Published in final edited form as:

Cancer. 2016 September 15; 122(18): 2819–2827. doi:10.1002/cncr.30118.

Breast Intraductal Papillomas without Atypia in Radiologic-Pathologic Concordant Core Needle Biopsies: Predictors of Upgrade to Carcinoma at Excision

Fresia Pareja, MD PhD^{1,*}, Adriana Corben, MD^{1,*}, Sandra Brennan, MB², Melissa P. Murray, DO¹, Zenica Bowser, MS¹, Kiran Jakate, MD³, Christopher Sebastiano, MD¹, Monica Morrow, MD⁴, Elizabeth Morris, MD², and Edi Brogi, MD PhD¹

¹Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

²Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³Department of Pathology, St. Michael's Hospital, Toronto, Canada

⁴Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Background—The surgical management of breast intraductal papilloma without atypia (IDP) identified at core needle biopsy (CNB) is controversial. We assessed the rate of upgrade to carcinoma at surgical excision, and identified parameters predictive of upgrade.

Methods—We identified women with CNB diagnosis of intraductal papilloma without atypia or carcinoma at our center between 2003 and 2013. Radiologic-pathologic concordance was assessed for all cases, and discordant cases were excluded. We correlated the radiologic and clinicopathologic features of patients with CNB diagnosis of IDP with upgrade to carcinoma at surgical excision.

Results—Our study population consists of 189 women with 196 IDPs; 166 women (171 IDPs) underwent excision. The upgrade rate was 2.3% (4/171). The upgrade lesions were 2 invasive lobular carcinomas and 2 cases of ductal carcinoma in situ (DCIS). One case of DCIS involved the residual IDP, whereas the other 3 carcinomas were 8 mm away. Twenty-four women (25 IDPs) did not undergo excision, and had stable imaging at follow-up (median of 23.5 months).

Address correspondence to: Edi Brogi, MD PhD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Tel: (212)-639-5363, brogie@mskcc.org.

*These authors have contributed equally to this work

Conflict of interest disclosure: The authors declare no conflict of interest

Author Contributions:

- FP, ADC, SB, MPM and EB contributed to the planning of the study.
- FP, ADC, SB, MPM, ZB, KJ, CS and EB contributed to the conduct of the study.
- FP, ADC, SB, MPM, ZB, KJ, CS, MM, EM and EB contributed to the reporting of the study.
- FP, ADC and EB are responsible for the overall content of the study as guarantors.

Conclusions—The upgrade rate at excision of IDP diagnosed at CNB with radiologic-pathologic concordance is 2.3%. Our findings suggest that observation is appropriate for patients with radiologic-pathologic concordant CNB yielding IDP, regardless of its size.

Keywords

Breast; papilloma; biopsy; core needle; atypia; upgrade; excision; carcinoma

Introduction

The standard of care for the management of atypical papilloma at CNB is surgical excision (EXC), as numerous studies have demonstrated high rates of upgrade to carcinoma¹⁻⁵. The surgical management following CNB diagnosis of IDP, however, remains controversial.

EXC of all IDPs is recommended by most investigators, due to the high reported rates of upgrade in some series⁶⁻⁸, and the inability of imaging studies to accurately classify the lesions⁹. However, most of the published series did not take into account radiologic-pathologic concordance of the lesions¹⁰, which may lead to falsely high upgrade rates. The integrated evaluation of imaging and CNB histological findings directs the management of patients with breast lesions, and radiologic-pathologic discordant findings always mandate EXC¹¹. A few more recent series have reported low upgrade rates at EXC of lesions yielding IDP at CNB^{12,13}, concluding that EXC is not required, and imaging surveillance is sufficient. A number of radiologic and histologic features predictive of the upgrade of IDP have been suggested, including size ≥ 1.5 mm on imaging¹⁴, presence of microcalcifications¹³, and older patient age¹⁵.

This study aimed to determine the upgrade rate at EXC of IDP diagnosed at CNB in a large series of cases with radiologic-pathologic concordance, and to identify clinical, histologic or radiologic variables predictive of upgrade at EXC.

Materials and Methods

Identification of cases

The Institutional Review Board approved this study. A computerized search of the Pathology Department database identified 385 women who underwent CNB of a breast lesion at our center between July 2003 and December 2013, and received a diagnosis of “papilloma”.

We excluded from the study 155 patients who had carcinoma in the CNB material, no slides available for review, or who underwent EXC at another institution, and 12 patients who did not undergo EXC and had no follow-up imaging at our institution. We conducted a pathology review of 218 cases, and excluded seven cases of papillary usual ductal hyperplasia, 12 atypical papillomas or IDPs with adjacent atypia in the CNB material. Three radiologic-pathologic discordant cases were also excluded.

Clinical information, including gender, race, age at diagnosis, symptoms, and personal history of breast carcinoma, was retrieved from the electronic medical records.

Radiology review and CNB procedure

A breast radiologist (S.B.) reviewed all available pre- and post-CNB imaging studies and assessed the size of the lesion and its distance from the nipple, indication for biopsy (calcifications, mass, non-mass enhancement [NME], asymmetry), and presence of a residual target after CNB. The distribution and morphology of calcifications, the shape and margins of masses, and the pattern of NME were also noted. Lesion enhancement kinetics were also evaluated. The mode of biopsy, biopsy modality, needle gauge, and number of tissue cores were also recorded.

Pathology review

Review of CNB material—Two breast pathologist (A.C. and F.P.), blinded to the EXC diagnosis, reviewed the hematoxylin and eosin (H&E) slides of all CNB cases included in the study. Lesions consisting of arborizing fibrovascular cores lined by epithelium and myoepithelium were categorized as intraductal papillomas¹⁶, and further classified based on the presence of epithelial atypia as either IDP or atypical papilloma. Cases showing atypical papilloma, a high risk lesion (i.e. atypia, LCIS, or radial scar) or papillary usual ductal hyperplasia in the CNB material were excluded from the study. We assessed the histologic features of the IDPs, including size (greatest dimension in a single core), complete removal at CNB, fragmentation, and associated calcifications.

Review of surgical excision specimens—The H&E slides of all EXC specimens were reviewed to assess for the presence of residual IDP and its size, biopsy site, atypia and carcinoma. The nature of the atypia or high risk lesion, along with its spatial relationship to the residual IDP or biopsy site was annotated. Upgrade was defined by the presence of invasive carcinoma and/or DCIS in the EXC specimen. We recorded the characteristics of the carcinoma (tumor type, size, histologic grade) and its spatial relationship with the residual IDP.

The slides of CNB and EXC specimens of the cases with upgrade were also reviewed together with two additional breast pathologists (E.B. and M.M.).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0; Armonk, NY. Fisher's exact test was used to assess the association of categorical variables with upgrade; one-way analysis of variance (one-way ANOVA) was used to evaluate continuous variables. Statistical significance was defined as a p value <0.05. Due to the small number of cases with upgrade to carcinoma on excision (n=4), correction of p values for multiple comparisons was not performed. In patients with more than one IDP, the analysis of the radiologic and histopathologic features was based on the number of CNBs and IDPs. The analysis of the clinical characteristics was performed per patient. For one patient with bilateral metachronous IDPs, we used the age at the time of first diagnosis of IDP for analysis.

Results

Patient characteristics

The study population consists of a total of 189 women with CNB diagnosis of IDP (183 patients had one IDP, 5 had two IDPs, and one had 3 IDPs). The total number of IDPs was 196. Mean patient age at diagnosis was 51.8 ± 0.9 years (range 25-85). Most women (166) underwent EXC of the radiologic target lesion. Twenty-four women did not undergo EXC, but were followed clinically and radiologically. One woman had EXC of two synchronous IDPs, but did not undergo EXC of a third IDP, that was detected two years later.

Patients who underwent surgical excision

Clinical Characteristics—One hundred sixty-six patients with 171 IDPs underwent EXC. The mean age was 51.8 ± 0.9 years (25-85); 89 (53.6%) patients were ≥ 50 years. Most patients (108; 65.5%) were of Caucasian ethnicity, 38 (23%) were African-American, 11 (6.7%) Asian/Indian, and 8 (4.8%) Hispanic; no information was available for one patient. Only 16 (9.6%) women reported symptoms, including 8 with nipple discharge. Fifty-eight (34.9%) patients had either prior (30; 18.1%) or concurrent (28; 16.9%) breast carcinoma. The latter was ipsilateral in 12 (7.2%) patients (Table 1).

Radiologic characteristics of the target lesion—The mean size of the radiologic target was 9 ± 0.5 mm (range 2-43). In 20 cases (11.8%), the radiologic target measured ≥ 15 mm. The mean and median distance between the nipple and the radiologic target was 38.9 ± 2 , and 30 mm (range 10-140), respectively; 109 lesions (64.1%) were >20 mm from the nipple. The radiologic targets were 102 masses (59.6%), 34 calcifications (19.9%), 33 NMEs (19.3%), and 2 asymmetries (1.2%).

The radiologic features were not associated with upgrade (Table 2, supplementary Table 1).

Core Needle Biopsy Procedure Characteristics—Seventy-eight (45.6%) biopsies were US-guided, 57 (33.3%) MRI-guided, and 36 (21.1%) stereotactic. One hundred (58.5%) IDPs were sampled by VAB and 71 (41.5%) by ACB. The needle gauge ranged from 9 to 18. The median number of cores per procedure was 6 (range 1-20). The CNB procedure characteristics were not associated with upgrade (Table 2 and supplementary Table 2).

Histopathologic characteristics of IDPs in the CNB samples—The mean microscopic size of the IDPs was 3.4 ± 0.1 mm (range 0.4-9); 144 (84.2%) IDPs were ≥ 2 mm. Eighty-one IDPs were fragmented (47.7%), 56 (32.7%) had calcifications, and 20 (11.7%) appeared completely removed at CNB. The mean size of fragmented IDPs (3.7 ± 0.2 mm) was greater than the size of non-fragmented IDPs (3.1 ± 0.2 mm; $p=0.03$) (Table 3).

Histopathologic characteristics of upgrade lesions in surgical excision specimens—The upgrade rate to carcinoma (2 invasive lobular carcinomas and 2 DCIS) in the EXC specimen was 2.3% (4/171 cases). All carcinomas measured ≥ 2 mm. A DCIS

involved the residual IDP in one case (true upgrade). The other 3 carcinomas were at least 0.8 mm from the residual IDP (incidental upgrades) (Table 4 and Figures 1 and 2).

Additional histopathologic findings in surgical excision specimens—Upon review of the EXC specimens, biopsy site was documented in all cases. A residual IDP was present in 107 (62.6%) EXC specimens, and had a mean histologic size of 5.5 mm (range 0.4–17 mm) (Table 3). Thirty-nine cases (22.8%) harbored a high risk lesion (19 ADH, 7 ALH, 4 LCIS, 1 columnar cell change with atypia, and 8 radial scars), which was not present on the initial CNB.

Analysis of features predictive of upgrade

Clinical features: The age of patients with and without upgrade was comparable (52.8 ± 1.8 versus 51.7 ± 0.9 , respectively). Concurrent ipsilateral breast carcinoma was the only clinical parameter associated with upgrade. Two of the four patients with upgrade had concurrent ipsilateral breast carcinoma, versus only 10/162 (6.2%) of the patients without upgrade. None of the patients with upgrade was symptomatic (Table 1).

Radiologic features and core needle biopsy procedure characteristics: There were no statistically significant differences in the radiologic characteristics of the lesions with and without upgrade. The radiologic target of the CNB was a mass in two of the four cases with upgrade (50%), and in 100 (59.9%) cases without upgrade. The CNB of two cases with upgrade targeted a mass. One mass was oval with circumscribed margins; the other had irregular shape and was not circumscribed. The other two CNBs with upgrade at EXC targeted clustered fine linear calcifications, and linear NME with plateau kinetics. The mean size of the imaging target was similar in cases with (9.8 ± 2.4 mm) and without upgrade (9 ± 0.5 mm); no imaging target size threshold correlated with upgrade. The IDPs were >20 mm from the nipple in most cases with (3; 75%) and without upgrade (106; 63.9%).

All four radiologic targets with upgrade at EXC were sampled by vacuum-assisted CNB (VAB) (One CNB was stereotactic, two US-guided, and one MRI-guided). The mean size of the imaging target sampled by VAB (9.9 ± 0.9 mm) was significantly greater than the mean size of the lesions sampled by ACB (7.7 ± 0.5 mm) ($p=0.043$). The needle gauge in the cases with upgrade ranged from 9 to 12. None of these parameters was predictive of upgrade (Table 2, supplementary Tables 1 and 2).

Histopathologic findings: In the CNB material, all IDPs with upgrade measured ≥ 2 mm. The mean size of the IDP was similar for cases with and without upgrade (3.4 ± 0.1 mm; $p=0.981$). IDP fragmentation was the only histologic parameter associated with upgrade. All four IDPs with upgrade and 77/167 (46.1%) IDPs with upgrade were fragmented ($p=0.048$). Complete IDP removal at CNB, and calcifications in the IDP were not associated with upgrade at EXC.

In the EXC specimen, residual IDP was identified in all four cases with upgrade, and in 103 (61.7%) cases without upgrade. The mean size of the residual IDP was similar in the two groups (Table 3).

Patients who did not undergo follow-up surgical excision

Twenty-four women with IDP and radiologic-pathologic concordant CNB did not undergo EXC, and were followed with imaging studies. The mean age was 55.3 ± 2.7 years (range 27–83). Three patients (12.5%) had concurrent contralateral breast carcinoma, and none had concurrent ipsilateral breast carcinoma. Two patients (8.3%) had history of contralateral breast carcinoma. One patient had a longstanding history of spontaneously resolving nipple discharge, which had recurred again and triggered the CNB. The patient chose not to undergo EXC. The mean lesion size by imaging was 7 ± 1 mm (range 2–20). The radiologic targets included 13 mass-lesions (52%), 9 calcifications (36%) and 3 NME-lesions (12%). Ten (40%) CNBs were stereotactic, 8 (32%) US-guided, and 7 (28%) MRI-guided. The CNB was VAB in 18 (72%) cases and ACB in 7 (28%) cases, with needle gauge ranging from 9 to 14. A residual post-CNB lesion was noted by imaging in 8 patients (32%). The IDP in the CNB material was fragmented in five cases (20%).

Median follow-up time was 23.5 months (range 6–132). Review of follow-up imaging studies showed stability of the lesions and no additional ipsilateral findings.

Discussion

While EXC of atypical papillomas identified in a CNB sample is mandated, regardless of radiologic-pathologic concordance³, the management of IDPs remains contentious.

Many investigators have assessed the upgrade rate of IDP at EXC with conflicting results. In this study we evaluated a large cohort of patients with IDPs diagnosed at radiologic-pathologic concordant CNB. DCIS or invasive carcinoma was identified in the EXC specimen corresponding to four out of 171 CNBs, with a 2.3% upgrade rate to carcinoma.

Our findings confirm that the upgrade rate at EXC of IDP with a radiologic-pathologic concordant CNB is very low. Swapp et al. observed no upgrades in a cohort of 77 radiologic-pathologic concordant IDPs. Moreover, 100 patients with radiologic-pathologic concordant CNB of IDP were stable by imaging during a mean follow-up time of 36 months¹². In a series of 85 radiologic-pathologic concordant IDPs there were two upgrades (2.4%)¹⁴, and none in a prospective series of 49 cases¹⁷. Several other smaller series of radiologic-pathologic concordant cases have also reported similar findings^{4,18,19}. A study of 80 radiologic-pathologic concordant IDPs, however, reports an upgrade rate of 18.8%²⁰. Of note, 12/15 upgrade lesions were papillary carcinomas, raising the possibility of undersampling or underdiagnosis at CNB. The latter study did not include MRI-guided CNBs. In our series, the upgrade rate without MRI-guided CNBs is 2.63% (3/114).

Rizzo et al. reported an upgrade rate of 9 %⁶, in a study of 234 IDPs. MRI-detected IDPs, and IDPs <1–2 mm in CNB material were excluded from their study. In our series, 27 (15.8%) IDPs measured <2 mm at CNB, and none was upgraded at EXC. MRI-guided CNBs accounted for 57 IDPs (33%), and only one had upgrade at EXC. If we exclude the aforementioned cases, the upgrade rate in our series is 3.2% (3/93). Our series includes only radiologic-pathologic concordant cases, whereas Rizzo et al. do not specifically indicate radiologic-pathologic concordance as a selection criterion.

We studied clinical, radiologic and histopathologic variables to identify patients with CNB diagnosis of IDP and high risk of upgrade at EXC. Some studies suggested that age correlates with upgrade at EXC ^{6,21}. In our series, age was not significantly related to upgrade, but all patients with carcinoma were 50 years old. Most patients with upgrade in the study of Rizzo et al. had symptoms⁶, but all of our patients with upgrade were asymptomatic.

Our institution is a cancer center, and a significant percentage of the patients in our study had prior or concurrent breast carcinoma (58; 34.9%). Ten patients (6.2%) without upgrade had concurrent ipsilateral breast carcinoma, compared to 2 (50%) patients with upgrade ($p=0.027$). In contrast, Cyr et al. found that prior/concurrent breast carcinoma was not associated with atypia or carcinoma at EXC ²². When worrisome symptoms, such as palpable mass or nipple discharge are present, the need for surgical excision of a concurrent breast carcinoma should be taken into account in the surgical management of the papilloma.

Most patients in our study were of Caucasian ethnicity, and 38 (23%) were African-American. Li et al. ¹³ studied a population of similar ethnic composition (77% Caucasian, and 19.5% African American), and reported a 1.9% upgrade rate, similar to our study. In contrast, 70% of patients in the study of Rizzo et al. were African American, and the upgrade rate was higher ⁶. It is possible that patient ethnicity correlates with different genetic characteristics, and/or with differences in the access to health care.

Twenty-six (16%) patients without upgrade at EXC had concurrent breast carcinoma, compared to 2 (50%) patients with upgrade. Even though this variable did not reach statistical significance, possibly due to the low number of upgrades in our study, we believe it prudent to offer EXC of IDP to patients with concurrent breast carcinoma.

Several efforts have been made to define a radiologic target lesion size threshold predictive of upgrade, but results are conflicting. Chang et al. reported no upgrades at EXC of IDPs <15 mm by imaging¹⁴. Likewise, Kil et al. found that most atypical and malignant papillary lesions measured 15 mm by imaging, whereas most benign papillary lesions were <15 mm ². Glenn et al ²¹, however, described an upgrade rate of 4.7% in IDPs measuring <15 mm, but did not report radiologic-pathologic concordance. Other authors have shown that size by imaging is not predictive of upgrade ^{13,21}. In our study, the mean imaging size of lesions with and without upgrade was comparable (9.8 ± 2.3 mm vs 9 ± 0.5 mm, respectively). None of the lesions with upgrade was 15 mm, but 3/4 lesions (75%) were 10 mm, compared to 51/167 (30.7%) of the lesions without upgrade. However, no imaging size threshold was predictive of upgrade. Altogether, we found that no radiologic feature was significantly associated with upgrade. Other investigators have also indicated that no mammographic and sonographic findings can distinguish benign from malignant papillary lesions ⁹, and that no radiologic parameter is predictive of carcinoma at EXC ²³.

Holley et al.²⁴ report a lower median number of cores obtained at CNB of IDPs without upgrade (3; range 1-7) compared to IDPs with upgrade (5; range 2-21). The median number of cores in our cohort was 6 (range 2-16), similar to the median number of cores in a study of 80 IDPs and no upgrades by Wiratkapun et al. (6; range 2-16)²⁵. In the study by Kim et

al.²⁶, 12 of 131 (9.1%) IDPs sampled by ACB showed upgrade on excision, while none of 5 IDPs sampled by VAB showed upgrade on excision. One hundred (58.5%) IDPs in our study were sampled by VAB. In our series the biopsy modality did not correlate with upgrade. It is thus possible that undersampling might contribute to high upgrade rates in some studies.

The histologic size of the IDP in CNB material was not predictive of upgrade. Jaffer et al. report no upgrades at EXC of incidental papillomas measuring <2 mm²⁷, and none of the 27 IDPs spanning <2 mm in CNB material in our series showed upgrade at EXC. In our series, all four IDPs with upgrade had a histologic size $\geq$ 2 mm at CNB, however 140 (83.8%) IDPs without upgrade did as well, and we found not histologic size cutoff which was significant for upgrade.

In the study of Weisman et al²⁸, IDPs completely removed in a single core (“micropapillomas”) showed no upgrade at EXC, and there were no upgrades at EXC of 28 fragmented IDPs. In our study, none of the IDPs with upgrade was completely removed at CNB, but incomplete removal of the IDP was not predictive of upgrade. IDP fragmentation in CNB material depends on the size of the IDP, as the mean size of fragmented IDPs in our series was significantly greater than the size of non-fragmented IDPs. It is not possible to determine if a fragmented IDP is removed completely by CNB. Our data show that neither IDP histological size in CNB material, nor complete IDP removal at CNB predicts upgrade. IDP fragmentation in CNB material, however, appears significantly correlate with upgrade ($p=0.048$). All four IDPs with upgrade in our study were fragmented, versus 77 (46.1%) IDPs without upgrade. Histologic evidence of IDP fragmentation in the CNB might be a factor to consider when deciding on the need of EXC, although the high observed frequency of IDP fragmentation in the CNB material limits the utility of this parameter.

Ming et al. report the presence of microcalcifications detected by CNB histology and imaging to be associated with upgrade¹³. Our results did not confirm this observation.

Information about the extent and severity of the carcinomas found in the EXC specimen of patients with CNB diagnosis of IDP is scarce. In our study, the upgrade lesions were two invasive lobular carcinomas and two DCIS, each measuring $\geq$ 2 mm. Three of the carcinomas were away from the residual IDP, and did not involve it, suggesting that, at least in our cohort, most upgrades were incidental (Table 4). Lewis et al. showed that there was no significant increase in the incidence of subsequent ipsilateral breast carcinoma in patients with IDP. The relative risk of developing carcinoma following the identification of IDP in an excisional biopsy specimen was 2.01, comparable to the risk in patients with proliferative disease without atypia (1.90)²⁹.

Our study is retrospective, and examined the patient population of a cancer hospital, where close imaging surveillance is routinely implemented and diagnostic expertise is readily available. Due to the limited number of cases with upgrade to carcinoma on excision in our series, our observations on the association of upgrade to carcinoma with concurrent ipsilateral breast cancer and with evidence of IDP fragmentation on CNB should be regarded as preliminary and hypothesis generating. Further evaluation of these parameters in relation

to upgrade to carcinoma on excision in a series with a larger number of upgrades is warranted.

Experience in the diagnosis of mammary lesions plays a role in the accuracy of the diagnosis of breast papillary lesions. Jakate et al. showed that the upgrade rate of IDP to carcinoma at EXC was different if breast pathologists (2.5%) versus non-breast pathologists (6.9%) evaluated the same cases³⁰. Our study cases were all reviewed by breast pathologists and this might account at least in part for the low rate of upgrade. Nakhli et al.¹⁰ observed no upgrades at EXC of IDPs in radiologic-pathologic concordant CNB samples, that were evaluated by an expert breast pathologist. Taken together, our results show that the risk of carcinoma associated with IDP diagnoses in radiologic-pathologic concordant CNB is low. Our data suggest that close radiologic follow up constitutes appropriate management for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Patrick Hilden, Research Biostatistician from the Department of Epidemiology and Biostatistics at MSKCC for his comments on the statistical evaluation of this study.

Funding support: Research reported in this publication was supported in part by the Cancer Center Support Grant of the National Institutes of Health/National Cancer Institute under award number P30CA008748

References

1. MacGrogan G, Tavassoli FA. Central atypical papillomas of the breast: a clinicopathological study of 119 cases. *Virchows Archiv : an international journal of pathology*. Nov; 2003 443(5):609–617. [PubMed: 13680220]
2. Kil WH, Cho EY, Kim JH, Nam SJ, Yang JH. Is surgical excision necessary in benign papillary lesions initially diagnosed at core biopsy? *Breast*. Jun; 2008 17(3):258–262. [PubMed: 18054232]
3. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? *The American journal of surgical pathology*. Sep; 2002 26(9):1095–1110. [PubMed: 12218567]
4. Renshaw AA, Derhagopian RP, Tizol-Blanco DM, Gould EW. Papillomas and atypical papillomas in breast core needle biopsy specimens: risk of carcinoma in subsequent excision. *American journal of clinical pathology*. Aug; 2004 122(2):217–221. [PubMed: 15323138]
5. Page DL, Salhany KE, Jensen RA, Dupont WD. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. *Cancer*. Jul 15; 1996 78(2):258–266. [PubMed: 8674001]
6. Rizzo M, Linebarger J, Lowe MC, et al. Management of papillary breast lesions diagnosed on core-needle biopsy: clinical pathologic and radiologic analysis of 276 cases with surgical follow-up. *Journal of the American College of Surgeons*. Mar; 2012 214(3):280–287. [PubMed: 22244207]
7. Jung SY, Kang HS, Kwon Y, et al. Risk factors for malignancy in benign papillomas of the breast on core needle biopsy. *World journal of surgery*. Feb; 2010 34(2):261–265. [PubMed: 19997916]
8. Shiino S, Tsuda H, Yoshida M, et al. Intraductal papillomas on core biopsy can be upgraded to malignancy on subsequent excisional biopsy regardless of the presence of atypical features. *Pathology international*. Jun; 2015 65(6):293–300. [PubMed: 25801805]
9. Lam WW, Chu WC, Tang AP, Tse G, Ma TK. Role of radiologic features in the management of papillary lesions of the breast. *AJR American journal of roentgenology*. May; 2006 186(5):1322–1327. [PubMed: 16632726]

10. Nakhlis F, Ahmadiyeh N, Lester S, Raza S, Lotfi P, Golshan M. Papilloma on core biopsy: excision vs. observation. *Annals of surgical oncology*. May; 2015 22(5):1479–1482. [PubMed: 25361885]
11. Liberman L, Drotman M, Morris EA, et al. Imaging-histologic discordance at percutaneous breast biopsy. *Cancer*. Dec 15; 2000 89(12):2538–2546. [PubMed: 11135213]
12. Swapp RE, Glazebrook KN, Jones KN, et al. Management of benign intraductal solitary papilloma diagnosed on core needle biopsy. *Annals of surgical oncology*. Jun; 2013 20(6):1900–1905. [PubMed: 23314624]
13. Li X, Weaver O, Desouki MM, et al. Microcalcification is an important factor in the management of breast intraductal papillomas diagnosed on core biopsy. *American journal of clinical pathology*. Dec; 2012 138(6):789–795. [PubMed: 23161711]
14. Chang JM, Moon WK, Cho N, et al. Risk of carcinoma after subsequent excision of benign papilloma initially diagnosed with an ultrasound (US)-guided 14-gauge core needle biopsy: a prospective observational study. *European radiology*. May; 2010 20(5):1093–1100. [PubMed: 19890638]
15. Arora N, Hill C, Hoda SA, Rosenblatt R, Pigalarga R, Tousimis EA. Clinicopathologic features of papillary lesions on core needle biopsy of the breast predictive of malignancy. *American journal of surgery*. Oct; 2007 194(4):444–449. [PubMed: 17826053]
16. Collins LC, Schnitt SJ. Papillary lesions of the breast: selected diagnostic and management issues. *Histopathology*. Jan; 2008 52(1):20–29. [PubMed: 18171414]
17. Chang JM, Han W, Moon WK, et al. Papillary lesions initially diagnosed at ultrasound-guided vacuum-assisted breast biopsy: rate of malignancy based on subsequent surgical excision. *Annals of surgical oncology*. Sep; 2011 18(9):2506–2514. [PubMed: 21369740]
18. Mercado CL, Hamele-Bena D, Singer C, et al. Papillary lesions of the breast: evaluation with stereotactic directional vacuum-assisted biopsy. *Radiology*. Dec; 2001 221(3):650–655. [PubMed: 11719659]
19. Ahmadiyeh N, Stoleru MA, Raza S, Lester SC, Golshan M. Management of intraductal papillomas of the breast: an analysis of 129 cases and their outcome. *Annals of surgical oncology*. Aug; 2009 16(8):2264–2269. [PubMed: 19484312]
20. Skandarajah AR, Field L, Yuen Larn Mou A, et al. Benign papilloma on core biopsy requires surgical excision. *Annals of surgical oncology*. Aug; 2008 15(8):2272–2277. [PubMed: 18473143]
21. Glenn ME, Throckmorton AD, Thomison JB 3rd, Bienkowski RS. Papillomas of the breast 15 mm or smaller: 4-year experience in a community-based dedicated breast imaging clinic. *Annals of surgical oncology*. Apr; 2015 22(4):1133–1139. [PubMed: 25316488]
22. Cyr AE, Novack D, Trinkaus K, et al. Are we overtreating papillomas diagnosed on core needle biopsy? *Annals of surgical oncology*. Apr; 2011 18(4):946–951. [PubMed: 21046266]
23. Agoff SN, Lawton TJ. Papillary lesions of the breast with and without atypical ductal hyperplasia: can we accurately predict benign behavior from core needle biopsy? *American journal of clinical pathology*. Sep; 2004 122(3):440–443. [PubMed: 15362376]
24. Holley SO, Appleton CM, Farria DM, et al. Pathologic outcomes of nonmalignant papillary breast lesions diagnosed at imaging-guided core needle biopsy. *Radiology*. Nov; 2012 265(2):379–384. [PubMed: 22952379]
25. Wiratkapun C, Keeratitragoon T, Lertsithichai P, Chanplakorn N. Upgrading rate of papillary breast lesions diagnosed by core-needle biopsy. *Diagnostic and interventional radiology*. Sep-Oct; 2013 19(5):371–376. [PubMed: 23748032]
26. Kim MJ, Kim SI, Youk JH, et al. The diagnosis of non-malignant papillary lesions of the breast: comparison of ultrasound-guided automated gun biopsy and vacuum-assisted removal. *Clinical radiology*. Jun; 2011 66(6):530–535. [PubMed: 21353213]
27. Jaffer S, Bleiweiss IJ, Nagi C. Incidental intraductal papillomas (<2 mm) of the breast diagnosed on needle core biopsy do not need to be excised. *The breast journal*. Mar-Apr; 2013 19(2):130–133. [PubMed: 23336823]
28. Weisman PS, Sutton BJ, Siziopikou KP, et al. Non-mass-associated intraductal papillomas: is excision necessary? *Human pathology*. Mar; 2014 45(3):583–588. [PubMed: 24444467]

29. Lewis JT, Hartmann LC, Vierkant RA, et al. An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. *The American journal of surgical pathology*. Jun; 2006 30(6):665–672. [PubMed: 16723843]
30. Jakate K, De Brot M, Goldberg F, Muradali D, O'Malley FP, Mulligan AM. Papillary lesions of the breast: impact of breast pathology subspecialization on core biopsy and excision diagnoses. *The American journal of surgical pathology*. Apr; 2012 36(4):544–551. [PubMed: 22314186]

Figure 1.

Intraductal Papilloma without Atypia at Core Needle Biopsy with Incidental Carcinoma in the Excision specimen. (a) A minute intraductal papilloma without atypia is present in the core needle biopsy sample. No cytologic atypia is evident at high magnification (inset). (b) The excision specimen contains a 1 mm focus of invasive lobular carcinoma, away from the residual intraductal papilloma (★) and biopsy site (*). A close view of the invasive lobular carcinoma is shown (inset).

Figure 2.

Intraductal papilloma without Atypia at Core Needle Biopsy with a True Upgrade to Carcinoma. (a) A minute intraductal papilloma without atypia is present in the core needle biopsy sample. A magnified view of the intraductal papilloma is shown in the inset. (b) The excision specimen contains a 2 mm focus of DCIS involving the papilloma (★), near the biopsy site (*).

Table 1
Clinical Characteristics of Patients according to Upgrade at Excision

	Total	No Upgrade	Upgrade	p value
Patients	166 (100%)	162 (100%)	4 (100%)	
Age				
Mean $\pm$ SEM	51.8 $\pm$ 0.9	51.7 $\pm$ 0.9	52.8 $\pm$ 1.8	0.864
Median (Range)	50.5 (25-85)	50 (25-85)	51.5 (50-58)	
<i>50 years old</i>	89 (53.6%)	85 (52.5%)	4 (100%)	0.124
<i>< 50 years old</i>	77 (46.4%)	77 (47.5%)	0	
Ethnicity^a				
Caucasian	108 (65.5%)	105 (65.2%)	3 (75%)	0.352
African American	38 (23%)	38 (23.6%)	0	
Asian/Indian	11 (6.7%)	10 (6.2%)	1 (25%)	
Hispanic	8 (4.8%)	8 (5%)	0	
Symptoms				
No	150 (90.4%)	146 (90.1%)	4 (100%)	1.000
Yes	16 (9.6%)	16 (9.9%)	0	
<i>Nipple discharge</i>	8 (50%)	8 (50%)	0	-
<i>Palpable mass</i>	7 (43.8%)	7 (43.8%)	0	
<i>Pain</i>	1 (6.3%)	1 (6.3%)	0	
Personal History of Breast Cancer				
Yes	58 (34.9%)	55 (34%)	3 (75%)	0.123
No	108 (65.1%)	107 (66%)	1 (25%)	
Concurrent				
<i>Yes</i>	28 (16.9%)	26 (16%)	2 (50%)	0.133
<i>No</i>	138 (83.1%)	136 (84%)	2 (50%)	
Concurrent and Ipsilateral				
<i>Yes</i>	12 (7.2%)	10 (6.2%)	2 (50%)	0.027
<i>No</i>	154 (92.8%)	152 (93.8%)	2 (50%)	
Prior				
<i>Yes</i>	30 (18.1%)	29 (17.9%)	1 (25%)	0.553
<i>No</i>	136 (81.9%)	133 (82.1%)	3 (75%)	

Abbreviation: SEM, standard error of the mean.

^aInformation for 165 patients.

Table 2
Radiologic Characteristics of the Target Lesions and Characteristics of Core Needle Biopsy Procedure according to Upgrade at Excision

	Total	No Upgrade	Upgrade	p value
Target Lesions	171 (100%)	167 (100%)	4 (100%)	
Size (mm)^a				
Mean ± SEM	9±0.5	9±0.5	9.8±2.4	0.834
Median (Range)	7 (2-43)	7 (2-43)	11.5 (3-13)	
15 mm	20 (11.8%)	20 (12%)	0	1.000
<15 mm	150 (88.2%)	146 (88%)	4 (100%)	
10 mm	54 (31.8%)	51 (30.7%)	3 (75%)	0.095
<10 mm	116 (68.2%)	115 (69.3%)	1 (25%)	
Distance from nipple (mm)^a				
Mean ± SEM	38.9±2	38.6±2.1	47.5±13.1	0.514
Median (Range)	30 (10-140)	30 (10-140)	55 (10-70)	
> 20 mm	109 (64.1%)	106 (63.9%)	3 (75%)	1.000
20 mm	61 (35.9%)	60 (36.1%)	1 (25%)	
CNB target lesion				
Mass	102 (59.6%)	100 (59.9%)	2 (50%)	0.972
Calcifications	34 (19.9%)	33 (19.8%)	1 (25%)	
NME	33 (19.3%)	32 (19.2%)	1 (25%)	
Asymmetry	2 (1.2%)	2 (1.2%)	0	
Mode of biopsy				
US-guided	78 (45.6%)	76 (45.5%)	2 (50%)	0.936
MRI-guided	57 (33.3%)	56 (33.5%)	1 (25%)	
Stereotactic	36 (21.1%)	35 (21%)	1 (25%)	
Biopsy modality				
VAB	100 (58.5%)	96 (57.5%)	4 (100%)	0.142
ACB	71 (41.5%)	71 (42.5%)	0	
Needle gauge				
Mean +SEM	11.5±0.2	11.5±0.2	11±0.7	0.667
Median (Range)	11 (9-18)	11 (9-18)	11.5 (9-12)	
Number of cores^b				
Mean +SEM	7.1±0.3	7.1±0.3	8±2.6	0.666
Median (Range)	6 (1-20)	6 (1-20)	9 (3-12)	

Abbreviations: SEM, standard error of the mean; CNB, core needle biopsy; NME, non mass enhancement; VAB, vacuum-assisted biopsy; ACB, automated core needle biopsy.

^a Only 170 cases were evaluable.

^b Information available for 153 cases.

Table 3
Histopathologic Characteristics of IDPs according to Upgrade at Excision

	Total	No Upgrade	Upgrade	p value
IDPs	171 (100%)	167 (100%)	4 (100%)	
CNB Specimen				
IDP Size (mm)				
Mean ± SEM	3.4±0.1	3.4±0.1	3.4±0.6	0.981
Median (Range)	3 (0.4-9)	3 (0.4-9)	3.5 (2-4.5)	
2 mm	144 (84.2%)	140 (83.8%)	4 (100%)	1.000
<2 mm	27 (15.8%)	27 (16.2%)	0	
Complete removal of IDP				
Yes	20 (11.7%)	20 (12%)	0	1.000
No	151 (88.3%)	147 (88%)	4 (100%)	
IDP Fragmentation				
Yes	81 (47.4%)	77 (46.1%)	4 (100%)	0.048
No	90 (52.6%)	90 (53.9%)	0	
Calcifications in IDP				
Yes	56 (32.7%)	53 (31.7%)	3 (75%)	0.103
No	115 (67.3%)	114 (68.3%)	1 (25%)	
EXC Specimen				
Residual IDP				
No	64 (37.4%)	64 (38.3%)	0	0.298
Yes	107 (62.6%)	103 (61.7%)	4 (100%)	
Size (mm)				
Mean±SEM	5.5±0.3	5.5±0.3	4.9±1.6	0.745
Median (Range)	0.4-17	0.4-17	0.7-8	

Abbreviations: IDP, intraductal papilloma without atypia; CNB, core needle biopsy; SEM, standard error of the mean; EXC, excision.

Table 4
Clinical, Radiologic and Histopathologic Characteristics of Patients with Upgrade

	1	2	3	4
Clinical Characteristics				
Age (Years)	50	51	52	58
Symptoms	No	No	No	No
Personal History of Breast Cancer	No	Yes (IDC)	Yes (IDC)	Yes (IDC)
Laterality	N/A	Ipsilateral	Ipsilateral	Ipsilateral
Temporal relationship	N/A	Prior (24 months)	Concurrent	Concurrent
Radiologic Characteristics of Target Lesion				
Reason for biopsy	Mass	NME	Mass	Calcifications
Size (mm)	13	10	13	3
Distance from nipple (mm)	50	60	10	70
Histopathologic Characteristics				
IDP in CNB Specimen				
Size (mm)	4	2	3	4.5
Completely removed	No	No	No	No
Fragmented	Yes	Yes	Yes	Yes
Calcifications in IDP	Yes	Yes	No	Yes
EXC Specimen				
Upgrade lesion	DCIS	DCIS	ILC	ILC
Size (mm)	2	2	1	2
Grade of invasive carcinoma	N/A	N/A	Mod diff	Mod diff
DCIS architecture	Cribriform	Flat and micropapillary	N/A	N/A
DCIS nuclear grade	Low	Intermediate to high	N/A	N/A
Distance from IDP (mm)	Involves IDP	11	8	15
Residual IDP size (mm)	7	0.7	8	4
Type of Upgrade	True	Incidental	Incidental	Incidental

Abbreviations: IDC, invasive ductal carcinoma; NME, non mass enhancement; IDP, intraductal papilloma without atypia; CNB, core needle biopsy; EXC, excision; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; N/A, not applicable; Mod diff, moderately differentiated.