



Prognostic Factors of Phyllodes Tumors of the Breast: Analysis of 170 Cases

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Authors' contributions

This work was carried out in collaboration between all authors. Author KR designed the study. Authors TD and AH performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors JBH, MH and AG managed the analyses of the study. Authors MC and RC managed the literature searches. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Background: Phyllodes tumors (PT) of the breast are rare and their prognosis and treatment are still subject of discussion. The purpose of this study is to determine the prognostic factors of this rare tumor.

Patients and Methods: We retrospectively reviewed the medical records of 170 patients who had histologically confirmed PT, collected over a period of 24 years in one single Institute (Salah Azaiz Institute).

Results: The mean age was of 38.7 years (14-75 years). The mean tumor size was 82.6 mm (15-300). According to criteria of WHO classification, tumors were classified into three groups: benign (97 cases, 57.1%), borderline (22 cases, 12.9%) and malignant (51 cases, 30%). One hundred and twenty eight patients (75.2%) were treated conservatively (96 benign, 17 borderline and 15 malignant) and 42 (24.7%) by radical surgery (6 borderline and 36 malignant). For malignant PT treated by local excision with or without reexcision of the tumor bed, the 5-year overall and recurrence free survivals were 46.2% and 44.2% vs. 55 and 63.8% when the surgery was radical (mastectomy with or without axillary dissection) (P=not significant and P=0.01). The rate of recurrence

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was 15.3 % (26) after a mean follow-up of 40 months (6 benign, 6 borderline and 14 malignant). Twelve patients developed metastases (7%). The 5-year overall and recurrence free survivals were 92.8% and 91.7%, respectively. In univariate analysis, age and recurrences are not of prognostic value for survival, while tumor size, histotype, necrosis, stromal overgrowth, cytonuclearatypia, tumor margins and number of mitosis were significant prognostic factors for survival. In multivariate study, stromal overgrowth and cytonuclearatypia remained independent predictors for survival. The tumor size and margins status were independent predictors for local recurrence.

Conclusion: According to our results, the most important factor for local recurrence is the tumor size and the margins status and for the overall survival is the stromal overgrowth and the cytonuclearatypia. The best treatment remains wide local excision for the benign forms while total mastectomy appears to be correlated to better recurrence free survival in large malignant PT.

Keywords: Phyllodes tumor; surgery; prognosis; breast neoplasm.

1. INTRODUCTION

Phyllodes tumors (PT) of the breast are rare fibroepithelial neoplasms of the breast that accounts for 2-3% of fibroepithelial breast tumors and 1% of all breast tumors [1]. Histologically, they are similar to mammary fibroadenomas but differ in their biological behaviour [2]. They are characterized by a leaf-like appearance with more abundant and cellular stroma than that of an fibroadenoma [3]. Given their rarity, epidemiologic data are scant. In a study from Los Angeles county over a 17-year period, the average annual incidence rate was 2.1 per million women [1,4]. The outcome and clinical behaviour of PT remains unclear because of their unexpected behaviour and histological heterogeneity [5]. This is a reanalysis of our previous study published in the American Journal of Surgery with additional patients and longer follow up. It aims to study to the clinicopathologic characteristics of PT and determine therapeutic and prognostic factors of this disease [6].

2. PATIENTS AND METHODS

This is a retrospective study about 170 patients with histologically confirmed PT collected over a period of time of 24 years ranging between 1986 and 2010. The tumors were classified into benign, borderline and malignant according to the world health organization criteria [3].

The histological diagnosis was done either on frozen section examination at the moment of surgery or on final pathology report and only in five cases on micro biopsy prior to surgery.

The indication of radical or conservative treatment depends on the ratio of the tumor volume over the breast volume, the consent of the patient and recently we introduced surgical oncoplastic techniques to increase the breast conservation surgery. In our center, we didn't perform mastectomy for benign PT whatever the tumor size is. Specimen margins were assessed by histological examination of shavings obtained from the circumferential margins of the specimens. Negative margins are defined by a distance of 10 mm or more microscopically. Statistical analysis was performed with SPSS software version 19 for Mac. Pearson chi-squared was used to investigate the relationship between age and histological type of PT. ROC curves was used to determine the statistical cut-off points of numeric

variables. Survivals were calculated according to the Kaplan-Meier method. Patients who died of intercurrent disease or who were lost to follow-up were censored at the time of last known follow-up. Comparison between curves was assessed using Log rank test. Multivariate analysis was performed using Cox regression model including variables which are significant on the univariate analysis. A p value of < 0.05 was considered to be statistically significant.

3. RESULTS

3.1 Clinical Characteristics (Table 1)

All patients were female with a median age of 38.7 years (range 14–75). The mean ages for benign, borderline and malignant PT were 37, 39 and 42 years, respectively. Malignant and borderline PT occurred in 73.5% of cases in patients older than 35 years vs. 55% for benign PT (p=0.014, odds ratio 6). Nulliparity was found in 42% of premenopausal women. The skin was involved in 21% of cases. No patient had metastatic disease at diagnosis.

Table 1. Patients characteristics and treatment modalities

Average duration of symptoms: months (range)	7 months (2-185)
Symptoms	
Breast lump	139 (82%)
Mastodynia	5 (3%)
Laterality	
Right	75 (44.1%)
Left	94 (55.3%)
Bilateral	1 (0.6%)
Menopausal status	
Pre-menopausal	118 (69.4%)
Menopausal	52 (30.5%)
Personal history of breast disease	
Present	10 (5.8%)
Absent	160 (94.2%)
Type of surgery	
Conservative	128 (75.3%)
benign	96
borderline	17
malignant	15
Radical	42 (24.7%)
Radical mastectomy	19
Simple mastectomy	23
Axillary dissection	
Yes	19 (11%)
No	151 (89%)

3.2 Treatment Modalities (Table 1)

Surgery was performed in all cases. Among the 128 patients having conservative surgery 25 underwent an enucleation (24 benign, 1 malignant) and 103 patients had wide local excision.

Radical surgery was achieved in 42 cases. The relationship between the type of surgery and histotype is shown in Table 2.

Table 2. Correlation between the type of surgery and the tumor grade

		Type of surgery		P value	Total
		Conservative (5 year recurrence free survival)	Radical (5 year recurrence free survival)		
Tumor grade	1	96	0	-	96
	2	17 (43.5)	6 (55)	ns	23
	3	15 (44.2)	36 (63.8)	0.01	51
Total		128 (77.7)	42(64.2)	ns	170

Radical surgery was carried out in 46.5% of tumors larger than 10 cm. The correlation between surgical treatment and tumor size is represented in Table 3. No patient received adjuvant radiotherapy or chemotherapy.

Table 3. The correlation between the tumor size and the type of surgery

		Type of surgery		Total
		Conservative	Radical	
Tumor size (cm)	<5	47 (90.4%)	5 (9.6%)	52 (100%)
	5-10	58 (77.3%)	17 (22.7%)	75 (100%)
	>10	23 (53.5%)	20 (46.5%)	43 (100%)
Total		128 (75.3%)	42 (24.7%)	170 (100%)

3.3 Histopathological Features

The mean histological tumour size of was 82.6 mm (range 15–300). The tumour margins were involved in four cases of which three were malignant PT. Tumor bed re-excision was involved in two cases. Viable residual tumor was observed in four mastectomy specimens of which three were malignant PT and one borderline PT. The histological extemporaneous examination was concordant with the final pathological report in 75.4% of cases. The pathologic variables studied after 5 years of follow-up are summarized in Table 4.

3.4 Local Recurrence

Local recurrence was noted in 26 patients (15.2%) after a mean follow-up of 40 months (1-216). The distribution according to the tumor grade was as following: 27.5% (14/51) in patients with malignant PT, 26% (6/23) with borderline and 6.2% (6/96) with benign PT.

The 5-year local recurrence free survival was 91.7%. After univariate analysis, the prognostic factors for local recurrence were tumor size larger than 100 mm ($p<0.003$), borderline and malignant forms ($p=0.014$), cytonuclear atypia ($p=0.018$), the presence of necrosis and haemorrhage ($p<0.0001$), number of mitosis ($p<0.0001$), stromal overgrowth ($p<0.0001$) and involved tumor margins ($p=0.007$).

With cox regression model analysis only tumor size and margins status were independent predictors for local recurrence.

For borderline and malignant PT the 5-year local recurrence free survival rates were 43.2% and 64.6% after conservative and radical surgery respectively (p=0.014).

For benign PT, the 5-year local recurrence rate was 93.8 after local excision and reexcision procedure and 88.7% after enucleation of the tumor bed (p=0.95).

Table 4. Histopathological parameters according to the tumor histotype

Histopathologic parameters	Benign	Borderline	Malignant
Tumor size			
<5	38	7	7
>10	11	8	24
5-10	48	7	20
No. of mitosis			
<5	85	16	15
>10	2	6	27
5-10	10	0	9
Cytonuclear Atypia			
No atypia	62	3	8
slight (+)	24	10	4
Moderate (++)	9	6	12
Severe (+++)	2	3	27
Tumor margins			
Not involved	88	11	33
Involved	9	11	18
Remaniement Hyalin			
Absent	91	17	39
Present	5	5	12
Necrosis+Hemorrhage			
Absent	91	15	19
Present	6	7	32
Stromal overgrowth			
Absent	88	18	35
Present	9	4	16
Tumor margins			
Not involved	31	13	9
Involved	1	0	1
heterologue component			
Absent	95	16	35
Present	2	6	16

3.5 Distant Metastasis (DM)

The 5-year metastasis free survival was 87.5%. DM developed in 12 (7%) patients within an average period of 27 months (range 5-58) of the initial treatment. All patients received palliative chemotherapy. Tumors were initially malignant in 10/53 (19%) cases and initially diagnosed borderline in two cases out of 23 (8.6%).

DM affected lung and bone in 90.5% and 9.5%, respectively. Eleven out of twelve patients with metastatic disease died within a mean period of 17 months (range 6-45) from the metastases onset.

In univariate analysis, seven prognostic factors for metastatic spread were identified: Tumor size more than 100 mm ($p=0.01$), borderline and malignant PT ($p<0.0001$), number of mitosis exceeding 15 ($p<0.0001$), presence of cytonuclear atypia ($p<0.0001$), presence of necrosis and haemorrhage ($p<0.0001$), involved tumor margins ($P=0.03$) and stromal overgrowth ($p=0.017$) (Table 5).

Table 5. The 5-year local recurrence and distant metastasis free survivals of treated patients with PT of the breast related to several clinicopathological variables

Factor	5-year LRFree survival (%)	P value univariate	5-year DM survival (%)	P value univariate
Age		ns		ns
> 50	70		90.4	
≤ 50	85.7		74.7	
Histotype		0.001		<0.0001
Benign	90.4		100	
Borderline	50.2		86.4	
Malignant	57.2		66	
Tumor size		0.003		0.01
< 100 mm	86		95.2	
> 100 mm	48.5		70.4	
Necrosis + hemorrhage		<0.0001		<0.0001
Present	42.5		52.1	
Absent	85		100	
Tumor margins		0.007		0.03
Not involved	82.7		92.3	
Involved	54.7		72.5	
Cytonuclear atypia		0.018		<0.0001
No or slight	81.7		98.7	
Moderate to Severe	61.9		68.3	
No. of mitosis		<0.0001		<0.0001
<15	84.5		92.8	
> 15	37.8		42	
Stromal overgrowth		<0.0001		0.017
Present	83.1		63.1	
Absent	38.6		92	

ns: not significant; LR: local recurrence; DM: distant metastasis

Based on cox regression model, a number of mitosis exceeding 15 per 10 hpf remained an independent factor for DM free survival.

3.6 Overall Survival

The median follow up time was 43,2 months (1-216 months). The 5-year overall was 92.8%. The 5-year overall survival related to several clinicopathological variables are shown in Table 6.

Univariate analysis showed tumor size, histotype, necrosis, stromal overgrowth, cytonuclear atypia, number of mitosis and tumor margins were significant prognostic factors.

Table 6. The 5-year overall survival of treated patients with PT of the breast related to several clinicopathological variables

Factor	5-year overall survival (%)	P value univariate
Age		ns
> 50	83.2	
≤ 50	86.7	
Histotype		<0.0001
Benign	100	
Borderline	82.5	
Malignant	72.5	
Tumor size		0.006
< 100 mm	94.5	
> 100 mm	76.8	
Necrosis + hemorrhage		<0.0001
Present	59.2	
Absent	99	
Cytonuclear atypia		<0.0001
No or slight	96.8	
Moderate to Severe	74	
No. of mitosis		<0.0001
<15	98.4	
> 15	51.1	
Stromal overgrowth		ns
Present	80	
Absent	98.2	
Recurrences		ns
Yes	90.4	
No	76.7	

ns: not significant

The multivariate analysis of significant prognostic factors in univariate analysis showed that Cytonuclear atypia and stromal overgrowth were directly related to the overall survival.

4. DISCUSSION

Phyllodes tumors (PT) are rare, occurring at any age, with a peak incidence between 30 and 40 years; a decade later than the average presentation of fibroadenoma and a decade earlier than that of invasive ductal or lobular carcinoma [4]. In our series, the mean age at diagnosis was 38.7 years (range 14–75); Malignant and borderline PT occurred in 73.5% of cases in patients older than 35 years vs. 55% for benign PT ($p=0.014$, odds ratio 6). Our findings showed that the malignancy rate increased significantly with age and the risk was multiplied by 6 when the age was more than 35 years.

Breast lump was the most common complaint found in 90% of cases [4]. In our series, 82% of women consulted for palpable breast mass. In the literature, the mean tumor size varies between 50 and 72 mm [7]. In our series, the mean tumor size was 82,6 mm (15-300).

Some authors reported the contribution of the core biopsy and fine needle cytology for the pre-operative diagnosis [8]. In our study the core biopsy was done only in five cases and in the other cases the diagnosis is made either on the frozen section examination or on the final histology report after local excision. Our attitude is explained by the difficulty of the diagnosis on the core biopsy especially to precise the tumor grade.

Complete excision, with accurate histologic examination and continued follow-up care, is the best way to treat phyllodes tumors. The risk of recurrence exists in PT whatever the tumor grade is, though it is low in benign forms, varying from 4.7 to 30%, and remarkably higher in borderline and malignant forms ranging from 30 to 65% [9]. In our series, the local recurrence rates according to the tumour grade were 27.5% in patients with malignant PT, 26% with borderline and 6.2% with benign PT. We found that there is no difference in term of recurrence free survival in benign PT after enucleation procedure or local excision and re-excision of the tumor bed. It is commonly recommended wide local excision for benign PT but when the diagnosis is made after enucleation of the benign forms, most authors favour the wait and see attitude because of the low recurrence rate even in this setting [10].

While the management of benign PT represents a subject of consensus, the management of borderline and malignant PT is still debated. Some authors favour the conservative surgery for borderline and malignant PT followed by adjuvant radiotherapy in case of clear margins [2]. Barth reports a local recurrence rate of 0% after wide local excision followed by external radiotherapy [11]. Conversely Belkacemi in his large series concluded that total mastectomy is correlated with better local outcome in borderline and malignant PT [9]. Our results are consistent with those of Belkacemi who suggested that total mastectomy is associated with better local recurrence rate for borderline and malignant forms [9].

Many authors consider that axillary lymph node dissection is not useful, while others prefer to use it only in case of clinically suspect adenopathy or invasive carcinoma within PT [12-14]. In light of our previous publication on PT we don't perform anymore the axillary lymph dissection only in case of palpable adenopathy.

The frequency of local recurrences varies between 0 and 60 % according to various series in the literature [7,11,15-17]. In our series, recurrences occurred 15.2% of cases, 83 % of which during the first three years following initial treatment. Our results are close with that of Belkacemi and Tan who reports a 5-year local recurrence rate of 14% [9,18].

In the literature, malignant PT recur in 24 to 58% of cases, while benign PT recur only in 4.3 to 27% of cases [5,18-20]. In our series, we report local recurrence rates of 27.5% in patients with malignant PT, 26% with borderline and 6.2% with benign PT. Other factors are identified to be risk factors for local recurrences such as surgical margins, nuclear atypia and stromal overgrowth [21]. In our study, local recurrence was significantly increased with tumors larger than 100 mm, borderline and malignant forms, cytonuclear atypia, the presence of necrosis and haemorrhage, number of mitosis, stromal overgrowth and involved tumor margins. Tumor size and margins status were independent predictors for local recurrence. In contrast age of patient showed no significant relation with local control.

The distant metastases rate varies considerably, from 6.6 to 70% and most of them occur in lung (84.5%) and bone (39%) [22]. In our series, metastases were observed in 7% of our population and occurred in lung in 90.5% and bone in 9.5% of cases.

According to some authors, patients with local recurrence do not develop distant metastases [2]. On the contrary, in previously reported series, 60 to 85% of patients with metastatic disease had already developed local recurrences [12,23,24]. This discordance in results could be explained by the different type of surgery used, and therefore others factors must be investigated to predict which of PT can metastasize or not. Our study demonstrates that the risk of distant spread is correlated to histotype, tumor size, cytonuclear atypia, presence of necrosis and haemorrhage, tumor margins, stromal overgrowth and number of mitosis. No relationship between age, type of surgery, recurrences and risk of metastasis was found in our study; this is consistent with the findings of Tan and Hart and Belkacemi [9,25,26].

The evolution of metastases is always fatal in spite of chemotherapy and radiotherapy. Death occurs within 24 months following the appearance of metastases. In our series, all but one patient died of metastasis within an average period of 17 months (range 6-45) from the diagnosis of metastatic spread. The last patient died because of huge local recurrence invading the mediastinum and the heart after total mastectomy.

The five-year disease free and overall survival varies, according to other series, ranges from 60 % to 92 % [12]. In our study, the five-year local recurrence free and overall survivals were 91.7% and 92.8% respectively. We agree with other studies that age is not of prognostic value. Conversely, prognosis was significantly correlated to histotype, tumor size, tumor necrosis and haemorrhage, tumor margins, cytonuclear atypia and high mitotic rate. Only cytonuclear atypia and stromal overgrowth remained independent predictors for survival. The occurrence of recurrences is not related to a dismal prognosis.

Belkacemi and al have reported that the mitotic index is an independent factor for disease free survival either in the whole population or in the borderline and malignant tumors subgroup, whereas tumor necrosis decreased overall survival in the whole population [9]. Some authors found tumor necrosis, tumor margins, histotype and tumor margins to be of prognostic value [7,27]. Other factors, such as beta-catenins and E-cadherin, are under investigation to further clarify the prognosis of PT [28].

5. CONCLUSION

According to our results, the most important factor for local recurrence is the tumor size and the margins status and for the overall survival is the stromal overgrowth and the cytonuclear atypia. Surgery is the cornerstone of the treatment based on wide local excision for benign forms while for the borderline and malignant PT, our study supports the conclusion that total mastectomy is associated to better outcome in borderline and malignant tumors especially those that are larger than 10 cm. There is no need to carry out a re excision of the tumor bed if the diagnosis of a benign tumor is done on the final histological report after enucleation. Our conclusions have to be interpreted with caution because our study has the limitations of a retrospective review and the large tumor size of our population. The place of adjuvant treatment is not clear and the radiotherapy has to be taken in account according to surgical margins, size, and pathologic criteria of the tumor, such as mitotic index, stromal overgrowth, cellular atypia, and tumor necrosis. Further studies are warranted to explore other prognostic factors to better precise the clinical behavior of this rare entity.

CONSENT

Not applicable.

ETHICAL APPROVAL

The ethical approval was obtained from the medical committee of the Salah Azaiz Institute.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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