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## Criteria for Excision of Suspicious Calcifications Using the Breast Lesion Excision System (BLES)

Alexandra Christou<sup>\*a</sup>, Vassilis Koutoulidis<sup>b</sup>, Dimitra Koulocheri<sup>c</sup>, Afrodite Nonni<sup>d</sup>,  
Constantinos George Zografos<sup>e</sup>, Georgios Constantinos Zografos<sup>f</sup>

<sup>a</sup> Brighton and Sussex University NHS Hospitals, Brighton, UK

<sup>b</sup> Department of Radiology, National and Kapodistrian University of Athens, Athens, Greece

<sup>c</sup> Department of Radiology, Breast Unit Hippokraton Hospital, Athens, Greece

<sup>d</sup> Department of Pathology, National and Kapodistrian University of Athens, Greece

<sup>e</sup> Department of Surgery, Nikaia General Hospital, Athens, Greece

<sup>f</sup> Department of Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece

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### ABSTRACT

**Background:** The aim of the study was to retrospectively evaluate possible imaging and histopathology criteria that can be used in a clinical basis to assess the success of excision of suspicious calcifications using the breast lesion excision system (BLES).

**Methods:** We investigated 400 BLES stereotactic biopsies of suspicious calcifications with the mean size of 15.38 mm (st. dev.= 13.579 mm, range 3-78 mm) using a 20 mm probe performed in our department between January 2014 and 2016. The mean age of our population was 58.5 years old (range 39-78 years). The pathology results of BLES specimens were compared with the final surgical results to assess excision success rates. Possible imaging and histopathology criteria for removal were statistically analyzed (mammographic size, disease free margins, grade, comedo phenotype, molecular type).

**Results:** The results showed that 90/400 (22.5%) biopsies were cancers (80% DCIS) and 38/400 were lesions with cell atypia (9.5%) of which 29/38 had subsequent surgery and were included in the study. Excision was achieved in 31/90 cancers (34.4%) and in 23/29 lesions with cell atypia (76.3%). The imaging and histopathology criteria for BLES excision that could be potentially clinically assessed were the initial mammographic size ( $p<0.001$ ), the distance of the lesion from the specimen margins ( $p<0.001$ ), the presence of comedo necrosis ( $p=0.014$ ) and the grade of the cancers ( $p=0.021$ ). The underestimation rate was 15.5%.

**Conclusion:** the mammographic size, grade, comedo presence and disease-free margins, were the main criteria for BLES success rate of excision of suspicious calcifications.

### Introduction

Breast lesion excision system (BLES) biopsy technique has been used in recent years for percutaneous biopsy of suspicious breast lesions

either under stereotactic or ultrasound guidance with high effectiveness and safety. It has been shown that it is a good alternative to core needle biopsy (CB) and vacuum assisted biopsy (VAB) techniques with similar accuracy and complication rates.<sup>1-5</sup> The underestimation rates of the technique are also comparable to those of VAB regarding high-risk lesions and ductal carcinoma in situ (DCIS).<sup>6,7</sup>

Moreover, due to its unique advantage of excising an intact piece of breast tissue with preserved tissue margins, the effectiveness of the

**\* Address for correspondence:**

Alexandra Christou, MD, PhD

Address: 177 Preston Rd, Brighton BN1 6AG, United Kingdom

Tel: +44 1273 664773

Email: [alexandrachristou@gmail.com](mailto:alexandrachristou@gmail.com)



technique in excision of the targeted breast lesions has been recently shown. The literature has reported that BLES performance in excision of suspicious breast lesions is promising and suggestive of potential use of the technique in excision of small breast benign and malignant lesions.<sup>7-10</sup>

A 2-mm disease free margin and no ink on tumor are considered the standards for an adequate surgical margin in DCIS and invasive cancer respectively.<sup>11,12</sup> As a result of these limited disease free margins that have been recently required for safe excision of breast cancer and the decrease in the volume of the breast tissue needed to be removed, the role of BLES technique as a potential therapeutic tool has emerged. The probes that are currently used for BLES biopsy are 12 mm, 15 mm or 20 mm. According to the BLES manufacturer guidelines, a spheroid piece of intact breast tissue can be removed weighing 1.1 gr and with dimensions 12 mm x 17 mm in case of a 12 mm probe; 2.1 gr weight and 15 mm x 21 mm dimensions in case of 15 mm probe; and 3 gr weight with 25 mm x 20 mm dimensions in case of 20 mm probe.<sup>13</sup>

The aim of this study was to evaluate the potential role of BLES using a 20 mm probe under stereotactic guidance to excise suspicious microcalcifications and identify potential imaging and histopathology criteria that could be used in a clinical basis to assess the possible success or failure of the excision.

## Methods

Between January 2014 and 2016, 394 women (mean age 58.5 years old; range from 39 to 78 years old) undergone stereotactic breast biopsy due to suspicious calcifications found on mammogram at our breast unit. A total number of 400 cases of calcifications (6 women had 2 areas of suspicious calcifications) were biopsied under stereotactic guidance using the BLES device during that period.

The main criteria for avoiding a BLES biopsy have been previously reported in papers from our unit, with the lesion positioning and the thickness of the breast being the most frequent ones.<sup>14,15</sup>

The inclusion criteria for the study were only first BLES biopsies and histologically proven cases to be either malignant or high-risk lesions with cell atypia and subsequent surgery (90 malignant and 29/38 high-risk lesions); the surgical result was used to determine the final pathology result in all cases. The lesions with no surgical result were excluded from the study (n=9 high risk lesions with cell atypia). The high-risk lesions with no cell atypia, such as benign papillomas (n=33) were not included in the study either and categorized as benign.

Informed consent for the percutaneous biopsy was obtained from all patients and ethical approval for the conduction of the study was also obtained.

The biopsy equipment consisted of the Fischer prone digital stereotactic device (Mammotest;

Fischer Imaging) and the BLES device (Breast Lesion Excision System® -B.L.E.S.-; Intact Medical).

All BLES biopsies were performed with an 8-gauge probe and 20 mm baskets by two experienced radiologists working in the department with 8 and 3 years of experience, respectively. All patients were placed in a prone position.

The procedure has been previously described in reports from our department.<sup>14,15</sup> Briefly, after careful stereotactic localization of the targeted area in order to be centrally positioned, 20 ml of local anesthetic (lidocaine 2%) is applied around the area (12, 3, 6 and 9 o'clock positions). A post anesthesia stereotactic image is then taken to assess the accuracy of the positioning. In case of deviation of the targeted lesion from the initial position relocation is obtained. Then the BLES stereotactic biopsy is performed. Through a small skin cut, the end-sharp probe is navigated through the breast tissue to the targeted area and, using radiofrequency (RF), an intact piece of breast specimen is retrieved and harvested inside the BLES basket at the end of the probe, which separates and removes the tissue. Due to RF application, a patient return electrode is applied to the upper back on the contralateral side of the breast to be biopsied.

After the biopsy, a radiographic image of the removed specimen is performed to assess the presence of the target lesion and a clip marker is positioned in the cavity through the biopsy channel. The sample is then placed in formalin and sent to the pathology department for histopathology test.

The patient follows the post biopsy treatment with local compression, dressing the skin incision site and applying a compressive bandage. Post biopsy control mammogram of the breast is performed to show the correct placement of the clip marker at the cavity site and the presence or absence of residual calcifications and any immediate biopsy complications. A post procedure clinical follow up appointment 48 hours after the biopsy is then booked to check the healing of the skin incision and deal with any complications, such as hematoma or infection.

The histopathology analysis of the specimen consists of the macroscopic measurement of the size of the BLES biopsy specimen and inking of the margins of the specimen. Microscopically, the presence and the type of cancer or cell atypia, the size of the included lesion and its distance from the margins (mm) are mentioned in all pathology reports. The distance of the lesion from the margins mentioned in the pathology result is the shortest distance of the lesion from the ink of the margins. Thermal artefacts if present and significant for the pathology diagnosis are also noted in the final report. Regarding cancers, the grade (G1-G3, high, intermediate and low grades DCIS) and the molecular type (luminal cancers, HER2 positive cancers and triple negative cancers)

**Table 1.** The main characteristics of the tumors and the relevant percentages

Tumour Characteristics	Number	Percentage
DCIS	72/90	80%
DCIS +Microinvasion	10/72	
DCIS + Invasion	13/72	
Invasion	18/90	20%
Intraductal	12	
Lobular	3	
Tubular	2	
Papillary	1	
Comedo	21/90	23.3%
Grade 1	23/90	25.5%
Grade 2	41/90	45.5%
Grade 3	26/90	28.8%
Luminal	69/90	76.6%
Her 2 Positive	18/90	20%
Triple Negative	3/90	3.3%
Mean Size (N=90)	15.38 mm (st. dev.= 13.579 mm, range 3-78 mm)	

are reported. In the surgical results, the presence or absence of the cavity from the previous BLES biopsy and any residual disease (malignancy or benign high-risk lesion) around the cavity are mentioned in the report. The size (in mm) of the residual disease is also mentioned.

The statistical analysis parameters were as follows: A) the mean values and the respective standard deviations were used to describe scale measurements such as the mammographic size and the margins in mm; B) frequencies and percentages were used for categorical variables such as BLES and surgical results and the lesion types; C) the mammographic size, the distance (mm) of the targeted lesion from the margins of the specimen, the grade and the molecular type of the cancers and the presence of comedo necrosis were the imaging and histopathology criteria that were statistically analyzed for the purposes of the study. For statistical reasons, the high, intermediate, and low grades DCIS were mentioned as grade 3, 2 and 1, respectively along with the grade of the invasive cancers. The statistical analysis of the cancers and the high risk lesions was performed separately (the results are reported for 90 cancers and 29 high risk lesions, separately). Mann Whitney test, Pearsons Chi-Square and Fisher's test were used to assess statistical differences and associations. ROC analysis was used for the estimation of effective cut off sizes of the variants and their associated sensitivity and specificity; D) SPSS v22.0 Software was used for the analysis and the statistical significance was set at 0.05.

## Results

There were 90 confirmed malignant cases and 29 confirmed high-risk lesions with cell atypia with subsequent surgery. The main characteristics of the cancers are presented in Table 1.

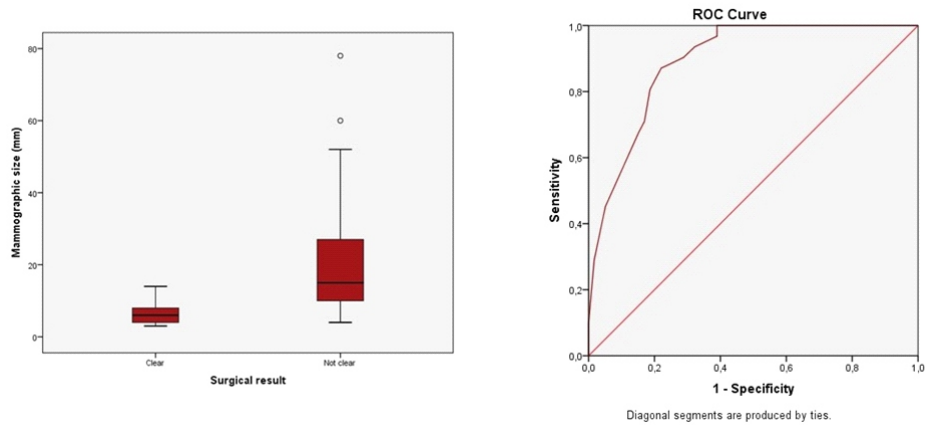
The high-risk lesions included in the study were mainly flat epithelial hyperplasia (13); lobular neoplasia type 1 and 2 (8); atypical ductal hyperplasia (4), papillomas with cell atypia (3) and mucocele like lesion with atypia (1).

BLES excision was achieved in 31/90 (34.4%) cancers and in 23/29 (79.3%) high risk lesions with cell atypia. From these cancers, 25 were pure DCIS, 3 were pure invasive cancers (1 tubular, 1 IDC and 1 ILC) and 3 were invasive cancers with additional DCIS.

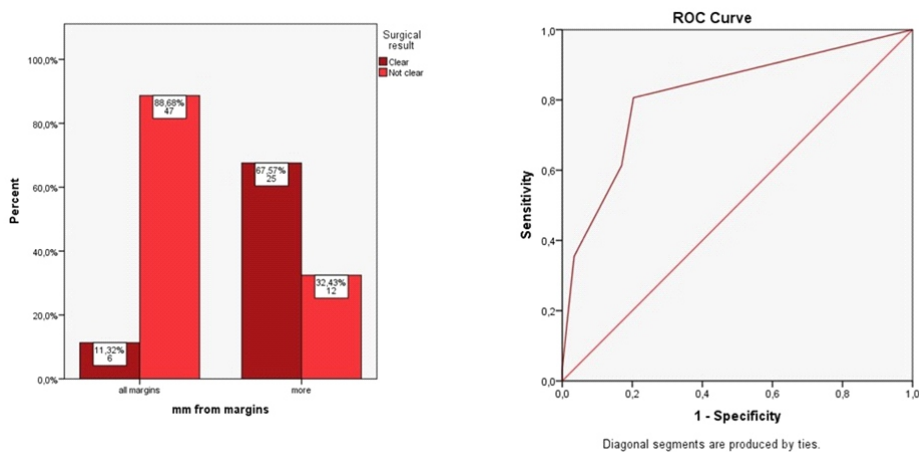
There was a statistically significant association between the initial mammographic size and the achievement of excision (Mann Whitney test,  $p < 0.001$ ). The size of the lesions that were excised was significantly smaller (mean size = 6.32 mm) than the size of the lesions that were not excised (mean size 20.14 mm) (Table 2, Figure 1). ROC analysis showed a cut off size of 14 mm over which none of the tumors were excised (sensitivity 100% , specificity 39% and area under curve (AUC) 0.892) (Figure 1). The success rate of excision was increased with the decrease in the size of the tumor. Specifically, 57.4% cases were excised with a size smaller than 14 mm, 71.8% at a cut off size of 8 mm (sensitivity 80.6 % , specificity 81.4%) and 95.7% at a cut off size of 4.5 mm (sensitivity 29% , specificity 98.3%).

**Table 2.** The mean mammographic size of the cancers that were excised and the cancers that were not excised using the BLES device

Mean Mammographic size / std deviation	Number of cases n=90
6.32mm / 2.737mm	Excised cases n=31
20.14 mm/ 14.568mm	Not excised cases n=59



**Figure 1.** Box plots of the mean size of the tumors that were completely removed with the BLES device (clear) and size of the tumors that were not excised (not clear) according to the surgical result and the associated ROC analysis.



**Figure 2.** Bar charts of the distance in mm of the tumours from the specimen margins (mm from margins) of disease-free BLES specimen margins (more) and of involved BLES specimen margins (all margins) and the achievement of BLES removal of the cancers (clear-not clear on surgical result) and the associated ROC analysis.

**Table 3.** Number of tumors with involved BLES specimen margins and with disease-free BLES specimen margins and the achievement or failure of BLES removal according to the final surgical result.

BLES specimen margins	Excision on surgical specimen	Residual disease on surgical specimen
Margins involved	6	47
Disease free margins	25	12

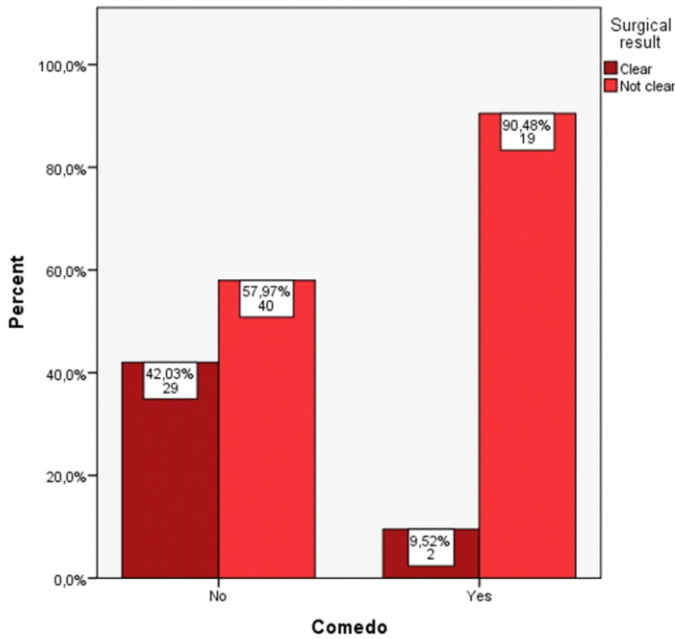
There was a statistically significant association between the distance of the tumors from the BLES specimen margins and the achievement of excision. In cases where the margins were disease-free the achievement of excision was 67,57% (25 cases) and in cases where the margins were involved was 11,32% (6 cases) (Pearson Chi-Square test,  $p < 0.001$ ). ROC analysis showed that at a cut off distance of 0.75 mm the specificity was 96,6%, the

sensitivity was 35.5% and the AUC was 0,816 (Table 3, Figure 2).

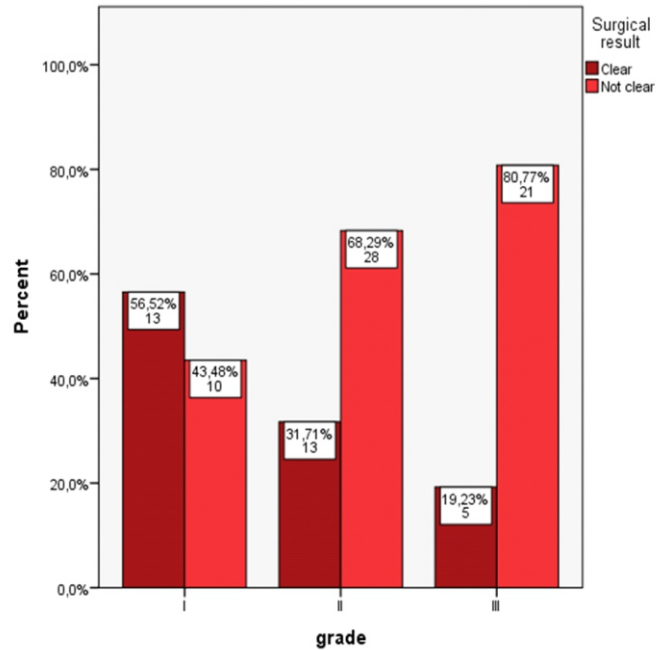
There was a statistically significant association between the presence of comedo necrosis and the failure of excision (Pearson Chi-Square,  $p = 0.006$ ). In comedo cases, the failure of excision was higher (90,48% ,19 cases) whereas in cases where comedo necrosis was absent the failure of complete removal was lower (57,97%, 40 cases) (Table 4, Figure 3).

**Table 4.** Comedo necrosis cases (present/not present) and the achievement or failure of BLES excision in the final surgical result (excision/residual disease)

Comedo necrosis cases	BLES excision	Residual disease
Present	2	19
Not present	29	40



**Figure 3.** Bar charts of the cases with and with no comedo necrosis and the achievement or failure of BLES excision (clear-not clear on surgical result).



**Figure 4.** Bar charts of G1-G3 cancers and the achievement of BLES excision (clear-not clear on surgical result).

**Table 5.** Correlation of the grade of the tumor (I-III) and the achievement or failure of BLES excision according to the final surgical result (excision/residual disease)

Grade of tumors	BLES excision	Residual disease
I	13	10
II	13	28
III	5	21

There was a statistically significant association between the grade of the cancers and the achievement of complete removal (Pearson Chi-Square,  $p=0.021$ ). In G3/high grade DCIS cases, the failure of excision was statistically higher (80,77%, 21 cases) whereas in G1/low grade DCIS cases, the failure was lower (43,48%, 10 cases) (Table 5, Figure 4).

No statistical association was seen between the molecular type and the BLES excision (Pearson Chi-Square,  $p=0.797$ ) (Table 6).

The only statistically significant finding for the achievement of excision of the high-risk lesions was the distance of the lesion from the specimen margins ( $p=0,041$  Mann Whitney test). Also, 94.7% of the cases (18/19 lesions) were removed when the

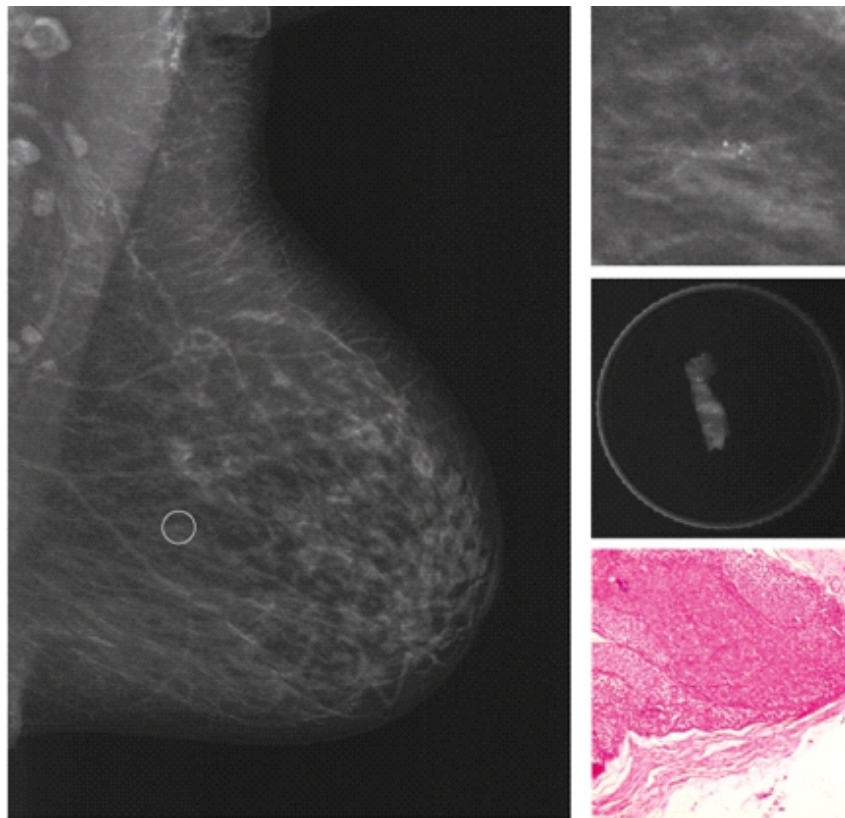
distance was over 1 mm, whereas 50% of the cases (5/10 lesions) were removed when the distance was 0.5 mm or 0 mm from the specimen margins.

The underestimation rate of cancers was 15.5% (14/90 cases); 7.7% (7/90 cases) was the underestimation rate of DCIS to invasive cancer; 3.3% (3/90) was the underestimation rate of DCIS to microinvasion; and 4.4% (4/90) was the underestimation rate of microinvasion to invasive cancer. No underestimation rate was found regarding the high-risk lesions. The complication rate was 8.75%.

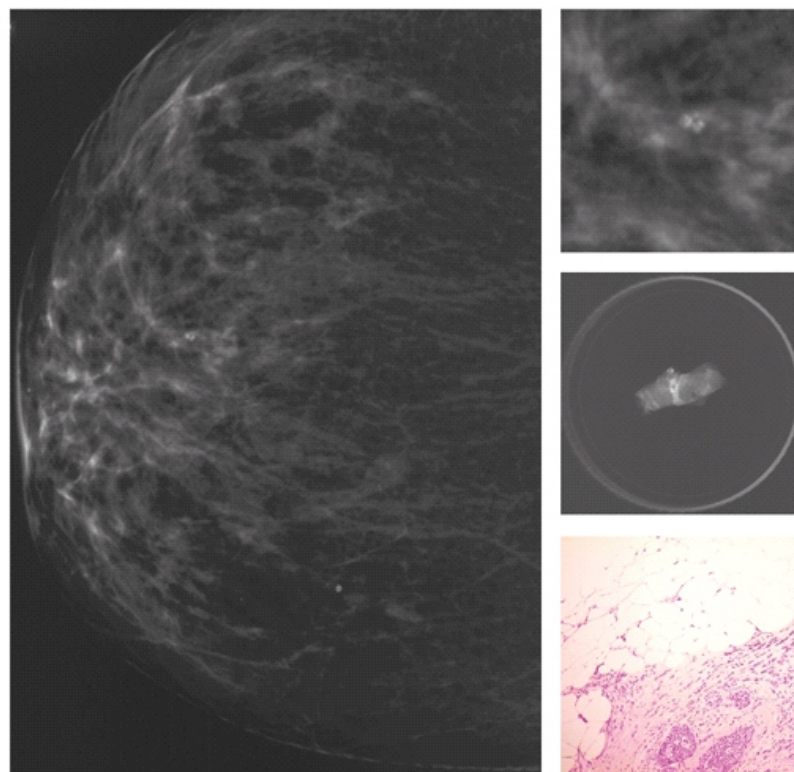
Figures 5 and 6 illustrate cases of calcifications found to be DCIS and ILC respectively, which were completely removed using the BLES device (Figures 5, 6).

**Table 6.** Correlation of the molecular type of the cancers and the achievement or failure of BLES removal according to the final surgical result (excised/residual disease)

Molecular type	BLES excision	Residual disease
Luminal	25	44
HER2 positive	5	13
Triple negative	1	2



**Figure 5.** Mediolateral view (MLO) of the left breast shows a small group of suspicious calcifications (left image). Magnification view of the group of suspicious calcifications (right upper image). BLES specimen X-RAY shows that the group of the calcifications is totally included in the specimen (right middle image). Magnification view (x 100) of the histopathology image of the BLES specimen reveals pleiomorphic LCIS (DCIS) was completely removed (right lower image). Subsequent surgery confirmed the achievement of complete removal and no residual disease was found.



**Figure 6.** Right craniocaudal (CC) view shows a 5 mm cluster of suspicious calcifications (right image). Magnification view of the cluster of the calcifications (left upper image). BLES specimen X-RAY shows that the cluster of the microcalcifications is included in the specimen (right middle image). Histopathology image of the BLES specimen shows ILC with 1mm free disease margins (lower left image). No residual disease was found in the final surgical result.



## Discussion

We report a study of 90 histopathologically proven cancers and 29 high risk lesions with cell atypia that underwent subsequent surgical excision. According to our results, the main criteria that could potentially be used in a clinical basis to assess BLES effectiveness in suspicious calcifications removal are the mammographic size, the distance of the lesion from the BLES specimen margins, the grade and no comedo phenotype.

We achieved complete removal of cancers in 31/90 cases (34.4%) and of high risk lesions with cell atypia in 23/29 cases (79.3%) using the intact BLES biopsy device.

Regarding cancers, the BLES success rate of excision is in agreement with previously published results with rates between 30% and 66%.<sup>5, 7-10</sup> Our study included calcifications only and no size limitation of the target lesion and this can explain the relatively low effectiveness of the method as there were lesions larger than the size that potentially the BLES probe can excise. The rationale behind this was to identify effective cut off sizes and other possible criteria, such as the grade and molecular type of the tumor, the presence of comedo necrosis and the distance of the tumor from the margins which either alone or in combination could be useful to assess the potential successful excision using the BLES device.

We found the size of the target lesion with a cut off size at 14 mm to be a major factor in excision. In cases smaller than 14mm, the success of excision was 57.4% (31/54 cases) and over that size, none of the cases was excised. Sub-analysis of smaller sizes showed a high success rate of excision of 71.4% at a cut off size of 8mm with specificity of 81.4% and in even smaller cases -less than 4.5mm-the excision rate was 95.7% with specificity of 98.3%. Apart from the probe size limitation, another reason that could explain the higher success rate of excision of smaller lesions is that a centrally targeted position of smaller lesions in the specimen can be potentially more easily achieved and thus more frequently disease free margins can be observed. The mean size of the excised tumors was 6.32 mm. The safest cut off size we found was 4.5 mm with specificity of 98.3%. However, in order to clinically assess the success of excision, radiology-pathology correlation should be in place taking into consideration other factors as well, such as the disease-free margins, the aggressiveness and the nature and type of the tumor (DCIS, invasive, invasive with DCIS, calcified-non calcified part of DCIS).

The distance of the lesion from the specimen margins was the main criteria we found for adequate excision of the target lesions. In cases of disease free margins, the achievement of excision was 67.5%. We found a safe cut off point of 0.75 mm distance of disease free margins with specificity of 96.6%. It is

known that both the type of tumor excised and the distance of the margins are significant factors in residual disease found on re-excision; invasive cancers have a lower rate of residual disease than DCIS.<sup>16</sup> We had only 6 cases of invasive tumors (3 of them with additional DCIS) that were completely excised. Most of our excised cases were small cases of DCIS (25 cases with size <10mm). However, it has been suggested that histopathologically small areas of DCIS show lower incidence of residual disease in re-excision when found close to the margins.<sup>17,18</sup>

The lower grade of the tumors and the absence of comedo necrosis were found to be the criteria for complete removal. This is in agreement with results from surgical excisions that have previously shown that factors such as the high nuclear grade and the presence of comedo necrosis are associated with increased risk of residual disease in re-excisions and presence of microinvasion, respectively.<sup>19-21</sup> In fact, in our population, 3/4 cases with microinvasion upgraded to invasion in the final result had shown comedo necrosis in the initial BLES specimen. Also, the tendency of the lower grade tumors to show higher excision rates could be potentially related to the more accurate imaging estimation of the extent of these tumors and thus the more accurate targeting.<sup>22</sup>

Regarding the high risk lesions, we found that the distance of the lesion from the specimen margins was the only criteria for the adequate excision using the BLES device and as reported previously from our department, high risk lesions were mainly removed when the distance of the lesion from the margins was over 1mm.<sup>23</sup> High risk lesions belong to a heterogeneous group of unknown potential of malignancy and adequate sampling with potential complete removal is the main clinical practice in order to rule out upgrading. No underestimation was found for the high-risk lesions which is the lowest of previously reported underestimations (0-9.5%)<sup>5, 7-10</sup>, supporting the adequate sampling. The safe removal of the high risk lesions supports the view of future potential use of the method to excise malignant lesions as well.

The underestimation rate of the cancers was 15.5% which is in agreement with previously reported underestimations, ranging from 3.2–21.4%<sup>2,3,7,9,10</sup>; however, the underestimation of DCIS to invasion was only 7.7%. The complication rate was also low, i.e., 8.75%. Both the underestimation and the complication rates have been previously reported in a study from our department.<sup>14</sup>

There are several limitations in the study. Firstly, only cases of calcifications were included, so solid masses were not investigated. Secondly, we included all sizes of calcifications and not only small clusters that can be potentially excised with the BLES probe; therefore, further research on the performance of



BLES in small groups of calcifications is required. Thirdly, we did not analyse the subtypes of DCIS apart from the comedo necrosis as this type is the most aggressive one and, instead, we analyzed the grade of the cancers. However, both the grade of DCIS and invasive cancers were included in the same groups to simplify the statistical analysis. Fourthly, we included the data and the analysis of the high-risk lesions with cell atypia separately in this study to present an overview of the performance of BLES in excision of calcifications, thereby avoiding the mixing of the data analysis. Finally, our study is a retrospective one, so a possibility of bias cannot be excluded.

In conclusion, the small size and low grade of the cancers no comedo presence and disease free specimen margins were found to be the main criteria for suspicious calcifications excision using the BLES device, supporting the idea that potential consideration of these factors can play a role in the future clinical assessment of BLES as a possible removal tool in selected cases of suspicious calcifications.

#### Conflict of Interest

None.

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