Stereotactic vacuum-assisted biopsy (SVAB) of Nonpalpable Breast Microcalcifications: Advantage of clip placement (Prospective study)

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Faculty of Medicine, University of Ulm

Presented by
Liu Fang
Wuhan, P. R. China
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Amtierender Dekan: Prof. Dr. med. Klaus-Michael Debatin
Berichterstatter: PD Dr. med. Roman Sokiranski
Berichterstatter: Prof. Dr. med. Wolfgang Pirsig
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For my Family
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<th>Description</th>
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<tr>
<td>ADH</td>
<td>atypical ductal hyperplasia</td>
</tr>
<tr>
<td>BI-RADS</td>
<td>breast imaging reporting and data system</td>
</tr>
<tr>
<td>CC</td>
<td>craniocaudal</td>
</tr>
<tr>
<td>CNB</td>
<td>core needle biopsy</td>
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<tr>
<td>DCIS</td>
<td>ductal carcinoma in situ</td>
</tr>
<tr>
<td>FN</td>
<td>false negative</td>
</tr>
<tr>
<td>FP</td>
<td>false positive</td>
</tr>
<tr>
<td>LN</td>
<td>lobular neoplasia</td>
</tr>
<tr>
<td>ML</td>
<td>mediolateral</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>SVAB</td>
<td>stereotactic vacuum-assisted biopsy</td>
</tr>
<tr>
<td>TN</td>
<td>true negative</td>
</tr>
<tr>
<td>TP</td>
<td>true positive</td>
</tr>
<tr>
<td>UDH</td>
<td>usual ductal hyperplasia</td>
</tr>
<tr>
<td>VAB</td>
<td>vacuum-assisted biopsy</td>
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</table>
1. Introduction

1.1 The present state of diagnosis and therapy for breast cancer
The diagnosis and therapy for breast carcinoma has evolved. Previously, breast carcinomas were detected by clinical examination of the breast. The lesions were usually large and had typically radiological features. The patients received a radical mastectomy as a result. In recent years, with the widespread using of screening mammography, many suspicious and clinically nonpalpable breast lesions were detected. Early carcinomas often display an uncharacteristic appearance. These lesions need further pathologic work-up to distinguish benignancy or malignancy. Malignant lesions in early stage are locally excised and treated with postoperative neoadjuvant chemotherapy.

As the result of the present state of breast cancer, the surgeon is faced with the challenge of performing therapeutic excision in the most accurate and efficient manner with the least morbidity to the patient. Also, the radiologist is faced with the challenge of making more standardized and more precise diagnosis with a more accurate localization of the tumors for subsequent breast conserving surgery.

1.2 Standard language of breast lesion: BI-RADS Categories
The Breast Imaging Reporting and Data System (BI-RADS) was proposed by the American College of Radiology (the 4th edition, 2003) [2] to provide a common language to describe mammographic lesions and the level of suspicion.
BI-RADS Category 0: the lesions need “additional imaging evaluation”.
BI-RADS Category I or II: the lesions have “negative mammogram” or “benign findings”, with a normal interval follow-up recommended.
BI-RADS Category III: the lesions have “probably benign finding” with a recommendation for 6-month interval follow-up.
BI-RADS Category IV or V: the lesions have “suspicious abnormality” or “highly suspicious of malignancy” with a recommendation for biopsy or surgical examination.
1.3 More precise diagnosis: Biopsies and their histological results

1.3.1 History of breast biopsy

Percutaneous breast biopsy was first performed with fine needle aspiration to establish a cytologic diagnosis for mammographically suspicious lesions [9, 66]. Fine needle aspiration could not remove the entire target lesions. In addition, fine needle aspiration could not differentiate between ductal carcinoma in situ (DCIS) and invasive carcinoma [66]. Other disadvantages include a failure rate of 0% to 22%, a positive margin rate of approximately 50%, and vasovagal reactions of approximately 20% [32]. In 1990, Parker et al. [59] first introduced the automated core needle breast biopsy (CNB). A small target lesion might be removed entirely with this technique. An even higher frequency of total excision of all visible target lesions has been reported after the stereotactic vacuum-assisted breast biopsy (SVAB), which was firstly reported by Liberman, Parker, Jackman, and Burbank in 1997 [12, 13, 28, 45, 61].

1.3.2 Stereotactic biopsy: CNB or VAB?

Vacuum-assisted breast biopsy (VAB) has proved more accurate and useful than CNB [11, 27, 29, 50, 63]. The first reason is that CNB requires the pinpoint accuracy, while VAB system can compensate for an inaccurate needle position [27]. The second reason is that a greater tissue volume is obtained with VAB than with CNB. The mean specimen weight is 17 mg for the 14-gauge CNB [11], 35-45 mg for the 14-gauge VAB [11], and 90-100 mg for the 11-gauge VAB [14]. The third reason is that CNB has limitations in making a correct diagnosis of microcalcifications compared to SVAB [29, 50, 63]. However, VAB is much more expensive than fine-needle and CNB.

1.3.3 Stereotactic biopsy: 14-, 11- or 8-gauge needle?

As described before, 11-gauge needle can harvest more tissue than 14-gauge. Burbank [14] and Jackman et al. [31] published comparative studies of the 11 and 14-gauge needle. The larger tissue volume minimized sampling error and improved compensation for any sampling shift. In addition, there was no increase in procedure time, and no complications with the 11-gauge needle. Therefore, SVAB should be performed with 11-gauge vacuum technique. 8-gauge needle can harvest more tissue than 11-gauge and has the same technical success rate as
11-gauge. However, the complication rate with the 8-gauge needle is slightly increased [21].

1.4 Accurate localizing of the lesions: clip marker
1.4.1 Introduction of markers
SVAB must be followed with a definitive procedure (open biopsy or mastectomy) for cancer, high risk lesions or when mammography and pathology are discordant [4]. In order to get a better rate of margin clearance, the radiologist’s role in accurately localizing the tumor is becoming vital.

The common used marker recently is metallic clip made of titanium or stainless steel, which was approved by the US Food and Drug Administration on 1995. Clip markers that are deployed through the biopsy probe can be divided into two kinds. One kind is a clip alone, such as the MicroMark II clip (Ethicon Endo-Surgery INC, OH, USA), which traps tissue with its limbs. Another kind is a clip with additional Ultrasound visible collagen materials, such as the Gel Mark Ultra (SenoRx INC, CA, USA), which fill the cavity to fix the clip.

There were alternative localization methods including carbon marking [56], methylene blue dye [54], radioactive seed placement [25], and the hematoma caused by biopsy [32]. Carbon marking and methylene blue dye stain the biopsy site and needle tract. As a result, the entire biopsy site and needle tract must be removed. Radioactive seed localization is based on an accurate clip placement and requires a second procedure for location and gamma expertise. However, it has been shown to have a lower rate of margin clearance compared with standard needle localization. The hematoma caused by biopsy remains visible only to 56 days and is not suitable for long term follow-up.

1.4.2 The purpose of clip placement
The indications for marking clip placement include the following: (a) to mark the lesion site if all imaging findings are removed; (b) to mark the tumor bed for additional surgery; (c) to mark the tumor bed which shows complete clinical regression after neoadjuvant chemotherapy; (d) to confirm the tumor bed for the pathologist and surgeon on the radiograph of the mastectomy specimen; (e) to
provide ultrasonographic and mammographic correlation of lesions; (f) to allow monitoring for changes in benign lesions on follow-up mammograms; and (g) to provide imaging documentation of prior biopsy when an imaging history is unavailable [15, 19, 23, 44, 53, 57, 67, 69].

1.4.3 Clip displacement: measurement systems
The clips deployed as a marker should be put into the intended site and must remain close to it to mark the biopsy site accurately. However, clip displacement from the biopsy site is not uncommon. Clips may migrate immediately after biopsy or later to the same or another quadrant than where the lesion was [7, 16, 41, 65].

Several measurement systems have been reported to assess the accuracy of clip placement. The first system is the post-biopsy screening film measurement [67]. Distances between clip to biopsy site were directly measured on the craniocaudal (CC) and mediolateral (ML) mammograms obtained immediately after the biopsy. This measurement reflected the clinical practice and closely illustrated the maximum clip displacement on z axis. The second system is the Pythagorean Theorem system [32]. Distances between clip to lesion site were measured in the x, y, and z axis on CC and ML mammograms. The three-dimensional distances of clip and lesion in the breast were calculated by the Pythagorean Theorem. This measurement reflected the three-dimensional localization of clip. However, it would underestimate the dislocation of clip in z axis [67]. The third system is the mask measurement system [15]. A mask is used, which was created by marking the location of the clip on post-biopsy image and the location of the lesion on pre-biopsy images in both projections. The distance from the clip to the lesion on the mask is used to determine the distance of the lesion. The true distance between the clip and the lesion is calculated as the mean distance of target minus a correction factor.

1.5 Aims of this study
Since the first report of SVAB published at 1997, many experiences have been summarized in journals and conferences. Most published studies confirming the efficacy of SVAB have focused on the use of dedicated prone units. Caines et al. [17] first described upright-type CNB using a conventional mammography unit with
an add-on stereotactic device. Only two other articles [22, 70] described experiences with an add-on stereotactic device for CNB. However, nobody applied the lateral-type SVAB with an add-on stereotactic device as we known. We introduced the lateral-type biopsy unit and wanted to evaluate its feasibility for microcalcifications.

There is still a debate about the indication of clip deployment. Most of scholars claimed to put clips only in the lesions which have radiologically been completely removed [23, 67, 53]. Some insisted on putting clips in every lesion [15, 69], and others preferred different methods for marking lesions [25, 32, 54, 56]. In addition, it is difficult to judge whether the lesion was completely taken out during the stereotactic biopsy because of the limited view and the obscure field due to a hematoma. These different opinions and technical difficulties have left clip deployment with some problems: in which patients clips are required? We prospectively deployed clips in each biopsy site and tried to predict which patients require clip deployment.

Clip displacement from the site of deployment is not an uncommon finding. However, few articles [53] were found about comparison of different clips and deployment techniques. In our study, we utilized two kinds of clips, MicroMark II and Gel Mark Ultra. We analyzed the post-biopsy mammograms to compare these two kinds of clips for placement accuracy.
2 Materials and Methods

2.1 Patients

In the Hospital Traunstein Germany, between July 2002 and March 2006, 162 women (mean age, 62±11.2; range 34-85 years) underwent mammography which showed nonpalpable suspicious microcalcifications in their breasts. The diagnostic strategy for nonpalpable breast microcalcifications is showed as the flowchart (Figure 1).

Figure 1: The diagnostic flowchart for nonpalpable microcalcifications in the Traunstein Institution.

172 suspicious (BI-RADS category IV) and 5 highly suspicious of malignant (BI-RADS category V) microcalcifications were obtained by stereotactic vacuum-assisted biopsy by five physicians. Each patient had given informed consent. 12 patients had two sites biopsied in one breast and 3 patients had two sites biopsied in each breast because of separate microcalcifications. 42 lesions for which the biopsy histology showed malignant or high-risk alterations were surgically excised.
no later than two weeks after biopsy. 26 of remaining 135 benign lesions (19.3%) were followed up after a mean of 6.8 months (range 3-45 months).

2.2 Stereotactic biopsy procedure
Two projections mammograms, CC and ML projections, were each obtained before biopsy with a conventional mammography unit (Mammomat 3000 Nova, Siemens, Germany) for accurate three-dimensional localization of the lesion. Biopsies were performed with the patient in a lateral lying position. An add-on digital stereotactic imaging unit (Mammomat 1000/3000 Nova Opdima digital biopsy and spot imaging system unit, Siemens-Elema. AB, Sweden) was employed to combine with Mammomat 3000 Nova. After the lesions had been targeted, Scandicain® (0.5%, 9 ml) mixed with Suprarenin® (1:500,000, 1 ml) was deeply injected into the lesions for local anesthesia. We used an 11-gauge vacuum-assisted needle (Mammotome System Control Module with SmartVac, Ethicon Endo-Surgery INC, OH, USA) to harvest tissues. For cluster microcalcifications, the biopsy needle was inserted in the center of the lesion. For diffuse microcalcifications, the region most suspected of cancer was targeted for biopsy. The probe was always inserted at the 12-o’clock position. The sampling chamber was continuously moved in 2-hour increments (60°), thus, 6 specimens were obtained per 360° needle rotation. We obtained a standard of 12 specimens per lesion for two rotations. After sequentially harvested 12 specimens, we kept the biopsy probe in the initial position, and a pair of stereotactic images was obtained to determine if the mammographic lesion was excised. On the other hand, the excised tissue specimens were roentgenized on a plate to verify if they contained calcifications. More specimens with an additional rotation were obtained basing on assessment of stereotactic images, the results of radiography of the specimens and visual inspection of the specimens (Figure 2).
After the tissue harvest, we reduced the pressure on the breast by about 15-20% of the initial pressure. The biopsy probe was retracted back for 5mm, then a 2-mm-size clip was inserted through the probe. We adopted two kinds of clips into each biopsy site. MicroMark™ II (Ethicon Endo-Surgery INC, OH, USA) clips were utilized from January 2004 to December 2004. From July 2002 to March 2006, we utilized Gel Mark® Ultra, (SenoRx INC, CA, USA) clips (Figure 3). Subsequently, a pair of stereotactic images was obtained to confirm the clip deployment. In
addition, final CC and ML mammograms were also obtained to verify placement and accuracy.

Figure 3: Two kinds of clips were utilized in our study.

a. Gel mark Ultra clip (SenoRx INC, CA, USA).
b. Gel Mark Ultra consists of a “S” shaped stainless steel marker, and 10 ultrasound visible pellets.
c. Micro Mark II clip (Ethicon Endo-Surgery INC, OH, USA).
d. Gel mark Ultra (arrow) and Micro Mark II clip (double arrow) on mammogram.

The specimens were divided into containing calcifications specimens (collected in container A) and without calcifications specimens (collected in container B) and sent to pathology.

After all the procedures, the breasts were compressed for 24 hours with bandages.

2.3 Evaluation
The data about patients included: age, history, diagnosis of mammograms, ultrasonography and other examinations, records of biopsy procedure,
complications if applicable, histological findings, therapeutic records and follow-up mammography findings.

We obtained the pre- and post-biopsy mammograms of 123 lesions in 108 patients. Two radiologists (they had respectively 19 and 3 years experience of mammography diagnosis) retrospectively evaluated the mammograms. Different opinions of them and discordance of documents and mammograms were resolved by consensus discussion. From the pre-biopsy mammograms we evaluated the details of mammographic features of lesions: (a) diameter of microcalcifications (was measured as the mean longest length diameter on CC and ML views and was recorded as <10 mm, 10-20 mm, >20 mm.), (b) morphology of microcalcifications (pleiomorphic, branching and punctuate), (c) distribution of microcalcifications (clustered, segmental and diffuse) and (d) present type of microcalcifications (mono-focal or multi-focal type). Mono-focal type means one area of calcification in one breast. Multi-focal type means several areas of calcifications which can be separated, visible in the same or different quadrants in one breast at least on one mammogram).

From the post-biopsy mammograms we evaluated the information about: (a) whether the microcalcifications were excised (b) localization of clip (the distance of clip-to–biopsy site was measured in a line from the center of the target to the clip on CC and ML views respectively, and was recorded as <10 mm, 10-20 mm, >20 mm, and (c) complications if happened.

We allocated all lesions to three mono-focal groups according to their diameter of <10 mm (group 1), 10-20 mm (group 2), >20 mm (group 3) and one multi-focal group (group 4) (Figure 4).
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Figure 4: Four groups of microcalcifications according to their diameters and distribution
a. group 1 (mono-focal microcalcifications smaller than 10 mm)
b. group 2 (mono-focal microcalcifications with diameter of 10-20 mm)
c. group 3 (mono-focal microcalcifications larger than 20 mm)
d. group 4 (multi-focal microcalcifications)
The biopsy target is marked by a broken circle

2.4 Histological classification

**Benign findings** (any specific or nonspecific benign epithelial or mesenchymal abnormality):
- fibrocystic change
- usual ductal hyperplasia (UDH)
- stromal fibrosis
- fibroadenoma

**High risk lesion** or benign finding with anticipated tissue-sampling error necessitating further excision:
- lobular neoplasia (LN), remains un-operated
- ductal hyperplasia with atypia (ADH)
- radial scar
- phyllodes tumor
Malignant lesions:
- ductal carcinoma in situ (DCIS)
- invasive malignancy of any origin (including invasive ductal or lobular cancer).

2.5 Statistical analysis
We analyzed our data with descriptive statistics (SPSS 10.0 statistics software, SPSS INC., Chicago, USA). Chi-square tests were used to analyze: (a) differences of microcalcificatons morphology, distribution on diagnosis; (b) differences of two kinds of clips on localization; and (c) differences of BI-RADS categories on malignancy. T-tests were used to compare with lesion size in the different diagnoses. Results were considered statistically significant if the P value was <0.05.

Using the definitions of Brenner et al. [8], we calculated the overall sensitivity, specificity and accuracy on the basis of the SVAB yielded histologic results. A SVAB diagnosis of a benign lesion that subsequently proved to be malignant was considered to be a false-negative result (FN), whereas those with benign results were classified as true-negative result (TN). Atypical or malignant lesions that subsequently proved to be malignant were considered true-positive results (TP), whereas those with benign or atypical results at pathology were classified as false-positive results (FP). As shown in Table 1, sensitivity was determined as follows: TP/TP+FN; specificity: TN/TN+FP; accuracy: (TP+TN) / (TP+FN+TN+FP).

Table 1: definitions of sensitivity and specificity

<table>
<thead>
<tr>
<th>Biopsy findings</th>
<th>Surgery or follow-up findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>True-positive (TP)</td>
</tr>
<tr>
<td>Negative</td>
<td>False-Negative (FN)</td>
</tr>
</tbody>
</table>
3. Results

3.1 Histological results following SVAB and surgery

The histological results (SVAB) of the 177 breast microcalcifications showed benign ones in 135 (76.3%), malignant ones in 39 (22.0%) and high risk lesions (atypical ductal hyperplasia, ADH) in 3 (1.7%) biopsies. Among the 39 malignant lesions, DCIS was diagnosed in 25/39 (64.1%), and invasive cancer in 14/39 (35.9%) biopsies (Figure 5). All the histological results corresponded to the mammographic findings.

![SVAB histological finds](image)

Figure 5: Histological results of 177 microcalcifications.

In each breast, we chose the suspicious microcalcifications as biopsy target. Twelve patients had two sites biopsed in one breast. Six patients had two benign lesions each, three patients had two malignant lesions each and three patients had benign and malignant lesions each (Figure 6).
Figure 6: 64-year-old woman underwent SVAB for multi-focal microcalcifications in the right breast.

a: Pre-biopsy ML mammogram showed one area of microcalcifications (circle) with diameter of 4mm and another area of microcalcifications (pane) with diameter of 6mm.
b: Post-biopsy ML mammogram of the first biopsy. The microcalcifications were completely removed and a clip was placed at the biopsy site.
d: Pre-biopsy ML mammogram of the second biopsy target.
e: Post-biopsy ML mammogram of the second biopsy (8 days interval). The calcifications were completely removed and a clip was placed at the second biopsy site.
c: and f: X-ray films of the first and second biopsy specimens. Calcifications were contained in specimens. The histological results for both of the biopsies were DCIS.

42 malignant or ADH lesions diagnosed by biopsy histology were surgically excised. Histological results showed that 3 DCIS and 1 ADH were underestimated and were finally diagnosed as invasive carcinoma. 26 of 135 benign lesions (19.3%) were followed up after a mean of 6.8 months (range 3-45 months) and
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were found benign because the microcalcifications did not change on the follow-up mammograms. 109 benign microcalcifications were not followed up. All SVAB findings were correlating with surgical findings except one atypical SVAB finding which was found malignant after surgery.

The sensitivity, specificity, accuracy were 100%, 92.9% and 97.1% respectively.

3.2 Clinical features

Among the 177 microcalcifications, 172 lesions were BI-RADS IV and 5 lesions were BI-RADS V. In 172 microcalcifications classified as BI-RADS IV, malignant lesions were 34 (19.8%). Among them, DCIS was diagnosed in 23/34 (67.6%), and invasive cancer in 11/34 (32.4%). All the microcalcifications classified as BI-RADS V were malignant lesions. Among them, DCIS was diagnosed in 2/5 (40%), and invasive cancer in 3/5 (60%). There is no significant difference between DCIS and invasive cancer in BI-RADS IV and V category (P=0.48) (Table 2).

Table 2: Frequency of malignant diagnosis according to BI-RADS Categories.

<table>
<thead>
<tr>
<th>BI-RADS Category</th>
<th>DCIS</th>
<th>Invasive carcinoma</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>23 (67.6)</td>
<td>11 (32.4)</td>
<td>34</td>
</tr>
<tr>
<td>V</td>
<td>2 (40.0)</td>
<td>3 (60.0)</td>
<td>5</td>
</tr>
<tr>
<td>total</td>
<td>25 (64.1)</td>
<td>14 (35.9)</td>
<td>39</td>
</tr>
</tbody>
</table>

3.3 Mammographic features

The mean diameter of microcalcifications was 13 mm (range 3-50 mm) and 60% of lesions were smaller than 10 mm. The mammographic features of microcalcifications are shown in Table 3. Differences between microcalcifications morphology and distribution of diagnosis were not significant (P>0.05).
Results

Table 3 Comparison of mammographic features of benign and malignant lesions.
Data represent the number of lesions. Numbers in parentheses are percentages.

* Data are the range. Numbers in parentheses are the mean.

<table>
<thead>
<tr>
<th>Features</th>
<th>Benign (n=105)</th>
<th>Malignant (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mm)*</td>
<td>3-50 (13.4)</td>
<td>3-25 (13.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clustered</td>
<td>66 (62.9)</td>
<td>9 (50.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>segmental</td>
<td>23 (21.9)</td>
<td>3 (16.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>diffuse</td>
<td>16 (15.2)</td>
<td>6 (33.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pleomorphic</td>
<td>8 ( 7.6)</td>
<td>1 ( 5.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>branch</td>
<td>12 (11.43)</td>
<td>2 (11.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>punctuate</td>
<td>86 (81.9)</td>
<td>15 (83.3)</td>
<td>0.53</td>
</tr>
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</table>

66/123 (53.7%) lesions were mono-focal microcalcifications. In group 1 (mono-focal microcalcifications with diameter <10 mm, n=26), 23 lesions (88.5%) were completely removed (Figure 7). In group 2 (mono-focal microcalcifications with diameter 10-20 mm, n=22), 18 lesions (68.2%) were completely removed (Figure 8), while in group 3 (mono-focal microcalcifications with diameter >20 mm, n=18), no lesion was completely removed (Figure 9), (Table 4). The mean diameter of microcalcifications was significantly smaller in the completely removed lesions than in the incompletely removed lesions (8.1 mm± 4.3 versus 19.3 mm± 9.8, p<0.01). 57/123 (46.3%) lesions were multi-focal microcalcifications.

Table 4 Outcomes of microcalcifications mammographically excised from 123 lesions
Numbers in parentheses are percentages of completely removed microcalcifications

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>mono-focal</th>
<th>multi-focal</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>completely removed</td>
</tr>
<tr>
<td>&lt;10</td>
<td>26</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>10-20</td>
<td>22</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>18</td>
<td>0 (0)</td>
</tr>
<tr>
<td>total</td>
<td>66</td>
<td>41 (62.1)</td>
</tr>
</tbody>
</table>
Figure 7: 67-year-old woman underwent SVAB for small clustered mono-focal microcalcifications.

a: Pre-biopsy craniocaudal mammogram showed a small clustered microcalcifications with diameter of 3 mm.
b: Post-biopsy mammogram showed the microcalcifications completely removed and a clip deployed at the biopsy site.
c: X-ray film of specimens showed that one of the specimens contained microcalcifications. The histological result was fibrocystic hyperplasia.

Figure 8: 68-year-old woman underwent SVAB for mono-focal microcalcifications.

a: Pre-biopsy mediolateral mammogram showed microcalcifications with diameter of 13 mm.
b: Post-biopsy mammogram showed the microcalcifications completely removed and a clip deployed.
c: X-ray film of specimens showed microcalcifications in the specimens. The histological result was fibrocystic hyperplasia with sclerosing adenosis.
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Figure 9: 76-year-old woman underwent SVAB for mono-focal microcalcifications.

a: Pre-biopsy mammogram showed microcalcifications with the longest diameter of 25 mm.
b: Post-biopsy mammogram showed the microcalcifications partly removed and a clip deployed
c: X-ray film of specimens showed specimens with microcalcifications.

The histological result was sclerosing adenosis.

Three DCIS and one ADH were histologically underestimated as to their degree of malignancy. While one lesion of 10 mm diameter was completely removed, the other 3 lesions were larger than 20 mm and not completely removed.

The mean number of specimens obtained per lesion is 19.5 (range 6-65, some of specimens were fragmental, thus the total number of specimen is greater than the excised number). In every case, we obtained at least one specimen containing calcifications. 20.6% of the specimens were containing calcifications on x-ray films. We separated specimens into those containing microcalcifications (Container A) and those without visible microcalcifications (Container B).

For the specimens obtained by SVAB from 39 malignant lesions, all the specimens containing microcalcifications were diagnosed as malignant, while 60.8% (372/611) of specimens without visible microcalcifications were diagnosed as malignant. The rate of malignant diagnosis was significantly higher in specimens containing microcalcifications than in specimens without visible microcalcifications (P<0.001).

In 4 cases, the calcifications were identified on specimen radiographs while no calcifications were seen by the pathologist. The most probable reason was that
Results

Microcalcifications were lost during the preparation of tissue sections for histological examination.

3.4 Clip placement

In each of 113 lesions with complete series of pre- and post-biopsy mammograms, a clip was deployed at the end of the vacuum biopsy. The localization of clip was evaluated on the CC and ML mammograms immediately after biopsy. However, 5 clips could not be detected on the post-biopsy mammograms although they were confirmed in biopsy site on stereotactic images. Among these missing clips, 3 of them were MicroMark II. In the remaining 108 clips, 79 clips were Gel Mark Ultra and 29 clips were MicroMark II.

75 clips (69.4%, 75/108) were located within 10 mm distant from the biopsy site on both projections. Among these 75 accurately localized clips, 57 clips were Gel Mark Ultra clip and 18 clips were MicroMark II clip. There was no significant difference between the two kinds of clips as to the accurate placement (Gel Mark Ultra clip: 72.2% vs MicroMark II clip: 62.1%, P=0.36). 33 (30.5%, 33/108) clips were dislocated on at least one projection and 28/33 (84.8%) clips were dislocated only on CC projection (Table 5, Figure 10). There was no significant difference between the two kinds of clips as to the inaccurate placement on CC projection (Gel Mark Ultra clip: 91.3% vs MicroMark II clip: 72.7%, P=0.30).

Table 5 Accuracy of the two kinds of clip deployment at breast post-biopsy mammograms with the lateral compression

<table>
<thead>
<tr>
<th>Distance of clip from biopsy site (mm)</th>
<th>MicroMark II (n=29)</th>
<th>Gel Mark (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>ML</td>
</tr>
<tr>
<td>&lt;10</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>10-20</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 10: 73-year-old woman who underwent SVAB, showed clip dislocated along the biopsy needle tract immediately after biopsy in the left breast.

a: and b: Pre-biopsy ML and CC mammograms show branched calcifications with segmental distribution, marked by a circle.

c: Post-biopsy ML mammogram shows that microcalcifications were partly removed. There is an air cavity in the biopsy site and a clip is placed in the air cavity (circle).

d: Post-biopsy CC mammogram shows the clip dislocated along the needle tract for about 15 mm. The upper arrow marks the biopsy site and the lower arrow marks the migrating clip.
3.5 Complications
Only one patient could not be completely biopsied after 6 tissue samples obtained because of bleeding. In no patient the biopsy procedure had to be interrupted because of pain or vasovagal reaction. Minor bleeding was common during the procedure. Four patients developed hematomas after biopsy which measured at least 2 cm in diameter. The hematomas were resorbed without surgical intervention. No inflammation had occurred.
4. Discussion

4.1 Feasibility of lateral-type add-on device SVAB
Breast calcifications are a common finding in all aging women, which remain challenges to the radiologists. In clusters of microcalcifications, precise differentiation by their mammographic features is impossible, even by Ultrasound and Magnetic Resonance Imaging (MRI) [34]. Our results with the 11-gauge needle proved that all the mammographic features, such as lesion size, morphology and distribution have no statistically significant correlate with the malignant diagnosis (P>0.05). SVAB has been established as a reliable and cost-effective method in the management of suspicious breast microcalcifications [29, 33, 34, 50, 63, 68].

The prone-type SVAB provides a very high success rate and became a standard for biopsy in many countries. However, prone-type biopsy units are much more expensive and not suitable for routine mammographic examination, which is performed most of the time at a diagnosing center. Furthermore, the room requirements for a prone system are significantly greater than those required for an add-on system [27, 35]. The combination with an add-on stereotactic device to conventional mammography unit on upright position has shown as good as the prone-type unit [35]. However, upright-type biopsy units had some difficulties in psychological support and in maintaining the patient in a stable position [27]. Considering these disadvantages, we utilized lateral-type biopsy in our study. It is easy for patients to maintain the stable positions. Additional, the patients cannot see the biopsy procedure and psychological problem is not as serious as in the upright-type.

4.1.1 Diagnostic accuracy and inaccuracy
In our data, all the microcalcifications were nonpalpable (59.6% lesions were <10mm) and 64.1% of the lesions with malignant diagnosis were noninvasive carcinomas. That is to say, very early lesions were detected. 23.7% malignant and high risk lesions versus 76.3% benign lesions is fully within the range of previously published results [3, 6, 10, 33, 38]. In addition, the percentage of patients with
malignancies found within BI-RADS IV and V category corresponds well with the percentages reported in the literature [33, 37, 46, 58].

According to our results, the sensitivity and specificity were 100% respectively 92.9%, which are higher than in a published multi-center results of over 4000 cases prone-type SVAB (95% confidence interval of sensitivity was 92.9%-95.5%; 95% confidence interval of specificity was 86.6-89.6%) [18]. 12% (3 cases) of patients were upgraded from DCIS to invasive carcinoma, which is similar to other reported results (5–18%) [6, 30, 33, 48, 64]. 33.3% (1 case) of patients were upgraded from ADH to invasive carcinoma, which corresponds to results reported in the literature (7-35%) [5, 18, 62, 63].

The major limitation of our study is that the follow-up is not complete: only 19.3% of the patients with benign lesions were followed-up for a mean of 6.8 months. Among the few followed-up patients there is no false-negative result. Maybe this is also the reason that our sensitivity and specificity were higher than the published results. Our data together with the other results published previously [11, 33, 50, 55] suggest that a negative diagnosis using SVAB is reliable and avoids to perform for the majority of patients open surgery biopsies for benign lesions.

In our study, all the invasive carcinomas were confirmed by surgery. No false-positive results occurred. This result prompted that the minimally invasive SVAB provides the accurate information to plan surgical treatment. These precise histological diagnoses before operation can help the surgeons to plan the surgical intervention, and also, the patients can be better emotionally prepared for the procedures. However, 3 patients of DCIS and 1 patient of ADH were histologically underestimated because they were invasive carcinomas and not carcinomas in situ resp. ADH. These results slightly decrease the value of SVAB for treatment planning because invasive carcinomas imperatively need an axillary lymph node dissection. In the case of DCIS and ADH an axillary lymph node dissection is not required. Whereas, histological underestimation cannot be avoided completely even if more tissue harvested by SVAB. The reason for this is that microcalcifications tend to occur in areas of DCIS and/or adjacent benign tissue rather than in invasive tumors [40]. Therefore, histological underestimation will
occur because SVAB specifically targets microcalcifications. For the cases of DCIS and ADH diagnosed via SVAB, an open biopsy is required before definite surgery (see decision tree Figure 11). On the other hand, Lee et al. [40] found that the histological underestimation rate of SVAB with the 11-gauge needle was not significantly different from the underestimation rate of open surgical biopsy. Thus, the 11-gauge SVAB is the less invasive method to get a reliable diagnosis for malignant lesions.

Figure 11: The flowchart (decision tree) for the procedure following the results of SVAB with the 11-gauge needle in our institution
4.1.2 Procedure safety
The side effect of lateral-type VAB is minimal. In our data, only 4 patients developed hematoma (larger than 2 cm) after biopsy, which is within the range of the reported results (0.8-3%) [31, 33, 34, 51]. No case with hematoma needed operative intervention. In our institution, injecting Suprarenin® with local anesthnesia and compressing breasts after procedure help to reduce the formation of hematoma. Other side effects reported include inflammations [33, 34] and vasovagal reactions [33, 51]. In our study, no inflammation and vasovagal reaction occurred.
In summary, the lateral-type SVAB performed on a conventional mammography unit with an add-on stereotactic device is a safe, reliable, and accurate method for evaluation of nonpalpable suspicious microcalcifications. Comparing to a dedicated prone biopsy system, an add-on device has advantages of significant cost and space-saving.

4.2 Quality assurance of SVAB
The high accuracy and reliability of VAB is depended on the quality assurance.

4.2.1 SVAB procedure counterchecks
There are three counterchecks for lesion biopsies and clip localization. The first countercheck are the two orthogonal pre-biopsy mammograms (CC and ML) for accurate three-dimensional localization of the lesion. The second countercheck are the stereotactic images during biopsy for validating the removal of lesion and clip deployment. The final countercheck are the post-biopsy mammograms (the same two projections as pre-biopsy) for further confirming the correct sampling and clip localization. In case of malignancy, the post-biopsy mammograms may support the wire localization before surgery [26, 33]. In our study, one patient was sampled by mistake. The cavity and clip on post-biopsy mammograms comparing the pre-biopsy mammograms reminded us of the error. This patient was rebiopsied the next day. This case emphasizes the importance of quality assurance of SVAB procedure.
4.2.2 Specimens quality assurance
How many samples and what kind of samples are needed for a reliable diagnosis for VAB with 11-gauge needle? The range of the sample number varied from 12 to 20 [26, 33, 51, 52]. In our study, 12 specimens per lesion were obtained as a standard procedure. Actually, mean 19.5 specimens were obtained per lesion. The sensitivity and specificity and underestimation rate of malignancy were full within the range of previously reported results. Therefore, we suggest that the average number of specimens should be no less than 12 per lesion.

Our goal of biopsy is to remove the small clustered microcalcifications as far as possible. In our data, the overall complete removal rate of calcifications was 54.5% and the complete removal rate of lesions <10 mm was 85.4%. Complete removal rather than sampling of microcalcifications was associated with a significantly lower frequency of imaging-histologic discordance [49].

In our study, the operator continued to extract samples until at least one sample revealed microcalcification on a radiograph of the specimen. Liberman et al. [42] reported that a specific histological diagnosis was obtained significantly higher in the specimens containing calcifications than the specimens without calcifications. Our results also showed that the rate of malignant diagnosis was significantly higher in specimens containing calcifications. The radiograph of the specimen allowed a first confirmation for lesions containing microcalcifications. Identification of calcifications on radiographs of specimens provides proof that the targeted lesion was sampled [33, 36]. Failure to identify calcifications on radiographs of specimens is considered an unsuccessful biopsy [40, 42].

4.2.3 Follow-up
A follow-up mammogram (standard screening mammograms, including CC and ML or MLO) should be carried out till 3 to 9 months after SVAB [26]. A small percentage (1.1-7%) of cases diagnosed as benign with biopsy will changed on follow-up mammograms [39, 60]. Some of them were malignancy on repeated biopsy. Therefore, follow-up mammograms can prevent false-negative results as the last countercheck.
The problem of patients dropping out of follow-up is common to most biopsy studies, with rates ranging from 25–39% [1, 20, 24, 39, 43]. Lacking of complete follow-up of benign lesions was our main limitation, which made it difficult to assess the true accuracy of SVAB with an add-on unit. The absent follow-up is not determined by the patient’s choice bias. Some patients lived far from our hospital and preferred to perform their follow-up examination in nearby clinic. Some patients could not be reached by phone or mail. Nevertheless, we will continue our efforts to further complete the existing follow-up data.

4.3 Clip deployment indicators
We classified all the microcalcifications into four groups depend on the diameter and distribution type. In each biopsy site, a clip was deployed. Consequently, this classification enables to indicate clip deployment. We found that microcalcifications smaller than 20 mm and all multi-focal microcalcifications are useful indicators to deploy clips. Only mono-focal microcalcifications larger than 20 mm do not need clips as marker.

Mammograms showing microcalcifications may underestimate the extent of the suspicious lesion, because some carcinomas extent into the non-calcified tissue [40, 51]. Other “non-calcified” areas cannot be recognized as suspicious because only microcalcifications larger than 150 \( \mu \)m can be seen on mammograms [36]. This means that even the complete removal of a lesion with mono-focal microcalcifications as performed in 88.5% of our group 1 and in 68.2% of our group 2 is no guaranty that the whole suspicious lesion has been removed. Previous investigations have shown that among cancers in which the mammographic targets were removed, surgery revealed residual cancer in 50-80% [47, 51]. Two groups of researchers reported the complete removal of the suspicious target by 11-gauge SVAB in 46-89% of all lesions [40, 68]. According to our data, the microcalcifications were completely removed in 54.5% of all lesions and in 77.1% of microcalcifications smaller than 20 mm. Based on these data, and the insecurity whether all suspicious tissue has been removed, we recommend using microcalcifications smaller than 20 mm (group 1 and 2) as indicators for clips for a better recognition of the site of breast biopsy even after a long follow-up.
period, which is partly in agreement with Schulz-Wendtland et al. [69], who also recommended deploying clips in lesions smaller than 10 mm. For microcalcifications larger than 20 mm (group 3), no lesions were completely removed. Therefore, mono-focal microcalcifications larger than 20 mm do not need clip deployment.

Furthermore, we recommend deploying clips into alterations with multi-focal microcalcifications (group 4), especially when they are distributed in the same quadrant, independently whether they have been completely removed or not. Thus the biopsy site is clearly marked. According to our data, 46.3% of the lesions were multi-focal microcalcifications. In 12 patients with multi-focal microcalcifications, the biopsy had to be performed twice for different microcalcifications. 6/12 patients had at least one malignant lesion each. For these patients, clips can help to improve the exact surgical excision.

4.4 Clip displaced immediately after biopsy
We utilized two kinds of clips to mark the biopsy cavity through the probe needle. They have different components and shapes. Gel Mark Ultra consists of 11 pellets. The sixth pellet is a stainless steel marker, which is visible on radiographs as “S” form. This is designed to mark the biopsy cavity for a long term. The other 10 pellets are absorbable poly-lactic and poly-glycolic acid pellets, which are visible via ultrasound and are absorbed by about 6 weeks. The syringe-like applicator fits within the 11-gauge vacuum-assisted cannula to access the biopsy cavity. The Gel Mark Ultra pellets were pushed lightly by the syringe-like applicator into the biopsy site and filled the cavity to limit clip movement. Micro Mark II is a clip alone with two shapes depending on whether it is open or closed. When open, the marker clip resembles a “U” shape. When closed, the two limbs are pinched together, forming a diamond shape. The MicroMark II clip assembly consists of a deployment grip, a pull wire attached to the deployment grip at one end and attached to the marker clip at the other end, and a plastic sheath that separates the deployment grip from the marker clip. As tension is applied to the pull wire by squeezing the deployment grip, the marker clip changes from the open shape to the closed shape. As progressively more tension is applied, the marker clip breaks free from the pull wire and traps the breast tissue by its limbs, then attached to the tissue. In practice, the process occurs almost instantaneously.
In short, these two kinds of clips were deployed though different techniques. The Gel Mark Ultra clip did not trap the tissue as MicroMark II clip did. In our study, there is no significant difference between these two kinds of clips concerning their accurate localization and displacement (p>0.05). We suppose that the device without trap to surrounding tissue is not a major reason for displaced. Because Gel Mark Ultra clip is cheaper than Micro Mark II clip and can be identified not only by mammogram but also by ultrasound and magnetic resonance, we prefer Gel Mark Ultra clip to localize the biopsy site.

As described in the introduction section, there are several methods to measure the distance of clip to biopsy site. We used the same method as Rosen et al. [67]. This method reflects the clinical practice and closely illustrates the maximum clip displacement on z axis. According to our result, 30.5% of clips were displaced on at least one projection, which is similar to the results of Rosen et al. [67]. Essermen et al. [23] described different mechanisms of clip migration, which include the following: the accordion effect, clip migration in the biopsy track, a clip floating in a hematoma, clip displacement by a hematoma, change in the clip site due to resorption of air at the biopsy cavity, change in the clip site after neoadjuvant chemotherapy, change in the clip site after reduction mammaplasty, and clip displacement by another clip.

We found that 84.8% of the displaced clips were located along the probe needle track on CC projection mammogram. This high percentage of the dislocated clips seems to prove that the major reason for dislocation may be the “accordion” effect. The clip is inserted at the end of the biopsy with the breast compressed in the craniocaudal or lateral plane. When the compression is released, the breast expands to its original shape and the clip may migrate in the direction of compression, which is along the direction of needle track [15, 23, 44, 67]. In our investigations, all the biopsies were performed with lateral compression (ML), which means that only in the CC projection the direction of the needle is visible. In order to minimize this effect, as to our experience, compression should be partially released prior to clip deployment.
Another reason is the post-biopsy hematoma, which is reported in the literature with in the range of 0.8% to 3% [31, 33, 34, 51]. According to our data, 4 cases (2.3%) developed large hematomas during biopsy (diameters of 25-50 mm). Only in one case the clip was accurately localized. In two of the 4 cases the clips got lost. In one case the clip could precisely mark the target on ML image, but was far from the biopsy site for more than 20 mm on CC image. The formation of a large hematoma at the biopsy site may cause significant mass effects and displace the clips from their deployed sites. In some cases, the clips cannot attach well to tissue and float in the cavity of the biopsy with the hematoma. These results show that it is necessary to prevent hematoma in order to reduce the rate of clip displacement.

In our investigation of 12 cases with 2 biopsies and 2 clips inserted respectively, the first clip did not migrate due to the second clip. There were 3 clips displaced at both CC and ML projections. We think that one reason is related to technical problems. Another reason in a few cases was a physician with minor experience.

In post-biopsy mammograms, we found that 5 clips had been lost. One of the patients concerned was diagnosed with DCIS. Fortunately, and helpful for the surgeon, there were residual microcalcifications in the biopsy site. Problems can be expected if the clip loss occurs in a patient, who required the clip as an indicator for surgery or as a marker for chemotherapy. No articles were found which explained the important phenomenon of clip loss. Two of our missing clips were associated with large hematomas. Therefore, we hypothesize that the clips may float out of the breast with the blood immediately after the deployment. We may not forget that the size of the clip is two millimeters. Consequently, it is important to control bleeding during biopsy not only for an accurate localization of the clip, but also for reducing the risk of losing the clips.

Because of the limited follow-up data, we could not offer credible results about the long-term stability of clips. Nevertheless, one case was observed with a late clip migration along the track needle due to a late hematoma (Figure 12).
64-year-old woman underwent SVAB for multi-focal microcalcifications in the right breast. (the same patient as Fig 6)
a: Pre-biopsy CC mammogram showed one area of microcalcifications (circle) with diameter of 4 mm and another area of microcalcifications (pane) with diameter of 6 mm.
b: Post-biopsy CC mammogram of the first biopsy. The microcalcifications were completely removed and a clip was placed at the biopsy site.
c: Pre-biopsy CC mammogram of the second biopsy (8 days interval). There was a late hematoma (red ellipse) and the first clip migrated along the needle track.
d: Post-biopsy CC mammogram of the second biopsy. The microcalcifications were completely removed and a clip was placed at the biopsy site.
6. Summary

Purpose:
(a) to evaluate the feasibility of an add-on stereotactic breast biopsy on lateral lying position for suspicious microcalcifications; (b) to predict which patients requiring clip deployment; (c) to compare two kinds of clips for accurate localization.

Materials and Methods:
For 177 suspicious microcalcifications from 162 women (mean age, 62±11.2; range 34-85 years) breast biopsy was performed. The malignant or high-risk lesions proved by histology, were surgically excised. 26 benign lesions were followed up after a mean of 6.8 months (range 3-45 months). Biopsies were performed with an 11-gauge needle and an add-on stereotactic vacuum-assisted device on lateral lying position. At least 12 specimens were excised for each lesion. The specimens were examined by X-rays and divided into specimens containing calcifications and specimens without calcifications. After the tissue harvest, one of the two kinds of clips, Gel Mark® Ultra and MicroMark™ II, was deployed into the biopsy site. Two projections mammograms, craniocaudal and mediolateral, were obtained before and immediately after biopsy. The information including the lesion’s mammography features, microcalcifications removement, clip localization and complications were evaluated on these mammograms. All lesions were classified into three mono-focal groups according to their diameter of <10 mm (group 1), 10-20 mm (group 2), >20 mm (group 3) and one multi-focal group (group 4). The outcomes were evaluated by Chi-Square test and T-tests. Results were considered statistically significant if the P value was <0.05.

Results:
(a) Histological results: Histology showed benign results in 135 (76.3%) biopsies, malignancy in 39 (22.0%) and atypical ductal hyperplasia (ADH) in 3 (1.7%) biopsies. Furthermore, histology results after surgery showed 3 ductal carcinoma in situ (DCIS) and 1 ADH were upgraded to invasive carcinoma. The working sensitivity, specificity, accuracy were 100%, 92.9% and 97.1% respectively. (b) Clinical features: 172 lesions were BI-RADS IV and 5 lesions were BI-RADS V
category. (c) Mammographic features: The mean diameter of microcalcifications was 13 mm (range 3-50 mm) and 60% of lesions were smaller than 10 mm. 66/123 (53.7%) lesions were mono-focal microcalcifications. In group 1 (n=26), 23 lesions (88.5%) and in group 2 (n=22), 18 lesions (68.2%) were completely removed, while in group 3 (n=18), no lesion was completely removed. The mean diameter of microcalcifications was significantly smaller in the completely removed lesions than in the incompletely removed lesions (8.1 mm ± 4.3 versus 19.3 mm ± 9.8, p<0.01). 57/123 (46.3%) lesions were multi-focal microcalcifications (group 4). The mean number of specimens obtained per lesion was 19.5 (range 6-65). The rate of malignant diagnosis was significantly higher in specimens containing calcifications than specimens without calcifications (P<0.01). (d) Clip placement: 79 clips were Gel Mark Ultra and 29 clips were MicroMark II. 75 clips (69.4%) were located within 10 mm distance from the biopsy site on both craniocaudal and mediolateral projections. 33 (30.5%) clips were dislocated on at least one projection and 84.8% clips were dislocated only on CC projection. There was no significant difference between the two kinds of clips as to accurate placement, also as to inaccurate placement. (e) Complications: Four patients developed large hematomas. The hematomas were resorbed without surgical intervention. No inflammation and vasovagal reaction had occurred.

Conclusions: (a) An add-on stereotactic vacuum-assisted biopsy on lateral lying position is a highly effective and minimally invasive diagnostic procedure for nonpalpable breast microcalcifications. (b) Microcalcifications smaller than 20 mm and all the multi-focal microcalcifications are useful indicators to deploy clips. Only mono-focal microcalcifications larger than 20 mm do not need clip deployment. (c) The major influent factor of clip displacement is the “accordion effect” during the biopsy procedure. There is no significant difference of the two kinds of clips as to accurate localization.
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