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ORIGINAL ARTICLE

Ultrasonographic Features Predictive of Malignancy in Intraductal Papillary Neoplasm of the Breast

İsmail Yurtsever[1], Şeyma Yıldız[1], Abdusselim Adil Peker[1], Hafize Otçu Temur[1], Bahar Atasoy[1], Serdar Balsak[1], Özlem Toluk[2]

[1]Department of Radiology, Bezmialem Vakıf University, İstanbul, Türkiye
[2]Department of Bioistatistics, Bezmialem Vakıf University, İstanbul, Türkiye

Abstract

Introduction: To detect and evaluate features of gray scale B-mode ultrasonographic examination findings that may predict malignancy in intraductal lesions of the breast.

Methods: In this retrospective study, 650 cases examined at Bezmialem Vakıf University Department of Radiology between January 2018 and December 2019 were scanned. Fifty-two female cases who were diagnosed with intraductal papillary lesions on gray scale B-mode US examination and underwent core biopsy were included.

Results: Lesions were evaluated according to their largest size (4-50 mm, median 13 mm); the largest size of the lesion was found to be higher in the malignant group than in the benign group (p=0.008). As a result of our ROC analysis in terms of predicting benign and malignant outcomes with the largest size of the lesion, AUC=0.764, sensitivity 81.8%, specificity 70.7%, and cut-off>10.5 mm (p=0.001). According to this result, lesions over 10.5 mm are more likely to be malignant.

Discussion and Conclusion: There is a lot of benign/malignant overlap in the radiological features of papillary lesions. We found the lesion size to be the most important feature in this distinction. Therefore, in cases that warrant suspicion, performing a core needle biopsy may be indispensable.

Keywords: Breast cancer; breast papillary neoplasm; core needle biopsy; ductal carcinoma in situ; papilloma.

Among solid breast tumors, intraductal papillary neoplasms (PN) are uncommon, occurring less than 3% of the time[1,2]. Breast PN comprises a diverse array of tumor forms, and diagnosing them pathologically might provide challenges at times. A variety of tumor types, from benign intraductal papilloma to invasive papillary carcinoma, are classified as PN of the breast[2]. There are six different types of papillary lesions that can be identified: encapsulated papillary carcinoma, papilloma, papilloma with atypical ductal hyperplasia/ductal carcinoma in situ (DCIS), papillary DCIS, solid papillary carcinoma (both in situ and invasive), and invasive papillary carcinoma[3]. Due to its unique clinical and radiological characteristics, papillary breast lesions can present differently. A palpable mass in papillary lesions or nipple discharge may be observed on a clinical examination[1].

Papillomas mostly show larger lesions as solitary masses, typically in the retroareolar region. They typically have round or oval-shaped masses that are highly defined, along with benign features[1,2]. Peripherally located

Correspondence: İsmail Yurtsever, M.D. Bezmialem Vakıf Üniversitesi, Radyoloji Anabilim Dalı, İstanbul, Türkiye
Phone: +90 212 453 17 00 **E-mail:** isyurtsever@gmail.com
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multiple masses may also appear, especially in multiple intraductal papillomas which originate from terminal ductal lobular units[1,4].

PN of the breast are categorized as one of these lesions at high risk[5]. Papillary breast lesions are a clinically, histologically, and biologically diverse group of breast diseases[6].

Determining the nature of a papillary breast lesion-whether benign, premalignant, or malignant-and further categorizing it as invasive or non-invasive are the primary goals of diagnosis. Basically, the presence of myoepithelial cells is important to rule out invasive growth. Along the fibrovascular cores of benign papillary lesions, myoepithelial cells coexist with luminal cells[6].

The presence of cellular atypia, especially in association with DCIS, is marked by a decrease and, in certain cases, an absence of myoepithelial cells. Myoepithelial cells in papillary DCIS are only seen on the outside of the impacted ducts. Encapsulated papillary carcinomas exhibit an absence of myoepithelium along the cyst wall, a characteristic shared by the nests of solid papillary carcinomas and invasive papillary carcinoma[6].

PN on core needle or vacuum-assisted biopsy may be difficult to diagnose. It is not possible to rule out the possibility of cellular atypia in a different area of a benign papillary lesion, even if pieces of the lesion are discovered in a biopsy specimen. Because of the uncertainty surrounding the diagnosis, benign papillary lesions in biopsies are now classified as lesions of uncertain malignant potential, or B3 on a 5-scale, in Europe[6]. This classification applies even in cases where cellular atypia is present[6]. Furthermore, atypical epithelial proliferations can be difficult to diagnose from a biopsy.

MRI, mammography, and ultrasound (US) frequently show a broad range of appearances for papillary lesions. In addition, some benign and non-papillary tumoral lesions may share imaging characteristics with papillary lesions; as a result, it can be challenging to distinguish papillary lesions using imaging[1].

US is more sensitive than other modalities in detecting all types of papillary lesions[1]. US appearances generally follow one of three basic patterns, though they can vary[1,7]. With or without ductal dilatation, an intraductal mass is the most typical pattern. If there was bleeding, echogenic fluid might be present in the dilated ducts. When a patient presents with serosanguinous nipple discharge, a single dilated duct (>3 mm) is a good indicator of an intraductal papillary lesion[1,7]. Papillary breast lesions can also present as an intracystic mass or a focal hypoechoic mass[1].

The purpose of this study is to review both benign and malignant papillary intraductal lesions of the breast, evaluate US features predictive of malignancy, and examine the shape, size, and contour characteristics of the papillary components.

Materials and Methods

In this retrospective study, 650 cases examined at Bezmialem Vakıf University Department of Radiology between January 2018 and December 2019 were scanned. The exclusion criteria of the study were whether the patients accepted core biopsy or not. Patients who did not have pathology results, surgery, or a two-year follow-up were also excluded. Fifty-two female cases who were diagnosed with intraductal papillary lesions on gray scale B-mode US examination and underwent core biopsy were included. Diagnosis, pathology results, and radiological data were confirmed. The primary endpoint was the frequency at which malignancy (DCIS or invasive disease) was identified after complete surgical excision. All cases were examined using an ultrasound scanner (Aplio 500 Toshiba/Canon, Japan), which runs B-mode gray-scale US modalities. Linear high-frequency transducers (14 MHz) were used for all examinations. Informed written consent was obtained from all cases before core biopsy. The procedures were used following the guidelines of the Helsinki Declaration on human experimentation. Ethics approval was granted by the local ethics committee at the university (05/12/2023-306).

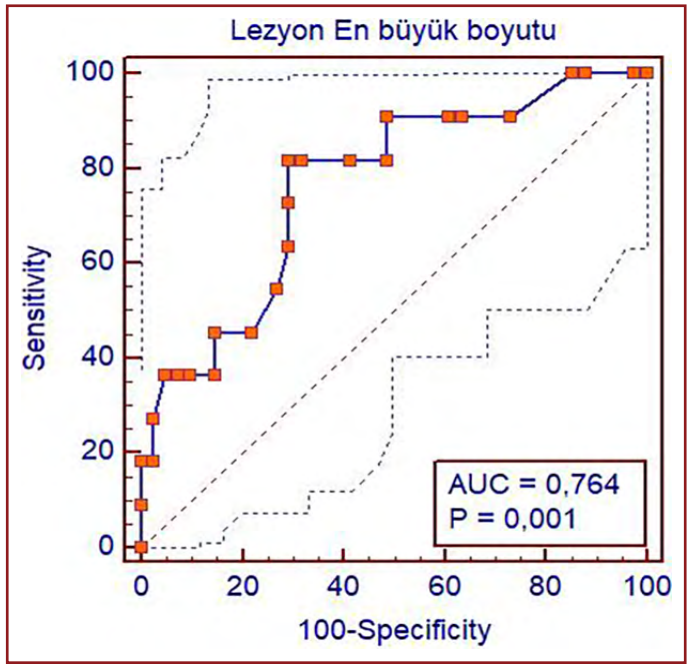

Figure 1. ROC analysis chart.

ROC: Receiver operating curve.

Statistical Analysis

Descriptive statistics were given with median (minimum-maximum) and frequencies with percentages. Comparisons were analyzed with Fisher's exact test, Fisher Freeman Halton test, Mann Whitney U test, and Kruskal Wallis test. Relationships between the largest size of the lesion and the distance from the nipple were examined with the Spearman correlation coefficient. We performed a Receiver Operating Curve (ROC) to evaluate whether the maximum size of the lesion was predictive of malignancy (Fig. 2). Youden's J Index was used for the cut-off value. SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) and MedCalc version 19.6.1 software were used for analysis. The Type-I error rate was taken as α=0.05.

Table 1. Comparisons made with the largest size of the lesion

	The largest size of the lesion	p
Shape		0.861
Oval	9.5 (4.0-36.0)	
İrregular	9.0 (5.5-50.0)	
Contour		0.624
Regular	9.5 (4.0-36.0)	
İrregular	9.0 (6.0-50.0)	
Result		0.008
Benign	8.0 (4.0-24.0)	
Malign	13.0 (6.0-50.0)	

No statistically significant difference was shown between the largest size of the lesion and its shape and contour (p=0.861 and p=0.624, respectively).

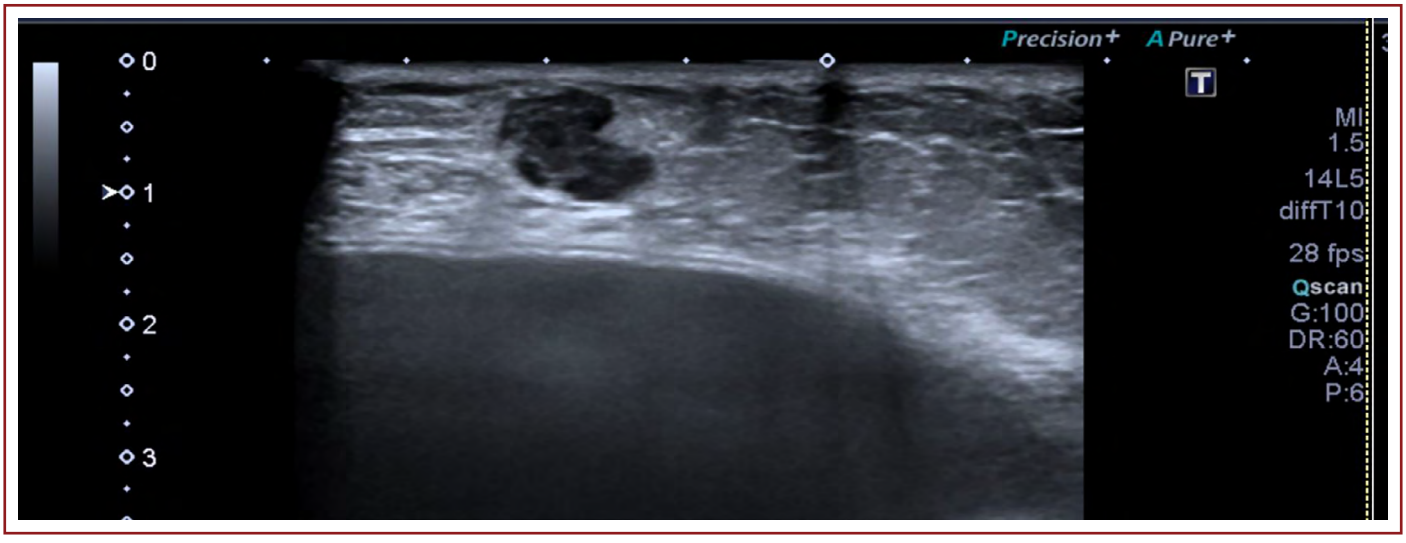

Figure 2. Solid lesion located perpendicular to the skin with a smooth contour containing micro cysts.

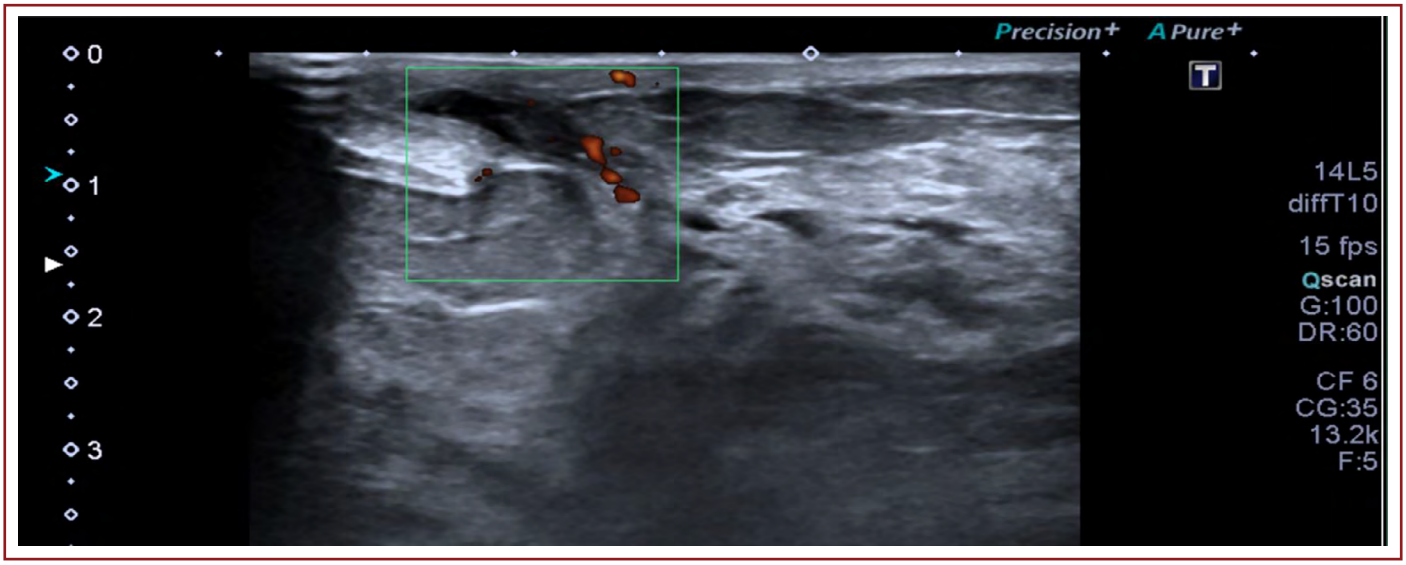

Figure 3. Solid lesion in an intraductal location with significant vascularization on color Doppler examination.

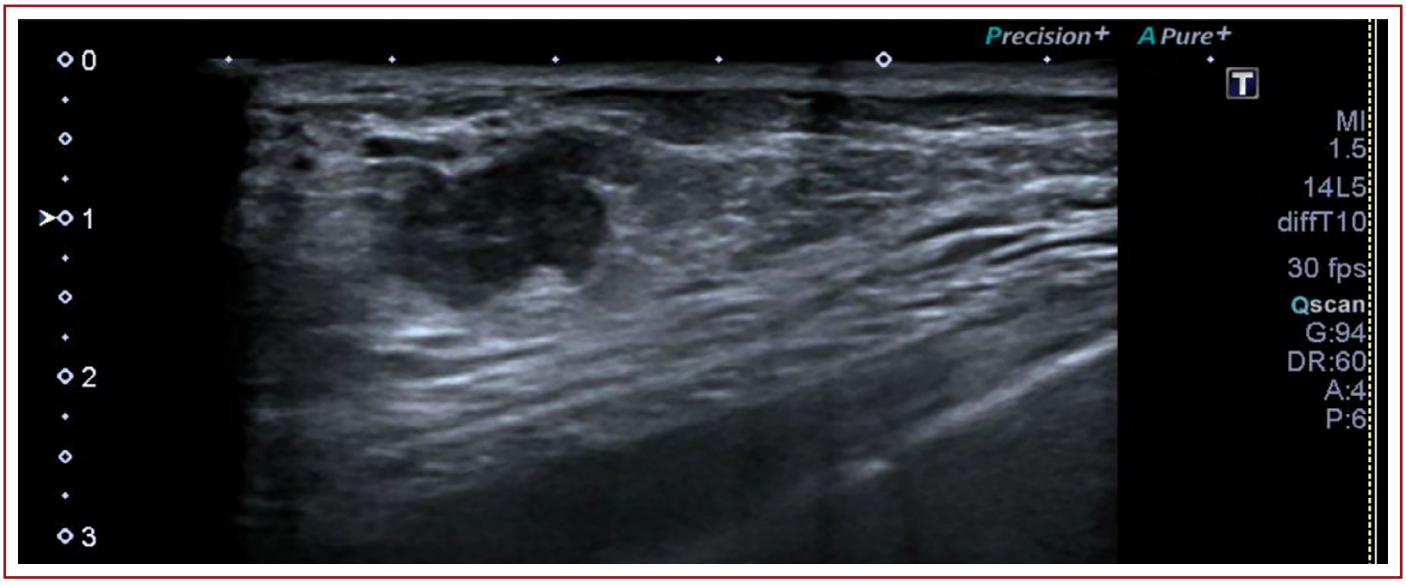

Figure 4. Solid lesion located parallel to the skin with unclear contours.

Results

Lesions were evaluated according to their largest size (4-50 mm, median 13 mm); the largest size of the lesion was found to be higher in the malignant group than in the benign group (p=0.008). As a result of our ROC analysis in terms of predicting benign and malignant outcomes with the largest size of the lesion, AUC=0.764, sensitivity 81.8%, specificity 70.7%, and cut-off>10.5 mm (p=0.001) (Fig. 1). According to this result, lesions over 10.5 mm are more likely to be malignant.

Distribution of lesions according to nipple distance: The distance of the lesions to the nipple was found to be <3 cm in 41 cases and >3 cm in 11 cases. No significant statistical relationship was found between the distance of the lesions to the nipple, their shape, contour, and pathology result (p>0.05) (Table 1).

Shape and contour features: The shape features of papillary lesions were found to be 38 oval and 14 irregular, and the contour features were found to be 40 regular and 12 irregular.

Ductal ectasia was present in 17 of the cases. Ductal ectasia was accompanied by only one of the malignant cases.

Malignant results after core biopsy: 3 cases were intraductal papillary carcinoma (Fig. 2), 5 cases were DCIS (Fig. 3), and 3 cases were encapsulated papillary carcinoma.

Benign results after core biopsy: 41 cases of papillomas (Fig. 4).

During the 12-month follow-up (average 9-24 months), 41 cases whose results did not change and 11 cases with an upgrade after surgery were identified.

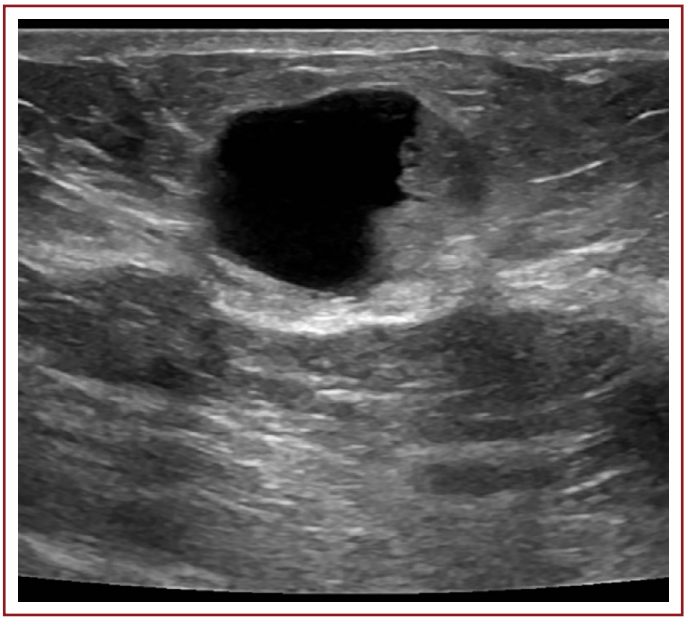

Figure 5. Cystic lesion containing a solid component.

Discussion

Accurate diagnosis based on breast imaging continues to be difficult for PN of the breast. According to published reports, tissue sampling is typically necessary to differentiate between benign and malignant papillary lesions because MG, US, and conventional DCE-MRI are deemed unreliable methods[8]. Surgical excision is generally considered necessary when a CNB specimen reveals atypical papillary lesions or papillary carcinomas[8].

The duct dilated with an intraductal mass or the complex cyst with an intracystic solid component are characteristic

features of intraductal papillary lesions. Pseudoinvasion can cause hazy borders in benign papillary lesions. Intraductal papillary lesions may resemble a solid mass if the mass is so big that it can fill the cyst or the dilated duct, making it difficult to distinguish between the peripheral ductal or cystic component[1,7].

Papillary carcinomas may be detected as a hypoechoic or heterogeneous solid mass or as a complex cyst that US shows septae or mural-based papillary projections[1,2]. There could be an atypical border and contour. One may observe posterior acoustic shadowing or enhancement[1]. Solid parts of the lesion frequently exhibit increased internal vascularity on Doppler ultrasonographic imaging (Fig. 3).

Differentiating between benign and malignant papillary breast lesions may not be feasible using US due to their varied appearances and significant imaging feature overlap. Benign papillary lesions are less likely to be present in older age groups when a larger solid component and evidence of intracystic hemorrhage are present[1,9].

A PN frequently manifests as a cylindrical mass that is consistent with a dilated duct that extends to the nipple. Benign papillomas can show focal architectural distortion[1,4]. Benign PN may exhibit large, irregular, coarse calcifications as well as clustered amorphous or punctate calcifications[1,10]. On rare occasions, pleomorphic microcalcifications can become malignant[1,11]. Microcalcifications may be linked to DCIS in papillomas[1].

Papillomas are usually centrally/subareolarly located as single lesions, can reach significant sizes, and become symptomatic. In contrast, peripheral lesions are usually smaller but may also be multiple and recurrent[10,12]. Papillomas are often accompanied by marked epithelial hyperplasia and/or periductal sclerosis, resulting in microscopically complex lesions[12].

Over the past 20 years, there has been a significant shift in the management of breast lesions, with minimally invasive CNB taking the place of routine surgical biopsy for diagnosis. Nevertheless, the concern of undersampling in CNB has emerged as a significant issue, particularly in the context of high-risk lesions[5]. It is noteworthy that a subset of these lesions may undergo histopathological upgrading subsequent to the comprehensive surgical excision of the entire affected region. While these fibrovascular nuclei are a characteristic feature of breast PN, the lesions they represent are a heterogeneous group of diseases that include malignant, atypical, and benign lesions[5].

Also known as high-risk or B3 lesions, breast lesions with unclear malignant behavior are made up of a range of pathologies with varying probabilities of comorbid malignancy. Over the last few decades, there has been a notable rise in the diagnosis of B3 lesions due to the extensive adoption of screening programs and the development of new imaging modalities[13]. According to reports, B3 lesions make up between 3 and 21% of all breast lesions and have a 0.2 to 5% chance of developing a related malignancy[13].

There may be similarities between the morphologic characteristics and enhancement patterns of benign papillomas and papillary carcinomas[8]. A histological examination is typically necessary because a reliable diagnosis to distinguish malignant and benign PN could not be made due to the variety of imaging findings of PN[14].

Up to 25% of patients may experience papillary lesions that deteriorate after excision. A CNB can reveal a benign papilloma. Overtreatment and needless surgical excisions may result from this correlation[14]. The necessity of routine excision of papillary neoplasms has been questioned in recent years because the existing literature reports variable progression rates ranging from 0.8% to 33% after surgical excision of PN diagnosed with CNB[5].

The majority of early researchers suggested that intraductal papillomas were either benign lesions or lesions that might eventually turn into carcinomas. More recent research on intraductal papillomas, however, has demonstrated that these lesions raise the risk of developing carcinoma, just like other types of proliferative breast disease. It has been proposed by some researchers that papillomas can function as direct precursor lesions[12]. Similarly, in our case, after wide local excision of a cystic lesion containing a solid component, the pathology specimen revealed the presence of intraductal papilloma and low-grade DCIS in the surrounding tissue (Fig. 5).

Pareja et al.[15] examined the association of imaging size of the PN and upstaging to malignancy and concluded that observation is appropriate for PN with no atypia and radiologic-pathologic concordance, regardless of size[5,15]. Khan et al.[16] concluded that palpability of the mass and presence of nipple discharge were not predictive of upstaging[5,16]. Hong et al.[17] found that age, size on US, and density on mammography were associated with upstaging, specifically in patients older than 54 years, and a lesion size greater than 1 cm[5,17].

Current research examined the necessity of excision versus merely imaging follow-up following a biopsy, as well

as upgrade rates. Eleven out of the 327 PN undergoing excision had DCIS, 2.4% had invasive carcinomas, and 9.5% of them had high-risk lesions[6]. When a lesion measured more than 1 cm, showed a palpable mass, or was more than 5 cm away from the nipple, women over 50 were more likely to have an upgrade to DCIS or invasive carcinoma[6]. In our study, similar results were found by performing CNB on PN. As a result of our ROC analysis, we found that lesions larger than 10.5 mm have a high risk of malignancy.

Tissue sampling is typically necessary because radiological imaging may not be able to accurately distinguish between benign and malignant papillary lesions due to the varied appearance of these lesions.

Study Limitations

The present study had some limitations. First of all, this study had a relatively small sample size. Secondly, it was impossible to avoid patient selection bias because all of the data were obtained from a single center. In some cases, there were insufficient sampling or suspicious results in core biopsy. Thirdly, the retrospective nature of the study was another limitation. Fourthly, surgery was not performed in all cases.

Conclusion

There is a lot of benign/malignant overlap in the radiological features of papillary lesions. We found the lesion size to be the most important feature in this distinction. Therefore, in cases that warrant suspicion, performing a core needle biopsy may be indispensable.

Ethics Committee Approval: The study was approved by the Bezmialem Vakıf University Ethics Committee (no: 306, date: 05/12/2023).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: İ.Y.; Design: Ş.Y.; Supervision: İ.Y.; Fundings: H.O.T.; Materials: A.A.P.; Data Collection or Processing: B.A.; Analysis or Interpretation: Ö.T.; Literature Search: S.B.; Writing: İ.Y.; Critical Review: Ş.Y.

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Conflict of Interest: None declared.

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References

1. Toprak H, Yidiz S, Aralasmak A, Aydin S, Bilgin S. Imaging spectrum of breast papillary lesions: With special emphasis on atypical appearances. Curr Med Imaging Rev 2016;12:1–6.
2. Brookes MJ, Bourke AG. Radiological appearances of papillary breast lesions. Clin Radiol 2008;63:1265–73. [CrossRef]
3. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020;77:181–5. [CrossRef]
4. Agoff SN, Lawton TJ. Papillary lesions of the breast with and without atypical ductal hyperplasia: Can we accurately predict benign behavior from core needle biopsy? Am J Clin Pathol 2004;122:440–3. [CrossRef]
5. Liu C, Sidhu R, Ostry A, Warburton R, Pao JS, Dingee C, et al. Risk of malignancy in papillary neoplasms of the breast. Breast Cancer Res Treat 2019;178:87–94. [CrossRef]
6. Kulka J, Madaras L, Floris G, Lax SF. Papillary lesions of the breast. Virchows Arch 2022;480:65–84. [CrossRef]
7. Ganesan S, Karthik G, Joshi M, Damodaran V. Ultrasound spectrum in intraductal papillary neoplasms of breast. Br J Radiol 2006;79:843–9. [CrossRef]
8. Yildiz S, Toprak H, Ersoy YE, Malya FÜ, Bakan AA, Aralaşmak A, et al. Contribution of diffusion-weighted imaging to dynamic contrast-enhanced MRI in the characterization of papillary breast lesions. Breast J 2018;24:176–9. [CrossRef]
9. Schneider JA. Invasive papillary breast carcinoma: mammographic and sonographic appearance. Radiology 1989;171:377–9. [CrossRef]
10. Cardenosa G, Eklund GW. Benign papillary neoplasms of the breast: mammographic findings. Radiology 1991;181:751–5.
11. Lam WW, Chu WC, Tang AP, Tse G, Ma TK. Role of radiologic features in the management of papillary lesions of the breast. AJR Am J Roentgenol 2006;186:1322–7. [CrossRef]
12. Lewis JT, Hartmann LC, Vierkant RA, Maloney SD, Shane Pankratz V, Allers TM, et al. An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. Am J Surg Pathol 2006;30:665–72. [CrossRef]
13. Catanzariti F, Avendano D, Cicero G, Garza-Montemayor M, Sofia C, Venanzi Rullo E, et al. High-risk lesions of the breast: Concurrent diagnostic tools and management recommendations. Insights Imaging 2021;12:63. [CrossRef]
14. Gültekin MA, Yabul FÇ, Temur HO, Sari L, Yilmaz TF, Toprak H, et al. Papillary lesions of the breast: Addition of DWI and TIRM sequences to routine breast MRI could help in differentiation benign from malignant. Curr Med Imaging 2022;18:962–9.
15. Pareja F, Corben AD, Brennan SB, Murray MP, Bowser ZL, Jakate K, et al. Breast intraductal papillomas without atypia in radiologic-pathologic concordant core-needle biopsies: Rate of upgrade to carcinoma at excision. Cancer 2016;122:2819–27. [CrossRef]
16. Khan S, Diaz A, Archer KJ, Lehman RR, Mullins T, Cardenosa G, et al. Papillary lesions of the breast: To excise or observe? Breast J 2018;24:350–5. [CrossRef]
17. Hong YR, Song BJ, Jung SS, Kang BJ, Kim SH, Chae BJ. Predictive factors for upgrading patients with benign breast papillary lesions using a core needle biopsy. J Breast Cancer 2016;19:410–6. [CrossRef]