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

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1 **Keywords**

2 Phyllodes tumour, fibroadenoma, surgical excision, margin

3 **Introduction**

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

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

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

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

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

43 **Methodology**

44 A prospective database of consecutive ultrasound visible masses was used to identify
45 lesions with a core biopsy suggestive of a phyllodes tumour in a single unit between May
46 2010 and January 2019. Masses with an ultrasound core biopsy result of B3, raising the
47 possibility of a phyllodes tumour were included.

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

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

55 Mammographic features assessed included presence of a mass; calcification; margin
56 definition and BIRADS score. Breast density was assessed using the BIRADS
57 classification(19) and a Visual Analogue Scale (VAS). (20) Breast density or composition,
58 was assessed in terms of the proportion of fibroglandular tissue with the least dense breast
59 graded as BIRADS density 'a' and the most dense graded as BIRADS density 'd'. In
60 addition, a 10cm visual analogue scale presented on paper sheets was used, with the
61 approximate percentage of dense breast tissue marked with the right side of line marking
62 100% density and the left marking 0% density. Inter-rater agreement was achieved via
63 discussion.

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

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

74 **Results**

75 31 patients with 31 lesions meeting the inclusion criteria were identified. Of these, 6 lesions
76 were screen-detected, all of which were benign, and 25 were symptomatic. There were 13
77 lesions requiring a margin (6 malignant, 7 borderline) and 18 benign lesions not requiring a

78 margin (13 benign phyllodes, 4 fibroadenoma and 1 other). The average age of study
79 patients was 53 years old, (range 22- 84 years). 25 patients had mammograms performed,
80 with the lesion being mammographically occult in 3, leaving 22 to be included in analysis. All
81 31 patients had a breast ultrasound.

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

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

86 The following ultrasound features were found significantly more frequently in those lesions
87 that were borderline/malignant phyllodes as shown in table 1; an irregular margin [8/13
88 (62%) vs 3/18 (17%) $p=0.01$], presence of micro-lobulations [7/13 (54%) vs 3/18 (17%) $p=$
89 0.028], mixed echogenicity [9/13 (69%) vs 1/18 (6%) $p=0.0002$], echogenic clefts [6/13
90 (46%) vs 1/18 (6%) $p=0.007$], BIRADS score of more than 3 [11/13 (85%) vs 9/18 (50%)
91 $p=0.047$], posterior enhancement (9/11 (82%) vs 6/18 (33%) $p=0.01$].

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

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

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

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

102 **Discussion**

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

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

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

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

124 The lack of a radiological, well-defined margin in borderline and malignant phyllodes mirrors
125 the pathological findings of infiltrative margins and stromal overgrowth in such tumours. (21)

126 The posterior enhancement may reflect the desmoplastic growth of tumour stromal cells in

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

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

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

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

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

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

153 **Conclusion**

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

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236

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

239

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

242

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

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

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

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

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

² One lesion was unassessable.

³ Two lesions were unassessable.

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

245

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

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

⁴ Two lesions were unassessable.

⁵ 3 lesions were mammographically occult.

<i>Poorly defined, mixed</i>			
BIRADS density			
<i>a-b</i>	3/10 (30)	7/15 (47)	>0.05
<i>c-d</i>	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)	

248 ¹ 3 lesions were mammographically occult.
249