Preoperative prediction of margin requirement following a core biopsy result suggestive of a phyllodes tumour

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Introduction

Phyllodes tumour is a rare fibroepithelial breast tumour which arises from the periductal stroma of the breast, it accounts for less than 1% of all primary breast tumours. (1,2) They can occur at any age but are most frequent in the fourth decade with earlier onset in those of Asian origin.(3,4) Phyllodes tumours can be divided into benign, borderline and malignant subtypes, depending on histological parameters such as nature of tumour borders, degree of stromal cellularity and atypia, mitotic count and stromal overgrowth. (5,6) Fibroadenoma is a very common fibroepithelial tumour which shares some characteristics with phyllodes tumour, but has a younger age distribution.(1) Differentiating between phyllodes and fibroadenoma tumours is difficult as clinical, radiological and histopathologic appearance may mimic each other with a definitive diagnosis only being made after microscopic analysis of the entire excised lesion.(1) Despite their similarities, fibroadenomas are benign and are managed either conservatively or by enucleation without surgical margins while phyllodes tumours require excision with clear margins to avoid recurrence particularly in the borderline and malignant subtypes. (7–11) Accurate identification pre-operatively is critical for appropriate surgical planning to avoid complications from overtreatment or inadequate excision.(10)

Imaging modalities used in the assessment of breast disease include mammography, ultrasound and Magnetic Resonance Imaging (MRI). Ultrasound elastography is the most recent imaging modality employed in differentiating between malignant and benign lesions by assessing the stiffness within lesions which has proved an accessory tool in assessing breast masses.(1) Studies evaluating the use of MRI suggests that both phyllodes and fibroadenoma show similar findings.(12) Immunohistochemical markers have been

suggested to increase accuracy in distinguishing between fibroepithelial tumours but histology remains the gold standard.(8,13)

Recent guidelines suggest benign phyllodes tumours do not need excision with margins but borderline and malignant phyllodes require excision with a clear margin to reduce the risk of local recurrence and potential distant metastases.(14) However, core biopsy cannot reliably differentiate between fibroadenomas and phyllodes tumour subtypes, which can be explained pathologically due their heterogeneity.(15) As such, it can be difficult for the surgeon to predict whether a margin is required or not from the preoperative information. If a more accurate prediction of the likely nature of the lesion as fibroadenoma or benign phyllodes versus borderline or malignant phyllodes were available, this could reduce unnecessary margin excision and cosmetic compromise, or avoid second operations to achieve clear margins.

Previous studies have compared the imaging features of fibroadenomas and phyllodes tumours (1,16,17) but none has compared the imaging features of those lesions requiring excision with a margin and those which do not.(18) In this study, we aimed to identify ultrasound and mammographic features associated with borderline and malignant phyllodes versus benign phyllodes and fibroadenomas to aid surgical planning.

Methodology

A prospective database of consecutive ultrasound visible masses was used to identify lesions with a core biopsy suggestive of a phyllodes tumour in a single unit between May 2010 and January 2019. Masses with an ultrasound core biopsy result of B3, raising the possibility of a phyllodes tumour were included.

The breast ultrasound features assessed were: mass shape and size; orientation; margin definition; presence of macro-lobulations and micro-lobulations; echogenicity; cystic spaces; echogenic clefts; skin involvement; surrounding oedema; Breast Imaging Reporting And Data System (BIRADS) score(19); posterior features and vascularity. BIRADS score allows

for unambiguous reporting of breast imaging and is graded from incomplete to proven malignancy, with scores of 0 to 6 respectively. For this study, only lesions with a BIRADS score of at least 3 were included.

Mammographic features assessed included presence of a mass; calcification; margin definition and BIRADS score. Breast density was assessed using the BIRADS classification(19) and a Visual Analogue Scale (VAS). (20) Breast density or composition, was assessed in terms of the proportion of fibroglandular tissue with the least dense breast graded as BIRADS density ‘a’ and the most dense graded as BIRADS density ‘d’. In addition, a 10cm visual analogue scale presented on paper sheets was used, with the approximate percentage of dense breast tissue marked with the right side of line marking 100% density and the left marking 0% density. Inter-rater agreement was achieved via discussion.

Excision surgical pathology was recorded, and lesions were classified, using definitions described earlier (5,6) as a benign phyllodes/ fibroadenoma or as a borderline/malignant phyllodes if a margin was required. Ultrasound and mammographic features in these 2 groups were compared. Statistical analysis used Chi-square, Fisher’s exact test and receiver-operating curve (ROC).

Attention was paid to features previously described to be suggestive of a phyllodes tumour. Imaging features were carried out by an experienced consultant radiologist who was blinded to the final pathology outcomes. For our study, benign phyllodes and fibroadenoma were grouped as not needing a margin whereas borderline and malignant phyllodes were grouped as needing a margin.(8,14)

Results

31 patients with 31 lesions meeting the inclusion criteria were identified. Of these, 6 lesions were screen-detected, all of which were benign, and 25 were symptomatic. There were 13 lesions requiring a margin (6 malignant, 7 borderline) and 18 benign lesions not requiring a

margin (13 benign phyllodes, 4 fibroadenoma and 1 other). The average age of study patients was 53 years old, (range 22- 84 years). 25 patients had mammograms performed, with the lesion being mammographically occult in 3, leaving 22 to be included in analysis. All 31 patients had a breast ultrasound.

Table 1. Categorical ultrasound features assessed in borderline/malignant phyllodes and fibroadenoma/benign phyllodes.

Table 2. Categorical mammographic features assessed in borderline/malignant phyllodes and fibroadenoma/benign phyllodes.

The following ultrasound features were found significantly more frequently in those lesions that were borderline/malignant phyllodes as shown in table 1; an irregular margin [8/13 (62%) vs 3/18 (17%) p= 0.01], presence of micro-lobulations [7/13 (54%) vs 3/18 (17%) p = 0.028], mixed echogenicity [9/13 (69%) vs 1/18 (6%) p = 0.0002], echogenic clefts [6/13 (46%) vs 1/18 (6%) p = 0.007), BIRADS score of more than 3 [11/13 (85%) vs 9/18 (50%) p=0.047], posterior enhancement (9/11 (82%) vs 6/18 (33%) p=0.01].

Large ultrasound size was significantly associated with borderline and malignant phyllodes tumours with an area under the curve (AUC) of 0.76, p=0.003 as shown in figure 1.

Stiffness at shock wave elastography (SWE) was also associated with borderline and malignant phyllodes, AUC 0.71, p=0.026 as shown in figure 2.

On mammography, fibroadenoma and benign phyllodes tumours had well-defined margins compared to the borderline/ malignant Phyllodes tumours [7/9 (78%) vs 4/13 (31%), p=0.04] as shown in table 2. No other mammographic features were statistically significant.

Mode of presentation was a significant factor with symptomatic lesions being more likely to require a margin than screen-detected lesions [13/13 (100%) vs 6/18 (33%) p=0.005], respectively.

Discussion

In this study, we have identified multiple pre-operative features that are significantly different between lesions requiring a margin and those that do not. In this study we grouped benign phyllodes and fibroadenoma as lesions not needing a margin and borderline and malignant phyllodes as lesions needing a margin. A previous study found that although differentiating between fibroadenomas and phyllodes tumours is difficult even for pathologists specialised in breast pathology, there is a inter-rater agreement when fibroadenomas and benign phyllodes are distinguished from malignant and borderline subtypes. (8)

This study shows that there are a number of pre-operative differentiating features between fibroadenoma and benign phyllodes versus borderline and malignant phyllodes found on ultrasound. The features suggesting borderline and malignant phyllodes, and thus the need for a surgical excision with margin include an irregular shape, micro-lobulations, high echogenicity, BIRADS score > 3, distal enhancement, large size and stiffness on SWE. In addition, a mammographic poorly-defined margin and symptomatic presentation suggest the need for a margin at excision.

We found increasing size to be a significant factor in predicting the need for a surgical margin. This is in agreement with a previous study which found that mean lesion size increased when comparing benign, borderline and malignant phyllodes tumours.(18) However, this study did not include any fibroadenomas.

As the number of differentiating factors shown is high, a multivariate analysis to find those with independent significance would be helpful. Unfortunately, our dataset is too small for multivariate analysis to be performed.

The lack of a radiological, well-defined margin in borderline and malignant phyllodes mirrors the pathological findings of infiltrative margins and stromal overgrowth in such tumours. (21) The posterior enhancement may reflect the desmoplastic growth of tumour stromal cells in

borderline and malignant lesions as it is known that posterior enhancement is found more frequently in high grade invasive cancers than low grade. (22)

Micro-lobulations are probably a reflection of an infiltrative margin as they are common features of an invasive cancer but uncommon in fibroadenomas. When found in fibroadenomas, they are thought to be due to hyalinisation or infarction leading to fibrous changes that increase the stromal component.(23) The high ultrasound BIRADS score in the borderline and malignant phyllodes is likely to reflect both infiltrative margins and the increased heterogeneity seen in these lesions.

Increased stiffness in invasive breast cancer has been shown to reflect active tumour stromal interaction.(24) Although tumour stromal interaction in malignant phyllodes is not well understood, it is possible that increased stiffness at shear wave elastography reflects activated tumour associated fibroblasts and the production of stiff collagen.(25,26) Stiffness on shear wave elastography may also reflect the increased cellularity of the stroma in phyllodes tumour compared to fibroadenoma.(1)

Although the number of screening-detected lesions in the study is small, it is striking that they were all benign phyllodes or fibroadenomas. The reason for this is not clear but may reflect their small size and impalpability.

Although peri-lesional oedema was not found to be a significant feature in our study, some studies(16,27) have found that rapidly growing tumours have surrounding interstitial oedema due to the compressed lymphatics or mammary ducts best seen on T2-weighted MRI images. Patients in this study did not routinely undergo MRI and, as such, this could not be studied in this cohort.

The small sample size from a single centre is the largest limitation in this study. Further studies should aim to include more cases from multiple centres. A larger sample size would enable multivariate analysis to identify independent factors. In addition, there were not enough MRI scans for this modality to be evaluated.

Conclusion

We have identified multiple ultrasound and mammographic features that may be used to guide surgeons' decisions regarding the use of a margin when excising lesions suggestive of a phyllodes tumour. Due to our small sample size, further studies involving larger numbers are required to validate our results.

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Figure 1: Receiver Operating Curve showing the association between ultrasound size of the lesion and borderline and malignant phyllodes tumour subtypes.

Figure 2: Receiver operating curve (ROC) showing the association between stiffness of the lesion and borderline and malignant phyllodes tumour subtypes.

Table 1: *Categorical ultrasound features assessed in borderline/malignant phyllodes and fibroadenoma/benign phyllodes.*

Lesion characteristics	**Borderline/malignant phyllodes (%)**	**Fibroadenoma*l* benign phyllodes (%)**	**p-value**
Mass shape			
Oval and round	5/13 (38)	15/18 (83)	0.01
Irregular	8/13 (62)	3/18 (17)	

Orientation[1] *Taller than wide* *Not taller than wide*	 0 12/12 (100)	 0 18/18 (100)	 >0.05
Margin *Well-defined* *Poorly defined, mixed*	 6/13 (46) 7/13 (54)	 12/18 (67) 6/18 (33)	 >0.05
Micro-lobulations *Yes* *No*	 7/13 (54) 6/13 (46)	 3/18 (17) 15/18 (83)	 0.028
Macro-lobulations *Yes* *No*	 9/13 (69) 4/13 (31)	 7/18 (39) 11/18 (61)	 >0.05
Echogenicity *Hypodense* *Mixed*	 4/13 (31) 9/13 (69)	 17/18 (94) 1/18 (6)	 0.002
Cystic spaces *Yes* *No*	 5/13 (38) 8/13 (62)	 2/18 (11) 16/18 (89)	 >0.05
Echogenic clefts			

[1] One lesion could not be assessed as it was too large to accurately determine the orientation.

Yes *No*	6/13 (46) 7/13 (54)	1/18 (6) 17/18 (94)	0.007
Skin changes *Yes* *No*	 2/13 (15) 11/13 (85)	 1/18 (6) 17/18 (94)	 > 0.05
Bright surrounding fat/oedema[2] *Yes* *No*	 1/12 (8) 11/12 (92)	 0 18/18 (100)	 >0.05
BIRADS score *3* *4a, 4b, 4c and 5*	 2/13 (15) 11/13 (85)	 9/18 (50) 9/18 (50)	 0.047
Posterior features *None, shadowing* *Enhancement*	 2/11 (18) 9/11 (82)	 12/18(67) 6/18 (33)	 0.01
Vascularity Penetrating vessels[3] *Yes* *No*	 9/11 (82) 2/11 (18)	 6/9 (67) 3/9 (33)	 >0.05

[2] One lesion was unassesable.
[3] Two lesions were unassesable.

Surrounding vessels[4] *Yes* *No*	 7/9 (78) 2/9 (22)	 7/9 (78) 2/9 (22)	>0.05
Laterality *Left* *Right*	 7/13 (54) 6/13 (46)	 7/18 (39) 11/18 (61)	>0.05

Table 2: *Categorical mammographic features assessed in borderline/malignant phyllodes and fibroadenoma/benign phyllodes*.

Lesion characteristics	**Borderline/malignant phyllodes (%)**	**Fibroadenoma/benign phyllodes (%)**	**p-value**
Presence of mass *Yes* *No*	 9/10 (90) 1/10 (10)	 13/15 (87) 2/15 (13)	>0.05
Calcification *Yes* *No*	 3/10 (30) 7/10 (70)	 3/15 (20) 12/15 (80)	>0.05
Margin[5] *Well defined*	 2/9 (22) 7/9 (78)	 9/13 (69) 4/13 (31)	0.04

[4] Two lesions were unassesable.
[5] 3 lesions were mammographically occult.

Poorly defined, mixed			
BIRADS density			
a-b	3/10 (30)	7/15 (47)	>0.05
c-d	7/10 (70)	8/15 (53)	
BIRADS score			
1-3	5/10 (50)	12/15 (80)	>0.05
4	5/10 (50)	3/15 (20)	

[1] 3 lesions were mammographically occult.