

Phyllodes tumors of the breast treated in a tertiary health care center: case series and literature review

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Abstract

Objective: This study was performed to determine the subtypes of phyllodes tumor (PT) in patients at a single tertiary healthcare center in Lebanon and to describe their characteristics along with a review of the literature.

Methods: This single-institution retrospective cohort study included all cases of PT of the breast treated at the American University of Beirut Medical Center from 1 January 2010 to 31 December 2014. The patients' demographic data, tumor characteristics, treatment data, and pathology reports were analyzed.

Results: Thirty patients were enrolled. Their median age was 42 years. In total, 66.7% had benign disease and 22.3% had malignant disease. Twenty-seven patients underwent surgery, four received radiotherapy, and one received systemic chemotherapy after PT progression. Twenty-seven patients had no recurrence at the last follow-up, two had local recurrence, and one had metastatic disease. All three patients with recurrence had an adequate negative surgical margin at the first excision.

Conclusion: This is the first cohort of patients with PT described in Lebanon and one of few in the Middle East. Our findings provide insight into the epidemiology, treatment modalities, and prognosis of PT in this geographical region.

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Keywords

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Introduction

Phyllodes tumors (PTs), previously known as cystosarcoma phyllodes, account for 0.5% to 1.0% of all breast tumors and 2.5% of all fibroepithelial tumors.^{1,2} They derive their neoplastic potential from mesenchymal cells and are thus histologically distinguished from adenocarcinoma of the breast.² PTs are histologically classified by the World Health Organization (WHO) as benign (35%–64%), borderline, and malignant (10%–30%). Malignant PTs tend to recur and metastasize at a higher frequency than the other forms of PT.³ Surgical excision with negative surgical margins is the mainstay of treatment and is associated with relatively high disease-free survival and long-term survival rates and a low recurrence rate.^{4,5} Radiation therapy (RT) is often used because PT tends to be locally aggressive.^{6–8} The role of chemotherapy and hormonal therapy has not been established.

Study aims

Given the paucity of data regarding PT in general and in the Middle East in particular, the aims of this study were as follows:

1. Review the cases of PT in patients treated at a single tertiary health care center in Lebanon
2. Describe the histological subtypes of PT according to the WHO classification, the characteristics of PT, and the survival of patients with PT treated at a single tertiary health care center in Lebanon

3. Compare the characteristics of patients with PT treated at our center with the data available in the literature

Methodology

This single-institution retrospective cohort study was based on a chart review of all cases of PT of the breast treated at the American University of Beirut Medical Center (AUBMC), a tertiary health care center, from 1 January 2010 to 31 December 2014. Ethical approval for the study was obtained from the American University of Beirut Medical Center's institutional review board. Patients were enrolled in the study after they provided verbal informed consent.

Patients of all ages with a histologically proven PT of the breast were eligible for inclusion. A list of patients with PT of the breast treated at AUBMC was obtained from the hospital's medical records department. Patients were enrolled in the study after they provided verbal informed consent. Each patient's hospital medical chart was reviewed for demographic data, clinical data, and pathological findings. Pathology reports were reviewed to obtain data on the histological type, WHO tumor grade, and Ki-67 value. Each patient's treatment was also evaluated (surgery, RT, systemic therapy, combined-modality treatment, or observation).

The data were compiled with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) using identification numbers. No patient names or case

numbers were collected or used at any point. Statistical analysis was performed using SPSS. Descriptive analyses of demographics, treatment modalities, and tumor characteristics were conducted.

Results

Patient characteristics

We identified 61 patients in our medical registry with a diagnosis of PT. However, 31 of these patients did not undergo pathological studies or surgical procedures at our institution; rather, they presented for a consultation. Thus, our study cohort comprised 30 patients with histologically proven PT. The median age of the study population was 42 years (mean, 43 years). Only five (16.7%) patients had a history of previous cancer; one of these five had a history of breast cancer (non-PT). Four patients had a family history of breast cancer. None of the patients had previously received RT. Additionally, only one patient had a history of oral contraceptive pill use, and none had used hormonal replacement therapy. The patients in the study had a mean of two pregnancies (median, 1 pregnancy; range, 0–6 pregnancies) (Table 1).

Tumor characteristics

Of the 30 patients, 19 (63.3%) had left breast disease, 10 (33.3%) had right breast disease, and 1 (3.3%) had bilateral disease. Twenty-one (73.3%) of the 30 patients

underwent a biopsy at our center, while the rest of the patients brought biopsy results that had been obtained at another medical center. Twenty-seven (90.0%) patients underwent surgical tumor removal. Of these 27 patients, 23 (85.2%) underwent partial mastectomy and 4 (13.3%) underwent simple mastectomy. The median size of the patients' tumors was 4.5 cm, and the mean was 5.0 cm. Of the 27 patients who underwent surgery, pathological examination of the surgical specimen showed that 5 (18.5%) patients had positive surgical margins. According to the WHO grading system, 18 (66.7%) of the resected tumors had benign features, 3 (11.1%) had borderline features, and 6 (22.2%) showed malignant features.

In our study population, four (13.3%) patients received RT. Only one (3.3%) patient received a combination of surgery, RT, and systemic chemotherapy because of progressive disease and the malignant nature of the tumor. The three patients who did not receive surgery were observed, and their disease was still stable on the date of the last follow-up (Table 2).

Current status

Twenty-seven of 30 (90.0%) patients were stable at the last follow-up and had no disease recurrence. Three (10.0%) patients had progressive disease with local tumor recurrence. One of these three patients had a malignant tumor at the first diagnosis and later developed metastasis to the thoracic

Table 1. Patient characteristics

Patient characteristics		
Median age, years	42	
History of cancer	Yes 16.7% (n = 5)	No 83.3% (n = 25)
Family history of breast cancer	Yes 3.3% (n = 1)	No 96.7% (n = 29)
Oral contraceptive pill use	Yes 3.3% (n = 1)	No 96.7% (n = 29)
History of ionizing radiation	Yes 20.0% (n = 6)	No 80.0% (n = 24)

Table 2. Tumor characteristics and treatments

Tumor characteristics and treatments			
Side of breast tumor	Left 63.3% (n = 19)	Right 33.3% (n = 10)	Bilateral 3.3% (n = 1)
Biopsy at our center	Yes 73.3% (n = 21)	No 22.7% (n = 9)	
Surgery	Yes 90.0% (n = 27)	No 10.0% (n = 3)	
Type of surgery	BCS 85.2% (n = 23)	Mastectomy 14.8% (n = 4)	
Positive margins following resection	Yes 18.5% (n = 5)	No 81.5% (n = 22)	
WHO grade	Benign 66.7% (n = 18)	Borderline 11.1% (n = 3)	Malignant 22.2% (n = 6)

BCS, breast-conserving surgery; WHO, World Health Organization

spine. The patient underwent resection of the metastatic tumor followed by chemotherapy. Another patient had a borderline tumor at the first diagnosis; the tumor recurred twice in the same breast, and the patient thus underwent surgical excision twice. Positive margins were found following the last excision, and the patient was being closely observed with no recurrence at the time of this writing. The third patient with recurrence had a benign histology at the first diagnosis; the tumor recurred once in the same breast, and she underwent surgical excision. She was still being closely observed with no recurrence at the time of this writing.

Discussion and review of the literature

PT accounts for 0.5% to 1.0% of all breast tumors and 2.5% of all fibroepithelial tumors.^{1,2} It is composed of epithelial and mesenchymal elements, the latter giving it its neoplastic features.² The WHO identified three types of PT on the basis of its histologic characteristics: benign, borderline, and malignant.⁹⁻¹¹ These types help to predict the likelihood of developing local recurrence, metastatic disease, or both. Many PTs are benign (35%–64%); the benign and borderline types almost never recur. Malignant tumors account for

10% to 30% of all PTs, and they have a higher chance of recurrence and metastasis.³

PT occurs most frequently in women aged 35 to 55 years and presents as a well-circumscribed, smooth, firm, and rarely painful mass.^{3,12} Hispanic and Asian women and women with prior radiation exposure to the chest are more prone to developing PT.^{2,13}

Because even benign PT is known to be locally aggressive, it was historically treated by mastectomy to ensure high rates of local control and disease-free survival. However, mastectomy has been replaced by breast-conserving surgery (BCS) with adequate surgical margins as the treatment of choice, and the two techniques have been found to provide comparable survival benefits.¹⁴⁻¹⁷ The most common site of metastases of PTs is the lung, followed by the bone, heart, and liver.¹⁸ Because axillary lymph node metastasis occurs in <1% of patients with PT, axillary lymph node dissection is not routinely performed.^{19,20} Patients with clinically palpable axillary nodes require axillary dissection; sentinel node biopsy may be performed if nodes are not palpable.²¹

The optimal treatment for PT is resection with a ≥ 1 -cm margin all around, particularly for borderline and malignant PT. The size of the tumor determines the choice of surgery (lumpectomy versus wide local

excision versus simple mastectomy).²² Notably, when tumor-free margins of at least 1 cm cannot be achieved by BCS or adjuvant RT for malignant PT, mastectomy is indicated.²³

The likelihood of local recurrence and distant metastasis in patients with PT is mainly determined by the histotype of the tumor and the margins after resection.^{17,24–27} In two studies, all patients with recurrence of PT had positive surgical margins.^{4,21} Thus, negative margins might improve long-term survival and disease-free survival and reduce recurrence.^{4,5}

Management of PT metastasis is governed by the same principles as management of soft tissue sarcoma.²⁸ Wide local excision is the first-line surgical treatment regardless of histological grade; however, mastectomy is necessary if the disease recurs.²⁹

Role of chemotherapy

A role for adjuvant chemotherapy or hormonal therapy in PT has not yet been established. The epithelial cells of adenocarcinoma express estrogen receptor- α , which responds to hormonal therapy. In contrast, the malignant nature and metastatic behavior of PT are due to the expression of estrogen receptor- β by stromal cells.^{30,31}

The earliest data on the use of systemic chemotherapy came from case reports and case series in the 1980s and 1990s, in which diverse regimens and combinations of cytotoxic chemotherapy were used with variable responses. In one case series of three patients with metastatic malignant cystosarcoma phyllodes, a significant clinical response was observed in two patients who received cisplatin and etoposide.³² In another case series of four patients who received ifosfamide alone, complete remission was achieved in two patients.³³

A study of 162 patients in India revealed no improvement in survival in some patients with metastatic disease who

received doxorubicin and ifosfamide, but the authors provided no statistics or further details in relation to this finding.³⁴ A retrospective observational study in Tunisia enrolled 30 patients with primary breast sarcoma, 18 of whom had phyllodes sarcoma.³⁵ Ten patients (33%) received adjuvant doxorubicin and ifosfamide, but no data on outcomes in relation to chemotherapy alone were reported.³⁵ A retrospective study of 165 patients from Institut Curie in France included eight patients who received six cycles of adjuvant doxorubicin with ifosfamide for 6 cycles, but the benefit of chemotherapy remained unproven.³⁶ Another study at Institut Curie included 25 patients, 13 (52%) of whom received anthracycline-based adjuvant chemotherapy; however, the authors could not determine the role of chemotherapy in overall and progression-free survival.²⁷

Only one observational study on the role of chemotherapy in the treatment of PT of the breast has been published.³⁷ This study enrolled 28 women; 17 underwent adjuvant chemotherapy, while the remaining 11 women were only clinically followed up. The outcomes of the women in the adjuvant chemotherapy arm were worse than those of the women in the observation arm: the 5-year recurrence-free survival rate was 58% in the chemotherapy group versus 86% in the observation group, but the difference was not statistically significant. The 5-year overall survival rate was 58% in the chemotherapy group versus 69% in the observation group.³⁷ It is important to note that this study was nonrandomized and underpowered, and the differences failed to achieve statistical significance.

The above findings clearly indicate that definitive evidence regarding the role of chemotherapy, the indications for chemotherapy, and the best treatment regimen has yet to be published. Molecular studies might offer an answer in the future. For example, next-generation sequencing of metastatic

malignant PT at MD Anderson Cancer Center in the United States revealed high expression of markers of sensitivity to taxane-based therapies (*TLE3*) and especially to albumin-bound paclitaxel (*SPARC*).³⁸

Role of radiation therapy

Because of the absence of large prospective trials, the role of adjuvant RT remains debatable despite its common use in patients with positive or close resection margins. Postoperative RT after BCS needs to be considered irrespective of the margin status because it offers better local control despite the absence of convincing evidence of a survival benefit.⁶⁻⁸

A review of the Surveillance, Epidemiology, and End Results Program (SEER) data from 1983 to 2002 indicated that patients who received postoperative RT had poorer treatment outcomes than those who did not.¹ However, the sample size was small and there were some missing data for crucial pathologic factors that could not be included in the multivariate analysis. A prospective study of margin-negative BCS followed by RT showed no local recurrence at the 5-year follow-up,⁷ whereas two other studies revealed a 22% to 50% local recurrence rate of malignant PT of the breast after margin-negative BCS.^{39,40}

Belkacémi et al.³⁹ also reported that additional RT provided local control in patients with malignant and borderline PT who had undergone wide excision and had a tumor-free margin of ≥ 1 cm (10-year local control rate of 86% in those who received RT and 59% in patients without RT, $p = 0.02$); however, additional RT had no effect on disease-free survival or overall survival.

A meta-analysis of eight studies showed a significant decrease in the risk of local recurrence in patients with borderline and malignant PTs who received adjuvant RT after BCS (hazard ratio [HR], 0.31; 95%

CI, -0.10 – 0.72), but there was no difference in the combined HR for local recurrence in the total mastectomy group with versus without RT (HR, 0.68; 95% CI, -0.28 – 1.64). However, overall survival and disease-free survival were not altered by adjuvant RT in either group.⁴¹

An analysis of the National Cancer Database demonstrated reduced local recurrence (HR, 0.43; 95% CI, 0.19–0.95) in patients who received adjuvant RT (14.3% of the study population), but adjuvant RT had no impact on disease-free survival or overall survival.⁸ Mitus et al.²³ reported a similar 5-year disease-survival rate (83.3%) in patients with tumor-free margins of < 1 cm who underwent BCS along with RT and in patients with tumor-free margins of ≥ 1 cm who only underwent BCS.

An analysis of the updated SEER 18 data (1983–2013), which involved 1974 patients with malignant PT of the breast, showed that patients with more adverse prognostic factors were treated with postoperative RT and that BCS was not statistically different from the non-RT group, regardless of the type of surgery.⁴²

Our study population

The median age of our study population (42 years) is consistent with the median age range of 35 to 55 years reported in the literature.^{3,12} Most of the tumors in our study population (66.7%) were benign according to the WHO grading system, slightly exceeding the 35% to 64% rate of benign disease cited in the literature.³ This discrepancy may be related to the small sample size of our population. Our finding that 22.2% of patients had malignant disease is consistent with previous studies, which showed that 10% to 30% of patients with PT have a malignant course.³

As stated earlier, total mastectomy and BCS offer comparable survival benefits.¹⁴⁻¹⁷ Most of the patients in the

present study underwent BCS, and only 13.3% underwent mastectomy. The preference for BCS is not related to the overall survival benefit but rather to advantages of BCS that are unrelated to the disease.

Chemotherapy was not shown to have a significant role in the treatment of PT. Multiple retrospective studies and case series have produced conflicting reports concerning the benefit of chemotherapy.^{30–33,38} Hence, in our study population, the physicians' choice to not prescribe chemotherapy for most patients was justified. Only one patient received chemotherapy as part of her treatment; therefore, the sample size was not sufficient to determine the survival benefit of chemotherapy in our study.

Four patients in our population received adjuvant RT. Other studies have indicated that RT for PT offers no survival advantage over surgery alone. However, RT needs to be considered to boost the effect of surgery and improve local disease control.^{6–8} While most patients in our study did not develop disease recurrence despite the absence of RT, the sample size was not large enough to determine the benefit of RT in terms of local control.

Finally, studies have shown that negative margins following resection might improve long-term survival and reduce disease recurrence.^{4,5,21} However, the patients with positive margins in our study did not develop disease recurrence, while the three patients with progressive or recurrent disease had previously attained negative margins following surgical tumor resection. This could again be explained by the rather small size of our sample because no statistical significance was extrapolated from these data.

As noted above, this study is limited by the small number of patients included in the analysis. This limitation is caused by the rather small population in Lebanon, the rarity of PT, and the inclusion of only one hospital center. The data extraction

relied solely on a review of paper-based medical records, with the inherent limitations and operator-dependence of these medical records. Nevertheless, this remains the first cohort of patients with PT described in Lebanon and one of few described in the Middle East, and it provides helpful insight into the epidemiology, treatment modalities being used, and prognosis of PT in this geographical region.

Conclusion

PTs are locally aggressive and mostly benign breast tumors with significant survival and cure rates. BCS and mastectomy are the first line of treatment for such tumors. Patients may receive RT to improve local control and decrease local recurrence rates. Chemotherapy has not been shown to play a definitive role in the treatment of PT to date. Despite the small sample size of our study population, it remains mostly consistent with the available literature regarding the epidemiology, tumor characteristics, and treatment course of PT.

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Consent for publication

This manuscript contains no individual person's data in any form; therefore, consent for publication was not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HA conceived of the study and participated in its design, patient recruitment, and manuscript drafting and functioned as the main study coordinator. RS participated in the study design, patient recruitment, data collection, and drafting of the manuscript. FS participated in the study design, patient recruitment, data collection, statistical analysis, and drafting of the manuscript. MS participated in the patient recruitment, data collection, and drafting of the manuscript. JA participated in the patient recruitment and drafting of the manuscript. NS participated in the study design, patient recruitment, and drafting of the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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