Phyllodes Tumors of the Breast: Clinicopathological Analysis of 35 Single-Center Cases

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Abstract

Aim: This study was conducted with the aim of to evaluate demographics of patients with phyllodes tumor (PT), clinical and histopathologic characteristics of tumors, and to share treatment approach to PTs from the experience of our center.

Method: In the study, the demographic, clinicopathological characteristics and treatment approaches of the patients who were treated between 2006 and 2017 at the Oncology Institute, Istanbul University with the diagnosis of PT were evaluated retrospectively by examining the patient files and pathology records.

Results: The median age was 39.7±11.1 years. For diagnosis, 6 patients underwent excisional biopsies, 1 patient incisional biopsy, and 27 patients core biopsies. Twenty seven patients underwent breast-conserving surgery (BCS), whereas 8 patients had mastectomy. Re-excision was added to one lumpectomy, and 2 cases who had BCS were converted to mastectomy due to margin positivity. The mean PT size was 55.3 mm (13 mm - 210 mm). The PT subtypes were as follows: benign (n=15, 42.9%), borderline (n=7, 20.0%), and malignant (n=13, 37.1%). Among those with malignant PTs, 3 patients received chemotherapy (CT) and radiotherapy (RT) following mastectomy, one patient with lumpectomy had CT and RT, and 2 patients received only RT. Patients with PT were followed for an average of 70 months (12 months- 184 months). Seven local recurrences (LR) (2 benign PT, 1 borderline PT, and 4 malignant PT), 1 single distant metastasis (malignant PT), and 1 LR plus distant metastasis (malignant PT) were observed in follow-up.

Conclusion: Negative surgical margin of ≥1cm is the most important step in the management of PTs. The survival benefit of adjuvant CT or RT are contraversial and need further investigation.

Keywords: Phyllodes tumor, breast surgery, local recurrence.

Özgün Araştırma Makalesi (Original Research Article)
Geliş / Received: 19.04.2023 & **Kabul / Accepted:** 28.07.2023
DOI: https://doi.org/10.38079/igusabder.1278840
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ETHICAL STATEMENT: Ethical approval for the study was gathered from Istanbul Faculty of Medicine, Ethical Committee (form number: 2023/402).

Memenin Filloides Tümörleri: Tek Merkezden 35 Olgunun Klinikopatolojik Analizi

Öz

Amaç: Bu çalışma, filloid tümörlü (FT) hastaların demografik özelliklerini, tümörlerin klinik ve histopatolojik özelliklerini değerlendirmek ve merkezimizin deneyimlerinden yola çıkarak PT'lere tedavi yaklaşımlarını paylaşmak amacıyla yapılmıştır.

Yöntem: Çalışmada İstanbul Üniversitesi Onkoloji Enstitüsü'nde 2006-2017 yılları arasında FT tanısı ile tedavi edilen hastaların demografik, klinikopatolojik özellikleri ve tedavi yaklaşımları hasta dosyaları ve patoloji kayıtları incelenerek retrospektif olarak değerlendirildi.

Bulgular: Medyan yaş 39,7±11,1 yıl idi. Tanı için 6 hastaya eksizyonel biyopsi, 1 hastaya insizyonel biyopsi ve 27 hastaya kor biyopsi uygulandı. 27 hastaya meme koruyucu cerrahi (MKC), 8 hastaya mastektomi uygulandı. Bir lumpektomiye yeniden eksizyon eklendi ve MKC olan 2 olgu sınır pozitifliği nedeniyle mastektomiye çevrildi. Ortalama FT boyutu 55,3 mm (13 mm - 210 mm) idi. FT alt tipleri benign (n=15, %42,9), borderline (n=7, %20,0) ve malign (n=13, %37,1) olarak belirlendi. Malign FT'li hastalardan 3'üne mastektomi sonrası kemoterapi (KT) ve radyoterapi (RT), lumpektomili bir hastaya KT ve RT, 2 hastaya sadece RT uygulandı. FT'li hastalar ortalama 70 ay (12 ay-184 ay) takip edildi. Takipte 7 lokal nüks (LN) (2 benign FT, 1 borderline FT ve 4 malign FT), 1 tek uzak metastaz (malign FT) ve 1 LN artı uzak metastaz (malign FT) gözlendi.

Sonuç: Negatif ≥1cm'lik cerrahi sınır, FT'lerin tedavisinde en önemli adımdır. Adjuvan KT veya RT'nin sağkalıma yararı tartışmalıdır ve daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: Filloides tümör, meme cerrahisi, lokal nüks.

Introduction

Phylloides tumor (PT) of the breast are uncommon sarcomatoid lesions that account 2-3% of all fibroepithelial neoplasias[1]. Radiologically, PTs show similar findings with benign fibroadenomas (FA) but they differ from FAs histologically by the presence of high cellularity and stromal components. In addition, clinically, PTs carry a substantial risk of local recurrence (LR) and metastatic spread. World Health Organization (WHO), classified 3 types of PTs[2]: benign, borderline and malignant. Malignant phyllodes with high relapse potential account for 25% of all PTs[3] (Table 1).

Table 1: WHO subclassification of phyllodes tumors

[a]		Benign	Borderline	Malign
Mitosis of Per 10 HPF		<5	5-9	≥10
Stromal overgrowth		Absent	Absent/focal	Present
Stromal atypia		Mild	Moderate	Marked
Stromal cellularity		Mild	Moderate	Marked
[b]				
Stromal atypia	**Mild**	Twice cellularity of normal perilobular stroma with evenly spaced nuclei without overlapping		
	Moderate	Intermediate in degree between mildly and markedly		
	Marked	Stromal cells in close contiguity with nuclei appearing to touch and overlapping		
Stromal cellularity	**Mild**	Small, uniform nuclei, with absent or inconspicuous nucleoli		
	Moderate	Intermediate in degree between mildly and markedly		
	Marked	Marked variation in nuclear size and shape, irregular nuclear membrane, and prominent nucleoli		
Intratumoral heterogenity		Variability in structure and stromal cellularity or atypia in a single tumor		
Tumor margin		Projections of tumor stroma into the peritumoral stroma or adipose tissue		
Leaflike pattern		Enhanced intracanalicular pattern, characterized by projection of cellular stroma into epithelial-lined clefts of cystic spaces		

[a] Grading System for Phyllodes Tumors Based on 2012 World Health Organization Classification, HPF: High power field. [b] Increase at least 50% of the stroma compared with typical fibroadenoma

Surgical removal should be the mainstay of management. Removal of tumors with a clear surgical margin is essential in surgery and requires re-excision if the surgical margin is not secured because LR mainly occur when a clear surgical margin cannot be obtained[4,5]. Barth Jr RJ reported the LR rates after breast-conserving surgery (BCS) for as 8% for benign PTs and as 21-36% for borderline & malignant types[6].

Contribution of adjuvant radiotherapy (RT) remains controversial. Although it is considered not necessary in benign PTs when the tumor is properly excised, RT is thought to reduce the risk of LR, especially in cases where it is suspected that a clear surgical margin can be obtained in

borderline and malignant tumors following BCS or even after mastectomy due to large tumor size. Studies in the current literature suggest RT to reduce the risk of LR in these cases[7].

The role of chemotherapy (CT) in these cases has also not been fully elucidated. CT can be used in malignant tumors that are predicted to be aggressive, but CT can be used in these tumors by discussing the profit and loss issue with the patient. Adjuvant hormone therapy may be used in hormone-sensitive tumors with a epithelial component, but its contribution has not been demonstrated[8].

This study aimed to present the clinicopathological findings and treatment approach of cases diagnosed with PT who admitted to our clinic.

Material and Method

Study Paticipants

The demographic, clinicopathological characteristics and treatment approaches of the 35 patients who were admitted to the Oncology Institute, Istanbul University Department of Breast Surgery between February 2006 and December 2017 and were treated with the diagnosis of PT were evaluated retrospectively by examining their tracking data.

Ethical approval for the study was gathered from Istanbul Faculty of Medicine, Ethical Committee (form number: 2023/402; Date: 17.03.2023).

Diagnosis

The patients were diagnosed radiologically and pathologically. Radiologically, mainly ultrasound (US), mammogram (MG) and magnetic resonance imaging (MRI) were used. Excisional biopsy, mainly core biopsy were preferred for pathological diagnosis.

Surgery

Following preliminary diagnosis, wide tumor excision (lumpectomy) with a macroscopic 1 cm surgical margin has been tried to obtain or re-excision if the surgical margin is close or positive or the surgical margin is unknown; Mastectomy (+/- reconstruction) was performed in cases where BCS was not suitable in terms of tumor size/breast ratio. Depending on the surgeon's preference, axillary intervention was performed in unique cases.

Pathological Examination

Pathologically, phyllodes tumor types are classified as benign, borderline and malignant with the following criteria (2): a) benign: <5 mitosis/ 10X magnification area, with low stromal excess with minimal stromal atypia and cellularity. signs of growth and surgical margins are intact, b) borderline: 5-9 mitoses in the field of 10X magnification, moderate stromal atypia and cellularity and excessive growth / surgical margins are intact or infiltrated, c) malignant: >10 mitosis / medium or infiltrated in the field of 10X magnification advanced stromal cellularity, atypia,

pleomorphism, stromal overgrowth and surgical margins infiltrating. Ki-67 index was also included in the pathological examinations in available cases. These stromal features were examined in the tumors within the study, but not every different parameter was examined in every tumor.

In addition, all specimens were evaluated for surgical margin and pectoral muscle invasion. In the period during which these cases were operated, the surgical margin was accepted positive if the tumor is in the ink at any margin, or the surgical margin was <2mm, and re-excisions were performed. The surgical margin was considered as negative if ≥2mm.

Adjuvant Therapy

Among the malignant phyllodes cases, unique cases, those who underwent BCS received RT to the breast and the tumor bed, among the cases who underwent mastectomy, RT to the chest wall in cases with a high mitotic index, which was thought to have an aggressive course, and additional CT was used to some of them, depending on their aggressive tumor characteristics.

Statistical Analyzes

Demographics of patients, tumor features, surgical approaches, and postoperative progression of tumors were gathered. Microsoft Excel software (Microsoft Luxembourg S.a.r.l., 20 Rue Eugene Ruppert, Luxembourg) was used to record the data. Parameters was tested using Fisher's exact test / the Chi-square test in two-tailed univariate analyses. Student's t-test (independent sample t- test) was used to compare the mean values of two independent groups. Variables that were available for total of cases and significant as a result of univariate analyses were included in multivariate analyses, and binary logistic regression analysis was performed. A p value less than 0.05 was considered as statistically significant. The Statistical Package for the Social Sciences (SPSS) program, version 21.0 (SPSS Inc., Chicago, IL, USA) was used in statistical analyzes.

Results

Clinicopathological features of the patients, treatment approaches, and data on follow-up are shown in Table 2 as benign vs. borderline & malignant. For diagnosis, 6 patients underwent excisional biopsies, 1 patient incisional biopsy, and 27 patients core biopsies. The subtypes of PTs were: benign (n=15, 42.9%), borderline (n=7, 20.0%), and malignant (n=13, 37.1%). The median age was 39.7±11.1, and without difference between benign and borderline & malignant PTs (p=0.06). The mean PT size was 55.3 mm (13 mm - 210 mm). Borderline & malignant PTs were larger in size than benign ones (p=0.019). Higher mitotic number was counted in borderline & malignant PTs (p<0.001). Marked stromal atypia (p<0.001), cellular pleomorphism (p=0.002), and stromal overgrowth (p=0.004) out of available data tended to be more in borderline & malignant PTs. The Ki-67 index of borderline & malignant PTs was found to be higher than the benign ones (p<0.001). Twenty seven patients had BCS, whereas 8 patients underwent mastectomy. Surgical axillary sampling was performed in three patients, and no nodal metastases

were detected in any of them. One re-excision was added to BCS, and 2 cases who had BCS were converted to mastectomy due to margin positivity. Thus, a total of 3/27 (11.1%) margin positivity was detected in conservative surgeries, 2 for malignant PTs, 1 for borderline PT. While the rate of mastectomy performed primarily in benign PTs was similar when compared with borderline & malignant PTs (p=0.055), it was seen that patients with borderline & malignant PT had significantly more mastectomy when the patients who underwent mastectomy due to positive margin were added (p=0.015). LR was observed at a similar rate in patients with benign PT and patients with borderline & malignant PT during the follow-up period (p=0.23).

Table 2: Clinicopathologic differences between benign and borderline & malignant phyllodes tumors

		Benign n=15	**borderline & malignant n=20**	**p**
Age, mean		36.6 (±10.4)	41.6 (±11.3)	0.06
Tumor size mm, mean		39.7 (±21.1)	67.0 (±62.4)	0.019
Mitotic number of Per 10 HPF, mean		2.3 (±0.7)	22.5 (±18.2)	<0.001
Stromal atypia	**mild/ moderate**	15 (100.0%)	9 (45.0%)	<0.001
	marked	-	11 (55.0%)	
Cellular pleomorphism	**no**	8 (100.0%)	5 (31.3%)	0.002
	yes	-	11 (68.8%)	
Stromal overgrowth	**no**	7 (100.0%)	4 (28.6%)	0.004
	yes	-	10 (71.4%)	
Ki-67, mean		1.1 (±0.3)	16.2 (±12.1)	<0.001
Initial surgery	**BCS±re-excision**	14 (93.3%)	13 (65.0%)	0.055
	Mastectomy	1 (6.7%)	7 (35.0%)	
Overall mastectomy (positive margin)		1 (6.7%)	9 (45.0%)	0.015
Local recurrence		2 (13.3%)	6 (30.0%)	0.23
Distant metastasis		-	2 (10.0%)	0.32

Among the patients with malignant PT, 3 patients received CT and RT following mastectomy, one patient with lumpectomy had CT and RT, and 2 patients received only RT. The median follow-up period was 70 months (range, 12 to 184 months). Lung metastases were detected in one patient at the eleventh month who underwent mastectomy and received CT. Bone metastasis was detected

at the eighth month in the patient who underwent lumpectomy and received CT. Seven LRs (2 benign PT, 1 borderline PT, and 4 malignant PT), 1 single distant metastasis (malignant PT), and 1 LR plus distant metastasis (malignant PT) were observed in follow-up. 1 LR developed following mastectomy and the remaining 7 following BCS.7

When variables that were available for all cases and significant as a result of univariate analyses were evaluated in multivariate analyses for the developement of LR, large tumor size (≥5cm) (p=0.032) and high mitotic number (≥5 Per 10 HPF) (p=0.025) were found to be more important factors to predict LR. These associations between significant factors and LR are summarized in Table 3.

Table 3: Multivariate logistic regression analysis

	OR	**Sig.**	**95% C.I. for EXP(B)**	
			Lower	**Upper**
Tumor size ≥50mm	2.94	0.032	1.29	7.76
Mitotic number of ≥5 Per 10 HPF	3.04	0.025	1.18	8.42
Stromal atypia (mild/moderate vs. marked (1))	0.89	0.23	0.80	1.38
Nagelkerke R Square		0.557		
Hosmer and Lemeshow Test		0.754		

Discussion

PTs of the breast are rare tumors that can be seen from young ages to advanced ages, most commonly in the middle ages between 35-55 years of age[9]. In our series, the median age was found to be around 40 in general; in addition, when the cases are examined as benign, borderline & malignant, no significant difference was found between the diagnosis ages of the two groups.

Preoperative radiological evaluation can be used to differentiate the tumor structure and diagnosis from possible FA. In our series, US and MG were requested for radiological imaging for all patients, except MG, which was not requested for 6 patients under 35 years of age. The shape of a PT on MG is a generally smooth, maybe lobulated view such as a FA, is reporting similar about 40-50% on MGs as a probably benign lesion (BIRADS 3). Therefore, in distinguishing these tumors from FAs could be difficult in radiological examinations such as US and MG performed in differential diagnosis. In studies performed with MRI, no significant differences were found in MRI findings between benign PTs and FAs, but it was found that malignant PTs had a higher contrast enhancement pattern in T1-weighted sections compared to benign PTs[10]. In our series,

MRI was performed in all patients diagnosed as mixed histology or malignant PT with preoperative biopsy but not in all cases with benign PT diagnosis.

In this study, PTs were divided into benign, borderline and malignant subtypes according to the WHO definitions[2]. While in other series, approximately 60% mostly benign PTs were detected[11], this rate was 31.5% in our series, with a higher rate of borderline or malignant PTs. This may be explained by the tendency of surgeons to probably not refer patients diagnosed with benign PT to a cancer center.

The mean size of phyllodes tumors has been reported in the literature to be between 4 and 7 cm[12]. In addition, Mallick et al. reported a median size may rise up to 13.6 cm of malignant phyllodes[13]. The median tumor size of our PTs was 55.3 mm, larger for borderline & malignant PTs (67.0 mm) compared with the benign subtype (39.7 mm). These relatively smaller tumor sizes were interpreted as a result of the rapid admission of patients in our case series.

Demian et al.[14] reported positive margin rates for malignant PTs and borderline PTs, of 24% and 15 %, respectively. Similarly, in our study, the probability of margin positivity following BCS is higher with malignant PT compared to borderline (25% vs. 20%). Also in the same study, total mastectomy rates were for borderline PTs as 23% and for malignant PTs as 81%. Although there was a lower rate for malignant PTs in this study, the overall mastectomy rates for the benign, borderline, and malignant PTs were 7%, 28%, and 54%, respectively, possibly due to increasing growth pattern.

Although there are studies in the literature showing that adjuvant RT reduces the LR rate for borderline and malignant PTs, its contribution is still controversial. In our study, RT was used in 6 cases of malignant phyllodes. LR was observed in 2 of them during the follow-up period. Likewise, it is a controversial issue that CT has a positive effect on tumor-specific disease during the follow-up period[15]. In our series, CT was used in 4 cases of malignant phyllodes, but distant metastasis developed in 2 patients and LR in 1 patient, possibly due to the existing aggressive tumor features. So our study could not support the hypothesis that RT and CT have an absolute positive effect.

The overall LR rate of the study was 22.9% (8/35) and 28% (7/25) following conservative surgery, which is a relatively high rate compared to the literature (8%-19%) (15). In the NCCN guidelines[16], it is stated that a minimum of 1 cm negative surgical margin should be provided to reduce the risk of recurrence. In our cases in the process of our retrospective study, the tumor-free clear margin limit for re-excision was accepted as 2mm, so a clear margin of 1 cm was not obtained in all cases. This high recurrence rate can be explained in this way.

According to the large meta-analysis by Yu C-Y et al. marked stromal atypia and high cellularity, stromal overgrowth, ≥5 of mitotic number, border irregularity, and margin positivity were found to be risk factors to develope recurrence, except larger tumors of 5 cm[17]. In our study, although a

negative margin of 1 cm was not obtained in all cases, high mitotic activity was found to be independent factor for recurrence in accordance with this meta-analysis, but tumor size larger than 5 cm was also found to be a significant factor.

Conclusion

PTs are an uncommon breast tumors that tend to grow rapidly, to occur in younger women compared to classical breast adenocarcinomas. Surgery is the mainstay of management. The study may extrapolate that large tumors with high mitotic activity should be excised with optimum negative clear margin. The survival benefit of adjuvant CT or RT are still contraversial and need further investigation.

Ethical approval for the study was gathered from Istanbul Faculty of Medicine, Ethical Committee (form number: 2023/402; Date: 17.03.2023). All patients provided written informed consent for participation in the study.

Authors declare no conflict of interest.

Funding: None

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