BREAST SURGERY

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Diagnosing phyllodes tumours of the breast: how successful are our current preoperative assessment modalities?

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assessment, biopsy, breast, mammography, phyllodes tumours, ultrasound.

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Abstract

Background: To assess the efficacy of the diagnostic modalities used in the preoperative assessment of phyllodes tumours.

Methods: In this retrospective study of patients treated at Princess Alexandra Hospital, 51 phyllodes tumours in 49 patients diagnosed between 2005 and 2016 were reviewed with regard to their preoperative findings to assess which modalities, including clinical findings, mammography, ultrasound, fine needle aspiration and core biopsy, were most diagnostically discriminating. Data on demographics and management were also collected.

Results: While 90.2% of lesions were clinically palpable and an abnormality was seen in 86.1% of lesions subjected to mammography, the findings in relation to these two modalities were essentially those of non-discriminatory masses. Furthermore, although 100% of the phyllodes lesions were sonographically visible, suspicion of a phyllodes tumour was only noted in 21.6% of cases. Fine needle aspiration yielded results suspicious for phyllodes in 21.1% of cases while core biopsy resulted in confirmed or suspected phyllodes tumour diagnoses in 69.2% of instances. Serial measurements of phyllodes tumours yielded an average growth rate of 8.04 mm per 365 days.

Conclusion: In the preoperative diagnosis of phyllodes tumours of the breast, ultrasound was a more discriminating imaging modality compared to mammography, and core biopsy demonstrated a superior accuracy of diagnosis over fine needle biopsy. A significant increase in lesion size over a short timeframe should also alert to the possibility of a phyllodes tumour.

Introduction

Phyllodes tumours of the breast are biphasic lesions composed of both stromal and epithelial components and they comprise 0.3–1% of all breast tumours and account for 2–3% of all fibroepithelial lesions.[1,2] They can occur at any age but are most commonly seen in women aged 35–55 years[2] (approximately 20 years later than fibroadenomas), although in Asian communities a younger age of presentation has been reported.[3]

Over the past 180 years or so, phyllodes tumours of the mammary gland have been described by more than 60 different synonyms. In 1838, Muller provided the first detailed description of this lesion which he termed *cystosarcoma phyllodes mammae,*[4] because of the overt leaf-like pattern of growth. In Muller's time the term 'sarcoma' implied only a fleshy tumour with no connotation of malignancy; however, it subsequently became apparent that both benign and malignant variants occurred. Histologically phyllodes tumours arise from the periductal stroma with only sparse lobular elements and they are characterized by increased cellularity of the stroma together with elongated epithelium-lined clefts.[5]

On the basis of the World Health Organization classification, phyllodes tumours are classified as either benign, borderline or malignant based on various features including tumour margins (pushing or infiltrating), stromal overgrowth, tumour necrosis, cellular atypia and the number of mitosis per high power field.[5] While phyllodes tumours of all grades have a tendency to recur, it is generally observed that benign phyllodes tumours can recur locally but do not metastasize, whereas borderline or malignant phyllodes can both recur locally and metastasize. Indeed local recurrences as high as 20% have been reported for benign lesions following surgical excision and for this reason wide local excision is recommended in the surgical management of all grades of phyllodes tumour.[6,7] Hence it is important to be able to make the preoperative diagnostic distinction between fibroadenoma and a phyllodes tumour as the

Table 1 Demographic details of total patient study group

	Total number of phyllodes tumours	Benign	Borderline	Malignant	*P*-value
Number of patients	49	31	13	5	
Age at diagnosis					0.858
Mean	43.8	40.0	50.3	50.4	
Median (range)	43 (17–67)	41 (17–58)	51 (36–67)	52 (40–61)	
Menopausal status					0.276
Premenopausal	34	24	7	3	
Perimenopausal	1	1	0	0	
Post-menopausal	14	6	6	2	
Parity (mean)	1.77	1.87	1.92	0.8	0.712
No. of children (mean)	1.71	1.81	1.83	0.8	0.771
Family history, % of patient with >1 first or second degree relative with breast cancer (%)	26.1	31.0	16.7	20	0.588

surgical management strategies for these two lesions are different. Whereas a fibroadenoma can be optionally managed by observation, close surgical excision/enucleation or even by a vacuum-assisted excision; by contrast phyllodes tumours need to be excised with a rim of uninvolved surrounding breast tissue, preferably in the order of 1 cm.[8]

However, readily achieving a preoperative diagnosis of phyllodes tumours continues to present a challenge as detailed in a number of recent studies showing the usual breast imaging modalities to have variable reported success rates but with core needle biopsy generally having better accuracy than fine needle aspiration biopsy.[8–10] Hence while triple assessment, that is, clinical features, radiological imaging and needle biopsy has proven to be successful in the assessment of most breast lesions, the efficacy of the components of this assessment process both individually and in combination would notionally seem to be less reliable in the diagnosis of phyllodes tumours.

The purpose of this study was to undertake a retrospective study of the efficacy of the various diagnostic modalities used to preoperatively assess phyllodes tumours in patients presenting with this condition in a large teaching hospital.

Methods

An electronic search was performed of the records of the Pathology Department at Princess Alexandra Hospital, Queensland, of breast biopsies reported with the diagnosis of phyllodes tumours in the period of 2005–2016. The pathology records were correlated with accessible medical records and the cases included in this study were those who had a diagnosis of a phyllodes tumour on a final surgical excisional biopsy. Data were extracted from the pathology records and medical records using a standard data template. Information collected included patient demographics, tumour characteristics including benign borderline or malignant grading, and the results of preoperative diagnostic investigations including clinical findings, the results of mammographic and ultrasound imaging, and the results of fine needle aspiration cytology and core biopsy. Interval size change for each tumour was recorded where serial ultrasound data was available.

Statistical significance was determined using analysis of variance and multinomial logistic regression for continuous and categorical data, respectively. Statistical significance was defined as a *P*-value less than 0.05. Analyses were performed using SPSS Statistics (IBM Corp., Armonk, NY, USA) and Excel (Microsoft, Redmond, WA, USA).

Results

There were a total of 51 phyllodes tumours identified in 49 patients in this study with two patients having two synchronous lesions in the same breast. There were 32 lesions recorded as benign phyllodes tumours, 13 were borderline lesions and six were malignant phyllodes tumours. The overall mean size of the tumours was 38.6 mm.

Patient demographics

Mean age of patients at diagnosis was 43.8 years. However, patients with benign phyllodes tumours tended to be younger with a mean age of 40.0 years where as borderline and malignant cases occurred in older women with mean ages of 50.3 and 50.4 years, respectively, although this age disparity did not reach significance ($P = 0.858$). Table 1 provides the median ranges for age in the different categories.

All patients in the series were female with 34 (69.4%) women being premenopausal, 14 (28.6%) being post-menopausal and one (2%) patient was perimenopausal.

Patients having benign and borderline lesions tend to have higher parity rates (1.87 and 1.92), respectively, compared to women with malignant phyllodes tumours whose mean parity rate was 0.8.

In this series, 26.1% of patients had a family history of breast cancer (first or secondary relative) although there was no significant difference between women with benign, borderline or malignant tumours.

Clinical findings

The majority of phyllodes tumours in this series were recorded as being clinically palpable (90.2%) but the degree of palpability ranged from 87.5% for benign lesions up to 100% for the six malignant tumours. However, although malignancy was suspected in these latter six cases, a specific diagnosis of phyllodes tumour type was not able to be established clinically.

Overall imaging outcomes

Mammography was performed in 35 of 49 patients which included 36 lesions. Of these 36 tumours, a non-specific mass lesion was identified in 31 instances (86.1%). However, phyllodes tumours were not suspected in any of these cases. For five lesions mammography was negative. The mean size of the lesions detected by mammography was 40.3 mm (Table S1).

Ultrasound was performed on all 51 phyllodes tumours, and in all cases a mass lesion was identified; however, a phyllodes tumour was suspected for only 11 lesions (21.6%) following ultrasound imaging. Often the appearance was that of a non-specific hypoechoic but solid lesion (Fig. S1).

Overall cytological and core histological diagnoses

Fine needle aspiration biopsy (FNAB) was performed on only 19 lesions (37.3% overall) and phyllodes tumour was suspected in four instances (21.1%) but with a further three lesions (15.8%) showing atypical cytological findings. A further nine FNABs were non-specific/benign (47.4%), while three results (15.8%) were non-diagnostic. Thus of the 19 lesions in which FNAB was performed, there were seven instances (36.9%) where either a phyllodes tumour was suspected or atypia was identified, thus prompting surgical excision (Table S2).

Core biopsy was performed on 39 lesions (76.5%). All core biopsies were performed using the standard technique without vacuum assistance. Phyllodes tumour was suspected in 12 (30.8%) lesions and actually diagnosed in 15 (38.4%) of the lesions biopsied. The remaining 12 lesions (30.8%) yielded non-specific or benign results.

In eight instances both FNAB and core biopsies were performed. Of these eight interventions, FNAB yielded seven non-specific/benign or non-diagnostic results. Subsequent core biopsies on the remaining seven lesions resulted in one phyllodes diagnosis, three phyllodes suspected and three non-specific/benign results. For one lesion only, phyllodes was suspected on both FNAB and core biopsy.

In one case, neither FNAB nor core biopsy was performed and surgical management was carried out based on clinical indications.

Results by subcategories: benign, borderline, malignant

Benign phyllodes tumours

A total of 32 benign phyllodes lesions were identified (62.7%). Of those benign phyllodes lesions on which imaging was performed, 84.2% were visible on mammography and all cases were visible on ultrasound with six lesions suspected of being of phyllodes tumours cases (18.8%). The mean size of benign phyllodes tumours was 31.0 mm and the median was 25.0 mm.

For those lesions that were subjected to FNAB, the result was non-specific/benign in 33.3%, non-diagnostic in 25%, atypical in 16.7% with phyllodes suspected in 25% of cases. Core biopsy findings were non-specific/benign in 37.5% of instances, suspicious of phyllodes tumour in 41.7% and diagnostic of phyllodes in 20.8%.

Borderline phyllodes

Of the 13 lesions identified, 11 underwent mammography and of these nine (81.8%) were visible. However, all lesions were visible on ultrasound with only two cases (15.4%) being suspected to be phyllodes. The mean size of borderline phyllodes tumours was 39.5 mm with a median of 30.0 mm.

In the five lesions that underwent FNAB, the result was non-specific/benign in 60%, atypical in 20%, with phyllodes suspected in 20% of instances. Core biopsy findings in this borderline group demonstrated a high degree of accuracy with 22.2% of lesions being suspicious for phyllodes and in 77.8% of lesions a diagnosis of phyllodes was made. There were no benign or non-specific diagnoses in this group.

Malignant phyllodes

Of the six malignant phyllodes lesions in this series, all tumours were visible on mammography but only as non-specific masses, and all were visible on ultrasound with suspicion of phyllodes in three cases. The mean size of malignant phyllodes was 77.3 mm with a median of 55.5 mm.

Of the two lesions that were subjected to FNAB, both offered non-specific/benign results. Core biopsy provided a diagnosis in three (50%) of the cases, with the remaining three resulting in non-specific/benign results.

Lesion size change

In this series there were nine lesions where it was possible to calculate serial ultrasound measurements to determine interval size change; five were benign phyllodes lesions and four were borderline phyllodes. The average size change extrapolated over 12 months (365 days) was 8.04 mm.

Multifocal lesions

Multifocality was observed in two patients, both of whom had two lesions and in both cases the lesions were located in the same breast. In one of the patients, the two lesions were malignant, with the tumours measuring 120 and 68 mm, while the other patient had two benign lesions measuring 50 and 135 mm.

Surgical management

The 31 benign cases were treated by wide local excision with no further re-excision being undertaken. While the 13 borderline lesions were all managed by means of wide local excision, three of these patients required a re-excision to improve margins. Of the five cases of malignancy four were ultimately treated by mastectomy, with one patient being managed with wide local excision only.

Discussion

The preoperative diagnoses of phyllodes tumours of the breast continue to represent a major challenge for both the surgeon and the pathologist. While our imaging and interventional techniques have improved significantly in recent years, the results of this study

demonstrate that significant limitations in our diagnostic acumen for phyllodes tumours remain, and re-affirm that diagnostic diligence with a high index of suspicion is required in the discovery and management of these lesions. The results of this study, which are consistent with some other recent reports, demonstrate that in the diagnosis of phyllodes tumours clinical assessment has limited value, ultrasound examination is superior to mammography but with a diagnostic sensitivity of only 21.6%; FNAB had a similar yield to ultrasound (21.1%), while core needle biopsy demonstrated the most superior diagnostic modality with a suspected or confirmed diagnoses in 69.2% of cases. The only other discriminating clinical diagnostic parameter identified in this study was a breast lesion size of >3 cm, and an interval increase in lesion size averaging 8 mm or greater over a 12-month period.

The importance of establishing a preoperative diagnosis of phyllodes tumours relates to their clinical behaviour and their subsequent recommended surgical management. While the clinical course of phyllodes tumours is somewhat unpredictable, some measure of predictability can be ascertained from the World Health Organization classification of phyllodes tumours[6] which recognizes benign, borderline and malignant categories based on the degree of stromal cellular atypia, mitotic activity, the degree of stromal overgrowth, tumour necrosis and margin appearance. These features do correlate with the risk of local recurrence and obviously in the case of malignancy there is also a risk of distant metastatic disease. Even benign and borderline phyllodes tumours are associated with a risk of local recurrence, with local recurrence rates of up to 20% being reported. It has also been recognized that recurrent lesions tend to be of a higher grade version than the original reported tumour with previous reports observing that recurrent tumours tended to show more aggressive features with a higher mitotic rate and greater degree of nuclear pleomorphism than the original lesions.[6,11] In a review of a series of 37 recurrent phyllodes tumours, Tan *et al.*[12] found that 19% developed a malignant recurrence from an initially benign or borderline tumour.

This knowledge further accentuates the importance of excising phyllodes tumours with an adequate margin, and several reports have confirmed that excision with a larger histological margin results in lower rates of recurrence.[13–15] It is therefore usually recommended that phyllodes lesions be excised with a local resection margin of at least 1 cm or greater. Histological identification of phyllodes tumour at excision margins is a strong predictor of local tumour recurrence, and where excision has been inadequate re-excision is advised. This unusual biological behaviour of phyllodes tumours is therefore an important driver for the achievement of a preoperative diagnosis of phyllodes, so that appropriate surgical intervention can be performed in the first instance with avoidance of the need for re-excision and to minimize the risk of recurrence. It is also important to establish or rule out the possibility of malignancy prior to undertaking surgical intervention, so that more appropriate and effective treatments can be planned preoperatively.

The results of our study suggest that apart from accessing interval size changes, breast imaging with mammography and ultrasound have their limitations in regard to diagnosing phyllodes tumours. However, ultrasound was shown to be of greater diagnostic value than mammography. All 51 lesions in this study were seen on ultrasound, and while 78.4% was seen as a non-specific mass, 21.6% were considered suspicious of phyllodes. However, of the 36 lesions for which mammography was performed, while a non-specific mass was noted in 86.1% of instances, the possibility of phyllodes tumour was not countenanced in any of these mammographic examinations, and 13.9% of the lesions were not seen at all. The imaging features which might herald the presence of a phyllodes tumour are a solid nodule with lobulated margins, a heterogeneous hypoechoeic texture, the presence of cystic spaces and the absence of microcalcification.[16] However, there remains substantial overlap in these sonographic features with a fibroadenoma. A recent report[17] has suggested that the combination of shear-wave elastography and colour Doppler may offer improved diagnostic accuracy over conventional ultrasound with the mean elasticity and maximum elasticity scores being significantly lower for fibroadenomas than for phyllodes tumours. In that study shear-wave elastography was reported to have a higher sensitivity, specificity and positive corrected value compared to standard B Mode ultrasound.

The role of magnetic resonance imaging (MRI) in differentiating fibroadenomas from phyllodes tumours is still undergoing review with recent reports indicating that the MRI characteristics of a phyllodes tumour might include increased enhancement, the presence of cystic spaces and the absence of internal septations.[18,19] Kamitani *et al.*[19] in a comparative study of the MRI features of fibroadenomas and phyllodes tumours found that the presence of a cystic component, strong lobulation and heterogeneity on delayed-phase contrast-enhanced T1W1 were more suggestive of phyllodes tumours. However, to date standard MRI would seem to have limited specificity in differentiating phyllodes tumours from fibroadenomas.

Analysis of needle biopsy interventions in our study has demonstrated a sensitivity for FNAB of only 21.1%, whereas core biopsy had a better success rate of 69.2%. These results are not too dissimilar from a report by Foxcroft *et al.*[9] which demonstrated a sensitivity for FNAB of 23% and for core biopsy of 65%. A recent report by Fashid *et al.*[20] which retrospectively analysed phyllodes tumours detected in a BreastScreen Australia service, also highlighted the lack of specificity of mammography in identifying phyllodes tumours, with fine needle aspiration biopsy indicating the presence of a fibro-epithelial lesion in only 21.7% of instances, and with core biopsy diagnosing or favouring phyllodes tumours in 62.5% of lesions. However, the sensitivity of core needle biopsy in diagnosing phyllodes tumours has varied greatly with some reports indicating a sensitivity as high as 83%[10] with other reports indicating an accuracy as low at 13.3%.[21] It would appear that diagnostic sensitivity is improved by combining the radiological and the cytohistological results in a similar way to the triple assessment strategy used for other breast lesions. In a study by Ward *et al.*,[22] the sensitivity of fine needle aspiration cytology, core needle biopsy and imaging for diagnosing phyllodes tumours was 40%, 63% and 65%, respectively, combining cytohistological and radiological tests improved sensitivity to 76%. There is promising evolving evidence for the use of vacuum-assisted biopsy (VAB)[23] in the management of phyllodes tumours with improved diagnostic outcomes, however, further studies on the role of VAB in this setting are required.

Being a retrospective study from a large institution teaching hospital, this study is subject to the usual limitations and biases associated with this type of retrospective review such as the difficulty of tracking all the appropriate records over the specified time period, and with the analyses being based on the recorded reports of radiological imaging which are often varied in their content and detail.

In conclusion, the preoperative diagnosis of phyllodes tumours of the breast continues to remain a somewhat elusive ambition with the findings of this report indicating that ultrasound is a more useful diagnostic tool than mammography and core needle biopsy is superior to fine needle aspiration biopsy. The importance of being able to diagnose phyllodes tumours preoperatively is related to the fact that this knowledge does impact on the type of surgical intervention to be undertaken, specifically in relation to the need to achieve clear margins of resection. The value of newer diagnostic modalities such as shear-wave elastography, MRI and VAB need to be further evaluated to determine if they can add value to the diagnostic process for this somewhat enigmatic tumour of the breast.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Non-specific hypoechoic ultrasound appearance of borderline phyllodes tumour in 24-year-old female right breast done at 12 O'clock.

Table S1. Mammographic and ultrasound imaging findings.

Table S2. Fine needle aspiration biopsy and core biopsy outcomes.