








## Evaluation of the Clinicopathological Features of Patients with Phyllodes Tumor of the Breast: A Retrospective Study From a Single Center

### Memenin Filloides Tümörü Tanılı Hastalarda Klinikopatolojik Özelliklerin

#### Değerlendirilmesi: Tek Merkezli Retrospektif Çalışma

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#### ABSTRACT

**INTRODUCTION:** Phyllodes tumors are very rare neoplasms in the breast. It is classified into subgroups as benign, borderline and malignant phyllodes tumors. The aim of our study is to investigate the clinicopathological features of all patients with phyllodes tumor treated and followed in our clinic and to compare them with the data in the literature.

**METHODS:** The data of 36 patients who were operated for phyllodes breast tumor in our clinic between January 2009 and September 2021 were analyzed retrospectively. The patients were evaluated in terms of age, gender, side and quadrant localization of the mass in breast, radiological preliminary diagnosis, pathological diagnosis, tumor size, follow-up periods, recurrence and metastasis status.

**RESULTS:** 23 (63.9%) patients were diagnosed as benign, 5 (16.6%) patients with borderline and 7 (19.4%) patients with malignant phyllodes tumor. There was no statistically significant difference between the benign, borderline and malignant phyllodes tumor groups in terms of patient age, the quadrant in which the tumor was located, the type of surgery performed, the diameter of the tumor, the radiological diagnosis and the follow-up period ( $p>0.05$ ). When the exitus status was examined, it was observed that the exitus status was significantly higher in the malignant group ( $p<0.05$ ).

**DISCUSSION AND CONCLUSION:** Subgroups of the disease play an important role in the follow-up and treatment of patients with phyllodes tumor. After surgical treatment, recurrence, metastasis and exitus status in malignant phyllodes tumors are much more common than other phyllodes tumors. Complete surgical resection with clean surgical margins is the recommended treatment.

**Keywords:** phyllodes tumor, malignant, benign, borderline, breast tumor

#### ÖZ

**GİRİŞ ve AMAÇ:** Filloides tümörler memede çok nadir görülen neoplazmlardır. Benign, borderline ve malign filloides tümörü şeklinde alt gruplara sınıflandırılmıştır. Çalışmamızın amacı kliniğimizde takip ve tedavi edilen tüm filloides tümörlü hastaların klinikopatolojik özelliklerini incelemek ve literatürdeki verilerle karşılaştırmaktır.

**YÖNTEM ve GEREÇLER:** Kliniğimizde Ocak 2009- Eylül 2021 tarihleri arasında filloides meme tümörü nedeniyle opere edilen 36 hastanın verileri retrospektif olarak incelendi. Hastalar yaş, cinsiyet, meme de taraf ve kadran lokalizasyonu, radyolojik öntamı, patolojik tanı, tümör çapı, hastaların takip süreleri, nüks ve metastaz durumu ve malign hastalarda hayatta kalma durumu ve süreleri açısından değerlendirildi. Veriler SPSS programı kullanılarak istatistiksel olarak değerlendirildi.

**BULGULAR:** Hastaların tümü kadın cinsiyeteydi. 23 hastaya benign, 5 hastaya borderline ve 7 hastaya da malign filloides tümörü tanısı konuldu. Tüm hastaların ortalama yaşı  $42.0 \pm 14.6$  olarak bulundu. 20 hastada sağ meme yerleşimli 16 hastada da sol meme yerleşimli kitle mevcuttu. Ortalama tümör çapı bütün hastalarda  $65.0 \pm 37.3$  mm olarak bulundu. Malign Filloides tümörü olan 5 Hastada uzak metastaz saptandı ve bu hastaların tamamı takiplerinde eksitus oldu. Hasta yaşı, tümörün yerleştiği kadran, yapılan cerrahinin çeşidi, nodül çapı, radyolojik tanı ve takip süresi açısından benign, borderline ve malign Filloides tümörü grupları arasında istatistiksel olarak anlamlı farklılık bulunmadı ( $p>0.05$ ). Sağkalmı incelendiğinde malign grupta eksitus durumunun anlamlı olarak yüksek olduğu görüldü ( $p<0.05$ ).

**TARTIŞMA ve SONUÇ:** Filloides tümörlü hastaların takip ve tedavisinde hastalığın alt grupları önemli rol oynamaktadır. Malign Filloides tümörlerde cerrahi tedavi sonrası nüks, metastaz ve eksitus durumu diğer filloides tümörlere göre çok daha fazla görülmektedir. Sağlam cerrahi sınırlarla komplet cerrahi rezeksiyon önerilen tedavidir.

**Anahtar Kelimeler:** adenokarsinom, EGFR, kanparametreleri

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## INTRODUCTION

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breast. They constitute less than 1% of all breast tumors (1). Although it is a tumor that can be seen in all women from adolescence to advanced age, it is most commonly seen in the 35-55 age range (2). Very few cases have been reported in the male gender (3). PTs were classified into benign, borderline and malignant subgroups by the World Health Organization (WHO) in 1982 according to various criteria such as cellular atypia, mitotic activity, and stromal overgrowth (4).

Clinical, radiological and histological examination methods are used in the evaluation of patients. Diagnosis is made mainly by histopathological examination. While the diagnosis can mostly be made with core biopsy examinations, some conditions such as benign PTs and fibroadenoma may be difficult to differentiate. In general, most PTs have benign behavior, but there is a possibility of local recurrence in all PTs (5). While local recurrence and distal metastasis are rarely seen in benign PTs, they are more common in borderline and malignant PTs. Surgery with clean resection margins remains the mainstay of treatment for PTs of the breast. Excision with a clean surgical margin of 1 cm or more is often recommended for all phyllodes tumors (6).

The aim of our study is to analyze the clinicopathological features, treatments, recurrence and metastasis status and general results of patients who were operated on with the diagnosis of breast PT in our clinic and compare them with the data in the literature.

## MATERIAL AND METHODS

The data of 36 patients who were operated for phyllodes breast tumor in Sakarya University Faculty of Medicine Training and Research Hospital between January 2009 and September 2021 were analyzed retrospectively. The patients were evaluated in terms of age, gender, laterality and quadrant localization of the tumoral mass in the breast, radiological preliminary diagnosis,

pathological diagnosis, tumor diameter, follow-up periods of the patients, and survival status and duration in malignant patients. Patients who were thought to have a preliminary diagnosis of phyllodes breast tumor as a result of the initial evaluation but who were found to have another benign or malignant breast pathology due to the histopathological evaluation were excluded from the study. Approval for the study and data collection was obtained from the Sakarya University Faculty of Medicine Ethics Committee with the application number (71522473/050.01.04/83315/512).

## Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. Accordingly, the Student-t-Test for parametric independent numeric variables and the Mann-Witney U test for nonparametric numeric independent variables were used to compare groups. The parametric and nonparametric numeric variables were presented as mean  $\pm$  standard deviation, minimum, maximum. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A p-value  $<0.05$  was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.)

## RESULTS

In total, all 36 patients were female. 23 (63.9%) patients were diagnosed with Benign PT, 5 (16.6%) patients with Borderline PT and 7 (19.4%) patients with malignant PT. The mean age of all patients was  $42.0 \pm 14.6$ . While the mean age was  $37.57 \pm 12.2$  in the benign PT group, it was  $47.33 \pm 10.9$  in the borderline PT group and  $52.0 \pm 19.5$  in the malignant PT group.

There was a mass in the right breast in 20 (55.5%) patients and a mass in the left breast in 16 (44.4%) patients. The mass was located in the upper outer quadrant in 17 (47.2%) patients, in the upper inner quadrant in 4 (11.1%) patients, in

the lower inner quadrant in 3 (8.3%) patients, in the lower outer quadrant in 4 (11.1%) patients, retro areolar in 7 (19.4%) patients, and the lower outer quadrant in 4 (11.4%) patients. It was located in more than one quadrant in 1 (2.7%) patient. In surgical treatment, breast-conserving surgery (BCS) was performed in 30 (83.3%) patients, oncoplastic surgery in 1 (2.7%) patient, mastectomy in 4 (11.1%) patients, mastectomy in 1 (2.7%) patient, and breast prosthesis placement in the same session.

The mean tumor diameter was  $65.0 \pm 37.3$  mm in all patients. It was determined as  $60 \pm 36.2$  mm in benign patients,  $86.6 \pm 38.8$  mm in borderline patients, and  $62.86 \pm 38.6$  mm in malignant patients.

The surgical margin was clean in 32 (88.8%) patients in the histopathological examination. In 20 (55.5%) patients, clear surgical margins were found more than 1 cm at the surgical margin, while in 12 (33.3%) patients, the surgical margin was clean but less than 1 cm. Four (11.1%) patients were reoperated because the postoperative surgical margin was positive. Distant metastases were detected in 5 (13.8%) patients with malignant PT. Lung metastases were observed in all five patients. In addition to lung metastasis, vertebral metastasis was also seen in one patient. 4 patients received adjuvant Chemotherapy and Radiotherapy. Local recurrence developed in 2 patients.

The mean follow-up period was  $52.3 \pm 36.6$  months. Five (13.8%) of our patients died due to causes related to their diseases. All patients who died were patients with malignant PTs. The mean survival of our patients who died due to malignant PTs was  $29 \pm 20.2$  (min:8, max:82) months.

There was no statistically significant difference between the Benign, Borderline, and Malignant PT groups in terms of patient age, the quadrant in which the tumor was located, the type of surgery performed, tumor diameter, radiological diagnosis, and follow-up period. When the survival was examined, it was seen that the exitus status was significantly higher in the malignant group.

## DISCUSSION

Although PTs can be seen in all age groups, the age range of 35-45 is the age when this disease is most common. It is usually seen in women, but very rarely male cases have also been reported (2,3). In accordance with the literature, our patients were in this age group and all of them were female. While benign PT patients in our patient group were relatively younger, the mean age was higher in borderline patients. The mean age was also higher in patients with malignant PTs than in other groups.

Patients usually present with the complaint of a rapidly growing, painless palpable mass. The mass usually originates from a single focus and involves the upper outer quadrant of the breast (7). Although very rare, bilateral and multifocal tumors have also been reported (8,9). In our patients, patients presenting with a single-focal mass located in the upper outer quadrant are prominent. In addition, patients also state that the mass grows rapidly in a short time.

In radiological evaluation, mammography, ultrasonography, and magnetic resonance imaging (MRI) methods are used. MRI is preferred in the differential diagnosis of suspected phyllodes lesions. However, the diagnosis of PT cannot always be made clearly with radiological evaluation. Particularly, there are difficulties in distinguishing between fibroadenoma and PT(10,11). Our patients have similar situations in radiological evaluation. Definitive diagnosis is made by histopathological examination (12). In our patients, the diagnosis was made by methods such as core biopsy and excisional biopsy.

The primary treatment for PTs is surgery. While more extensive surgical treatments such as simple mastectomy were used in borderline and malignant PTs in the past, nowadays breast-conserving surgery is the more preferred appropriate surgical treatment even in patients with malignant PTs where complete resection is possible (13). BCS was applied to the majority of our patients. Although BCS is often preferred, mastectomy may be required in patients with large malignant tumors or in patients with an inappropriate tumor-to-breast tissue ratio (14). In addition, mastectomy is the preferred treatment in recurrent cases. Sentinel lymph node biopsy or axillary lymph node dissection is not

recommended as part of routine surgical treatment because PT spreads mainly by the hematogenous route and nodal involvement is extremely rare (15). However, axillary lymph node dissection can be performed in patients with malignant PT with axillary metastases (16). In our series, clinical and radiological axillary lymph node metastases were not detected in any patient, and axillary lymph node dissection was not performed.

Since the margin of surgical resection is thought to be associated with local recurrence of PTs, the extent of surgery to be performed is controversial. Many clinical studies, along with the National Comprehensive Cancer Network (NCCN) guidelines, recommend extensive removal of the tumor with a clear margin of 1 cm (6,17,18). However, recent studies show that there is no direct correlation between the local recurrence rate and the width of negative surgical margins (19,20). There are also studies suggesting that a clean surgical margin of 1 cm is overtreatment (21). In the majority of our patients, the surgical margins were clean and above 1 cm. In our patients whose surgical margins were clean but less than 1 cm, reexcision was not performed because the pathology result was compatible with benign PT, and these patients were followed up. However, patients with positive surgical margins in the pathological examination were re-operated.

The sizes of PTs vary between 5 and 7 cm on average, although cases between 0.5 cm and 30 cm in size have been reported (19, 22). The relationship between tumor size and malignancy is controversial; however, rapid growth can be detected in malignant tumors (23). The mean tumor size in our cases is also consistent with the literature. However, no relationship was found between tumor size and malignancy. In addition, it is stated by our patients that the mass grows very rapidly in all of our patients with a malignant diagnosis. In some studies, it has been reported that distant metastases are seen in approximately 10% of patients (15, 24). In another study, distant metastases were found at a rate of 14% (25). The most common sites of metastasis are lung, bone, brain, liver, and other organs, respectively (24). In our patients, metastasis

was observed in 5 patients (13.8%) at a rate similar to the literature. Lung metastases were also observed in 5 patients with metastasis. In addition to lung metastasis, vertebral metastasis was observed in 1 patient. Metastatic patients have a poor prognosis and mean overall survival ranges from 5 to 17 months (26). In our series, the mean survival of five patients who died due to metastatic disease was 29 months.

Adjuvant Chemotherapy is not the standard treatment for malignant PT. There are not enough clinical studies on this subject. It can be offered as an option in patients with tumor size greater than 5 cm, stromal overgrowth, and positive surgical margin status without the opportunity for re-surgical resection, by co-decision with the patient (27). The subject of Adjuvant Radiotherapy is still one of the controversial issues. NCCN guidelines and some studies recommend the use of Adjuvant Radiotherapy in cases of recurrent malignant PT(28). Another study recommends Adjuvant Radiotherapy to reduce the likelihood of local recurrence in patients with both borderline and malignant phyllodes tumors treated with BCS(29). The effect of radiotherapy on overall and disease-free survival has not been demonstrated. On the other hand, Adjuvant Radiotherapy is also recommended in patients with malignant phyllodes tumor treated with surgically wide excision (30). Four of our patients also received Adjuvant Chemotherapy and Adjuvant Radiotherapy.

The limitations of our study are the retrospective nature of our study and the small number of cases.

In conclusion, PT is a pathology that should be carefully evaluated in the preoperative period. Surgical complete resection with an intact and clean surgical margin is the recommended treatment. While morbidity and mortality are much less common in the benign and borderline patient groups, mortality rates increase significantly in malignant tumors, especially in metastatic cases. Adjuvant radiotherapy and chemotherapy after surgery in patients with malignant PT are still controversial topics. Further studies are needed in a prospective nature with a higher number of cases.

**Table 1: Clinicopathological Characteristics of the Patients**

		Benign Phyllodes Tumor	Borderline Phyllodes Tumor	Malignant Phyllodes Tumor	Total	p value
<b>Age</b>		37.57 ± 12.2	47.33 ± 10.9	52.0 ± 19.5	42.0 ± 14.6	<b>0.52</b>
<b>Type of surgery</b>	Breast Conserving Surgery	21 (70%)	5 (16.7%)	4 (13.3%)	30	<b>0.20</b>
	Oncoplastic surgery	1 (100%)	0	0	1	
	Mastectomy	1 (25%)	1 (25%)	2 (50%)	4	
	Mastectomy + Breast Prosthesis	0	0	1 (100%)	1	
<b>Quadrant of the tumor</b>	Upper outer	10 (58.8%)	2 (11.8%)	5 (29.4%)	17	
	Upper inner	4 (100%)	0	0	4	
	Lower inner	3 (100%)	0	0	3	
	Lower outer	1 (25%)	3 (75%)	0	4	
	Retroareolar	5 (71.4%)	1 (14.3%)	1 (14.3%)	7	
	Multiple quadrants	0	0	1 (100%)	1	
<b>Tumor diameter</b>		60 ± 36.2	86.6 ± 38.8	62.86 ± 38.6	65.0 ± 37.3	<b>0.55</b>
<b>Radiological preliminary diagnosis</b>	Benign	19 (79.2%)	3 (12.5%)	2 (8.3%)	24	<b>0.16</b>
	Malignant	1 (14.3%)	3 (42.9%)	3 (42.9%)	7	
	Phyllodes Tumor	3 (60%)	0	2 (40%)	3	
<b>Follow-up period (Month)</b>		65.7 ± 37.01	31.8 ± 16.6	26.0 ± 26.1	52.3 ± 36.6	
<b>Survival</b>	Alive	23 (74%)	6 (19.4%)	2 (6.5%)	31	<b>&lt; 0.05</b>
	Exitus	0 (0%)	0 (0%)	5 (100%)	5	
<b>Total number of patients</b>		<b>23 (63.9%)</b>	<b>6 (16.6%)</b>	<b>7 (19.4%)</b>	<b>36</b>	

**Ethics Committee Approval:**

Sakarya University Clinical Research Ethics Committee (date:05.11.2021 and no:2019/512)

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