original article

Phyllodes tumor of the breast: a retrospective study of the impact of histopathological factors in local recurrence and distant metastasis

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BACKGROUND AND OBJECTIVES: The challenging issue for the breast surgeons is local recurrence of phyllodes tumor. The histological criteria to predict local recurrence has been a controversial issue. The objective of this study was to determine pathological parameters and surgical margins that influence outcome of local recurrence and distant metastasis in phyllodes tumor (PT).

DESIGN AND SETTING: Retrospective review between January 2003 to August 2008 at King Hussein Cancer Center-Jordan.

PATIENTS AND METHODS: Forty-two female patients diagnosed as having PT were classified to benign, borderline and malignant. The medical records were reviewed in relation to the surgical management, recurrence, follow-up, the histological features of the tumor and grading of tumours based on the following histological parameters: mitotic count, stromal cellularity, stromal overgrowth, cellular pleomorphism, nuclear grade, tumor necrosis, tumor margin, and surgical margin status. All patients underwent wide local excision of the tumor or mastectomy.

RESULTS: Forty-two patients with PT (16 benign, 9 borderline, 17 malignant PT) were followed up for 30 months. The mean age was 39.8 years, and the average tumor size was 6.6 cm. The recurrence rate of PT in our study was 21% at a mean time of 11 months. Nine patients had local recurrence; 2 benign, 6 malignant and 1 borderline. Cellular pleomorphism had correlation with recurrence rate (*P*=.045). We had six patients (14%) with distant metastasis. All had malignant PT. Metastasis in PT has a relationship with histological grade (*P*=.02).

CONCLUSIONS: We conclude that patients with moderate and severe cellular pleomorphism had higher local recurrence, while metastatic PT occur more in patients with high nuclear grade.

Mammary phyllodes tumors (PTs) are uncommon biphasic, fibroepithelial neoplasms composed of epithelium and a spindle-cell stroma that accounts for 0.3-1% of all primary breast tumors.[1] The behavior of PTs in all forms (benign, borderline, and malignant) is unpredictable[2] and the distinction between benign, borderline and malignant tumors is often difficult and does not always reflect the clinical behavior. Triple assessment by clinical, radiological and histological examination forms the fundamental basis for the evaluation of PTs. Treatment could be either by wide excision or mastectomy provided that clear histological margins are achieved. Wide local excision with at least 1 cm clear margin is currently the standard of treatment of PT in most institutions.[3-5] To date, the local recurrence rate in PT is approximately 15%.[6-8] Local recurrence usually occurs within the first few years following surgery, especially if it was with incomplete excision.[3] Some authors argue that histological criteria can be used to predict the likelihood of local recurrence.[9] Local recurrence can usually be controlled by another surgery including wider excision or even mastectomy.[2] It is unclear whether malignant PTs are associated with high recurrence rate[10,11] or whether the positive margins are responsible for this recurrence.[2,5] Approximately 20% of patients with malignant PTs develop distant metastasis.[4-6,12] Most distant metastasis develops without evidence of local recurrence, while several studies have shown that local recurrence is a strong predictor of metastatic spread.[13-15] The most

common sites for distant metastasis are the lung, bone, limbs and rarely to the abdominal viscera.[16] The objective of this study was to determine pathological parameters and surgical margins that influence outcome of local recurrence and distant metastasis in PT patients managed at King Hussein Cancer Centre.

PATIENTS AND METHODS

This was a retrospective study involving 42 consecutive patients with PT. The database from department of surgery and anatomical pathology at King Hussein Cancer Center, Amman, Jordan was utilised to identify 42 patients diagnosed with PT by histopathology from January 2003 to August 2008. The study was conducted with prior approval of the institutional review board. Each individual case history was reviewed from hospital records to obtain demographic and clinical data which are illustrated in **Table 1**. The tumors were classified into benign, borderline and malignant according to the WHO classification.[17] The medical records were reviewed according to the surgical management, the histological features of the tumor as well as recurrence and follow-up. Triple assessment was obtained by clinical, ultrasonography and/or mammography and true-cut biopsy. All patients underwent wide local excision of the tumor or mastectomy based on the breast-to- tumor ratio, grade of the tumor, margin status and recurrence. All of the original haematoxylin and eosin slides were prepared using formalin fixed paraffin embedded. Routine haematoxylin and eosin staining procedure was done and reviewed blindly by a single pathologist using 3 μm thick paraffin sections. Cases with no archived paraffin blocks were excluded. The pathological diagnosis and grading of tumors were reviewed based on the following histological parameter: mitotic count (per 10 high power field [HPF]) using 40× lens Olympus BX 41 microscope, stromal cellularity (low-intermediate-high). The grades of stromal cellulariy were selected based on the a) amount of the cells. Typically, the stroma shows a variable degree of stromal cellularity, with some areas being hypocellular and other areas being hypercellular, b)the stromal cells may show variable nuclear pleomorphism, ranging from a bland appearance to frankly sarcomatous morphology, c) mitotic activity, d) stromal overgrowth (present or absent; defined as at least one 40× field of stroma without epithelium),[18] scromal nuclear atypia/cellular pleomorphism (mild-moderate-severe), nuclear grade (low grade: well differentiated and mitotic figure 2-5/HPF), (intermediate grade: moderate differentiated and mitotic figure 5-10/HPF), (high grade: mitotic figure >10/HPF with bizarre looking cells and hyperchromatism in the nucleus with irregular nuclear borders) and other features including tumor necrosis, tumor margin (infiltrative versus pushing with compression adjacent tissues), surgical margin status (positive or negative) <1 mm versus >1 mm. We considered a microscopic safety margin of 1 mm as a cutpoint. Typically a benign PT has low stromal cellularity, low mitotic count (less than 2-5/10HPF), around margin, abscence of stromal cell atypia or nuclear pleomorphism, abscence of stromal overgrowth, and abscence of necrosis or malignant heterologous elements. On the other hand, malignant PT shows stromal hypercellularity, significant stromal cell atypia or nuclear pleomorphism, high mitotic count(>10/HPF), stromal overgrowth, an infiltrative margin and necrosis or malignant heterologous element. Many patients do not possess all the features for malignancy, and are labelled as having borderline PT. Following review of the 42 patients diagnosed with PT, 16 were classified as benign, 9 as borderline and 17 as malignant. These pathological variables were assessed as predictors of local recurrence and metastases in addition to other parameters such as tumor size and surgical margins.

Comparisons of categorical variables such as stromal cellularity, stromal proliferation, nuclear grade, cellular pleomorphism and tumor necrosis were performed using the chi-square test. A comparison of continuous variables, such as mitotic figures was carried out using Kruskal-Wallis test. All tests were carried out using SAS software (version 9.1). A *P* value of less than .05 was considered significant.

RESULTS

Forty-two women were diagnosed with PT between January 2003 to August 2008 with ages ranging between 12-59 years (mean=39.8 years, median=43.5 years). Thirty-seven (88%) were premenopausal while the remaining 5 (12%) were postmenopausal. Both breasts were almost equally involved with PT in our study, but the upper outer quadrant was the most common site (43% in comparison to other sites in the breast). A family history of breast cancer was reported only in 5 patients (12%). The tumor size ranged between 2 to 29 cms (mean=6.68 cm, median 5.0 cm) with median duration of 6 months. The mean follow-up period was 30 months. Mitotic figure, stromal cellularity, stromal proliferation, nuclear grade, cellular pleomorphism and tumor necrosis were compared among the pathological types. After analysis, there were significant differences between the pathological types; 16 benign (38%), 9 borderline (21%) and 17 malignant PT (40%) with (P<.05) in most variables (**Table 1**). All 42 cases were

Table 1. Distinction between phyllodes subtypes based on histopathological criteria (n=42).

Pathological criteria	Total	Benign (B)	Borderline (BR)	Malignant (M)	Chi-square/ Kruskal-Wallis	*P*
Mitotic figures					0.000	
	Mean (Min, Max)	1.97 (0.5)	12.9 (2.30)	23.9 (4.78)		
Stromal cellularity	Low	6	6 (37.5%)			
	Intermediate	20	10 (62.5%)	7 (77.8%)	3 (17.6%)	.000
	High	16		2 (22.2%)	14(82.4%)	
Stromal proliferation	?	1			1 (5.9%)	
	Present	19	4 (25.0%)	3 (33.3%)	12 (70.6%)	.037
	Absent	22	12 (75.0%)	6 (66.7%)	4 (23.5%)	
Nuclear grade	Low	15	14 (87.5%)		1 (5.9%)	
	Intermediate	16	2 (12.5%)	8 (88.9%)	6 (35.3%)	.000
	High	11		1 (11.1%)	10 (58.8%)	
Cellular pleomprphis	Mild	20	13 (81.3%)	5 (55.6%)	2 (11.8%)	
	Moderate	13	3 (18.8%)	3 (33.3%)	7 (41.2%)	.001
	Severe	9		1 (11.1%)	8 (47.1%)	
Margin type	?	3	1 (6.3%)		2 (11.8%)	
	Pushing	35	15 (93.8%)	9 (100%)	11 (64.7%)	.082
	Infiltrating	4			4 (23.5%)	
Tumor necrosis	?	2			2 (11.8%)	
	Yes	11	1 (6.3%)	1 (11.1%)	9 (52.9%)	.004
	No	29	15 (93.8%)	8 (88.9%)	6 (35.3%)	
Margin status	?	4	1 (6.3%)		3 (17.6%)	
	Negative	28	8 (50.0%)	9 (100%)	11 (64.7%)	.050
	Positive	10	7 (43.8%)		3 (17.6%)	
Positive margin	?	3	2 (28.6%)		1 (33.3%)	
	Focal	6	4 (57.1%)		2 (66.7%)	.788
	Diffuse	1	1 (14.3%)			

?: Unknown B: Benign PT BR: Borderline PT M: Malignant PT

treated by surgical resection either with wide local excision or mastectomy with adequate safety margin.

The recurrence rate for all PT in our study was 21%. The duration between the date of surgery and local recurrence was about 11 months. Nine patients had local recurrence; 2 benign, 6 patients had malignant type and 1 borderline (**Table 2**). After studying these recurrent cases with all pathological parameters including margin status and the size we conclude that only cellular pleomorphism has correlation with recurrence. Patients with moderate and severe cellular pleomorphism had higher recurrence rate (*P*=.045) (**Table 2**). We consider a microscopic safety margin of 1 mm as a cutpoint, so even a negative margin could harbor a risk of recurrence that reached up to 14.3% in our study. It was found that 6 cases (14%) metastasized, and all were malignant. They were detected by regular follow-up in high-risk patients, which is predetermined by tumor biology[6] using a bone scan, chest and abdomen computerized tomography scan. The duration between the date of sur-

Table 2. Pathological review of 42 patients with PT and local recurrence (n=42).

Pathological criteria	Total	No Recurrence (NR)	Recurrence (R)	Chi-Square / Kruskal-Wallis	*P*
Size	?	10	4	6	.15
	10 cm	5	4 (80.0%)	1 (20.0%)	
	5-10 cm	11	9 (81.8%)	2 (18.2%)	
	< 5 cm	16	16 (100%)		
Mitotic figures	<5	18	16 (88.9%)	2 (11.1%)	.137
	5-10	8	7 (87.5%)	1 (12.5%)	
	>10	16	10 (62.5%)	6 (37.5%)	
Pathology Diagnosis	Benign	16	14 (87.5%)	2 (12.5%)	.195
	Borderline	9	8 (88.9%)	1 (11.1%)	
	Malignant	17	11 (64.7%)	6 (35.3%)	
Stromal Cellularity	Low	6	5 (83.3%)	1 (16.7%)	.475
	Intermediate	20	17 (85.0%)	3 (15.0%)	
	High	16	11 (68.8%)	5 (31.3%)	
Stromal Proliferation	?	1		1 (100%)	.094
	Present	19	14 (73.7%)	5 (26.3%)	
	Absent	22	19 (86.4%)	3 (13.6%)	
Nuclear grade	Low	15	14 (93.3%)	1 (6.7%)	.172
	Intermediate	16	12 (75.0%)	4 (25.0%)	
	High	11	7 (63.6%)	4 (36.4%)	
Cellular Pleomprphis	Mild	20	19 (95.0%)	1 (5.0%)	.045
	Moderate	13	8 (61.5%)	5 (38.5%)	
	Severe	9	6 (66.7%)	3 (33.3%)	
Margin type	?	3	2 (66.7%)	1 (33.3%)	.276
	Pushing	35	29 (82.9%)	6 (17.1%)	
	Infiltrating	4	2 (50.0%)	2 (50.0%)	
Tumor necrosis	?	2	1 (50.0%)	1 (50.0%)	.474
	Yes	11	8 (72.7%)	3 (27.3%)	
	No	29	24 (82.8%)	5 (17.2%)	
Margin status	?	4	2 (50.0%)	2 (50.0%)	.199
	Negative	28	24 (85.7%)	4 (14.3%)	
	Positive	10	7 (70.0%)	3 (30.0%)	
Positive Margin	?	3	1 (33.3%)	2 (66.7%)	.240
	Focal	6	5 (83.3%)	1 (16.7%)	
	Diffuse	1	1 (100%)		
Negative Margin	?	9	8 (. %)	1 (. %)	.596
	Size ≤1 mm	9	8 (88.9%)	1 (11.1%)	
	Size >1 mm	10	8 (80.0%)	2 (20.0%)	

R: Recurrence NR: Non recurrence :Not known

gery and metastatic date was a mean of 15.9 months. Three cases metastasized to the lung only, one to the bone and the other two cases metastasized to more than two organs such as bone, lung, thigh and intestine. Metastasis in PT had an association with histological grade, so that high-grade PTs had metastasis (**Table 3**).

DISCUSSION

The clinical behavior of PT is poorly understood. Fibroadenoma is a benign solid breast tumor composed of fibroglandular tissue in young women.[19] Fibroadenoma and PT differ in their biological behavior; the latter has a propensity to recur locally and is able to metastasize[3] and therefore, the management of PT is individually based.[3] Triple assessment is the standard and core biopsy employed with sensitivity reached up to 70%, while false negative results reached up to 30% in our study. Gatta G et al confirmed that an ultrasound-guided core needle biopsy is highly sensitive and specific to differentiate between fibroadenoma and PT.[20] Until the late 1970s, mastectomy was the standard surgical treatment for all PT, irrespective of tumor size or histological type.[21] Today more conservative surgical options have been adopted to assess which operation is suitable for a PT patient. There is no definite agreement regarding the appropriate surgical procedure, since PTs are rarely multifocal. In literature review, wide local excision is currently being suggested to be an appropriate primary surgical procedure for all histological types of PTs[12,22] with minimal 1 cm safe margins,[4,5,12,23] taking advantage of breast conserving surgery where feasible. For borderline, malignant PT, greater than 10 cm in size,[22] or in cases of local tumor recurrence, mastectomy and immediate breast reconstruction may become the preferred option,[24] depending on the breast to tumor ratio. It has been suggested that mastectomy is no longer required, even for malignant PT, provided adequate resection margins can be achieved.[25] Local recurrence can usually be controlled by further wide excision[26] and mastectomy is not invariably required. Re-excision is recommended in cases with a positive surgical margin, stromal overgrowth and malignancy.[27] In few instances, more radical surgery will be required for optimal control. Axillary lymph node dissection was unnecessary because lymph node metastasis to the axilla reached up to 14% in our series. There is no consensus on specific grading system that predicts the behavior of PTs and even benign PT may metastasize.[1] The expression of many biological markers has been explored to discriminate between different grades of PTs and to predict their behavior. Recently Puay Hoon Tan et al[8] established a predicted monogram based on three histological criteria (stromal atypia, mitosis, overgrowth) and surgical margin (AMOS criteria) to calculate recurrence-free survival in women diagnosed with PT. The recurrence rate in our study was 21% at an average time of 11 months, which matches the WHO recurrence rate.[1] A local recurrence rate of 10% to 40% has been reported making average of 15%.[6,8,28] A follow-up period of 30 months was used because the median time for recurrence is less than 24 months in almost all of the studies.[5,12,13,29,30] Margins affect the choice of the procedure, so borderline and malignant tumor types should not be considered an absolute indication for mastectomy. De Roos et al[29] noticed that patients with recurrence have margin involvement on histological examination, but not all patients with the margin involvement developed recurrence. Achievement of clear surgical margins in management of malignant PT is important and recommended to be at least 1 cm;[5,12,31,32] therefore, there is some evidence that excision with a negative margin will result in decreased recurrence rates[8,14,28] even though this alone offers no guarantees. In contrast, other studies failed to establish any relationship between margin involvement and local recurrence of PT.[2,3] Some previous studies suggest that tumor size is not necessarily

Table 3. Histopathological parameters in PT patients with distant metastases (n=6).

Pathological criteria	Grade			Mitotic figure			Cellular pleomorphism		
	Low	Intermediate	High	<5	5-10	>10	Mild	Moderate	Severe
Total	15	16	11	18	8	16	20	13	9
No Metastasis (NM)	13 (36.1%)	16 (44.4%)	7 (19.4%)	18 (50.0%)	6 (1607%)	12 (33.3%)	18 (50.0%)	11 (30.6%)	7 (19.4%)
Metastasis (M)	2 (33.3%)	-	4 (66.7%)	-	2 (33.3%)	4 (66.7%)	2 (33.3%)	2 (33.3%)	2 (33.3%)
P value (chi-square test)		.029			.072			.678	

M: metastasis NM: Non metastasis

associated with local recurrence risk.[12,33-35] The relationship between the size of PT and local recurrence is controversial. In contrast, others found that larger tumors were more likely to develop a local recurrence.[5,13,14,29] Kaprisi et al concluded that tumor size and surgical margins found to be the principal determinant of local recurrence and distant metastasis.[12] In our study, tumor size and surgical margins were not correlated with local recurrence as shown in **Table 2**. Different studies have considered that stromal overgrowth,[36-38] infiltrating margins,[38] high mitotic rate,[39] and degree of stromal atypia[40,41] are important predictors of recurrence and/or prognosis, while others have disagreed with these findings.[13,42] tumor size, degree of mitotic activity and stromal atypia have been described as predisposing factors for the development of distant metastasis.[12,29,34,36] In our study, metastasis was related to the histological grade (**Table 3**) and local recurrence was not found to be a predictive sign of distant metastases. However, both borderline and malignant PTs are known to metastasize, whereas, not all PTs classified as malignant will metastasize.[43]

The role of chemotherapy, radiotherapy and hormonal manipulation in both the adjuvant and palliative settings remain to be defined. The role of adjuvant treatment is unclear and has not been the subject of large randomized controlled trials.[6,33,43] Although Barth et al concluded that margin-negative resection combined with adjuvant radiotherapy is very effective therapy for local control of borderline and malignant PT.[7]

To sum up, this is a single institution experience of a rare tumor, the first study to shed light on cellular pleomorphism and recurrence rate in PT. The local recurrence rate is within the range reported in previous series. We conclude that only cellular pleomorphism had a correlation with local recurrence of PT while metastatic PT had relation with histological grade. The surgical management needs to be tailored to the clinical situation with more aggressive management reserved for higher grade or recurrent tumors. If satisfactory cosmosis cannot be obtained, then mastectomy is mandatory. Current studies have found that new genetic mutation and intratumoral genetic heterogeneity can develop within the same tumor.[44] These mutations could be the explanation of malignant behavior or recurrence of PT; for example, loss of expression of (P16INK4a) gene was found frequently in malignant PT,[44] also activation mutations in and overexpression of epidermal growth factor receptor gene (egfr) are associated with progression in the grade of breast PT.[45] Up to now, only correlations between expression of P53, Ki 67,c-Kit, PDGF, VEGF and CD10 with tumor grade[46-50] have been described. We recommend more prospective studies to determine the specific triggers that responsible for aggressive behavior of PT, and to study mutations in (egfr) gene to be considered as a prognostic indicator for metastatic PT.

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