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Is the extent of surgical resection important in patient outcome in benign and borderline phyllodes tumors of the breast?

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Background/aim: Phyllodes tumors (PTs) of the breast are rare, and their diagnosis and treatment remain controversial. This retrospective study aims to examine the clinical outcome of benign and borderline PTs, according to the surgical margins.

Materials and methods: We examined the medical records of 122 patients in our clinic, who had histologically confirmed benign and borderline PTs between 1994 and 2017.

Results: The mean age of the patients was 40.6 years (range 18.0–81.0, ±12.1 standard deviation [SD]) and the mean tumor size was 25.8 mm (range 9–65, ±10.3 SD). All patients underwent a breast-conserving procedure and the median follow-up was 51 months. Tumor margins were positive (tumor touching the ink) in 43 patients (35%). Only 16 patients (13%) had margins ≥10 mm. The margins were between 2 and 10 mm in most patients (40%) and ≤1 mm in 12% of the patients.

Conclusion: Although no re-excision was performed to obtain grossly clear margins, local recurrence was not observed in any patients. Therefore, revision surgery for close or positive surgical margins for benign and borderline PTs should not be performed as a rule. As most tumors recur within 2 years of diagnosis, we propose a close clinical and imaging follow-up during this period.

Key words: Phyllodes tumor, surgery, surgical margins

1. Introduction

Phyllodes tumors (PTs) are rare fibroepithelial tumors of the breast that account for less than 1% of all primary breast tumors (1,2). They were first described by Johannes Muller in 1838 as "cystosarcoma phyllodes" (3). However, in 1982, the World Health Organization (WHO) declared a more suitable term of "phyllodes tumor", which has been widely accepted (4).

Benign PTs are more frequent, with an incidence of 35%–85%. Borderline PTs, on the other hand, account for 7%–40% of cases (5). Local recurrence rates vary in the literature, and are reported to be approximately 8% for benign PTs and 21% for borderline cases (6).

The macroscopic appearance of most PTs is that of a circumscribed, round to oval multinodular mass that lacks a true histologic capsule. Most PTs are indistinguishable from fibroadenomas (FAs) on gross examination. Histologically, PTs of the breast show the characteristic appearance of leaf-like architecture, increased stromal overgrowth, cellularity, atypia, and mitosis (7). According to the WHO, three histologic types are identified based on histopathological features: benign, borderline, and malignant (4).

Diagnosis of PTs with imaging methods is generally difficult and they are often confused with FAs. On mammography (MG), PTs have smooth, round-to-oval margins with lobulation. On ultrasonography (US), PTs are generally heterogeneous, well-defined, hypoechoic oval lesions surrounded by a capsule or pseudocapsule, and show lobulation. However, internal echoes and calcifications are absent (8).

Surgery is the main treatment for PTs of the breast. Nevertheless, the extent of initial resection and the necessity for re-excision to have adequate margins remain controversial. Both PTs and FAs are on the same morphological spectrum; hence, it can be very difficult to differentiate these entities clinically, radiologically, and in terms of tissue sampling. Patients usually undergo enucleation of this innocuous breast lump, the diagnosis of which results from PTs. The question regarding these

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patients is whether or not to obtain wide excision margins to achieve local disease control and spare them the potential cosmetic and psychological problems that may arise with resurgery.

In this retrospective study, we aimed to investigate clinical outcomes of 122 benign and borderline PTs of the breast, treated and followed-up in a single institution, to better characterize both surgical management patterns and clinical behavior of these rare tumors, according to surgical margins at first resection.

2. Materials and methods

The medical records of 122 patients with histologically confirmed benign and borderline PTs operated on at our clinic between 1994 and 2017 were retrospectively reviewed. Informed consent was obtained from all patients during hospitalization.

The clinical data analyzed included patient demographics, radiologic methods used for diagnosis, tumor size, localization, and type of surgery. Histopathologic features of the tumor, as well as patient follow-up data and outcomes, were evaluated.

Preoperative MG and US were evaluated by our breast radiologist in the Department of Radiology, Dokuz Eylül University. All patients were evaluated according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS). Atlas (5th edition) was used in all imaging methods.

As PTs may be difficult to distinguish preoperatively from cellular FAs due to their heterogeneous nature, neither fine needle aspiration cytology (FNAC) nor core needle biopsy was performed as the initial management.

Operative treatment was defined as wide local excision (WLE), enucleation, or wire-guided surgery (WGS). Patients with palpable mass underwent WLE. WGS, which has abnormal radiologic findings without palpable mass, was used in patients. Enucleation of the tumor was performed in patients that had been diagnosed with FAs peroperatively.

All the histologic slides were examined by our breast pathologist in the Department of Pathology, Dokuz Eylül University. The tumors were classified according to the WHO classification of breast tumors. Data on tumor size and margins (negative or positive, and minimum tumor-free margin) were obtained.

We subdivided the tumors into 4 groups based on the nearest resection margins: (1) positive resection margin, (2) resection margin ≤ 1 mm, (3) resection margin between 2 mm and <10 mm, and (4) resection margin ≥ 10 mm.

Regular clinical and imaging follow-up of all the patients were similar during the first 2 years after surgery.

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 20.0 was used for statistical analyses. Categorical variables were expressed as percentages and continuous variables as means, median, standard deviation (SD), and range.

3. Results

3.1. Clinical characteristics

From 1994 to 2017, a total of 122 female patients with a mean age of 40.6 years (range 18.0–81.0, ±12.1 SD) were included in the study. The mean ages for benign and borderline PTs were 39.3 and 50.5 years, respectively. The characteristics of the patients are summarized in Table 1.

Most patients (90%) presented with palpable, mobile, and painless masses in their breasts. In 12 (10%) patients, the diagnosis was based on abnormal radiologic findings.

In 58 (47.5%) patients, the tumor was located in the right breast, and in 64 (52.5%), it was located in the left breast. All patients presented with a unilateral breast lump at diagnosis.

3.2. Imaging findings

MG was performed in 46 (37.7%) patients, of whom 33 (71.7%) were classified as suspicious (BI-RADS ≥ 4). In US imaging, this was performed in all patients, 105 (86.0%) of which were classified as suspicious (Table 1). PTs were suspected in 63 (51.6%) patients during imaging analyses.

3.3. Primary treatment

All patients underwent surgery. A total of 67 (55.0%) patients were treated with WLE, 43 (35.0%) with enucleation, and 12 (10.0%) with WGS (Table 2).

No patients underwent axillary lymph node dissection. Adjuvant therapy was not given.

3.4. Histopathologic features

The histopathologic characteristics of the cases are summarized in Table 2. One hundred and eight (88.5%) tumors were benign PTs and 14 (11.5%) were borderline on histopathological analyses. The mean tumor size was 25.8 mm (range 9–65, ±10.3 SD). Surgical margin data were available for all patients.

(1) 35% (n = 43) of patients had positive surgical margins after surgery (tumor touching the ink). All patients with positive margins had benign PTs.

(2) 12% (n = 14) of patients had margins ≤ 1 mm (close margins, but no tumor on ink).

(3) 40% (n = 49) of patients had margins between 2 and <10 mm.

(4) 13% (n = 16) of patients had margins ≥ 10 mm.

3.5. Follow-up

The median follow-up was 46 ± 57.6 months (range 0–277) in benign PTs and 133 ± 67.2 months (range 36–240) in borderline PTs (Table 2).

All 43 patients with positive margins had benign histology. Re-excision was not performed in these patients, who were closely followed-up by physical examination

Table 1. Patient and lesion characteristics (n = 122).

		Mean ± SD (range)	n (%)
Age mean (years)		40.6 ± 12.1 (18–81)	
Preoperative diagnostic modalities	By palpation		110 (90)
	By radiologic findings		12 (10)
Mammographic impression (n = 46)	BI-RADS 3		13 (28.4)
	BI-RADS 4a		27 (58.6)
	BI-RADS 4b		4 (8.7)
	BI-RADS 4c		2 (4.3)
Echographic impression (n = 122)	BI-RADS 3		17 (13.9)
	BI-RADS 4a		99 (81.1)
	BI-RADS 4b		4 (3.3)
	BI-RADS 4c		2 (1.6)
Tumor laterality	Left		64 (52.5)
	Right		58 (47.5)

Table 2. Histopathological characteristics (n = 122).

		Benign (n = 108)	Borderline (n = 14)	Total (n = 122)
Size		26.1 ± 10.6	23 ± 7.5	25.8 ± 10.3
Mean ± SD (range)		(9–65)	(11–35)	(6–5)
Mitosis, n (%)	0–4	108 (89)	4 (3)	112 (92)
	5–10	-	9 (7)	9 (7)
	>10	-	1 (1)	1 (1)
Surgical margins, n (%)	Positive	43 (35)	-	43 (35)
	≤1 mm	13 (11)	1 (1)	14 (12)
	2–<10 mm	40 (33)	9 (7)	49 (40)
	≥10 mm	12 (10)	4 (3)	16 (13)
Type of surgery, n (%)	Enucleation	43 (35)	-	43 (35)
	Wide local excision	55 (45)	12 (10)	67 (55)
	Wire guided	10 (8)	2 (2)	12 (10)
Follow-up (months)	Median	46 ± 57.6	133 ± 67.2	51 ± 63.1
	Range	(0–277)	(36–240)	(0–277)

and imaging methods. The median follow-up within this group of patients was 39 months (range 1–277). There was no local recurrence during the follow-up period.

4. Discussion

PTs of the breast are rare, representing <1% of all breast neoplasms (1,2). The WHO categorizes these tumors as benign, borderline, and malignant, based on histopathologic characteristics (4). Their prognosis and clinical outcome are still associated with much uncertainty and variability. In addition, malignant PTs commonly show more aggressive behavior, both locally and systemically, compared to their benign and borderline counterparts (9). In this study, we investigated benign and borderline PTs of the breast treated, diagnosed, and followed-up at our institution, to better characterize both surgical management patterns and the clinical behavior of these tumors.

PTs may occur at any age, with a mean age ranging between 30 and 52 years (10). In our study, all patients were female with a mean age of 40.6 years at diagnosis, which is similar to other series.

Painless palpable mobile mass in the breast was the most common presenting symptom in our series (90.0%). Tumor size ranged from 9 to 65 mm, with a mean size of 25.8 mm. In several studies in the literature, the size of PTs of the breast varies between 0.5 and 27 cm, with a mean between 5 and 7.2 cm (11). In contrast, the mean tumor size in our series seems to be considerably smaller.

PTs were localized in either breast in almost equal proportion (47.5% vs. 52.5%) in our study, similar to several other series (12).

The role of imaging is uncertain in diagnosis due to lack of specific characteristics. PTs and FAs have similar MG and US features (8). We performed US as the first-step imaging method in all patients in our study. MG was performed only in patients aged more than 40 years. Diagnosis of PTs was suspected in 63 (51.6%) patients during imaging analyses in our series, a ratio that was higher than that in the literature (13). WGS was performed on 12 (10%) patients who presented with abnormalities detected during imaging analyses without a palpable mass.

FNAC of the breast has low sensitivity (72.0%) to differentiate the type of histology (14,15). Moreover, false-negative results can be obtained when sampling is performed in an area of hypocellular stroma (11). Core needle biopsy is more acceptable than FNAC for obtaining a correct diagnosis, as it can provide specific histopathologic findings. However, its false negative rates are reported as high as 30.0% in the literature (16).

As PTs may be difficult to diagnose with cytologic and histologic methods preoperatively due to their heterogeneous nature, none was the preferred choice of first-line management in our institution. Instead, excisional biopsy was performed to achieve an accurate diagnosis with examination of the entire mass. This approach increased cost-effectiveness.

Surgery remains the cornerstone of treatment for PTs of the breast. However, due to their unpredictable clinical presentation, uncertain pathological behavior, and inaccurate preoperative diagnosis, there still seem to be dilemmas in their treatment plans (11). Enucleation of the tumor is frequently preferred, since the majority of these lesions are diagnosed as FAs preoperatively (15). The question in PT cases, however, is whether or not all these patients should undergo a second operation to provide adequate clear margins. In the literature, there is no consensus about the necessity of a surgical revision of margins in such cases.

Numerous clinical studies recommend wide excision of the tumor with a 10-mm clear margin (12,17–21), which causes major difficulties in achieving good cosmetic results. However, recent data show that there is no direct relationship between the margin status or width of negative margins and recurrence (22,23). Kim et al. have suggested that recurrence rates are very low for benign PTs, regardless of margin status, even for patients treated with local excision (24). In addition, Yom et al. have reported that margin status is not associated with risk of local recurrence (15). In their series of 164 PT cases, Jang et al. found that a 10-mm negative margin thickness did not confer any local control advantage over a narrower negative margin (22). Onkendi et al. have shown that the extent of surgical resection did not affect disease-free survival in patients with borderline and malignant PTs (23). In addition, there are certain series in the literature that report recurrence in PT cases with negative margins at initial surgery (12,17). In their largest series, Zurrida et al. advocated a wait-and-see policy for patients with benign and low-grade tumors and positive surgical margins, due to lower recurrence rates (25,26). In our series, we performed complete surgical resection with safe margins in clinically and radiologically suspected benign PTs or tumors of undetermined clinical significance.

In our study, 35% of patients had positive surgical margins and 12% had close margins of less than 1 mm. This might be explained by the fact that the majority of benign tumors were diagnosed peroperatively as FAs, and enucleation of the tumors were, therefore, performed. None of the patients underwent reoperation to increase the margin. In agreement with this, Tan et al. suggest a conservative approach to benign PTs that have initially been enucleated without margins, and excision with negative margins should be achieved for recurrent and malignant PTs (14). This is supported by the MD Anderson Cancer Center clinical practice algorithm for PTs, which recommends that if initial excision has a negative margin in benign PTs, further surgery is not required (15). Despite positive and very close margins (47.0%) in our study, we have no local recurrence, whereas local recurrence rates in other series vary from 8.0% to 13.0% (6,12,19,21). This may be explained by the fact that these studies do not separate benign or borderline PTs from high-grade malignant PTs in evaluation (12,22,27).

Several factors have been found to be related to local recurrence. Tumor size and mitotic activity were found to be independently associated with local recurrence, whereas margin status and surgical procedure were not. The risk of local recurrence is higher in larger tumors and tumors with >10 mitosis per 10 high power fields. In our series, mean tumor size was 25.8 mm and 121 (99.0%) patients had <10 mitosis per 10 high power fields. In agreement with our results, several authors have proposed that re-excision should be performed in tumors with high mitotic activity (15,20,21). Moreover, local recurrence of benign

and borderline tumors can be well managed by further surgery (either breast-conserving surgery or mastectomy).

PTs show unpredictable behavior of histotypes. Metastases are more common in malignant PTs. In a similar manner, we have no metastases in our series (17,21,22). Nevertheless, several authors have described local recurrence and even distant metastases of benign and borderline tumors (18,19,21,22).

In this study, the median follow-up was 46 months in benign and 133 months in borderline PTs. The mean duration of time-to-recurrence varies in the literature, but most tumors recur within 2 years from diagnosis (20,21,25–27). Therefore, it seems that most recurrences can be detected during this time frame with appropriate follow-up.

Our findings suggest that patients with benign and borderline PTs have a less aggressive disease course and low risk of local recurrence, irrespective of margin status. Reoperation with wider resection in healthy tissue is not justified in selected patients. There is no evidence-based recommendation for delineating an optimal length of follow-up or follow-up intervals. Nevertheless, beginning with clinical and radiological reviews at 6 months and continuing for the first 2 years after surgery, follow-up of yearly evaluation may be an appropriate practice suggestion.

Our study may lead to new perspectives in the surgical management of patients with benign or borderline PTs of the breast, enable patients feel good about their breast cosmesis, and prevent tumor recurrence efficiently.

However, our data have limited capacity for making firm assumptions, as this is a retrospective study. The results of prospective trials and similar studies are warranted to support our results.

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