J Exp Clin Med 2014;6(5):161–165

Contents lists available at ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

ORIGINAL ARTICLE

Surgical Treatment of Phyllodes Tumor of the Breast with the Trend

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ARTICLE INFO

Article history:
Received: Jul 25, 2014
Revised: Aug 11, 2014
Accepted: Aug 13, 2014

KEY WORDS:
breast;
phyllodes tumor;
recurrence;
wide excision

Objective: Phyllodes tumors are composed of a benign epithelial component and a cellular spindle cell stroma that form a leaf-like structure. The purpose of this study was to define changes in patient characteristics, histopathologic parameters, and the outcome during two periods: before and after the introduction of core needle biopsy for preoperative diagnosis.

Methods: Records were reviewed of 170 patients with phyllodes tumors who were managed surgically. Patients treated from 1997 to 2004 ($n = 101$) were compared with patients treated from 2006 to 2013 ($n = 69$).

Results: The analysis of the two treatment periods revealed that the tumor size at diagnosis increased from 4.6 cm during the earlier period to 7.0 cm during the recent period ($p < 0.05$). The number of patients undergoing wide excision significantly increased during the recent period. Multivariate analysis revealed that a positive surgical margin was the only independent predictor of recurrence with an increased hazard of 4.8.

Conclusion: Wide excision with a clear margin is the first choice of current treatment for phyllodes tumors, even for malignant phyllodes tumors. However, this strategy does not further reduce local recurrence effectively, and core needle biopsy cannot be overstated in avoiding inappropriate initial surgery.

1. Introduction

A phyllodes tumor of the breast is a rare neoplasm with an incidence of less than 1% of all primary breast tumors.[1] The key features of a phyllodes tumor are a hypercellular stroma and glandular elements that project into the stroma in a leaf-like fashion.[2] In 1982, the World Health Organization declared "phyllodes tumor" as the most appropriate term from among more than 60 synonyms.[3] The World Health Organization subclassified the tumor histologically as benign, borderline, or malignant.[2,4,5] The relatively high recurrence rate despite surgical resection is also an unresolved management problem. In various reports, local recurrences develop in 8–40% of patients, and distant metastases occur in 0–21% of patients, depending on the number of patients in the study and the proportion of aggressive lesions.[6] Local recurrence is not a necessary antecedent event to the development of systemic metastases. Local recurrence is nonetheless deleterious because of a tendency for recurrent lesions to have a higher histologic grade than the primary tumor.[7–10]

Fatality because of the extension of a recurrent tumor to vital organs in the absence of distant metastasis has been reported.[11] This propensity to recur makes proper and adequate treatment imperative, even though local recurrence generally does not reduce survival.[8,11,12] A sharp distinction between the benign and malignant categories is not always possible. Several investigators have attempted to define factors predicting local relapse and distant metastasis.

Phyllodes tumors are histologically fibroepithelial tumors that likely originate from the terminal ductolobular unit and may be stroma-derived.[4] The stromal component microscopically may be bland and resemble a fibroadenoma, or may be atypical and resemble a soft-tissue sarcoma, or may vary between these extremes and (often) resemble a low-grade sarcoma. Grading is usually based on the semiquantitative evaluation of the following criteria in the stromal component: nuclear pleomorphism, mitotic rate, overgrowth, cellularity, and aspects of tumor margins. Ward and Evans[13] first reported stromal overgrowth as a putative additional factor of prognosis. In 1991, Cohen-Cedermark et al[14] included tumor necrosis and the presence of stromal elements (other than fibromyxoid tissue) among the prognostic factors.

Conflicts of Interest: Authors declare no conflicts of interests on this article.

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http://dx.doi.org/10.1016/j.jecm.2014.08.002

However, it is unknown whether the recognition of risk factors can be translated into practical ways to improve the outcome. The rationale for this study was to evaluate the features and outcomes during the treatment period before and the treatment period after the introduction of core needle biopsy for preoperative diagnosis, and to investigate whether the recurrence rates changed with increasing experience.

2. Methods

2.1. Study patients and procedures

We retrospectively analyzed the data of 170 patients with phyllodes tumor of the breast who were surgically managed from 1997 to 2013. Patients who were referred after primary therapy were not included in this series. To clarify the changing profile of phyllodes tumors, patients were placed in two groups: (1) before the introduction of core needle biopsy for preoperative diagnosis and (2) after the introduction of core needle biopsy for preoperative diagnosis. Diagnosis was confirmed histologically on the surgical specimens. Stromal overgrowth was defined as an absence of ductal elements in a 40 × low-power field. Follow up was obtained by internal database clinical collection and by interviews. The overall group was divided into two periods: (1) from March 4, 1997 to October 19, 2004 (period A) and (2) from March 6, 2006 to August 24, 2013 (period B). We then compared the patients treated during these two periods to determine if there was a change in either the tumor characteristics or the rates of local recurrence. The Mackay Memorial Hospital Institutional Review Board (Taipei, Taiwan) approved this study (approval number: 13MMHIS154).

2.2. Statistical analysis

Clinical features, histologic parameters, and the type of primary surgical intervention were correlated with local recurrence and compared for the two periods. Data from the two periods were compared by the Student *t* test, the Fisher's exact test, and the Chi-square test, as appropriate. Kaplan–Meier analysis for local recurrence was analyzed for the time until the first local recurrence. The significance of clinical and pathologic factors were compared using the log-rank test. Cox proportional-hazards modeling was employed to investigate major prognostic factors. Statistical significance was considered to have been achieved when $p < 0.05$. All statistical analyses were performed with SPSS for Windows, version 22.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

All 170 patients were female, and included two patients with synchronous bilateral tumors. The age at diagnosis of primary phyllodes tumor ranged from 12 years to 76 years (mean age, 39 years). Sixteen (9%) patients were under 20 years old. The mean age of the patients with benign phyllodes tumor was 36 years (age range, 12–76 years); the mean age for patients with a borderline tumor was 45 years (age range, 14–73 years); and the mean age for patients with malignant tumor was 42 years (age range, 18–63 years). These differences were not statistically significant. No patient had lymph node metastasis or distant metastasis at the time of presentation.

During treatment period A, a mastectomy was usually performed when a frozen section was malignant or when an excisional biopsy revealed a borderline or malignant tumor. At times, the breast lump was so large that a mastectomy was performed with clinical suspicion of carcinoma. Mastectomy was generally performed in a skin-sparing fashion so that skin grafts were unnecessary. For recurrent benign tumors, the choice of operation depended on a surgeon's preference. Some surgeons performed a mastectomy, and other surgeons performed a local or wide excision to achieve a negative margin. During this period, all patients undergoing mastectomy had concurrent axillary lymph node dissection.

During treatment period B, most operations were performed after the core needle biopsy to rule out malignant disease. A mastectomy was performed only when a malignant tumor was diagnosed with tissue proof. A huge benign lesion rarely required a mastectomy to attain a clear margin. Axillary lymph node dissection was performed when a core needle biopsy specimen was malignant. If a phyllodes tumor had been suspected pre- or perioperatively, a wide excision was performed with a margin of healthy tissue (greater than 1.0 cm). When the margin of the excised benign or borderline tumor was less than 0.5 cm, reoperation was undertaken if the patient agreed. Further details about the patient population are listed in Table 1.

Of the 32 patients with malignant tumors, 17 (53%) patients underwent mastectomy. Of 138 patients with nonmalignant histology, 124 (90%) patients were treated by breast-conserving surgery ($p < 0.05$). During the earlier period, mastectomy was performed on 11 (73%) of 15 patients with a malignant tumor. During the recent period, 11 (65%) of 17 patients with malignant disease underwent breast-conserving surgery; however, one patient developed local failure. All pathology of the mastectomy specimens indicated clear margins with normal breast tissue surrounding the tumor. In 18 patients, axillary lymph node dissection was performed at the time of the mastectomy, but no nodal metastases were found. For patients treated by breast-conserving surgery, eight patients in the earlier period and 21 patients in the recent period had margin involvement. They were either not offered further treatment or refused it.

The tumor size ranged 1.0–40 cm in the largest dimension [median size, 4.0 cm (period A); mean size, 6.0 cm (period B)]. Benign tumors, borderline tumors, and malignant tumors had mean diameters of 4.5 cm, 7.1 cm, and 7.5 cm, respectively ($p = 0.002$, ANOVA *F* test). The average size was 4.6 cm during

Table 1 Clinical characteristics of 172 patients with a phyllodes tumor during the two treatment periods

Parameter	Period A (1997–2004) ($n = 101$)	Period B (2006–2013) ($n = 69$)
Age (y), mean (SD)*	36 (13)	42 (13)
Tumor size*		
≤5 cm	80	31
>5 cm	21	38
Laterality*		
Right	46	43
Left	53	26
Bilateral	2	0
Quadrant		
Upper outer	48	40
Lower outer	15	7
Upper inner	19	7
Lower inner	9	2
Central	10	13
Treatment*		
Local excision	52	8
Wide excision	32	48
Total mastectomy	5	7
MRM	12	6
Margin status*		
Negative	93	48
Positive	8	21

All data (except for age) are presented as the number.
* Indicates significance at $p < 0.05$.
SD = standard deviation.

treatment period A and 7.0 cm during period B. The tumor size increased significantly in the recent period ($p < 0.05$).

For the 139 patients treated by breast-conserving surgery, the tumor size ranged 1.0–15.0 cm (mean size, 4.3 cm). For the 31 patients treated by mastectomy, the tumor size ranged 1.5–40.0 cm (mean size, 11.2 cm; $p < 0.05$). During treatment period B, the mean tumor size was 13.8 cm for eight nonmalignant lesions treated by mastectomy. Tumor classification showed that 106 (62.4%) phyllodes tumors were benign, 32 (18.8%) tumors were borderline malignant, and 32 (18.8%) tumors were malignant. The two periods had differences in histology type, stromal cellularity, and mitosis (Table 2). Twenty-one patients developed a local recurrence after a median of 18.9 months (range, 0.8–65.3 months); among these patients, only nine patients had a recurrence within the 1st year of follow up. One tumor treated by mastectomy recurred. The median time to recurrence was 24.1 months (12 patients) in treatment period A and 11.9 months (9 patients) in treatment period B ($p > 0.05$). Figure 1 illustrates the actuarial local control for both periods. Among the parameters studied, a positive surgical margin showed an increased hazard of 4.8, whereas none of the other prognostic factors were statistically significant (Table 3). Figure 2 shows the local outcome by margin status for the overall series.

Most (48%) recurrences were of the same grade. Upgrading to the next category was observed in 40% of recurrences. Three originally benign phyllodes tumors recurred locally as histologically malignant tumors; they were treated by mastectomy and neither has recurred. Two originally benign phyllodes tumors recurred locally as histologically borderline tumors. One tumor was treated by wide local excision without subsequent recurrence. The other tumor was treated by local excision but without a negative margin; it recurred as a malignant lesion (Table 4). The second recurrent episode was eventually controlled by mastectomy. Distant metastasis was not found in any patient who underwent mastectomy. In addition, two patients subsequently developed invasive ductal carcinoma of the breast (median interval, 3.5 years).

Table 2 The pathologic parameters of 172 patients with a phyllodes tumor during the two treatment periods

Parameter	Period A (1997–2004) ($n = 101$)		Period B (2006–2013) ($n = 69$)	
Histology type*	No.	%	No.	%
Benign	79	78	27	39
Borderline	7	7	25	36
Malignant	15	15	17	25
Tumor borders				
Pushing	81	80	59	86
Infiltrative	20	20	10	14
Stromal cellularity*				
Mild to moderate	74	73	62	90
Marked	27	27	7	10
Nuclear atypia				
Mild to moderate	93	92	67	97
Marked	8	8	2	3
Mitoses (per 10 HPF)*				
0–4	76	75	36	52
5–9	12	12	15	22
≥0	13	13	18	26
Stromal overgrowth				
Absent	89	88	49	71
Present	12	12	20	29
Heterologous elements				
Absent	99	98	67	97
Present	2	2	2	3
Tumor necrosis				
Absent	96	95	63	91
Present	5	5	6	9

* Indicates significance at $p < 0.05$.
HPF = high power field.

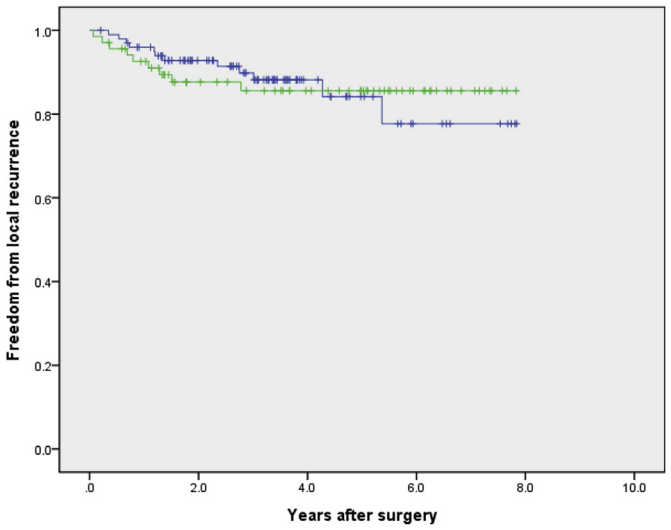

Figure 1 The graph shows the actuarial freedom from local recurrence for patients after treatment of their phyllodes tumor during the two periods. Curves are plotted based on the Kaplan–Meier method. The log-rank test shows no significant difference. The blue line is treatment period A ($n = 101$) and the green line is treatment period B ($n = 69$).

4. Discussion

Phyllodes tumor is a rare tumor that represents approximately 1% of mammary neoplasms and 2.5% of fibroepithelial lesions.[11] Some authors believe that histopathologic features that predict prognosis are fundamental in optimizing the management of phyllodes tumors.[2,4,7–13,15,16] Other authors emphasize the poor correlation between the biological behavior of the tumor and its histologic appearance.[6,17,18] All such tumors should be treated as potentially malignant. In the present study, the histopathologic parameters

Table 3 Multivariate Cox hazard analysis for local recurrence in 170 patients with a phyllodes tumor

Characteristics	Hazard ratio	95% CI
Treatment period		
Period A	1.0	—
Period B	0.67	0.26–1.73
Age		
≤40 y	1.0	—
>40 y	1.7	0.70–4.15
Tumor size		
≤5 cm	1.0	—
>5 cm	0.91	0.35–2.36
Surgical margin		
Negative	1.0	—
Positive	4.83	1.86–12.55
Tumor borders		
Pushing	1.0	—
Infiltrative	0.43	0.10–1.86
Nuclear atypia		
Absent	1.0	—
Present	0.55	0.19–1.65
Mitosis (per 10 HPF)		
≤10	1.0	—
>10	0.36	0.08–1.60
Stromal cellularity		
Mild to moderate	1.0	—
Marked	0.25	0.03–1.88
Tumor necrosis		
Absent	1.0	—
Present	0.68	0.09–5.09

For all comparisons, $p < 0.05$.
CI = confidence interval; HPF = high power field.

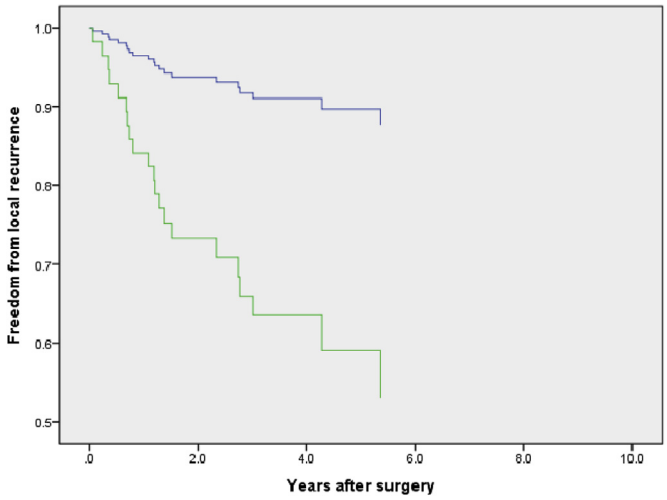

Figure 2 The graph shows the actuarial freedom from local recurrence for patients after treatment of their phyllodes tumor. The surgical margin is expressed as a categorical variable. The presence of a positive margin indicates a significantly increased likelihood of recurrence. The blue line indicates a negative margin ($n = 141$) and the green line indicates a positive margin ($n = 29$).

during the two periods were similar, and Cox regression analysis showed that no factor, except a positive surgical margin, was prognostic of local recurrence.

Certainly the small number of patients in the subsets may produce a beta (type II) error effect. In addition, the limitation of the current study is its retrospective nature. The inability to demonstrate a relation to the surgical procedure may result from a selection bias for type of surgery (the more malignant the tumor, the more likely a patient was to undergo radical surgery), which makes it difficult to propose specific treatment recommendations, based on our study. Tumor size has generally been considered of prognostic significance,[4,9] but this has not been reliably verified.[11,12]

Core needle biopsy has had a very vital role in the histological assessment of phyllodes tumor in preoperative settings and in differentiating phyllodes tumor from cellular fibroadenomas.[19] The sensitivity of core needle biopsy in diagnosing malignant phyllodes tumor is as high as 99%.[20] Benign lesions may grow to a considerable size, and small lesions may be histologically malignant. Sometimes patients present with a rapidly enlarging tumor at the site of a preexisting mass. In our series, the size of the phyllodes tumor also increased with increasing degree of malignancy, but the size was not a predictive factor for local recurrence. A further observation was the recent trend toward larger lesions at diagnosis. This may be explained by the change in patients' medical-seeking behavior during the second treatment period. The tumor size was not correlated with recurrence, although it is easy to understand that an increased tumor size at diagnosis makes it difficult to achieve a negative surgical margin with breast-conserving surgery. Before the 1980s, mastectomy was widely used,[4] but wide surgical excision with free margins is now advocated as the primary treatment.[6,21] Furthermore, it is believed that few phyllodes tumors are multifocal, and local recurrences are usually controlled by repeat excision.[22]

Table 4 Changes in the histologic grade of phyllodes tumors in women with locally recurrent disease

Change in diagnosis	Recurrence			Total	%
	First	Second	Third		
Benign to benign	11	0	0	11	44
Benign to borderline	2	1	1	4	16
Benign to malignant	3	1	0	4	16
Borderline to benign	1	0	0	1	4
Borderline to borderline	1	0	0	1	4
Borderline to malignant	1	1	0	2	8
Malignant to benign	2	0	0	2	8
Total	21	3	1	25	

We previously tended to treat all malignant tumors by mastectomy. During the recent period, breast-conserving surgery was undertaken if the surgeon was comfortable with the surgical margins. Our experience suggests that a large tumor-to-breast ratio still necessitates mastectomy to achieve negative margin status or a better cosmetic result. Axillary lymph node dissection is generally not recommended because malignant phyllodes tumors usually spread by a hematogenous route rather than a lymphatic route, although mastectomies for malignant tumors in period A and period B had concurrent axillary dissection. This is because our experience showed that the frozen section is very unreliable for diagnosing phyllodes tumors.[15]

A change in attitude among surgeons was demonstrated by the fact that 32% of patients underwent wide excision during the earlier period whereas 70% of patients underwent wide excision during the recent period. However, the positive margin rate did not consistently decrease over time, although surgeons typically strive to achieve a 1–2-cm distal clearance margin. A problem we encountered was that it was difficult to persuade patients to undergo additional radical surgery, even in patients with marginal involvement. Many patients declined when they realized that further operation did not guarantee that there would be no recurrence. In the literature, most tumors do recur within 2–5 years.[4,8,11–13,15] The median time to recurrence in the present study was similarly 18.9 months. Some authors have suggested mastectomy for the recurrence of borderline and malignant tumors.[7,12] Regarding the grade progression in the recurrent tumors, the present results showed that 10 (40%) of 25 recurrences were upgraded. Two metachronous breast cancers were concomitantly observed. In 1976, Hajdu and collaborators[8] reported the malignant transformation of a previously benign tumor that had recurred. Azzopardi et al[2] thereafter suggested that tumors could undergo malignant transformation. Malignant transformation of the epithelial component of the tumor has been reported in cases of ductal carcinoma *in situ*, infiltrating ductal carcinoma, and lobular carcinoma *in situ*.[4,5,23,24] The incidence of carcinoma transformation in phyllodes tumor is believed to be only 1–2% of all phyllodes tumors.[23]

Additional studies are required to identify the factors that promote malignant progression in the epithelial and stromal components of phyllodes tumors. With regard to adjuvant therapy, one patient with a borderline tumor in our series received postoperative radiotherapy. Two patients (one patient with a borderline tumor and one patient with a malignant tumor) received adjuvant chemotherapy for contralateral breast cancer. To date, neither patient has developed a recurrence or metastasis. There is no evidence of a role for chemotherapy.[6,18,21,25] The use of radiotherapy is also controversial. Some authors[17] believe that additional radiotherapy does not improve the prognosis and is unnecessary, whereas other authors[26] suggest that adjuvant radiation therapy may be appropriate for high-risk patients with margins less than 0.5 cm of tumors greater than 10 cm in diameter, or after the resection of recurrent disease.

Progesterone receptors are present in nearly all cases of phyllodes tumor and estrogen receptors in approximately one-third of phyllodes tumor cases.[27] However, the role of hormonal therapy is uncertain. Kersting and colleagues[28] found that activating mutations in the epidermal growth factor receptor gene and overexpression of the epidermal growth factor receptor are associated

with the grade progression of phyllodes tumors. However, numerous studies have attempted to determine whether immunohistochemical markers may be useful in predicting the clinical outcome of the patients, but all of these markers have failed to attain any clinical validation.[29]

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