Benign and malignant papillary lesions of the breast: Radiographic differentiation by mammography and sonography

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Background	:	*There has been limited data regarding the radiographic features related to malignant papillary lesions and no features to definitely differentiate between benign and malignant papillary lesions.*
Objective	:	*To determine the mammographic and sonographic features and their detection rate for differentiation of benign and malignant papillary lesions.*
Design	:	*A retrospective analytic study*
Setting	:	*Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
Methods	:	*We retrospectively reviewed mammography and sonography of 89 surgically proven benign papillary lesions and 44 malignant papillary lesions from January 1, 2005 to December 31, 2014 at our institution. Radiographic findings were analyzed according to the Breast Imaging Reporting and Data System.*

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Results : *Of these 133 papillary lesions, 50.4% (67/133) and 97.7% (130/133) could be detected on mammography and sonography, respectively. An irregular shape, non-circumscribed margin, high density of mass and suspicious calcification were more frequently found on mammography in malignant lesions (P < 0.05). As for sonography, an irregular shape, complex or heterogeneous echo of mass, intralesional vascularity and suspicious calcification were more frequently found in malignant lesions (P < 0.05). When combining interpretation of mammography and sonography, they gave a sensitivity of 97.7%, specificity of 36%, positive predictive value of 43%, and negative predictive value (NPV) of 97%.*

Conclusions : *Although there were some overlaps of radiographic features between benign and malignant papillary lesions, we found the features significantly indicative of malignant papillary lesions and gave high sensitivity and NPV. In the future, if histopathologic diagnosis of the papillary lesions is benign on core-needle biopsy and concordant with benign radiographic findings, conservative management with follow-up imaging instead of surgical excision may be considered.*

Keywords : *Breast, papillary neoplasm, mammography, sonography.*

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ธิติ ทองส่งโสม, จตุพร ชยะกุลคีรี. การจำแนกพยาธิสภาพของรอยโรคปาปิลลารี่ของก้อนเนื้อเต้านมโดยใช้ภาพทางรังสีวิทยา. จุฬาลงกรณ์เวชสาร 2559 ก.ค. – ส.ค.;60(4): 373 – 87

เหตุผลของการทำวิจัย : *การศึกษาลักษณะภาพทางรังสีวิทยาของรอยโรคปาปิลลารี่ของก้อนเนื้อเต้านม ในปัจจุบันยังมีน้อยและไม่สามารถใช้แยกรอยโรคชนิดอันตรายออกจากชนิดไม่อันตรายได้*

วัตถุประสงค์ : *เพื่อค้นหาลักษณะภาพทางรังสีวิทยาของแมมโมแกรมและอัลตราซาวน์ที่สามารถใช้แยกรอยโรคปาปิลลารี่ของก้อนเนื้อเต้านมชนิดอันตรายออกจากชนิดไม่อันตรายได้ และหาอัตราการตรวจพบของรอยโรคชนิดอันตราย*

รูปแบบการวิจัย : *การศึกษาวิจัยเชิงวิเคราะห์แบบย้อนหลัง*

สถานที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร*

ตัวอย่างและวิธีการศึกษา : *ผู้ป่วยที่ได้รับการผ่าตัดก้อนเนื้อเต้านมและผลพยาธิวิทยาวินิจฉัยว่าเป็นรอยโรคปาปิลลารี่ในโรงพยาบาลจุฬาลงกรณ์ จำนวน 132 คน 133 รอยโรค ตั้งแต่ ปี พ.ศ. 2548 ถึง พ.ศ. 2557 เป็นรอยโรคชนิดไม่อันตราย 89 รอยโรค และชนิดอันตราย 44 รอยโรค ภาพแมมโมแกรมและอัลตราซาวน์ของรอยโรคก่อนการผ่าตัดถูกวิเคราะห์และเก็บข้อมูลแบบย้อนหลัง*

ผลการศึกษา : *ในจำนวน 133 รอยโรคปาปิลลารี่ พบว่าร้อยละ 50.4 (67/133) สามารถตรวจพบได้จากแมมโมแกรม และร้อยละ 97.7 (130/133) สามารถตรวจพบได้จากอัลตราซาวน์ ลักษณะภาพของแมมโมแกรมที่พบได้บ่อยกว่าอย่างมีนัยสำคัญทางสถิติในกลุ่มรอยโรคชนิดอันตราย ได้แก่ รูปร่างขรุขระ ขอบเขตไม่ชัดเจน ก้อนมีความหนาแน่นสูง และพบกลุ่มหินปูนที่มีลักษณะน่าสงสัย (P < 0.05) ลักษณะภาพจากอัลตราซาวน์ที่พบได้บ่อยกว่าอย่างมีนัยสำคัญทางสถิติ ในกลุ่มรอยโรคชนิดอันตราย ได้แก่ รูปร่างขรุขระ แอคโคเป็นแบบผสม มีเส้นเลือดอยู่ภายในรอยโรค และพบกลุ่มหินปูนที่มีลักษณะน่าสงสัย (P < 0.05) เมื่อใช้ลักษณะภาพของแมมโมแกรมร่วมกับอัลตราซาวน์เพื่อตรวจหารอยโรคชนิดอันตราย พบว่าให้ความไวเท่ากับร้อยละ 97.7 ความจำเพาะเท่ากับร้อยละ 36 ค่าพยากรณ์ผลบวกเท่ากับร้อยละ 43 และค่าพยากรณ์ผลลบเท่ากับร้อยละ 97*

สรุป   :   *แม้ว่าลักษณะภาพทางรังสีวิทยาจะมีการทับซ้อนกันระหว่างรอยโรค*
ปาปิลารี่ชนิดไม่อันตรายและชนิดอันตราย   แต่การใช้แมมโมแกรม
ร่วมกับอัลตราซาวน์เพื่อตรวจหารอยโรคชนิดอันตรายให้ค่าความไว
และค่าพยากรณ์ผลลบสูงมากในอนาคตหากรอยโรคปาปิลารี่ได้รับ
วินิจฉัยว่าเป็นชนิดไม่อันตราย จากการเจาะชิ้นเนื้อและสอดคล้องกับ
ลักษณะภาพทางรังสีวิทยาว่าไม่อันตราย การติดตามรอยโรคด้วย
แมมโมแกรมและอัลตราซาวน์แทนการผ่าตัดอาจพิจารณาเป็นทาง
เลือกหนึ่งของการรักษา

คำสำคัญ   :   *เต้านม, รอยโรคปาปิลารี่, แมมโมแกรม, อัลตราซาวน์.*

Papillary lesions of the breast are considered uncommon. The incidence is up to 5% of the breast lesions undergone biopsy. These tumors have a wide spectrum of pathology from benign to malignancy and are classified into subtypes including intraductal papilloma, papilloma with atypical ductal hyperplasia (ADH), papilloma with ductal carcinoma in situ (DCIS), papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma.[1, 2] Their histologic characterizations reveal an arborescent structure composed of fibrovascular stalks, covered by a layer of epithelial cells with or without an intervening myoepithelial cell layer. [3] It is hard to definitely differentiate between benign and malignant papillary lesions by imaging because of the overlapping appearances.[4 - 6]

In our knowledge, few studies have demonstrated the radiographic features related to malignant papillary lesions.[7, 8] However, there has been no feature to definitely differentiate between benign and malignant papillary lesions. The purpose of our study was therefore to determine the mammographic and sonographic features and their detection rate for differentiation of the two groups of papillary lesions.

Materials and Methods

Study Population

The histopathologic reports of all breast lesions from January 1, 2005 to December 31, 2014 at our institution were retrieved. Of 264 histopathologically proved papillary lesions, 131 (49.6%) lesions were excluded from this study due to no mammography or sonography before surgery or mixed histopathologic type. The clinical presentation and radiographic findings of breast imaging of 133 surgically proven papillary lesions in 132 patients (age, 25 - 89 years; mean age, 53 years) were found. One patient had bilateral breast papillary lesions. All mammography and sonography of the patients were retrieved for retrospective interpretation by consensus of two radiologists with up to 7 years of experience in breast imaging.

This study has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (approval No. 584/57).

Of 89 benign papillary lesions, 84 lesions were intraductal papilloma and 5 lesions were papilloma with ADH. Of 44 malignant papillary lesions, 2 were papilloma with DCIS, 17 were papillary DCIS, 3 were encapsulated papillary carcinoma, 3 were solid papillary carcinoma and 19 lesions were invasive papillary carcinoma. (Table 1)

Mammographic Interpretation

Two reviewers interpreted all mammographic examinations by consensus. The mammographic features were analyzed according to the Breast Imaging Reporting and Data System (BI-RADS).[9] The presence of mass, shape, margin and density of mass, presence of suspicious calcification, architectural distortion, soft tissue change and duct change were recorded.

Sonographic Interpretation

Two reviewers retrospectively interpreted all sonographic examinations by consensus. The sonographic features were analyzed according to the BI-RADS. The presence of mass, shape, orientation, margin, echo and posterior feature of mass, presence of calcification, architectural distortion, duct change, vascularity and soft tissue change were recorded.

Table 1. Result of 133 histopathologic examination of papillary lesions.

Benign lesion	N (89)	Malignant lesion	N (44)
Intraductal papilloma	84	Papilloma with DCIS	2
Papilloma with ADH	5	Papillary DCIS	17
		Encapsulated papillary carcinoma	3
		Solid papillary carcinoma	3
		Invasive papillary carcinoma	19

Statistical analyses

SPSS version 20.0 (Statistical Package for the Social Sciences, IBM corporation, United State) was used for statistical analysis. Chi-square and Fisher's exact tests were used to determine the radiographic features related to malignant papillary lesions, and $P < 0.05$ was considered statistically significant.

Results

The mean age of the patients with benign papillary lesions was 50.0 years (range, 25 - 83 years), and that of those with malignant papillary lesions was 59.2 years (range, 37 - 89 years).

Of the 89 patients with benign papillary lesions, 12 (13%) had palpable mass and 31 (35%) had nipple discharge. Of the 43 patients with malignant papillary lesions, 18 (42%) had a palpable mass and 10 (23%) had nipple discharge. The rest of them presented for screening mammography.

Sixty-seven (50.4%) of 133 papillary lesions were detected on mammography including 30 (33.7%) of 89 benign lesions and 37 (84.1%) of 44 malignant lesions. The mammographic features of these lesions are listed in Table 2.

Table 2. Mammographic features of benign and malignant papillary lesions.

Features	Benign papillary lesions (n = 30)	Malignant papillary lesions (n = 37)	P
Mass, n (%)	27/30 (90)	35/37 (95)	
Shape			< 0.001
Oval	16/27 (59)	2/35 (6)	
Round	0/27 (0)	1/35 (3)	
Irregular	11/27 (41)	32/35 (91)	
Margin			< 0.001
Circumscribed	10/27 (37)	3/35 (8)	
Obscured	8/27 (30)	1/35 (3)	
Microlobulated	5/27 (18)	15/35 (43)	
Indistinct	4/27 (15)	15/35 (43)	
Spiculated	0/27 (0)	1/35 (3)	

Table 2. Mammographic features of benign and malignant papillary lesions. (Continuous)

Features	Benign papillary lesions (n = 30)	Malignant papillary lesions (n = 37)	P
Density			0.002
High	11/27 (41)	28/35 (80)	
Equal	16/27 (59)	7/35 (20)	
Calcification, n (%)			0.041
Presence of suspicious	4/30 (13)	13/37 (35)	
Absent	26/30 (87)	24/37 (65)	
Architectural distortion, n (%)			0.684
Present	2/30 (7)	4/37 (11)	
Absent	28/30 (93)	33/37 (89)	
Duct change, n (%)			1.000
Present	1/30 (3)	1/37 (3)	
Absent	29/30 (97)	36/37 (97)	
Soft tissue change, n (%)			1.000
Present	1/30 (3)	2/37 (5)	
Absent	29/30 (97)	35/37 (95)	

An irregular shape, non-circumscribed margin and high density of mass, and presence of suspicious calcification were more frequently found on mammography in malignant lesions than in benign lesions ($P < 0.05$)(Figure 1). When any of these features was presented to indicate malignancy, interpretation of mammography gave sensitivity of 84.1% (95% CI, 69.9% - 93.4%), specificity of 77.5% (67.4% - 85.7%), positive predictive value (PPV) of 64.9% (51.1% - 81.9%), and negative predictive value (NPV) of 90.8% (81.9% - 96.2%) for detection of malignant papillary lesions.

An architectural distortion, duct change and soft tissue change were rarely found on mammography and their differences between the two groups were not statistically significant ($P > 0.05$).

Only 3 lesions (2%) were not detected on sonography. Of 130 papillary lesions detected on sonography, 88 (98.9%) were benign and 42 (95.5%) were malignant. The sonographic features of these lesions are listed in Table 3.

An irregular shape, complex or hetero-geneous echo of mass, intralesional vascularity, and presence of suspicious calcification were more frequently found on sonography in malignant lesions than in benign lesions ($P < 0.05$)(Figure 1). When any of these features was present to indicate malignancy, interpretation of sonography gave sensitivity of 93.2% (95% CI, 81.3% - 98.6%), specificity of 41.6% (31.2% - 52.5%), PPV of 44.1% (33.8% - 54.8%), and NPV of 92.5% (79.6% - 98.4%) for detection of malignant papillary lesions.
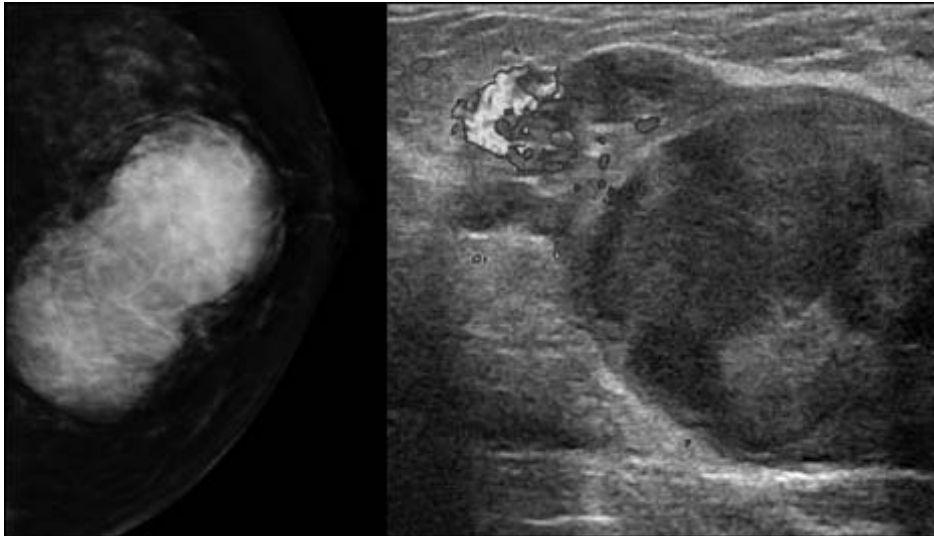
Figure 1. A 50-year-old female presented with palpable mass. (Right) Mammography on CC view showed a large
lobulated hyperdense mass occupying from subareolar to inner part of the left breast containing suspicious
microcalcifications. (Left) As for sonography, this mass showed lobulated margin, heterogeneous echo,
and intralesional vascularity. Excision confirmed invasive papillary carcinoma.

Table 3. Sonographic features of benign and malignant papillary lesions.

Features	Benign papillary lesions (n = 88)	Malignant papillary lesions (n = 42)	P
Mass, n (%)	50/88 (57)	41/42 (98)	
Shape			0.006
Oval	17/50 (34)	4/41 (10)	
Round	0/50 (0)	0/41 (0)	
Irregular	33/50 (66)	37/41 (90)	
Orientation			0.062
Parallel	5/50 (10)	0/41 (0)	
Not parallel	45/50 (90)	41/41 (100)	
Margin			0.051
Circumscribed	16/50 (32)	5/41 (12)	
Indistinct	9/50 (18)	15/41 (37)	
Lobulated	24/50 (48)	20/41 (49)	
Angular	1/50 (2)	1/41 (2)	
Echo			0.001
Anechoic	1/50 (2)	0/41 (0)	
Hypoechoic	38/50 (76)	17/41 (42)	
Complex	11/50 (22)	21/41 (51)	
Heterogeneous	0/50 (0)	3/41 (7)	

Table 3. Sonographic features of benign and malignant papillary lesions.(Continuous)

Features	Benign papillary lesions (n = 88)	Malignant papillary lesions (n = 42)	P
Posterior feature			0.212
Enhancement	12/50 (24)	12/41 (29)	
Shadowing	0/50 (0)	2/41 (5)	
None	38/50 (76)	27/41 (66)	
Calcification, n (%)			0.002
Presence of suspicious	1/88 (1)	7/42 (17)	
Absent	87/88 (99)	35/42 (83)	
Architectural distortion, n (%)			0.323
Present	0/88 (0)	1/42 (2)	
Absent	88/88 (100)	41/42 (98)	
Duct change, n (%)			0.001
Present	44/88 (50)	8/42 (19)	
Absent	44/88 (50)	34/42 (81)	
Vascularity, n (%)			< 0.001
Present	20/88 (23)	24/42 (57)	
Absent	68/88 (77)	18/42 (43)	
Soft tissue change, n (%)			0.323
Present	0/88 (0)	1/42 (2)	
Absent	88/88 (100)	41/42 (98)	

As for the benign papillary lesions, 44 (49.4%) lesions showed a duct change on sonography; 7 focal dilated duct, 18 focal dilated duct with internal echo, and 19 focal dilated duct with intraductal nodule. Most of them were in subareolar area, and an intraductal nodule showed oval shape, circumscribed margin, and hypoechoic echo (Figure 2). The rest of benign lesions demonstrated a solid mass in an extraductal location without adjacent duct dilatation (Figure 3).

An orientation, margin and posterior features of mass on sonography had no statistically significant difference between the two groups ($P > 0.05$). An architectural distortion and soft tissue change were rarely found on sonography and their differences between the two groups were not statistically significant ($P > 0.05$).

When any suspicious mammographic or sonographic features were presented to indicate malignancy; interpretation of both mammography and sonography gave sensitivity of 97.7% (95% CI, 88% - 99.9%), specificity of 36% (26.1% - 46.8%), PPV of 43% (33.1% - 53.3%), and NPV of 97% (84.2% - 99.9%) for detection of malignant papillary lesions. The combining interpretation of both mammography and sonography increased the sensitivity and negative predictive value but the diagnosis became less specific.
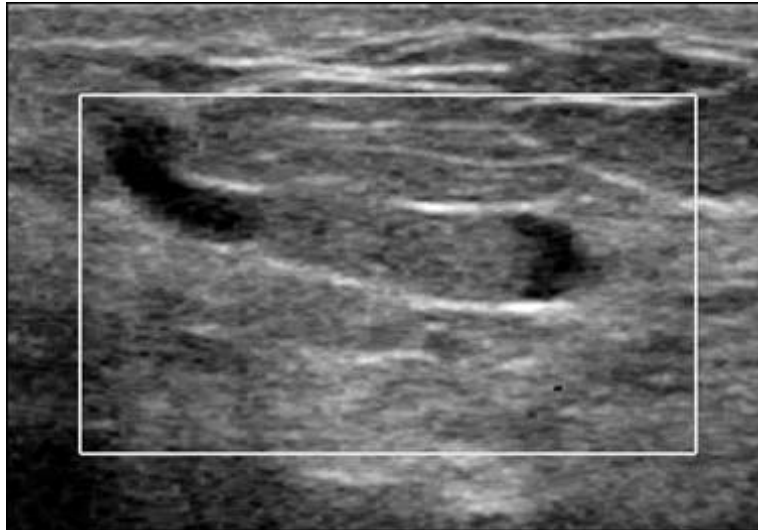
Figure 2. A 62-year-old female presented for check-up. Sonography revealed a single dilated duct with an intraductal nodule at subareolar area of right breast. No intralesional vascularity is seen. Excision confirmed intraductal papilloma.
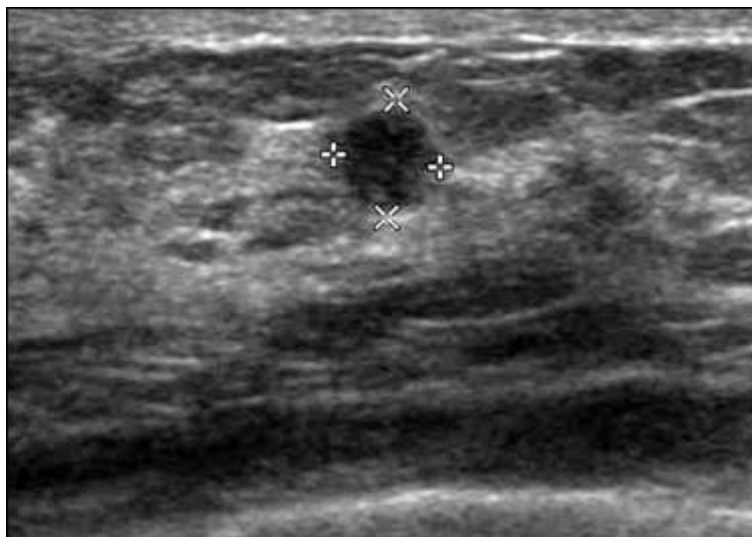

Figure 3. A 52-year-old female presented for check-up. Sonography revealed a circumscribed hypoechoic mass at lower inner quadrant of right breast. Excision confirmed intraductal papilloma.

Discussion

Papillary lesions of the breast are considered uncommon, however, the lesions have a wide spectrum of pathology.[1] A few studies have demonstrated the radiographic features related to malignant papillary lesions, but there has been no feature to definitely differentiate between benign and malignant lesions. [4 – 8] Nowadays, we have higher resolution technology of imaging which gives more detail of the lesions. This study was designed to determine the mammographic and sonographic features and their detection rate for differentiation of the two groups of papillary lesions.

Most papillary lesions are small and can be undetected by mammography or sonography. The detection rate of papillary lesions on mammography from our study was 50.4%. According to Lam et al. [7] abnormal mammographic findings were seen in 21 of 56 patients (37.5%) with papillary lesions, lower than our study. This could be due to new digital mammography that has improved the detection rate. As for sonography, the overall sensitivity to detect papillary lesions is 98%.

Even in the case that the papillary lesion is detectable on mammography, the sensitivity or specificity is not sufficient to precisely differentiate between malignancy and benignity. In the study by Lam et al. [7], the characteristics of microcalcifications were slightly more sensitive than those of the mass in differentiating between benign and malignant lesions. On the contrary, the findings from our study indicated that characteristics of the mass on mammography including shape, margin and density were more sensitive than those of suspicious calcifications in differentiating between the two groups.

Shin HJ et al. [10] demonstrated that the echo pattern was a significant sonographic feature ($P = 0.003$). In their study, benign papillary lesions showed hypoechoic, isoechoic or hyperechoic, while malignant papillary lesions showed mixed hyperechoic-hypoechoic or complex echo. Our results also indicated that the echo pattern was a significant feature ($P = 0.001$). A complex echo or heterogeneous echo was more frequently found in malignant papillary lesions.

In the study by Han et al. [11], 26 (65%) of 40 benign papillary lesions showed a circumscribed margin on sonography. Kim et al. [8] reported the similar findings, in which 31 of 46 benign papillomas (76.4%) showed a circumscribed margin. In addition, 12 of 21 papillary carcinomas (57.1%) also displayed a circumscribed margin, so that it was not a significant feature ($P = 0.27$) from this study. Likewise, our results indicated that the margin of mass on sonography was not a significant feature. A circumscribed margin was found in 16 (32%) of 50 benign papillary lesions and 5 (12%) of 41 malignant papillary lesions ($P = 0.051$) in our study. These suggested that the margin of mass on sonography could not be used for differentiation of benign and malignant papillary lesions (Figure 4).

In the study by Lee et al. [12], posterior enhancement was a significant feature, frequently found in malignant lesions. In contrast, our results showed that posterior enhancement had no significant difference between the two groups ($P > 0.05$). We found that benign papillary lesions with a cystic component could also have a posterior enhancement. (Figure 5)

In the study by Kuzmiak CM et al. [13] intralesional vascularity was found to be a significant feature to differentiate the two groups of papillary lesions. Most of their malignant lesions were associated with intralesional vascularity, unlike benign lesions. Our results support this finding that intralesional vascularity was a significant sonographic feature ($P < 0.001$) in malignant papillary lesions. Intralesional vascularity can also be identified in the fibrovascular core of an intraductal papilloma, but Color Doppler images were not demonstrated in all lesions, especially in the small ones. It is worth noting that their presence might be shown in the large benign papillary lesions (Figure 5).
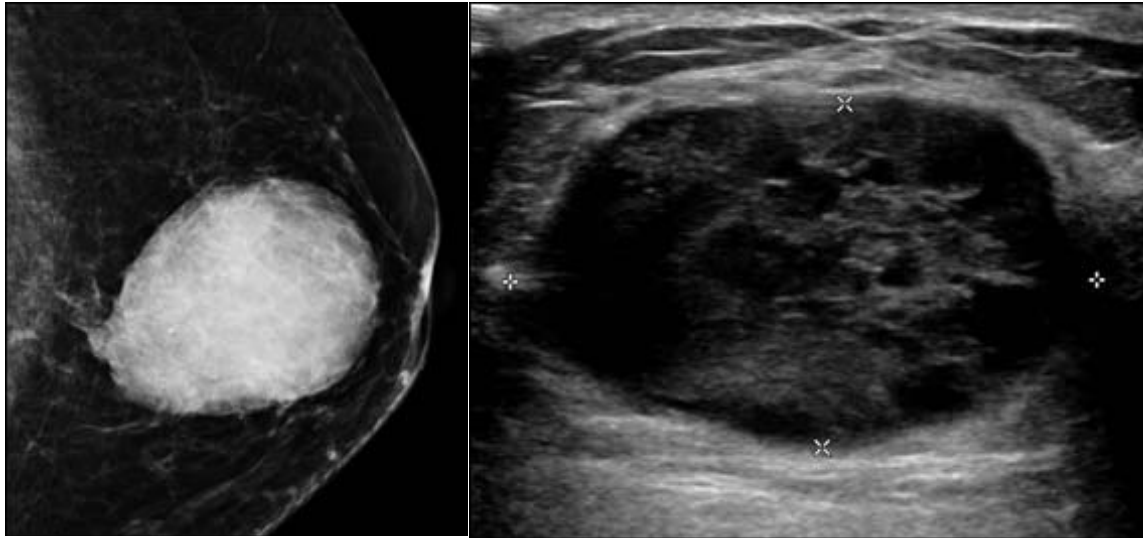
Figure 4. A 66-year-old female presented with palpable mass. (Right) Mammography revealed a circumscribed hyperdense mass at central part of left breast. (Left) For sonography, this mass showed a circumscribed heterogeneous-echoic appearance. Mastectomy confirmed invasive papillary carcinoma.
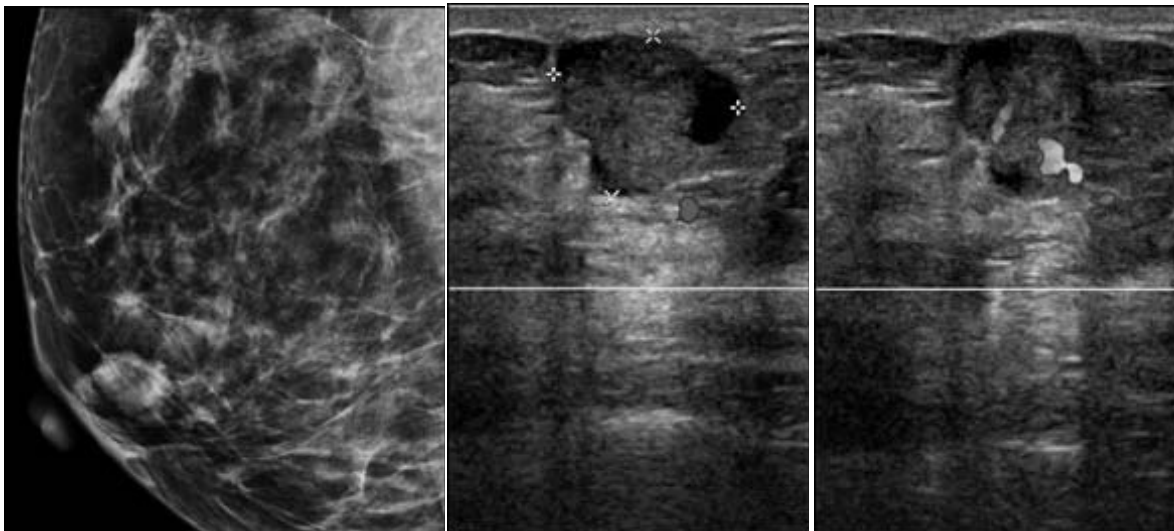

Figure 5. A 48-year-old female presented for check-up. (Right) Mammography revealed a circumscribed oval isodense mass at subareolar area of right breast. (Middle and left) As for sonography, this mass showed a complex cystic-solid echo, posterior enhancement and vascularity in solid component. Excision confirmed intraductal papilloma.

In our study, 19 of 89 benign papillary lesions demonstrated the common finding of intraductal papilloma - a solid nodule within a single dilated duct in the subareolar area. [9] However, benign papillary lesions which appeared as a mass in an extraductal location without adjacent duct dilatation may resemble malignant lesions, especially if the lesions show irregular shape, non-circumscribed margin or complex echo (Figure 6).
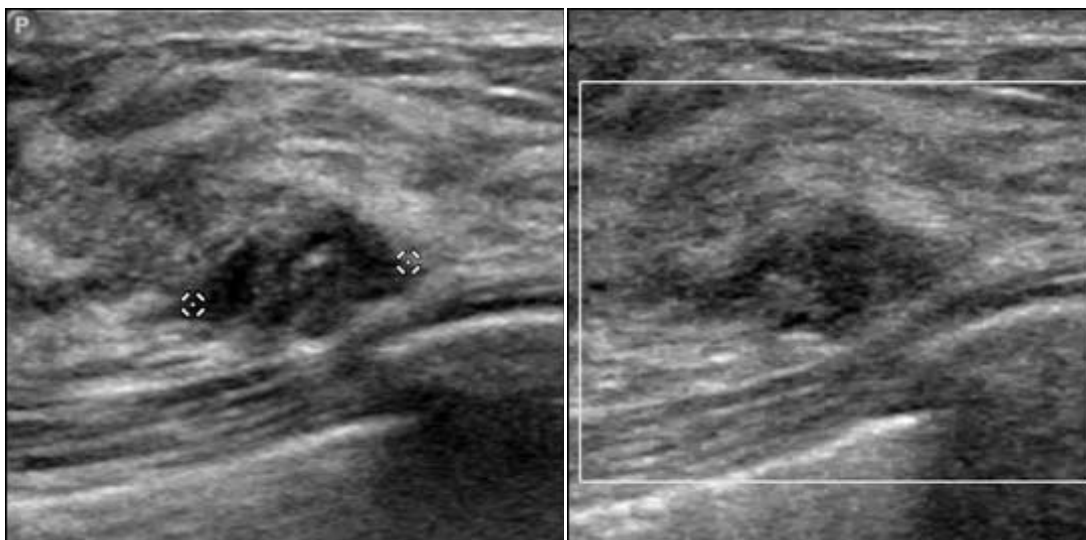
Figure 6. A 38-year-old female presented for check-up. (Right) Sonography showed a microlobulated hypoechoic mass at lower mid part of right breast. (Left) No intralesional vascularity is seen. Excision confirmed intraductal papilloma.

There has been a controversial papillary lesion treatment. Some have reported that benign papillary lesions diagnosed by using core needle biopsy should be excised because of a sufficient number of excisions revealed a histopathologic upgrade. [7, 15] On the contrary, other studies have concluded that when the histopathologic diagnosis is benign by using core needle biopsy and concordant with radiographic findings, the lesions could be safely followed by imaging instead of surgical excision. [1,16,17]

From our finding, radiographic features are significant indicative of malignant papillary lesions were: 1) on mammography - an irregular shape, non-circumscribed margin, high density of mass and presence of suspicious calcification; and, 2) on sonography -an irregular shape, complex or heterogeneous echo, vascularity of mass and presence of suspicious calcification. Combining the interpretation of both mammography and sonography, the sensitivity of 97.7%, specificity of 36%, a PPV of 43%, and an NPV of 97%. With a high NPV, our results supported the conservative treatment of the benign papillary lesions diagnosed by using core needle biopsy and concordant with radiographic findings that these lesions could be followed by imaging.

There were a few limitations in our study, however. Firstly, our sample size was small, i.e., only 132 patients with 133 lesions passed our inclusion criteria. A further research with a larger sample size is therefore needed. Another limitation is that our study was a retrospective interpretation, especially for sonographic findings. Therefore, some sonographic features were not evaluated in the examinations.

Conclusion

Although there were some overlaps of radiographic features between benign and malignant papillary lesions; we found that features such as characteristics of mass on mammography, complex

or heterogeneous echo and intralesional vascularity on sonography were significantly indicative of malignant papillary lesions and gave high sensitivity and NPV. In the future, if histopathologic diagnosis of the papillary lesions is benign on core-needle biopsy and concordant with benign radiographic findings, conservative management with follow-up imaging instead of surgical excision may be considered.

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