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Improved evaluation of patients with small clusters of microcalcifications on mammograms: Implementation of vacuum assisted excision with "cavity margins shaving" technique

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ABSTRACT

Rationale and Objectives: The purpose of our study is to assess the diagnostic performance and treatment effectiveness of vacuum assisted excision (VAE) under digital breast tomosynthesis (DBT) guidance with "cavity margins shaving" technique to ensure total lesion removal in patients with ≤ 15 mm clusters of microcalcifications.

Materials and Methods: Patients with a single cluster of microcalcifications (BI-RADS > 3) < 15 mm who underwent DBT-guided VAE were enrolled. The "cavity margins shaving" technique was used: 12 focus samples (FS) and 12 cleaning samples (CS) were taken and the histopathologic assessment of the FS and CS was performed separately. The presence of residual disease within the CS was assessed. The surgical excision results were compared according to the CS status.

Results: A total of 72 patients were included, with 12 benign (16.7%), 45 B3 (62.5%) and 15 malignant (20.8%) lesions. Among the 13 ductal carcinomas in situ (DCIS) and 17 atypical ductal hyperplasia (ADH) cases without residual disease within the CS (21/30, 70%), in 2 cases residual pathology was detected in the subsequent surgery, without any case of upgrade.

Comparing the presence of malignant disease (residual DCIS or upgrade of ADH) at surgical excision according to the CS status, the rates were 1/5 (20.0 %) and 4/5 (80.0 %) respectively for negative and positive CS (P = 0.007). The NPV of the absence of residual lesion in the CS was 95.24 % (95 %CI: 76.39 %-99.20 %).

Conclusion: VAE with cavity margins shaving technique could represent a valuable alternative to surgical excision in selected patients (such as those with ADH or low-grade DCIS) who met the radiologic and histologic criteria.

1. Introduction

Vacuum assisted biopsy (VAB) under stereotactic guidance is the gold standard for percutaneous biopsy of suspicious breast microcalcifications [1–5]. Vacuum Assisted Excision (VAE) is the same procedure but aims to remove the amount of tissue equivalent to a surgical biopsy (i.e. about 4 g of tissue) which can yield a final diagnosis in the majority of cases [6].

However, underestimation, that is the finding of more severe disease (upgrade) at surgical excision, may occur after percutaneous diagnosis of atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS) [7,8]. The finding of ADH and DCIS, which are both commonly associated with clustered calcifications, increased dramatically following the introduction of breast cancer screening programs [7]. ADH is a "lesion of uncertain malignant potential" or B3 lesion found in about 5 % to 20 % of breast biopsies and DCIS accounts for approximately 20 % of screen

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detected breast cancers [9,10]. ADH and low-grade DCIS share cytological and architectural similarities and their distinction is based on partial/uniform involvement of terminal duct lobular units and size/extent criteria [11].

When biopsy histology returns a diagnosis of ADH or DCIS, surgical excision is still recommended, due to the risk of underestimation, reported to be 20.9 % for ADH and 11.2 % for DCIS [12].

About DCIS, during the last few decades, it has become increasingly clear that a substantial fraction of mammographically detected DCIS lesions is slowly progressing or indolent [13]. In particular, whilst high-grade DCIS may progress to invasive cancer, there is greater uncertainty surrounding the behavior of low- and low-intermediate-grade DCIS. Indeed, the latter, now considered Stage zero breast cancer, could be downgraded to pre-cancer, deserving of being watched closely and not automatically treated [14,15]. To reduce overtreatment of non-progressive DCIS, four international prospective study protocols (LORIS, COMET, LORD, and LORETTA) are currently evaluating the possibility to avoid surgery, especially when complete removal of microcalcifications on the post-biopsy mammogram was achieved [16–19]. However, the complete removal of microcalcifications alone does not rule out residual DCIS in the final surgical specimen [20].

About ADH, the recommendations are conflicting, with the third international consensus conference on B3 lesions and AGO guidelines advising surgical excision (even if the lesion appears to be excised on VAB) and the UK guidelines of the NHSBSP multidisciplinary working group and European guidelines suggesting that VAE could be a safe alternative to surgery [6,21–24]. Different nomogram including various factors have been developed to predict ADH upgrade but no one with a sufficient strength to definitely define which cases could safely avoid surgery [25,26]. The use of magnetic resonance imaging and contrast-enhanced mammography may help in ADH management, with the presence of residual post-biopsy enhancement indicating the necessity of surgery, but they are not conclusive [27–29].

In the era of de-escalation, the focus changed from maximizing cancer detection to minimizing overtreatment [13,30]. This emphasizes the need to identify women who are more likely to have cancer and really need surgical excision, avoiding unnecessary surgical procedures with surgical risk and distress for the patient and healthcare costs.

The purpose of our study is to assess the diagnostic performance and treatment effectiveness of VAE under digital breast tomosynthesis (DBT) guidance with "cavity margins shaving" technique to ensure total lesion removal in patients with $\leq$ 15 mm clusters of microcalcifications.

2. Materials and methods

2.1. Study population

This was an observational retrospective study approved by the local Institutional Review Board (IRB) (Protocol number 155–2024, 4/11/2024). Data collection and aggregation were performed in a fully anonymized manner and in line with international legislation. The study was performed in accordance with the Declaration of Helsinki statement for medical research involving human subjects.

Patients with a single cluster of microcalcifications $\leq$ 15 mm (BIRADS $>$ 3) which underwent VAE under DBT-guidance identified from consecutive patients of the screening program from January 2023 to November 2024 were eligible [31].

Patients were included when surgical histopathological examination of the entire lesion was available. Exclusion criteria included a synchronous ipsilateral or contralateral breast cancer or incomplete imaging/pathology details.

Data were collected from medical records, radiology reports and pathology reports.

All B5 lesions and ADH cases underwent surgery. The other B3 lesions were discussed at the multidisciplinary team meeting to ensure radiological and pathological concordance; if complete removal of microcalcification was documented on post-biopsy mammogram and no evidence of malignancy on VAE was seen, the patients were sent to annual mammographic surveillance.

2.2. VAE procedure with "cavity margins shaving technique"

DBT-VAB was performed in a prone position using the Giotto Class 30,000 system, with a 9-gauge vacuum biopsy device (Eviva; Hologic, Bedford, MA, USA) with an aperture of 20 mm or 12 mm. The biopsy approach was chosen on the basis of breast thickness and lesion location. DBT was performed to identify the target lesion and the DBT section with the best target visualization was chosen. When the position of the target was selected, coordinates were automatically determined by the biopsy software system, including z-axis location. After skin disinfection, local anesthetic was induced with 10 mL of carbocaine. DBT was repeated to re-identify the target lesion to avoid errors due to the lesion movement subsequent to anesthetic injection and biopsy coordinates were recalculated. After inserting the biopsy needle, the pre-fire control was performed with two stereotactic images (+15◦ and − 15◦). Finally, post-fire control was performed with two stereotactic images (+15◦ and − 15◦). In the study group, the "cavity margins shaving" technique was used: the first 12 specimens were taken with macroscopic excision of the focus (focus samples, FS); then 12 "cleaning" samples (CS), shaving the cavity margins, were taken without removing the biopsy needle but using a second sample container. Post Biopsy X-rays of the specimens were obtained for the FS and CS separately, to verify the correct sampling of the target microcalcifications and to separate the specimens with microcalcifications from those without.

A clip marker (Securmark for Eviva; Hologic) was placed in all patients and a post-biopsy mammogram was performed to check the clip position. After two weeks, two mammograms' projections (cranio-caudal and latero-medial or medio-lateral views) were obtained to check the clip position and to evaluate the complete/incomplete removal of the target lesion.

2.3. Pathologic evaluation

All the specimens were immediately placed in fixative solution (formalyn 10 %), processed in the laboratory of Pathology and paraffin embedded; four 2-μm sections were obtained and stained with haematoxylin and eosin analyzed by dedicated breast pathologists.

The histopathologic assessment of the specimens of the FS and CS was performed separately. Results were classified from B1 to B5, according to the European guidelines [32].

For lesions sent to surgery, the presence of any residual disease in the surgical specimen was evaluated.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 12.0 software (SPSS, Chicago, IL).

Statistical analysis was applied to the subset of DCIS and ADH cases. The VAE examination results were compared with the surgical pathological results to assess upgrade or residual malignant disease. "Upgrade" means that at surgical excision a more severe disease was found as compared with VAE results, that is invasive carcinoma at surgery in case of DCIS or ADH at VAE and DCIS or invasive carcinoma in case of ADH.

The surgical excision results (residual malignant disease/upgrade or not) were compared according to the CS status (positive/negative) using the chi-square test. The significance level was set at $p < 0.05$. Negative predictive value (NPV) of CS status was calculated.

3. Results

A total of 72 patients (mean age of 60 years, range 51–74 years) who

underwent DBT breast biopsy between January 2023 and November 2024 for single clusters of BI-RADS > 3 microcalcifications measuring up to 15 mm were included.

The histological assessment on specimens showed 12 benign lesions (12/72, 16.7 %), 45 B3 lesions (45/72, 62.5 %, consisting of 17 ADH and 28 other B3 lesions) and 15 malignant lesions (15/72, 20.8 %, consisting of 1 invasive carcinoma, 1 DCIS with micro-invasion and 13 DCIS) (Table 1).

Surgery was performed on 33/72 (45.8 %) lesions (all B5 and 18 B3 lesions). In both the 2 cases of invasive carcinoma and G3 DCIS with micro-invasion (invasive focus ≤ 1 mm), cancer was found also in the CS; at surgical excision, residual 2 mm invasive cancer was found in the first case and residual G3 DCIS in the second case.

Table 2 shows the presence of residual lesions in the CS and the surgical outcome for the DCIS and ADH lesions. No residual disease at surgical excision was found in 9/13 (69.2 %) of DCIS and 13/17 (76.5 %) of ADH cases. Among the 13 DCIS cases, cancer involved the CS in 5 cases (5/13, 38.5 %) while the CS were disease-free in 8 cases (8/13, 61.5 %). The subsequent surgical excision revealed micro-foci of invasive cancer in 1/13 cases (7.7 %) (upgrade); DCIS was still present in 3 cases (3/13, 23.1 %) while in 9 cases (9/13, 69.2 %) the final histological assessment found only benign changes and post-biopsy sequelae (Fig. 1). Among the 17 ADH cases, ADH was found also in the CS in 4 cases (4/17, 23.5 %), with 1 case of upgrade (G1 DCIS) and 2 cases of residual ADH at the subsequent surgical excision; in 13 cases (13/17, 76.5 %) the CS were disease-free and in 1/13 cases ADH was found at the final histological assessment. In particular, among the DCIS and ADH cases with no residual disease found within the CS (21/30, 70 %), in only 2 cases residual pathology was detected in the subsequent surgery (one residual G1 DCIS and one residual ADH), without any case of upgrade.

When we compared the presence of malignant disease (residual DCIS or upgrade of ADH) at surgical excision according to the CS status, the rates were 1/5 (20.0 %) and 4/5 (80.0 %) respectively for negative and positive CS (P = 0.007) (Table 3). The NPV of the absence of residual lesion in the CS was 95.24 % (95 %CI: 76.39 %-99.20 %).

4. Discussion

Our study supports the use of the "cavity margins shaving" technique in VAE as a good option for percutaneous stereotactic biopsy of small clusters of suspicious microcalcifications. Vacuum-assisted techniques are an alternative and cost-effective non-surgical method for the provision of a greater volume of tissue for histological evaluation through the use of a large bore hollow needle and vacuum assistance to draw tissue into the specimen chamber [7,8,33]. VAE has recently been introduced into the NHSBSP as an alternative to a diagnostic surgical excision for selected B3 lesions. Indeed, when a B3 lesion is diagnosed, further sampling is usually necessary to exclude associated malignancy but for many women, the traditional approach of an open diagnostic surgical excision represents overtreatment. VAE offers a safe and effective pathway for the management of B3 lesions, reducing the number of open surgical procedures [XX].

The use of "cavity margins shaving" technique not only allows multiple contiguous samples to be obtained with a single needle insertion but also permits the evaluation of the margins of the bioptic cavity. Indeed, the split sampling of the first 12 FS and the 12 CS and their separate histopatological analysis allows the evaluation of the cavity margins, to ensure complete removal of the target lesion. This is the first study about the use of this technique applied to VAE. Previous studies analyzed the effectiveness of this technique applied to breast surgery, where the surgeon performed an additional circumferential resection of the tissue within the excision cavity, to evaluate its potential benefits on the rates of positive resection margins and reexcisions in breast cancer patients [34,35].

In our series, underestimation occurred for 1/32 DCIS (7.7 %), better with respect to a significant *meta*-analysis by Brennan et al. that reported up to 26 % of patients with biopsy-confirmed DCIS with invasive carcinoma in surgical specimens [36]. This difference is probably due to the use of VAE in our study instead of simple VAB that can significantly reduce the rate of diagnostic underestimation. Moreover, it is interesting to note that in this case of underestimation, the microcalcifications seem to be all removed at post-biopsy mammogram, confirming that this radiological criterion alone does not rule out residual DCIS in the final surgical specimen [20].

Residual disease (G1 DCIS) at surgical excision was seen in only 1/8 (12.5 %) cases of patients with negative CS. Re-evaluating the post-biopsy mammogram of this case, we noticed residual microcalcifications not completely removed during the VAE procedure. This underlines the importance of associating the two criteria of "negative CS" and "no residual evidence of microcalcifications on post-biopsy mammogram" to ensure a correct selection of patients who can safely avoid surgery.

Looking at ADH in our study, we found 1/17 (5.9 %) cases of upgrade in the group with residual disease in the CS vs no upgrade in the group without residual disease in the CS. These findings not only support the idea that VAE is a reliable option for excision of small ADH lesions, as suggested by the UK and European guidelines, but also suggest that "cavity margins shaving technique" can allow to select a subset of patients who can be safely sent to surveillance [6,8,23]. In recent years, many studies examined the radiological and histologic characteristics of ADH on percutaneous breast biopsies to determine features that would predict the risk of upgrade at surgical excision and different predictive models were developed [26,37–39]. However, VAE with "cavity margins shaving technique" should not be seen as a "predictive" tool but as a safe alternative to surgical excision when histologic (negative CS) and radiologic (no residual microcalcification) criteria are met. Moreover,

Table 1
Histological data of vacuum assisted excision case series.

Histology	N° cases	%
Malignant lesions	15	20.8
Invasive carcinoma	1	1.4
DCIS with micro-invasion	1	1.4
G1 + G2 DCIS	13	18
B3 lesions	45	62.5
ADH	17	23.6
FEA	18	25
ALH/LCIS	9	12.5
FEA + RS	1	1.4
Benign lesions	12	16.7
Adenosis/fibrosis	7	9.7
UDH	3	4.2
Fibroadenoma	2	2.8
TOTAL	72	100

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma in situ; FEA, flat epithelial atypia; LCIS, lobular carcinoma in situ; RS, radial scar; UDH, usual ductal hyperplasia.

Table 2
Histopatological results of the cleaning samples at VAE for DCIS and ADH and findings at subsequent surgical excision.

VAE		Surgical excision			Total
Histology	CS status	No residual disease	Residual disease	Upgrade	
DCIS (n = 13)	Positive	2	2	1	5
	Negative	7	1	0	8
ADH (n = 17)	Positive	1	2	1	4
	Negative	12	1	0	13
Total		22	6	2	30

ADH, atypical ductal hyperplasia; CS, cleaning samples; DCIS, ductal carcinoma in situ; VAE, vacuum assisted excision.

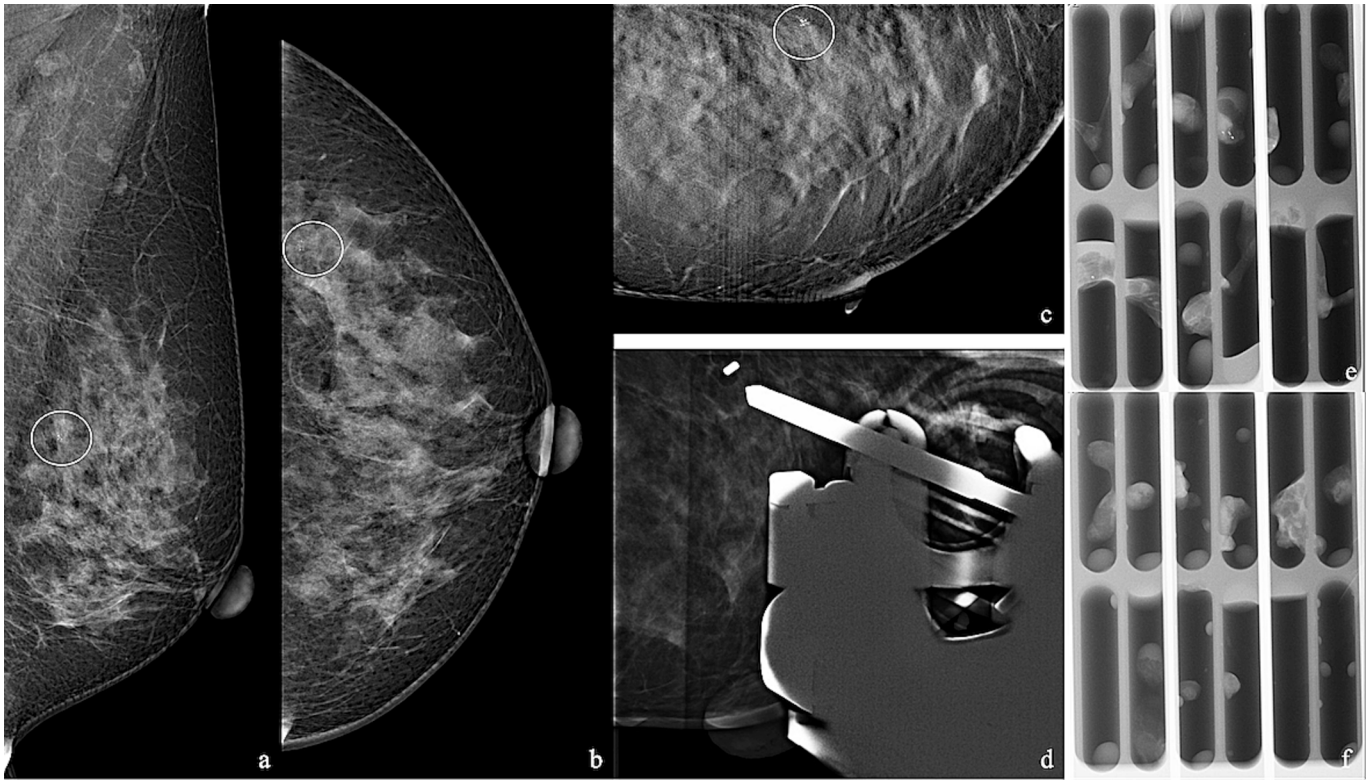

Fig. 1. 52 years old women. MLO (a) and CC (b) mammographic views showing a single cluster of BIRADS 4b microcalcifications (round circle) measuring 5 mm. DBT section with the best target visualization was chosen (c) and VAE procedure was performed with the "cavity margins shaving" technique. Post Biopsy X-rays of the specimens were obtained for the focus samples (d) and cleaning samples (e) separately, showing all the microcalcifications in the focus samples. A clip marker was placed and a post-biopsy mammogram was performed to check the clip position (f), showing no residual microcalcifications. Histology revealed G2 DCIS, with disease-free cleaning samples. The subsequent surgery found only benign changes and post-biopsy sequelae, without residual disease.

Table 3
Histopatological results of the cleaning samples at VAE for DCIS and ADH and presence of malignant disease (residual DCIS or upgrade of ADH) at surgical excision.

VAE		Surgical excision		Total
Histology	CS status	Residual malignant disease/Upgrade (n = 5)	No malignant disease (n = 25)	
DCIS or ADH	Positive n = 9	4	5	9
	Negative n = 21	1	20	21

ADH, atypical ductal hyperplasia; CS, cleaning samples; DCIS, ductal carcinoma in situ.

patients with ADH have a 4-fold increased risk of breast cancer [40,41] and the long-term risk is higher for the affected breast but increased for both breasts [42]. In this scenario, VAE with cavity margins shaving technique can play a crucial role in reducing the diagnostic underestimation of biopsies and consequently avoid surgical excision in a group of patients with a generally increased risk of breast cancer (not only in the site of ADH excision).

Our study has a few limitations. First, it is a retrospective observational study and not a prospective study aimed to compare traditional VAE with VAE with cavity margins shaving technique. Second, the numbers of DCIS and ADH are small, so larger prospective studies are needed to assess the validity of our inferences. Larger prospective studies comparing "standard" VAE and VAE with "cavity margins shaving technique", with the experimental group focusing not only on the complete removal of the target microcalcifications (radiologic criterion) but also on the separate histopathological analysis of the CS (histologic criterion) will clarify if this technoque could help to significantly reduce undeestimation. Third, all our DCIS cases were Grade 1 or 2.

5. Conclusions

The "cavity margins shaving technique" goes beyond the limits of standard VAE because not only permits the evaluation of a greater amount of tissue but also allows both the radiological (throw the presence/absence of residual microcalcification at the post-biopsy mammogram) and the histological (throw the presence/absence of residual lesion in the CS) evaluation of the removal of target lesion. In this way, VAE with "cavity margins shaving technique" could represent a valuable alternative to surgical excision in selected patients (such as those with ADH or low-grade DCIS) who met the radiologic and histological criteria. By eliminating surgical excision for properly selected patients with ADH or low-grade DCIS, radiologists can play a crucial role to safely reduce patient distress, discomfort, and healthcare costs. Larger prospective studies are needed to assess the validity of our inferences and to definitely identify patients who could benefit from this technique to safely avoid surgery.

CRediT authorship contribution statement

Rossella Rella: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Giovanna Romanucci:** Validation, Data curation. **Paolo Belli:** Supervision. **Mariagrazia Ramunno:** Investigation. **Josè Nunnari:** Investigation. **Gianluca Russo:** Data curation. **Francesca Morciano:** Visualization, Data curation. **Sebastiano Croce:** Writing – review & editing, Data curation. **Lucrezia Papalia:** Data

curation. **Francesca Fornasa:** Writing – review & editing. **Oscar Tommasini:** Project administration. **Marco Conti:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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