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Original contribution

# Upgrade rate of intraductal papilloma diagnosed on core needle biopsy in a single institution☆,☆☆

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**Abstract** The management of intraductal papilloma (IDP) diagnosed on core needle biopsy (CNB) is controversial due to the variable upgrade rates to breast carcinoma (BC) on subsequent surgical excision reported in the literature. The purpose of our study was to investigate the upgrade rate of IDP diagnosed on CNB to BC in subsequent surgical excision and the impact of clinical, pathologic, and radiologic variables. This is a retrospective cohort of all women who had a diagnosis of IDP on a CNB between 2005 and 2018 in a tertiary academic center with subsequent surgical excision. Upgrade was defined as ductal carcinoma in situ (DCIS) and invasive carcinoma on surgical excision. Statistical analyses included Pearson's chi-square, Wilcoxon rank-sum, and logistic regression. A total of 216 women with IDP in a CNB were included. Nineteen patients (8.8%) upgraded to BC in the overall cohort, including 14 DCIS and 5 invasive carcinomas. An upgrade rate of 27% was found in atypical IDP (14 of 51 cases), while only 3% of pure IDP upgraded to BC (5 of 165 cases). Older age (>53 years) at the time of biopsy (odds ratio [OR] = 1.05, 95% confidence interval [CI] = 1.01–1.09, $p = 0.027$) and concomitant atypical ductal hyperplasia (ADH) (OR = 9.69, 95% CI = 3.37–27.81, $p < 0.0001$) were significantly associated with upgrade. Our results support surgical excision of IDP on CNB when associated with ADH or diagnosed in women aged older than 53 years. The low surgical upgrade rate of 3% for pure IDP on CNB in younger women should be part of the management discussion.


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## 1. Introduction

The management of intraductal papilloma (IDP) diagnosed on core needle biopsy (CNB) is controversial [1−3]. Some investigators advocate routine surgical excision based on an upgrade risk of up to 33% on subsequent surgical resection [4−6]. Several factors might influence this upgrade rate, such as size of the lesion, clinical presentation, presence of concomitant high-risk lesions, and radiologic-pathologic discordance [7]. Other authors suggest that with all the confounding factors considered, the upgrade risk of a pure IDP (excluding cases with atypical hyperplasia) may be as low as 2.3% [3,8−10].

Routine surgical excision might lead to unnecessary surgeries and higher cost, while forgoing excision may overlook malignancy. Therefore, identifying potential risk factors to better determine the surgical upgrade potential of IDP can help guide patient management and tailor treatment options [2,11].

Here, we report our findings based on the analysis of 216 cases of IDP diagnosed by percutaneous CNB with subsequent surgical excision and with consideration of the clinical, radiological, and histologic factors implicated in the pathological upgrade of IDP.

## 2. Materials and methods

This study was approved by the New York University Institutional Review Board. A retrospective review of the pathology database at New York University Langone Health, a tertiary academic center, from January 1, 2005 to December 31, 2018, targeted women aged 18 years or older who had a breast IDP diagnosed on CNB and underwent subsequent excision. Cases of pure IDP and atypical papilloma, whether associated with atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH)/lobular carcinoma in situ (LCIS), were included and analyzed separately. Cases of IDP associated with mucocele-like lesion and radial scar were excluded. Cases of IDP associated with ductal carcinoma in situ (DCIS) and invasive carcinoma in the same biopsy specimen were also excluded.

Patient charts were reviewed for clinical information, including age, family history of breast cancer, radiologic and histologic characteristics, and menopausal status.

Two independent subspecialized breast pathologists (U.O., F.D.) reviewed all the CNB slides to confirm the diagnosis and measure the IDP on the slide. Pathologic diagnosis of IDP was made if there was a benign lesion arising within a duct, composed of papillary projections with fibrovascular cores, covered by an epithelial and myoepithelial layer [12]. CNB pathology was compared with the subsequent surgical excision; a pathological upgrade was defined as DCIS or invasive carcinoma on subsequent surgical excision specimen. The surgical histopathology slides were reviewed for all CNBs diagnosed as pure IDP that were upgraded at excision. All CNB procedures were image guided and used 9G (78%), 11G (1%), 12G (8%), and 14G (13%). Patients' breast imaging studies including mammography, ultrasound, and/or magnetic resonance imaging (MRI) were reviewed by a dedicated breast radiologist (J.L.), who interpreted the pathologic-radiologic correlation as either concordant or discordant.

The following variables were analyzed: age, family history, *BRCA1/2* mutation status, diagnostic imaging modality, radiologic-pathologic discordance, and size of IDP measured on the slide. The association between upgrade of IDP and a concomitant breast carcinoma (BC) diagnosed in a separate biopsy site (either ipsilateral or contralateral) from the IDP specimen was also evaluated.

Statistical analyses included Pearson's chi-square and Fisher's exact tests to assess the association of categorical variables with an upgrade to carcinoma. Wilcoxon rank-sum and logistic regression were used to evaluate continuous variables. Statistical significance for all analyses was defined as a p-value $<0.05$.

A relevant literature search of 2000−2019 was performed in Medline, Embase, and Cochrane Library for publications analyzing surgical upgrade rate of pure IDP and atypical papilloma diagnosed with CNB.

## 3. Results

A total of 216 women (mean and median age: 53 years; range 24−82 years) with IDP in a CNB were included in the study. Of the 216 cases of IDP, 51 (24%) had associated atypia (41 with ADH and 10 with either ALH or LCIS). Overall, there were 165 (76%) patients with pure IDP with no concomitant atypia (Table 1).

Nineteen cases (8.8%) upgraded to BC in the overall cohort, including 14 DCIS (two with microinvasion) and 5 invasive carcinomas (2 ductal, 2 lobular, and 1 papillary carcinoma) (Table 2). DCIS cases were of nuclear grade 1 (2; 14%), nuclear grade 2 (11; 79%), and nuclear grade 3 (1; 7%) with a median size of 5 mm (mean: 11 mm; range 2−50 mm). Four of the invasive carcinomas were grade 2 and one (invasive papillary carcinoma) was grade 1. The size of the invasive carcinomas ranged from 3 mm to 10 mm (mean: 5 mm; median 4 mm). Except for case 2, the upgraded lesions were noted in the tissue surrounding the IDP (refer Table 2 and Discussion). When analyzing cases of IDP with respect to associated atypia, upgrade rates of 32% (13 of 41), 10% (1 of 10), and 3% (5 of 165) were found in IDP with ADH, ALH/LCIS, and no atypia, respectively. The overall upgrade rate for all atypia was 27% (14 of 51).

One hundred and ninety-seven patients (91%) had imaging available for analysis. Six (3%) of those patients had a discordant imaging result when correlated to the pathologic finding in CNB. One patient with discordant

**Table 1** Clinicopathologic characteristics of patients with intraductal papilloma on initial biopsy in relation to surgical excision final pathology.

| Variables | IDP without upgrade on surgical excision (n = 197) | IDP with upgrade on surgical excision (n = 19) | *P*-value |
|---|---|---|---|
| Age at biopsy (years) | | | |
| Median (range) | 51 (24−82) | 61 (29−80) | 0.0298 |
| Strong family history (1st degree) | | | |
| Yes, n (%) | 45 (24.1) | 5 (27.8) | 0.7749 |
| No, n (%) | 142 (75.9) | 13 (72.2) | |
| Nipple discharge | | | |
| Yes, n (%) | 11 (5.6%) | 3 (16%) | 0.1127 |
| No, n (%) | 186 (94%) | 16 (84%) | |
| *BRCA1/2* status | | | |
| Positive, n (%) | 4 (2) | 0 (0) | 1.0000 |
| Negative, n (%) | 192 (98) | 19 (100) | |
| Menopause | | | |
| Yes, n (%) | 105 (53.3%) | 13 (68.4%) | 1.0000 |
| No, n (%) | 92 (46.7%) | 6 (31.6%) | |
| Imaging modality | | | |
| Mammogram, n (%) | 72 (36.5) | 9 (47.4) | 0.7371 |
| Ultrasound, n (%) | 38 (19.3) | 3 (15.8) | |
| MRI, n (%) | 87 (44.2) | 7 (36.8) | |
| Radiologic-pathologic correlation | | | |
| Concordant, n (%) | 188 (96.4) | 18 (94.7) | 0.5309 |
| Discordant, n (%) | 7 (3.6) | 1 (5.3) | |
| Size of IDP (mm) | | | |
| Mean (range) | 2.97 (0.5−13.0) | 2.92 (1.0−7.8) | 0.9171 |
| Associated ADH | | | |
| Yes, n (%) | 28 (14.5) | 13 (68.4) | <0.0001 |
| No, n (%) | 167 (85.5) | 8 (31.6) | |
| Associated ALH/LCIS | | | |
| Yes, n (%) | 9 (4.7) | 1 (5.3) | 1.0000 |
| No, n (%) | 186 (95.3) | 20 (94.7) | |
| Concomitant ipsilateral breast carcinoma | | | |
| Yes, n (%) | 10 (5.1) | 1 (5.3) | 1.0000 |
| No, n (%) | 187 (94.9) | 18 (94.7) | |
| Concomitant contralateral breast carcinoma | | | |
| Yes, n (%) | 31 (15.7) | 4 (21.1) | 0.5204 |
| No, n (%) | 166 (84.3) | 15 (78.9) | |

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma in situ; IDP, intraductal papilloma; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging.

pathologic imaging upgraded to BC in the surgical excision, although this patient had ADH adjacent to IDP in the CNB.

When analyzing factors that might influence the upgrade rate of IDP on multivariate analysis, older age (>53 years) at the time of biopsy (odds ratio (OR) = 1.05, 95% confidence interval (CI) = 1.01−1.09, p = 0.027) and concomitant ADH (OR = 9.69, 95% CI = 3.37−27.81, $p < 0.0001$) were the only variables significantly associated with upgrade to BC in subsequent excision. The latter association remained significant even after adjusting for age. There was no association between upgrade to BC and having a concomitant ipsilateral or contralateral BC, concomitant lobular neoplasia, IDP microscopic size, imaging modality, and reason for biopsy. Although there was a higher proportion of upgrade among menopausal women (68.4%), the difference was not statistically significant (Table 1).

Review of the CNB slides of the 41 cases of IDP with associated ADH revealed three general patterns of ADH: ADH involving the IDP (atypical papilloma; 16 cases; Fig. 1A), ADH distant from the IDP (17 cases; Fig. 1B), and mixed (8 cases). The pattern of atypia did not correlate with upgrade rate on surgical excision (Table 2).

## 4. Discussion

The management of breast papillary lesions is controversial due to conflicting upgrade rates of IDP reported in

**Table 2** Clinicopathologic characteristics of 19 cases of intraductal papilloma that upgraded to breast carcinoma on surgical excision.

| Case number | Age (years) | Laterality | Reason for biopsy | Imaging modality | Biopsy needle size | Radiologic-pathologic correlation | IDP microscopic size (mm) | Associated high-risk lesion | Concomitant carcinoma | Final pathology on surgical excision (size) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 70 | Right | Calcification | MMG | 9-G | Concordant | 2.7 | None | Ipsilateral IDC | DCIS (6 mm) |
| 2 | 80 | Left | Mass | US | 14-G | Concordant | 2.2 | None | None | Invasive papillary carcinoma (5 mm) |
| 3 | 71 | Right | NME | MRI | 9-G | Concordant | 2 | None | Contralateral IDC | IDC (3 mm), DCIS (6 mm) |
| 4 | 31 | Right | Mass | MRI | 9-G | Concordant | 1 | None | None | DCIS-MI (2 mm and <1 mm respectively) |
| 5 | 72 | Right | Calcification | MMG | 9-G | Concordant | 3.5 | None | None | DCIS (50 mm) |
| 6 | 48 | Left | Mass | US | 9-G | Concordant | 1 | LCIS | None | ILC (multifocal, 3 mm), LCIS |
| 7 | 62 | Left | Mass | US | 14-G | Concordant | 3.6 | AIDP-ADH | None | DCIS (5 mm) |
| 8 | 71 | Left | NME | MRI | 9-G | Concordant | 5.8 | ADH | None | DCIS (2 mm) |
| 9 | 70 | Right | Mass | MMG | NA | Concordant | 2.8 | AIDP-ADH | None | DCIS (3 mm) |
| 10 | 54 | Left | Calcification | MMG | NA | Concordant | 7.8 | AIDP-ADH | Contralateral IDC | DCIS (3 mm) |
| 11 | 60 | Left | Calcification | MMG | 9-G | Concordant | 1 | ADH | None | DCIS (15 mm) |
| 12 | 29 | Right | Mass | US | 12-G | Concordant | 2 | ADH | None | DCIS (4 mm) |
| 13 | 61 | Left | Calcification | MMG | NA | Concordant | 2.7 | AIDP | None | DCIS (3 mm) |
| 14 | 67 | Left | NME | MRI | 9-G | Concordant | 2.1 | AIDP | None | DCIS-MI (40 mm and <1 mm respectively) |
| 15 | 49 | Right | Mass | MRI | NA | Concordant | 3.4 | AIDP-ADH | Contralateral IDC | DCIS (2 mm) |
| 16 | 54 | Left | Calcification | MMG | 9-G | Concordant | 3 | ADH | None | IDC (multifocal, 4 mm), DCIS (25 mm) |
| 17 | 48 | Left | Calcification | MMG | 9-G | Concordant | 1.8 | ADH | None | DCIS (5 mm) |
| 18 | 61 | Left | NME | MRI | 9-G | Discordant | 3 | ADH | Contralateral IDC | ILC (10 mm), DCIS (2 mm) |
| 19 | 64 | Left | Calcification | MMG | NA | Concordant | 3.3 | AIDP | None | DCIS (12 mm) |

AIDP, atypical intraductal papilloma (ADH involving IDP); ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; G, gauge; IDC, invasive ductal carcinoma; IDP, intraductal papilloma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; MI, microinvasion; MMG, mammography; MRI, magnetic resonance imaging; NA, not available; NME, nonmass enhancement; US, ultrasound.

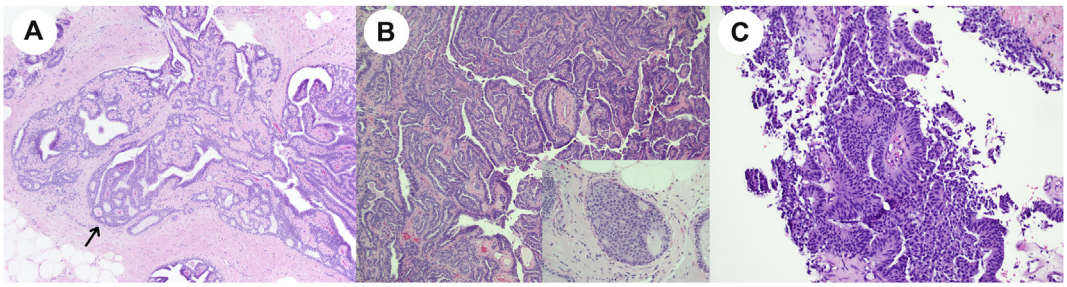


**Fig. 1** A), Case 15 showing an intraductal papilloma (IDP) involved by focal atypical ductal hyperplasia (ADH) (arrow) (hematoxylin & eosin, X200). (B), Case 8 showing an IDP (hematoxylin & eosin, X100). Inset shows a focus of ADH not associated with IDP (hematoxylin & eosin, X200). (C), Case 2 showing a papillary lesion with a monotonous population of ductal cells with low nuclear grade and nuclear stratification (hematoxylin & eosin, X200). This case was upgraded to invasive papillary carcinoma on surgical excision.

**Table 3** Literature review of pure intraductal papillomas and atypical papillomas with subsequent surgical excision from 2000 to 2019.

| Authors | Upgrade rate in pure IDP | Upgrade rate in atypical papillomas |
|---|---|---|
| Agoff and Lawton [36] | 0% (0/11) | 48% (12/25) |
| Masood et al. [37] | 16.7% (1/6) | 50% (2/4) |
| Ivan et al. [16] | 0% (0/6) | 75% (6/8) |
| Renshaw et al. [14] | 0% (0/45) | 28.6% (2/7) |
| Lewis et al. [38] | 10.7% (34/318) | 20.4% (11/54) |
| Arora et al. [28] | 0% (0/18) | 30.3% (20/66) |
| Ashkenazi et al. [39] | 20% (4/20) | 60% (9/15) |
| Eun et al. [40] | 2.3% (1/43) | 44.4% (8/18) |
| Valdes et al. [41] | 16.7% (6/36) | 25% (4/16) |
| Sydnor et al. [9] | 2.6 (1/38) | 66.7% (10/15) |
| Shin et al. [42] | 15.4% (12/73) | 6.7% (1/15) |
| Kil et al. [20] | 8.8% (6/68) | 37.5% (3/8) |
| Sakr et al. [43] | 14.6% (7/48) | 66.7% (2/3) |
| Ahmadiyeh et al. [10] | 3.5% (1/29) | 22.5% (9/40) |
| Bernik et al. [44] | 8.5% (4/47) | 53.8% (7/13) |
| Bode et al. [45] | 0% (0/11) | 57.9% (11/19) |
| Cheng et al. [18] | 3.9% (3/77) | 50% (4/8) |
| Tseng et al. [46] | 29.2% (7/24) | 71.4% (5/7) |
| Tse et al. [32] | 10.3% (7/68) | 54.5% (6/11) |
| Chang et al. [47] | 0% (0/49) | 18.2% (2/11) |
| Kim et al. [48] | 9.1% (12/131) | 33.4% (5/15) |
| Richter-Ehrenstein et al. [13] | 4.4% (2/45) | 9.1% (1/11) |
| Brennan et al. [49] | 4.5% (2/44) | 8.7% (2/23) |
| Fu et al. [19] | 5.9% (12/203) | 15.4% (10/65) |
| Rizzo et al. [2] | 2.6% (5/193) | 38.1% (16/42) |
| Weisman et al. [50] | 0% (0/37) | 28.6% (2/7) |
| Wiratkapun et al. [15] | 0% (0/91) | 30.1% (12/39) |
| Glenn et al. [34] | 4.8% (7/146) | 21.7% (5/23) |
| Nakhlis et al. [17] | 6.7% (3/45) | 21.1% (11/52) |
| Shiino et al. [4] | 33.3% (4/12) | 45.4% (10/22) |
| Hong et al. [51] | 5.9% (14/234) | 26.8% (11/41) |
| Seely et al. [52] | 4.7% (5/107) | 14.8% (4/27) |
| Han et al. [22] | 1.9% (3/154) | NA |
| Khan et al. [53] | 7.5% (8/107) | 18.6% (8/43) |
| Kiran et al. [54] | 2.9% (4/136) | 14.2% (2/14) |
| Chen et al. [55] | 2.3% (6/265) | 22.2% (2/9) |
| Park et al. [56] | 8.9% (14/158) | 33.3% (7/21) |
| Present study | 3.0% (5/165) | 27% (14/51) |
| Overall | 6.1% (200/3281) | 29.5% (256/868) |

NA, not available.

the literature, ranging from 0 to 33% in cases of pure IDP and 9−75% in cases of atypical papilloma [4,13−16] (Table 3). Owing to the risk of undersampling in a CNB and underestimation of papillary lesions, IDP has been traditionally treated with surgical excision [10,17].

In this study, the overall upgrade rate of IDP was 27% in atypical papillomas and 3% in pure IDPs. Patients with IDP and ADH had significantly higher likelihood of harboring BC in the surgical excision with an odds ratio of 9.69, in accordance with the current literature that suggests surgical excision for all cases with atypia [2,18−21]. These findings further support that ADH, and not IDP, drives the risk of upgrade to carcinoma.

In the compiled data of 38 published studies with similar design as the present study (Table 3), comprising more than 2000 IDPs, the overall upgrade rate was 6.1% in pure IDP and 29.5% in atypical papilloma, which included those with focal atypia, ADH, ALH, or LCIS. Comparative analysis of this body of literature is confounded by the lack of standardization in methodology (e.g. pure IDP versus atypical papilloma, biopsy slide review, radiologic-pathologic correlation, and so on). That said, the more recent and well-controlled studies of the topic indicate a low upgrade rate for pure papillomas. For instance, in a large study by Han et al. [22], the upgrade rate of pure papilloma to malignancy was reported as low as 0.8%.

Owing to the low risk of upgrade rate in some studies, expectant management with clinical and radiological follow-up has been proposed for patients with pure IDP [3]. Imaging methods traditionally do not seem to be able to accurately distinguish between benign papillary lesions and those with malignant potential [23], as we did not find an association between imaging findings and upgrade rate in this study. However, the vast majority of cases in the present study (97%) had imaging results concordant with pathologic findings, which is reassuring when it comes to patient follow-ups. Nakhlis et al. [17] reported that all cases of pure IDP that upgraded to BC in their study had discordant radiologic-pathologic findings. Some studies found an association between mass-forming lesions on imaging with subsequent histologic upgrade in excision specimen [24,25]. The presence of calcifications seems to be controversial when related to upgrade with some studies suggesting a positive association between the calcifications and the upgrade [26,27], while others show the reverse [24]. Of the 19 cases that upgraded to carcinoma on surgical excision in our study, only one case was deemed discordant on radiologic-pathologic correlation. This case (case 18) had a 2.6-cm nonmass enhancement on MRI with the subsequent CNB showing a 3-mm IDP in association with ADH. There was a 10-mm invasive lobular carcinoma and a 2.0-mm focus of DCIS on surgical excision specimen (Table 2). Overall, we did not find a significant association between the upgrade rate and radiologic-pathologic correlation or the reason for biopsy (i.e. mass or calcifications) possibly due to the overwhelmingly concordant cases (Table 1).

After review of the surgically excised specimen slides for the five pure IDP cases with upgrade, we categorized the discrepancy as possible incidental in four cases (cases 1, 3, 4, 5) and misinterpretation ("*undercalling*") of the CNB findings in one case (case 2). In all four cases with incidental upgrade, a 9-gauge needle was used, yielding *multiple* cores. All four cases showed radiologic-pathologic concordance. Therefore, we believe that undersampling did

not play a role in the upgrade. In the misinterpreted case (case 2), a monomorphic population of ductal cells with focal stratification in a papillary arrangement is noted (Fig. 1C). In retrospect, the case should have been called atypical papilloma (Table 2).

We found older age (>53 years) to be a risk factor for surgical upgrade. In the study by Ahmadiyeh et al. [10], patients with atypical papilloma were significantly older than those with no atypia. Several studies suggested that older age is a risk factor for pathological upgrade in papillary lesions [18,28,29]. Conversely, Leithner et al. [30] did not find a significant association between upgrade to carcinoma and age; however, their study is limited by a relatively small sample size. Our study supports this finding and underlines the significance of age as a talking point during breast management consultation.

Surprisingly, risk factors that had been classically associated with upgrade to BC, such as concomitant diagnosis of BC and the microscopic size measured on the slide, did not reach statistical significance in this study. Several authors have reported that larger IDP lesions are associated with higher upgrade rate [20,29,31,32]. The study by Jaffer et al. [33] found no risk of upgrading in 46 patients with IDP smaller than 2 mm. In contrast, Glenn et al. [34] reported an upgrade rate of 7% in IDP smaller than 5 mm, showing that there is no threshold in which IDP can be ignored. In the present study, we decided to use the microscopic size of IDP measured on the slide for our analysis. The decision was based on the lack of consistency in the imaging modalities, abnormal findings, and measurement reporting. For example, more than half of our patients were biopsied because of calcifications and non-mass enhancements. Interestingly, in the study by Li et al. [35], only the size measured on the slide, not the radiologic size, was predictive of upgrade.

In summary, our results support surgical excision of IDP on CNB when associated with ADH or diagnosed in women aged older than 53 years. The low surgical upgrade rate of 3% for pure IDP on CNB in younger women should be part of the management discussion.

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