Positive Predictive Value for the Malignancy of Mammographic Abnormalities Based on the Presence of an Ultrasound Correlate

Original Article

Alshafeiy T et al. Positive Predictive Value for the Malignancy of Mammographic Abnormalities Based on the Presence of an Ultrasound Correlate Ultrasound Int Open 2022; 8: E8–E14 | © 2022. The Author(s)

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Key words
breast, AREAS, STRUCTURES & SYSTEMS, mammography, METHODS & TECHNIQUES, ultrasound, METHODS & TECHNIQUES

received 29.06.2021
accepted after revision 18.04.2022

Bibliography
Ultrasound Int Open 2022; 8: E8–E14
DOI 10.1055/a-1832-1808
ISSN 2199-7152
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ABSTRACT

Purpose To compare the outcomes of different mammographic lesions based on the presence of an ultrasound (US) correlate and to estimate how often targeted US can identify such lesions.

Materials and Methods This retrospective study included all consecutive cases from 2010 to 2016, with Breast Imaging Reporting and Database System (BI-RADS) categories 4 & 5 who underwent US as part of their diagnostic workup. We compared the incidence of malignancy between lesions comprising a US correlate that underwent US-guided core needle biopsy (CNB) and those without a correlate that underwent stereotactic CNB.

Results 833 lesions met the study criteria and included masses (64.3%), architectural distortion (19%), asymmetries (4.6%), and calcifications (12.1%). The CNB-based positive predictive value (PPV) was higher for lesions with a US correlate than for those without (40.2% [36.1, 44.4%] vs. 18.9% [14.5, 23.9%], respectively) (p < 0.001). Malignancy odds for masses, asymmetries, architectural distortion, and calcifications were greater by 2.70, 4.17, 4.98, and 2.77 times, respectively, for the US-guided CNB (p < 0.001, p = 0.091, p < 0.001, and p = 0.034, respectively). Targeted US identified a correlate to 66.3% of the mammographic findings. The odds of finding a correlate were greater for masses (77.8%) than architectural distortions (53.8%) (p < 0.001) or calcifications (24.8%) (p < 0.001).

Conclusion The success of targeted US in identifying a correlate varies significantly according to the type of mammographic lesion. The PPV of lesions with a US correlate was significantly higher than that of those with no correlate. However, the PPV of lesions with no US correlate is high enough (18.9%) to warrant a biopsy.
Introduction

Targeted breast ultrasound (US) is frequently used as an adjunct to diagnostic mammography because of its ability to characterize lesions [1]. Moreover, the use of US in addition to mammography increases the sensitivity and specificity of breast cancer diagnosis from 63 % to 95 and 89 % to 92 %, respectively [2]. Moreover, it increases the cancer detection rate from 3 % to 5 % [3].

If abnormal findings are observed on screening mammography, the patients are recalled for diagnostic evaluation. Supplemental mammographic views are traditionally obtained with targeted breast US (if required). The goal of targeted US during the evaluation of a mammographic lesion is to achieve a more specific diagnosis of the cause of a mammographic abnormality, to prevent unnecessary biopsies, and to detect more carcinomas.

Despite a meticulous mammographic-sonographic correlation and skilled personnel, targeted US may not identify mammographic findings. Sampling must be performed by either stereotactic, tomosynthesis-guided biopsy or primary surgical incisional biopsy for lesions without a US correlate. Institutions that lack special equipment to perform stereotactic or tomosynthesis-guided biopsy may hesitate to perform a surgical intervention in the absence of a US correlate [4]. We aimed to compare the outcome of different mammographic lesions based on the presence of a US correlate and to assess how often targeted US can identify these lesions.

Patients and Methods

This retrospective study was approved by our Institutional Review Board and was in compliance with the Health Insurance Portability and Accountability Act. A waiver of consent was granted based on its retrospective design.

Patient selection

We included all attending consecutive cases over 7 years that had been assigned Breast Imaging Reporting and Database System (BI-RADS) categories 4 and 5 on diagnostic mammography because of abnormal screening mammography (BI-RADS 0) and underwent a US examination as part of the diagnostic workup. We excluded lesions that were detected only on screening US or magnetic resonance imaging (MRI).

We reviewed patient medical records for the type of mammographic abnormalities, as stated in the diagnostic report, the presence of a US correlate, biopsy guidance, and biopsy results. Mammographic abnormalities were classified according to the BI-RADS lexicon [5] as masses, asymmetries, architectural distortions, and calcifications. The lesion was classified according to the dominant component in the diagnostic study when it included two more findings, such as a mass with associated calcifications (►Fig. 1). Moreover, the term calcification was only used for pure calcifications without associated findings.

We calculated and compared the positive predictive value (PPV) for malignancy between patients with and without a US correlate. In general, patients with a US correlate underwent US-guided core needle biopsy with post-biopsy marker deployment upon completion of the procedure. In contrast, those without a correlate underwent stereotactic biopsy. All US-guided core needle biopsy procedures were done using a 14-gauge automatic needle, while all stereotactic biopsy procedures were performed using 11-gauge vacuum-assisted needles. Typically, 5 samples were enough for US-guided biopsy, whereas 6–12 samples were taken in stereotactic procedures. In cases including a subtle US correlate, stereotactic biopsy may have been chosen over US guidance at the discretion of the radiologist. Upon the completion of all US- and stereotactic-guided biopsy procedures, a clip tissue marker was placed to mark the biopsy site. A post-biopsy mammogram with two basic views (CC and MLO) was also obtained.

Imaging Technique and Interpretation

All patients underwent screening mammography (2D only or both 2D and 3D). The mammograms were interpreted using the BI-RADS lexicon by dedicated breast radiologists with one to 23 years of experience [5]. Patients with abnormal findings identified on screening mammography were assigned BI-RADS 0 and recalled for diagnostic mammography, which included additional mammographic views and/or targeted US (if required). US examinations were performed by four fellowship-trained breast imaging radiologists with 5 years to 20 years of experience in breast imaging and performing breast US. Linear multi-frequency transducers of US machines dedicated to breast imaging were used. During this period, we used Philips IU 22 and Siemens Acuson S2000.

Patients who did not undergo breast US, those assigned final categories BI-RADS 1, 2, or 3 following the diagnostic workup, and patients with incomplete data including declined or failed biopsy and unavailable results were excluded from the study.

Statistical analyses

Categorical data are presented as frequencies and relative frequencies (i.e., percentages). We used the confidence interval method of Agresti and Coull (1998) to construct 95 % confidence intervals for PPVs of the US-guided CNB and stereotactic CNB malignancy classifications [6]. Furthermore, we conducted inter-imaging-modality comparisons of diagnostic relative frequencies (e.g., PPV) based on conventional chi-square frequency tests. A p ≤ 0.05 decision rule was established a priori as the null hypothesis rejection rule for inter-imaging-modality diagnostic comparisons of relative frequencies. All statistical analyses were conducted using the Spotfire Splus version 8.2 statistical package (TIBCO Inc., Palo Alto, CA).

Results

Following abnormal mammography screening, 2,092 lesions underwent diagnostic workup during the study period. We excluded 1,259 lesions because of a lack of US examination in the diagnostic workup, lack of a biopsy, or incomplete data. 833 lesions in 811 patients met our inclusion criteria. The mean patient age was 59.1 years (range: 31 to 86 years; SD: 11.9 years). Mammographic lesions included masses (64.3 %, n = 536), asymmetries (4.6 %, n = 38), architectural distortions (19 %, n = 158), and calcifications (12.1 %, n = 101).

A US correlate was identified for 552 lesions (66.3 %), which varied significantly according to the original mammography finding (p < 0.001) (►Table 1). The PPV of a US correlate was significantly greater for a mass (77.8 %) than for architectural distortions (53.8 %) (p < 0.001) or calcifications (24.8 %) (p < 0.001). Similarly, the likelihood of finding a US correlate was significantly greater for an...
asymmetry (65.8 %) or architectural distortion (53.8 %) than for calcifications (24.8 %) (p < 0.001 for both) (Table 1).

While lesions with a US correlate (66.3 %, n = 552) underwent US-guided CNB, those without a correlate (33.7 %, n = 281) underwent stereotactic biopsy.

Comparing the pathological outcomes of mammographic lesions based on biopsy guidance

The overall malignancy rate of lesions that underwent US-guided CNB was significantly higher than that of those that underwent stereotactic biopsy (40.2 vs. 18.9 %, respectively) (p < 0.001) (Table 2).

Moreover, we estimated the pathological outcomes for each mammographic finding. Masses that underwent US-guided CNB demonstrated a significantly higher PPV for malignancy than those that underwent stereotactic CNB (39.3 vs. 19.3 %, respectively) (p < 0.001) (Table 3).

Similarly, architectural distortions that underwent US-guided CNB were more likely to have higher malignancy rates than lesions that underwent stereotactic biopsy (PPV, 41.2 vs. 112.3 %, respectively) (p < 0.001) (Table 3).

Asymmetries that underwent US-guided CNB revealed a significantly higher PPV for malignancy than those that underwent stereotactic CNB (44.0 vs. 15.4 %, respectively) (p = 0.019) (Table 3).

Likewise, calcifications that underwent US-guided CNB had a significantly greater likelihood of malignancy than those that underwent stereotactic biopsy (PPV, 48 vs. 25 %, respectively) (p = 0.034) (Table 3).

There were no significant differences in the incidence of high-risk lesions between lesions that underwent US- or stereotactic-guided CNB (p = 0.713).

| Presence of a US correlate based on mammographic findings. |
|-----------------|-----------------|----------|----------------|
| US correlate    | No US correlate | Total    | PPV [95 % CI]  |
| Masses          | 417             | 119      | 536             | 77.8 % [74.0, 81.2 %] |
| Asymmetries     | 25              | 13       | 38              | 65.8 % [48.6, 80.4 %] |
| Architectural distortions | 85     | 73       | 158             | 53.8 % [45.7, 61.8 %] |
| Calcifications  | 25              | 76       | 101             | 24.8 % [16.7, 34.3 %] |
| Total           | 552             | 281      | 833             |                      |

p < 0.001; PPV: positive predictive value; US: ultrasound.
Benign discordant lesions identified following targeted US-guided CNB

We identified benign discordant results in 54 cases that underwent targeted US-guided CNB (9.8 %, n = 54 of 552). 19 (35.2 %, 19 of 54) cases were upgraded to malignancy based on surgical excision or repeated biopsy under stereotactic guidance (▶ Table 4). Invasive ductal carcinoma (IDC), tubular carcinoma, invasive lobular breast cancer, and ductal carcinoma in situ were observed in 12, 1, and 3 cases, respectively.

On reviewing the clip site in the aforementioned cases, the clip was found to be misplaced (off) in 20 cases (37 %, 20 of 54). In other words, the presumed US correlate was wrong, and the exact lesion was not observed on mammography (▶ Fig. 2). In contrast, the clip was found to be in a good place in 34 cases (63 %).

27 (50 %) patients underwent surgical excision for benign discordant biopsy. While 16 (29.5 %) patients underwent repeated biopsy under stereotactic guidance, 3 (5.5 %) underwent MRI to verify if the original mammographic lesions were benign. Moreover, 8 (15 %) patients refused surgery and chose follow-up. We performed follow-up by mammography for at least 2 years (2–5 years).

Misplacement of a post-biopsy clip is more likely to result in an upgrade in the subsequent surgical excision (65 %, 13 of 20) than in the case of discordant lesions with the clip in place (21.4 %, 6 of 28) (p = 0.001)

Discussion

Our findings demonstrate that, despite being common for screen- ing-detected masses, asymmetries, and architectural distortions, the presence of a US correlate is less common for calcifications. Moreover, the PPV for biopsy is much higher for all lesion types when a US correlate is detected. The lack of a US correlate does not indicate consideration of follow-up over biopsy due to a > 2 % rate of malignancy.

**Table 2** Biopsy outcomes by imaging guidance method.

<table>
<thead>
<tr>
<th></th>
<th>Malignant</th>
<th>High-risk lesions</th>
<th>Benign</th>
<th>Total</th>
<th>PPV [95 % CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-guided CNB</td>
<td>222 (40.2 %)</td>
<td>53 (9.6 %)</td>
<td>277 (50.2 %)</td>
<td>552</td>
<td>40.2 % [36.1, 44.4 %]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stereotactic CNB</td>
<td>53 (18.9 %)</td>
<td>30 (10.7 %)</td>
<td>198 (70.5 %)</td>
<td>281</td>
<td>18.9 % [14.5, 23.9 %]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>275 (33.0)</td>
<td>83 (10.0)</td>
<td>475 (57.0)</td>
<td>833</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNB: core needle biopsy; PPV: positive predictive value; and US: ultrasound.

**Table 3** Pathological outcomes of different mammographic findings by biopsy guidance method.

<table>
<thead>
<tr>
<th></th>
<th>Malignant</th>
<th>High-risk lesion</th>
<th>Benign</th>
<th>Total</th>
<th>PPV [95 % CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Masses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-guided CNB</td>
<td>164 (39.3 %)</td>
<td>33 (7.9 %)</td>
<td>220 (52.8 %)</td>
<td>417</td>
<td>39.3 % [34.6, 44.2 %]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stereotactic CNB</td>
<td>23 (19.3 %)</td>
<td>8 (6.7 %)</td>
<td>88 (73.9 %)</td>
<td>119</td>
<td>19.3 % [12.7, 27.6 %]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>187 (34.9 %)</td>
<td>41 (7.6 %)</td>
<td>308 (57.5 %)</td>
<td>536</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Architectural Distortions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-guided CNB</td>
<td>35 (41.2 %)</td>
<td>13 (15.3 %)</td>
<td>37 (43.5 %)</td>
<td>85</td>
<td>41.2 % [30.6, 52.4 %]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stereotactic CNB</td>
<td>9 (12.3 %)</td>
<td>9 (12.3 %)</td>
<td>55 (75.3 %)</td>
<td>73</td>
<td>12.3 % [5.8, 22.1 %]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44 (27.8 %)</td>
<td>22 (13.9 %)</td>
<td>92 (58.2 %)</td>
<td>158</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asymmetries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-guided CNB</td>
<td>11 (44.0 %)</td>
<td>3 (12.0 %)</td>
<td>11 (44.0 %)</td>
<td>25</td>
<td>44.0 % [24.4, 65.1 %]</td>
<td>0.019</td>
</tr>
<tr>
<td>Stereotactic CNB</td>
<td>2 (15.4 %)</td>
<td>2 (15.4 %)</td>
<td>9 (69.2 %)</td>
<td>13</td>
<td>15.4 % [1.9, 45.4 %]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 (34.2 %)</td>
<td>5 (13.1 %)</td>
<td>20 (52.6 %)</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calcifications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-guided CNB</td>
<td>12 (48.0 %)</td>
<td>4 (16.0 %)</td>
<td>9 (36.0 %)</td>
<td>25</td>
<td>48.0 % [27.8, 68.7 %]</td>
<td>0.034</td>
</tr>
<tr>
<td>Stereotactic CNB</td>
<td>19 (25.0 %)</td>
<td>11 (14.5 %)</td>
<td>46 (60.5 %)</td>
<td>76</td>
<td>25.0 % [15.8, 36.3 %]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31 (30.7 %)</td>
<td>15 (14.9 %)</td>
<td>55 (54.4 %)</td>
<td>101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNB: core needle biopsy; PPV: positive predictive value; and US: ultrasound.
Bahl et al. [7] investigated factors that influence the outcome of architectural distortions. Architectural distortions detected by screening mammography are less likely to represent malignancy than those detected by diagnostic mammography (67.0 vs. 83.1 %, respectively, \( p < 0.001 \)). Targeted US could identify 304 of 347 (87.6 %) architectural distortions. Moreover, distortions without a sonographic correlate were less likely to represent a malignant lesion than those with a correlate (27.9 vs. 82.9 %, respectively, \( p < 0.001 \)).

Targeted US could identify a correlate in 53.8 % of architectural distortions. Similarly, the malignancy rate was significantly lower for distortions without a US correlate compared to those with a correlate (41.2 vs. 12.3 %, respectively, \( p < 0.001 \)). However, the rate was not low enough to forgo biopsy (Fig. 3).

Chesebro et al. [8] evaluated the outcomes of developing asymmetries and found that US could characterize 30 out of 201 lesions with an accuracy of 15 %. Moreover, they established an association between developing asymmetries with US correlates and an increased risk of malignancy, with 57 % malignancy versus 37 % for asymmetries without a correlate.

### Table 4 Association between upgrading to malignant and original mammographic findings.

<table>
<thead>
<tr>
<th>Mammographic finding</th>
<th>Upgraded</th>
<th>Not upgraded</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masses</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Architectural distortions</td>
<td>5</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Asymmetries</td>
<td>5</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Calcifications</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>19</td>
<td>35</td>
<td>54</td>
</tr>
</tbody>
</table>

\( p = 0.232 \).
Shetty et al. [9] investigated the role of US in the evaluation of focal asymmetries among 36 women. They observed a solid mass, complicated cyst, echogenic tissue, and no US correlate in 41.7 % (15 of 36), 5.6 % (2 of 36), 25.0 % (9 of 36), and 27.8 % (10 of 36) of cases, respectively. Excisional biopsy of focal asymmetries showed IDC in seven patients (19.4 %, 7 of 36). Two of these patients (28.6 %) revealed no abnormality during US, thereby supporting the idea that negative US does not exclude malignancy and should not prevent biopsy.

A series by Soo et al. [10] mentioned that 23 % of the calcifications observed on mammography were detected by US. In addition, US-detected calcifications were three times more likely to be malignant and invasive than those detected by mammography alone.

Bae et al. [11] reviewed 336 patients with suspicious microcalcifications who underwent biopsy under image guidance. Only 17.5 % of the calcifications could be identified on targeted US. In contrast, 74 % were mammography only findings. The remaining 8.5 % of cases demonstrated an association between a mass and calcifications during US. In addition, the lesions visible on US were more likely to represent malignancy (66.2 % vs. 23.2 %, respectively; p < 0.001) and depicted higher BI-RADS categories than those not detected by US (61.0 vs. 22.2 %, respectively; p < 0.001).

Our findings correspond with the findings of previous studies that mammographic lesions with no US correlates were associated with significantly lower malignancy rates than those with correlates. However, the rates were high enough to recommend biopsy.

The rate of upgrades to malignancy among patients who underwent surgical excision for benign discordant results demonstrated a significant association with post-biopsy clip position (p = 0.001). Misplaced clips following biopsy were associated with an upgrading rate of 65 % (13 cases of 20) at the time of surgical excision. Post-biopsy, misplaced clip markers should alert radiologists to the fact that the finding sampled under targeted US guidance is not the same as the lesion primarily detected by mammography.

However, surgeons should still excise discordant lesions with a good clip position. This can be attributed to the upgrading rate of 21.4 %, which is not negligible. Good position of the clip should not prevent the surgical excision of a benign discordant biopsy result. Nonetheless, a misplaced clip should definitely prompt action, either re-biopsy under stereotactic guidance or surgical excision.

Misplaced clips should be documented and followed with placement of another clip. Cases of migrated clips are challenging if the lesion is no longer palpable or detectable by imaging. It is nearly impossible to perform breast-conserving surgery with no intraoperative guidance. Some surgeons perform blind wide lumpectomy with the aid of intraoperative fluoroscopy. Tomosynthesis does not usually improve the accuracy of marker placement [12].

Previous studies mentioned that all benign discordant results should be surgically excised, owing to the substantial cancer detection rate in subsequent surgical excision 15–50 % [13–22].

Previous studies showed an acceptable interobserver agreement regarding BI-RADS lexicon since its introduction in 1993 for mammography and its redesign for mammography in 2003 [23–27]. The current study included a relatively wide range of radiologist experience in breast imaging reflecting the real practice of radiology in most institutions. The effect of inter- and intraobserver variability may have influenced the results. Palazuelos et al. [28] criticized the Choi et al. study [24] for the evaluation of interobserver agreement emphasizing the importance of using a well-designed and dedicated study design to evaluate this point.

However in the current study, the mammography and US results were homogeneously distributed among the radiologists for various BI-RADS categories with no predilection for any category to be assigned to a specific level of experience. Correlating the efficacy of clip placement with the level of radiologist experience would have also enriched the study and influenced its results. This issue requires a different study design.

Our study had several limitations. The study had a retrospective design and was performed at a single institution. Moreover, targeted US was not performed in all cases. We only included lesions that underwent US examination. Therefore, the incidence of a US correlate did not predict the overall finding on diagnostic imaging.

Moreover, we only included suspicious and malignant lesions, so that the data did not predict the incidence of overall malignancy in screening. In addition, we could not accurately evaluate lesions with subtle correlates on US as they underwent stereotactic biopsy and were considered with no US correlates. Evaluation of inter-reader variability and the effect of the “number of years of experience of the performing radiologist” on the accuracy of targeted US and on targeted US-guided biopsy would have enriched the study. This, however, could not be achieved, because in our institution the radiologist who performed the diagnostic workup is not necessarily the same one who performed the procedure.

The strengths of this study include that all targeted US examinations were performed by dedicated breast imaging radiologists. Moreover, this is the first study to compare the PPV of all mammographic findings based on the presence of a US correlate.

The study findings are clinically relevant as targeted US could identify a correlate in only 66 % of cases. The incidence of malignancy is significantly lower for lesions with no US correlate, although it is still high enough to recommend biopsy. The PPV was not low enough to prevent biopsy.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

References


