Peer Review File

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Reviewer Comments

Comment 1: What is the real purpose of treatment on lesions that, in almost all cases, will remain benign? Some international Consensus (Rageth CJ et al. First and Second International Consensus Conference on lesions of uncertain malignant potential in the breast - B3 lesions) highlight the possibility of complete exeresis with second-line VABB 7-8 G but on dubious lesions (B3), of small size and with cellular atypia in order to reduce diagnostic underestimation. In this study it does not seem that we are looking for this.

Reply 1: Firstly, in spite of the benign lesions, the patients will still spend much time and money on regular US examinations for follow-up. Some lesions cause severe anxiety and some larger lesions affect appearance. Cellular atypia is a dangerous factor but we don't know that before the VABB. So we should take measures on those "benign lesions" on US images.

Secondly, this study is retrospective and the pathological classification of all the lesions remains unknown preoperatively. We postoperatively selected 31 mammary hamartomas pathologically from all the 3388 lesions resected by VABB in order to evaluate the efficiency to treat hamartomas. Several studies have demonstrated that there were recurrences and malignant transformation when treating fibroadenoma and phyllodes tumor by VABB, partly because of the large size. But how about hamartomas? Our results proved the outstanding complete resection rate and little malignant transformation rate in all hamartomas lesions. So this finding indicates that we can use VABB to treat hamartomas confidently as an alternative for surgery, regardless of the large size (5.5cm in our study), because it's excellent in oncology safety and complications. So we may amplify the indication, particularly in the size. Actually we have concluded the features of hamartomas in US images (Liu G, et al. J Cancer Res Ther. 2019; 15: 864-70). So if we find a lesion like hamartomas in US, in spite of the large size, just treat it by VABB.

Changes in the text: We have modified our text as advised (see Page 13, line 16)

Comment 2: The proposed treatment is performed on large lesions, up to 5 cm. This raises some concerns about both the actual excision and potential complications. Have you experienced different results on major injuries? If so, which ones?

Reply 2: Before the procedure we also had those concerns, but the results demonstrated that we had a good complete excision rate and little complications. The excision may be linked with pathology: intraductal papilloma and phyllodes tumor represent lower complete excision rate than hamartoma (Wang, et al. Breast J. 2019, 25(5):807-812 & Shang, et al. Breast. 2020, 49:242-245). As for the complications, we didn't experience different results on major injuries, just pain, hematomas and ecchymosis. We added hemocoagulase and adrenaline to the anesthetic, squeezed the hematoma area and bandaged the breast tightly for 24-48 hours, in order to prevent those injuries.

Changes in the text: This part is explained on Page 10, line 2 & Page 13, line 16.

Comment 3: The evaluation of the efficacy of the treatment, from what emerges, would be entrusted to the ultrasound follow-up: this appears to be a limit, if we consider that these are underdiagnosed lesions because they are often indistinguishable from the surrounding tissue. The total exeresis of the lesion could in fact be demonstrated in my opinion only with the histological analysis following the surgical exeresis of the treated area. Have you verified from this point of view doubtful cases of complete excision after ultrasound treatment?

Reply 3: If the pathology results report atypical hyperplasia or any malignancy characteristic, we will perform extra surgeries on these lesions after VABB. But in this study, patients accepted VABB instead of surgery because of its minimal invasive vantage. So if no potential danger is reported pathologically, we think US follow-up is complete enough.

Changes in the text: We have modified our text as advised (see Page 13, line 10)

Comment 4: The presence of microcalcifications is suggested by the proposed literature in a not insignificant portion of hamartomas. It is important to identify this

presence as this could indicate a malignant modification of the lesion. However, microcalcifications are better observed in mammography, where, moreover, it is often possible to visualize this type of lesion, classically capsulated. Therefore mammography should be mentioned in your study and radiomics studies and reporting aid systems that highlight microcalcifications well should also be mentioned. Here are some studies of this type that I recommend adding to your references:

• Basile TMS, Fanizzi A, Losurdo L et al. “Microcalcification detection in full-field digital mammograms: A fully automated computer-aided system” Physica medica Vol. 64, August 2019, Pages 1-9

• Fanizzi A, Basile TMS, Losurdo L et al. “A machine learning approach on multiscale texture analysis for breast microcalcification diagnosis” BMC Bioinformatics Vol. 21, 11 March 2020, Article n. 91

Reply 4: Given the denser breast tissue, US is the primary tool for screening breast diseases in China. Because no microcalcifications were found pathologically in our study, we didn’t conduct mammography examinations. But we agree that microcalcifications are significant indicators of malignant modification. Thank you greatly for your suggestions and we will add this part to our article.

Changes in the text: We have modified our text as advised (see Page 13, line 5& Page 18, line 10)