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# Rates of upgrade to malignancy in surgical excision of intraductal papillomas of the breast: A retrospective cohort study

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**Ethics Committee Approval**
Ethical approval was obtained from the Haydarpaşa Numune Training and Research Hospital Education Planning Board (Approval number: August 25, 2023-223051729). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Intraductal papillomas (IDP) of the breast, though benign, share an association with the duct epithelium, similar to some breast malignancies. Percutaneous biopsies often fail to fully characterize these lesions. The decision to perform surgical excision for IDP of the breast is frequently based on the presence of atypia observed during percutaneous biopsy. However, consensus remains lacking regarding the management of IDP of the breast without atypia. This study was undertaken to share findings on IDP, contributing to a better understanding of their nature and guiding treatment approaches.

**Methods:** We conducted a retrospective evaluation of data from 42 female patients diagnosed with intraductal papilloma through percutaneous biopsy, who subsequently underwent surgical excision between January 1, 2015, and August 25, 2023. Patients not diagnosed with intraductal papilloma, those with prior breast malignancy diagnoses, and those identified incidentally during other surgical procedures were excluded from the study. Data recorded included patient ages, the largest lesion diameters measured by ultrasonography, the percutaneous biopsy method (Fine needle aspiration biopsy [FNAB] or Core needle biopsy [CNB]), atypia status observed during percutaneous biopsy, histopathological features observed during surgical excision, and lesion diameter in cases where malignancy was upgraded. If ductal carcinoma in situ (DCIS) or invasive cancer was identified in the surgical excision specimen, it was classified as an upgrade.

**Results:** The median age of the patients was 48.5 years (range: 12.9 years). FNAB was performed in ten cases (23.8%), while CNB was used in 32 cases (76.2%). There was no significant difference in the detection of atypia when comparing FNAB and CNB ($P$=0.57). Eight patients (19%) were diagnosed with atypical intraductal papilloma. Among them, three patients with atypia and two patients without atypia exhibited an upgrade to malignancy. The study revealed a malignancy upgrade rate of 37.5% for IDP with atypia and 5.9% for those without atypia. Furthermore, the average age of patients with malignancy upgrades was higher than that of patients with benign lesions ($P$=0.02).

**Conclusion:** In light of the malignancies detected in cases of breast IDP, even in the absence of atypia, opting for surgical excision, particularly in older patients, can help prevent the oversight of these cancers.

**Keywords:** breast cancer, intraductal papilloma, upgrade, excision, atypia

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## Introduction

Breast cancer stands as the most frequently diagnosed cancer among women worldwide [1,2]. Within the realm of breast pathology, papillary lesions can manifest as either benign, atypical, or malignant. Intraductal papillomas (IDP), specifically, represent benign lesions characterized by finger-like fibrovascular cores enveloped by layers of epithelial and myoepithelial cells [3]. Discrepancies between the findings from needle biopsies and surgical excisions for papillary breast lesions have led to diverse treatment strategies for intraductal papillomas (IDP). The consensus in the management of IDP, diagnosed through needle biopsy, revolves around surgical excision when atypia is present [4,5]. For those IDP lacking atypia, close monitoring is typically recommended, although surgical removal may also be considered due to the observed rates of upgrades detected in surgical excision specimens [6]. The literature reports upgrade rates to malignancy ranging from 0% to 33% for IDP cases without atypia in needle biopsy results [7,8]. Some experts contend that the limited tissue fragments obtained in imaging-guided needle biopsies may not always provide a comprehensive sampling of the entire lesion, potentially leading to missed cancer diagnoses [9].

No established parameters exist for predicting the progression to malignancy. Consequently, the significance of data derived from lesions diagnosed as intraductal papilloma in contributing to the literature cannot be overstated.

This study presents the rates of upgrades to malignancy detected through surgical excision in 42 patients diagnosed with IDP via percutaneous needle biopsy. Additionally, a retrospective analysis of data believed to be associated with these upgrades is provided.

## Materials and methods

The retrospective study protocol received approval from the Haydarpaşa Numune Training and Research Hospital Education Planning Board (EPB) on August 25, 2023, with reference number 223051729. This study retrospectively assessed the data of 42 patients who were diagnosed with intraductal papilloma through percutaneous biopsy between January 1, 2015, and August 25, 2023, and whose surgical procedures were conducted by a single surgeon. Data for this analysis were sourced from the hospital database and physician records. Inclusion criteria encompassed patients diagnosed with intraductal papilloma through percutaneous needle biopsy guided by ultrasonography, who subsequently underwent surgical excision. The surgical excisions for all patients were performed by the same surgeon following ultrasound-guided wire marking.

Exclusion criteria for this study were defined as individuals with a prior malignancy diagnosis and incidental IDP discovered during procedures unrelated to percutaneous biopsy. Parameters examined in the study included patient ages, ultrasonographically measured maximum lesion diameters, the central or peripheral location of lesions relative to the nipple areola in ultrasonographic imaging, Breast Imaging Reporting and Data Systems (BIRADS) categories as indicated in radiological reports, the percutaneous biopsy method (Fine needle aspiration biopsy [FNAB] or Core needle biopsy [CNB]), atypia status in percutaneous biopsies, surgical excision pathology results, histopathological features, and the diameter of the detected lesion if an upgrade was identified.

In ultrasonographic imaging, IDPs were categorized as central or peripheral based on their location. Lesions described as retroareolar, periareolar, and situated less than 2 cm from the nipple were classified as centrally located, while lesions positioned 2 cm or more distant from the nipple were categorized as peripherally located. Additional pathological findings, such as microcalcifications, radial scars, and complex sclerosing lesions, were also recorded in the surgical excision specimen. Notably, instances of detecting ductal carcinoma in situ (DCIS) or invasive cancer in the surgical excision specimen were documented as upgrades.

**Statistical analysis**

Statistical analysis for the cases included in the study was conducted using IBM SPSS (version 22.0; IBM, Armonk, NY, USA). Categorical data were assessed using Chi-square and Fischer's exact test. In cases where numerical data adhered to a normal distribution, the student t-test was applied. Conversely, when numerical data did not follow a normal distribution, the Mann-Whitney U test was employed. A significance level of *P*-value <0.05 was deemed statistically significant.

## Results

The median age of the 42 female patients included in the study was 48.5 (12.9) years, with an age range of 18-81 years. All patients underwent diagnosis through percutaneous needle biopsy guided by ultrasonography. It was determined that ten (23.8%) of the biopsies were performed using FNAB, while 32 (76.2%) were conducted using CNB. Eight (19%) of the patients were found to have atypical intraductal papilloma. Among these eight patients, three were subsequently upgraded to malignancy. Specifically, one patient was detected with FNAB, and the other two were identified through CNB.

Interestingly, the two cases that were upgraded to malignancy through surgical excision did not exhibit any atypia in their initial biopsies, both of which were performed using CNB. Notably, there was no statistically significant difference found when comparing the ability of FNAB and CNB to detect atypia ($P$=0.57).

The average lesion size determined through ultrasonography was 10.6 (5.1) mm, with a range of 6-22 mm. Specifically, the ultrasonographic diameter measured 9.9 (4.3) mm for benign lesions and 14.8 (6.9) mm for malignant lesions. Notably, the ultrasonographic diameter was found to be larger in patients whose lesions were upgraded to malignancy when compared to those with benign lesions, although this difference did not reach statistical significance ($P$=0.155).

Following surgical excision, malignancy was identified in five out of 42 patients diagnosed with IDP, representing an incidence of 11.9%. Among these five patients with malignancy, three presented with IDP accompanied by atypia, while two had IDP without atypia. The specific malignancy types observed in these cases included three with DCIS, one with tubular carcinoma, and one with encapsulated papillary carcinoma in conjunction with DCIS.

Interestingly, it was determined that IDP were most frequently upgraded to DCIS, accounting for 9.52% of cases. The

average tumor diameter among those with malignancy upon surgical excision measured 13 mm, with a range spanning from 5 to 25 mm. Moreover, the mean age of the five patients who experienced an upgrade to malignancy was 64.6 (9.5) years, whereas the mean age of the 37 benign patients without malignancy was 46.3 (11.9) years. This difference in mean ages between the two groups was statistically significant ($P$=0.02).

Out of the IDPs, 22 (52.4%) were identified as centrally located, while the remaining 20 (47.6%) were situated peripherally. Among the cases that upgraded to malignancy, two (9.1%) were centrally located, and three (15.0%) were found in peripheral locations. It is worth noting that there was no statistically significant difference observed between central and peripheral locations in terms of cases upgrading to malignancy ($P$=0.65).

Of the two IDPs without atypia that progressed to malignancy, one was centrally located, while the other was peripherally situated.

All patients in the study were classified as BIRADS 4. When examining the subgroup distribution within this category, it was found that 25 patients were classified as BIRADS-4a (59.5%), three as BIRADS-4b (7.1%), and four as BIRADS-4c (9.5%). Notably, ten patients (23.8%) did not fall into any specific subgroup within BIRADS-4.

Among the patients diagnosed with malignancy, three were categorized as BIRADS-4 with no specified subgroup, one was classified as BIRADS-4a, and one was designated as BIRADS-4c.

During surgical excision, the diagnoses of 20 out of the 37 patients with IDP remained unchanged, whereas 17 patients were found to have additional pathologies that were not initially detected. Importantly, all five patients who underwent an upgrade to malignancy also had additional pathologies identified during surgical excision. This observation yielded a statistically significant result ($P$=0.041). The additional pathological findings are detailed in Table 1.

Table 1: Distribution of additional pathologies in benign and malignant cases.

| Additional pathology | Benign (n/%) | Malignant (n/%) | Total (n/%) |
|---|---|---|---|
| **None** | 20 / 54.1 | 0 / 0.0 | 20 / 47.6 |
| **Microcalcification** | 11 / 29.7 | 2 / 40.0 | 13 / 31.0 |
| **Radial scar** | 1 / 2.7 | 2 / 40.0 | 3 / 7.1 |
| **Complex sclerosing lesion** | 1 / 2.7 | 0 / 0.0 | 1 / 2.4 |
| **Fibroadenoma** | 2 / 5.4 | 1 / 20.0 | 3 / 7.1 |
| **Microcalcification + Complex sclerosing lesion** | 1 / 2.7 | 0 / 0.0 | 1 / 2.4 |
| **Microcalcification + Fibroadenoma** | 1 / 2.7 | 0 / 0.0 | 1 / 2.4 |
| **Total** | 37 / 100.0 | 5 / 100.0 | 42 / 100.0 |

$P$=0.041

The upgrade to malignancy was observed in three (37.5%) out of eight patients diagnosed with IDP that included atypia. In contrast, among the 34 patients diagnosed with IDP without atypia, 2 (5.9%) experienced an upgrade to malignancy. When considering the entire cohort of 42 patients diagnosed with IDP, whether with or without atypia, a total of five cases (11.9%) were upgraded to malignancy, as summarized in Table 2.

Table 2: Atypia conditions and upgrade rates of cases.

| Atypia | No upgrade (n/%) | Upgrade to malignancy (n/%) | Total (n/%) |
|---|---|---|---|
| **No** | 32 / 94.1 | 2 / 5.9 | 34 / 100 |
| **Yes** | 5 / 62.5 | 3 / 37.5 | 8 / 100 |
| **Total** | 37 / 88.1 | 5 / 11.9 | 42 / 100 |

$P$=0.040

## Discussion

In this study, we assessed the rates of malignancy progression during surgical resection in patients diagnosed with IDP through imaging-guided needle biopsy. Our findings revealed that patients who underwent an upgrade to malignancy were generally older. This observation aligns with previous research suggesting a correlation between advanced age and progression. For instance, Ahmadiyeh et al. [10] noted a significantly higher average age among individuals with atypical papillomas compared to those without atypia. Multiple studies have also reported advanced age as a risk factor for pathological advancement in papillary lesions [7,11,12]. Our study supports the existing literature by confirming a significant association between advanced age and the likelihood of an upgrade.

This study concluded that there was no significant difference in the diagnostic accuracy between FNAB and CNB when used for percutaneous biopsy in diagnosing IDP, as compared to the histopathological examination results of surgical excision material. In a related study, Şimşir et al. [13] asserted that breast papillary lesions could be effectively classified as either benign or atypical through the use of FNAB.

In another study assessing biopsies of papillary breast lesions, it was reported that both FNAB and CNB yielded comparable outcomes [14]. This study observed no significant difference between the performance of FNAB and CNB in distinguishing between the benign and atypical characteristics of breast papillary lesions.

The ultrasonographic diameter was measured at 9.9 (4) mm for benign papillomas and 14.8 (6.9) mm for lesions that progressed to malignancy. This study revealed a trend where the diameters of IDPs that advanced to malignancy tended to be larger than those that did not progress to malignancy. In a separate investigation involving 520 cases, a lesion size of 1.5 cm on imaging was identified as an independent predictor of malignancy [15]. Another study indicated an increased likelihood of atypia when the lesion size exceeded 1.2 cm [16]. Jaffer et al. [17] reported no instances of upgrade in 46 patients diagnosed with IDP lesions smaller than 2 mm. In a study involving 102 cases, lesions that eventually progressed to malignancy were typically 1.7 cm in size [9].

Chen et al. [18] discovered that peripheral localization of IDPs in lesions without atypia was linked to higher upgrade rates in postmenopausal women. However, in our study, no significant relationship was identified between central and peripheral localization and the progression to malignancy.

Moseley et al. [9] reported that DCIS accounted for 69% of intraductal papilloma upgrades. In our study, among the malignancies identified, DCIS was the most prevalent upgrade, accounting for 80% of cases.

Surgical excision specimens of breast IDPs often reveal the presence of other accompanying lesions. Microcalcifications are commonly associated with IDPs and were found to be the most frequently occurring accompaniment in this study. Additional accompanying lesions included radial scar, complex sclerosing lesion, and fibroadenomas. Notably, microcalcifications and radial scar were more frequently observed in cases where IDPs progressed to malignancy. The literature supports the notion that

microcalcification is the most common accompanying lesion in the progression of IDPs to malignancy [19].

A meta-analysis has indicated that the risk of malignancy in IDPs escalates in BIRADS-4b and BIRADS-4c cases [20]. However, it is important to note that this study did not conduct a BIRADS subgroup analysis for all patients, preventing a comprehensive evaluation in this regard.

There is a consensus regarding surgical excision when atypia is identified through percutaneous biopsy in cases of IDP [4,5]. However, differing opinions emerge when atypia is not detected in percutaneous biopsy results.

In cases of atypical IDP, the literature reports upgrade rates to malignancy ranging from 45.4% to 22.5% [7,10]. Conversely, for IDP without atypia, a series of 407 cases in the literature suggests a relatively lower upgrade rate of 5.8% following surgical excision of benign papillary breast lesions [21]. In their study involving 102 cases, Moseley et al. [9] reported a malignancy upgrade rate of 2.9% and a high-risk benign lesion upgrade rate of 7.8% after surgical excision in cases without atypia on biopsy. Our study's upgrade findings align with the current literature [6,9,10,21]. It is also imperative to emphasize the importance of close monitoring and informed communication with patients in cases where atypia is not detected in percutaneous biopsy and surgical intervention is not pursued.

**Limitations**

Our study has a limitation in that it is retrospective. Furthermore, due to the lack of specified BIRADS subgroups in all cases, an assessment pertaining to the subgroups was not feasible. To gain a more comprehensive understanding of the clinical progression of the disease, there is a need for randomized prospective studies on this subject. Another limitation of our study is its relatively small sample size in terms of the number of cases.

**Conclusion**

IDP cases represent benign lesions identified through radiological or pathological examinations. While surgical excision is a well-established treatment option for cases containing atypia, a clear treatment approach is not evident for cases lacking atypia. This study revealed that surgical excision, particularly in older age groups, promptly aided in diagnosing malignancy in cases of IDP without atypia.

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