TRANSLATIONAL CANCER RESEARCH

Peer Review File

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Reviewer A:

In general, VABB is a diagnostic tool, which is not used for therapy. Please provide the reason for which you chose to do this study.

It's too short time to analyze overall survival. It's better to mention only disease-free survival. It is suggested that the language in this paper to be re-checked by a English-native speaker.

Response: Thank you for your advice on our manuscript. There has been a trend of breast surgery with minimal invasion, which aims to reduce surgical complications and improve aesthetic effects. Various techniques are now being explored for patients with early breast cancer, such as radiofrequency ablation and endoscopic surgery. Some researchers have also tried mammotome-assisted endoscopic breast surgery (1). Meanwhile, some young patients with small tumors wonder if they could avoid open surgery after VABB, so we used retrospective data to evaluate the safety of VABB therapeutic use for breast cancer. However, because of a high rate of residual tumor, we conclude that VABB should only be used as a diagnostic tool for breast cancer and that standard open surgery should be performed after VABB.

With regard to your second comment, we have deleted the data related to the overall survival and mentioned only disease-free survival (see Page 6, lines 113–117 and Page 21, lines 455–465).

The English of this manuscript has been re-edited by native speakers.

Responses and changes in the text according to specific comments:

(1) row 42-43: The sentence is incorrect. (Improvements .... have improved...)

Changes in the text: We have modified our text as advised (see Page 3, line 43).

(2) row 54: It would be better to show some previous studies if available.

Changes in the text: We added some data as advised (see Page 3–4, lines 54–66).

(3) row 62: ultrasound guided VABB? You should add the information of the machine, gauge, the number of biopsy samples.

We have described the details of VABB operation, including information about the machine, gauge, and number of biopsy samples.

Changes in the text: We added some data as advised (see Page 4–5, lines 78–87 and Page 6, line 126–127).

(4) row 65: Is there no patients who underwent NAC?

Our cohort only had one patient with bilateral stage IV breast cancer of stage who underwent NAC. We excluded this case due to potential interference of survival analysis.

Changes in the text: We have added neoadjuvant chemotherapy as an exclusion criterion (See Page 5, line 95-96).

(5) row 68: Please add the reference
Changes in the text: We have added the reference as advised (see Page 5, line 93).
(6) row 69: Please add the reference
Changes in the text: We have added the reference as advised (see Page 5, line 94).
(7) row 72: Please add the reference
Changes in the text: We have added the reference as advised (see Page 5, line 103).
(8) row 73: Please explain what is targeted therapy
Here the targeted therapy mainly referred to adjuvant trastuzumab in the treatment of Her-2 positive breast cancer patients.
Changes in the text: We have modified our text as advised (see Page 6, lines 106–107).
(9) row 76: Is the follow-up tool only US?
We have an individualized follow-up plan for breast cancer patients mainly based on their postoperative pathology results. We also give our patients a booklet containing information about their follow-up time and examinations after surgery.
Changes in the text: We added some data as advised (see Page 6, lines 112–113).
(10) row 85: Please add original lesion size (mean, size)
Changes in the text: We added the original lesion size as advised (see Page 6, line 126).
(11) row 90: Please add the reference
Changes in the text: We have added the reference as advised (see Page 7, line 135).
(12) row 97: 52.6% is pretty high. it would be better to delete "only"
Changes in the text: We have modified the text as advised (see Page 7, line 143).
(13) row 104: Please add time (mean, range) between VABB and surgery
Changes in the text: We added the time between VABB and surgery as advised (see Page 7, lines 149).
(14) row 109: Please add the reference
Changes in the text: We have added the reference as advised (see Page 8, line 156).
(15) row 122-124: The sentence (However....) is not results. Please move to discussion"
Changes in the text: We have modified our text as advised (see Page 13, lines 262-264).
(16) row 156: You wrote "controversial". Is there any research paper that VABB is recommended for therapy?
Changes in the text: We have added the reference and modified our text as advised(see Page 3–4, lines 54–66).
(17) row 103: Please explain what is liquid biopsy
Changes in the text: We have added the reference and modified our text as advised (see Page 12, lines 244–251).
(18) row 210-212: You did not mention the cost analysis of VABB so far. You should mention that in the discussion.
Changes in the text: Since many patients will have to pay for VABB in the outpatient department at their own expenses, we have explained about the cost analysis of VABB (see Page 12, lines 252–257).

Reviewer B

In this study, the authors investigated the potential of VABB as a therapeutic tool in early breast cancer. While the topic is interesting, the manuscript suffers from

essential drawbacks regarding the study design and conclusions. Therefore, I do not think that this paper is ready for publication yet.
See comments below:

Materials and methods:

1. The benign results after VABB biopsy are not listed in the exclusion criteria, what was the procedure when B3 lesions (with uncertain malignant potential) were detected after VABB at histology? It is known that they could be associated with in situ or invasive malignancy, so they would require further surgical assessment.

Response 1: Thank you for the careful review of our manuscript. We are sorry for the confusion caused by the inclusion criteria. We only enrolled the patients who were initially diagnosed as having breast cancer after VABB, and we have rearranged the description of the patients included in our study. As for B3 lesions (with uncertain malignant potential) detected after VABB at histology, consensus conferences on B3 lesions have been held regularly, and we could communicate with these patients based on both their personal preferences and the consensus. In the second consensus on B3 lesions (2), experts recommend that for flat epithelial atypia (FEA), classical lobular neoplasia (LN), papillary lesions (PL), and radial scars (RS) diagnosed on core-needle biopsy (CNB) or vacuum-assisted biopsy (VAB), excision by VAB is preferred to open surgery. On the other hand, for atypical ductal hyperplasia (ADH) and phyllodes tumors (PT) diagnosed at VAB or CNB, first-line treatment is open surgical excision (OE) with follow-up surveillance imaging for 5 years. Since our study was mainly focused on patients with diagnosed breast cancer who should receive open surgical excision after VABB, we did not describe lesions with uncertain malignant potential in the manuscript.
Changes in the text: We have modified our text about inclusion criteria as advised (see Page 5, lines 88–100).

2. There is not enough information how patients were divided into the two groups, exact group definition is lacking.

Response 2: Thank you for your comment. We divided the patients into groups based on whether there were residual tumors in the postoperative pathology of open surgical excision.
Changes in the text: We have modified our text about the group definitions as advised (see Page 6, lines 108–111).

3. There is no distinction or explanation if only mass lesions were included in the study, or also microcalcifications were included in the study.

Response 3: Mass lesions with microcalcifications may have a higher residual tumor rate using ultrasound-guided VABB, since microcalcifications are not always easy to detect under ultrasound. Therefore, we only included mass lesions in our study.
Changes in the text: We have modified our text as advised (see Page 4, lines79–80).

4. How many samples were retrieved at VABB, always the same number, or the number of samples varied? This can also influence the degree of tumor resection based

on how much tissue is removed from the lesion.

Response 4: The mean number of specimens was 8.9±6.6 in our study, since most of the tumors were less than 2 cm in size. The number of samples varied due to the size and shape of different lesions; precise positioning is also an important factor when considering removing the number of specimens. We would also review the ultrasound at the end of the VABB operation to ensure that there are no residual lesions under ultrasound view.

Changes in the text: We have modified our text about details of VABB operation as advised (see Page 4–5, lines 78–87 and Page 6, lines 126–127).

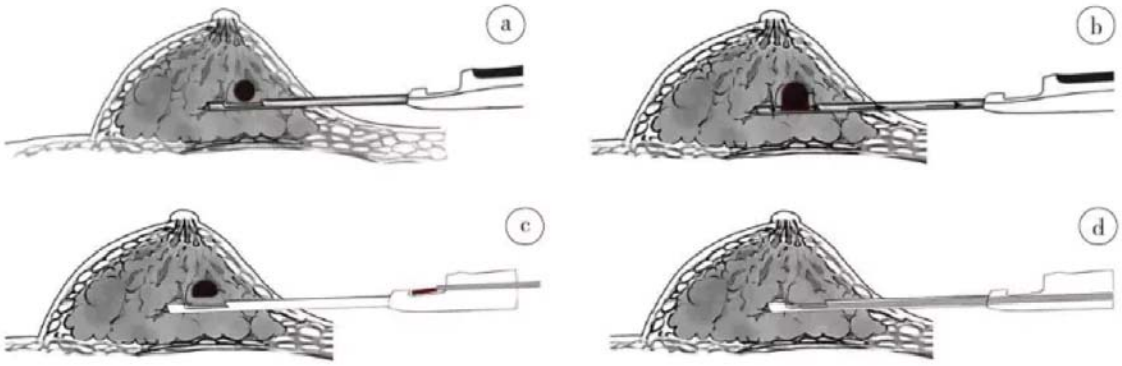
Results:

1. Section Patients characteristics, row 89, at VABB or surgery, and how was the "maximum resected tumor size" evaluated, it is also stated that were no significant differences in the maximum resected tumor size, while at row 94 it is stated that breast sonography revealed significant inter-group difference in the lesions' maximum diameter. It is not clear, please explain.

Response 1: Maximum resected tumor size here referred to the size of resected tumor evaluated during the operation of VABB, while the lesions' maximum diameter was evaluated by the preoperative ultrasound of tumor bed before open surgical excision. The maximum diameter detected by the preoperative ultrasound before open surgical excision referred to the size of suspicious lesions of residual tumors. If there were no suspicious lesions and the original tumor bed had only hematoma or subcutaneous exudate, the maximum diameter was recorded as zero.

2. Can the authors provide an explanation in which way the shape of the tumor, irregular vs. regular influence the degree of total vs. partial resection at VABB?

Response 2: The figure below shows the standard operation of VABB in the latest Chinese consensus guidelines (2017 edition) (3) and may illustrate our explanation. If a tumor (black dots) is regular as shown in the figure (a–d), we could resect it in a relatively easy way since there is a clearer visual field during the operation, which helps a complete resection. However, some breast cancer tumors have unclear borders and even blurry or crab foot shapes. For these patients, it would be difficult to resect their tumors completely with negative margins even in open surgical excision.



3. It is to assume that the size of the tumor plays a decisive role in the success of total resection with VABB, this why the number of samples can influence the results, also if the lesions were larger, there is a decreased probability that the entire lesion would be removed. Can the authors provide subgroups of patients (e.g. lesions 1, and between 1 and 2 cm) and see how this could influence the rate of total resection of the lesions.
Response 3: We have made subgroup analyses to see how tumor size could influence the rate of total resection of the lesions. From Table 3, we could see a rising residual rate with an increasing tumor size. Based on our experience, VABB should not be considered for malignant breast tumors with a diameter of >2 cm.
Changes in the text: We have modified our text about subgroup analyses as advised (see Page 8, lines 160–162 and Page 21, lines 447–448).

4. Can the authors explain how many patients showed a hematoma after VABB, this can also be influenced by the number of samples retrieved and can influence the size and the vascularity of the lesions post VABB. How were the lesion size and vascularity measured in the presence of post-bioptical hematoma?
Response 4: In this study, there were 8 out of 89 patients who had a hematoma after VABB and the hematoma rate was 8.99%, slightly lower than that in a recent systematic review and meta-analysis (4). We do agree that the hematoma rate can also be influenced by the number of samples retrieved and that can influence the size and the vascularity of the lesions post VABB. So, we do our best to reduce the hematoma rate, such as a precise positioning of breast lesion and a compression of tumor bed within a week after VABB. After removing the compression, we would evaluate if there is a hematoma or subcutaneous exudate and sometimes there should be a further fine-needle aspiration of suspicious liquid. Most of the hematomas may result from an inadequate compression or fixation, and they would gradually resolve in a short time. Since the mean time from VABB to surgery was 29.97±11.73 days, the existence of hematoma had little influence on measuring the lesion size and vascularity in the preoperative ultrasound.

Reviewer C
The management of breast cancer has evolved over the last few decades, with needle biopsy interventions now including vacuum-assisted breast biopsy (VABB). In the manuscript “Reconsidering the therapeutic use for vacuum-assisted breast biopsy in breast cancer patients: A retrospective single-center study”, the authors evaluated the residual tumor rate and prognosis of breast cancer patients who underwent VABB-based resection.
A number of improvements need to be made before the manuscript can be accepted.

Response: Thank you for the careful review. The files you provided are helpful as well.
1. The introduction is too simple. Please add relevant content to further enrich this part.

Response 1: Thank you for your helpful comment.
Changes in the text: We added some data as advised (see Page 3–4, lines 54–66).

2. In the paper, why were only 89 patients who underwent VABB between January 2011 and December 2018 chosen?
Response 2: Thank you for this comment. This was not expressed clearly enough in the Abstract. As shown in the Methods, we only enrolled malignant lesions and the 89 breast cancer patients were chosen based on the inclusion and exclusion criteria.
Changes in the text: We have modified our text as advised (see Page 1, lines 14–15 and Page 5, lines 88–89).

3. How is VABB performed in patients with breast cancer? Please describe this in detail in the 'Methods' section.
Response 3: We have described the details of VABB operation in the Methods, including information about the machine, gauge, and the number of biopsy samples (also advised by Reviewer A).
Changes in the text: We have modified our text as advised (see Page 4–5, lines 78–87 and Page 6, lines 126–127).

4. What progress has been made with breast cancer diagnosis? Relevant content should be supplemented in the discussion.
Response 4: Progress in breast cancer diagnosis has been supplemented in the Discussion.
Changes in the text: We have added the progress as advised (see Page 12, lines 244–251).

5. The paper is not unique enough. One of the references (reference 11) has already reported on 5,232 patients who underwent VABB, and found that VABB could be used to detect early breast cancer and as a clinical diagnostic technique. What is the novel idea in this paper? Relevant content should be supplemented in the discussion.
Response 5: Thank you for this comment. In the reference (5), 61 malignant lesions were identified among the 5,232 patients who underwent VABB and the authors mainly focused on the diagnostic indication of VABB. Our study included 89 breast cancer patients with survival data, and we also found an association between the time from VABB to open surgery with disease-free survival in the residual group, which has seldom been provided in previous studies.
Changes in the text: We have modified our text as advised (see Page 12, lines 258–259).

REFERENCES

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