ANTICANCER RESEARCH *40*: 1719-1729 (2020)
doi:10.21873/anticanres.14125

Evaluation of Ultrasound-guided 8-Gauge Vacuum-assisted Excision System for the Removal of US-detectable Breast Lesions

TOMMASO PERRETTA[1*], FELICIANA LAMACCHIA[1*], DONATELLA FERRARI[1*], EMANUELA BENINATI[1], FEDERICA DI TOSTO[1], VINCENZO DE STASIO[1], ROSARIA MEUCCI[1,2], CARLA DI STEFANO[1], ORESTE CLAUDIO BUONOMO[3], GIANLUCA VANNI[3] and CHIARA ADRIANA PISTOLESE[1]

[1]*Diagnostic Imaging Unit, Policlinico Tor Vergata, Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy;*
[2]*Applied Medical-Surgical Sciences, Tor Vergata University of Rome, Rome, Italy;*
[3]*Breast Unit-Department of Surgical Science, Policlinico Tor Vergata (PTV) University, Rome, Italy*

Abstract. *Aim: To assess the ability of ultrasound (US)-guided vacuum-assisted breast excision (VAE) to remove Breast Imaging Reporting and Data System (BI-RADS) ≥3 breast lesions in order to analyze US features most frequently associated with complete excision. Materials and Methods: A total of 266 BI-RADS ≥3 lesions without microcalcifications underwent US-VAE. US-VAE and gold standard pathological results were compared. US features of lesions were analyzed. Results: The complete excision rate was 93.61%; the VAE agreement rate was 99.62%. Circumscribed margins, regular shape, parallel orientation, and the absence of posterior features were favorable US features associated with complete excision. Lesions completely excised were: BI-RADS 3 ≤21.10 mm and BI-RADS 4 ≤18.70 mm with one unfavorable US characteristic, and BI-RADS 4 lesions ≤13.5 mm with two unfavorable US features hindered complete removal. Two atypical ductal hyperplasias (<10 mm, one unfavorable feature) and eight ductal carcinomas in situ (≤8.7 mm, one/two unfavorable features) were completely removed. Conclusion: US-VAE is highly accurate for diagnostic purpose and, in some cases, highly successful for complete lesion excision. This success also depends on the US characteristics and size of the lesion.*

*These Authors contributed equally to this study.

Correspondence to: Feliciana Lamacchia, MD, Department of Biomedicine and Prevention, UOC of Diagnostic Imaging, Tor Vergata University of Rome, Viale Oxford 81, 00133, Rome, Italy. Tel: +39 0620902400, e mail: lamacchia.feliciana@gmail.com

Key Words: Vacuum-assisted excision, vacuum-assisted breast biopsy, ultrasound, breast lesions, lesions of uncertain malignant potential, breast cancer.

The use of surgical excisional biopsy has been overtaken by needle biopsy and the introduction of the vacuum-assisted breast biopsy (VABB) system (1-3), in the mid 1990s (4). In the past few years several authors have shown a significant increase of diagnostic accuracy of VABB compared to fine-needle aspiration cytology (FNAC) and core needle biopsy (2, 5-8). Compared to conventional biopsy methods, the VABB system has several advantages, including the ability to acquire more samples with a single needle insertion, to obtain a more reliable histological diagnosis and more tissue (9, 10).

Its main use is sampling of benign or suspicious, clinically palpable or not palpable but imaging-detectable breast lesions, offering the advantage of complete removal of the lesion (11). In fact, it provides mammary tissue samples for histological examination, whilst also performing complete or partial removal of the breast lesion.

VABB can be performed under the guidance of different imaging modalities, in fact all VABB devices work according to the same suction mechanism principle and this system can be used under stereotactic, ultrasound (US) and magnetic resonance guidance.

One of the most common diagnostic indications for VABB are palpable or non-palpable lesions of Breast Imaging and Reporting Data System (BI-RADS) category 3 and 4 (12). US-VABB is often performed after inadequate or inconclusive FNAC, in cases of discrepancy between imaging and cytological/histological diagnosis after FNAC/core needle biopsy and for small breast lesions (<5 mm) (13-15). In addition, preoperative US-VABB system can be used for biopsy of the ducts beneath the nipple areola complex in women with invasive or *in situ* carcinoma requiring conservative mastectomy in order to determine if it is possible to save the nipple (16).

Excisional VABB, also known as vacuum-assisted excision (VAE), may be a better option for patients who have difficulty complying with follow-up (pregnant women, or women planning to undergo breast plastic surgery), patients with a lesion that changes in size or shape during the follow-up, extremely apprehensive patients, symptomatic patients, and patients with a family or personal history of breast cancer (17). VAE for therapeutic purposes includes treatment of fibroadenomas (18), nipple discharge (19), and B3 lesions (especially lesions such as flat epithelial atypia, classical lobular neoplasia, papillary lesions, and radial scars) (20, 21).

This system has gained popularity due to its high sensitivity and specificity, low costs, tolerability by patients and esthetic result of scars (22). The use of this system is not only able to reduce the need for open surgical biopsy or excision but can also minimize the costs of operating room or hospital admissions associated with surgical excision (11).

At our Institute, when VABB is required for a lesion with a maximum diameter of less than 25 mm, VAE is carried out with an 8-G needle; the VAE protocol is completed when there is no US evidence of the lesion at the end of the procedure. The 8-G needle can collect 250 to 310 mg of tissue, which is three times the amount collected using 11-G needles, and this makes them capable of resecting both palpable or non-palpable breast lesions that are smaller than 3 cm (23). However, limited data exist in the literature.

The purpose of our retrospective study was: i) To assess the ability of a US-guided 8-G VAE system to completely remove BI-RADS category ≥3 US-detectable breast mass lesions without microcalcifications; ii) to analyze which US features are most frequently associated with a complete excision; iii) to evaluate this system for diagnostic and therapeutic purposes.

Materials and Methods

This retrospective study was carried out at Tor Vergata University Hospital (Rome, Italy).

Study population. The study group consisted of 266 women with 266 recent-onset breast lesions, classified as BI-RADS category 3, 4 or 5, and who had undergone US-guided VAE at our Center in the period between March 2016 and March 2019.

Inclusion and exclusion criteria. All patients included in the study group were women with a BI-RADS category ≥3 US-detectable breast lesion, who completed the excisional protocol with no evidence of lesion at the end of the procedure, and who underwent surgery or US follow-up 6 months later at our Institute. Patients who did not undergo surgery at our Institute or were lost during US follow-up were excluded. Women with target lesions associated with a cluster of microcalcifications on mammography were also excluded, since it would not have been feasible to establish the complete excision of microcalcifications by US at the end of the procedure.

Management of BI-RADS category 3, 4, and 5 lesions. All BI-RADS 4 and 5 lesions required histological verification (unlike BI-RADS 3 lesions for which there were eventually reassuring instrumental findings and anamnestic data) received close instrumental follow-up (after 6 months, then every 6 and 12 months for 2 years). Once stability was demonstrated for at least 2 years, the lesion was downgraded to BI-RADS 2 (benign). Otherwise, if the lesion developed suspicious features, then it was upgraded to BI-RADS 4 or 5 and its modification represented an indication for histological characterization (12). Moreover, indications for VAE in those with BI-RADS 3 findings included lesions that patients wished to be removed (24).

US-VAE procedure. The procedure was performed in an ambulatory care setting by a radiologist with >10 years of experience in breast imaging and US-guided biopsy. All patients underwent appropriate coagulation tests before US-VAE and were asked to discontinue medications that would interfere with coagulation or clotting function for at least 1 week before biopsy. All patients gave their informed consent for the procedure. An US examination was performed 14 days after the biopsy, when patients came to get their biopsy results.

After disinfecting the area and administering local anesthetic (10 ml of lidocaine hydrochloride), a 5 mm skin incision was performed using a scalpel to guarantee appropriate access for the needle insertion. The excision was achieved using a Mammotome® vacuum-assisted system (Devicor Medical Products, Inc., Cincinnati, OH, USA), with an 8-G needle, under the guidance of high-resolution US equipment (MyLab™ 9 XP; Esaote SpA, Genoa, Italy, with 5-13 MHz linear array transducer and My LabTM Twice; Esaote SpA, Genoa, Italy with 10-13 MHz linear array transducer), obtaining a minimum of 12 samples, until there was no US evidence of the lesion. The procedure finished when evidence of complete resection under US was achieved, if no complication occurred. At the end of sampling, the operator released a magnetic resonance-compatible titanium clip. The average time required to perform US-VAE was 13 min (range=10-15 min). Thereafter, the biopsy site was compressed manually for at least 10 min until complete hemostasis. The incision site was closed with sterile adhesive skin closures and locoregional therapy with ice and antibiotic therapy were recommended.

Histopathological diagnosis. Histopathological results were classified into the five diagnostic categories stipulated by the Fourth Edition of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis (25) and correlated with US features of the lesions. Therefore, our histological results were classified into f: Unsatisfactory/normal breast tissue (B1), benign (B2), benign but of uncertain malignant potential (B3), suspicious of malignancy (B4), and malignant (B5). Finally, they were grouped into three categories: Benign (B1, B2), high risk (B3), and malignant including ductal carcinoma *in situ* (DCIS), and invasive cancer (B4 and B5, according to the histological report).

Post-VAE management. In the case of lesions found to be malignant at percutaneous biopsy (B4-B5), definitive surgery was performed. B3 lesions underwent surgical biopsy. When benign histological results at percutaneous biopsy (B2) agreed with the iconographic characteristics, US follow-up after 6 months was recommended.

Data analysis. We compared the pathological results of US-VAE with the gold standard results after surgery or follow-up. Gold standard results were considered the final pathological results after surgical excision for B3, B4 and B5 lesions, and US follow-up after 6 months for B2 lesions; no evidence of lesion recurrence or malignancy at US follow-up was considered as a benign gold standard result.

Subsequently, we calculated the high-risk underestimation rate, both for atypical ductal hyperplasia (ADH) and non-ADH high-risk lesions (when high-risk lesions diagnosed by VAE were upgraded to DCIS or invasive cancer after subsequent surgery); the DCIS underestimation rate (proportion of lesions diagnosed as DCIS by VAE that were upgraded to invasive carcinoma after surgical excision); the false-negative rate of US-guided VAE (the proportion of all invasive cancer and DCIS diagnosed by surgery or on follow-up biopsy, after a benign diagnosis on US-guided VAE); and the agreement rate (the proportion of lesions that were not classified as DCIS underestimation, high risk underestimation, or false-negative diagnosis). The malignancy rate after US-VAE and after surgery, the positive predictive value, and the negative predictive value of US-VAE were also analyzed. We evaluated US features of the lesions, including the echo pattern, circumscribed or not circumscribed margins, regular or irregular shape, parallel or not parallel orientation, presence and absence of posterior features, and maximum diameter.

Statistical analysis. The above-mentioned variables were statistically analyzed for association with complete removal of the lesion. Descriptive and comparative statistics were performed. Summary statistics were performed for the study population, using frequencies and percentages for categorical variables. Data are expressed as the mean±standard deviation for continuous variables. Statistical analysis was performed with the Fisher exact test for categorical variables. In the case of bivariate analysis between categorical and quantitative variables, the Student *t*-test was applied according to the normality conditions. A value of $p<0.05$ was considered statistically significant.

Results and Discussion

Study patients. Our study included 266 US-detectable breast masses without calcifications in 266 women (average age=38.70 years; range=19-69 years). All patients underwent US-VAE and completed the study protocol without US evidence of the lesion after the procedure.

Complications. Complications after VABB may include bleeding or pain during the procedure, as well as postoperative pain, hemorrhage, hematoma (23), vasovagal response (22) and infections.

None of the patients included in our study experienced significant complications after the procedure (infection or hematoma requiring aspiration). However, 20 patients reported post procedural pain the day after the VAE, resolved with paracetamol, and 17 patients reported hematoma <20 mm, demonstrated by US as a fluid cavity at the biopsy site, not requiring aspiration.

Table I. *Pathological classification of breast lesions after vacuum-assisted excision (VAE) (n= 266) and correlation with Breast Imaging and Reporting Data System (BI-RADS) (12).*

Pathological classification	No. of lesions after VAE*, n (%)	BI-RADS category, n		
		3	4	5
Benign lesions	182 (68.42%)	141	41	0
Fibroadenoma	119 (44.74%)	94	25	0
Fibrocystic disease	53 (19.92%)	41	12	0
Ductal epithelial hyperplasia	6 (2.26%)	6	0	0
Sclerosing adenosis	4 (1.50%)	0	4	0
High-risk lesions	63 (23.68%)*	31	32*	0
Papillary lesion	44 (16.54%)	25	19	0
Phyllodes tumor	9 (3.38%)	6	3	0
Atypical ductal hyperplasia	5 (1.88%)*	0	5*	0
Lobular intraepithelial neoplasia	2 (0.75%)	0	2	0
Flat epithelial atypia	2 (0.75%)	0	2	0
Radial scar	1 (0.38%)	0	1	0
Malignant lesions	21 (7.89%)*	1	17*	3
Ductal carcinoma *in situ*	14 (5.26%)*	1	13*	0
Invasive carcinoma	7 (2.63%)	0	4	3

*These are the histopathological results after VAE. Histopathological results changed slightly after surgery. One case of BI-RADS 4 atypical ductal hyperplasia was found to be ductal carcinoma *in situ* after surgery. Therefore, definitive histological results yielded atypical ductal hyperplasia in four patients (1.50%) and ductal carcinoma *in situ* in 15 (5.64%), for a total of 62 high-risk lesions (23.31%), and 22 malignant lesions (8.27%). Among BI-RADS 4 lesions, 31 were high-risk including four atypical ductal hyperplasia, 18 were malignant including 14 ductal carcinomas *in situ*.

BI-RADS category assessment and histological results after VAE. Breast lesions were classified as follows: 173 BI-RADS category 3, 90 BI-RADS category 4, three BI-RADS category 5.

After US-VAE, the pathological diagnosis was benign in 182 lesions (68.42%), high risk in 63 lesions (23.68%), and malignant in 21 lesions (7.89%), which were 14 DCISs (5.26%), and seven invasive cancers (2.26%). The pathological results of US-guided 8-G VAE are reported in Table I. The malignancy rate of all lesions submitted to US-VAE was 7.89% (n=21/266); in particular, a malignant outcome after VAE was observed in 1/173 (0.57%) BI-RADS 3, 17/90 (18.87%) BI-RADS 4 and 3/3 (100%) BI-RADS 5 findings.

Results of gold standard evaluation (open excision and 6-month US follow-up). Out of 266 breast findings, 182 benign lesions after VAE were referred for US follow-up, showing no evidence of lesion recurrence on US examination after 6 months (Figure 3); therefore, they were considered successfully removed (100% of benign lesions).

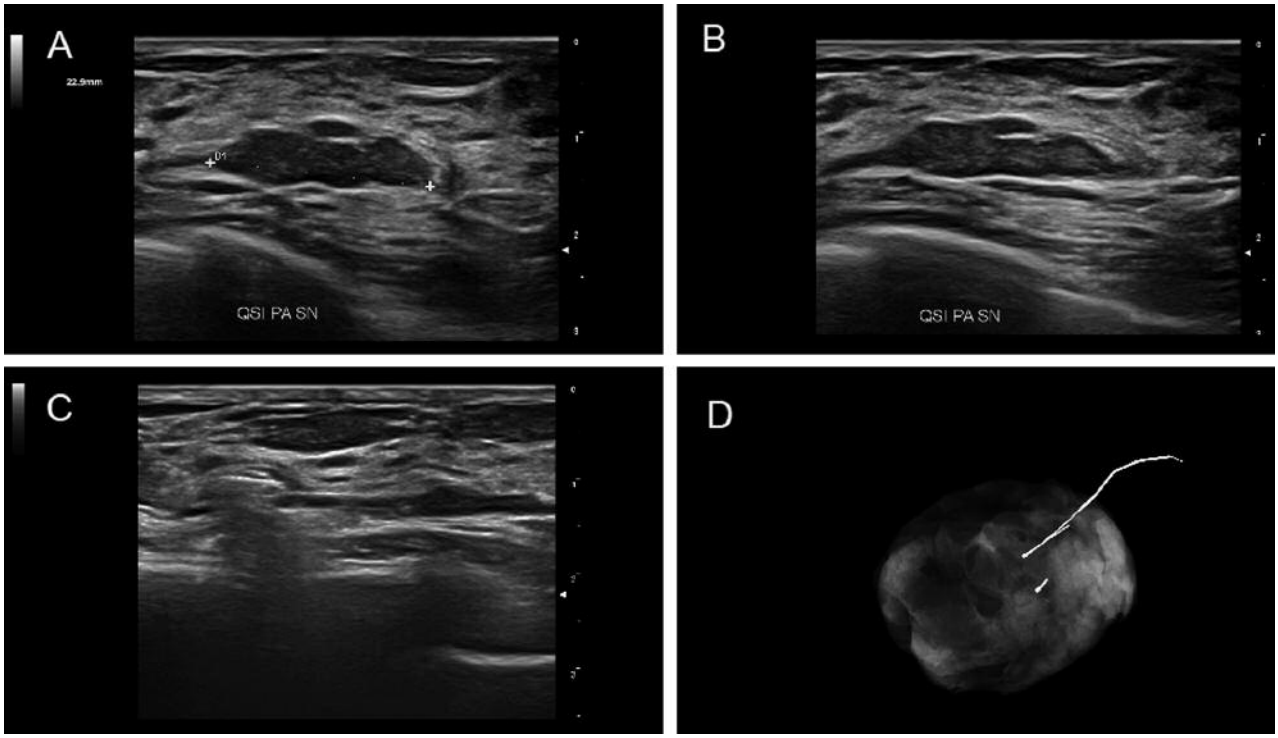

Figure 1. *Ultrasound (US) evaluation showed a solid hypoechoic lesion, 22.90 mm in maximum diameter, with regular shape, parallel orientation, no posterior features and circumscribed margins, classified as BI-RADS category 3 (A) and which underwent US-guided 8-G vacuum-assisted excision (B). At the end of the procedure the lesion appeared to have been completely removed and the metallic marker clip was released (C); the histological examination yielded a diagnosis of phyllodes tumor. X-Ray evaluation of the surgically resected specimen; (D) with residual lesion at histopathological analysis.*

After US-VAE, 63 high-risk lesions underwent surgery and in 93.65% of cases (n=59/63), the final pathological diagnosis revealed no evidence of the lesion removed by US-VAE, including two cases of ADH. In the remaining cases (6.35%; n=4/63) the lesions were not completely excised. In fact, after surgery, two cases of ADH were still present at the definitive histological report; moreover, a further case of not completely removed ADH was DCIS. In one case of phyllodes tumor, the largest lesion in our study, with a maximum diameter of 22.9 mm (BI-RADS category 3), a remnant was present after the excisional biopsy (Figure 1).

Lesions with a malignant outcome after US-VAE (n=21) underwent surgery: In two cases of invasive cancer after US-VAE, the final pathological diagnosis was DCIS, probably because the US-VAE removed the entire invasive cancer component; in eight cases of DCIS no malignancy was found after surgery, achieving complete excision of the malignant lesions (Figure 2); in the remaining malignant cases (n=11), there was no substantial change in the histological diagnosis established after VAE but the lesions were not completely removed (Table I). Therefore, among all malignant lesions (n=22), including the aforementioned DCIS that was underestimated as ADH after VAE, 36.36% (n=8 DCIS) were removed without remnant by US-VAE. Therefore, the gold standard evaluation revealed benign diagnoses for 182 lesions, high-risk pathology in 62, DCIS in 15, and invasive carcinoma in seven lesions, as shown in Table II. After gold standard evaluation, the malignancy rate of all lesions was 8.27% (n=22/266).

Gold standard results and VAE evaluation. The rate of completely removed lesions with US-guided 8-G VABB was very high at 93.61% (n=249/266): 99.42% for BI-RADS 3 (n=172/173) and 85.56% (n=77/90) for BI-RADS 4 findings. A complete removal was achieved in 100% (n=182/182) of benign lesions, 95.16% (n=59/62) of high-risk lesions, and 36.36% (n=8/22) of malignant lesions. The rate of residual lesions after VAE was 6.39% (n=17/266): 0.57% (n=1/173) for BI-RADS 3, 14.44% (n=13/90) for BI-RADS 4, and 100.00% (n=3/3) for BI-RADS 5.

Lesions with remnant after US-VAE were high=risk lesions in 17.65% (n=3/17), and malignant lesions in 82.35% (n=14/17). The false-negative rate was 0: No benign pathological diagnosis at VAE turned out to be malignant. The high-risk underestimation rate of US-VAE was 1.59% (1/63), while the ADH underestimation rate was 20.0% (1/5).

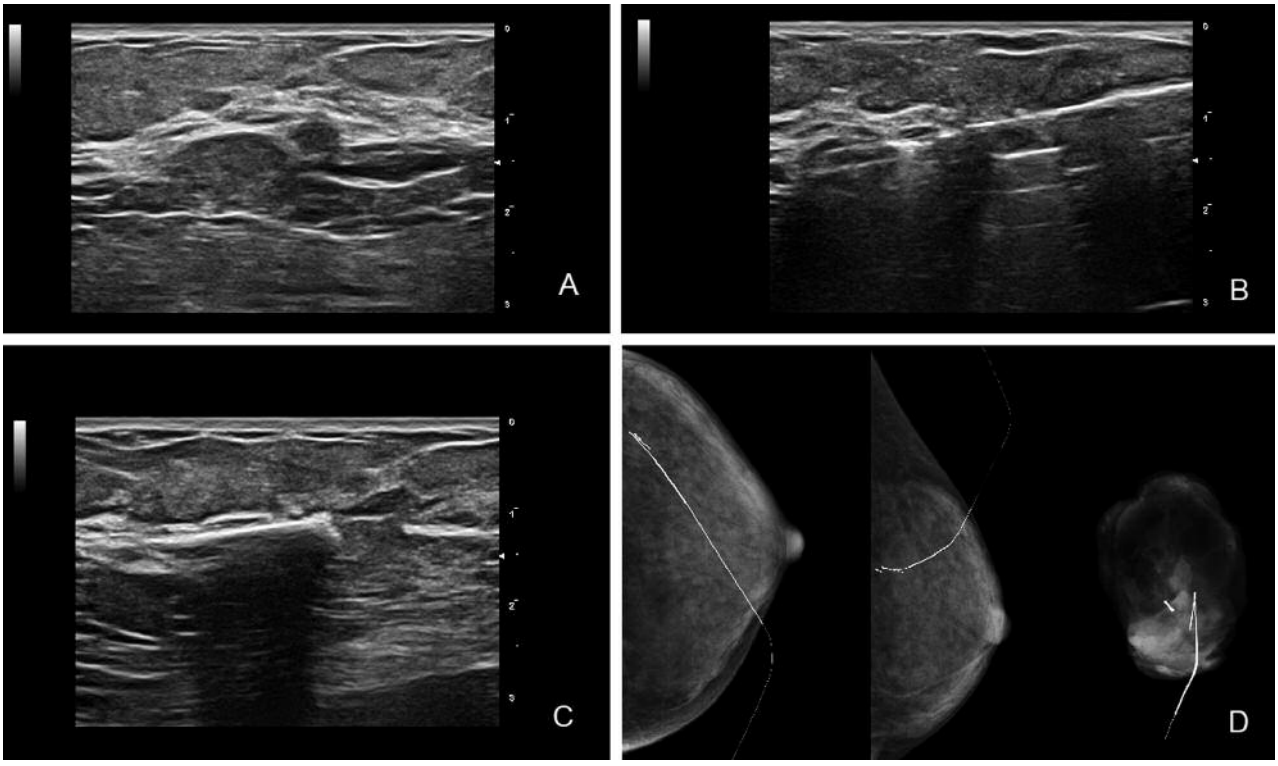

Figure 2. *Ultrasound (US) evaluation showed a solid hypoechoic lesion, with regular shape, parallel orientation, no posterior features and no circumscribed margin, classified as BI-RADS category 4 (A) which underwent US-guided 8-G vacuum-assisted excision (B). At the end of the procedure the lesion appeared to have been completely removed and the metallic marker clip was released (C); the histological examination yielded diagnosis of a ductal carcinoma in situ. Cranio-caudal and medio-lateral projections of the upper outer quadrant of the left breast: the metallic landmark was placed in the area previously subjected to vacuum-assisted excision; X-Ray evaluation of the surgical resected specimen, without residual lesion at histopathological analysis (D).*

Table II. *Comparison of pathological results of 266 ultrasound-guided vacuum-assisted excisions (US-VAE) with gold standard diagnosis (surgery for high-risk and malignant lesions; 6-12 months ultrasound follow-up for benign lesions).*

Histological result after US-VAE, n	Gold standard, n			
	Benign lesion	High-risk lesion	Invasive carcinoma	Ductal carcinoma *in situ*
Invasive carcinoma	0	0	7	0
Ductal carcinoma *in situ*	0	0	0	14
High-risk lesion	0	62	0	1
Benign	182	0	0	0

The non-ADH high-risk lesion underestimation rate and the DCIS underestimation rate were both 0. Finally, the agreement rate was 99.62% (n=265/266), the positive-predictive value of US-VAE was 100%, and the negative-predictive value of US-VAE was 99.59%.

This greater success of excision is most likely attributed to several factors, including the exclusive use of the 8-G device (26) and the experience of the operators. Therapeutic VABB for complete excision of palpable breast lesions or conducted due to the patient's desire to remove a breast lesion seems to be a suitable method that is safe and effective (24). Some authors reported that after removal of US evidence of breast lesions with a 11-G VABB device, there was a substantial probability that the residual lesion, which was not visualized during the procedure, would later be found at surgery or follow-up imaging (27). On the contrary, we demonstrated that in most cases, complete lesion removal is feasible, probably thanks to the use of a larger needle as well as the operator's

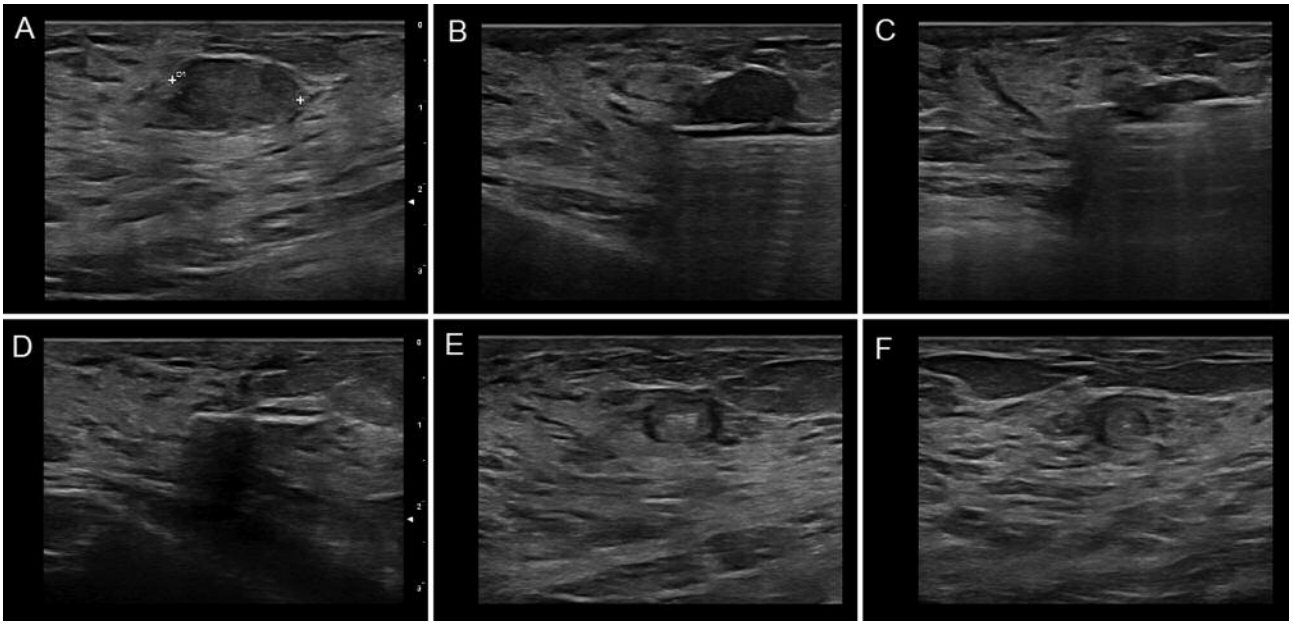

Figure 3. *Ultrasound (US) evaluation showed a solid hypoechoic lesion, with regular shape, parallel orientation, no posterior features and no circumscribed margin, classified as BI-RADS category 3 (A) which underwent US-guided 8-G vacuum-assisted excision (B and C). At the end of the procedure, the lesion appeared to have been completely removed and the metallic marker clip was released (D); the histological examination yielded fibroadenoma. Axial (E) and longitudinal (F) US scans after 12 months follow-up showed the presence of the metallic clip with adjacent tissue reaction, without any solid lesions.*

experience. The use of US-VAE varies between Institutes, our Center has subspecialized breast imaging radiologists with long-term experience with US-VABB. The high concordance between the final pathological diagnosis and the histological results of US-VAE allows us to state that this procedure is associated with a very low risk of underestimating B3 lesions. In fact, in our series, no non-ADH lesion was underestimated and almost all were successfully removed, as confirmed by surgery. In line with the recent (2018) "Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions)", for the treatment of B3 lesions with classical lobular neoplasia, flat epithelial atypia, radial scar, and papillary lesion type (21), the statistical analysis of our data demonstrated that it was possible to therapeutically excise these lesions by VABB instead of open surgery. On the other hand, ADH lesions are usually removed by open surgery because of the lack of sufficient evidence on whether they are suitable for VAE . The ADH underestimation rate of US-VAE in our study was 20.0% (1/5), still suggesting that histological underestimation after US-VAE should be considered for this subtype of lesion.

Statistical analysis of US features. Among the 266 lesions, those presenting a remnant after gold standard evaluation (n=17) were significantly larger than those completely removed by VAE (n=249) (maximum diameter=15.89±3.78 mm, range=7.10-22.90 mm, and 13.21±3.82 mm, range=5.20-21.10 mm, respectively; p=0.0055). This shows that a lesion's dimensions play an important role in achieving its complete excision.

All lesions in our study group had a hypoechoic echo pattern, the other US features are pointed out in Table III. Comparing all successfully removed and all not completely removed lesions, statistically significant factors associated with a complete excision included circumscribed margins (p<0.001), regular shape (p<0.001), parallel orientation (p<0.001), and the absence of posterior features (p<0.001) (Table IV). Therefore, these characteristics were considered favorable for complete lesion removal. On the contrary, not circumscribed margins, irregular shape, not parallel orientation, and the presence of posterior features were considered unfavorable for a complete excision.

BI-RADS category 3 findings have all the aforementioned US-favorable characteristics for achieving complete excision with US-guided 8-G VABB. The mean maximum diameter of successfully excised BI-RADS 3 lesions (n=172/173; 99.42%) was 14.05±3.68 mm (range=5.60-21.10 mm). In our series, almost all BI-RADS 3 lesions were successfully removed; in fact, only one BI-RADS 3 lesion with a maximum diameter of 22.90 mm was not completely excised, and it was the largest lesion in our dataset. Therefore, in our experience, it was possible to successfully remove BI-RADS 3 lesions with a maximum diameter up to 21.10 mm.

Table III. *Correlation between Breast Imaging and Reporting Data System (BI-RADS) (12) category, ultrasound features, definitive histological result and complete or not complete ultrasound-guided vacuum-assisted excision of 266 breast mass lesions.*

BI-RADS category	Ultrasound features	Definitive histological result	Completely removed, n (%)	Not completely removed, n (%)
BI-RADS 3 (n=173)	Regular shape, circumscribed margins, parallel orientation and not posterior features (n=173)	Fibroadenoma	94 (100%)	0
		Fibrocystic disease	41 (100%)	0
		Ductal epithelial hyperplasia	6 (100%)	0
		Papillary lesion	25 (100%)	0
		Phyllodes tumor	5 (83.33%)	1 (16.67%)
		Ductal carcinoma *in situ*	1 (100%)	0
BI-RADS 4 (n=90)	Circumscribed margins, regular shape, not parallel orientation and not posterior features (n=26)	Fibroadenoma	20 (100%)	0
		Papillary lesion	6 (100%)	0
	Circumscribed margins, irregular shape, parallel orientation and not posterior features (n=24)	Fibroadenoma	5 (100%)	0
		Fibrocystic disease	7 (100%)	0
		Papillary lesion	10 (100%)	0
		Atypical ductal hyperplasia	1 (100%)	0
		Ductal carcinoma *in situ*	1 (100%)	0
	Circumscribed margins, irregular shape, not parallel orientation and not posterior features (n=8)	Sclerosing adenosis	2 (100%)	0
		Radial scar	1 (100%)	0
		Ductal carcinoma *in situ*	0	3 (100%)
		Invasive carcinoma	0	2 (100%)
	Not circumscribed margins, regular shape, parallel orientation and not posterior features (n=18)	Fibrocystic disease	5 (100%)	0
		Papillary lesion	1 (100%)	0
		Phyllodes tumor	3 (100%)	0
		Atypical ductal hyperplasia	1 (100%)	0
		Lobular intraepithelial neoplasia	2 (100%)	0
		Flat epithelial atypia	2 (100%)	0
		Ductal carcinoma *in situ*	4 (100%)	0
	Not circumscribed margins, irregular shape, parallel orientation and not posterior features (n=11)	Papillary lesion	1 (100%)	0
		Sclerosing adenosis	2 (100%)	0
		Atypical ductal hyperplasia	0	2 (100%)
		Ductal carcinoma *in situ*	2 (40.00%)	3 (60.00%)
		Invasive carcinoma	0	1 (100%)
	Not circumscribed margins, regular shape, not parallel orientation and not posterior features (n=3)	Papillary lesion	1 (100%)	0
		Ductal carcinoma *in situ*	0	1 (100%)
		Invasive carcinoma	0	1 (100%)
BI-RADS 5 (n=3)	Not circumscribed margins, irregular shape, not parallel orientation and not posterior features (n=1)	Invasive carcinoma	0	1 (100%)
	Not circumscribed margins, irregular shape, not parallel orientation and posterior features (n=2)	Invasive carcinoma	0	2 (100%)

US features of BI-RADS category 4 findings are recorded in Table III. No BI-RADS 4 lesion had posterior features. Among BI-RADS 4 lesions (n=90), all those with one unfavorable US feature (n=68) and 40.91% (n=9/22) of those with two unfavorable US features were completely removed; in contrast, all BI-RADS 4 lesions showing a remnant after gold standard evaluation (n=13) had two unfavorable US characteristics ($p<0.001$). Hence, the presence of only one unfavorable characteristic allows complete excision for BI-RADS 4 lesions, therefore, it is more likely that breast lesions without calcification with only one unfavorable US feature can be successfully removed than those with two.

BI-RADS 4 lesions completely excised (n=77) had a shorter mean maximum diameter than those not completely removed (n=13) [11.33±3.45 mm (range=5.20-18.70 mm) *vs.* 16.82±2.02 mm (range=14.30-21.10 mm), respectively] and this difference was statistically significant ($p<0.001$). In particular, all BI-RADS 4 findings with one unfavorable US feature were completely excised and they presented a mean maximum diameter of 11.32±3.7 mm (range=5.20-8.70 mm). Moreover, out of all BI-RADS 4 findings with two unfavorable features, lesions with a remnant after VAE (n=13) had a statistically significantly larger maximum diameter compared to those completely removed (n=9)

Table IV. *Ultrasound features of lesions completely removed by vacuum-assisted breast excision and statistically analyzed (p<0.05 considered statistically significant). The percentage refers to the number of lesions with the specific variable that were completely removed at gold standard examination.*

Ultrasound variable	All lesions		Benign lesions		High-risk lesions		Malignant lesions	
	Removed, n/N (%)	*p*-Value	Removed, n/N (%)	*p*-Value	Removed, n/N (%)	*p*-Value	Removed, n/N (%)	*p*-Value
Circumscribed margins	225/229 (98.25%)	<0.001	173/173 (100%)	>0.99	48/49 (98.00%)	0.1086	1/6 (16.67%)	0.3512
Not circumscribed margins	24/37 (64.86%)		7/7 (100%)		11/13 (84.62%)		7/16 (43.75%)	
Regular shape	217/220 (98.63%)	<0.001	166/166 (100%)	>0.99	46/47 (97.87%)	0.1425	6/8 (75.00%)	0.0083
Irregular shape	32/46 (69.57%)		14/14 (100%)		13/15 (86.67%)		2/14 (14.29%)	
Parallel orientation	219/225 (97.33%)	<0.001	160/160 (100%)	>0.99	51/54 (94.44%)	>0.99	8/12 (66.67%)	0.0017
Not parallel orientation	30/41 (73.17%)		20/20 (100%)		8/8 (100%)		0/10 (0%)	
Posterior features	0/2 (0%)	<0.001	0	>0.99	0	>0.99	0/2 (0%)	0.5152
Not posterior features	249/264 (94.32%)		180/180 (100%)		59/62 (95.16%)		8/20 (40.00%)	

[16.82±2.02 mm (range=14.30-21.00 mm) *vs.* 11.43±2.35 mm (range=6.10-13.50 mm), respectively; $p<0.001$]. Based on our experience, BI-RADS 4 lesions with only one unfavorable characteristic among not circumscribed margins, irregular shape, and not parallel orientation and with a maximum diameter up to 18.70 mm were completely removed. Similarly, two unfavorable US features in BI-RADS 4 lesions with a maximum diameter up to 13.5 mm allowed removal without remnant. As can be seen from our results, BI-RADS 4 lesions with two unfavorable US features and a maximum diameter ≤13.50 mm were successfully removed, in fact, all the lesions larger than 13.5 mm had a remnant at the gold standard evaluation.

These results, from the imaging point of view, underline that the success of complete removal with VAE also depends on both the US characteristics and the size of the lesions, and that both these features should be taken into consideration in the use of US-VAE for therapeutic purposes.

Finally, BI-RADS category 5 findings included in our study (n=3) had more than two unfavorable US features, as reported in Table III, and an average maximum diameter of 9.57±1.77 mm (range=7.10-11.20 mm); the final diagnosis yielded invasive cancer in all three cases. No lesion with more than two unfavorable US features, was successfully excised; in contrast, 94.68% of lesions with two or fewer unfavorable US characteristics (n=249) were completely removed ($p=0.002$). Thus, from our data, it seems that the presence of more than two unfavorable US features strongly hinder complete excision with US-guided 8-G VABB.

Statistical analysis by definitive histological outcome. All benign lesions were successfully removed (141 BI-RADS 3 and 41 BI-RADS 4), as shown in Tables II and III. Among 182 benign lesions, 65.38% (n=119) were fibroadenomas, which usually appeared as solid lesions with regular shape, circumscribed margins and a parallel orientation, without posterior features. In our study, all lesions with a maximum diameter of less than 22.9 mm and the abovementioned characteristics were successfully removed. Breast fibroadenoma is an extremely common problem in young women, usually demonstrated as a palpable mass. After establishing a confident diagnosis, the patient is offered either surgical removal or conservative management with a close follow-up. Often in daily practice, solitary fibroadenomas in young females are surgically removed, principally to alleviate patient anxiety and because of patient lack of compliance with surveillance examinations or because of the extremely remote possibility of missing malignant transformation (28). In these patients, US-VABB using an 8-G needle represents an indispensable and conclusive diagnostic and therapeutic approach, allowing complete evaluation of the excised lesion, on the basis of ultrastructural, immunohistochemical and biochemical parameters. Most patients preferred the minimally invasive approach of US-VAE rather than surgery because they were able to have a definitive diagnosis and, in selected cases, removal of the lesion without undergoing surgery, in one session, reducing in this way the anxiety of needing a lesion to be monitored over time. Another advantage of the VAE procedure is a better esthetic result than surgery, in fact, the skin incision is only a few millimeters and the patients do not report evident scars.

At definitive histological evaluation, high-risk lesions (n=62) comprised 31 BI-RADS 3 and 31 BI-RADS 4. Out of 31 BI-RADS 3 high-risk lesions, 30 (96.77 %) were successfully removed (mean maximum diameter=15.11±2.18 mm; range=11.6-19.4 mm); the only one not totally removed was the largest lesion of our cohort, as previously reported, which was a phyllodes tumor. Among BI-RADS 4 high-risk lesions, all of those with one unfavorable feature (n=26) were successfully removed compared with 60.00% of those with two unfavorable characteristics (n=3/5) ($p=0.0215$)

(Table III). In detail, two high-risk lesions, with two unfavorable characteristics, showing a remnant after surgery were ADHs; in contrast, both ADH lesions with one unfavorable US feature were completely removed. However, this difference was not statistically significant (p=0.3333). In ADH lesions, a statistically significant difference was observed in maximum diameter: the completely removed ADHs were considerably smaller than those not removed, with a maximum diameter <10 mm [9.45±0.25 mm (range=9.20-9.70 mm) *vs*. 20.75±0.35 mm (range=21.00-20.40 mm)]. Finally, one BI-RADS 4 lesion with two unfavorable features, a maximum diameter of 14.30 mm and a final report of AHD after VAE, was found to be DCIS after surgical excision. Therefore, small ADH masses, without microcalcifications, with a maximum diameter <10 mm and only one unfavorable characteristic were successfully removed by US-guided 8-G VABB, according to our results.

Malignant lesions after surgery comprised one BI-RADS 3, 18 BI-RARD 4 and three BI-RADS 5. US features of malignant lesions are recorded in Table III. Successfully excised malignant lesions (n=8) were assigned BI-RADS category 3 in one case and BI-RADS category 4 in seven. All malignant findings completely removed were DCIS after histological analysis and none was invasive cancer (p=0.0225). Regular shape and parallel orientation were statistically significantly associated with complete removal of malignant lesions, in fact lesions completely removed had a regular shape in 75% of cases and parallel orientation in 66.67% of cases (p=0.0083 and p=0.0017, respectively), as summarized in Table IV. The BI-RADS 3 malignant lesion removed without remnant was 6.90 mm in maximum diameter and had all the favorable US features for achieving a complete excision. Moreover, all BI-RADS 4 malignant lesions with one unfavorable US feature (n=5) were removed with success, whereas only 15.38% (n=2/13) of BI-RADS 4 malignant lesions with two unfavorable US features were excised without remnant (p=0.0025). The average maximum diameter of completely and not completely removed malignant lesions were 6.55±1.11 mm (range=5.20-8.70 mm) and 14.71±3.02 mm (range=7.10-18.20 mm), respectively (p<0.001). Considering all DCIS, BI-RADS 4 lesions (with one or two unfavorable US features) (n=14), seven with a mean maximum diameter of 6.50±1.18 mm (range=5.20-8.70 mm) were completely excised, whereas seven with a mean maximum diameter of 16.70±1.08 mm (range=14.70-18.20 mm) had a remnant after surgery (p<0.001). Moreover, among DCIS BI-RADS 4 lesions with two unfavorable characteristics, those successfully removed (n=2) had an average diameter of 5.45±0.25 mm (range=5.20-5.70 mm), but those not completely excised had a greater average diameter of 16.70±1.08 mm (range=14.70-18.20 mm) (p<0.001).

It was observed that we were able to completely excise all DCIS <10 mm (n=8) but none >10 mm (n=7) (p<0.001).

In malignant cases, the diagnosis after VAE was accurate; in fact, only one case of DCIS was underestimated as ADH. Moreover, in two cases of invasive carcinoma, the infiltrating part was removed by VAE and only the DCIS component remained. Our data highlight an important result: the complete non-surgical excision of DCIS without microcalcifications with large core US-guided VABB. This study showed that it was possible, in some selected cases, to use the 8-G VABB procedure to remove small BI-RADS category 3 or 4 DCIS, with a maximum diameter of 8.7 mm or less, a hypoechoic echo pattern, parallel orientation, no posterior features, even if with both irregular shape and non-circumscribed margins. However, in our cases, regular shape and parallel orientation were statistically significant factors associated with complete excision of malignancy. Moreover, a smaller maximum diameter was relevant for the successfully excision of DCIS with two unfavorable US features. The possibility of removing selected DCIS with certain characteristics might be of great relevance in the narrow category of patients refusing surgery. Nevertheless, our cohort was too small to be able to make exact statistical deductions in this regard and further studies with a greater study population are required.

Study limitations. There are some limitations to our study: First of all, the small cohort and the retrospective nature of the study. Another limitation is that women with a benign histological diagnosis were assigned to US follow-up and only the check up after 6 months were considered, furthermore, the complete excision or the lesion was assessed only by US examination and not histologically.

Conclusion

US-guided 8-G VABB is highly accurate for diagnostic purposes for BI-RADS category 3 or higher lesions without microcalcifications and, in some cases, highly successful for complete excision. US features might be predictors of a successfully complete excision. The success of a complete removal with VAE also depends on both the US characteristics and lesion size, and both these features should be taken into consideration in the use of US-VAE for therapeutic purposes. Moreover, the presence of more than two unfavorable US features may strongly hinder complete excision. In our experience, it was not possible to completely remove BI-RADS category 5 lesions. Therefore, when a breast lesion is visible by US, we believe that the 8-G US-VABB system is the optimal tool both for accurate diagnosis of suspicious findings and for complete excision of benign lesions, in patients who wish them to be removed, and of some subtypes of high-risk lesions (such as lobular neoplasia, flat epithelial atypia, radial scars and papillary lesions) avoiding unnecessary surgery, risks associated with

it, and reducing healthcare costs. Moreover, selected ADH and DCIS might be successfully removed without leaving any remnant and this could be of great relevance for a narrow category of patients refusing surgery. However, further studies are required in this regard.

Conflicts of Interest

None to be declared.

Authors' Contributions

Tommaso Perretta performed VAE, conceived the original idea and supervised the project. Feliciana Lamacchia performed the statistical analysis and wrote the Results and Discussion. Donatella Ferrari and Federica Di Tosto collected the data. Donatella Ferrari designed the figures. Vincenzo De Stasio wrote the Materials and Methods. Emanuela Beninati wrote the Introduction. Rosaria Meucci and Carla Di Stefano aided in interpreting the results. Oreste Claudio Buonomo and Gianluca Vanni operated on the patients who underwent surgery. Chiara Adriana Pistolese is the Head of the Breast Radiology Department and gave her support in supervising the project. All Authors discussed the results and contributed to the final article.

Acknowledgements

This study was in part supported by a grant from the Italian Ministry of Health.

References

1 Meyer JE, Smith DN, Lester SC Kaelin C, DiPiro PJ, Denison CM, Christian RL, Harvey SC, Selland DL and Durfee SM: Large core needle biopsy of nonpalpable breast lesions. JAMA *281(17)*: 1638-1641, 1999. PMID: 10235159. DOI: 10.1001/jama.281.17.1638

2 Zannis VJ and Aliano KM: The evolving practice pattern of the breast surgeon with disappearance of open biopsy for nonpalpable lesions. AM J Surg *176(6)*: 525-528, 1998. PMID: 9926783. DOI: 10.1016/s0002-9610(98)00265-7

3 Abbate F, Cassano E, Menna S and Viale G: Ultrasound-guided vacuum-assisted breast biopsy: Use at the European Institute of Oncology in 2010. J Ultrasound *14(4)*: 177-181, 2011. PMID: 23397003. DOI: 10.1016/j.jus.2011.10.003

4 Burbank F, Parker SH and Fogarty TJ: Stereotactic breast biopsy: Improved tissue harvesting with the mammotome. Am Surg *62(9)*: 738-744, 1996. PMID: 8751765.

5 Yu YH, Liang C and Yuan XZ: Diagnostic value of vacuum-assisted breast biopsy for breast carcinoma: A meta analysis and systematic review. Breast Cancer Res Treat *120(2)*: 469-479, 2010. PMID: 20130983. DOI: 10.1007/s10549-010-0750-1

6 Hopper K, Baird D, Reddy V, Landis JR, Parker SH, Tyler HN, Jr, Ownbey JL, McCauslin MA, Yakes WF and Sabatelli FW: Efficacy of automated biopsy guns *versus* conventional biopsy needles in the pygmy pig. Radiology *176(3)*: 671-676, 1990. PMID: 2389024. DOI: 10.1148/radiology.176.3.2389024

7 Verkooijen HM, BorelRinkes IH, Peeters PH, Landheer ML, Van Es NJ, Mali WP, Klinkenbijl JH and van Vroonhoven TJ: Impact of stereotactic large core needle biopsy on diagnosis and surgical treatment of nonpalpable breast cancer. Eur J Surg Oncol *27(3)*: 244-249, 2001. PMID: 11393185. DOI: 10.1053/ejso.2000.1102

8 Povoski SP, Jimenez RE and Wang WP: Ultrasound-guided diagnostic breast biopsy methodology: Retrospective comparison of the 8-gauge vacuum-assisted biopsy approach *versus* the spring-loaded 14-gauge core biopsy approach. World J Surg Oncol *9*: 87, 2011. PMID: 21835024. DOI: 10.1186/1477-7819-9-87

9 Jackman RJ, Marzoni Jr FA and Rosenberg J: False negative diagnoses at stereotactic vacuum-assisted needle breast biopsy; Long-term follow--up of 1,280 lesions and review of the literature. Am J Roentgenol *192(2)*: 341-351, 2009. PMID: 19155393. DOI: 10.2214/AJR.08.1127

10 Jackman RJ, Burbank F, Parker SH, Evans WP III, Lechner MC, Richardson TR, Smid AA, Borofsky HB, Lee CH, Goldstein HM, Schilling KJ, Wray AB, Brem RF, Helbich TH, Lehrer DE and Adler SJ: Stereotactic breast biopsy of nonpalpable lesions: Determinants of ductal carcinoma *in situ* underestimation rates. Radiology *218(2)*: 497-502, 2001. PMID: 11161168. DOI: 10.1148/radiology.218.2.r01fe35497

11 Lui CY and Lam HS: Review of ultrasound-guided vacuum-assisted breast biopsy: Techniques and applications. J Med Ultrasound *18(1)*: 1-1, 2010. DOI: 10.1016/S0929-6441(10)60001-X

12 D'Orsi CJ, Sickles EA, Mendelson EB and Morris EA: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology, 2013.

13 Hahn M, Krainick-Strobel U, Toellner T, Gissler J, Kluge S, Krapfl E, Gissler J, Kluge S, Krapfl E, Peisker U, Duda V, Degenhardt F, Sinn HP, Wallwiener D and Gruber IV: Interdisciplinary consensus recommendations for the use of vacuum- assisted breast biopsy under sonographic guidance: First update 2012. Ultraschall Med *33(4)*: 366-371, 2012. PMID: 22723042. DOI: 10.1055/s-0032-1312831

14 Carder PJ and Liston JC: Will the spectrum of lesions prompting a "B3" breast core biopsy increase the benign biopsy rate? J Clin Pathol *56(2)*: 133-138, 2003. PMID: 12560393. DOI: 10.1136/jcp.56.2.133

15 Sebag P, Tourasse C, Rouyer N, Lebas P, Denier JF and Michenet P: Value of vacuum-assisted biopsies under sonography guidance: Results from a multicentric study of 650 lesions. J Radiol *87(1)*: 29-34, 2006. PMID: 16415777. DOI: 10.1016/s0221-0363(06)73966-x

16 Govindarajulu S, Narreddy S, Shere MH, Ibrahim NB, Sahu AK and Cawthorn SJ: Preoperative mammotome biopsy of ducts beneath the nipple areola complex. Eur J Surg Oncol *32(4)*: 410-412, 2006. PMID: 16516432. DOI: 10.1016/j.ejso.2006.01.013

17 Fine RE, Israel PZ, Walker LC, Corgan KR, Greenwald LV, Berenson JE, Boyd BA, Oliver MK, McClure T and Elberfeld J: A prospective study of the removal rate of imaged breast lesions by an 11-gauge vacuum-assisted biopsy probe system. Am J Surg *182(4)*: 335-340, 2001. PMID: 11720666. DOI: 10.1016/s0002-9610(01)00723-1

18 NHS National Institute for Health and Clinical Excellence: Image-guided Vacuum-assisted Excision Biopsy of Benign Breast Lesions. London, 2006. Available at: https://www.nice.org.uk/guidance/ipg156

19 Bonaventure T, Cormier B, Lebas P, Bonneau C and Michenet P: Benign papilloma: Is US-guided vacuum-assisted breast biopsy an alternative to surgical biopsy? J Radiol *88(9 Pt 1)*: 1165-1168, 2007. PMID: 17878878. DOI: 10.1016/s0221 0363(07)89928-8

20 Tennant SL, Evans A, Hamilton LJ, James J, Lee AH, Hodi Z, Ellis IO, Rakha EA and Wilson AR: Vacuum-assisted excision of breast lesions of uncertain malignant potential (B3) – an alternative to surgery in selected cases. Breast *17*: 546-549, 2008. PMID: 18829318. DOI: 10.1016/j.breast.2008.08.005

21 Rageth CJ, O'Flynn EAM , Pinker K, Kubik-Huch RA, Mundinger A, Decker T, Tausch C, Dammann F, Baltzer PA, Fallenberg EM, Foschini MP, Dellas S, Knauer M, Malhaire C, Sonnenschein M, Boos A, Morris E and Varga Z: Second international consensus conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast Cancer Res Treat *174(2)*: 279-296, 2019. PMID: 30506111. DOI: 10.1007/s10549-018-05071-1

22 Simon JR, Kalbhen CL, Cooper RA, and Flisak ME: Accuracy and complication rates of US-guided vacuum-assisted core breast biopsy: Initial results. Radiology *215(3)*: 694-697, 2000. PMID: 10831686. DOI: 10.1148/radiology.215.3.r00jn37694

23 Park HL and Hong J: Vacuum-assisted breast biopsy for breast cancer. Gland Surgery *3(2)*: 120-127, 2014. PMID: 25083505. DOI: 10.3978/j.issn.2227-684X.2014.02.03

24 Lee SH, Kim EK, Kim MJ, Moon HJ and Yoon JH: Vacuum-assisted breast biopsy under ultrasonographic guidance: Analysis of a 10-year experience. Ultrasonography *33(4)*: 259-266, 2014. PMID: 25036755. DOI: 10.14366/usg.14020

25 Perry N, Broeders M, de Wolf C, Törnberg S, Holland R and Von Karsa L: European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth Edition. Ann Oncol *19(4)*: 614-622, 2008. PMID: 18024988. DOI: 10.1093/annonc/mdm481

26 Povoski SP and Jimenez RE: A Comprehensive evaluation of the 8-gauge vacuum-assisted Mammotome® system for ultrasound-guided diagnostic biopsy and selective excision of breast lesions. World J Surg Oncol *5*: 83, 2007. PMID: 17663769. DOI: 10.1186/1477-7819-5-83

27 March DE, Coughlin BF, Barham RB, Goulart RA, Klein SV, Bur ME, Frank JL and Makari-Judson G: Breast masses: Removal of all US evidence during biopsy by using a handheld vacuum-assisted device – initial experience 1. Radiology *227(2)*: 549–555, 2003. PMID: 12676972. DOI: 10.1148/radiol.2272020476

28 Sperber F, Blank A, Metser U, Flusser G, Klausner JM and Lev-Chelouche D: Diagnosis and treatment of breast fibroadenomas by ultrasound-guided vacuum-assisted biopsy. Arch Surg *138(7)*: 796-800, 2003. PMID: 12860764. DOI: 10.1001/archsurg.138.7.796

Received January 12, 2020
Revised January 28, 2020
Accepted February 3, 2020