Rates of Presurgical Underestimation of Breast Cancer after Standardized Assessment of Breast Calcifications

Zusammenfassung

Ziel: Häufigkeitsbestimmung histopathologischer Brustkrebsunterschätzung nach Vakuumass-tested Biopsie (VSB) in der standardisierten Abklärung von Mikroverkalkungen der Brust im Vergleich zur postoperativen Diagnose.


Ergebnisse: Bei 91/119 Frauen (76,5 %) war die endgültige Histologie maligne. Der Anteil des duktalen Carcinoma in situ (DCIS) betrug 79,1 % (72/91), der Anteil der invasiven Karzinome 20,9 % (19/91). Bei 9/37 Frauen mit diagnostischen Exzisionen änderte sich die präoperative benign als unklare Dignität zu einer postoperativen Diagnose. In acht Fällen betraf die Diagnoseunterschätzung das DCIS (21,6 %) und in einem Fall invasives Brustkrebs (2,7 %). Sieben von neun unterschätzte Fälle (77,8 %) resultierten aus der diagnostischen Exzision atypischer epithelialer Proliferationen vom duktalen Typ (AEPDT, positiver prädiktiver Wert 30,4 % (7/23)). Bei präoperativer DCIS-Diagnose wurde bei 7/71 Frauen postoperativ invasiver Brustkrebs diagnostiziert (9,9 %). Bei 11/82 Frauen mit einer onkologisch geplanten Operation wurde invasiver Brustkrebs bereits durch die VSB diagnostiziert.

Schlussfolgerung: Die präoperative Unterschätzung einer DCIS-Diagnose nach VSB bei postope-

Abstract

Purpose: To determine the frequency of histopathological underestimation of breast cancer after vacuum-assisted biopsy (VAB) in standardized assessment of breast calcifications compared to postsurgical diagnosis.

Materials and Methods: The retrospective study included acquired data of 506 consecutively examined women, who underwent VAB for the assessment of pure calcifications after standardized digital mammographic and sonographic imaging. 119/506 (24.5%) women underwent further surgical procedures: 37 women had a surgical diagnosis of invasive cancer, 82 women a surgical procedure based on a therapeutic concept. Postsurgical results of VAB were compared with the postsurgical histopathological reports.

Results: In 91/119 women (76.5%) the final histology was malignant. The rate of ductal carcinoma in situ (DCIS) was 79.1% (72/91) and the rate of invasive carcinoma was 20.9% (19/91). In 9/37 women with diagnostic excision biopsy, the postsurgical status of benign or uncertain changed to a postsurgical diagnosis of malignant (24.3%). In eight cases underestimation included DCIS (21.6%) and in one case invasive cancer (2.7%). Seven of the nine underestimated cases (77.8%) resulted from excision biopsy of atypical epithelial proliferation of ductal type (AEPDT, positive predictive value 30.4% (7/23)). After surgery due to DCIS in 7/71 women invasive breast cancer was diagnosed (9.9%). In 11/82 women with oncological surgery, invasive cancer was already diagnosed by VAB.

Conclusion: Underestimation of invasive cancer in terms of presurgical DCIS diagnosis can be minimized by the standardized assessment protocol to about 10%. Underestimation of DCIS is mainly related to presurgical diagnosis of AEPDT.

Key Points:
- The standardized use of digital mammographic and sonographic imaging prior to vacuum-assisted biopsy is suitable for minimizing underestimation of invasive breast cancer. AEPDT represents a high risk diagnosis for underestimation of DCIS.

Citation Format:

Purpose

Previous reports have focused on lesion-related and device-related factors influencing underestimation after percutaneous biopsy in relation to postsurgical histology [1] defined as an upgrade of a benign lesion or a lesion with an uncertain malignant potential to a malignant diagnosis or upgrade of a diagnosis of ductal carcinoma in situ (DCIS) to invasive breast cancer. Underestimation of DCIS occurs more frequently with large-core biopsy than with vacuum-assisted biopsy (VAB) [2]. Further risk factors are high-grade lesion at diagnostic excision biopsy, lesion size greater than 20 mm in diameter at radiological imaging, palpability and mammographic masses [1].

In the course of the establishment of digital mammography techniques, the detection rate of breast lesions corresponding with calcifications increased [3]. VAB is the method of choice in the invasive assessment of calcifications. Because of a known association of small invasive breast cancers as well as DCIS, a precursor lesion of invasive breast cancer, with calcifications, VAB is a frequently used diagnostic tool in the assessment of mammography screening programs [4]. Therefore, the accuracy of presurgical histological results plays an important role in daily clinical practice in terms of adequate surgical planning, risk assessment regarding postsurgical changes to malignancy and informed discussion.

Therefore, we determined the frequency of underestimation of postsurgical histopathological results in comparison to presurgical histopathological diagnosis of vacuum-assisted biopsy in standardized assessment of pure breast calcifications.

Materials and Methods

Study group

The retrospective study included acquired data of 506 consecutively examined women, who underwent VAB for the assessment of pure calcifications after participation in one digital unit of the national mammography screening program [5, 6] within 30 months (January 2010 to June 2013). After VAB, correlation between imaging characteristics and histopathological morphology was proven in all cases by a multidisciplinary conference.

In 382 of 506 women (75.5 %) after VAB no further surgical procedure was recommended. 358 of these VABs were coded with the histopathological category B2 (benign lesions: cystic alterations, adenosis n = 298, fibroadenoma n = 51, fat necrosis n = 6, periductal mastitis n = 3) and 24 were coded with B3 (lesions of uncertain malignant potential: lobular neoplasia n = 16, small papilloma re-moved n = 4, small radial scar not depicted by imaging n = 4) as described by the European guidelines [5].

Follow-up of women with B2 lesions without recommended surgery was available for 305 of 358 women (85.2 %) as follows: 221 women had a normal screening mammogram two years later, 84 women had follow-up examinations after biopsy at the hospital during the screening interval; invasive breast cancer ≤ 10 mm in size was diagnosed in one woman in a different quadrant to the performed VAB at an interval of 15 months. Follow-up of women with B3 lesions without recommended surgery was available for 22 of 24 women (91.7 %) with the following results: 15 women had a normal screening examination two years later, 7 women had an individual follow-up scheme with shorter intervals than two years; no cancer occurred. No follow-up was available in 55 women (with B2 lesions n = 53, with B3 lesions n = 2).

In 124 of 506 women (24.5 %) after VAB further surgical procedures were indicated. In 119 of 124 women (96.0 %) surgery was performed and data were available for evaluation. 37 of 119 women (31.1 %) underwent a surgical diagnostic excision biopsy. Diagnostic excisions were indicated due to histological risk lesions (n = 36) or a histological benign lesion in the assessment of linear calcifications (n = 1) [5, 7] (Table 1). 82 of 119 women (68.9 %) had a surgical procedure based on a therapeutic concept (Table 1).

Standardized assessment of calcifications

Assessment took place at a specialized breast diagnostic unit at a university hospital. Two breast radiologists performed standardized additional imaging procedures for the assessment of calcifications, including digital magnification views cranio-caudal and latero-medial (Selenia; Dimensions; Hologic, Bedford, Mass) [8] and high-resolution ultrasound (Acuson S2000; Siemens Healthcare, Erlangen, Germany). Clinical examination and ultrasound of the whole breast were added systematically to verify the absence of an associated mass as well as to assess the axillary lymph nodes. With knowledge of additional imaging and clinical examination during the assessment process, radiologists documented the lesion morphology in the screening software (MaSc; KVIT, Dortmund, Germany). Calcifications without an additional mass, identified by described imaging, were called pure calcifications. For study purposes lesion data were extracted from the screening software. Diameters of areas of suspicious calcifications were estimated on the magnification views pre-VAB. In cases of pure suspicious calcifications, vacuum-assisted biopsy was performed by two breast radiologists (96, mean number of samples 12, range 7 to 20). Post-biopsy mammograms cranio-caudal and latero-medial were obtained. Samples were examined by two specialized pathologists. Lesions were categorized according to the B categories as described by the European guidelines (Table 1).
Table 1 Distribution of pathological B categories and histological lesions after performance of vacuum-assisted biopsy of women with further recommendation for surgical procedure.

<table>
<thead>
<tr>
<th>category of vacuum-assisted biopsy</th>
<th>histological lesion</th>
<th>number/ frequency N/(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2: benign lesion</td>
<td>adenosis¹</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>B3: lesions of uncertain</td>
<td>atypical epithelial proliferation of ductal type²</td>
<td>21 (17.6)</td>
</tr>
<tr>
<td>malignant potential</td>
<td>papillary lesion³</td>
<td>9 (7.6)</td>
</tr>
<tr>
<td></td>
<td>radial scar³</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td></td>
<td>mucocoele-like lesion³</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>flat epithelial atypia³</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>B4: suspicious of malignancy</td>
<td>atypical epithelial proliferation of the ductal type, suspicious for ductal carcinoma in situ</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>B5a: malignant, in situ lesion</td>
<td>ductal carcinoma in situ</td>
<td>71 (59.7)</td>
</tr>
<tr>
<td>B5b: malignant, invasive breast lesion</td>
<td>invasive breast cancer</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>119 (100)</td>
</tr>
</tbody>
</table>

¹ Histologically benign lesion in the assessment of linear calcifications, correlation was based on non-comedo calcifications in dilated ducts; surgery revealed that the DCIS had a weak correlation of DCIS with calcifications.  
² Histologisch gutartige Läsion resultierend aus der Abklärung linearer Mikroverkalkungen, die Korrelation basierte auf Non-Komedonekrosen in dilatierten Gängen; die Operation erbrachte, dass das DCIS eine schwache Mikrokalkkorrelation aufwies.  
³ Diagnostic excision biopsy was indicated independently of residual parts of the lesion by imaging.  
Diagnosticen Exzisionen wurden unabhängig von mammografischen Restverkalkungen indiziert.  

All biopsy results were confirmed for agreement between radiological and pathological diagnosis in a multidisciplinary conference [5]. If indicated, therapeutic or diagnostic surgery was planned by the multidisciplinary team. According to our previously described diagnostic protocol, all lesions of atypical epithelial proliferation of ductal type (AEPDT) were recommended for surgical excision. Diagnostic excision was recommended for radial scars (RS), papillary lesions (PAP), mucocoele-like lesions (MUC) and flat epithelial atypia (FEA) when lesion remnants were visible on post-interventional imaging [7].

Analysis
Histopathological diagnosis after surgery was compared with presurgical histopathological diagnosis of VAB. Underestimation of histological breast lesions after VAB in comparison to further surgery was defined as follows:

► Diagnostic excision biopsy: A histologically benign lesion or a lesion of uncertain malignant potential obtained by VAB changed postsurgery to a malignant histology, including DCIS and invasive breast cancer.

► Therapeutic surgery: A DCIS diagnosis obtained by VAB changed postsurgery to an invasive breast cancer diagnosis.

The rates of underestimation were determined separately for diagnostically relevant excision biopsy and therapeutic surgery. In each case, the presurgical result of VAB was compared with the postsurgical histopathological report.

Table 2 Distribution of histopathological pre- and postsurgical lesions of performed diagnostic excision biopsies.

<table>
<thead>
<tr>
<th>histological lesion</th>
<th>planned diagnostic excision surgery</th>
<th>underestimation</th>
<th>underestimation per lesion type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number N</td>
<td>number N/pT category</td>
<td>frequency %</td>
</tr>
<tr>
<td>adenosis⁴</td>
<td>1</td>
<td>1 (pTis)¹</td>
<td>100</td>
</tr>
<tr>
<td>atypical epithelial proliferation of ductal type²</td>
<td>23</td>
<td>6 (pTis)²</td>
<td>30.4</td>
</tr>
<tr>
<td>papillary lesion³</td>
<td>9</td>
<td>1 (pTis)⁴</td>
<td>11.1</td>
</tr>
<tr>
<td>radial scar³</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mucocoele-like lesion³</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>flat epithelial atypia³</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>37</td>
<td>9</td>
<td>24.3</td>
</tr>
</tbody>
</table>

pT: pathological tumor category according to the TNM classification.  
¹ Ductal carcinoma in situ, nuclear grade: intermediate (n = 1).  
² Ductal carcinoma in situ, nuclear grade: low (n = 2), intermediate (n = 2), high (n = 2).  
³ Ductal carcinoma in situ, nuclear grade: gering (n = 2), intermediär (n = 2), hoch (n = 2).  
⁴ Invasive ductal carcinoma, grade: 2.  
Invasiv duktales Karzinom, Grad: 2.  
Duktales carcinoma in situ, nuclear grade: low (n = 1).  
Duktales carcinoma in situ, Kernenmalignitätsgrad: gering (n = 1).

Sizes of areas of suspicious calcifications on magnification views pre-VAB were measured to calculate the median and range. Post-VAB the mammographic complete versus incomplete removal of calcifications was determined.

Results

In 91 of 119 women undergoing surgery (76.5 %), the final histology was malignant. Among these diagnoses, the rate of ductal carcinoma in situ (DCIS) was 79.1 % (72/91) and the rate for invasive carcinoma was 20.9 % (19/91).

Diagnostic excision biopsy

Of the 37 women who had a diagnostic excision biopsy, the presurgical benign diagnosis was confirmed in 28 cases (75.7 %). In 9 of 37 women the final diagnosis was underestimated and the presurgical non-malignant diagnosis changed to a postsurgical malignant diagnosis (24.3 %). Of these nine cases, underestimation included the diagnosis of DCIS (mean 9 mm, range 5 – 32 mm) in eight cases (21.6 %) and the diagnosis of an invasive cancer of 5 mm in size in one case (2.7 %). Seven of the nine underestimated cases (77.8 %) resulted from excision biopsy after the diagnosis of atypical epithelial proliferation of ductal type (AEPDT). The positive predictive value for malignancy of AEPDT was 30.4 % (7/23) (Table 2).

In the case of atypical epithelial proliferation of ductal type, the median mammographic diameter of calcifications without...
a postsurgical upgrade (n = 16) was 15 mm (range 3 mm to 50 mm), and that of those with a postsurgical upgrade (n = 7) was 28 mm (range 4 mm to 51 mm). In 2 of 10 (20.0 %) AEPDT diagnoses without residuals classifications post-VAB, the upgrade occurred postsurgically, while 5 of 13 (38.5 %) AEPDT diagnoses with residual classifications had a postsurgical upgrade.

**Oncological surgery**
In 11 of the 82 women who received oncological surgery, an invasive cancer was already diagnosed by VAB. Postsurgical diagnoses included invasive ductal carcinoma (n = 9), invasive lobular carcinoma (n = 1) and invasive micropapillary carcinoma (n = 1). In 71 women surgery was planned on the base of a presurgical DCIS diagnosis. After surgery due to DCIS, invasive breast cancer was diagnosed in 7 of those 71 women (9.9 %) and the pre-surgical result underestimated the presence of invasion (mean diameter 11 mm, range 2 – 37 mm). In 28.6 % (n = 2) of the underestimated cases, the nuclear grade was reported as intermediate, and in 57.1 % (n = 4) as high. In one case the nuclear grade was not available (14.3 %) (Table 3).

The median mammographic diameter of calculations of DCIS cases without a postsurgical upgrade (n = 64) was 24 mm (range 4 mm to 96 mm). Among the DCIS cases with an upgrade (n = 7), the median mammographic diameter of calculations was 36 mm (range 7 mm to 79 mm).

Of all VAB-related DCIS diagnoses, underestimation occurred in 2 of 16 cases (12.5 %) of mammographic lesion size over 50 mm. In 2 of 15 DCIS lesions (13.3 %) without residual classifications post-VAB, an upgrade occurred postsurgically (pT1a, pT1b). In 5 of 56 DCIS lesions (8.9 %) with residual classifications post-VAB, an upgrade was diagnosed postsurgically.

**Discussion**
Standardized assessment of mammographic pure breast calcifications with exclusion of an associated mass by ultrasound and consecutive performance of vacuum-assisted biopsies underestimated final histological lesions of diagnostic excision biopsies in 24 % of cases, so that postsurgical modification of histology required oncological surgery. The leading constellation consisted of postsurgical DCIS diagnosis after excision biopsy due to atypical epithelial proliferation of ductal type resulting from vacuum-assisted biopsy. In primary DCIS diagnoses obtained by vacuum-assisted biopsy, 90 % were estimated precisely whereas in 10 % of cases presurgical invasive breast cancer was underestimated.

The assessment of breast calcifications resulted in 28 benign (23.5 %) and 91 malignant (76.5 %) postsurgical diagnoses. Postsurgical malignancy should be monitored, especially since calculation-related breast lesions are known to be associated with higher rates of lesions of uncertain malignant potential (B3) than masses [9] and therefore may carry a higher probability for a benign surgical excision compared to masses or a mixture of mammographic lesion types.

Similarly to previous results, we found AEPDT to be the B3 lesion with the highest rate of finally detected malignancy (40 % [7], 50 % [10]). 30.4 % (7/23) of the diagnoses of AEPDT in minimally invasive biopsy were not proved as atypical ductal hyperplasia (ADH) after excision surgery but were upgraded to a malignant diagnosis, mainly to DCIS diagnosis (85.7 %). Kohr et al. concluded that surgical excision should be recommended even when ADH involves fewer than three foci and all mammographic calculations have been removed by needle biopsy, because the upgrade rate was still 12 % [11]. Our results support that finding.

Brennan et al. performed a meta-analysis of the underestimation of invasive breast cancer with ductal carcinoma in situ at needle biopsy. The pooled estimate was 25.9 %. Preoperative variables that showed significant univariate association with higher underestimation included the use of a 14-gauge core biopsy device versus the use of an 11-gauge vacuum-assisted biopsy with an underestimation of 30.3 % versus 18.9 % (P < 0.001), respectively [1]. Our results, using a 9-gauge device, show an underestimation of 10 %. Underestimation occurs in constellation with and without residual classifications post-VAB. The low rate of underestimation may not only be related to the large biopsy device. The meta-analysis defined risk constellations for underestimation as palpable versus impalpable lesions, presence of mammographic masses versus the absence and stereotactic image guidance of biopsy versus ultrasound or clinical guidance. Our study collective was restricted to cases of pure calcifications. The absence of associated masses was proved by additional magnification imaging and ultrasound. Therefore, we suppose that the standardized imaging protocol was useful to select cases of low risk for underestimation.

After DCIS diagnosis in VAB, the multidisciplinary team has to define a recommendation for surgery including breast surgery and facultative axillary staging by sentinel lymph node biopsy. Guidelines recommend sentinel lymph node biopsy in cases of presurgical DCIS diagnoses and planned mastectomy [12, 13]. For our above described collective without stratification of lesion size or nuclear grade, the risk of underestimation of invasion did not exceed 10 % so that a general recommendation of a sentinel lymph node biopsy in combination with a breast-conserving biopsy in terms of a DCIS diagnosis and sonographically normal axillary lymph nodes does not seem adequate. Kotani et al. concluded that because of a low prevalence of metastatic involvement, the cessation of SLNB is a reasonable consideration in patients initially diagnosed with DCIS by stereotactic VAB [14]. In concordance, the American Society of Clinical Oncology recently updated a clinical practice guideline and recommends that women with DCIS should not undergo SLNB when breast-conserving surgery is planned [12].
Nevertheless, constellations with higher probabilities for invasion of over 50 % for palpable lesions should be carefully evaluated by the multidisciplinary team regarding axillary staging [1, 15]. SLNB may be considered as part of the primary surgical procedure when preoperative variables show a tumor larger than 2 cm [1, 16]. The national working group of gynecological oncologists suggests discussion of sentinel lymph node biopsy in the planning of a breast-conserving therapy only for cases of DCIS lesions ≥5 cm or >2.5 cm in combination with high grade subtypes [13]. Our data support that restrictive recommendation since invasive cancer was underestimated in only about 13 % of all DCIS lesions ≥5 cm, resulting in a secondary recommendation of SLNB. Despite dedicated imaging before biopsy and the use of large devices, invasive cancer, mostly less than 10 mm in size (85.7 %), was still underestimated in 10 % of all VAB-related DCIS diagnoses. The frequency of upgrade was comparable for cases with total removal of calcifications by VAB (13.3 %). Our study provides a risk estimation which might also be useful for presurgical dialog with patients. In addition, MRI may be a useful tool in mammography screening assessment [17 – 19]. The strengths of our study are that results are based on a standardized procedure with high quality assurance: clearly defined guidelines, specially trained radiologists and pathologists. Furthermore, we exclusively used direct radiography digital magnification techniques and high-resolution breast ultrasound. A limitation of the study is due to the fact that we analyzed data of one assessment unit only. The possibility to transfer the results is limited. Due to the limited number of cases, we did not evaluate subgroups of risk estimation by statistical tests.

Conclusion

Underestimation of DCIS (21.6 %) in diagnostic excision biopsies is mainly related to presurgical diagnosis of AEPDT. Underestimation of invasive cancers in diagnostic excision biopsies is rare (2.7 %). Underestimation of invasive cancer in terms of presurgical DCIS diagnosis can be minimized (9.9 %) by standardized assessment protocols including mammographic and sonographic imaging prior to vacuum-assisted biopsy.

Acknowledgements

The authors would like to thank Ms. Stefanie Michalk for the administrative help provided.

Clinical relevance

The establishment of digital mammography in breast cancer screening identified and clarified microcalcifications more often compared to the currently outdated analogue mammography technique. Protocols define vacuum-assisted biopsy as the method of choice for assessment of microcalcifications. The accuracy of a preoperative diagnosis compared to the postoperative end diagnosis is relevant for patient counseling, for planning of surgery – especially with the objective to minimize follow-up surgeries, and for the indication of sentinel lymph node biopsy. The integration of additional digital mammography views and high-resolution ultrasound imaging can achieve a selection of low risk for non-identification of invasive breast cancer after vacuum-assisted biopsy.

References

7. Weigel S, Decker T, Korsching E et al. Minimal invasive biopsy results of “uncertain malignant potential” in digital mammography screening: high prevalence but also high predictive value for malignancy. Fortschr Röntgenstr 2011; 183: 743 – 748