Peer Review File

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Reviewer A

Comment 1: The methylene blue location technique improved the outcome of deep-seated benign breast tumor resection under endoscopy: A retrospective, single-institution analysis

The authors compare methylene blue guided endoscopic excision of tumors to skin mark endoscopic excision. The paper has many problems, including incomprehensible English, problematic methodology and need for extensive editing of the paper.

Reply 1: Thanks for your valuable suggestions, we purchased English language copy editing service from "American journal editor (AJE)" company to improve and polish the manuscript, revised portion are marked in the paper, we hope the Editor-in-Chief can see the best version of our manuscript.

Changes in the text 1: We have modified our text as advised, revised portion are marked in the paper, and new version was uploaded.

Comment 2: the discussion should be re-written in a concise fashion summarizing the findings and the literature written refraining from incusing data that is not relevant, such as the paragraph on atypia and high risk.

Reply 2: Thank you for your important comments which improve our paper a lot, we rewrote the second paragraph of the discussion section, and the paragraph on atypia and high risk was removed.

Changes in the text 2:

We have modified our text as advised, (see Page 8, line 213-220) "Vacuum-assisted breast biopsy (VABB) is method to remove small benign breast masses, patients can avoid general anesthesia and have a small incision,[15,16] and international guidelines recommend the use of vacuum-assisted excision for breast lesions with a maximum

diameter of 25 mm,[17,18] while endoscopic surgery has the advantage in the resection of benign tumors with a diameter greater than 25 mm or multiple benign tumors, and can achieve complete resection of the tumor along with its envelope, and remove a small amount of normal breast tissue to avoid residual tumor envelope and recurrence".

Comment 3: the 4 videos are repetitive.

Reply 3: Thanks for your valuable suggestions. Due to the large memory of the long video (2.76GB), which exceeds the limit of "WeTransfer" and cannot be uploaded. It is divided into 4 short videos (1a,1b,1c,1d), they are continuous, describing 4 parts of the endoscopic resection process guided by methylene blue. Thanks for your kind considerations will be greatly appreciated.

Changes in the text 3: We retransfer the videos (1a,1b,1c,1d) again.

Comment 4: The main problem with this paper is that it describes a procedure that is not indicated: In the introduction the authors talk about benign lesions:" Surgical excision is the definitive procedure performed for symptomatic benign breast tumors to alleviate anxiety regarding potential for growth or malignancy as well as physical discomfort. Surgical excision is the definitive procedure performed for symptomatic benign breast tumors to alleviate anxiety regarding potential for growth or malignancy as well as physical discomfort". Most benign breast lesions are not precancerous and do not need to be excised. It is not clear what the authors mean by symptomatic as if the lesion is palpable there is no need for any kind of pre-operative marking.

Reply 4: We feel great thanks for your professional review work on our article. Patients with benign breast tumors may cause breast pain or discomfort, and the pain is usually localized, lasting for a period of time or recurring. Patients with benign breast tumors classified as BI-RADS1-2 are usually not treated. In patients with associated pain or discomfort and classified as BI-RADS3-4a, we recommend resection. Deep-seated benign breast tumor is generally untouchable, sometimes is palpable, skin marking before ultrasound is a way to guide endoscopy to find a lump during surgery. For example, when endoscopy is looking for a lump, pressing the skin marking site will

give the endoscopy a better guide.

Changes in the text 4: We have modified our text as advised, (see Page 2, line 39-44), “Surgical excision is the definitive procedure performed for benign breast tumors (classified as BI-RADS3-4a) with associated pain or discomfort to alleviate anxiety regarding potential for growth or malignancy as well as physical discomfort.”

Comment 5: In the methods section the inclusion criteria include cancer:" Eligible patients were those who had breast cancer (ductal carcinoma in situ (DCIS), BI-RADS range from Class 3 to 4A), and the tumor distance from the pectoralis major was less than or equal to 5mm or on the surface of the pectoralis major, no evidence of multiple lymph node metastasis, and no evidence of skin or chest wall invasion".

The surgical technique describes a fibroadenoma. The results describe a cohort of patients with benign disease:" 65 women with fibroadenoma, 10 with adenosis of the mammary glands, 15 with fibrocystic breast disease, 7 with tissue hyperplasia, 3 with foliate tumors, 5 with papilloma, and 2 with sclerosing adenosis."

Reply 5: Thanks for your valuable feedback, we described surgical technique on breast tumor, this is a writing error, please excuse this clerical error. The eligible patients in this study were those who had breast tumor, all the data shown in Table 1, which did not involve malignant tumors or lymphatic node metastasis, thank you for indicating this typo, we have corrected it as below:

Changes in the text 5: We have modified our text as advised, (see Page 3, line 76-78), “Eligible patients were those who had breast tumor, Breast Imaging-Reporting and Data System (BI-RADS) range from Class 3 to 4A)”, (see Page 5, line 120-122), “The surgeon incised the gland behind the tumor, exposed the tumor envelope, and then separated the tumor forward and upward to the initial point”. Thanks for your valuable suggestion!

Reviewer B

Comment 1: The paper describes two large cohorts of patients that have been operated

for deep benign? breast tumors with endoscopic resection. One cohort used methylene blue as a surgical localization guide, while the other had “line marking method”. More than 200 patients are included, which should allow good assessment of the two techniques. I have a few major concerns:

It is not reported how patients were allocated to one of the two groups, thus there is no randomization involved. This is a fundamental methodological problem if the authors wish to compare the two methods.

Reply 1: We feel great thanks for your professional review work on our article. This work is a retrospective study, the research method tends to be matched control. We hope to conduct a RCT prospective study in the future. Thanks!

Changes in the text 1: We polished the manuscript include methodology and extensive editing of the paper by “American journal editor (AJE)” company, revised portion are marked in the paper, and new version was uploaded.

Comment 2: I think the title exaggerates when stating that the use of MBL IMPROVES the outcome of surgery. The only differences between the groups were in surgery duration and blood loss. None of these measures are important outcomes, at least not when considering the absolute values which were minimal. If you corrected for multiple comparisons, like you perhaps should, the differences may not have been significant. The main message and title should therefore not claim that MBL method is better than the other, but equally good.

Reply 2: Thank you for your valuable suggestions to improve the quality of our manuscript. We would like to revised our title like below: “The application of methylene blue location technique in deep-seated benign breast tumor resection under endoscopy: A retrospective, single-institution analysis”. Thanks!

Changes in the text 2: We have modified our text as advised, (see Page 1, line 1-2),

Comment 3: I would like to know more about the line marking method. In many countries this is not used, instead wire localization or wire-less markers are used with a search probe. I am not sure that “line marking method” is the relevant comparison to

methylene blue.

Reply 3: Thank you for your professional comments, "line marking method": The tumor was determined by B-ultrasonography before surgery, and the corresponding position of the breast surface was marked, the methylene blue was not used in the "line marking method". During the intraoperative endoscopic search for tumor, press into the breast at the marking point, which can guide the probe forward direction. This method minimizing the injury of breast compare to wire localization.

Comment 4: It is very confusing that in the headline and abstract you write about patients with benign tumors, but in line 82 you write that you included patients with breast cancer. Then for the rest of the paper it is only benign disease. Assuming this is a mistake, and that you included only patients with presumed benign disease, it is surprising that you do not have any patients that had malignant disease on final histopathology (Table 1).

Reply 4: Thank you for your professional comments. The eligible patients in this study were those who had benign breast tumor under the evaluation, which did not involve malignant tumors or lymphatic node metastasis, thank you for indicating this typo!

Changes in the text 4: We have modified our text as advised, (see Page 3, line76-79), "Eligible patients were those who had breast tumor, Breast Imaging-Reporting and Data System (BI-RADS) range from Class 3 to 4A)".

Comment 5: Line 46-47 "Benign breast disease is a common entity that places women at an elevated risk for breast cancer" – try rephrasing

Reply 5: Thank you for your professional comments, we rephrase this expression: "Most of benign tumor were evaluated at Breast Imaging-Reporting and Data System (BI-RADS) 3 or 4A, which always indicates benign lesions before the biopsy, but with the final pathological confirmation of malignancy, and proven by many studies from multiple countries."

Changes in the text 5: We have modified our text as advised, (see Page 2, line 39-41), "Most of benign tumor were evaluated at Breast Imaging-Reporting and Data System

(BI-RADS) 3 or 4A, which always indicates benign lesions before the biopsy, but with the final pathological confirmation of malignancy, and proven by many studies from multiple countries. [5,6]"

5. Grady I, Gorsuch H, Wilburn-Bailey S. Long-term outcome of benign fibroadenomas treated by ultrasound-guided percutaneous excision. Breast J. 2008 May-Jun;14(3):275-8. doi: 10.1111/j.1524-4741.2008.00574. x. Epub 2008 Apr 6. PMID: 18397185.

6. Pandit P, Murkey SP, Agarwal A, Jaiswal A, Agrawal S. Understanding Fibroadenoma of the Breast: A Comprehensive Review of Pre-operative and Post-operative Clinicopathological Correlations. Cureus. 2023 Dec 30;15(12): e51329. doi: 10.7759/cureus.51329. PMID: 38288219; PMCID: PMC10823311.

Thanks!

Comment 6: Line 53: Endoscopic techniques? Or Endoscopy

Reply 6: Thanks for your valuable suggestions. We have corrected "endoscopic techniques" to "Endoscopy"

Changes in the text 6: We have modified our text as advised, (see Page 2, line 47-48), Endoscopy has been widely used in breast tumor surgery to achieve curative partial resection and preserve the cosmetic appearance of the breast, the appearance of endoscopy allows wide excision without compromising the aesthetic outcome of the breast; (see Page 9, line 230-232), The breast endoscopy not only achieves the therapeutic effect of invasive surgery but also conserves the aesthetic appearance of the breast.

Comment 7: Line 56: It is not clear what you mean by "touchable". Same phrase used in abstract

Reply 7: Thanks for your valuable suggestions. We have revised this word like below: "the long visual distance in endoscopic surgery makes it difficult to touch the tumor".

Changes in the text 7: We have modified our text as advised, (see Page 9, line 239-241), However, the long visual distance in endoscopic surgery makes it difficult to

touch the tumor, limiting the widespread use of this technique.

Comment 8: Table 2 is truncated in a way that makes it hard to read. Line 235: I do not understand what adverse effects of radiation you are talking about. It is not reported what kind of group statistics that is used. Are all numbers average (not mean) with standard deviation, or do you use standard error of the mean?

Reply 8: Thanks for your valuable suggestions. “adverse effects of radiation” is a writing mistake, please excuse this clerical error. We have revised the sentence as “the MBL group had a lower volume of blood loss than the SML group”. Average with standard deviation was used to analysis surgical features and patient-reported cosmetic results. We have revised this word like below: the MBL group had a lower volume of blood loss than the SML group, in which the blood loss with a mean of 10.07 ml in the MBL group compared to 13.83 ml in the SML group ($p=0.004 < 0.05$).

Changes in the text 8: We have modified our text as advised, (see Page 8, line 221-223), the MBL group had a lower volume of blood loss than the SML group, in which the blood loss with a mean of 10.07 ml in the MBL group compared to 13.83 ml in the SML group ($p=0.004 < 0.05$).

Reviewer C

Comment 1: First of all, I am honored to have the opportunity to review your excellent study.

However, I am curious about a few things and hope that they can be corrected in the future.

I wonder how many doctors performed SML and BML (only one breast surgeon, 2~3 or more breast surgeons). And also, I want to specify whether it was performed by only one breast surgeon, or with the cooperation of a radiologist.

Reply 1: Thank you for your positive comments and valuable suggestions to improve the quality of our manuscript. There are five doctors in our department, our chief

performed the surgery, another surgeon responsible for the endoscopy, with the cooperation of a nurse, and no radiologist involved.

Comment 2: I didn't hear about 'full moon position'. Maybe, that means 'supine position', I guess. If it's right, it is better to change the word that used in field more frequently.

Reply 2: Thank you for your valuable suggestions. We have revised 'full moon position' to 'supine position'.

Changes in the text 2: We have modified our text as advised, (see Page 5, line 113), "The patient was placed in full supine position after anesthesia".

Comment 3: Is 'absorbable beauty thread' the official product name?

Did you use a specific thread used for facial lift in the field of plastic surgery?

If there is no need to insert the word 'beauty', it would be better to only write absorbable thread.

Reply 3: Thank you for your valuable suggestions. We have revised 'absorbable beauty thread' to 'absorbable thread'.

Changes in the text 3: We have modified our text as advised, (see Page 5, line 125-126), "The incision was closed with absorbable thread".

Comment 4: I think the other parts of the paper come to excellent conclusions without any problems. However, it is fundamentally questionable whether this method is more effective than excision using local anethesia such as VABB. Of course, excision through endoscopic surgery is suitable for evaluating the pathologic features of the whole lesion, and also, is an excellent method for making a smaller incision than conventional skin incision. However, for most patients in this study, they had a pathologic outcome that can be removed by VABB. If surgeons use VABB, those patients can avoid the general anesthisia and the incision can be smaller. So, if you can compare to VABB, you can find the advantages of endoscopic surgery such as bleeding control, complete wide excision for borderline breast disease (ADH or atypical intraductal papilloma) that

could be diagnosed by accidently postoperative pathologic report.

In the future, I hope to design a prospective study comparing conventional surgery, VABB and endoscopic surgery using BML. It is great honor to review your paper. Thank you.

Reply 4: Thank you for your professional comments, we added the comparison and discussion between cavity mirror and VABB, and rephrase this expression: Vacuum-assisted breast biopsy (VABB) system is used in breast tumors less than 3 mm in diameter, patients can avoid the general anesthesia and have small incision, while endoscopic surgery has the advantage in the resection for benign tumors with a diameter greater than 3 mm or multiple benign tumors, and can achieve complete resection of the tumor along with its envelope, and remove a small amount of normal breast tissue to avoid residual tumor envelope and recurrence**.**

Changes in the text 4: We have modified our text as advised, (see Page 8, line 210-213), "Vacuum-assisted breast biopsy (VABB) system is used in breast tumors less than 3 mm in diameter, patients can avoid the general anesthesia and have small incision, while endoscopic surgery has the advantage in the resection for benign tumors with a diameter greater than 3 mm or multiple benign tumors, and can achieve complete resection of the tumor along with its envelope, and remove a small amount of normal breast tissue to avoid residual tumor envelope and recurrence".