

RESEARCH ARTICLE

Comparison of Clinical Characteristics Between Benign Borderline and Malignant Phyllodes Tumors of the Breast

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Abstract

Background: Phyllodes tumors of the breast are rare fibroepithelial lesions, so relatively little is known about this disease entity. The present study was designed to identify differences in clinical features between benign borderline and malignant phyllodes tumors. **Materials and Methods:** Data from 246 women with phyllodes tumors of the breast treated in Cancer Hospital Chinese Academy of Medical Sciences between 2002 and 2012 were collected and analyzed, including age at presentation, age at treatment, course, size of primary tumor, location, histological type, type of surgery and treatment, local recurrence, distant metastasis, fibroadenoma history, disease-free survival and number of mitosis per 10hpf. There are 125 (55%) benign, 55 (24%) borderline and 47 (21%) malignant tumors. **Results:** In univariate analysis, average age at presentation, average age at treatment, size of primary tumor, ulceration or not, type of primary surgery, distant metastasis and number of mitosis per 10 hpf turned out to be statistically different among the three PT types ($p=0.014, 0.018, <0.000, 0.003, <0.000, 0.001$ and <0.000 , respectively), while recurrence and disease-free survival (DFS) demonstrated trends for statistical significance ($P =0.055$ and 0.060 , respectively). Multivariate analysis revealed distant metastasis and excision were significantly different in benign, borderline and malignant phyllodes tumors of the breast ($p=0.041$ and 0.018 , $OR=0.061$ and 0.051). At the same time, size of primary tumor with $p=0.052$ tended to be different between groups ($OR=1.127$). However, age at treatment, ulceration and DFS showed no statistically significant variation ($p=0.400, 0.286$ and 0.413 , respectively). **Conclusions:** Benign borderline and malignant phyllode tumors have different distant metastasis risk, different primary tumor size and different surgical procedures, and malignant PTs are more likely to be bigger and to metastasize.

Keywords: Phyllodes tumors of the breast - benign - borderline - malignant - disease free survival - recurrence

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Introduction

Phyllodes tumors (PTs) are one kind of rare fibroepithelial tumors of breast, which constitute only 0.3-0.9% of all breast tumors and 2-3% of fibroepithelial neoplasm (Lee et al., 1931; Rowell et al., 1993), however, a higher incidence rate (3.9%) of malignant cystosarcoma phyllodes only was once reported (Serey et al., 2011). Johannes Muller from Germany first described and named it cystosarcoma phyllodes (CSP) in 1838 (Müller et al., 1838). In 1931, the first case of pulmonary metastatic phyllodes tumor was identified, until then, the malignant biological behavior of CSP was known (Lee et al., 1931). The World Health Organization proposed a new name, that is phyllodes tumors (PT) (WHO, 1981) in 1981 and classified it into three types: benign, borderline and malignant in 2003 (Tavassoli et al., 2003) according to the degree of cellular atypia, mitotic activity, tumor margins and stromal overgrowth, Table 1. The tumor occurs usually in women aging 35-55 years (Reinfuss et al., 1996). Benign, borderline and malignant account

for 58.4%-74.6%, 15.0%-16.1% and 9.3%-31% of all phyllodes tumors (Tan et al., 2005; Taira et al., 2007; Karim et al., 2009), and the recurrence rate for three groups is 10%-17%, 14%-25%, 23-30% (Rowell et al., 1993), respectively. Of malignant tumors 1/3 to 1/2 will metastasize (Reinfuss et al., 1996).

Phyllodes tumors are well-circumscribed, painless, mobile masses that are surrounded by a pseudocapsule of compressed breast parenchyma (Rowell et al., 1993). Sometimes, lesion grows suddenly and dilated veins may be observed overlying large phyllodes tumors. Microscopically, PT contains both epithelial and stromal components. The stroma is much more cellular and contains nuclear atypia and mitotic activity, which differs from fibroadenoma.

PT has an overall good prognosis, while local recurrence is a common problem. Surgery is the standard treatment for PT. Generally, local excision is taken in benign and small tumors, while total mastectomy will be taken into account when it is borderline, huge, malignant or repeatedly recurrent. Axillary lymph node

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Table 1. Classification

	Margin	Stromal Atypia	Mitoses/ 10HPF	Stromal Overgrowth
Benign	Pushing	Minimal	<5	Absent
Borderline	Pushing/ Infiltrating	Moderate	5≤count<10	Present
Malignant	Infiltrating	Severe	≥10	Present

involvements are described in fewer than 5% of all patients with phyllodes tumors (Belkacemi et al., 2008; Suzuki-Uematsu et al., 2010), otherwise, malignant PTs are bloodvessle-borne metastasis, so routine axillary lymph node dissection seems unnecessary, unless there is certain metastases or clinical palpable lymph node. Although the histologic type is an established independent prognostic factor for survival (Chaney et al., 2000), the prognostic value of other parameters remains uncertain. Moreover, there are no definite predisposing factors and the etiology of phyllodes tumor is not clearly known. In this study, we aim to identify the difference in clinical features between benign, borderline and malignant phyllodes tumors and help to better explore this rare disease in the future.

Materials and Methods

Patients

Data from 246 women with PT of the breast treated in Cancer Hospital Chinese Academy of Medical Sciences between 2002 and 2012 was collected and analyzed retrospectively with a follow-up to May 20th, 2014, including age, tumor size, location, histological type, way of surgery and treatment, DFS. all of the patients are female. Of all of them, 61 patients have recurrence and one person has both local recurrence and distant metastasis. According to the World Health Organization classification (Tan et al., 2005) there are 125 (55%)benign, 55 (24%) borderline and 47 (21%) malignant cases in our study, respectively. 181 cases had complete follow-up. Follow-up data was obtained by telephone call and records of re-examination. The pathological diagnosis of intial neoplasms was fibroadenoma in 14 patients. Four patients with malignant PT died of distant metastases, 2 lung and 2 intial bone metastases.

Pathological methods

A pathological consultation will be performed when the masses are first resected not by our hospital. Patients with intial PT treated in our center are diagnosed by core needle biopsy or fast intraoperative frozen Haematoxylin-Eosin staining at first. Then after the operation, a routine paraffin pathology will be given to reassure the result. The pathological sections before 2003 are reviewed again to ensure a consistent application of standard histologic criteria.

Statistical analysis

Statistical analysis was carried out by SPSS, version 17.0. Differences in clinical features between three groups were assessed by the log-rank Pearson Chi-square test, Fisher exact test, ANOVA and Nonparametric Test. The *P*

Table 2. Patient Basic Characteristics

	Total Number	Average (range)
Age at presentation (yr)	235	40.7 (12-74)
Missing	11	
Age at treatment (yr)	246	42.0 (14-74)
Missing		
Course (m)		14.6 (0.25-216)
Missing	32	
Initial size of tumor (cm)	225	4.70 (1-32)
Missing	21	
Location of tumor		
Left	117	
Right	123	
Bilateral	1	
Axillary	2	
Missing	3	
Histological type		
Benign	125 (55%)	
Borderline	55 (24%)	
Malignant	47 (21%)	
Missing	19	
DFS (m)	181	44.7 (1-135)
Missing	65	
Number of mitosis per 10hpf		
<5	59	
5≤mitosis≤9	24	
≥10	21	
Missing	142	
Ulceration		
Yes	9	
No	218	
Missing	19	
Type of primary surgery		
Local excision	210	
Total mastectomy	26	
Modified radical mastectomy	8	
Missing	2	
Recurrence		
Yes	61	
No	133	
Missing	52	
Local Recurrence		
Yes	56	
No	138	
Missing	52	
Distant metastasis		
Yes	6	
No	188	
Missing	52	
With fibroadenoma (homolateral or contralateral)		
Yes	51	
No	195	
Pathological change during recurrence		
Yes	16	
No	211	
Missing	19	
Times of recurrence		
≤twice	32	
>twice	11	
Missing	203	
Treatment after surgery		
Chemotherapy	4	
Radiotherapy	6	
Chemo+radio	3	
NA	233	

value in test of parallel lines is 0.247 (>0.05). So Ordinal Logistic Regression was used on multivariate analysis. All tests were two-sided, when *p*<0.05, it's statistically significant.

Results

Demographic and clinical characteristics of 246 patients with PT treated at Cancer Hospital and Chinese Academy of Medical Sciences with follow-up are given in table 2.

Univariate analyses identified that average age at presentation, average age at treatment, size of primary tumor, ulceration or not, type of primary surgery, distant metastasis and number of mitosis per 10 hpf are statistically different in three PT types ($p=0.014, 0.018, <0.000, 0.003, <0.000, 0.001$ and <0.000 , respectively), while recurrence and disease-free survival (DFS) demonstrate a trend of statistical significance ($P=0.055$ and 0.060 , respectively), as is shown in Table 3.

Course=age at treatment–age at presentation, otherwise, recurrence includes both local recurrence and

distant metastasis. So there is colinearity in these parameters. Considering clinical significance and univariate analysis result, choose age at treatment, distant metastasis, type of primary surgery, ulceration, size of primary tumor and DFS into Ordinal Logistic Regression with test of parallel lines $p=0.247>0.05$. Meanwhile, the P value of this model is <0.000 and the P value of Pearson test and Deviation test are $0.443 (>0.05)$ and $0.976 (>0.05)$ respectively. It implies the matching effect of this model is preferable.

We can see from multivariate analysis in Table 4 distant metastasis and excision are significantly different in benign, borderline and malignant phyllodes tumors of the breast ($p=0.041$ and 0.018 , OR=0.061 and 0.051). At the same time, size of primary tumor with $p=0.052$ tends to be different in groups (OR=1.127). However, age at treatment, ulceration and DFS demonstrate no statistical significance in three groups ($p=0.400, 0.286$ and 0.413 , respectively).

Table 3. Univariate Analysis

		Benign	Borderline	Malignant	P value
Average age at presentation		39.7	45.2	39.6	0.014
Average age at treatment		41	46	40.9	0.018
Course		12.9	16.1	17.4	0.634
Location	Left	60	28	22	
	Right	62	27	23	
	Bilateral	1	0	0	
	axillary	1	0	1	
Size of primary tumor		3.7	4.8	7.5	<0.000
DFS (m)		49.8	41.1	47.1	0.055
Ulceration	Yes	1	2	5	
	No	122	48	35	
Type of primary surgery	Local excision	121	46	25	
	Total mastectomy	2	7	17	
	Modified radical mastectomy	0	2	5	
Recurrence	Yes	17	14	13	
	No	77	31	23	
Local Recurrence	Yes	17	13	9	0.326
	No	77	32	27	
Distant metastasis	Yes	0	1	5	0.001
	No	94	44	31	
With fibroadenoma (homolateral or contralateral)	Yes	23	6	5	0.278
	No	102	49	42	
Number of mitosis per 10hpf	<5	37	18	3	<0.000
	5≤mitosis≤9	2	20	2	
	≥10	0	1	20	
Times of recurrence	≤twice	9	7	6	0.62
	>twice	1	3	2	

Table 4. Multivariate Analysis

		Regression Coefficient	Wald	P	OR	OR 95%CI
Benign PT		-2.712				
Borderline PT		-1.068				
Age at treatment (y)		0.013	0.707	0.4	1.013	0.982-1.045
Recurrence	Yes	0				
	No	-2.798	4.174	0.041	0.061	0.004-0.892
Type of primary surgery	Local excision					
	Mastectomy	-2.976	5.622	0.018	0.051	0.004-0.597
	Modified radical mastectomy	-0.714	0.31	0.578	0.49	0.040-6.056
Ulceration	Yes	0				
	No	1.597	1.139	0.286	4.938	0.263-92.666
Size of primary tumor (cm)		0.12	3.788	0.052	1.127	1.000-1.273
DFS (m)		-0.005	0.669	0.413	0.995	0.984-1.007

Discussion

In our study, we found malignant phyllodes tumors were more likely to be bigger and develop distant metastasis comparing benign and borderline ($p=0.052$, $OR=1.127$ and $p=0.041$, $OR=0.061$, respectively). We also noted a trend toward more excision cases in benign patients ($p=0.018$, $OR=0.051$). Apart from stromal hypercellularity, mitoses, cytologic atypia, stromal overgrowth and tumor borders, which are categorical standard items, several authors have noted (Tan et al., 2005; Barrio et al., 2007) other histological characteristics, such as necrosis, hemorrhage, cystic degeneration, intratumoral pseudoangiomatous stromal hyperplasia etc, are different in three histologic PTs. Our study aims to find the differences in clinical features between benign borderline and malignant phyllodes tumors, so we excluded count of mitosis in Ordinal Logistic Regression Analysis.

The current series had 61 recurrent cases, including 56 local control failures, 6 distant metastases and 1 concurrent recurrence. The local recurrence rate for three groups were 18%, 29% and 25% ($p=0.326$), while distant metastases rate were 0, 2% and 14% ($p=0.001$). That is, benign borderline and malignant phyllodes tumors have different distant metastases, but not local recurrence. Jing Wei et al. in his study of 192 cases also states histotype is related with distant metastasis ($p<0.001$), while has no relationship with local recurrence ($p=0.139$) (Wei et al., 2014).

The mean size of primary tumor for three groups were 3.7, 4.8 and 7.5cm in univariate analysis with $p<0.000$. On multivariate analysis, patients with bigger masses are more likely to be malignant ($p=0.052$, $OR=1.127$). A retrospective study carried out by Memorial Sloan-Kettering Cancer Center in 2007 (Barrio et al., 2007) categorized phyllodes tumors into benign and malignant (including borderline and malignant) groups and tumor size into ≤ 3.0 cm and >3.0 cm, and they found malignant group was bigger than benign group ($p<0.0001$), so as another research done by Puay-Hoon Tan et al. with $p<0.001$ (Tan et al., 2005).

From the univariate analysis in our study, we can see benign phyllodes tumors accounts for 63% (121/192) excision, and the rates for borderline and malignant are 24% (46/192) and 13% (25/192), respectively. In mastectomy group, the constitute rates for benign borderline and malignant are 8% (2/26), 27% (7/26) and 65% (17/26) with $p<0.000$. That is benign phyllodes tumors are more likely to choose excision, however, for the malignant, mastectomy is favored. In the literature and NCCN (August et al., 2000; Hassouna et al., 2006; NCCN, 2014), the primary goal for treatment of phyllodes tumor is to achieve wide negative margin (tumor cells are present ≥ 1 cm from the closest surgical margin), mastectomy is recommended for malignant PT, which has worse prognosis, whereas for borderline and benign PT, treatment is based on wide local excision. In daily clinical work, we just treat PT mainly according to this standard. On multivariate analysis, excision ($p=0.018$, $OR=0.051$) is statistically significant, which from the other side proves our data is real and accurate.

From table 3, we can see average age at treatment is different in three groups, but in multivariate analysis this parameter doesn't show any statistical significance. A study including 363 cases undertook in Pakistan found the frequency of phyllodes tumor in adolescent girls and young women (less than and equal to 25 years of age) were identical (Khurshid et al., 2006). From these data, we can see benign, borderline and malignant PT have no difference in age and there is an equal distribution of three PTs in the population. In light of the rarity of this disease, large multi-center studies are needed to further confirm our findings.

In summary, besides histopathologic characteristics, benign borderline and malignant phyllodes tumors are different in clinical features, such as primary tumor size, distant metastasis and surgical procedure. Efforts should be made to explore the unpredictable performance of three histologic PTs and help to better know and treat further this rare disease.

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