has not been developed. These limitations inhibit extensive clinical applications of MRI during NAC response evaluation.

Methods

-Page 8, line 178: Why was a P value of 0.1 used to determine statistical significance in univariate analysis? This is unusual. Explain this.

Response: We thank for the great comments. A P value of 0.1 was used in univariate analysis to prevent missing significant variable during the selection of multivariable analysis. As described in the text (**Page8, Line 184**), The logistic regression was used for the selection of independent variables with entry P-value=0.05 and removal P-value=0.1. At the final model construction, the variable with P value<0.5 was considered as the predictive variable to the response of NAC.

Results

-Page 9, line 215: Inequality mark is missing, P value. Please check the whole manuscript.

Response: Thank you for your important suggestion. Inequality mark has been supplemented and the whole manuscript has been checked. The editing errors have also been corrected at Page7, Line 182(P<0.1); Page 10, Line 251 (143 cases);

Discussion

-Page 12, line 271: Authors focus on quantitative features of CEUS in this manuscript. However, The quantitative results of CEUS are subjective depending on the selection of the area of interest and depend on the ultrasound company's own program and analysis method. Add this limitation.

Response: Thank you for your constructive suggestion. We have add this limitation at Page 11, Line 286: Moreover, quantitative results of CEUS are subjective and are depending on the ROIs as well as on the ultrasound company's own program and analysis method.

1. Lee YJ, Kim SH, Kang BJ, et al. Contrast-Enhanced Ultrasound for Early Prediction of Response of Breast Cancer to Neoadjuvant Chemotherapy. *Ultraschall Med* 2018.