

Peer Review File

Available at <http://dx.doi.org/10.21037/gc-20-456>.

Reviewer #A:

Major point

Comment 1: This is an important point. Please clarify the purpose of this study in “Introduction” section. You should describe the novelty of this study.

Reply 1: Above all, thank you very much for your careful review and contributive comments for our paper. We agree with the reviewer about the weak point of novelty for this study. Considering the routine use of VABB in clinical practice, it was no longer a hot topic on the usefulness and safety of this technique in case of microcalcification. Therefore, the purpose and novelty of this study have been reconsidered and highlighted following reviewer’s request.

Changes in the text: see Page 4-5, line 64-73; Page 12-13, line 216-230.

Comment 2: Please describe the analysis method in this research in more detail.

Reply 2: Thank you for your comment. We have modified the method section in the text.

Changes in the text: see Page 8, line 139-141.

Comment 3: In this research, verification is also necessary for intrinsic subtypes as subjects.

(1) **Reply 3:** Thank you for your contributive advice. We agree with the reviewer on the importance of intrinsic subtype in case of calcifications. Classification of breast calcifications by **morphology and distribution** is useful in predicting the likelihood of malignancy. Due to the limitation of medical record extraction, the calcification morphology and distribution of all 594 lesions could not be completely listed in baseline characteristics. However, we adopted four descriptors (amorphous, coarse

heterogenous, fine pleomorphic, fine linear branching) of calcification morphology that usually indicate sufficient suspicion of malignancy to prompt a recommendation for biopsy (Ref 1). Therefore, associated descriptions and comment have been added in 'Table S1', 'Methods', 'Results' and 'Discussion' sections.

[Ref 1] Sickles E.A, D'Orsi C.J, Bassett L.W et al. ACR BI-RADS®Mammography 2013.

Changes in the text: see Page 5-6, line 85-87; Page 9, line 153-157; Page 13-14, line 244-248; Table S1.

Comment 4: Please clearly describe the indication of VABB. (Please clearly indicate the use of CNB and VABB)

Reply 4: Thank you for your advice. We have added this information in "Introduction" section.

Changes in the text: see Page 4, line 55-60.

Comment 5: Because the result of Figure is unclear, please consider again (Figure 3).

Reply 5: Thank you for your advice. We tended to present an integrated course of VABB procedure in case of malignant lesion in our center, so the authors decided to keep the figure in place.

Changes in the text: None, see Page 11, line 204.

Minor point

Comment 6 : The sentence of this paper has many careful mention errors. Please review it.

Reply 6: Thank you for your language advice. The manuscript has been sent for language editing by AJE (verification code 8499-1D90-EC68-AADE-CD2P). The editing certificate is attached along with revision files.

Changes in the text: The changes were shown by yellow color in the text.

Special thanks to you for your valuable comments.

Reviewer #B:

Comment 1 : Since its availability, stereotactic VABB has been used for approximately 20 years. Many studies have reported the usefulness and safety stereo-guided VABB. It can no longer be considered a new technique. It is difficult to accept a retrospective study of the usefulness and safety techniques of stereo-guided VABB for microcalcification. However, if you revise the point of the significance to obtain samples including calcification under stereo-guided VABB for microcalcification, this would be an interesting and highly suggestive paper. It needs major revision to add this point to the introduction and the discussion.

Reply 1: First of all, thank you sincerely for your rigorous review and precious advices. We agree with reviewer about the weakness of novelty for this paper. Considering the routine use of VABB in clinical practice, it was no longer a hot topic on the usefulness and safety of this device for microcalcification. In our initial version of manuscript, one of exploratory analysis was on the diagnostic consistencies of VABB specimens with or without calcifications, but not as the primary objective. Therefore, we have adjusted this point as the primary aim in the revised version. Associated corrections have been added in 'Introduction', 'Methods', 'Results', 'Discussion' and 'Table 3' sections.

Changes in the text: see Page 4-5, line 64-73; Page 7, line 111-117; Page 10-11, line 181-195; Page 12-13, line 216-230; Table 3.

Comment 2 : Line 53;

“Currently, vacuum-assisted breast biopsy (VABB) under stereotactic guidance has emerged as a reliable and safe diagnostic approach for mammographically visible lesions

(2-4).” These references are from 1996 to 2001. They cannot be considered as current.

Reply 2: Thank you for your comment. We agreed with your opinion. Considering that VABB was introduced in the mid-1990s (Ref 2), our expression was not rigorous enough. Modification has been made in the text.

[Ref 2] Parker SH, Lovin JD, Jobe WE, et al. Stereotactic breast biopsy with a biopsy gun. Radiology 1990; 176:741-7.

Changes in the text: see Page 4, line 54-55.

Comment 3 : Line 72, 145;

BI-RADS 0 means incomplete and requires an additional imaging evaluation or prior mammograms for comparison; therefore, it is not a target for VABB.

Reply 3: Thank you for your careful review and rigorous comment. Firstly, all the enrolled patients had mammographically detected calcifications. By reviewing the raw data, we found that the 7 cases with mammographic BI-RADS 0 category were all provided with additional imaging procedures (breast ultrasound and/or MRI). The final pathological results confirmed the presence of calcareous deposits in all 7 VABB samples. The detailed information is showed in **Table S3 (attached in the WORD format of response letter)**.

Changes in the text: see Page 6, line 88-91.

Comment 4 : Line 98;

“The malignancy rate, defined as the development of new malignant lesions during the short-term follow-up (<12 months) of patients with ADH diagnosed by VABB without residual calcifications conservatively managed.”

However, the malignancy rate represents the rate of the malignancy found in each BI-RADS category (same as lines 148, 168, and 228)

Reply 4: Thank you for your correction. We failed to make it clear in this context. The **false negative rate** should be the proper term instead of malignancy rate.

Changes in the text: see Page 7, line 121; Page 11, line 203; Page 15, line 272.

Comment 5 : Line 108;

“As there is no consensus in the management of the patients with a diagnosis of ADH (11), in our study, this group of patients with possibility of complete removal of calcifications was proposed to receive conservative management, while surgical excision was mandatory to patients either with residual calcifications of ADH or malignant lesions.” You have provided indications for stereo-guided VABB and a way of dealing with it at your institution. As a result of this policy, will you suggest the same concept of conservative or surgical procedures?

Reply 5: Thank you for your interesting question. The management of the patients with a diagnosis of ADH is still a controversial. Pathologically, ADH is considered to be precancerous but not equivalent to malignancy, therefore, it is uncertain whether follow-up or subsequent surgical biopsy has a better prognosis. In real-world clinical practice, we, surgeons, may prefer surgical excision rather than intense observation to avoid the risks of cancer transformation or biopsy underestimation. On the other side, some of the patients may choose to have follow-up because of a reluctance to undergo surgery. Schiaffino *et al.* (Ref 3) verified the conservative management in a significant group of patients with a single group of calcifications, without residual calcifications post-procedure and without the presence of multiple foci of hyperplasia or high proportion of hyperplasia at histopathological evaluation. This result is partly in line with data from our study. Considering the histopathological underestimation rate and false negative rate approximately equal to 5-6% in our data, this subset of patients might be regarded as the “probably benign” category and benefited from conservative management instead of surgical procedure. However, more specified RCTs are warranted in the future as well as longer period of follow-up.

[3] Schiaffino S, Massone E, Gristina L, et al. Vacuum assisted breast biopsy (VAB) excision of subcentimeter microcalcifications as an alternative to open biopsy for atypical ductal hyperplasia. *Br J Radiol* 2018;91:20180003

Changes in the text: None.

Comment 6 : Line 123;

A total of 594 stereotactic VABB procedures were performed for 594 lesions in 597 patients (mean age 46 years, range 21–80 years) (Figure 1).

→it has to be “594 lesions in 587 597 patients.”

→and please check the English of this phrase; A total of 594 stereotactic VABB procedures were performed for 594 lesions in 587 patients?

Reply 6: Thank you for your careful review and proper language advice. This was a writing error and we have modified this phrase.

Changes in the text: please see Page 8, line 146.

Comment 7 : Line 126 & S Table 1;

Calcifications with mass were excluded. Why is distortion included when it should be a case of calcification?

Reply 7: Thank you for your question. All the enrolled patients had mammographically detected calcifications. We did not make it clear in the supplementary Table 1. After checking the raw data, we found that the lesion type of all 7 cases manifested as architecture distortion with calcifications. The detailed information is showed below in **Table S4 (attached in the WORD format of response letter)**. We have further **removed** the column of lesion type in the Table S1.

Changes in the text: see Table S1.

Comment 8 : Line 136;

The underestimation rate for high risk lesion in total was 5.1% as two cases of ADH was upgraded to DCIS in the final surgical excision

Please check the English Language.

Reply 8: Thank you for your proper language suggestion. We have modified this phrase.

Changes in the text: see Page 10, line 170-171.

Comment 9 : Line 146 ;

As you mentioned “557 (93.8%) BI-RADS 4 lesions,” Is this value not an error? Is it not 470 according to Table 2, $4A + 4B + 4C = 387 + 59 + 24 = 470$?

Reply 9: Thank you for your careful review. This was a calculation error. We have modified the wrong data.

Changes in the text: see Page 9, line 152.

Comment 10 : Line 147, Table2;

You showed the number of cases in each BI-RADS category in Table 2. In addition, you mentioned only BI-RADS 4a as “BI-RADS 4a diseases accounted for 65.2% (387/594) of the total cases.” You need to further explain your intended meaning for this. You equally need to check the consistency in notation of BI-RADS, 4A or 4a.

Reply 10: Thank you for your questions. For the 1st one, we meant to describe the fact that nearly two-thirds of cases enrolled were classified as BI-RADS 4A mammographically. Due to the introduction of calcification morphology, this sentence has been replaced. For the 2nd one, the standardized notation of BI-RADS category 4 should be capitalized according to the Breast Imaging Reporting And Data System (BI-RADS) 5th edition of American college of radiology (ACR), and we have revised the wrong ones.

Changes in the text: see Page 9, line 153, 156, 158 & Table 2.

Comment 11 : Line 148;

You defined the malignancy rate as follows: the development of new malignant lesions during the short-term follow-up (<12 months) of patients with ADH diagnosed by VABB without residual calcifications conservatively managed in line 98. However, the malignancy rate in line 148 indicates the rate of malignancy found in each BI-RADS category. This is same as in lines 168 and 183.

Reply 11: Thank you for your correction. We failed to make it clear in this context. The **false negative rate** should be the proper term instead of malignancy rate.

Changes in the text: see Page 7, line 121; Page 11, line 203; Page 15, line 272.

Comment 12 : Line 154, Table3;

It is worth noting whether there is a difference between the pathological results of the lesion with and without calcification. This is highly suggestive by the diagnostic accuracy of the lesions without calcification using stereo-guided VABB targeting calcification. Therefore, clearly address this.

Were there samples that contained both calcifications and non-calcifications in all cases? Of the 84 malignant cases, 71 cases without calcifications were diagnosed as malignant; however, 13 cases without calcifications were not found malignant. This is understandable.

On the other hand, of the 471 benign cases, 458 cases without calcifications were diagnosed as benign. Therefore, what were the pathological results in the remaining 13 cases?

Reply 12: Thank you for your question and advice.

(1) Reply to **question:** In our study, each sample of VABB consisted of specimens with calcification lesions and paired specimens of adjacent tissue without calcifications, which were separately submitted to histopathologic assessment. Of 471 benign cases, 458 cases without calcifications were identically diagnosed as benign while the pathological results in the remaining 13 cases revealed normal breast tissue.

(2) Reply to **advice:** Analysis has been added to determine the difference between the

pathological results of the lesion with and without calcification as well as the diagnostic accuracy.

Changes in the text: see Page 10-11, line 181-195; Page 12-13, line 216-230; Table 3.

Comment 13 : Line 167;

The terminology “The calcification were openly biopsied.” is preferable to calcification lesions or lesions with calcifications.

Reply 13: Thank you for your helpful language editing. We have modified this phrase in the text.

Changes in the text: see Page 11, line 202.

Comment 14 : Line 168;

Same remark as lines 98 and 148.

Reply 14: Thank you for your correction. We failed to make it clear in this context. The **false negative rate** should be the proper term instead of malignancy rate.

Changes in the text: see Page 7, line 121; Page 11, line 203; Page 15, line 272.

Comment 15 : Line 190;

This guideline was published in 2007. Has it not been updated?

Reply 15: Thank you for this note. After searching the PubMed/Medline, we found that the European Society of Breast Imaging, EUSOBI, has issued a series of 5 recommendations for women’s information. The first (Ref 4) and the third (Ref 5) focusing on mammography, the second on breast MRI (Ref 6), and the fourth on breast ultrasound (Ref 7). The current version represents also an update of a previous EUSOBI guideline regarding diagnostic interventional breast procedures, published in 2007 (Ref 8). We have replaced our reference by the latest version.

[Ref 4] Sardanelli F, Helbich TH (2012) Mammography: EUSOBI recommendations for women's

information. Insights Imaging 3:7–10.

[Ref 5] Sardanelli F, Fallenberg EM, Clauser P et al (2017) Mammography: an update of the EUSOBI recommendations on information for women. Insights Imaging 8:11–18.

[Ref 6] Mann RM, Balleyguier C, Baltzer PA et al (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678.

[Ref 7] Evans A, Trimboli RM, Athanasiou A et al (2018) Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. Insights Imaging 9:449–461.

[Ref 8] Wallis M, Tarvidon A, Helbich T, Schreer I (2007) Guidelines from the European Society of Breast Imaging for diagnostic interventional breast procedures. Eur Radiol 17:581–588.

Changes in the text: see Page 13, line 237; Page 17, line 313-315.

Comment 16 : Line 193, 196;

See the submission guidelines. Please check in-text citation guidelines; (reference number) or [reference number].

Reply 16: Thank you for your submission format advice. We have modified the wrong reference number.

Changes in the text: see Page 13, line 232.

Comment 17 : Line 225;

Are these two new cases considered as primary, or was this diagnosis of ADH underestimated? In this manuscript, the study is based only on the BI-RADS category; however, the morphology is related to the case of calcification. Heterogeneous calcification may change in a short duration, while amorphous calcification would change slowly. It would be better to comment on the morphology.

Reply 17: Thank you for your question and contributive advice.

After revising the medical record, both of these 2 patients without residual calcifications post-VABB received eventually conservative management and developed new lesions of calcifications in the same breast within 12 months (**Table S5, attached in the WORD format of response letter**).

(1)). According to our definition, they should be considered as false negative events

rather than ADH estimation.

(2) We agree with the reviewer on the importance of morphology in case of calcifications.

Classification of breast calcifications by morphology is useful in predicting the likelihood of malignancy. Due to the limitation of medical record extraction, the calcification morphology of all 594 lesions could not be completely listed in baseline characteristics. But we adopted four descriptors (amorphous, coarse heterogenous, fine pleomorphic, fine linear branching) of calcification morphology that usually indicate sufficient suspicion of malignancy to prompt a recommendation for biopsy (Ref 9). Therefore, associated descriptions and comment have been added in 'Table S1', 'Methods', 'Results' and 'Discussion' sections.

[Ref 9] Sickles E.A, D'Orsi C.J, Bassett L.W et al. ACR BI-RADS®Mammography 2013.

Changes in the text: see Page 5-6, line 85-87; Page 9, line 153-157; Page 13-14, line 244-248; Table S1.

Comment 18 : Line237 ;

In the conclusion, objects should be written without omissions.

In conclusion, stereotactic VABB for microcalcification is an accurate and safe technique...

Reply 18: Thank you for language editing. We have modified this phrase in the text.

Changes in the text: see Page 15, line 281.

Special thanks to you for your helpful and contributive comments.

Table 3. Imaging features in seven cases of mammographic BI-RADS category 0

No.	Mammography	Imaging features		Pathological result of VABB
		Breast ultrasound	Breast MRI	
1	Suspicious clustered linear calcifications, BI-RADS 0	Dilated ducts with intraductal calcifications, BI- 4A	NA	DCIS
2	Multiple groups of suture calcifications, BI-RADS 0	Cystic mass, BI-RADS 3	NA	Hyperplasia with calcareous deposits
3	Scattered diffused calcifications with architecture distortion, BI-RADS 0	Fibrocystic changes, BI-RADS 3	NA	Fibrocystic changes with calcareous deposits
4	Clustered fine calcifications, BI-RADS 0	NA	NA	Ductasia with calcareous deposits
5	Scattered diffused punctate calcifications, BI-RADS 0	Adenosis, BI-RADS 2	Solid masse, BI-RADS 3	Ductasia with calcareous deposits
6	Clustered calcifications, segmental distribution, BI-RADS 0	Heterogenous masse with suspicious calcifications, BI-RADS 0	NA	Ductasia with calcareous deposits
7	Scattered diffused punctate calcifications, BI-RADS 0	Adenosis, BI-RADS 2	Cystic change, BI-RADS 1	Hyperplasia with calcareous deposits

Table S4. Mammographic features in 7 cases of calcifications with architecture distortion

No.	Lesion type	Mammographic BI-RADS category
1	Regional milk calcifications with architecture distortion	4A
2	Coarse heterogenous calcifications with architecture distortion	4B
3	Fine pleomorphic calcifications with architecture distortion	4B
4	Coarse heterogenous calcifications with architecture distortion	4B
5	Amorphous calcifications with architecture distortion	4B
6	Segmental punctate calcifications with architecture distortion	4A
7	Fine linear branching calcifications with architecture distortion	4C

Table S5. Baseline information of two false-negative cases

No.	MG before VABB	Pathology of VABB	DFI (mons)	MG before surgery	Pathology of surgery
1	Regional heterogenous calcifications BI-RADS 4B	coarse ADH	5	Suspicious calcifications with architecture distortion, BI-RADS 4A	IDC
2	Segmental calcifications, BI-RADS 4B	amorphous ADH	6	Fine linear branching calcifications with architecture distortion, BI-RADS 4C	IDC

MG: mammography; VABB: vacuum-assisted breast biopsy; ADH: atypical hyperplasia; DFI: disease-free interval; IDC: invasive ductal carcinoma.