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Breast papillary lesions: comparative analysis of core needle biopsy and surgical excision findings in a single-center retrospective cohort with literature review.

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Keywords: Papillary breast lesion; Core needle biopsy; Myoepithelial cell; Estrogen receptor; Excision.

Abstract. This retrospective study aimed to identify histopathological and immunohistochemical predictors of malignancy requiring surgical excision among papillary breast lesions diagnosed by core-needle biopsy (CNB). Fifty-three women with CNB-diagnosed papillary breast lesions who subsequently underwent surgical excision at the İzmir Bakırçay University Çiğli Hospital between January 2015 and January 2025 were included. Clinical, radiological, and pathological data were analyzed. Twenty-eight patients (52.8%) were ≤50 years of age, and 21 lesions (39.6%) were larger than 3 cm. Surgical excision revealed benign lesions in 24 cases, malignant lesions in 16 cases, and intracystic solid carcinoma or atypical ductal hyperplasia in 13 cases. The malignancy/atypia group (45.2%) showed a significantly higher frequency of myoepithelial cell loss ($p<0.001$) and microcalcifications ($p=0.028$), and uniform, strong estrogen receptor positivity (100%) on CNB. Benign lesions were more commonly peripherally located ($p=0.049$). No significant associations were observed with age, Breast Imaging Reporting and Data System (BI-RADS) category, or lesion size. These findings indicate that loss of myoepithelial cells and estrogen receptor positivity are strong predictors of malignancy and support the routine incorporation of immunohistochemical evaluation into CNB-based risk stratification.

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Lesiones papilares mamarias: análisis comparativo de los hallazgos de la biopsia con aguja gruesa y de la escisión quirúrgica en una cohorte retrospectiva de un solo centro, con revisión de la literatura.

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Palabras clave: Lesión papilar mamaria; Biopsia con aguja gruesa; Célula mioepitelial; Receptor de estrógeno; Escisión.

Resumen. Este estudio retrospectivo tuvo como objetivo identificar predictores histopatológicos e inmunohistoquímicos de malignidad que requieren escisión quirúrgica en lesiones papilares mamarias diagnosticadas mediante biopsia con aguja gruesa (BAG). Se incluyó a un total de 53 mujeres diagnosticadas con lesiones papilares mamarias por BAG que posteriormente fueron sometidas a escisión quirúrgica en el Hospital Çiğli de la Universidad de İzmir Bakırçay entre enero de 2015 y enero de 2025. Se analizaron datos clínicos, radiológicos y patológicos. Veintiocho pacientes (52,8%) tenían ≤50 años y 21 lesiones (39,6%) tenían un tamaño mayor a 3 cm. La escisión quirúrgica reveló lesiones benignas en 24 casos, lesiones malignas en 16 y carcinoma sólido intraquístico/hiperplasia ductal atípica en 13 casos. El grupo con malignidad/atipia (45,2%) presentó una frecuencia significativamente mayor de pérdida de células mioepiteliales ($p<0,001$) y de microcalcificaciones ($p = 0,028$), así como una positividad uniforme y fuerte para el receptor de estrógeno (100%) en la BAG. Las lesiones benignas se localizaron con mayor frecuencia en la periferia ($p = 0,049$). No se observaron asociaciones significativas con la edad, la categoría Sistema de Informes y Registro de Datos de Imagen de la Mama (BI-RADS) ni el tamaño de la lesión. Estos hallazgos indican que la pérdida de células mioepiteliales y la positividad para el receptor de estrógeno son predictores sólidos de malignidad y respaldan la incorporación sistemática de la evaluación inmunohistoquímica en la estratificación del riesgo basada en la BAG.

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INTRODUCTION

Breast papillary lesions encompass a broad spectrum of entities characterized by a papillary architecture with arborizing fibrovascular cores. These lesions range from benign intraductal papillomas to atypical papillary proliferations and overt papillary carcinomas. Clinical examination and imaging modalities lack sufficient specificity to reliably distinguish among these entities, making histopathologic evaluation essential for accurate diagnosis. Classification is primarily based on the nature of the proliferating epithelial component and the presence or absence of a basal myoepithelial cell layer, which is a critical discriminator among benign, *in situ*, and invasive lesions.

Benign papillary lesions include intraductal papillomas, which may be associated with epithelial hyperplasia, metaplasia, atypical ductal hyperplasia, or ductal carcinoma in situ (DCIS). Malignant papillary neoplasms include papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma (*in situ* and invasive), and invasive

papillary carcinoma. Despite this structured categorization, these lesions often show overlapping morphological and immunohistochemical features, posing substantial diagnostic challenges, particularly with limited tissue samples obtained by core-needle biopsy (CNB). In this setting, underdiagnosis is more common than overdiagnosis, especially when invasive components are focal or discontinuous [1].

Papillary neoplasms account for approximately 5% of all breast biopsies. However, their detection rate has risen in recent years, largely due to advances in image-guided percutaneous biopsy techniques and the widespread use of high-resolution breast ultrasonography [2]. According to the 5th edition of the WHO Classification of Breast Tumors, papillary neoplasms are classified into five major groups: intraductal papilloma, papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma, and invasive papillary carcinoma. Although unified by their characteristic papillary architecture, these lesions exhibit considerable morphological, immunohistochemical, and biological heterogeneity, reflecting a continuum from benign to malignant disease [2-4].

Accurate distinction between noninvasive and invasive papillary carcinomas is critical for prognostic assessment and therapeutic planning. Histologic features supporting invasion include irregular clusters, tongues, and nests of tumor cells that extend into the surrounding stroma beyond a well-defined boundary. Nevertheless, limited sampling, tissue fragmentation, and artifactual distortion in CNB specimens often complicate this distinction, even when myoepithelial immunohistochemical markers [5, 6] are used.

At the molecular level, papillary carcinomas predominantly align with luminal breast cancer subtypes, consistent with their generally low-grade biology and favorable clinical behavior [1]. Papillary carcinoma of the breast is a distinct, relatively uncommon subtype that occurs predominantly in postmenopausal women and accounts for a small proportion of all breast malignancies. Histologically, it is characterized by well-formed papillary structures lined by multilayered or pseudostratified neoplastic epithelial cells, supported by delicate fibrovascular cores [7]. Importantly, neither encapsulated papillary carcinoma nor solid papillary carcinoma with associated invasive foci should be classified as invasive papillary carcinoma, as true invasive papillary carcinoma is a separate, rare entity with an excellent prognosis, low recurrence rates, and prolonged disease-free survival [8].

Preoperative CNB is widely regarded as the standard diagnostic modality for evaluating breast lesions. However, discrepancies between CNB diagnoses and subsequent surgical excision specimens remain incompletely characterized, and the overall degree of diagnostic concordance between these modalities has not been fully elucidated [9]. As reliance on CNB has increased, management strategies for benign intraductal papillomas without atypia have shifted toward more conservative, surveillance-based approaches rather than routine surgical excision [10]. Nevertheless, papillary lesions remain among the most diagnostically challenging entities in breast pathology.

Given these challenges, identifying reliable histopathological and immunohistochemical predictors of malignancy risk in papillary lesions diagnosed by CNB is of substantial clinical importance. The present study aims to contribute to this ongoing effort by evaluating key diagnostic parameters that may help stratify malignancy risk and guide decisions regarding the necessity of surgical excision.

PATIENTS AND METHODS

Study design

Between January 2015 and January 2025, 53 female patients who received a histopathological diagnosis of papillary breast lesions on CNB in the Department of Medical Pathology at İzmir Bakırçay University

Çiğli Training and Research Hospital and subsequently underwent surgical excision at the same institution were enrolled in this retrospective study. Cases were identified through a systematic search of the institutional pathology database. Ethics committee approval for this study was obtained from the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee on 03 July 2024 (decision no. 1657).

Clinical, radiological, and pathological data were extracted from the electronic hospital information system. Collected variables included patient age at diagnosis, radiologically measured lesion size, anatomical localization within the breast parenchyma, and the Breast Imaging Reporting and Data System (BI-RADS) score assigned at the time of diagnostic imaging.

Histopathological evaluation of excision and CNB specimens included assessment of papillary architecture, the presence or absence of an intact myoepithelial cell layer, and any associated atypical or malignant epithelial proliferations. Myoepithelial cell status was determined by routine hematoxylin–eosin (H&E) staining, supplemented, when necessary, with immunohistochemical markers such as p63, CK5/6, or smooth muscle myosin heavy chain. Estrogen receptor (ER) expression was evaluated immunohistochemically in accordance with current ASCO/CAP guidelines and recorded semiquantitatively. All microscopic assessments were performed by at least two experienced breast pathologists.

Histopathologic evaluation was performed on tissue obtained via CNB. Tumors were classified by neoplastic nature, architectural features, and cytomorphologic characteristics. Biopsy sites were selected based on radiologic assessment, targeting lesions with high BI-RADS categories or clinically palpable abnormalities. CNB was the primary diagnostic procedure, with sampling directed toward the most suspicious radiologic or clinical regions.

Immunohistochemical (IHC) analysis was performed to assess estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. ER and PR positivity was defined as nuclear staining in ≥1% of tumor cells. HER2 status was interpreted using standard scoring criteria (0 to 3+), with equivocal (2+) cases further evaluated by fluorescence *in situ* hybridization (FISH).

Statistical analysis

Statistical analyses were conducted using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Descriptive statistics were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and as frequencies and percentages for categorical variables.

Comparisons among diagnostic groups (benign, *in situ*/atypical, and malignant) were conducted using the Chi-square test or Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U test for continuous variables, based on distributional characteristics. For multigroup comparisons, one-way ANOVA or the Kruskal–Wallis test was applied as appropriate.

The association between histopathological parameters (e.g., myoepithelial cell loss, ER expression), radiologic features, and final excision outcomes was examined using binary logistic regression to identify independent predictors of atypia or malignancy. A p-value <0.05 was considered statistically significant.

RESULTS

Among the 53 patients analyzed, 28 (52.8%) were ≤50 years of age, and lesions >3 cm were identified in 21 cases (39.6%). Based on excision pathology, patients were classified into benign (n = 24), malignant (n = 16), and in situ carcinoma (ISC)/

atypical ductal hyperplasia (ADH) (n = 13) groups. CNB results were classified into benign, borderline/atypical, and malignant categories, and then compared with the final excision diagnoses. This comparison allowed evaluation of diagnostic concordance and identification of underestimation or upgrade rates between biopsy and excision specimens. The grouped distribution of CNB diagnoses and their corresponding excision pathology outcomes is summarized in Table 1. A total of 53 cases were evaluated, and excision outcomes were analyzed in relation to their corresponding BI-RADS assessments to determine the association between radiological classification and final pathological diagnosis. The distribution of excision pathology results according to BI-RADS categories is presented in Table 2. Representative histopathological an d immunohistochemical features of DCIS with papillary features (Fig. 1), encapsulated papillary carcinoma (Fig. 2), and invasive encapsulated papillary carcinoma (Fig. 3) are shown.

Lesions with atypia or malignancy (combined ISC/ADH and malignant cohort; 45.2%) had a markedly higher rate of myoepithelial cell loss than benign lesions ($p<0.001$). Within this cohort, 20.7% of lesions exceeded 3 cm. The atypical group had a significantly higher frequency of microcalcifications ($p = 0.028$), and all cases (100%) showed strong ER immunoreactivity on CNB specimens, indicating uniform hormone receptor positivity.

Table 1. Distribution of core needle biopsy diagnoses and corresponding excision outcomes.

Tru-Cut Biopsi Diagnostic Group	Tru-Cut Biopsi Specific BX Diagnosis	Corresponding Excision Outcome(s)	n
Benign Papillary Lesions	IDP	IDP, ADH+IDP, FCD, Fibroadenoma, DCIS, Invasive EPC, NSTIC (rare upgrades)	23
	USD–associated papilloma	IDP	1
	Micropapilloma	FCD, FCD+fibroadenoma	2
Atypical Papillary Lesions	ADH	UDH/FCD, IDP	4
	Papillary neoplasia (atypia not excluded)	DCIS, DCIS+IDP, Sclerosing papilloma, NSTIC, EPC	8
In situ Malignant Lesions	DCIS	DCIS, DCIS+IDP, SPC, NSTIC	5
	DCIS + EPC	EPC	1
	DCIS + IDP	DCIS+IDP	1
Encapsulated / Papillary Carcinoma Spectrum	EPC ± invasive component	EPC, invasive EPC, invasive papillary carcinoma	5
	SPC	SPC	1
Invasive Carcinomas	NSTIC with EPC	Invasive EPC	1
	Invasive mucinous carcinoma with papillary component	Mucinous carcinoma	1
	Invasive papillary carcinoma	Invasive papillary carcinoma	1
Other Papillary/ Proliferative Lesions	Ductal hyperplasia with papillary structures	DCIS	1

IDP: Intraductal papilloma; ADH: Atypical ductal hyperplasia; FCD: Fibrocystic disease; NSTIC: Invasive carcinoma, no special type; EPC: Encapsulated papillary carcinoma; DCIS: Ductal carcinoma *in situ*; UDH: Usual ductal hyperplasia; SPC: Solid papillary carcinoma.

Table 2. BI-RADS-based distribution of excision results (n = 53).

BI-RADS	Benign	Malign	Total
2	5	1	6
3	6	8	14
4	14	16	30
5	2	1	3

Breast Imaging Reporting and Data System (BI-RADS).

Benign lesions were significantly more likely to be peripherally localized than atypical lesions (p = 0.049). No statistically significant intergroup differences were observed in age distribution, BI-RADS category, lesion size, or other parameters (all p>0.05).

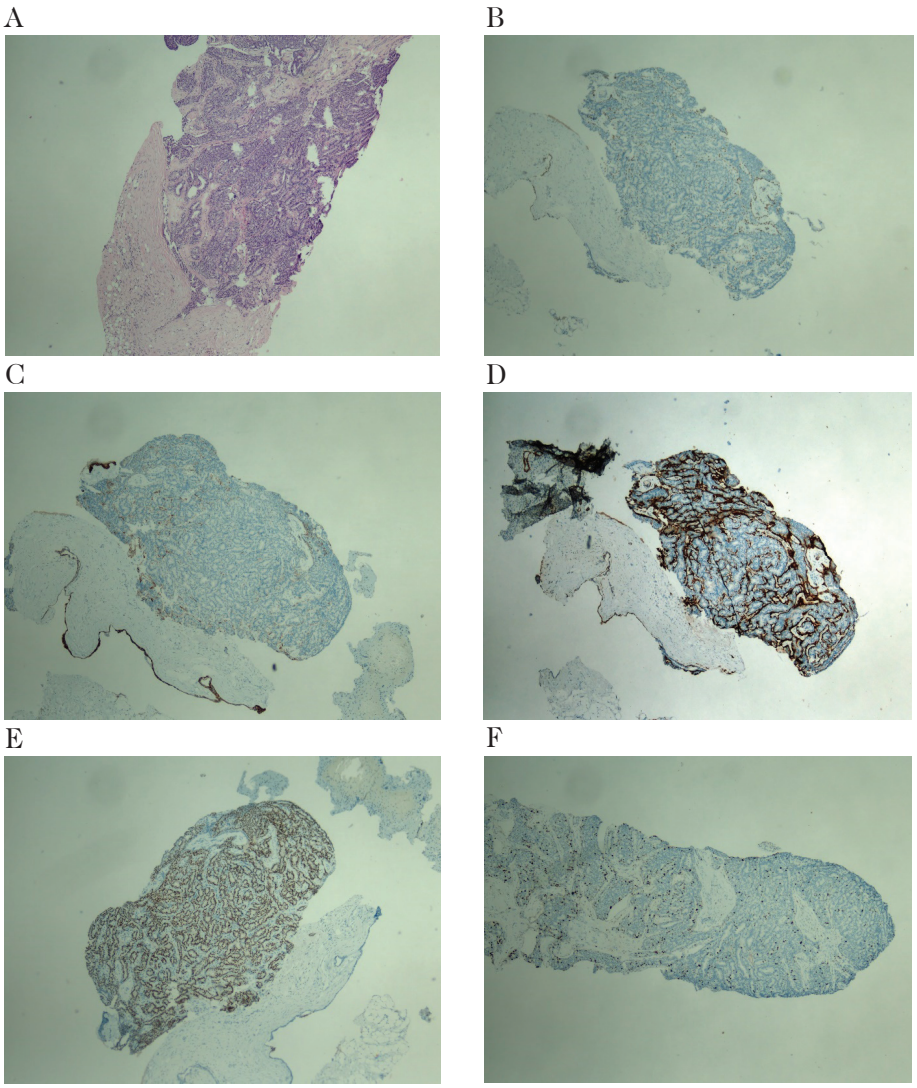

Fig. 1. Histopathological and immunohistochemical findings in a case of ductal carcinoma *in situ* with papillary features. **A:** A case diagnosed as grade 2 ductal carcinoma *in situ* on excisional biopsy; the Tru-Cut biopsy section primarily demonstrates papillary neoplasia *in situ*, stained with hematoxylin and eosin (×40); **B, C, D:** Immunohistochemical staining with p63 (B), CK5/6 (C), and smooth muscle myosin (D) demonstrating the presence of the myoepithelial layer (×40); **E:** Immunohistochemical staining for estrogen receptor (ER) showing 30% nuclear positivity (×40); **F:** Ki-67 immunohistochemical staining demonstrating a proliferative index of 10% (×40).

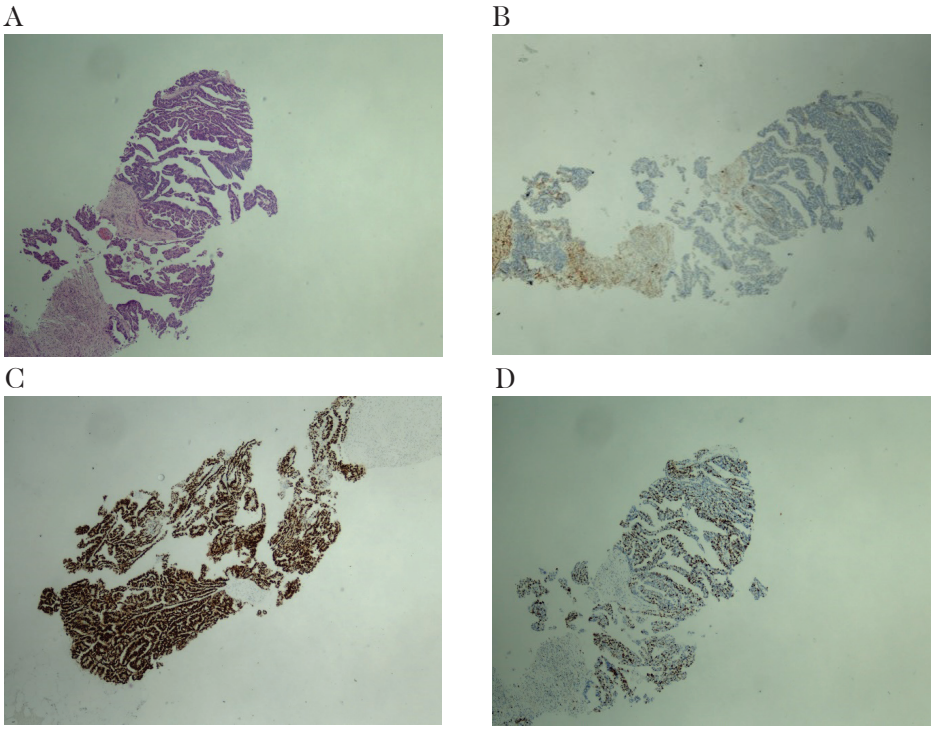

Fig. 2. Histopathological and immunohistochemical features of a case of encapsulated papillary carcinoma. **A:** Hematoxylin and eosin–stained section of a case in which encapsulated papillary carcinoma was initially suspected on Tru-Cut biopsy and subsequently confirmed on excisional material (×40); **B:** Immunohistochemical staining with p63 demonstrating absence of the myoepithelial layer (×40); **C:** Immunohistochemical staining for estrogen receptor (ER) showing diffuse, strong nuclear positivity (100%) (×40); **D:** Immunohistochemical staining for Ki-67 demonstrating a proliferative index of 30% (×40).

DISCUSSION

Papillary breast lesions constitute a diagnostically heterogeneous group, ranging from benign intraductal papillomas to atypical papillary proliferations and papillary carcinomas. Because of their complex architectural patterns and frequent histologic overlap, accurate classification based solely on CNB specimens remains challenging. Although CNB is widely accepted as a minimally invasive and effective initial diagnostic tool, its inherent sampling limitations may lead to underestimating atypia or malignancy in papillary lesions, particularly in those with focal or heterogeneous atypical components [11].

Although papillary breast lesions share a characteristic papillary architecture, they display a broad spectrum of morphological, immunohistochemical, and biological features [3,12]. Ongoing advances in diagnostic pathology, immunohistochemistry, and molecular techniques have substantially improved our understanding of these lesions; however, significant diagnostic and prognostic challenges remain. Over the past decades, numerous aspects of papillary tumor classification, biological behavior, and clinical management have been extensively investigated and, in some cases, remain controversial, with each new contribution offering incremental clarification [4,13].

More recently, molecular approaches have enabled genomic and transcriptomic characterization of papillary breast tumors, providing additional insights into their pathogenesis and potential clinical

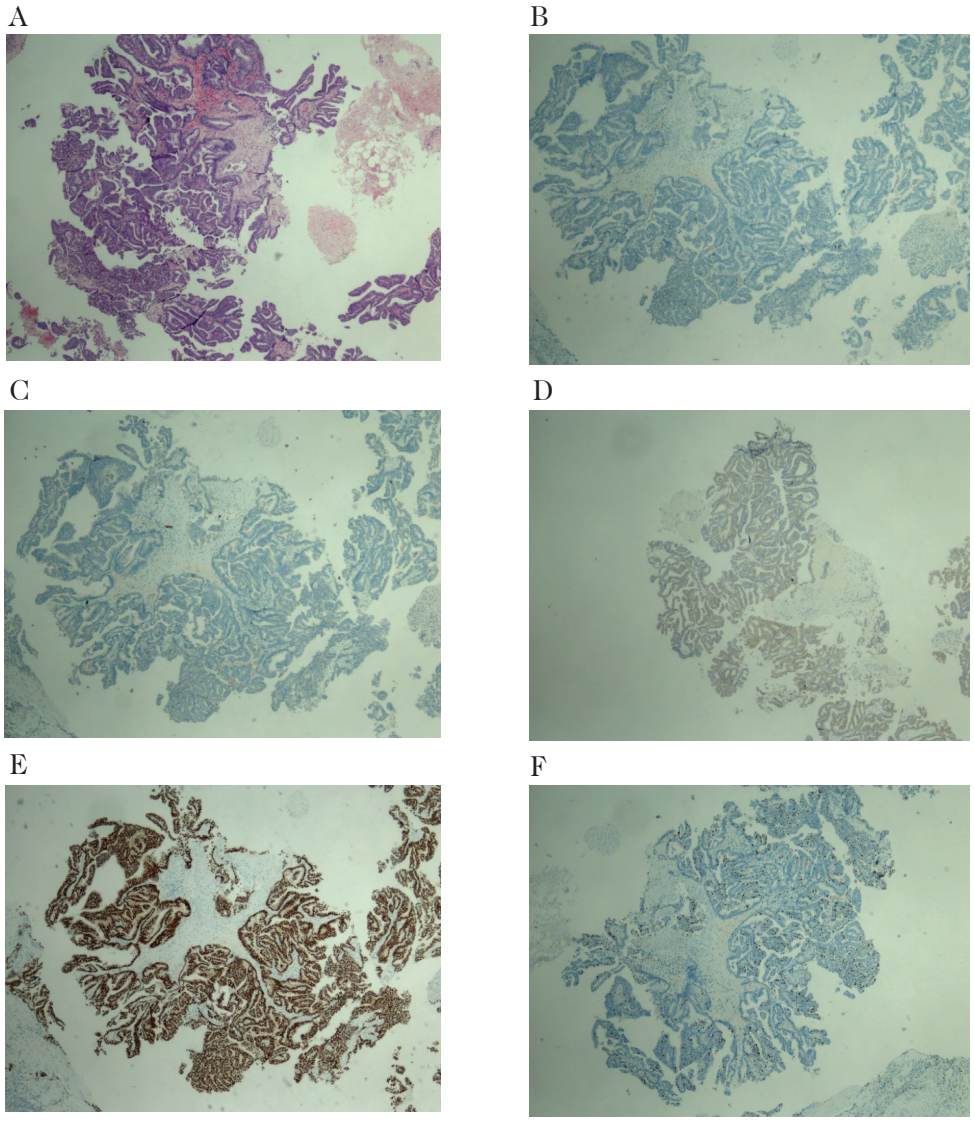

Fig. 3. Histopathological and immunohistochemical features of a case of invasive encapsulated papillary carcinoma. **A:** Hematoxylin and eosin stained Tru-Cut biopsy section (×40) from a case diagnosed with invasive encapsulated papillary carcinoma by both Tru-Cut biopsy and subsequent excisional biopsy; **B, C:** Immunohistochemical staining with p63 (B), CK5/6 (C) and SMM (**D**) showing absence of myoepithelial layer (×40); **E:** Immunohistochemical staining for estrogen receptor (ER) showing widespread strong nuclear positivity (100%) (×40); **F:** Immunohistochemical staining of Ki-67 showing a proliferative index of 15% (×40).

behavior[1,3,13,14]. Despite these advances, the biological significance and optimal management of certain papillary lesions—particularly those diagnosed from limited CNB material—remain incompletely understood, underscoring the ongoing need for comprehensive histopathological evaluation and clinicopathological correlation.

Numerous studies have examined the diagnostic performance and clinical management of papillary neoplasms identified on CNB; however, reported rates of underdiagnosis and diagnostic upgrade on excision vary widely across the literature. Epithelial atypia has consistently been associated with a substantially increased risk of upgrade to

DCIS or invasive carcinoma, supporting current recommendations for complete surgical excision in such cases. In contrast, the optimal management of papillary lesions without atypia diagnosed on CNB remains controversial, with no clear consensus on routine surgical excision versus imaging-based surveillance [2].

Consistent with the findings of Puccini et al. [2], our study showed that when diagnostic upgrades were limited to DCIS or invasive carcinoma, abnormal physical examination findings were significant predictors of malignancy. This observation underscores the limitations of CNB in fully characterizing papillary lesions and reinforces the concept that even papillary lesions without atypia diagnosed on CNB may carry a clinically meaningful risk of upgrade at excision.

Consistent with previous reports by Tian et al. [9], CNB in our cohort showed high concordance in distinguishing benign from malignant breast lesions, with only a small number of discordant cases. Notably, misclassification predominantly involved lesions with atypical ductal hyperplasia (ADH) or ADH combined with an intraductal papilloma. These lesions frequently lacked overtly suspicious sonographic features, and their maximum tumor diameter was generally less than 3 cm, factors that may partially explain the diagnostic challenges encountered.

Accurate discrimination between in situ and invasive carcinoma remains critical, as substantial differences exist in the therapeutic strategies applied to these entities [15]. Pathological grading plays a central role in guiding clinical management, influencing decisions about surgical extent, axillary evaluation, and the need for adjuvant therapy. Consequently, precise histopathological assessment is essential to optimizing patient outcomes.

Intralesional heterogeneity is a defining biological feature of papillary breast lesions and has important diagnostic implications[16]. Atypical papillary lesions, in particular, often show focal architectural atypia and localized disruptions of the myoepithelial cell layer. Immunohistochemical analysis may therefore reveal focal loss of CK5/6 expression confined to atypical regions. Similarly, proliferation indices show marked regional variability across benign, atypical, and malignant papillary lesions, with differences between low- and high-proliferative areas reported to reach up to 44%.

Collectively, these observations indicate that asymmetric growth and intralesional heterogeneity are intrinsic features of many papillary lesions. This heterogeneity highlights the inherent limitations of CNB, as limited sampling may miss the most diagnostically significant areas, potentially leading to underdiagnosis. These findings support continued recommendations for surgical excision when atypia is identified or when lesion heterogeneity raises concerns about sampling adequacy [17].

Managing patients diagnosed with benign intraductal papilloma on CNB remains particularly challenging. Although most of these lesions are truly benign, reported rates of upgrade to atypia or malignancy on excision are high enough to warrant concern. As a result, many clinicians favor routine surgical excision to establish a definitive diagnosis. However, this approach inevitably leads to overtreatment, given that the incremental breast cancer risk associated with a solitary benign papilloma is comparable to that of usual ductal hyperplasia. These considerations underscore the need for improved risk stratification strategies to more accurately identify patients who would benefit from surgical intervention [17].

Finally, the relatively low underestimation rates for DCIS and ADH reported with CNB have important implications for surgical planning. When subsequent excision is performed, surgeons may reasonably assume a low likelihood of occult invasive carcinoma, supporting breast-conserving surgical approaches. In such cases, axillary lymph node sampling may be safely omitted, given the low probability of invasive disease [18].

This review has several limitations. In several of the included studies, incomplete or inconsistent reporting limited a rigorous assessment of methodological quality and hindered accurate evaluation of the potential impact of bias on study findings. Furthermore, substantial heterogeneity in study designs, diagnostic thresholds, and histopathological criteria limited meaningful cross-study comparisons and likely contributed to variability in reported outcomes.

To strengthen the evidence base, future high-quality prospective diagnostic accuracy studies using standardized reporting frameworks are needed. Such studies would enable more robust validation of current findings and help mitigate the impact of residual methodological limitations.

In conclusion, given the well-documented potential for underestimation—not only of carcinoma but also of atypical proliferative lesions—surgical excision remains a justified and prudent management strategy for papillary breast lesions identified on CNB. When a papillary lesion is detected on CNB, surgical excision carries a substantial likelihood of revealing atypia or an associated malignancy, either within the index lesion or in adjacent breast tissue.

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Author's contributions

TD drafted the manuscript and conducted the statistical analyses. GE, SST, SCP, FUD, and EK contributed to the study's conception and design. All authors critically reviewed and approved the final manuscript.

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Conflict of interest

All authors participating in the study declare that there is no conflict of interest.

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