Original Article

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

Fresia Pareja, MD, PhD[1]; Adriana D. Corben, MD[1]; Sandra B. Brennan, MB[2]; Melissa P. Murray, DO[1]; Zenica L. Bowser, MS[1]; Kiran Jakate, MD[3]; Christopher Sebastiano, MD[1]; Monica Morrow, MD[4]; Elizabeth A. Morris, MD[2]; and Edi Brogi, MD, PhD[1]

BACKGROUND: The surgical management of mammary intraductal papilloma without atypia (IDP) identified at core-needle biopsy (CNB) is controversial. This study assessed the rate of upgrade to carcinoma at surgical excision (EXC). **METHODS:** This study identified women with a CNB diagnosis of intraductal papilloma without atypia or carcinoma at a cancer center between 2003 and 2013. Radiologic-pathologic concordance was assessed for all cases, and discordant cases were excluded. The radiologic and clinicopathologic features of patients with a CNB diagnosis of IDP were correlated with an upgrade to carcinoma at EXC. **RESULTS:** The study population consists of 189 women with 196 IDPs; 166 women (171 IDPs) underwent EXC. The upgrade rate was 2.3% (4 of 171). The upgraded 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 $\geq$ 8 mm away. Twenty-four women (25 IDPs) did not undergo EXC and had stable imaging on follow-up (median, 23.5 months). **CONCLUSIONS:** The upgrade rate at EXC for IDPs diagnosed at CNB with radiologic-pathologic concordance was 2.3%. These findings suggest that observation is appropriate for patients with radiologic-pathologic concordant CNB yielding IDP, regardless of its size. ***Cancer*** **2016;122:2819-27.** © *2016 American Cancer Society.*

KEYWORDS: atypia, biopsy, breast, carcinoma, core needle, excision, papilloma, upgrade.

INTRODUCTION

The standard of care for the management of atypical papilloma at core-needle biopsy (CNB) is surgical excision (EXC) because numerous studies have demonstrated high rates of upgrade to carcinoma.[1-5] Surgical management after a CNB diagnosis of intraductal papilloma without atypia (IDP), however, remains controversial.

EXC of all IDPs is recommended by most investigators because of the high reported rates of upgrade in some series[6-8] and the inability of imaging studies to accurately classify the lesions.[9] However, most of the published series did not take into account radiologic-pathologic concordance of the lesions,[10] 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 EXC.[11] A few recent series found low upgrade rates at EXC of lesions yielding IDP at CNB,[12,13] and the investigators concluded that EXC is not required and that imaging surveillance is sufficient. A number of radiologic and histologic features predictive of upgrade have been suggested; they include a size $\geq$ 1.5 mm on imaging,[14] the presence of microcalcifications,[13] and older patient age.[15]

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

Corresponding author: Edi Brogi, MD, PhD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; Fax: (929) 321-5012; brogie@mskcc.org

[1]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York; [2]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; [3]Department of Pathology, St. Michael's Hospital, Toronto, Ontario, Canada; [4]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

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F.P. and A.D.C. contributed equally to this article.
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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, had no slides available for review, or 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 7 cases of papillary usual ductal hyperplasia and 12 atypical papillomas or IDPs with adjacent atypia in the CNB material. Three radiologic-pathologic discordant cases were also excluded.

Clinical information, including the sex, 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, the indication for biopsy (calcifications, mass, nonmass enhancement [NME], and asymmetry), and the 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 noted. Lesion enhancement kinetics were evaluated. The mode of biopsy, biopsy modality, needle gauge, and number of tissue cores were recorded.

Pathology Review

Review of CNB material

Two breast pathologists (A.D.C. and F.P.), blinded to the EXC diagnosis, reviewed the hematoxylin and eosin slides of all CNB cases included in the study. Lesions consisting of arborizing fibrovascular cores lined by epithelium and myoepithelium were categorized as intraductal papillomas,[16] and they were further classified according to the presence of epithelial atypia as either IDP or atypical papilloma. Cases showing atypical papilloma, a high-risk lesion (ie, atypia, lobular carcinoma in situ, 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 the size (the greatest dimension in a single core), complete removal at CNB, fragmentation, and associated calcifications.

Review of surgical excision specimens

The hematoxylin and eosin slides of all EXC specimens were reviewed to assess the presence of residual IDP and its size as well as the biopsy site, atypia, and carcinoma. The nature of the atypia or high-risk lesion, along with its spatial relation with the residual IDP or biopsy site, was annotated. An upgrade was defined as the presence of invasive carcinoma and/or ductal carcinoma in situ (DCIS) in the EXC specimen. We recorded the characteristics of the carcinoma (tumor type, size, and histologic grade) and its spatial relation with the residual IDP.

The slides of CNB and EXC specimens of the cases with upgrades were also reviewed together by 2 additional breast pathologists (E.B. and M.M.).

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows (version 22.0; IBM, Armonk, NY). Fisher's exact text was used to assess the association of categorical variables with an upgrade; one-way analysis of variance (one-way ANOVA) was used to evaluate continuous variables. Statistical significance was defined as a P value $< .05$. Because of the small number of cases upgraded to carcinoma on EXC ($n = 4$), a correction of P values for multiple comparisons was not performed. For patients with more than 1 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 1 patient with bilateral metachronous IDPs, we used the age at the time of the first diagnosis of IDP for the analysis.

RESULTS

Patient Characteristics

The study population consisted of 189 women with a CNB diagnosis of IDP (183 patients had 1 IDP, 5 had 2 IDPs, and 1 had 3 IDPs). The total number of IDPs was 196. The mean patient age at diagnosis was 51.8 ± 0.9 years (range, 25-85 years). Most women ($n = 166$) underwent EXC of the radiologic target lesion. Twenty-four women did not undergo EXC but were followed clinically and radiologically. One woman underwent EXC of 2 synchronous IDPs but did not undergo EXC of a third IDP, which was detected 2 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 (range, 25-85 years); 89 patients (53.6%) were ≥ 50 years old. Most

TABLE 1. Clinical Characteristics of the Patients According to the Upgrade Status at Excision

	Total	No Upgrade	Upgrade	*P*
Patients, No. (%)	166 (100)	162 (100)	4 (100)	
Age				
Mean ± SEM, years	51.8 ± 0.9	51.7 ± 0.9	52.8 ± 1.8	.864
Median (range), years	50.5 (25-85)	50 (25-85)	51.5 (50-58)	
≥50 y, No. (%)	89 (53.6)	85 (52.5)	4 (100)	.124
<50 y, No. (%)	77 (46.4)	77 (47.5)	0	
Ethnicity, No. (%)[a]				
White	108 (65.5)	105 (65.2)	3 (75)	.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. (%)				
No	150 (90.4)	146 (90.1)	4 (100)	1.000
Yes	16 (9.6)	16 (9.9)	0	
Nipple discharge	8 (50)	8 (50)	0	
Palpable mass	7 (43.8)	7 (43.8)	0	
Pain	1 (6.3)	1 (6.3)	0	
Personal history of breast cancer, No. (%)				
Yes	58 (34.9)	55 (34)	3 (75)	.123
No	108 (65.1)	107 (66)	1 (25)	
Concurrent				
Yes	28 (16.9)	26 (16)	2 (50)	.133
No	138 (83.1)	136 (84)	2 (50)	
Concurrent and ipsilateral				
Yes	12 (7.2)	10 (6.2)	2 (50)	.027
No	154 (92.8)	152 (93.8)	2 (50)	
Prior				
Yes	30 (18.1)	29 (17.9)	1 (25)	.553
No	136 (81.9)	133 (82.1)	3 (75)	

Abbreviation: SEM, standard error of the mean.
[a] Information was available for 165 patients.

patients (108 or 65.5%) were of white ethnicity, 38 (23%) were African American, 11 (6.7%) were Asian/Indian, and 8 (4.8%) were Hispanic; no information was available for 1 patient. Only 16 women (9.6%), including 8 with nipple discharge, reported symptoms. Fifty-eight patients (34.9%) had either prior (30 or 18.1%) or concurrent breast carcinoma (28 or 16.9%). The latter was ipsilateral in 12 patients (7.2%; Table 1).

Radiologic characteristics of the target lesion

The mean size of the radiologic target was 9 ± 0.5 mm (range, 2-43 mm). In 20 cases (11.8%), the radiologic target measured ≥15 mm. The mean and median distance between the nipple and the radiologic target were 38.9 ± 2 and 30 mm (range, 10-140 mm), 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 an upgrade (Table 2 and Supporting Table 1 [see online supporting information]).

CNB procedure characteristics

Seventy-eight biopsies (45.6%) were ultrasound (US)-guided, 57 (33.3%) were magnetic resonance imaging (MRI)–guided, and 36 (21.1%) were stereotactic. One hundred IDPs (58.5%) were sampled by vacuum-assisted biopsy (VAB), and 71 (41.5%) were sampled by automated core-needle biopsy (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 an upgrade (Table 2 and Supporting Table 2 [see online supporting information]).

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 mm); 144 IDPs (84.2%) were ≥ 2 mm. Eighty-one IDPs (47.7%) were fragmented, 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; $P = .03$; Table 3).

TABLE 2. Radiologic Characteristics of the Target Lesions and Characteristics of the Core-Needle Biopsy Procedure According to the Upgrade Status at Excision

	Total	No Upgrade	Upgrade	*P*
Target lesions	171 (100)	167 (100)	4 (100)	
Size[a]				
Mean ± SEM, mm	9 ± 0.5	9 ± 0.5	9.8 ± 2.4	.834
Median (range), mm	7 (2-43)	7 (2-43)	11.5 (3-13)	
≥15 mm, No. (%)	20 (11.8)	20 (12)	0	1.000
<15 mm, No. (%)	150 (88.2)	146 (88)	4 (100)	
≥10 mm, No. (%)	54 (31.8)	51 (30.7)	3 (75)	.095
<10 mm, No. (%)	116 (68.2)	115 (69.3)	1 (25)	
Distance from nipple[a]				
Mean ± SEM, mm	38.9 ± 2	38.6 ± 2.1	47.5 ± 13.1	.514
Median (range), mm	30 (10-140)	30 (10-140)	55 (10-70)	
>20 mm, No. (%)	109 (64.1)	106 (63.9)	3 (75)	1.000
≤20 mm, No. (%)	61 (35.9)	60 (36.1)	1 (25)	
CNB target lesion, No. (%)				
Mass	102 (59.6)	100 (59.9)	2 (50)	.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, No. (%)				
US-guided	78 (45.6)	76 (45.5)	2 (50)	.936
MRI-guided	57 (33.3)	56 (33.5)	1 (25)	
Stereotactic	36 (21.1)	35 (21)	1 (25)	
Biopsy modality, No. (%)				
VAB	100 (58.5)	96 (57.5)	4 (100)	.142
ACB	71 (41.5)	71 (42.5)	0	
Needle gauge				
Mean ± SEM	11.5 ± 0.2	11.5 ± 0.2	11 ± 0.7	.667
Median (range)	11 (9-18)	11 (9-18)	11.5 (9-12)	
No. of cores[b]				
Mean ± SEM	7.1 ± 0.3	7.1 ± 0.3	8 ± 2.6	.666
Median (range)	6 (1-20)	6 (1-20)	9 (3-12)	

Abbreviations: ACB, automated core-needle biopsy; CNB, core-needle biopsy; MRI, magnetic resonance imaging; NME, nonmass enhancement; SEM, standard error of the mean; US, ultrasound; VAB, vacuum-assisted biopsy.
[a] Only 170 cases were evaluable.
[b] Information was available for 153 cases.

Histopathologic characteristics of upgraded lesions in surgical excision specimens

The upgrade rate to carcinoma (2 invasive lobular carcinomas and 2 cases of DCIS) in the EXC specimen was 2.3% (4 of 171 cases). All carcinomas measured ≤ 2 mm. DCIS involved the residual IDP in 1 case (true upgrade). The other 3 carcinomas were at least 0.8 mm from the residual IDP (incidental upgrades; Table 4 and Figs. 1 and 2).

Additional histopathologic findings in surgical excision specimens

Upon a review of the EXC specimens, the biopsy site was documented in all cases. A residual IDP was present in 107 EXC specimens (62.6%), and the mean histologic size was 5.5 mm (range, 0.4-17 mm; Table 3). Thirty-nine cases (22.8%) harbored a high-risk lesion (19 cases of atypical ductal hyperplasia, 7 cases of atypical lobular hyperplasia, 4 cases of lobular carcinoma in situ, 1 columnar cell change with atypia, and 8 radial scars) that was not present in the initial CNB sample.

Analysis of features predictive of an upgrade

Clinical features. The age of patients with and without upgrades was comparable (52.8 ± 1.8 vs 51.7 ± 0.9 y, respectively). Concurrent ipsilateral breast carcinoma was the only clinical parameter associated with an upgrade. Two of the 4 patients with an upgrade had concurrent ipsilateral breast carcinoma, whereas only 10 of the 162 patients without an upgrade (6.2%) did. None of the patients with an upgrade was symptomatic (Table 1).

Radiologic features and CNB procedure characteristics. There were no statistically significant differences in the radiologic characteristics of the lesions with and without upgrade. The radiologic target of CNB was a mass in 2 of the 4 cases with an upgrade (50%) and in 100 cases (59.9%) without an upgrade. In 2 cases with an upgrade, CNB targeted a mass. One mass was oval with circumscribed margins; the other had an irregular shape and was not circumscribed. For the other 2 cases with an upgrade at EXC, CNB targeted clustered fine linear calcifications in one case, and linear NME with plateau kinetics in the other. The mean size of the imaging target was similar in cases with an upgrade (9.8 ± 2.4 mm) and cases without an upgrade (9 ± 0.5 mm); no imaging target size threshold correlated with an upgrade. The IDPs were > 20 mm from the nipple in most cases with (3 or 75%) and without an upgrade (106 or 63.9%).

All 4 radiologic targets with an upgrade at EXC were sampled with VAB (1 CNB was stereotactic, 2 were US-guided, and 1 was 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; $P = .043$). The needle gauge in the cases with an upgrade ranged from 9 to 12. None of these parameters were predictive of an upgrade (Table 2 and Supporting Tables 1 and 2 [see online supporting information]).

Histopathologic findings. In the CNB material, all IDPs with an upgrade measured ≥2 mm. The mean size of the IDP was similar for cases with and without an upgrade (3.4 ± 0.1 mm; $P = .981$). IDP fragmentation was the only histologic parameter associated with an upgrade. All 4 IDPs with an upgrade and 77 of 167 IDPs (46.1%)

TABLE 3. Histopathologic Characteristics of IDPs According to the Upgrade Status at Excision

	Total	No Upgrade	Upgrade	*P*
IDPs, No. (%)	171 (100)	167 (100)	4 (100)	
CNB specimens				
IDP size				
Mean ± SEM, mm	3.4 ± 0.1	3.4 ± 0.1	3.4 ± 0.6	.981
Median (range), mm	3 (0.4-9)	3 (0.4-9)	3.5 (2-4.5)	
≥2 mm, No. (%)	144 (84.2)	140 (83.8)	4 (100)	1.000
<2 mm, No. (%)	27 (15.8)	27 (16.2)	0	
Complete removal of IDP, No. (%)				
Yes	20 (11.7)	20 (12)	0	1.000
No	151 (88.3)	147 (88)	4 (100)	
IDP fragmentation, No. (%)				
Yes	81 (47.4)	77 (46.1)	4 (100)	.048
No	90 (52.6)	90 (53.9)	0	
Calcifications in IDP, No. (%)				
Yes	56 (32.7)	53 (31.7)	3 (75)	.103
No	115 (67.3)	114 (68.3)	1 (25)	
EXC specimens				
Residual IDP, No. (%)				
No	64 (37.4)	64 (38.3)	0	.298
Yes	107 (62.6)	103 (61.7)	4 (100)	
Size				
Mean ± SEM, mm	5.5 ± 0.3	5.5 ± 0.3	4.9 ± 1.6	.745
Median (range), mm	0.4-17	0.4-17	0.7-8	

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

without an upgrade were fragmented ($P = .048$). Complete IDP removal at CNB and calcifications in the IDP were not associated with an upgrade at EXC.

In the EXC specimens, residual IDP was identified in all 4 cases with an upgrade and in 103 cases (61.7%) without an upgrade. The mean sizes of the residual IDPs were similar in the 2 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 y). Three patients (12.5%) had concurrent contralateral breast carcinoma, and none had concurrent ipsilateral breast carcinoma. Two patients (8.3%) had a 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 mm). The radiologic targets included 13 mass lesions (52%), 9 calcifications (36%), and 3 NME lesions (12%). Ten CNBs (40%) were stereotactic, 8 (32%) were US-guided, and 7 (28%) were MRI-guided. The CNB was VAB in 18 cases (72%) and ACB in 7 cases (28%), with the 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 5 cases (20%).

The median follow-up time was 23.5 months (range, 6-132 months). A review of follow-up imaging studies showed stability of the lesions and no additional ipsilateral findings.

DISCUSSION

Although EXC of atypical papillomas identified in a CNB sample is mandated, regardless of radiologic-pathologic concordance,[3] 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 with radiologic-pathologic concordant CNB. DCIS or invasive carcinoma was identified in the EXC specimen in 4 of 171 CNBs with a 2.3% rate of upgrading to carcinoma.

Our findings confirm that the upgrade rate at EXC of IDP with a radiologic-pathologic concordant CNB sample is low. Swapp et al[12] observed no upgrades in a cohort of 77 radiologic-pathologic concordant IDPs. Moreover, 100 patients with radiologic-pathologic concordant CNB for IDP were stable according to imaging during a mean follow-up time of 36 months. In a series of 85 radiologic-pathologic concordant IDPs, there were 2 upgrades (2.4%),[14] and there were none in a

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

prospective series of 49 cases.[17] Several other smaller series of radiologic-pathologic concordant cases have reported similar findings.[4,18,19] A study of 80 radiologic-pathologic concordant IDPs, however, reported an upgrade rate of 18.8%.[20] Notably, 12 of 15 upgrade lesions were papillary carcinomas, and this raises the possibility of undersampling or underdiagnosis at CNB. The latter study did not include MRI-guided CNB. In our series, the upgrade rate without MRI-guided CNB was 2.63% (3 of 114).

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

We studied clinical, radiologic, and histopathologic variables to identify patients with a CNB diagnosis of IDP and a high risk of an upgrade at EXC. Some studies have suggested that age correlates with an upgrade at EXC.[6,21] In our series, age was not significantly related to an upgrade, but all patients with carcinoma were ≥50 years old. Most patients with an upgrade in the study of Rizzo et al[6] had symptoms, but all of our patients with an 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 or 34.9%). Ten patients (6.2%) without an upgrade had concurrent ipsilateral breast carcinoma, whereas 2 patients (50%) with an upgrade did ($P = .027$). In contrast, Cyr et al[22] found that prior/concurrent breast carcinoma was not associated with atypia or carcinoma at EXC. When worrisome symptoms such as a palpable mass or nipple discharge are present, the need for EXC of a concurrent breast carcinoma should be taken into account in the surgical management of the papilloma.

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

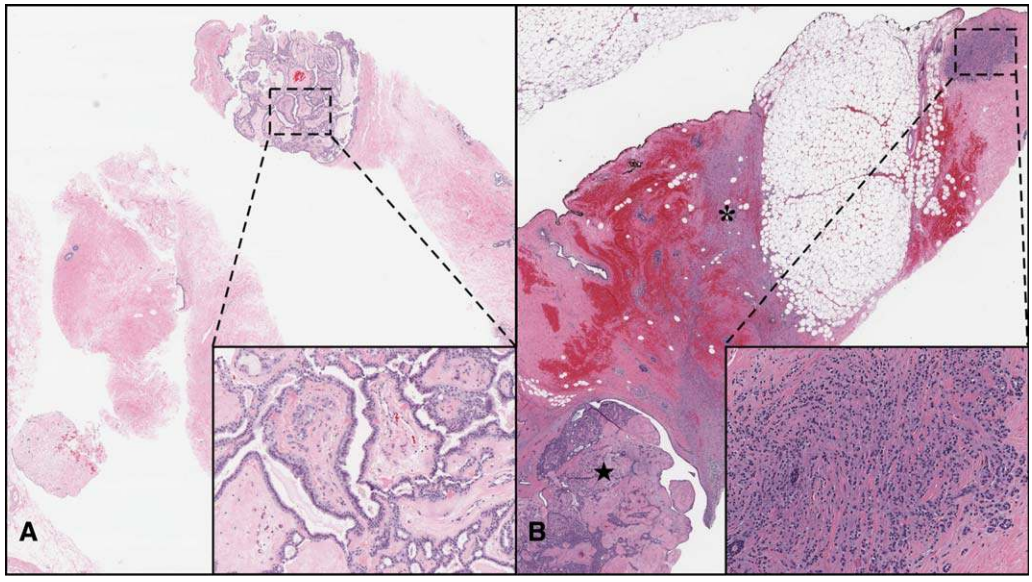

Figure 1. Intraductal papilloma without atypia on core-needle biopsy with an incidental carcinoma in the excision specimen. (A) A minute intraductal papilloma without atypia is present in the core-needle biopsy sample. *Inset*: No cytologic atypia is evident at a high magnification. (B) The excision specimen contains a 1-mm focus of invasive lobular carcinoma away from (⋆) the residual intraductal papilloma and (*) the biopsy site. *Inset*: A close view of the invasive lobular carcinoma is shown.

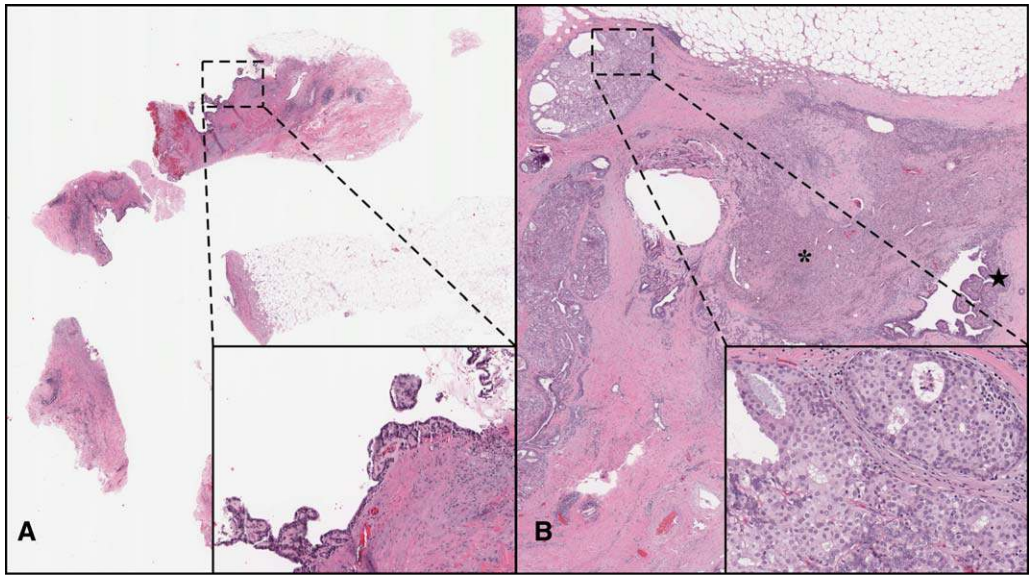

Figure 2. Intraductal papilloma without atypia on core-needle biopsy with a true upgrade to carcinoma. (A) A minute intraductal papilloma without atypia is present in the core-needle biopsy sample. *Inset*: A magnified view of the intraductal papilloma is shown. (B) The excision specimen contains a 2-mm focus of ductal carcinoma in situ involving (⋆) the papilloma near (*) the biopsy site.

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

Several efforts have been made to define a radiologic target lesion size threshold predictive of an upgrade, but the results are conflicting. Chang et al[14] reported no upgrades at EXC for IDPs < 15 mm according to imaging. Likewise, Kil et al[2] found that most atypical and malignant papillary lesions measured ≥ 15 mm by imaging, whereas most benign papillary lesions were < 15 mm.

Glenn et al,[21] however, described an upgrade rate of 4.7% in IDPs measuring < 15 mm, but they did not report radiologic-pathologic concordance. Other authors have shown that size by imaging is not predictive of an upgrade.[13,21] In our study, the mean imaging sizes of lesions with and without an upgrade were comparable (9.8 ± 2.3 vs 9 ± 0.5 mm, respectively). None of the lesions with an upgrade was ≥ 15 mm; however, 3 of the 4 lesions (75%) were ≥ 10 mm, whereas 51 of the 167 lesions (30.7%) without an upgrade were ≥ 10 mm. No imaging size threshold was predictive of an upgrade. Altogether, we found that no radiologic feature was significantly associated with an upgrade. Other investigators have also indicated that no mammographic and sonographic findings can distinguish benign papillary lesions from malignant ones,[9] and no radiologic parameter is predictive of carcinoma at EXC.[23]

Holley et al[24] reported a lower median number of cores obtained at CNB for IDPs without an upgrade (3; range, 1-7) versus IDPs with an upgrade (5; range, 2-21). The median number of cores in our cohort was 6 (range, 2-16), and this is similar to the median number of cores in a study of 80 IDPs and no upgrades by Wiratkapun et al[25] (6; range, 2-16). In the study by Kim et al,[26] 12 of 131 IDPs (9.2%) sampled by ACB showed an upgrade on EXC, whereas none of 5 IDPs sampled by VAB showed an upgrade on EXC. One hundred IDPs (58.5%) in our study were sampled by VAB. In our series, the biopsy modality did not correlate with an upgrade. It is 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 an upgrade. Jaffer et al[27] reported no upgrades at EXC of incidental papillomas measuring < 2 mm,[27] and none of the 27 IDPs spanning < 2 mm in CNB material in our series showed an upgrade at EXC. In our series, all 4 IDPs with an upgrade had a histologic size ≥ 2 mm at CNB; however, 140 IDPs (83.8%) without an upgrade did as well, and we found no histologic size cutoff that was significant for an upgrade.

In the study of Weisman et al,[28] IDPs completely removed in a single core (micropapillomas) showed no upgrade at EXC, and there were no upgrades of 28 fragmented IDPs at EXC. In our study, none of the IDPs with an upgrade were completely removed at CNB, but incomplete removal of the IDP was not predictive of an 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 that the size of nonfragmented IDPs. It is not possible to determine whether a fragmented IDP is removed completely by CNB. Our data show that neither the IDP histological size in CNB material nor complete IDP removal at CNB predicted an upgrade. IDP fragmentation in CNB material, however, appeared to significantly correlate with an upgrade ($P = .048$). All 4 IDPs with an upgrade in our study were fragmented, whereas 77 IDPs (46.1%) without an upgrade were. Histologic evidence of IDP fragmentation in the CNB material might be a factor to consider when one is deciding on the need for EXC, although the high observed frequency of IDP fragmentation in the CNB material limits the utility of this parameter.

Li et al[13] reported the presence of microcalcifications detected by CNB histology and imaging to be associated with an upgrade. Our results did not confirm this observation.

Information about the extent and severity of the carcinomas found in the EXC specimens of patients with a CNB diagnosis of IDP is scarce. In our study, the upgrade lesions were 2 invasive lobular carcinomas and 2 cases of DCIS, each measuring ≤ 2 mm. Three of the carcinomas were away from the residual IDP and did not involve it; this suggests that at least in our cohort, most upgrades were incidental (Table 4). Lewis et al[29] 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 after the identification of IDP in an excisional biopsy specimen was 2.01, which was comparable to the risk in patients with proliferative disease without atypia (1.90).

Our study was retrospective and examined the patient population of a cancer hospital at which close imaging surveillance is routinely implemented and diagnostic expertise is readily available. Because of the limited number of cases with an upgrade to carcinoma on EXC 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 an upgrade to carcinoma on EXC 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[30] showed that the upgrade rates of IDP to carcinoma at EXC were different when breast pathologists (2.5%) and non-breast pathologists (6.9%) evaluated the same cases. Our study cases were all reviewed by breast pathologists, and this might account at least in part for the low upgrade rate. Nakhlis et al[10]

observed no upgrades at EXC of IDPs diagnosed 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.

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The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Fresia Pareja: Planning of the study, conduct of the study, reporting of the study, and responsibility for the overall content of the study as a guarantor. **Adriana D. Corben**: Planning of the study, conduct of the study, reporting of the study, and responsibility for the overall content of the study as a guarantor. **Sandra B. Brennan**: Planning of the study, conduct of the study, and reporting of the study. **Melissa P. Murray**: Planning of the study, conduct of the study, and reporting of the study. **Zenica L. Bowser**: Conduct of the study and reporting of the study. **Kiran Jakate**: Conduct of the study and reporting of the study. **Christopher Sebastiano**: Conduct of the study and reporting of the study. **Monica Morrow**: Reporting of the study. **Elizabeth A. Morris**: Reporting of the study. **Edi Brogi**: Planning of the study, conduct of the study, reporting of the study, and responsibility for the overall content of the study as a guarantor.

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