

# The Treatment and Prognosis of Patients with Phyllodes Tumor of the Breast

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**Abstracts Objective** To study the treatment and prognosis of the breast phyllodes tumors. **Methods** clinical data, and the results of follow-up in 203 cases of breast phyllodes tumors were analyzed using Logistic analysis and Cox regression in SPSS statistic software. **Results** local recurrence and tumor mortality were in direct proportion to the pathologic grade of the tumor. There was a direct proportion between local recurrence and tumor infiltration, and between tumor caused-mortality and tumor mitosis and necrosis. Mitotic activity and tumors necrosis were the independent prognostic factor. After surgical resection 21.1% of patients with benign tumor, 45.2% of patients with borderline tumor, 64.3% of patients with malignant tumor suffered local recurrence. the 5-year survival rate was 100% in patients with benign phyllodes tumor, 92.0% with borderline, 33.3% with malignant. **Conclusion** local excision is not the appropriate treatment for phyllodes tumor. Patients with benign or borderline phyllodes tumor should with local excision including a margin of uninvolved tissue, and that with local recurrence borderline and malignant Phyllodes tumor is mastectomy.

**Key Words** Breast neoplasme; Surgical procedures; Prognosis

Phyllodes tumors (PT) remains a poorly understood tumor of the breast. there are two major question waiting for a definitive answer: identification of independent prognostic factors and determination of the best surgical approach to this questionable lesion. The aim of this retrospective study is to discuss the prognostic and therapeutic aspects of phyllodes tumors with clinical data, and the results of follow-up in 203 cases of breast phyllodes tumors which were analyzed using Logistic analysis and Cox regression.

## MATERIAL AND METHODS

### The clinical material

273 cases with phyllodes tumor of breast were collected among the 42,723 patients with breast diseases from 22 hospitals between January 1956 to December 2000<sup>[1]</sup>. Among them, female 200 and male 3. Their ages ranged from 13 to 68 years old, the median age was 39 years old. Breast tumor occurred in left side 103 cases, right side 97 cases, bilateral 2 cases (concomitantly occurred 1 case, successively occurred 1 case), and right sub-axillary region 1 case; single lesion was 194 cases, and multiple lesions 9 cases. One hundred and ninety-four cases were recorded the concrete region of the breast tumor, among them, 54.5% of cases

occurred in upper-lateral quadrant. Duration of symptoms varied from 1 week to 30 years, the median duration was 12 months.

### Surgery pattern

According to the initial record of the hospital, the surgery pattern was divided into three types: **a.** tylectomy (tumor resection only, i.e., simple enucleation), **b.** wide local excision (resection of the tumor with 2cm margins of normal mammary tissue) and **c.** mastectomy (include simple and radical mastectomy). The death cause of the patients was based on the final hospital in charge.

### Statistic analysis

Tumor pathologic morphology closely related with diagnosis of tumor in before study<sup>[1]</sup> (stromal overgrowth; stromal cellularity; tumor margin; mitosis number; nuclear pleomorphism; tendency of differentiation; tumor necrosis; number of thin vessels), and clinic factors closely related with prognosis (ages; surgery pattern; size of tumor; sudden increase of tumor; histotype of tumor) were utilized for Chi-square test, cluster, focater, logistic and Cox multivariate regression analysis using SPSS 10.0 system.

## RESULTS

### Result of follow-up

There were 273 cases diagnosed as the breast PT, and 203 patients with full follow-up came into our study. Of them, 133 cases were benign, 42 cases were borderline and 28 cases were malignant. The patients followed-up <5 years and >5 years

were 72 and 131 cases respectively; five-year survival rate of the patients with benign phyllodes tumor, borderline tumor and malignant tumors was 100% (82/82), 92.0% (23/25) and 33.3% (8/24) respectively.

### Histopathological changes

These histopathological changes were different in three histogrades of breast PT (Table 1).

**Table 1.** Pathological changes of different subtype of breast PT

Pathological changes	Benign	Borderline	Malignant	Total
Tendency of differentiation				
Fibroid	48	14	10	72
Mucoid	41	4	0	45
Lipoid	2	2	0	4
Complex of the above three	37	17	0	54
Liomyosarcomoid	5	2	0	7
Osteochondrosarcomoid	0	2	4	6
Malignant fibrous histocytomoid	0	0	6	6
Epitheliosarcomoid	0	0	2	2
Rhabdosarcomoid	0	0	1	1
No definite type	0	1	5	6
Mitosis(number/10HPF)				
0-4	133	3	0	136
5-9	0	39	3	42
>10	0	0	25	25
Nuclear pleomorphism				
Absent~slight	130	2	0	132
Moderate	3	40	1	44
Severe	0	0	27	27
Growth pattern				
Pushing	122	4	0	126
Infiltrative	11	34	26	71
Unidentified	0	4	2	6
Number of thin vessels				
3	0	12	1	13
4-6	0	9	7	16
>7	0	0	5	5
Tumor necrosis				
Spotty or focal	0	2	4	6
Fragmentary	0	2	16	18

**Table 2** Relationship between pathological changes and local recurrence or death

	severe cellular atypia (%)	mitosis number (average)	infiltrative (%)	tumor necrosis (%)	heterologous differentiation (%)
living without tumor	20.61	2.53	20.61	2.29	8.40
local recurrence	40.00	4.77	49.23	7.69	10.77
death for tumor	89.89	18.72	100.00	94.44	61.11

\*  $\chi^2$  of variety of living without tumor, local recurrence, and death for tumor (severe cellular atypia, mitosis number, infiltrative, tumor necrosis and heterologous differentiation) were 14.9098, 68.4040, 19.5081, 64.7697 and 21.3529 respectively,  $P < 0.01$ .

### Relationship between histopathological changes and local recurrence or death

The relationship between the histopathological basic changes and local recurrence or death was showed in table 2.

### Relationship between pathological histotype and surgery pattern

The degree of histotype and the extent of surgery were associated with prognosis of patients. The local recurrence increased with the elevation of histograde, and decreased with the extension of the surgery (Table 3).

### Statistic result

Logistic regression analysis proved that histograde of the tumor was related to the local recurrence and death, thus infiltrative growth of the tumor was associated with local recurrence ( $P<0.001$ ). That is to say, local recurrence and death increased with the elevation of the degree of histotype and the infiltrative extent of the tumor. In our study, local recurrences with infiltrative growth or pushing growth are 43/71 (60.5%) and 22/126(17.5%), respectively. In the patients with benign, boderline and malignant phyllodes tumors the local recurrence were 28/133 (21.1%), 19/42 (45.2%) and 18/28 (64.3%), respectively, tumor-related death was 0/133, 2/42(4.8%) and 16/28(57.1%) cases, respectively, the distant metastases was 0/133, 1/42 (2.4%) and 10/28(35.75) cases, respectively.

Cox model univariate analysis stated that surgery pattern, stromal cellularity, nuclear pleomorphism, mitotic activity, Nature of tumor margin, tumor necrosis, the number of thin vessels of the tumor, tendency of differentiation and histograde

were independent risk factors for prognostic (Table 4).

Logistic regression and Cox model analysis also demonstrated that tumor-related death was associated with mitotic activity and tumor necrosis, these two were independent factors to predict prognosis of the patient with PT. The tumor-related death in patients with mitoses  $>10$  and  $<10$ /PHF were 16/25(64%) and 2/178(1.1%) cases, and in patients with and without tumor fragmentationary necrosis were 15/16(93.8%) and 2/115(1.7%) cases, respectively. It suggests that increased mitoses rate and tumor fragmentationary necrosis could predict very poor prognosis.

## DISCUSSION

### Incidence, age and prognosis of breast PT

PT of the breast has much lower prevalence. In all the patients of our retrospective study<sup>[1]</sup>, the incidence was only 2.85 per 10,000, and it account 6.39% in breast diseases, 1.03% in breast tumor. The ratio of PT to fibroadenoma was 1:60. The median age in this group was 39 years, which is close to the Blacks in Europe or American, but is lower 10 years than the Whites<sup>[2]</sup>. This resembles to Chinese person in Taiwan<sup>[3]</sup>, which suggests that this lower age may be caused by racial factors.

By the univariate analysis of Cox model, the age, tumor size and the time of sudden increase of the tumor were not related to the prognosis, but surgery pattern, stromal cellularity, nuclear pleomorphism, mitotic activity, Nature of tumor margin, tumor necrosis, the number of thin vessels and tendency of tumor differentiation were correlated with

Table 3. Relationship between histotype and surgery pattern

Histotype	Tylectomy			Wide local excision			Mastectomy		
	No.	Local recurrence (%)	Death (%)	No.	Local recurrence (%)	Death (%)	No.	Local recurrence (%)	death (%)
Benign	101	28(27.7)	0	10	0	0	22	0	0
Borderline	24	18(75.0)	1(4.2)	4	1(25.0)	0	14	0	0
Malignant	18	17(94.4)	9(50.0)	--	--	0	10	1(10.0)	1(10.0)

Notes: 1. No cases in malignant group received wide local excision.

2. Seven cases in malignant group without local recurrence died of distant metastases have not listed in.

3.  $\chi^2$  between the same surgery pattern of three histotype and local recurrence was 13.1041,  $P<0.01$ .

$\chi^2$  of three surgery patterns were 8.4080, 9.3083 and 5.4771  $P<0.05$   $P<0.01$  and  $P<0.05$  respectively.

**Table 4.** Influence of clinical and pathological factors to 5-year survival rate

Factors	Degree of factors	Total/survival cases	Survival rate %	$\chi^2$ value	P value
Mitosis(number)	0-4	84/83	98.8	66.87	<0.01
	5-9	25/23	92.0		
	>10	22/7	31.8		
Nuclear atypia	Slight~moderate	88/85	96.6	48.82	<0.01
	Severe	24/9	37.5		
Tumor necrosis	Spotty or focal	5/4	80.0	11.42	<0.01
	Fragmentary	16/1	6.3		
Growth pattern	Pushing	81/81	100	28.32	<0.01
	Infiltrative	50/32	64.0		
Tendency of Differentiation	Homogenous	118/110	93.2	48.61	<0.01
	Heterologous	13/3	23.1		
Thin vessels (number)	<6	122/110	90.2	22.84	<0.01
	>7	9/3	33.3		
Size of tumor (cm)	<5	41/37	90.2	0.80	>0.05
	>5	90/76	84.4		
Sudden increase of tumor	Present	95/85	89.5	3.01	>0.05
	Absent	36/28	77.8		
Age(years)	<40	74/66	89.2	1.23	>0.05
	>40	57/47	82.5		
Histotype	Benign	82/82	100	14.0	<0.01
	Borderline	25/23	92.0		
	Malignant	24/8	33.3		

the prognosis significantly. And histograde, mitotic activity and tumor necrosis were independent risk factors for prognosis, these factors could influence the 5-year survival rate of the patients by itself or combined (table 3).

#### The treatment of PT

**To determine the histograde of tumor before operation** Our follow-up results showed that local recurrence increased with the elevation of histograde, and decreased with the extension of the surgery pattern. Therefore, histopathological subtype should be determined before operation. The only way to solve this problem is to perform intraoperative frozen section. In view of its importance, the pathologist should not only determine the histograde of tumor clearly, but also should inform more details such as mitoses, nature of tumor margin, tumor necrosis and other pathological findings possibly affecting survival rate as far as possible. This will help the surgeon to choose the adequate operation pattern.

**Tylectomy should not be adopted in PT** Our investigation suggested that in almost all the patients with tylectomy the local recurrence occurs.

With this surgery, the local recurrence in patients with benign, borderline and malignant tumor was 27.7%, 75% and 94.4%, respectively. In malignant group, four cases recurred several times, and then died with distant metastases in spite of repeated tylectomy each time, which suggested that tylectomy could not achieve the goal to cure the tumor, no matter what subtype it is. In the past decades in China, this operation was widely accepted due to many complex reason.

**Wide local excision should be the first place for benign and borderline PT** Our study showed that in benign tumor group, 10 cases with wide local excision and 14 cases with simple mastectomy had not recurred. Which means that both operation pattern will prevent recurrence efficiently, but it is obviously that wide local excision is much better because of its relatively less injuries. As to borderline tumor, our results showed that only one in four cases with wide local excision recurred, and it had not recurred by additional mastectomy. On the other hand, in 18 patients with recurrence by local tumor excision, there is no recurrence in 10 cases were was chosen additional mastectomy, and only one in seven cases who was chosen wide local ex-

cision recurred. The total recurrence rate in wide local excision was 18.2%. This suggests that most of borderline tumor should choose wide local excision at the beginning. Even if it recurred, it could also be cured by additional mastectomy. The borderline PT of the breast should be totally removed only if the tumor size does not allow either an adequate resection margin (2cm) or good cosmetic results by a less extensive procedure. Especially in some adolescent or mature women, wide local excision was of great importance to maintain the function of the breast. Otherwise in some elderly women, it might be better to choose simple mastectomy instead.

**Mastectomy should be chosen in malignant tumor** Optimum surgical therapy for malignant PT has been a subject of debate. In our study, 17 of 18 cases with local excision recurred, and 4 of them died even though they received repeated wide local excision. Five of 14 cases also died in spite of additional mastectomy. But only 1 case recurred in 10 patients who received mastectomy at the beginning. Therefore, considering its biological behavior, malignant tumor should firstly choose mastectomy. Only in several adolescent or mature women, if the diameter of the tumor is not more than 2cm, and its surrounding had enough mammary tissue, was the wide local excision permitted to perform. But it should also be under the strict surveillance. Once it recurred, additional mastectomy should be performed immediately.

In view of lymph node metastases only occurred in one of 22 patients in our group, we considered that it is of no necessity to perform radical mastectomy if there is no positive enlarged axillary lymph node. This is consistent with the literature.

In our study, 11 cases occurred distant metastases (lungs 9 cases, bones 1 case, lung and brain 1 case). Compared with lymph node metastases, distant metastases occurred more commonly. After operation, 4 cases received irradiation, 6 cases received chemical therapy and 13 patients received Chinese medicine treatment. It did not show significant difference in statistics, and further statistic analysis had not done because of small sample. In this respect, there are also many controversies. Although some authors proposed that post-radiotherapy will help for the patients<sup>[4]</sup>.

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