

Intraductal Papilloma Without Atypia on Image-Guided Breast Biopsy: Upgrade Rates to Carcinoma at Surgical Excision

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Keywords

Breast cancer · Imaging · Biopsy · Papilloma

Summary

Background: The management of intraductal papilloma without atypia (IDP) in breast needle biopsy remains controversial. This study investigates the upgrade rate of IDP to carcinoma and clinical and radiologic features predictive of an upgrade. **Methods:** Patients with a diagnosis of IDP on image-guided (mammography, ultrasound, magnetic resonance imaging) core needle or vacuum-assisted biopsy and surgical excision of this lesion at a certified breast center between 2007 and 2017 were included in this institutional review board-approved retrospective study. Appropriate statistical tests were performed to assess clinical and radiologic characteristics associated with an upgrade to malignancy at excision. **Results:** For 60 women with 62 surgically removed IDPs, the upgrade rate to malignancy was 16.1% (10 upgrades, 4 invasive ductal carcinoma, 6 ductal carcinoma in situ). IDPs with upgrade to carcinoma showed a significantly greater distance to the nipple (63.5 vs. 36.8 mm; $p = 0.012$). No significant associations were found between upgrade to carcinoma and age, menopausal status, lesion size, microcalcifications, BI-RADS descriptors, initial BI-RADS category, and biopsy modality. **Conclusion:** The upgrade rate at excision for IDPs diagnosed with needle

biopsy was higher than expected according to some guideline recommendations. Observation only might not be appropriate for all patients with IDP, particularly for those with peripheral IDP.

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Introduction

Papillary lesions of the breast include a wide range of benign, atypical, and malignant tumors, which cannot be reliably distinguished using imaging alone [1]. Surgical excision is generally recommended for atypical papilloma diagnosed with image-guided breast biopsy, due to its high upgrade rates to breast cancer [2–5]. However, the management of intraductal papilloma without atypia (IDP) on image-guided breast biopsy remains controversial due to divergent results in previous studies reporting upgrade rates to malignancy after excision ranging from 0 to 25% [6–11]. It has been suggested that image-guided biopsy is limited by tissue fragmentation and small specimen size and therefore might miss areas with atypia and breast cancer. Therefore excision of IDP found on image-guided biopsy is frequently recommended in interdisciplinary post-biopsy conferences. In contrast, other studies found low upgrade rates at surgical excision and concluded that imaging surveillance might be sufficient [6, 12, 13].

Previous studies investigated which clinical and imaging features are predictive for an upgrade to carcinoma and suggested

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characteristics such as larger lesion size [7], presence of microcalcifications [14], older patient age [5], and palpable mass lesions [11]. However, to our knowledge, almost all of these previous studies focused on only a single imaging modality, and there is still no consensus as to which imaging features warrant surgical excision.

Hence, this study aimed to investigate the upgrade rate to breast cancer at excision of IDP diagnosed on ultrasound(US)-, mammography(MG)-, and magnetic resonance imaging(MRI)-guided breast biopsy, and to identify clinical and imaging descriptors predictive of malignancy.

Patients and Methods

Study Population

The institutional review board approved this retrospective study with a waiver for written consent. A computerized search of the breast center database (ODS easy, Asthenis, Aschheim, Germany) identified 71 patients with a needle biopsy diagnosis of IDP and subsequent surgical excision of this lesion between 03/2007 and 03/2017. Thus, a total of 60 patients with 62 IDPs were included in the study.

Radiologic information was assessed in consensus by 2 radiologists with more than 10 years' experience in breast radiology, using the imaging modality with which the biopsy was conducted. Lesion laterality and size, nipple discharge, presence of calcifications, distance between nipple and lesion, and BI-RADS (Breast Imaging Reporting and Data System) category according to the revised American College of Radiology BI-RADS lexicon were evaluated. In patients with multiple IDP, all lesions were rated. Clinical information, such as age at diagnosis and menopausal status, were retrieved from the database. Characteristics of the carcinoma such as tumor type and grade were recorded. A malignant upgrade was defined as the presence of breast cancer and/or ductal carcinoma in situ (DCIS) in the surgically removed lesion.

Biopsy Procedure

Core needle biopsy (CNB) was used for mass lesions using a 14-gauge coaxial biopsy system (HistoCore, BIP, Tuerkenfeld, Germany). Vacuum-assisted biopsy (VAB) was performed for non-mass lesions using a 10-gauge coaxial needle system (Vacora, Bard Biopsy Systems, Tempe, AZ, USA) or a 9-gauge automated VAB system (ATEC, Hologic, Marlborough, MA, USA). 12 biopsy cylinders were sampled for each suspicious lesion. In the case of microcalcifications within the lesion, biopsy success was evaluated with a post-procedural radiograph of the specimen.

For both CNB and VAB, the imaging modality for needle guidance was chosen based on the best lesion visualization. US guidance (Logiq E9, GE Healthcare, Milwaukee, WI, USA), MG stereotactic guidance (FCR PROTECT CS Plus, Fujifilm, Minato, Japan; DMR Plus, GE Healthcare) with a panning angle of $\pm 15^\circ$, or MRI guidance (Symphony 1.5 Tesla, Siemens Healthcare, Erlangen, Germany) were used. Biopsies were performed by 2 board-certified breast radiologists with >10 and >20 years' experience, respectively.

Histopathologic Analysis

All patients included in the present study underwent subsequent surgical excision after initial biopsy for the following reasons: potential non-representative needle biopsy, pain, patient's wish, initial BI-RADS 5 classification with discordant findings after biopsy, size progress, nipple discharge.

Both the initial biopsy and the postoperative specimen were analyzed by a pathologist with >15 years' experience using standardized histologic techniques and additional immunohistochemical methods if necessary.

Statistical Analysis

Statistical tests were performed using IBM SPSS Statistics (version 22.0; IBM, Armonk, NY, USA). A Mann-Whitney test was used to assess the associa-

tion of continuous values with an upgrade, while categorical data was assessed using the chi-square test and the Fisher's exact test. A p value of <0.05 was considered as statistically significant. Continuous data is given as mean \pm standard deviation. For patients with 2 IDPs, analyses of radiologic features were performed for both lesions, whereas clinical characteristics were evaluated per patient.

Results

Patient Characteristics

The study population consisted of 60 women with 62 lesions with a CNB diagnosis of IDP (58 patients had 1 IDP, 2 had 2 IDPs). Mean patient age at diagnosis was 54.7 years (range 32–79 years). 20 (33.3%) patients were premenopausal, 4 (6.7%) were perimenopausal, and 36 (60%) were postmenopausal. Galactography was performed in 5 patients due to secretion. All lesions were surgically removed after an interval of up to 3 months (mean 2.1 months). The upgrade rate to carcinoma was 16.1% (10/62 lesions). Of those patients, 3 were premenopausal, while 7 were postmenopausal. Invasive ductal carcinoma was found in 4 lesions (2 grade 1, 2 grade 2), while the other 6 lesions showed DCIS after excision (1 grade 1, 4 grade 2, 1 grade 3).

Age and menopausal status were not associated with a malignant upgrade ($p = 0.174$, $p = 1.0$, respectively). When peri- and postmenopausal patients were considered together, again no association was found ($p = 0.871$) with age.

Radiologic Characteristics

The mean size of the target lesion was 11.5 mm (range 2–31 mm). The mean and median distance to the nipple were 41.5 and 40 mm (range 5–130 mm), respectively. 39 (62.9%) lesions had a distance of >2 cm to the nipple. All measurements were performed in the modality with which the biopsy was conducted. The lesions were 46 masses, 12 non-mass lesions, and 2 architectural distortions. Microcalcifications were present in 8 cases. 4 lesions were initially classified as BI-RADS 3, 54 lesions as BI-RADS 4, and 4 lesions as BI-RADS 5. 9 patients had a history of breast cancer in the contralateral breast.

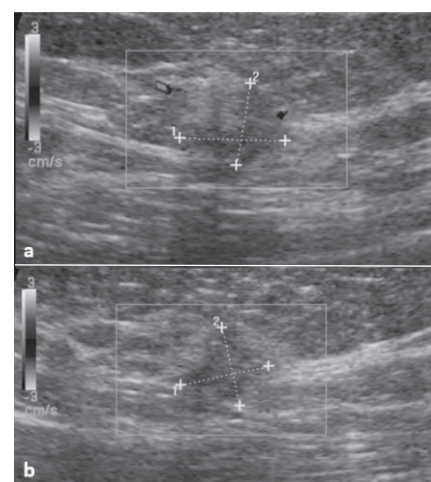


Fig. 1. Ultrasound-guided core needle biopsy of a BI-RADS 5 lesion (a transverse image; b longitudinal image) in a 65-year-old woman showing benign papilloma without atypia, which was considered a radiologic-pathologic discordance. Upgraded diagnosis after surgical excision was ductal carcinoma in situ.

Table 1. Assessment of intraductal papillomas without atypia according to the upgrade status at excision. Distance to the nipple in mm was significantly greater in lesions with an upgrade at excision, while the other characteristics did not reach significance

	Overall (n = 62)	No upgrade (n = 52)	Upgrade (n = 10)	p value
Age, mean ± SD, years	54.7 ± 12.6	53.8 ± 12.6	59.7 ± 11.7	0.174
Menopausal status, n				0.871
Premenopausal	20	18	3	
Peri-/postmenopausal	42	34	7	
Tumor size				
Mean ± SD, mm	11.5 ± 7.1	11.3 ± 7.0	12.3 ± 8.3	0.941
≥15 mm, n	15	9	2	1.000
<15 mm, n	47	43	8	
Distance to nipple ^a , mean ± SD, mm	41.5 ± 27.6	36.8 ± 24.2	63.5 ± 32.8	0.012
Tumor characteristics, n				0.808
Mass	46	40	6	
Non-mass	12	10	2	
Architectural distortion	2	2	0	
Microcalcifications, n				1.000
Yes	8	7	1	
No	54	35	9	
Initial BI-RADS category, n				0.805
BI-RADS 3	4	4	0	
BI-RADS 4	54	46	8	
BI-RADS 5	4	2	2	
History of breast cancer in the contralateral breast, n				0.629
Yes	9	7	2	
No	53	45	8	
Biopsy procedure, n				1.000
CNB	48	40	8	
VAB	14	12	2	
Biopsy guidance, n				0.901
US	45	37	8	
MG	12	10	2	
MRI	5	5	0	

^aDistance to the nipple in mm was significantly greater in lesions with an upgrade at excision, while the other characteristics did not reach significance.

SD = Standard deviation; CNB = core needle biopsy; VAB = vacuum-assisted biopsy; US = ultrasound; MG = mammography; MRI = magnetic resonance imaging.

IDPs with upgrade to carcinoma after excision showed a significantly greater distance between nipple and lesion (63.5 vs. 36.8 mm; $p = 0.012$). No association was found between imaging characteristics such as lesion size ($p = 0.941$), presence of microcalcifications ($p = 1.0$), initial BI-RADS category ($p = 0.805$), and malignancy after excision.

Biopsy Procedure Characteristics

US-guided biopsies were performed in 45 (71%) cases, 12 (3.2%) biopsies were MG-guided, and 5 (6.5%) biopsies were MRI-guided VAB. Overall, VAB was used for 14 (22.6%) IDPs, and 48 (77.4%) were sampled using CNB. Of the 10 malignant upgrades, 8 were biopsied with US-guided CNB, and 2 with MG-guided stereotactic VAB. No association between biopsy technique or guidance

and malignant upgrade was found ($p = 1.0$; $p = 0.901$). All details are outlined in table 1, and figures 1–3 show examples of imaging and biopsy findings in patients.

Discussion

It is undisputed that surgical excision is required when an atypical papilloma is found in breast biopsy material, due to the high risk for synchronous or metachronous carcinoma [15]. At the same time, the management of IDPs, which are regarded as benign proliferative disease, remains controversial, and patient numbers in previous studies are limited. An international consensus conference on B3 lesions decided that benign papilloma should undergo

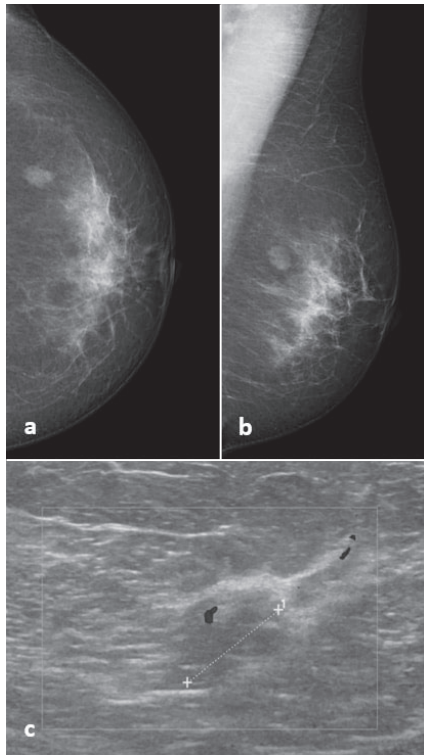


Fig. 2. 53-year-old woman with a 1.3-cm mass on **a, b** mammography and **c** ultrasound, initially classified as BI-RADS 4. Mammography-guided core needle biopsy revealed benign papilloma without atypia. Diagnosis was confirmed after surgical excision.

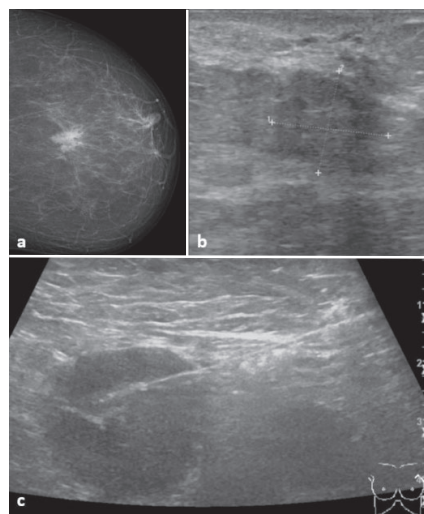


Fig. 3. 62-year-old woman with a BI-RADS 5 lesion on **a** mammography and **b** ultrasound. Benign papilloma without atypia was diagnosed with ultrasound-guided biopsy, whereas biopsy of a suspicious lymph node in the left axilla (**c**) revealed a metastasis of an invasive carcinoma. Subsequent surgical excision of the breast lesion confirmed this diagnosis.

therapeutic excision with VAB, or be removed when they are larger, symptomatic, or peripheral [16]. However, national recommendations differ from country to country; for instance, according to a guideline in Germany (Arbeitsgemeinschaft Gynäkologische Onkologie e.V., www.ago-online.de), surveillance is regarded as sufficient for solitary benign papilloma in CNB/VAB without radiologic-pathologic discordance. Many investigators suggested that areas of atypia or carcinoma may be missed in the limited tissue material gained with needle biopsy, thus requiring excisional biopsy for IDPs. Meanwhile, others suggested that IDPs with concordant benign imaging characteristics do not require excision [6, 17, 18]. To our knowledge, almost all previous studies investigated

IDP based on only a single imaging modality with a focus on US [19], while our study evaluated both CNB and VAB guided by MG, US, and MRI.

The upgrade rate to carcinoma at excision of IDP diagnosed with biopsy has been investigated in multiple previous studies with conflicting results. In a recent study, Pareja et al. [6] found a malignant upgrade rate of 2.3% in 171 radiologic-pathologic concordant lesions. In a study cohort of 77 patients, no malignant upgrades were reported, and 100 patients were stable according to imaging over the course of 36 months [20]. Prospective studies reported an upgrade rate of 4% in 100 IDPs [7], and no upgrades in 49 cases [21]. Other studies have reported similar findings, with upgrade rates of 2.6% in 230 lesions [12]. However, multiple studies report substantially higher upgrade rates such as 6.3% in 154 patients [11] or 8.9% in 234 patients [22]. In another 80 patients, an even higher upgrade rate of 19% was found [23]. Our results suggest that the upgrade rate to DCIS or invasive carcinoma at excision of IDP is substantial, suggesting that observation only might not be an appropriate management of all patients with an IDP diagnosed with biopsy.

Papillomas are classified as central and peripheral, or single and multiple, with peripheral lesions showing a significantly higher risk for breast cancer than central papilloma in previous studies [4, 24, 25]. In our study, a greater distance to the nipple was significantly associated with a higher upgrade rate (63.5 vs. 36.8 mm; $p = 0.012$). Due to the small number of patients with multiple IDP ($n = 2$), we could not evaluate potential differences in upgrade rate between solitary and multiple lesions.

It has been reported that larger lesions were more likely to be upgraded to malignancy [4, 7]. In our study, no association between lesion size and upgrade to carcinoma was found. Previous studies also suggested that older patients are at higher risk for atypia and carcinoma in papillary lesions [5]. In the present study, there was a trend for higher age in patients with an upgrade to carcinoma, although it did not reach statistical significance ($p = 0.174$).

Most previous studies investigated IDPs diagnosed with CNB, while our study additionally included IDPs verified with VAB. Regarding CNB lesions, we investigated only 14-gauge CNB, while in previous studies, no significant differences between the use of 11-gauge and 14-gauge CNB for IDP were found [26, 27]. It could be assumed that VAB might lead to less upgrades, providing a larger tissue sample than CNB. Vales et al. [28] found that malignancy was missed less frequently with VAB compared to CNB in a study investigating 80 patients ($p < 0.05$). In our study, we did not observe significant differences in upgrade rates between VAB ($n = 14$) and CNB ($n = 46$). Nevertheless, limitations of CNB with potential undersampling or underdiagnosis should be kept in mind.

In previous studies, the upgrade rate was substantially lower in cases with pathologic-radiologic concordance [6, 7]. In the present study, 2 patients with IDP and subsequent upgrade after excision showed initial BI-RADS 5, indicating pathologic-radiologic discordance after initial biopsy. However, there was no significant difference between the upgrade and non-upgrade group regarding

initial BI-RADS categorization. Thus, it should be taken into account that benign papilloma and papillary carcinoma have a considerable overlap in imaging features, and indication for surgery should be considered in any inconclusive case.

This study has some limitations additional to the retrospective study design and possible selection bias, which deserve mentioning. First, as in similar studies, our patient numbers and hence the number of upgrades to malignancy were limited, and associations with upgrade to carcinoma should therefore be regarded as preliminary. The small patient numbers could have influenced study results, so that no significant differences in upgrades between CNB and VAB or other characteristics could be found. Further studies with larger patient numbers are warranted to validate our findings. Second, we did not evaluate the upgrade to lesions of greater clinical

significance other than DCIS and invasive carcinoma, such as atypical ductal or lobular hyperplasia.

In conclusion, we found an upgrade rate to carcinoma at excision for IDPs diagnosed with image-guided biopsy of 16.1%. Lesions with an upgrade to malignancy after excision were significantly associated with a greater distance to the nipple. Our data suggest that observation only might not be adequate for the management of all patients with a diagnosis of IDP on biopsy. For patients with peripheral IDP, surgical excision should be considered.

Disclosure Statement

The authors have no potential conflict of interest to declare.

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