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Phyllodes Tumor of The Breast: Histopathological and Clinical Results of 13 Cases

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Abstract: Phyllodes tumors (PT) are biphasic tumors originating from cleft-like spaces lined by epithelial cells and the hypercellular stroma. PT is a very rare tumor of the breast. The World Health Organization (WHO) classifies it as benign, borderline, or malignant. In this research, we aimed to describe the radiological, pathological, and clinical results of patients, who were admitted to our hospital and diagnosed with PT and evaluate them in the light of the literature. A total of 13 PT patients diagnosed in the pathology laboratory of Konya Training and Research Hospital between January 2010 and December 2019 were retrospectively analyzed. The mean age of the patients was 42.69 years (range, 18-64). The tumor location was the right breast in 4 (30.7%) patients and the left breast in 9 (69.3%) patients. Of the malignant PT, 1 (20%) was located in the right breast and 4 (80%) were located in the left breast. Of the patients, 5 (38.5%) were diagnosed with benign PT, 3 (23%) with borderline PT, and 5 (38.5%) were diagnosed with malignant PT. The mean tumor size was 7.7 cm, and the diameter of each of the malignant PT was larger than 7.7 cm, with a mean diameter of 12.9 cm. PT should be correctly identified at initial diagnosis and treated effectively, as the risk of recurrence is high. To develop new treatment modalities, we should especially understand malignant lesions well, and also attach importance to patient education and awareness.

INTRODUCTION

Phyllodes tumors (PT) are biphasic tumors characterized by a leaf-like structure arising from cleft-like spaces lined by epithelial cells and the hypercellular stroma[1]. PT is a very rare tumor of the breast, accounting for less than 1% of all breast tumors and 2.5% of fibroepithelial tumors. It most commonly occurs in women between the ages of 40 and 50 years[1,2].

Benign PT account for 60% to 75% of all cases[1,3]. The local recurrence rate of benign PT has been reported to be approximately 20%. The prevalence of borderline PT ranges from 12% to 26% in different series. The local recurrence rate has been reported to be between 14% and 25%. Approximately 10% to 15% of PT are malignant, with a local recurrence rate ranging from 15% to 40%. Of malignant PTs, 9% to 27% metastasize to distant organs. The most common metastasis sites are the lungs, bone, brain, and liver[1].

The standard treatment of PT is the removal of the tumor with a negative surgical margin of at least 1 cm to reduce local recurrence [4,5]. If patients with positive surgical margins have benign or borderline histology, they can undergo re-excision or be followed up closely. Patients with a positive surgical margin and malignant histology should undergo further surgery to achieve clear surgical margins. Adjuvant treatment options include radiation therapy, which has been shown to reduce local recurrence [5,6]. However, the role of adjuvant radiotherapy and chemotherapy in malignant PT remains unclear. Most patients with metastases do not respond to standard chemotherapy and die within 3 years after the initial treatment [1,7].

Researchers have suggested that stromal induction may occur in PT due to growth factors produced by the mammary epithelium. Trauma, pregnancy, increased estrogen activity, and breastfeeding is among the factors that stimulate tumor growth. The effect of these factors has not been fully understood, but endothelin-1, a stimulator of breast fibroblast growth, may be a contributing factor. Although there have been reports of progression of the fibroadenoma (FA) to PT, it most likely develops de novo [3].

On ultrasonography (USG) and mammography (MM), it is usually visualized as large, round, well-demarcated masses with lobulated contours and higher density than adjacent tissue, sometimes a halo can be visualized around the tumor clearly due to rapid growth. The cystic component, heterogeneous content without microcalcification, and posterior acoustic enhancement suggest PT rather than FA, especially when associated with rapid growth and large volume [3,4,7]. Visualization of solid components with greater concentration in hemorrhagic cystic cavities on magnetic resonance imaging (MRI) suggests PT [2,8].

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Since PT are rare, there are discussions on their naming, histopathological diagnosis, radiological appearance, treatment options, and recurrence. In this study, we aimed to describe the radiological, pathological, and clinical results of patients, who were admitted to our hospital and diagnosed with PT and evaluate them in the light of the literature.

MATERIALS and METHODS

Thirteen PT patients diagnosed in the pathology laboratory of Konya Training and Research Hospital between January 2010 and December 2019 were retrospectively analyzed. The slides stained immunohistochemically with hematoxylin-eosin were re-evaluated. Histopathological diagnosis was made in excisional biopsy specimens. The World Health Organization (WHO) classifies this tumor as benign, borderline, or malignant based on histological characteristics such as stromal cellularity, stromal overgrowth, stromal atypia, the number of mitoses per high-power field, and tumor margin. In benign PT, 0-4 mitotic figures are seen per 10 high power field (HPF), and minimal stromal cellularity and minimal stromal atypia are observed. In borderline PT, 5-9 mitotic figures are seen per 10 HPF, and its stromal cellularity and atypia are moderate. In malignant PT, ≥10 mitotic figures are seen per 10 HPF, and it involves moderate or severe stromal cellularity and atypia. Also, stromal overgrowth and infiltration into surrounding tissues are observed [9]. We classified the tumors according to these parameters. Demographic information such as gender, age, tumor location and tumor size, and clinical information such as radiological imaging, the presence of recurrence and metastasis were obtained from the patient files in the hospital's electronic database.

The study was approved by the Non-pharmaceutical and Medical Device Research Ethics Committee of KTO Karatay University.

RESULTS

The mean age of the patients was 42.69 (range, 18-64) years. All of the patients were female. The tumor location was the right breast in 4 (30.7%) patients and the left breast in 9 (69.3%) patients. Of the malignant PT, 1 (20%) was located in the right breast and 4 (80%) were located in the left breast. All borderline PT were localized in the upper outer quadrant (UOQ). Of the malignant PT, 2 (40%) were occupying all quadrants, 2 (40%) were localized in the UOQ, and 1 (20%) in the lower outer quadrant (LOQ). Of the benign PT, 3 (60%) were localized in UOQ, 1 (20%) in the upper inner quadrant (UIQ), and 1 (20%) was localized in the lower inner quadrant (LIQ). The main reason for admission was palpable mass, and the most common physical examination finding was painless mobile mass. Breast USG was used on all patients as the imaging technique, and MM was additionally performed on those over 40 years of age, and MRI was used on 2 patients. On USG, all malignant PT were identified as BI-RADS 4, 4 of the benign PT as BI-RADS 3, and 1 patient as BI-RADS 4. Of the borderline PT, 1 was identified as BI-RADS 3, 1 as BI-RADS 4, and the one with tubular carcinoma was identified as BI-RADS 5 (Figure-1). Core needle biopsy technique was used for the preoperative histopathological diagnosis of 11 patients. Of these, 5 were diagnosed with fibroepithelial lesions (FEL), 2 with a malignant tumors, 1 with cellular fibroadenoma (CFA), 1 with spindle cell neoplasia, 1 with tubular carcinoma, and 1 was diagnosed with fibroadipose tissue. The comparison of the histopathological diagnoses and postoperative histopathological diagnoses of the patients evaluated with core needle biopsy is shown in Table 1. Other clinicopathological characteristics are presented in Table 2. Of the patients, 5 (38.5%) were diagnosed with benign PT, 3 (23%) with borderline PT, and 5 (38.5%) were diagnosed with malignant PT. The mean tumor size was 7.7 cm (range, 2.3-16.5), and the diameter of each of the malignant PT was larger than 7.7 cm, with a mean diameter of 12.9 cm (range, 8.5-16.5). Only one of the patients diagnosed with borderline PT had a positive surgical margin and underwent re-excision. Three patients diagnosed with malignant PT underwent wide excision to achieve a negative surgical margin, 1 patient underwent a segmental mastectomy, and 1 patient underwent a mastectomy. In 3 of those with a clean surgical limit, the distance of the tumor to the surgical limit was less than 1 cm. Only one patient had a positive surgical margin. During the follow-up, recurrence was also observed in the tumor with a negative surgical margin of more than 1 cm. All recurrences were followed up within 1 year following the first surgical intervention. Four (80%) patients with a diagnosis of malignant PT who developed recurrence after surgery underwent mastectomy during the second surgical procedure. Lung and brain metastases were seen 6 months after one of the recurrences (tumor diameter was larger), and lung metastasis was observed 1.5 years after one of the recurrences. These patients who developed lung metastasis after surgery received adjuvant chemotherapy and radiotherapy. The patient with brain metastasis died at the end of the third year after diagnosis. Two of the patients had coexisting benign PT-ductal carcinoma in situ (DCIS). The DCIS component was of solid and cribriform morphology and included both grade 1 and grade 2 areas. In one of the patients diagnosed with borderline PT, areas of tubular carcinoma were observed within the tumor. All patients were followed up with physical examination and appropriate imaging techniques of MM/USG/MRI at 3-month intervals in the first year, 6-month intervals in the second year, and once a year in the following years. Local recurrence and metastasis did not develop in borderline and benign PT.

Table 1. Comparison of histopathological diagnoses of core needle biopsy specimens with histopathological diagnoses of surgical specimens

Histopathological diagnoses of core needle biopsy	n †	Surgical method	Histopathological diagnoses of surgical specimens	Surgical margin status
Cellular fibroadenoma	1	Wide excision	Malignant PT ‡	Positive
Malignant tumor	2	Mastectomy	Malignant PT	Negative
		Segmental Mastectomy	Malignant PT	Negative
Fibroepithelial lesion	5	Wide excision	Benign PT(n=3)	Negative
			Borderline PT (n=1)	Positive
			Malignant PT (n=1)	Negative
Spindle cell neoplasia	1	Wide excision	Benign	Negative
Fibroadipose tissue	1	Wide excision	Borderline PT	Negative
Tubular carcinoma	1	Mastectomy	Borderline PT	Negative

†:Number of cases, ‡: Phyllodes tumor

Table 2. Clinicopathological characteristics of tumor types

Diagnosis	Age	Localization	Tumor size (cm)	BI-RADS (USG) †	The number of mi-toses /10 HPF	Ki67 PI‡ (%)	Relapse	Malignant epithelial component
Benign	47	Left UOQ§	2,5	3	1	*	Absent	Absent
	33	Left LIQ‖	5,5	3	2			Absent
	60	Left UOQ	2,8	3	1			Absent
	18	Right LIQ	3	3	3			DCIS**
	59	Left UOQ	2,3	4	2			DCIS
Borderline	38	Right UOQ	7,5	3	8	25	Absent	Absent
	47	Left UOQ	9	4	5	20	Absent	Absent
	64	Right UOQ	3,7	5	7	30	Absent	Tubular carcinoma
Malignant	35	Left UOQ	14,5	4	15	40	Present	Absent
	33	Left LOQ¶	11	4	55	40	Present	Absent
	21	Left all quadrants	14	4	17	50	Present	Absent
	59	Left UOQ	8,5	4	15	35	Present	Absent
	41	Right all quadrants	16,5	4	13	35	Absent	Absent

†:Ultrasonography, ‡:Proliferation index, §:Upper outer quadrant, ‖ :Lower ınner quadrant,
¶:Lower outer quadrant, **:Ductal carcinoma in situ
*:Ki67 immunohistochemical staining was not applied to benign phyllodes tumors

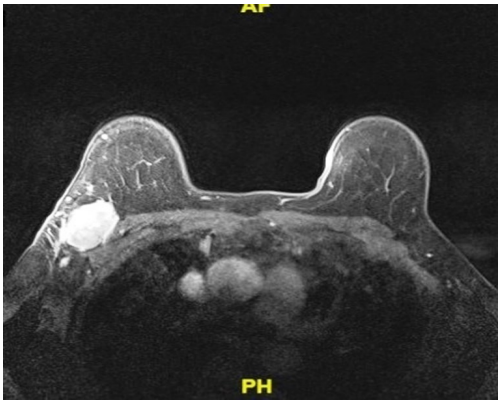

Figure 1. Hyperintense BI-RADS 5 tumor lesion with contour irregularity in the inferomedial part extending from the upper outer quadrant of the right breast to the axillary tail on T1A images, MRI

On macroscopic examination, cut surfaces of nodular masses with relatively well-circumscribed lobulated contours (Figure-2) were grayish-skin color and had a homogeneous appearance. They contained myxoid areas and cystic spaces. In addition to these findings, bleeding areas and necrosis were observed in malignant PT. Also, bulging was observed on the cut surface of the tumors.

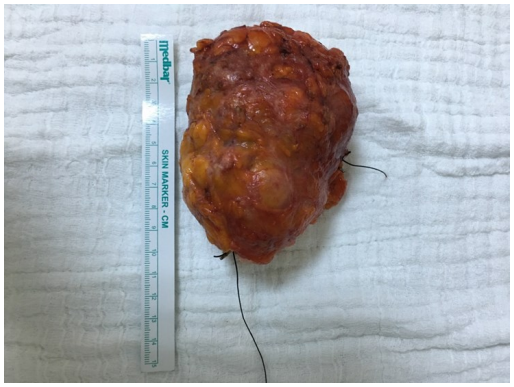

Figure 2. Macroscopic appearance of phyllodes tumor

The histopathological examination revealed epithelial and myoepithelial cell layers lining the branching cleft-like spaces, and stroma with increased cellularity around the cleft-like spaces in benign PT (Figure-3). Cytological atypia was not observed, and the mean mitotic figure number per 10 HPF was 1.8 (1-3). On the histological examination of borderline PT, increased stromal cellularity was noted (Figure-4), and the mean mitotic figure number per 10 HPF was 6.6 (5-8). Nuclear pleomorphism, prominent nucleoli, cytological atypia, bleeding, and necrosis were observed in malignant PT. The lesions had limited infiltration and the stroma was highly cellular, while the mean mitotic figure number per 10 HPF was 23 (13-55) (Figure-5). DCIS (solid and cribriform type) was identified in two benign phyllodes tumor patients (Figure 6), and tubular carcinoma in one borderline PT patient. Ki67 proliferation index was 30 for borderline PT and >30 for malignant PT.

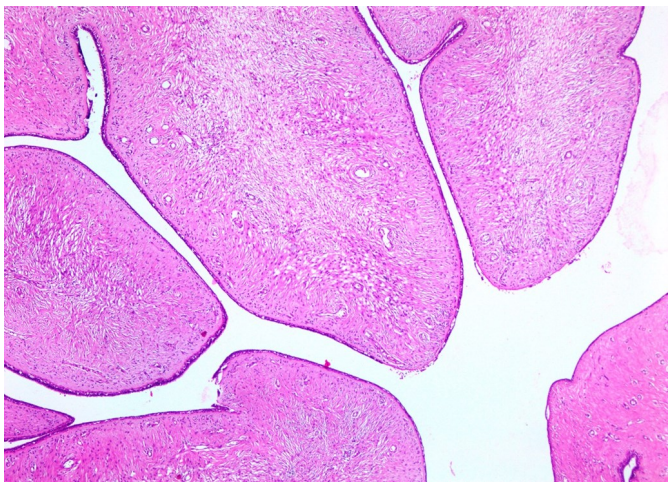

Figure 3. Epithelial and myoepithelial cell layers lining the branching cleft-like spaces and stroma with mildly increased cellularity around the cleft-like spaces, benign PT (H&E stain x40)

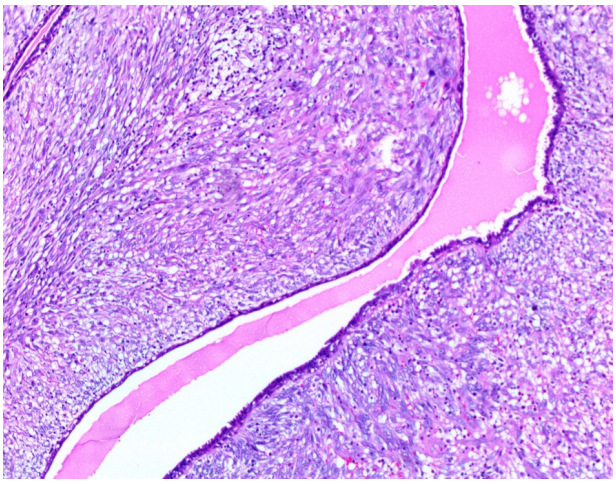

Figure 4. Moderately increased cellular stroma around the cleft-like spaces, borderline PT (H&E stain X100)

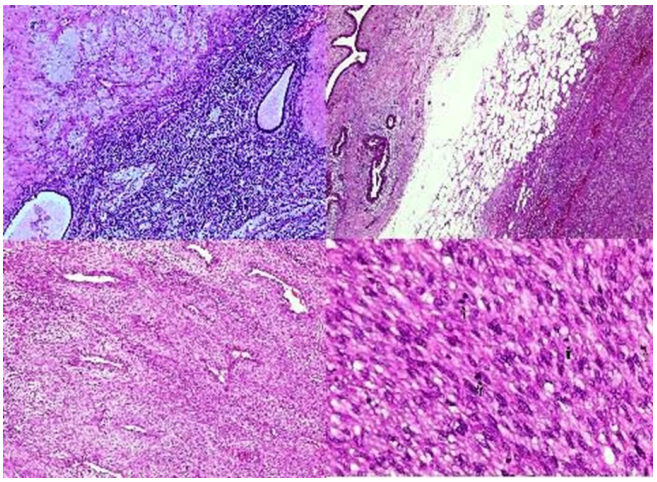

Figure 5. Prominent cytological atypia, infiltrative border, and cellular stroma, increased mitotic count, malignant PT (H&E stain)

DISCUSSION

PT are rare fibroepithelial tumors that make up less than 1% of all breast tumors. Clinically, they tend to present with unilateral, painless breast masses that stretch the overlying skin. In some cases, bloody nipple discharge caused by spontaneous infarction of the tumor has been described. Ulceration and nipple retraction are rare. While axillary lymphadenopathy is common, nodal metastases are rare[3,10].

Phyllodes tumors tend to appear as a large breast mass. The diameter of the mass can range from 1 to 45 cm and cover the entire breast. In their study including 145 benign, 33 borderline, and 15 malignant PT, Kim et al. found a mean tumor diameter of 4 cm and a mean tumor diameter of 6.2 cm for malignant PT[11]. In our series, the mean tumor diameter was 7.7 cm, the mean diameter of malignant PT was 12.9 cm, and both values were greater. In the literature, the most commonly affected site is the upper outer quadrant, and multifocality and bilaterality have been reported[12]. In our series, in line with the literature, the most commonly affected site was the upper outer quadrant, and all masses were unilateral. It most frequently occurs in the age range of 40-50 years, which is 20 years older than the age at which FA occurs[4,8,12]. In our patient group, the mean age at the diagnosis of the tumor was 42.69 years, and malignant PT tended to be seen at a younger age compared to breast cancer, as in the series of Weng et al[7].

The local recurrence rate of benign PT has been reported to be approximately 20%. The local recurrence rate of malignant PT varies between 15% and 40%[7]. Recurrent malignant PT may have a more aggressive biological behavior than the first tumor[12]. We only observed recurrence in our malignant PT cases, with a recurrence rate of 80%, which was quite high compared to the literature. Of malignant PT, 9% to 27% metastasize to distant organs[10]. The most common metastasis is to the lungs, and we found lung metastasis in 40% of our malignant PT cases.

There is no pathognomonic radiological finding that differentiates between FAs and benign, borderline, and malignant phyllodes tumors. Recent studies have reported that contrast-enhanced MRI findings such as a tumor size over 3 cm, poorly circumscribed and microlobular structure, heterogeneous appearance in echogenicity, hypervascularity, and the presence of internal cystic cavities support PT in the differential diagnosis of two tumors[6,10,12,13]. Moreover, solid components with greater concentration in hemorhagic cystic spaces on MRI suggest PT. On USG and MM, large, round, lobulated, well-circumscribed masses with a higher density than adjacent tissue are usually visualized. Cystic areas, heterogeneous content without microcalcification, and acoustic enhancement suggest PT rather than FA, especially when associated with rapid growth and large volume[2,8]. The American College of Radiology (ACR) BI-RADS lexicon classification is a standard reporting guideline widely used for the assessment and classification of breast lesions[13]. According to the results of a radiological evaluation of our cases, there were no findings that would differentiate between histological subtypes in the classification of BI-RADS.

Rarely, ductal and lobular carcinoma in situ and invasive carcinoma may develop from the PT epithelium. Rodrigues et al. reported a total of 11 patients with malignant epithelial transformation in a series of 183 cases[14]. DCIS or invasive breast carcinomas may develop in association with PT, but they are very rare and occur in only about 1% of patients with PT[12,15]. In our series, the concomitant malignant epithelial transformation was observed in 3 (23%) of 13 patients, which was significantly higher than those reported by other studies. In our series, the prevalence rates of benign, borderline, and malignant PT were 38.5%, 23%, and 38.5%, respectively. Among all PT, the prevalence rates of the others, except for borderline PT, were not consistent with the data in the literature.

PT is difficult to differentiate in core needle biopsy materials;increased stromal cellularity should be reported as FEL, and excision of the mass should be recommended. In our series, the most common core needle biopsy diagnosis made was FEL. Of the malignant PT patients, 1 was diagnosed with CFA, 1 with FEL, and 2 with malignant tumors[12]. Histological heterogeneity in stromal cellularity and structure in PT may cause difficulty in differentiating between PT and CFA in core needle biopsy. Stromal cellularity should be categorized as mild, moderate, or prominent, and the area with most cells should be assessed. The threshold for mild stromal cellularity is not well defined. Jacobs et al. evaluated the mildly increased stromal cellularity approximately twice the cellularity of normal perilobular stroma, with no or rare stromal nuclei appearing to touch each other[16]. While data on increased stromal cellularity are inconsistent, many studies have found that subepithelial condensation of stromal cells is a common characteristic of PT and that it may be the best predictor of PT in core needle biopsies. Stromal overgrowth, described as stromal proliferation without epithelial elements in at least 1 low power field (×40), is a characteristic of PT[1]. In our series, areas without epithelial space, areas defined as a stromal overgrowth in surgical specimens, were interpreted as malignant tumors in core needle biopsy.

The presence of heterologous sarcomatous elements (liposarcoma, chondrosarcoma, and osteosarcoma) alone qualifies a PT as malignant. The differential diagnosis of malignant PT includes sarcomas and sarcomatoid metaplastic carcinoma. The differentiation of malignant

PT from metaplastic carcinoma is based on morphology. Nuclear pleomorphism, abundant mitosis, and spindle cells with heterologous elements can be seen in metaplastic carcinoma, as in malignant PT. The heterologous sarcomatous element was not observed in any of our malignant PT cases. The presence of benign epithelium lining the leaf-like structure and cleft-like spaces is characteristic of PT, whereas if malignant epithelial elements are present, metaplastic carcinoma is more likely. Histopathologically, a stromal component rather than an epithelial component is present in the metastatic PT focus[12]. If there is no epithelial component, immunohistochemistry may be helpful, especially in core biopsy. It has been reported that CD34 is positive in approximately 75% of PT and negative in metaplastic carcinoma. However, CD34 positivity was observed in only 37% to 57% of malignant PT. CD34 was positive in 2 (40%) of the malignant PT patients in our series, with no CD117 expression observed in any of them. Multiple immunohistochemistry markers have been studied to improve the classification of PT and predict outcomes. Studies have shown that the expression of p53, Ki67, CD117, EGFR, p16, and VEGF are correlated with histological grades of PT, none have been proven to be clinically useful. Among these markers, p53 expression and Ki67 index have been reported to be significantly correlated with disease-free and overall survival in some studies, but other studies have found no correlation with relapse or clinical behavior. The Ki67 PI of recurrent malignant PT in our series was ≥35%. PAX3 and SIX1 expression by immunohistochemistry and gene expression analysis has recently been described in borderline and malignant phyllodes tumors and is associated with a poor clinical outcome[3,10].

PT may contain benign, borderline, and malignant foci intermingled within the same neoplasm, making careful gross examination and histologic sampling particularly important. Therefore, given PTs histologic heterogeneity, excision is required to accurately classify and grade PT. The primary treatment of PT is surgical excision. Large tumors require a mastectomy. Although the incidence of local recurrence secondary to breast-conserving surgery is higher, studies have shown no difference in metastasis-free survival or overall survival between breast-conserving surgery and mastectomy. Studies are stating that the scope of surgery is not related to disease-free survival or local recurrence as long as the surgical margins are disease-free; however, some studies recommend the removal of the tumor with a clean surgical margin of at least 1 cm to reduce local recurrence. PT shows hematogenous spread. The rate of axillary metastasis is low, and therefore it has been observed that axillary lymph node sampling is not required in PT cases[6,12]. The National Comprehensive Cancer Network(NCCN) recommends the use of RT in recurrent malignant PT cases. Some authors recommend adjuvant RT to reduce the likelihood of local recurrence in both borderline and malignant PT patients treated surgically[3,6,8,12]. Although there is no routine chemotherapy protocol for the treatment of PT, it is recommended that it be treated like sarcoma. Studies are indicating that the local recurrence rate is as low as 0-13% in benign PTs and that positive surgical margin is not associated with local recurrence. Therefore, local excision and close follow-up are sufficient for such cases[6].

The five-year and overall survival rates for patients with benign and malignant PT have been reported to be 91% -100% and 53.4% -91%, respectively[6]. One of our patients who was diagnosed with malignant PT died at the end of the third year after surgery.

Conclusion

Since most of the studies to date have a small number of specimens with borderline and malignant tumors, there is a need for further research including well-defined PT with follow-up data. A fast -growing, painless mass in the breast should be a warning sign for PT diagnosis. The contribution of imaging techniques is limited, and biopsy is required for diagnosis. PT should be correctly identified at initial diagnosis and treated effectively, as the risk of recurrence is high. To develop new treatment modalities, we should especially understand malignant lesions well, and also attach importance to patient education and awareness.

Conflict of interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in anyfirm.

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