Original Article

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Phyllodes Tumor of the Breast: Analysis of 48 Patients

Murat Özgür Kılıç, Serdar Gökay Terzioğlu, Betül Bozkurt, Gül Dağlar
Clinic of General Surgery, Numune Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: Phyllodes tumor (PT) is a rare biphasic breast neoplasm that accounts for less than 1% of all breast tumors. The aim of this study was to evaluate the clinicopathologic features, diagnostic difficulties, and therapeutic outcomes of patients with PT.

Materials and Methods: A total of 48 female patients who underwent surgery for PT were included in the study. Patient characteristics, clinicopathologic features of tumors, diagnostic findings, surgical outcomes, adjuvant therapies, and follow-up findings were retrospectively evaluated.

Results: The mean age of patients was 35 years. Painless breast mass was the most common (85.4%) presenting symptom. Total excision with at least 1 cm macroscopic clear margins was the most frequently performed (87.5%) surgery. Most patients (n=34, 70.8%) had benign PT; however, borderline and malignant tumors were found in 9 (18.8%) and 5 (10.4%) patients, respectively. During the mean follow-up period of approximately 30 months, local and distant recurrence was detected in three (6.3%) patients and one (2.1%) patient, respectively. Patients with malignant PT had larger tumors than those with benign and borderline PTs (p=0.010). No significant difference in other clinical, diagnostic, and pathologic characteristics was found between the groups.

Conclusion: PT can be easily confused with other breast masses such as fibroadenoma due to the non-specific clinical and radiologic findings. Surgical excision with at least 1 cm clear margins is of great importance to reduce the risk of local recurrence. However, recurrence can develop even after appropriate surgery, thus patients should be closely followed up after surgery.

Keywords: Breast, diagnosis, phyllodes tumor, treatment

Introduction

Phyllodes tumor (PT) is a rare breast neoplasm that accounts for less than 1% of all breast tumors (1). It was first described and named as "cystosarcoma phyllodes" in the 1800s due to its morphologic and histologic characteristics. However, its name was changed to PT by the World Health Organization in 1982 because most tumors have benign characteristics and this term did not clearly reflect the biologic behavior (2). PTs are biphasic tumors that comprise epithelial and mesenchymal components, and are classified into three categories, benign, borderline, and malignant, according to the mitotic activity, cellularity, stromal overgrowth, and the nature of the tumor margins (3, 4). Most PTs are benign, whereas malignant tumors comprise 10-25% of cases (1, 5). Surgery is the mainstay treatment; the major concern after surgical intervention is the high risk of local recurrence. Therefore, accurate preoperative diagnosis plays an important role in the management of these tumors, especially for those with borderline and malignant histopathology.

In this paper, we aimed to evaluate the clinicopathologic features, diagnostic difficulties, and therapeutic outcomes of patients with PT.

Materials and Methods

Patients

The medical records of 48 female patients who underwent surgery because of PT at Ankara Numune Training and Research Hospital between 2008 and 2015 were retrospectively evaluated. The patients' demographic data such as age, menopausal status, marital status, personal and family history of breast cancer, initial clinical findings, and duration of symptoms prior to diagnosis were recorded. This study was conducted

Address for Correspondence :
Murat Özgür Kılıç, e-mail: murat05ozgur@hotmail.com

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in accordance with the Helsinki Declaration. Informed consents of the patients were waived due to the retrospective nature of the study.

Diagnostic tests

A detailed breast examination that included the axillary region was routinely performed in all patients. Breast ultrasonography (US) was used in all patients, and mammography (MM) was performed in patients aged more than 35 years. The definitive diagnosis was based on fine-needle aspiration cytology (FNAC), core biopsy, or excisional biopsy with histopathologic confirmation.

Therapeutic approach and final histopathology

Total excision with at least 1 cm surgical margins and mastectomy were the surgical methods performed for the tumors. Patients who had positive surgical margins after the initial surgery underwent re-excision to obtain tumor-free margins.

Histopathologic types of PTs were classified into three categories: benign, borderline, and malignant, according to standard criteria previously reported (6) (Table 1). All resected specimens were also evaluated in terms of surgical margins and invasion of pectoral muscle.

Adjuvant therapies and follow-up period

All patients were discussed at local multidiciplinary oncology meetings. Adjuvant radiotherapy to the breast and tumor bed was administered to patients who underwent breast conserving surgery for malignant PT. In addition, patients who underwent mastectomy for malignant PT and had a high mitotic index received radiotherapy to the chest wall. A chemotherapy regimen containing doxorubicin and cyclophosphamide was also given to these patients.

All patients were evaluated at regular intervals during the follow-up period due to the high risk of local and/or distant metastasis. The type and time of recurrence was also recorded.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc.; Chicago, Illinois, USA) version 21 was used for statistical analysis. Descriptive analyses are presented as mean±SD/percentage for continuous variables and numbers/percentages for categorical variables. The Kruskal-Wallis test was used to compare continuous variables between three tumor groups. Categorical values were compared using the Chi-square test or Fisher's exact test. The patients were then classified as having benign, borderline/malignant PTs, and statistical analysis of these two groups was conducted using the Mann-Whitney U, Chi-square, and Fisher's exact tests. $P<0.05$ was considered statistically significant.

Results

A total of 48 female patients with a median age of 35 years (range, 18 to 58 years) were included in the study. The majority of patients (81.2%) were of reproductive age; only 18.8% of the patients were postmenopausal. No patients had a personal or family history of breast cancer. Painless breast mass was the most common (85.4%) presenting symptom. The median duration of symptoms prior to diagnosis was 4.5 months. All demographic and clinical characteristics of the patients are presented in Table 2.

US was the first-step imaging method in all patients, MG was performed in half (50%) of the patients owing to the limitation of age. Well-defined hypoechoic solid lesion (77.1%) was the most frequently reported sonographic finding. Similarly, well-circumscribed nodular

Table 1. Classification of PTs according to histopathologic features (6)

	Margin	Stromal atypia	Mitoses/10 HPF*	Stromal overgrowth
Benign	pushing	minimal	<5	absent
Borderline	pushing/ infiltrating	moderate	5-9	present
Malignant	pushing	severe	≥10	present

*HPF: high-power field

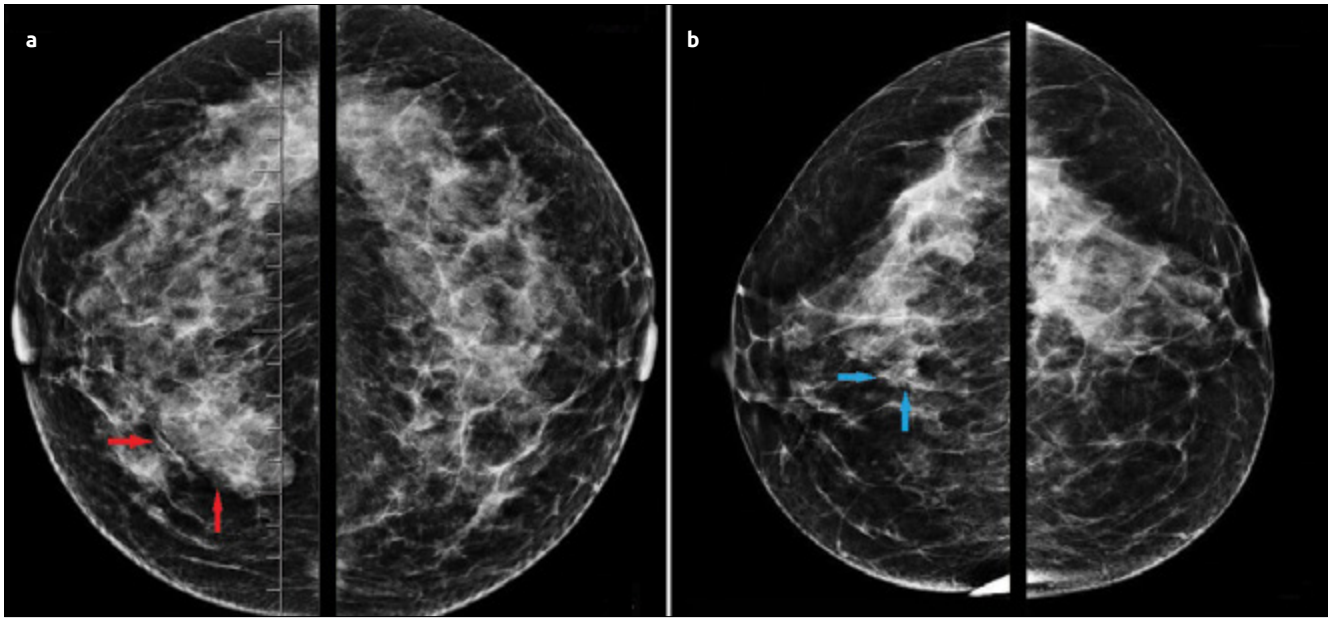

Figure 1. a, b. Mammographic images of PTs. (a) Benign PT: Well-defined nodulary opacity at the lower-inner quadrant of right breast (red arrows), (b) Poorly-defined lobulated nodulary opacity at the lower-inner quadrant of the right breast (blue arrows)

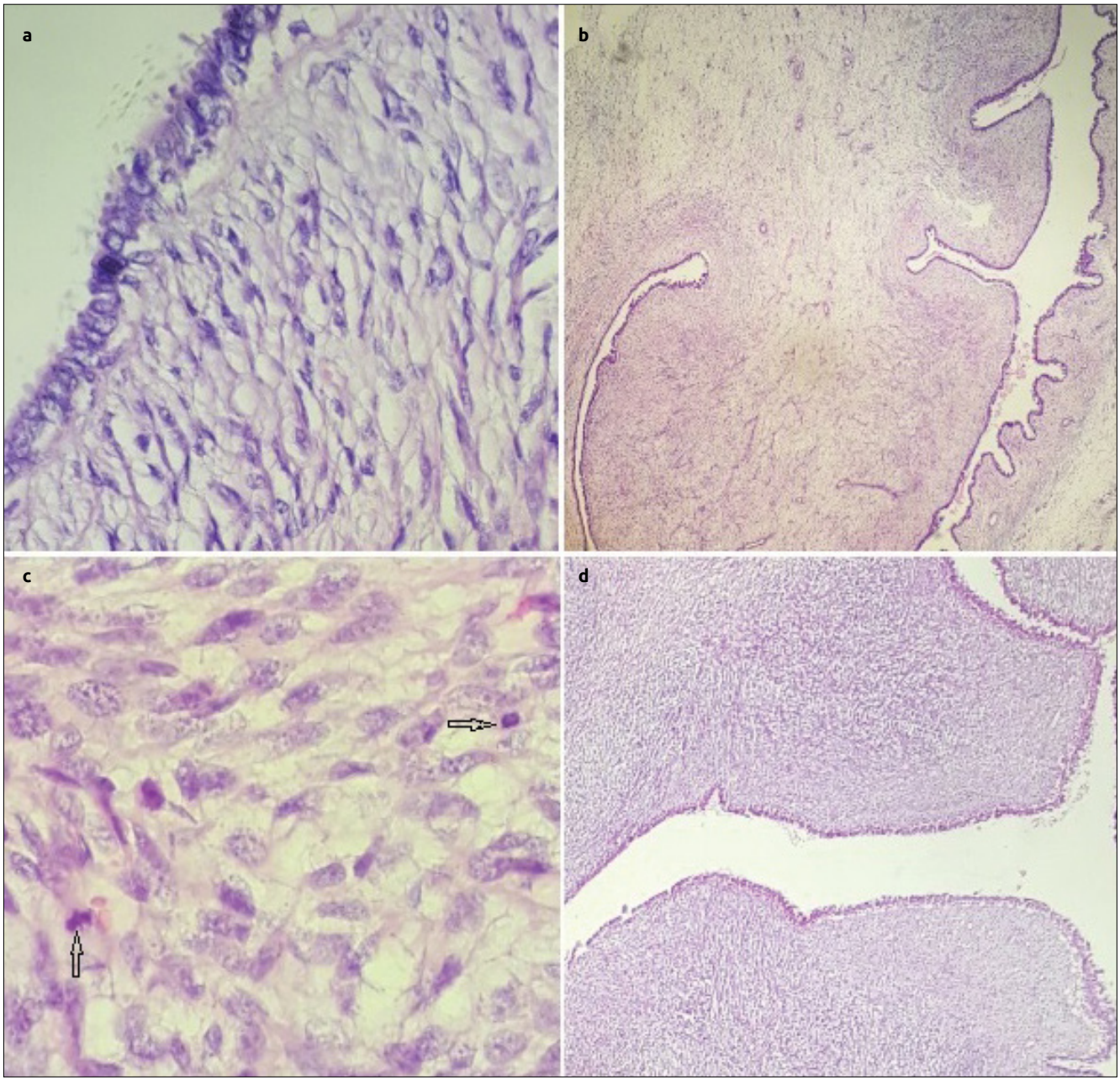

Figure 2. a-d. Microscopic illustrations of benign (a, b) and malignant (c, d) PTs. (a) Subepithelial proliferative stromal cells without nuclear atypia, (b) Leafy stromal fronds and surrounding proliferative epithelium, (c) Atypical stromal cells with pleomorphic enlarged nuclei and many scattered mitoses (arrows) (d) Atypical hypercellular stromal cells with stromal fronds

opacity was the most (33.3%) frequent radiologic finding in MG. All radiologic findings are presented in Table 3.

Histopathologic diagnoses, types of surgery, adjuvant therapies, and oncologic outcomes are summarized in Table 4. Core needle biopsy was the most commonly (n=27, 56.3%) used histopathologic diagnostic method, and suspicion of PT was reported in 21 (77.8%) patients. FNAC was only performed in two (4.2%) patients, one of which was benign, the other was non-diagnostic. The remaining 19 (39.6%) patients underwent excisional biopsy with normal surrounding tissue for both diagnosis and treatment of the masses.

Total excision with at least 1 cm macroscopic clear margins was the most frequent (87.5%) surgery. Although most patients (n=34, 70.8%) were diagnosed as having benign PT, borderline and malignant tumors were found in 9 (18.8%) and 5 (10.4%) patients, respectively. Mean tumor size was 38 mm (7-170 mm). During the mean follow-up time of 29.5 months, local and distant recurrence as detected in three (6.3%) patients and one (2.1%) patient, respectively. Local recurrence occured in patients with benign, borderline, and malignant PTs within the second year of surgery. A distant metastasis was detected the lung of a patient with malignant PT, 16 months after the operation.

Benign, borderline, and malignant PTs were statistically evaluated in terms of clinical, radiologic, and therapeutic characteristics. Malignant PT had a mean tumor size of 61.6 mm (47-90 mm), whereas benign and borderline PTs had a mean tumor size of 32.3 mm (7-170 mm) and 43.2 mm (17-150 mm), respectively. Tumor size was found statistically significantly different among the three histologic variants of PT (p= 0.010). However, other continuous parameters including age (p= 0.091)

Table 2. Basic demographic and clinical characteristics of the patients with PT (n=48)

Characteristics	n (%)
Age (years) (mean±SD)	35.06±12.1 y (18-58 y)
Menopausal status	
Premenopausal	39 (81.2%)
Postmenopausal	9 (18.8%)
Marital status	
Single	17 (35.4%)
Married	28 (58.3%)
Divorced/widowed	3 (6.3%)
Presenting symptom/sign	
Painless breast mass	41 (85.4%)
Painful breast mass	6 (12.5%)
Skin changes over the tumor	7 (14.6%)
Nipple discharge	1 (2.1%)
Incidental (during screening MG)	1 (2.1%)
Side of tumor	
Right	26 (54.2%)
Left	19 (39.6%)
Bilateral	3 (6.3%)
Location of tumor	
Upper-outer	28 (58.3%)
Retroareolar	10 (20.8%)
Other quadrants (total)	7 (14.7%)
More than one quadrants	3 (6.3%)
Duration of symptoms (median, 25-75% IQR)	4.5 mo (3-8 mo)

Age is presented as mean±SD, Duration of symptoms is presented as median (25-75% IQR), other variables are presented as n (%).

SD: standard deviation; MG: mammography; y: year; mo: month; IQR: Interquartile range

and duration of symptoms (p= 0.843) were similar between each tumor group. No statistical analyses of categorical parameters including menopausal and marital status, presenting symptoms, side and location of tumor, US and MG findings, or recurrence could be performed because of the small number of patients. Therefore, all patients were classified as having benign and borderline/malignant PTs to obtain better statistical results. No significant differences between these two groups were found in terms of those categorical parameters (p>0.05).

Discussion and Conclusion

PT is an uncommon breast neoplasm with considerable uncertainty about its biologic behaviour. These tumors usually occur in women aged 35-50 years; however, malignant PTs have a slightly older presentation than others (5-7). In our case series, 5 patients had malignant PT with an avarage age of 36 years; the mean age of patients with benign PT was 22 years.

Table 3. Sonographic and mammographic findings in patients with PT

Radiologic findings	n (%)
Ultrasonographic findings (n=48)	
Well-defined hypoechoic mass	37 (77.1%)
Lobulation	24 (50%)
Mass with irregular margins	11 (22.9%)
Heterogeneous internal echogenicity	6 (12.5%)
Axillary lymphadenopathy	6 (12.5%)
Increased vascularity in Doppler US	22 (45.8%)
Mammographic findings (n=24)	
Well-defined nodulary opacity	16 (66.6%)
Lobulation	7 (29.1%)
Asymmetric density	7 (29.1%)
Axillary lymphadenopathy	7 (29.1%)
Microcalcification	6 (25%)

US: ultrasonography

Table 4. Histopathologic diagnosis, surgical, and oncologic outcomes of the patients

Radiologic findings	n (%)
Type of histopathologic diagnosis	
Core needle biopsy	27 (56.3%)
Excisional biopsy	19 (39.6%)
FNAC	2 (4.2%)
Type of surgery	
Total excision with wide margins	46 (95.8%)
Mastectomy	2 (4.2%)
Re-excision after initial surgery	2 (4.2%)
Histopathologic tumor type	
Benign	34 (70.8%)
Borderline	9 (18.8%)
Malign	5 (10.4%)
Adjuvant radiotherapy	4 (8.3%)
Adjuvant chemotherapy	5 (10.4%)
Duration of follow-up	29.5±16.2 (8-59)
Recurrence	
Local	3 (6.3%)
Distance	1 (2.1%)

Duration of follow-up is presented as mean±SD (range); other variables are presented as n (%).

FNAC: fine needle aspiration cytology

Non-tender, sharply demarcated, and mobile breast lump is the most common clinical finding in patients with PT. Dilated breast veins can sometimes be observed through the underlying skin over the tumor. Although these tumors have an average size of 5 cm, lesions of up to 40 cm have been reported (8). The association between tumor size and malignancy is controversial; however, rapid growth may be detected in malignant tumors (5). In our study, the mean tumor size was 38 mm, consistent with previous studies, and the largest PT was 170 mm in diameter, which was diagnosed as benign PT. In addition, the mean size of malignant PTs was higher than that of the others, and the mean tumor sizes of benign, borderline, and malignant PTs were statistically significantly different. There are no clinical features to distinguish benign or malignant PT from other benign breast lesions. Enlarged axillary lymph node is also an infrequent clinical finding in PT. Similarly, a small number of patients in the present study had palpable axillary lymph nodes.

The upper outer quadrant of the breast is the most frequent location of PT, and both sides are often equally affected. Multifocality and bilaterality are seen infrequently (9, 10). In our study population, right breasts were affected slightly more than left breasts, and the most common tumor location was the upper outer quadrant. Additionally, both multifocality and bilaterality were found in a small number of patients, similar to previous reports.

In general, PT is difficult to diagnose using imaging methods due to the lack of specific radiologic characteristics. Radiologically, PT is often confused with fibroadenoma (FA), cysts, and well-circumscribed carcinoma. With US, the majority of PTs are described as well-defined hypoechoeic oval lesions surrounded by a capsule or pseudocapsule. Contrary to FAs, several sonographic findings including heterogeneous internal structure with irregular margins, septae, lobulation, and the absence of microcalcifications were reported to be associated with PT (11-13). In addition, increased intralesional vascularity with Doppler US is a frequent feature of these tumors. However, no specific color Doppler US finding was found to help differentiate PT from FA, or benign PTs from malignant (14). MG also has limited diagnostic value in differentiating PT and other benign breast lesions (12). In our study, US was used as the first-step imaging method in all patients, and MG was only performed in patients aged more than 35 years. The sonographic and mammographic findings were parallel to the literature; no specific radiologic feature was identified to differentiate the histologic subtypes of PTs. In addition, FA was the most commonly reported radiologic diagnosis with both US and MG, consistent with previous works (15-17). In recent years, several studies regarding the potential role of magnetic resonance imaging (MRI) in the diagnosis of PT have been published. However, no significant differences in MRI findings were found between benign PT and FA (18). MRI was not used in the diagnostic examinations of our patients.

FNAC, core needle biopsy, incisional and excisional biopsies were used in the preoperative histopathologic diagnosis of PT. Distinction of benign PT from cellular FA and malignant PT from spindle cell metaplastic carcinoma and primary breast sarcoma are the main problematic issues in the histopathologic evaluation (4). FNAC has quite low sensitivity due to the similarities with FA (19). Additionally, false-negative results can be obtained from FNAC when sampling is performed in an area of hypocellular stroma. PT can be histologically distinguished from FA by nuclear atypia, increased stromal cellularity, mitotic activity, and ratio of stroma to epithelium (20). Core needle biopsy is considered more reliable than FNAC in obtaining a correct diagnosis because it can provide specific histopathologic findings. However, its sensitivity was reported as approximately 65% in the definitive diagnosis of PT (21). Therefore, some surgeons advocate excisional biopsy for both diagnosis and surgical treatment of PTs. In our study, core needle biopsy was the most commonly used histopathologic diagnostic method, with an approximately 80% diagnostic accuracy for PT. Accordingly, in a study by Gatta et al. (14), core needle biopsy was found a valuable tool in the differential diagnosis of PT and FA, with high specifity and sensitivity rates. In our experience, core needle biopsy plays an important role in the preoperative histopathologic diagnosis of PTs. FNAC was only used in two patients, and excisional biopsy was preffered for PTs that were strongly considered as FA or another benign lesion in preoperative clinical and radiologic evaluations.

Wide surgical excision, generally defined as removal of tumor with at least 1 cm clear microscopic margins, is the primary treatment in PT (22). Mastectomy may be needed in patients with large malignant tumors or an inappropriate tumor-breast tissue ratio. In the present study, surgical excision with adequate surrounding tissue was the most commonly performed surgery, and mastectomy was needed in only two patients with large malignant tumors. Axillary dissection is not recommended as a routine surgical approach because PT mainly spreads via a hematogenous route and nodal involvement is extremely rare (23, 24). However, axillary dissection may be considered in patients with malignant PT who have axillary metastasis. In our study, axillary dissection was not performed in any patients due to the absence of axillary involvement both clinically and radiologically. Benign PTs with positive margins or less than 1 cm clear margin may not require re-excision; however, such patients should be closely followed up because of the local recurrence risk of up to 15% (23). On the other hand, it is mandatory to obtain at least 1 cm tumor-free margins in borderline and malignant PTs because the local recurrence rate was reported as 21% even when surgical borders were clear (25). The local recurrence rate in our study population was 5.3%, which was less than those reported in previous works. However, a recurrence rate of 6.3% was found in a recent study of approximately 500 patients with benign and borderline PTs, consistent with our results. An interesting result from that study was that wide excision margins of nonmalignant PTs were not found correlated with the development of local recurrence (26). In our study, re-excision after the initial surgery was performed in two patients with borderline PTs. Tumor-free surgical margins were achieved in all patients with borderline or malignant PTs. Three patients developed local recurrence during the follow-up periods, of whom one had malignant, one had borderline, and one had benign tumors. All recurrence occured within the 2nd and 3rd years of surgery, in agreement with the literature (5). The patient who had benign PT and developed local recurrence had a positive surgical margin after the initial operation. However, re-excision for positive margin was not performed the patient was unwilling to undergo surgery. The other two patients who developed local recurrence had undergone appropriate initial surgery with total removal of tumor and negative surgical margins. All three patients were premenopausal,aged under 50 years, and also had unifocal tumors of similar size. Re-excision with adequate surrounding tissue was performed for recurrent tumors of all patients. No further recurrence was observed in these three patients after re-excision during their mean follow-up periods of 1 year. Consequently, sufficient surgical margin is of great importance to minimize the risk of local recurrence. Distant metastasis can be seen in 10% of cases, which most often affects the lungs and bones (17). In our case series, distant metastasis was detected in only one patient with malignant PT, 16 months after surgery.

There is no global consensus on the role of adjuvant radiotherapy and chemotherapy in the management of PT (3, 24). However, application of radiotherapy to the breast after surgery for borderline and malignant PTs was shown to reduce the risk of local recurrence, without any significant survival benefit (27, 28). Therefore, adjuvant radiotherapy should be considered in patients with borderline and malignant PT on an indidualized basis (4, 5). Although there have been no randomized clinical trials on the role of systemic therapy in malignant PTs, various chemotherapy regimens containing doxorubicin, dacarbazine, cisplatin, iphosphamide, and etoposide are generally recommended for patients with malignant and/or metastatic disease. Adjuvant chemotherapy has no benefical effect on patient survival (1).

The 5-year overall-survival rates for benign and malignant PTs were reported to be approximately 90% and 80%, respectively (1). However, some authors reported lower survival rates for malignant tumors (29). In our study, no patients died during the mean follow-up period of 30 months.

In conclusion, PT has non-specific clinical and radiologic findings, and can easily be confused with other similar breast masses, particulary FA. Total excision with adequate clear margins is of great importance to reduce the risk of local recurrence. However, it should be always kept in mind that local recurrence can develop even after appropriate surgery for all histologic subtypes of PT. Therefore, these patients should be closely followed up at regular intervals after surgery.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

Author Contributions: Concept - M.Ö.K.; Design - M.Ö.K.; Supervision - M.Ö.K., S.G.T.; Materials - S.G.T., B.B., G.D.; Data Collection and/or Processing - S.G.T.; Analysis and/or Interpretation - M.Ö.K., G.D.; Literature Review - M.Ö.K.; Writing - M.Ö.K.; Critical Review - B.B., G.D.

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