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Original Contribution

Phyllodes tumor of the breast clinical experience and outcomes: A retrospective cohort tertiary hospital experience

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ABSTRACT

Background: Phyllodes tumor (PT) accounts for <1% of all breast tumors worldwide. Based on their microscopic features, these tumors are classified into benign, borderline, and malignant. This study aimed at evaluating the clinical experience and the clinicopathologic features of PT.

Methods: A retrospective cohort study of 46 female patients with histologically diagnosed PT. Data collection and evaluation was done on patient demographics, preoperative radiological assessment and pathology, surgical procedure, post-surgery pathological evaluation, radiation therapy (RT), and follow-up.

Results: The median age at diagnosis was 42 years and young premenopausal patients (median age 35 years) had malignant PT. Forty-five patients underwent core needle biopsy (CNB) with high sensitivity and the positive predictive value (82.2% and 97.4% respectively). Thirty-nine patients (86.7%) underwent conservative surgery and 6 (13.3%) had a mastectomy. Twenty-seven (58.6%) were classified as benign, 11 (23.9%) as borderline and only 8 (17.4%) as malignant PT. Malignant PT had the greatest median tumor size (13 cm). Mortality and recurrence rates were 4.3% and 2.2% respectively. RT was administered in 6 patients (13.0%), 5 having malignant and 1 borderline PT. The metastatic rate was found to be 6.5%.

Conclusion: PT are rare breast tumors with variable biologic behavior and heterogenous clinicopathological findings. Young, premenopausal women with large tumors may have malignant PT with a risk of recurrence and metastasis. Core needle biopsy is a reliable tool for diagnosis of PT with strict follow-up recommended for large tumors diagnosed as fibroadenoma on CNB. Surgical management must ensure a tumor-free margin on excision to reduce recurrence.

1. Introduction

Phyllodes tumors (PT) are rare biphasic breast tumors of fibroepithelial origin. The name is derived from its leaf-like morphology under a microscope. PT accounts for less than 1% of all breast tumors worldwide with a mean patient age of 40 years and ranges from 9 to 85 years [1-3]. The most common presenting symptom is a painless breast lump that grows quickly within weeks or months. Diagnosing PT requires initial clinical evaluation followed by radiological assessment (mammogram and breast ultrasound).

Core needle biopsy (CNB) or tissue evaluation is essential for definitive diagnosis. The histological evaluation is crucial since PT and fibroadenomas can be difficult to differentiate clinically and by imaging alone, or even with a core biopsy on occasions [4]. PT can be classified as benign, borderline, or malignant, depending on the grading system of histological features developed by the World Health Organization in 2012 [5] and revised in 2019 [6]. The histological features include tumor border (well-circumscribed or permeative), stromal cellularity

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and stromal cellular atypia (mild, moderate or marked), mitosis per 10 high power field (<5, 5–9 or ≥10), stromal overgrowth (present or absent, or focal), and malignant heterologous elements (present or absent).

The standard treatment for PT as per the National Comprehensive Cancer Network (NCCN) is surgical excision with a wide safe margin of 1.0 cm or more of normal breast tissue around the lump, without axillary staging [7]. A wide margin excision is crucial since a narrow surgical margin is associated with a risk of local recurrence [7]. Simple mastectomy may be necessary whenever a wide margin cannot be obtained or the lump is very large in size, or are multiple [7,8]. The use of radiation therapy (RT) is not supported by data from randomized control trials but the NCCN suggests the use of RT in case of recurrence and high risk of morbidity [7]. The WHO reported a local recurrence rate of 21% (17% in benign, 25% in borderline, and 27% in malignant) [5]. Tumor grading is the main factor in the prognosis and survival of PT patients [1]. Lung and bone metastases are the most common possible metastatic sites and the cause of death in PT patients [5]. Furthermore, PT-related deaths are usually seen within 5 years of diagnosis [5].

The aim of this study was to explore and evaluate the clinicopathological features; histopathological diagnosis and the histological subtypes; radiological imaging findings; risk and prognostic factors; treatments and outcome; and complications in patients with PT at a tertiary hospital.

2. Methods

This is a retrospective study of patients with pathologically proven PT. Data collection began after receiving approval from the institutional review board (IRB) at our tertiary hospital in Riyadh, Saudi Arabia. The hospital information system database was searched to retrieve pathologically diagnosed PT patients between April 2009 and May 2020, and 46 patients were identified for inclusion in the study. For each patient, data was collected from hospital's electronic medical record (EMR) and patient files, including patient demographics, personal and family history, physical examination, preoperative radiological assessment and pathology, surgical procedure, post-surgery pathological evaluation, radiation therapy (RT), and follow-up data.

The pre-operative radiological assessment was obtained through ultrasonography and/or mammography, followed by core needle biopsy. Lumpectomy with a safe margin of 1.0 cm where possible or mastectomy was performed to reach a definitive diagnosis and for proper classification/grading as part of the post-surgical pathological evaluation. The WHO classification was used to classify the tumors into benign, borderline, and malignant [5]. The revised WHO guidelines published in 2019 updated the assessment of mitotic activity as number of mitotic figures per mm^2 along with per 10 high power fields (HPFs). According to the latest WHO classification, benign PT has <2.5 mitoses per mm^2 (<5 mitosis HPFs), borderline PT has 2.5 to <5 mitoses per mm^2 (5–9 mitosis HPFs), and malignant PT has ≥5 mitoses per mm^2 (≥10 mitosis HPFs) [6]. Postoperative management included RT for a number of patients and none of our patients received systemic therapy. Finally, follow-up data was recorded from the date of diagnosis up to the date of the last visit. Categorical data was presented as numbers and percentages while the numerical data was presented as median and range.

3. Results

Out of the 46 patients, 27 (58.6%) were classified as benign PT, 11 (23.9%) as borderline PT and only 8 (17.4%) as malignant PT (Fig. 1 illustrates histopathological features of benign, borderline and malignant PT). Forty-five patients received close follow up and one patient lost follow-up after CNB. The median follow-up was 33 months (range 1–115 months).

All the 46 patients were females with a median age at diagnosis of 42 years (ranging from 16 to 69 years). Borderline PT had the highest median age of 54 years (range 37–69 years) whereas younger patients with a median age of 35 years (range 23–41 years) had malignant PT. The age group of cases with benign PT was similar to the median age group of the entire sample (42.5 years). Only 5 patients (10.9%) had a positive family history for cancer, and all belonged to the benign PT group. Out of these 5 benign PT cases, only 1 patient had a positive family history for breast cancer. Twenty-two patients were premenopausal, 5 were perimenopausal, 10 were postmenopausal, and 9 did not have their menopausal status documented. Out of 8 malignant PT cases, 6 were premenopausal and 2 had unknown menopausal status. None of the post-menopausal cases had malignant PT and an equal number of these cases belonged to benign and borderline PT (5 cases each). Most of the premenopausal and perimenopausal cases were benign PT.

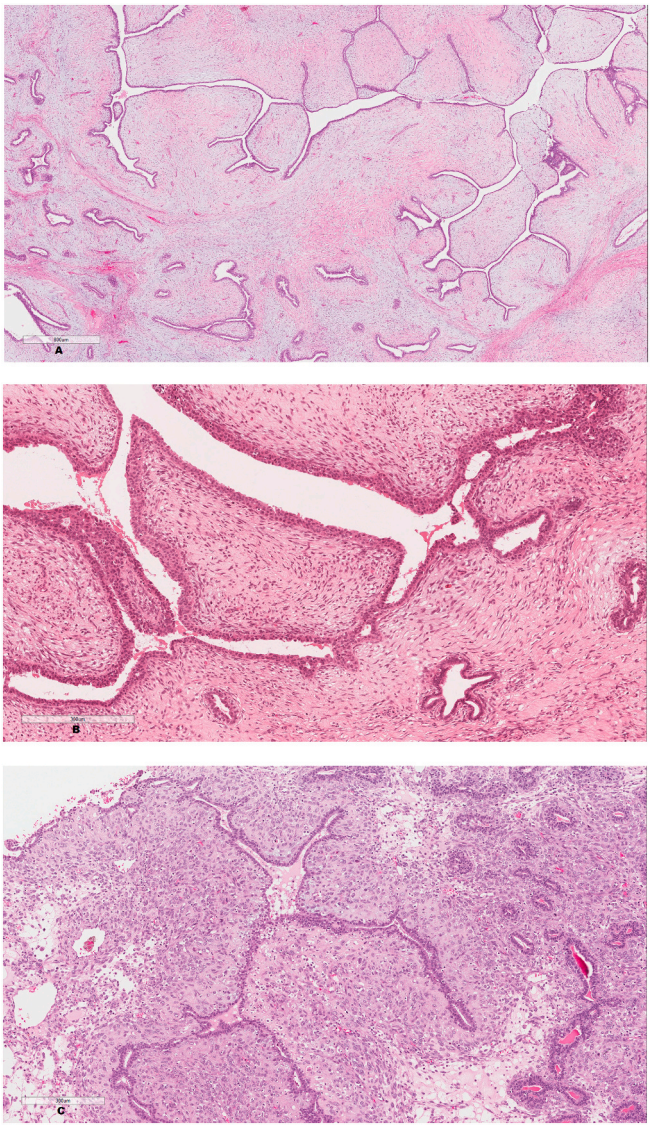

Fig. 1. Histopathological features of phyllodes tumor: A. Benign, B. Borderline, C. Malignant.

The demographic data of 46 cases diagnosed with Phyllodes tumor (PT) is summarized in Table 1.

Forty-five patients presented with symptomatic breast lump, and 1 patient was asymptomatic and diagnosed through breast cancer screening. Moreover, one patient had a bilateral tumor. Radiological evaluation by mammography revealed four tumors (8.5%) were BI-RADS 2, ten (21.3%) were BI-RADS 3, thirty-one (66.0%) were BI-RADS 4, and two (4.3%) were in BI-RADS 5 category (Fig. 2 illustrates

Table 1
Demographic data of 46 patients diagnosed with phyllodes tumor.

	All cases	Percentage out of total	Benign phyllodes (n)	Borderline phyllodes (n)	Malignant phyllodes (n)
Age (years)					
Median	42	–	42.5	54	35
Range	16–69	–	16–64	37–69	23–41
Family history of cancer (n)					
Yes	5	10.9%	5	0	0
No	41	89.1%	22	11	8
Total	46	100.00%	27	11	8
Family history of breast cancer (n)					
Yes	1	2.2%	1	0	0
No	45	97.8%	26	11	8
Total	46	100.00%	27	11	8
Menopausal status (n)					
Premenopausal	22	47.8%	12	4	6
Postmenopausal	10	21.7%	5	5	0
Perimenopausal	5	10.9%	4	1	0
Unknown	9	19.6%	6	1	2
Total	46	100%	27	11	8

mammogram of benign, borderline and malignant PT).

The histopathologic and surgical data is summarized in Table 2. Out of the 46 patients, 45 had CNB, and 1 patient had fine-needle aspiration (FNA) preoperatively. On CNB, 37 patients were diagnosed as PT, 6 as fibroadenoma, 1 as pseudoangiomatous stromal hyperplasia, and 1 as fibrocystic breast changes. The CNB sensitivity was 82.2% and the positive predictive value was 97.4%. For the one patient who had FNA, the lesion was diagnosed as fibroadenoma.

Forty-five patients underwent surgery, and one patient who was diagnosed on CNB as borderline PT never showed up thereafter. Initially, 40 had conservative surgery (88.9%) and 5 had a mastectomy (11.1%). After the initial surgery, 28 patients had positive surgical margins (62.2%), 27 of these underwent re-excision and 1 had a mastectomy. In total 39 patients (86.7%) underwent conservative surgery and re-excision, and 6 (13.3%) underwent a mastectomy. Mastectomy patients were equally distributed among the 3 subtypes, while the majority of the benign cases (92.6%) had conservative surgery.

The median tumor size of our PT cases was 6.5 cm (with a range of 0.8–30 cm). Malignant PT had the greatest median size followed by borderline and benign PT (13 cm, 7.5 cm and 4.5 cm respectively). One patient had a bilateral tumor and was among the 27 patients diagnosed histopathologically as benign PT.

Recurrence was observed in one patient (2.2%) who had a malignant tumor and underwent re-excision. Therefore, the risk for recurrence in our malignant PT was 12.5%. Forty-two patients were alive with no disease (93.3%), one was alive with disease (2.2%), and two died of the disease (4.3%). The 2 patients who died of the disease had distant metastasis, one had lung metastasis and the other had metastasis in lung, ovary, scalp and brain. Rate of distant metastasis was found to be 6.5% ($N = 3$).

Radiation therapy (RT) was administered to 6 patients (13.0%), one of which was borderline and five were malignant. All the five malignant patients who received radiation therapy had larger tumor sizes than the median and one of them experienced recurrence. The dose of RT was 60 Gy/30 fractions in four patients, one of whom was still under RT, and in two patients it was 50 Gy/25 fractions.

4. Discussion

Phyllodes tumors (PT) also known as Cystosarcoma Phyllodes, are a rare entity of breast tumors accounting for just 0.5% of the incidence of breast cancer [1,9]. What makes its diagnosis and management more challenging is its uncertain and heterogenous biologic behavior. Therefore, clinicians have heavily relied upon the reports from retrospective studies related to the behavior of this tumor to improve early diagnosis and use correct management strategies [2]. This study adds to the reported data, by exploring the clinicopathological characteristics, diagnostic accuracy, management options and outcome among 46 female patients diagnosed with PT at our tertiary hospital over a period of 11 years.

PT is more common among women between 35 and 55 years of age [10] with most of the cases aged between 25 and 49 years. In this study, the median age was 42 years (with a range from 16 to 69 years) which is in line with a similar study within the region, who reported a median age of 40 years [11]. Atalay et al. had a relatively younger cohort with a reported median age of 26 years [12], while the median age of 35 years has been reported by Kilic et al. and Ditsatham et al. [13,14]. Studies have also reported that it can affect younger women and adolescent girls [7]. In our cohort, only 2 cases were in that age group (16 and 18 years respectively) and both were classified as benign PT with variable pathological tumor size (1.6 and 6 cm respectively). On the other hand, the malignant PTs have been found to be associated with an older age group [15] but in our cohort, the median age for malignant PTs was just 35 years with the eldest being 41 years and youngest 23 years old. Whereas the median age for borderline PTs was comparatively much higher (54 years).

PTs mostly occur in females, but rare cases have been reported in men [8]. All 46 cases in our cohort were females, 47.8% ($N = 22$) of cases were premenopausal, which is in contrast with a much higher percentage of premenopausal cases of PT reported by other similar studies (80%, 93.3%, 81.2% and 88% respectively) [11,12,14,16]. In our study, half of the premenopausal patients had borderline and malignant PT and 75% of the malignant PT cases were premenopausal. This finding is in line with a study by Demian et al. who had a cohort with 97% of cases with borderline and malignant PT and 80% of these cases were premenopausal [11].

The mammographic assessment was performed for all 46 patients and only one of the patients had a bilateral tumor. Most of our cases ($N = 31$, 66.0%) were classified radiologically as BI-RADS 4 followed by 21.3% ($N = 10$) as BI-RADS 3. Despite many clinicopathological similarities with our cohort, contrary to our findings Demian et al. reported majority of their PTs were BI-RADS 3 (45.4%) followed by BI-RADS 4 (36.4%) [11]. In our cohort, 70% of cases belonged to BI-RADS 4 & 5 category and this may be one reason for a very high percentage of core needle biopsies and lumpectomy performed in our cohort.

Out of 45 patients who had a CNB, PT was diagnosed with accuracy in 37 patients (82.2%). Post-surgical biopsy specimen confirmed PT in all 45 patients, 82.2% of whom were previously diagnosed by CNB and 17.8% were missed. The CNB sensitivity in our cohort was quite high (82.2%), compared to what has been reported by Kilic et al. (77.8%) [14], Sawalhi et al. (70.0%) [16], and Lee et al. (72.0%) [17]. On the other hand, a comparatively much higher sensitivity of 99% has been

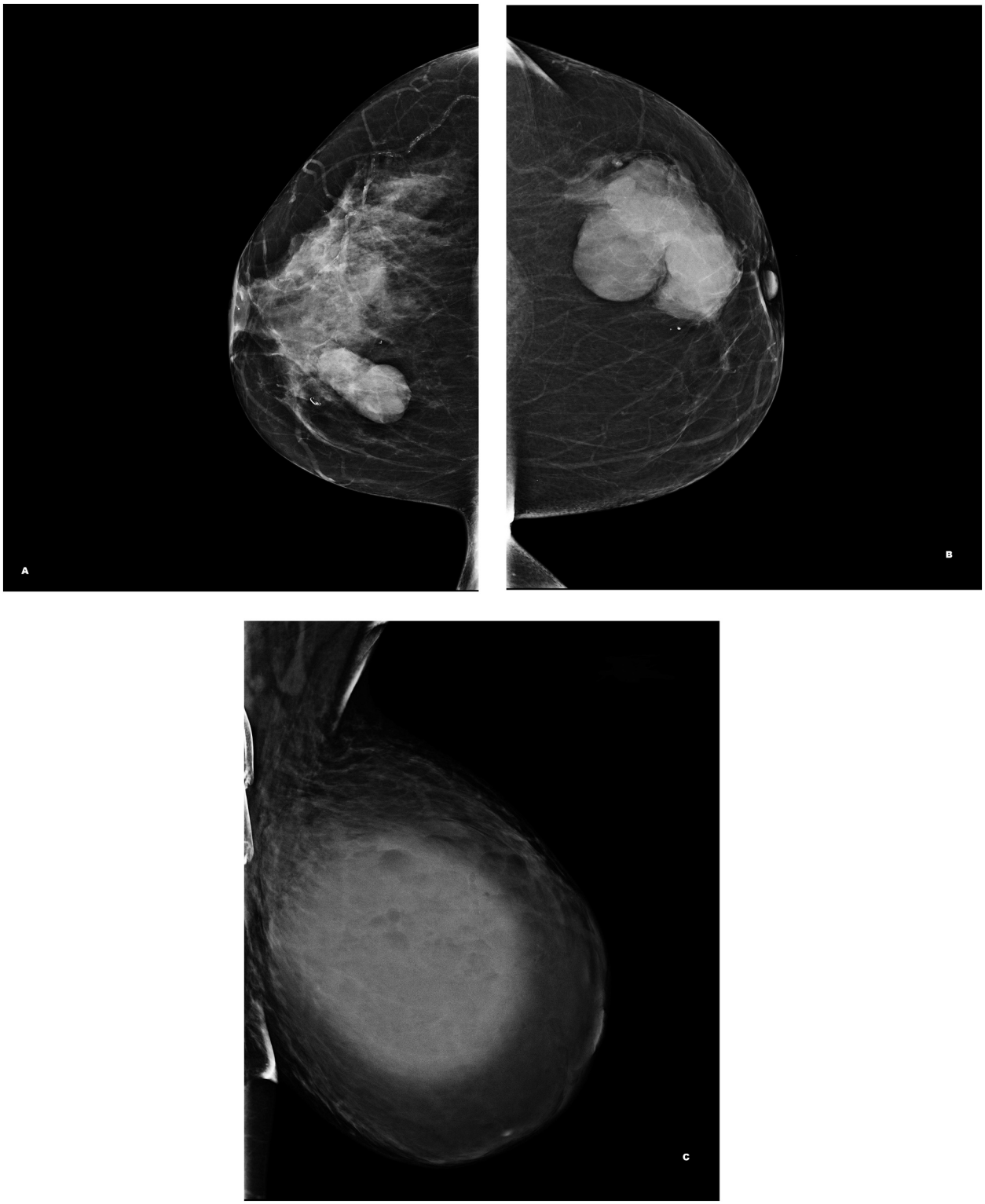

Fig. 2. Mammogram of phyllodes tumor: A. Benign, B. Borderline, C. Malignant.

reported by Komenaka et al. for the diagnosis of PT by CNB [18]. Only 1 patient in our cohort underwent FNA (Fine needle aspiration) as its role in the diagnosis of PT has been controversial with sensitivity rates reported to be as low as 63% [19]. Six cases of PT were wrongly diagnosed as fibroadenoma on CNB and 1 on FNA. Although CNB is more sensitive than FNA, still both are prone to miss the diagnosis between fibroadenoma and benign PT because of increased cellularity of stroma present in both. In line with this, in our cohort out of the 6 missed cases on CNB, 5 came out to be benign PT and 1 as borderline PT. Similarly, 1 case missed on FNAC was also proven to be benign PT on excisional biopsy. Correct differentiation of PT from fibroadenoma is a key target for better management and some studies have even reported the role of tumor markers like P53 and Ki67 in this as their expression is increased in PT and associated with poor prognosis [8].

In this study, based on surgical excision, benign phyllodes constituted 59.0% of the cases which are almost similar to the average

Table 2
Histopathologic and surgical data of 46 cases of phyllodes tumor.

	All cases	Percentage out of total	Classification based on post-surgical biopsy		
			Benign Phyllodes (n)	Borderline phyllodes (n)	Malignant phyllodes (n)
Core needle biopsy result					
Phyllodes tumor (PT)	37	80.4%	20	10	7
Fibroadenoma	6	13.0%	5	1	0
Pseudoangiomatous stromal hyperplasia	1	2.2%	0	0	1
Fibrocystic changes	1	2.2%	1	0	0
Fine needle aspiration					
Fibroadenoma	1	2.2%	1	0	0
Total	46	100%	27	11	8
Type of surgery					
Mastectomy	6	13.3%	2	2	2
Conservative	39	86.7%	25	8	6
Total	45	100.0%	27	10	8
Pathologic size (cm)					
Median	6.5	–	4.5	7.5	13
Range	0.8–30	–	0.8–27	1–15	7.5–30
Classification					
Benign	27	58.7%	–	–	–
Borderline	11	23.9%	–	–	–
Malignant	8	17.4%	–	–	–
Total	46	100.0%	–	–	–

percentage reported (35% to 75%) [4,8] but slightly lesser than what has been reported by Atalay et al. and Kilic et al. who found 70.0% and 70.8% PT to be benign [12,14]. On the other hand, the percentage of benign PT in our study is much higher than what has been reported by Sawalhi et al. who observed the benign subtype to be only 38% of the cases [16] and Demian et al. who reported only 1 benign tumor out of 35 (3%) patients, attributing it to the fact that surgeons adopted a wait and see approach for benign PT [11]. Among malignant phenotypes, we observed a slightly higher frequency (17.4%) than previously reported of 10% to 15% [4]. Ditsatham et al. reported a comparatively higher percentage of malignant PT (20%) in their cohort of 118 cases while their percentage of benign PT (62%) was almost like ours [13]. Most studies have reported the percentage of borderline PT to be between 12% and 25% of all PT cases, and our finding of 23.9% of borderline PT cases also strengthens these reports. In comparison with Ditsatham et al. our percentage of borderline PT was higher than what they reported (18%).

The median pathological tumor size in our patient cohort was 6.5 cm which was in line with the average size between 4 and 7 cm previously reported for PT [8,20]. It was highest for malignant tumors (13 cm) with the biggest tumor measuring 30 cm. Mallick et al. also reported a similar median size of 13.6 cm for their malignant PT [21]. Another interesting finding is that the biggest benign PT measured 27 cm. The bigger tumor size could be a reason for re-excision in 62.2% of cases and a relatively higher mastectomy rate (13.3%) as the tumor free margin could not be achieved.

Forty-five surgeries were performed and the rate of mastectomy in our cohort was 13.3%. Demian et al. reported a much higher percentage of mastectomy (57%) compared to our cohort [11]. On the other hand, our mastectomy rate was approximately 3 times higher than what has been reported by Atalay et al. (3.3%) and Kilic et al. (4.2%) [12,14]. Ditsatham et al. reported the lowest mastectomy rate (0.9%) among similar studies [13]. One of the reasons for our mastectomy rate was higher compared to these studies may be because more than half of cases had a bigger tumor size, where the margins could not be cleared and surgeons have to perform a mastectomy.

After the initial surgery, we found 28 patients (62.2%) had a positive margin, 27 of whom underwent re-excision and 1 mastectomy. Ogunbiyi et al. found recurrence in 24 out of 64 patients (37.5%), only 11 underwent re-excision and further surgery to clear the margin [2]. In our cohort, the percentage of tumors where tumor-free margin could not be achieved ($N = 28$; 62.2%) is significantly higher than what is reported by Ogunbiyi et al. Out of these 28 patients, 5 had malignant PT, another 5 had borderline and 18 had benign PT. Because of the fact that approximately 36% of the cases with positive margins were tumors with median tumor size of 7.5 cm and greater and even benign PT had relatively larger tumor size to what has been reported, we speculate that this may be the reason for a high percentage of cases with positive surgical margins and associated re-excision and mastectomy. Demian et al. reported that 7 patients showed inadequate surgical margin, 4 of whom underwent wider excision and 3 underwent a mastectomy, which means 75% of the cases with positive margins underwent mastectomy compared to only 3.6% in our cohort [11]. This could be attributed to an advanced and professional surgical re-excision despite large tumor size and positive surgical margin after the initial surgery. Similarly, Atalay et al. reported only 1 patient (3.3%) where a tumor-free margin couldn't be achieved multiple times and eventually, she underwent a simple mastectomy [12]. Contrary to these findings, Kilic et al. found post-surgical positive margin in 3 patients only (6.2%), and none underwent mastectomy as 2 of underwent re-excision and reached a tumor-free surgical margin, and 1 patient refused to undergo surgery again [14].

Radiation Therapy (RT) is not a usual modality in the treatment of PT, and its role has been controversial due to the lack of data from randomized control trials. But NCCN still suggests using RT in high-risk cases [7]. In our study, six patients (13.0%) received radiation therapy. Three out these 6 patients underwent a mastectomy and 3 had surgical excision, 5 had positive surgical margins, and average tumor size was 12.5 cm for these 6 patients. Five of those six had malignant tumors, and one had a borderline tumor, highlighting the importance of RT in specifically malignant PT which are aggressive and big tumors with a high risk of metastasis. None of these patients treated with RT developed metastasis or recurrence. This confirms the earlier reported findings of the beneficial role of RT in malignant and aggressive tumors along with the surgical excision with safe margins. Findings of RT use reported by Demian et al. (11.5%), Atalay et al. (6.67%) and Kilic et al. (8.3%) are not too different to ours concerning the percentage of PT cases treated with RT and its dose [11,12,14]. Four patients received a dose of 60 Gy/30 fractions and 2 patients received 50 Gy/25 fractions. Demian et al. also used an RT dose of 60 Gy/30 fractions in 1 patient and a dose of 50 Gy/25 fractions in 2 patients.

Overall local recurrence was observed in 1 patient (2.2%), who was 41 years old, had a malignant PT, a tumor size of 7.5 cm and did a re-excision of the tumor. The overall recurrence rate of our study was lower than the recurrence reported in other studies (14–40%) [8,11,12,14]. Pezner et al. reported a high recurrence rate of 36% [22].

Similar to our finding, Ogunbiyi et al. also recorded recurrence in 1 patient only (1.9%) who in contrast had a benign PT with positive surgical margin and followed the policy of wait and see [2]. Ditsatham et al. also recorded a relatively lower recurrence rate of 4.9%, where 5 out of the total 9 recurrences occurred in benign PT patients [13]. In line with our findings, they also reported that age of <45 years, malignant phenotype and larger tumor size are risk factors for recurrence. Our findings are consistent with theirs and strengthen their recommendations.

In addition to this, in our study the distant metastasis developed in 3 patients (6.5%) who all had malignant tumors and median tumor size of 10 cm (Range 9–16 cm). This finding is in line with the already reported metastatic rate (10%) for the PT and the fact that larger tumor size is associated with metastasis in malignant PT [8]. Contrary to our findings, Sawalhi et al. reported a higher rate of metastasis (16%), but similar to our study all the cases were also malignant [16]. Mishra et al. reported that 25% of all malignant PT will eventually metastasize and in contrast with this our rate of metastasis in malignant PT is very high (37.5%) [8]. Demian et al. and Kilic et al. each recorded one patient with metastasis, 3%, and 2.08% respectively, in their studies [11,14] and metastatic rate in our study was almost 2 to 3 times higher than these.

The median follow-up duration in this cohort was 33 months, which is quite similar to what has been reported earlier by Abdalla et al. (39 months) [23]. On the other hand, the median follow-up in our study is about twice as much as reported by Atalay et al. (18 months) and about half of what has been reported by Powell et al. (60 months) [12,24]. Forty-two patients (91.3%) were alive with no disease, one (2.2%) was alive with disease. Furthermore, two patients (4.3%) died of disease due to advanced malignant tumor one with lung metastasis and the other with metastasis in lung, ovary, scalp and brain. Similar to our findings, Salvadori et al. reported two deaths (4.2%) due to pulmonary metastasis and the mortality rate was almost the same as in our cohort [3]. Abdalla et al. reported 10 deaths (12.6%) all of whom had developed distant metastasis and their mortality rate was 3 times higher than our cohort and what has been reported by Salvadori et al. [23].

In conclusion, PTs are rare breast tumors with variable biologic behavior and heterogenous radiological and clinical findings. Histopathological characteristics and classification drive the management plan. Young (<40 years), premenopausal women with large tumors (>7.5 cm) may have malignant PT. Core needle biopsy is a reliable tool for diagnosis of PT but has its inherited limitation, therefore strict follow-up is recommended for large breast tumors (more than 3.0 cm) diagnosed as fibroadenoma on CNB. Surgical management must ensure a tumor-free margin on excision. Local recurrence with clear and safe margin is rare but recurrence and metastasis may occur in large tumors of malignant subtype among younger women. An in-depth analysis into behavior of phyllodes tumors is still lacking, and more studies are required to explore this rare breast tumor.

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Declaration of competing interest

None.

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