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ORIGINAL ARTICLE – BREAST ONCOLOGY

Predicting Outcome in Mammary Phyllodes Tumors: Relevance of Clinicopathological Features

Joshua Li[1], Julia Y. Tsang[1], Clement Chen[2], Siu-Ki Chan[3], Sai-Yin Cheung[4], Cherry Wu[5], Ava Kwong[2], Jintao Hu[6], Hong Hu[7], Dongxian Zhou[7], and Gary M. Tse[1]

[1]Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong; [2]Division of Breast Surgery, Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong; [3]Department of Pathology, Kwong Wah Hospital, Yau Ma Tei, Hong Kong; [4]Department of Pathology, Tuen Mun Hospital, Tuen Mun, Hong Kong; [5]Department of Pathology, North District Hospital, Sheung Shui, Hong Kong; [6]Department of Pathology, The Second Affiliated Hospital of Jinan University, Shenzhen People's Hospital, Shenzhen, China; [7]Department of Breast Surgery, The Second Affiliated Hospital of Jinan University, Shenzhen People's Hospital, Shenzhen, China

ABSTRACT

Background. Phyllodes tumors (PTs) of the breast are uncommon fibroepithelial neoplasms. Most behave in a benign fashion but they also have the potential to recur locally or to metastasize.

Methods. In the current study involving 290 PTs (181 benign, 76 borderline, and 33 malignant) from three hospitals over an 11-year period, we assessed the relationship between histologic parameters (including histologic features affecting grade and surgical margin status), postoperative adjuvant treatment, and local recurrences and distant metastases.

Results. An involved surgical margin was the only factor associated with increased risk of local recurrences (hazard ratio [HR] 4.673, $p = 0.003$), but not for distant metastases. For local recurrences, a wider margin did not confer additional benefits. None of the histologic factors were predictive for local recurrences. In contrast, distant metastases were correlated with histologic parameters, particularly an infiltrative border (HR 10.935, $p = 0.012$) and the presence of necrosis (HR 15.311, $p = 0.007$). In this series, all local recurrences were found in patients without radiotherapy, regardless of surgical margin status.

Conclusion. A negative surgical margin is mandatory for the effective local control of PT recurrence, and a minimal margin clearance may be sufficient. For distant metastases, the inherent characteristics of PTs are important, thus it may be prudent to evaluate additional histologic features, including necrosis, for patients' prognostication.

Phyllodes tumors (PTs) of the breast are uncommon fibroepithelial neoplasms accounting for 0.5–1.0% of primary female breast tumors,[1] with a higher incidence in the Asian population.[2] While most PTs behave in a benign fashion, some (approximately 21%) may recur locally and rarely metastasize (< 2%).[3] The current three-tier grading system is based on a combined assessment of mitotic count, stromal cellularity, stromal overgrowth, stromal cell pleomorphism, and border morphology.[4] Practical problems in grading exist as some PTs may fulfill some but not all criteria for each grade. In general, this grading shows good correlation with distant metastases,[2] but not with local recurrences as correlation of local recurrence with grade was not consistently reported.[3,4] A nomogram has been proposed that estimates the recurrence-free survival (RFS) of patients with PTs, but this nomogram only utilizes some, not all, histologic features used for PT grading, suggesting some histologic parameters may be more important than others, and further reflecting the limitations of this grading system.[3] While this nomogram has been validated,[5–7] it does not distinguish between local recurrences and distant

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G. M. Tse
e-mail: garytse@cuhk.edu.hk

metastases. Histologic factors have been variably reported to predict recurrence.[8–11] Due to the rarity of PTs, few studies were available evaluating the association of histologic factors with PT metastasis.[9,12,13]

Apart from the intrinsic histologic features, surgical margin clearance is critical for recurrence prediction.[2,14–16] A surgical margin $\geq$ 1 cm was recommended.[17] *Re-excision is suggested* for cases with a close/involved margin; however, in practice, there is no consensus on the definition of an adequate surgical margin. Some recent studies casted doubt on the influence of surgical margin status on recurrences in low-grade PTs.[11,18,19]

Given the lack of clear consensus in the prognostication and management of PTs, we evaluated the relationship between clinicopathologic parameters, treatment, and outcomes. Most studies only examined local recurrences,[8,11] while very few evaluated factors affecting local recurrences and distant metastases separately.[9,13] In the current study, we assessed grading, surgical margin status, and some additional histologic parameters, as well as postoperative adjuvant treatment, for their relationship with local recurrences and distant metastases. This may help to identify relevant clinicopathologic factors for optimal patient management.

MATERIALS AND METHODS

Patient Selection

PT excision specimens in the three involved institutions over an 11-year period (1999–2009) were obtained through a computerized search. Patient age at diagnosis, tumor size, postoperative adjuvant treatment, and follow-up data were recorded. For the outcome, RFS was defined as the time interval between the initial diagnosis and the first detection of recurrence, while local RFS (LRFS) was defined as the time interval between the initial diagnosis and the first detection of local recurrence. Distant metastasis-free survival (DMFS) was defined as the time between the initial diagnosis and the first detection of distant metastasis. This study was approved by the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee.

Histologic Features

The specimens were routinely processed, and all cases were reviewed for histological features to confirm the diagnosis. Tumor border was categorized as pushing or infiltrative, and mitotic count was the number of mitotic figures per 10 high-power fields (400×; Nikon Labophot, field area 0.19 mm^2). Stromal pleomorphism and cellularity were graded into mild, moderate, and marked. Stromal overgrowth was defined as the complete absence of an epithelial component in a low-power field (LPF) [40×; Nikon Labophot, field area 1.9 mm^2]. The tumors were graded into benign, borderline, and malignant based on the WHO criteria.[4] Additional histologic features, including the presence of myxoid changes, necrosis, hemorrhage, hyalinization, and pseudoangiomatous stromal hyperplasia (PASH), in the stroma were also assessed. The final surgical margin status was obtained from medical records, and was measured as the closest distance of the tumor to the inked resection margin, while clear margin (not involved) was defined as no tumor cells found at the painted margin.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA). The association of demographic and histologic parameters and surgical margins with local recurrences and distant metastases was carried out using the paired Chi-square test. The survival difference in RFS was examined with Kaplan–Meier survival analysis using the log-rank test, and multivariate analysis was performed using Cox regression. Correlation was considered significant if the p value was < 0.05.

RESULTS

Patients

This cohort included 290 PT cases. Mean patient age was 43.2 years (range 16–86), mean tumor size was 6.24 cm (range 1.2–33), and mean follow-up period was 75.2 months (range 1–248). There were 181 (62.4%) benign, 76 (25.2%) borderline, and 33 (11.4%) malignant PTs. No heterologous elements were detected in any of the cases (characteristics of the cohort are summmarized in Table 1). Excisional margin status was available in 270 cases, including 32 cases who underwent re-excision. Involved margin was found in 67 cases at final surgery.

Local recurrences and distant metastases were seen in 9.3% (n = 27) and 2.1% (n = 6) of patients, respectively (patient 39 had both local recurrences and distant metastasis). Among these patients, 18 had single local recurrences, 9 had multiple recurrences, and 5 had distant metastases.

The 18 cases of single recurrences arose from 12 benign and 6 borderline primary PTs. Of the 12 benign primary PTs that recurred, seven and three cases recurred as benign and borderline, respectively, and the two remaining cases

TABLE 1 Correlation of total recurrence, local recurrence, and distant metastasis with clinicopathological features in all cases and cases with clear surgical margins

	Total	Total recurrences			Local recurrences			Metastases		
		No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
All cases										
Age (years)										
Mean	43.2	43.6	41.1	*0.098*	43.7	39.0	**0.020**	43.1	51.2	NS
SD	12.2	12.2	12.4		12.4	9.3		12.0	18.8	
Range	16–86	16–86	19–86		16–86	19–54		16–86	29–86	
Median	44	45	41		45	40		44	48	
Tumor size										
Mean (mm)	62.4	61.5	70.2	NS	62.5	61.8	NS	61.5	110.8	NS
SD	45.1	44.2	52.2		46.1	33.6		43.3	101.1	
Range	12–330	12–330	20–280		12–330	20–150		12–330	44–280	
Median	50	50	55		50	55		50	55	
Surgical margin										
Not involved	203	190	13	**0.005**	195	8	< **0.001**	198	5	NS
Involved	67	55	12		55	12		66	1	
Diagnosis										
Benign	181	164	17	NS	164	17	NS	180	1	**0.007**
Borderline	75	64	11		66	9		73	2	
Malignant	34	30	4		33	1		31	3	
Mitotic count										
< 5	188	169	19	NS	170	18	NS	186	2	**0.029**
5–9	57	51	6		52	5		56	1	
> 9	45	38	7		41	4		42	3	
Pleomorphism										
Mild	127	117	10	NS	117	10	NS	126	1	**0.013**
Moderate	132	114	18		116	16		130	2	
Severe	31	27	4		30	1		28	3	
Cellularity										
Mild	132	121	11	NS	123	9	NS	129	3	NS
Moderate	107	92	15		92	15		107	0	
Severe	51	45	6		48	3		48	3	
Overgrowth										
No	183	167	16	*0.074*	167	16	NS	183	0	< **0.001**
Focal	68	59	9		59	9		67	1	
Present	39	32	7		37	2		34	5	
Border										
Pushing	169	154	15	NS	154	15	NS	169	0	< **0.001**
Focal infiltrative	72	63	9		64	8		70	2	
Infiltrative	29	24	5		28	1		25	4	
Myxoid stroma										
Absent	222	197	25	NS	202	20	NS	216	6	NS
Present	68	61	7		61	7		68	0	
Necrosis										
Absent	281	251	30	NS	254	27	NS	277	4	**0.012**

TABLE 1 continued

	Total	Total recurrences			Local recurrences			Metastases		
		No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
Present	9	7	2		9	0		7	2	
Hemorrhage										
Absent	276	245	31	NS	249	27	NS	271	5	NS
Present	14	13	1		14	0		13	1	
Hyalinization										
Absent	262	233	29	NS	238	24	NS	256	6	NS
Present	28	25	3		25	3		28	0	
PASH										
Absent	287	256	31	NS	260	27	NS	282	5	*0.061*
Present	3	2	1		3	0		2	1	
Treatment										
RT										
No	256	228	28	NS	229	27	*0.091*	254	2	**0.001**
Yes	30	26	4		30	0		26	4	
Surgery										
BCS	233	211	22	NS	211	22	NS	232	1	**0.001**
Mastectomy	36	30	6		34	2		32	4	
Cases with a clear surgical margin										
Age										
Mean		44.7	44.1	NS	44.9	38.9	*0.089*	44.5	52.4	NS
SD		11.5	15.3		11.8	8.7		11.4	20.7	
Range		17–86	21–86		17–86	21–47		17–86	29–86	
Median		45	44		45	41.5		45	49	
Tumor size										
Mean (mm)		61.7	80.1	NS	63.1	57.8	NS	61.6	124.8	NS
SD		44.6	73.5		47.2	38.9		44.3	111.1	
Range		12–330	20–280		12–330	20–130	12–330	44–280		
Median		50	45		50	43.5		50	87.5	
Diagnosis										
Benign		114	3	**0.028**	114	3	NS	117	0	**0.001**
Borderline		51	6		53	4		55	2	
Malignant		25	4		28	1		26	3	
Mitotic count										
< 5		121	4	< **0.001**	122	3	NS	124	1	**0.017**
5–9		37	3		38	2		39	1	
> 9		32	6		65	3		35	3	
Pleomorphism										
Mild		79	2	**0.024**	79	2	NS	81	0	**0.005**
Moderate		87	7		89	5		92	2	
Severe		24	4		27	1		25	3	
Cellularity										
Mild		84	4	NS	86	2	NS	86	2	NS
Moderate		69	4		69	4		73	0	
Severe		37	5		40	2		39	5	
Overgrowth										
No		123	4	**0.001**	123	4	NS	127	0	< **0.001**

TABLE 1 continued

	Total	Total recurrences			Local recurrences			Metastases		
		No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
Focal		41	2		41	2		43	0	
Present		26	7		31	2		28	5	
Border										
Pushing		111	5	**0.022**	111	5	NS	116	0	**< 0.001**
Focal infiltrative		50	4		51	3		53	1	
Infiltrative		17	4		21	0		17	4	
Myxoid stroma										
Absent		114	11	NS	149	6	NS	150	5	NS
Present		46	2		46	2		48	0	
Necrosis										
Absent		183	11	NS	189	8	NS	191	3	**0.016**
Present		7	2		9	0		7	2	
Hemorrhage										
Absent		182	12	NS	186	8	NS	190	4	NS
Present		8	1		9	0		8	1	
Hyalinization										
Absent		170	12	NS	175	7	NS	177	5	NS
Present		20	1		20	1		21	0	
PASH										
Absent		188	12	NS	192	8	NS	196	4	*0.072*
Present		2	1		3	0		2	1	
Treatment										
RT										
No		165	9	*0.071*	166	8	NS	173	1	**0.001**
Yes		22	4		26	0		22	4	
Surgery										
BCS		158	6	**0.001**	158	6	NS	164	0	**< 0.001**
Mastectomy		24	6		28	2		26	4	

p values reaching statistical significance (> 0.05) are bolded, *p* values showing marginal correlations (> 0.1 and < 0.05) are italicized

NS no statistical significance, *SD* standard deviation, *RT* radiotherapy, *BCS* breast-conserving surgery, *PASH* pseudoangiomatous stromal hyperplasia

had missing information regarding the recurrence. Of the six borderline primary PTs that recurred, five recurred as borderline and one recurred as benign.

The nine cases with multiple recurrences arose from six benign, two borderline, and one malignant primary PT. Of the six benign primary PTs, two recurred only as benign; two recurred twice as borderline; one recurred as borderline, then benign; and one (patient 39) recurred as benign, followed by borderline, malignant PT, and eventually developed bone metastasis. For the two borderline primary PTs, one had three benign recurrences, followed by one borderline recurrence, while the other case recurred as malignant, followed by benign, then malignant again. The single malignant primary PT had three borderline recurrences (electronic supplementary Table S1).

The local recurrence rates for benign, borderline, and malignant PTs were 9.4% (17/181), 12.0% (9/75), and 2.9% (1/34), respectively. Tumor grade had no significant correlation with local recurrence.

The six patients with distant metastases included one patient who had both local recurrences and distant metastases, as detailed in the previous paragraph (patient 39). The remaining five patients included three with malignant PTs and two with borderline primary PTs. All metastases occurred within 1 year after diagnosis (electronic supplementary Table S1). The distant metastases correlated with grade ($p = 0.006$) showed metastatic rates of 0.6% (1/181), 2.7% (2/75), and 8.8% (3/34) for benign, borderline, and malignant PTs, respectively.

Data on surgical treatment were available in 269 cases. Thirty six (13.4%) cases (11 benign, 12 borderline, and 13

malignant) had mastectomy, and 233 cases (154 benign, 60 borderline and 19 malignant) had breast-conserving surgery (BCS). Follow-up information on adjuvant treatment was available in 286 patients; 30 patients received adjuvant radiotherapy (RT), including 7, 10, and 13 patients with benign, borderline, and malignant PTs. There was a significant positive correlation of increasing tumor grade with RT treatment and surgery type ($p < 0.001$ for both).

Correlation with All Recurrences (Local Recurrences and Distant Metastases), Local Recurrences, and Distant Metastases

All recurrences (local recurrences and distant metastases) were associated with involved surgical margins ($p = 0.005$). A marginal correlation was found with younger age ($p = 0.098$) and stromal overgrowth ($p = 0.074$), however no correlation was observed with all other factors (Table 1).

Local recurrences were only associated with younger age ($p = 0.020$) and involved final surgical margin ($p < 0.001$). All histologic factors were not associated with local recurrences (Table 1).

Distant metastases were associated with higher tumor grade ($p = 0.007$), mitosis ($p = 0.029$), pleomorphism ($p = 0.013$), stromal overgrowth ($p < 0.001$), infiltrative tumor border ($p < 0.001$), presence of necrosis ($p = 0.012$), and postoperative RT ($p = 0.001$) (Table 1). A marginal correlation was found with PASH ($p = 0.061$), however the number of cases with PASH stroma was too low to draw a definite conclusion. Stromal overgrowth, infiltrative border, tumor necrosis, and PASH ($p \leq 0.046$) remained significantly associated with metastases in borderline and malignant PTs (electronic supplementary Table S2), suggesting these factors predicted metastases independent of the PT grade.

Survival analysis showed that patients with PTs involving surgical margins had shorter RFS (log-rank 8.582, $p = 0.003$) and LRFS (log-rank 15.294, $p < 0.001$) (Fig. 1). Higher tumor grade (log-rank 10.390, $p = 0.006$) (Fig. 1) and the relevant associated features (marked pleomorphism [log-rank 9.941, $p = 0.007$], stromal overgrowth [log-rank 25.072, $p < 0.001$], and infiltrative border [log-rank 24.079, $p < 0.001$]) [electronic supplementary Fig. S1] were associated with shorter DMFS. Multivariate analysis showed surgical margin was an independent prognostic factor for all events (hazard ratio [HR] 2.639, $p = 0.018$) and for local recurrences (HR 4.673, $p = 0.003$). In contrast, distant metastases were independently associated with infiltrative border (HR 10.935, $p = 0.012$) and the presence of necrosis (HR 15.311, $p = 0.007$), but not with surgical margin (Table 2). The presence of PASH areas (HR 55.328, $p = 0.007$) was also an independent prognostic factor for distant metastases; however, the number of cases with PASH stroma was too low.

Correlation with Local Recurrence and Distant Metastasis According to Margin Status

In cases with positive margins, there was no association between any histologic features and all recurrences, except younger age ($p = 0.040$) [electronic supplementary Table S3].

In cases with clear margins, all recurrences (local recurrence and distant metastasis) were associated with higher tumor grade ($p = 0.028$), mitotic count ($p < 0.001$), pleomorphism ($p = 0.024$), overgrowth ($p = 0.001$), and infiltrative border ($p = 0.022$). Postoperative RT ($p = 0.071$) showed a marginal correlation, while surgery type showed a significant correlation ($p = 0.001$) (Table 1). For local recurrences, none of these factors showed a significant correlation. Conversely, distant metastases were associated with grade, mitosis, pleomorphism, overgrowth, infiltrative border, and necrosis ($p \leq 0.016$) (Table 1).

Overall, 253 patients had complete data regarding treatment and margin status. Among these patients, 19 had local recurrences. It is interesting to note that all cases that recurred locally did not receive RT. Table 3 shows details regarding treatment and margin status in relation to local recurrence and PT grade.

Survival analysis showed that in the cases with a clear surgical margin, distant metastases were associated with higher tumor grade (HR 6.342, $p = 0.009$), infiltrative border (HR 16.729, $p = 0.005$), high mitotic count (HR 3.134, $p = 0.041$), pleomorphism (HR 7.253, $p = 0.013$), PASH (HR 18.918, $p = 0.009$), necrosis (HR 15.406, $p = 0.003$), and larger tumor size (HR 1.011, $p = 0.027$) (Table 2). The low number of distant metastases precluded further multivariate analysis. No factors showed an independent prognostic impact for local recurrences.

Information regarding surgical margin clearance was available for 153 cases. The mean clearance was 0.4 cm, and 19 cases had a wide surgical margin (≥ 1 cm). Clearance from the surgical margin did not show a correlation with any events (electronic supplementary Table S4). The rate of recurrence in cases with a wide margin (5.3%) was similar to those with narrow margins (0.1 to < 1 cm) (6.7%). Regarding local recurrences, 149 cases had complete data regarding RT, surgery, and margin clearance. Among these, five local recurrences were observed and none received RT. Two benign and two borderline cases with local recurrences had BCS with a narrow margin, while one borderline case had mastectomy with a narrow margin (Table 4).

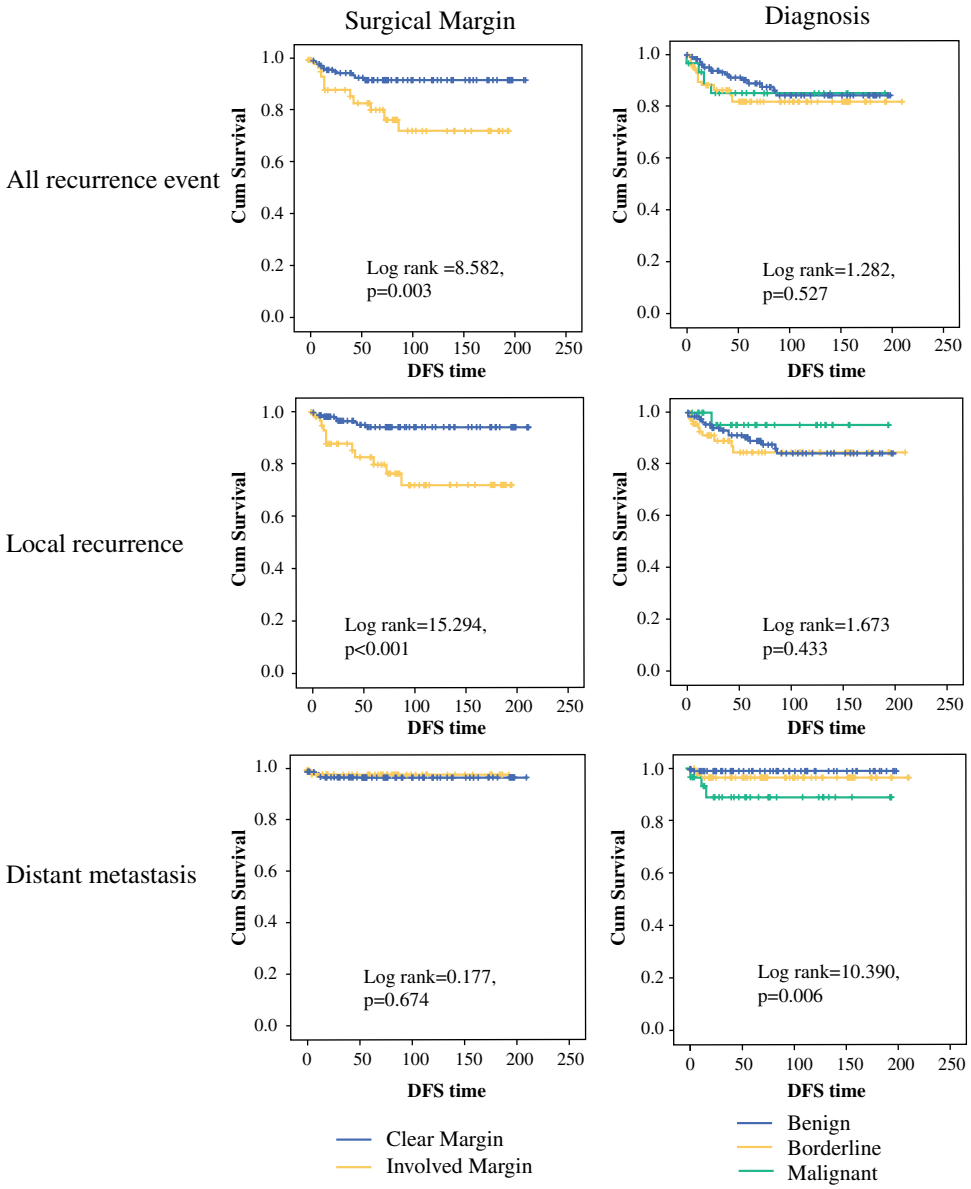

FIG. 1 Kaplan–Meier analysis on patients' survival according to margin status and diagnosis. *Cum* cumulative, *DFS* disease-free survival

DISCUSSION

The mainstay for treatment of PTs is surgical excision, and the goal is always a balance of minimizing cosmetic and functional morbidities and recurrence risk. Traditionally, a 10 mm resection margin was regarded as adequate,[17,20] however, in practice, achieving such wide margins may be impractical.[21] Thus, to date, the attainment of a negative margin in all PTs is still debatable.[22]

In the current series, involved margins were only associated with an increased risk of local recurrences, but not distant metastases, similar to other previous reports.[3,8–10,16] Furthermore, although an involved surgical margin was associated with local recurrences, a wider margin did not confer additional benefits. These findings echoed recent studies showing a lack of relationship between margin width and disease recurrence.[16,23] Thus re-excision for close, but not involved, margins may not be justified.

Local recurrences were also associated with younger patient age, as previously reported.[13,15] Younger patients might have a potentially lesser extent of excision, as evidenced by a higher rate of positive surgical margins, thus leading to an increased local recurrence risk.

In PTs, local recurrences are more common than distant metastases. Many factors, including patient age, tumor size, stromal mitosis, stromal overgrowth, necrosis, and

TABLE 2 Cox regression analysis on histological factors related to recurrence-free survival for all cases

	Univariate				Multivariate			
	HR	Lower 95% CI	Upper 95% CI	*p* value	HR	Lower 95% CI	Upper 95% CI	*p* value
All cases								
All recurrences								
Surgical margin	2.841	1.290	6.255	**0.010**	2.639	1.178	5.910	**0.018**
Diagnosis	1.203	0.742	1.951	NS				
Border	1.546	0.940	2.543	*0.086*	1.595	0.930	2.735	*0.090*
Overgrowth	1.389	0.904	2.136	NS				
Cellularity	1.210	0.759	1.929	NS				
Pleomorphism	1.342	0.808	2.229	NS				
Mitosis	1.138	0.738	1.757	NS				
Tumor size	1.003	0.996	1.009	NS				
Age	0.981	0.953	1.011	NS				
PASH	2.670	0.363	19.648	NS				
Hyalinization	0.758	0.225	2.556	NS				
Hemorrhage	0.502	0.068	3.686	NS				
Necrosis	2.258	0.539	9.466	NS				
Myxoid stroma	0.822	0.354	1.909	NS				
Local recurrences								
Surgical margin	4.559	1.870	11.309	**0.001**	4.673	1.582	10.304	**0.003**
Diagnosis	0.791	0.433	1.444	NS				
Border	0.927	0.487	1.765	NS				
Overgrowth	0.923	0.544	1.568	NS				
Cellularity	1.070	0.639	1.793	NS				
Pleomorphism	0.970	0.548	1.715	NS				
Mitosis	0.886	0.529	1.483	NS				
Tumor size	0.999	0.990	1.008	NS				
Age	0.966	0.936	0.998	**0.035**				
PASH	0.049	< 0.001	> 1000	NS				
Hyalinization	0.899	0.262	3.083	NS				
Hemorrhage	0.045	< 0.001	46.339	NS				
Necrosis	0.048	< 0.001	> 1000	NS				
Myxoid stroma	1.021	0.430	2.429	NS				
Metastases								
Surgical margin	0.634	0.074	5.430	NS				
Diagnosis	4.142	1.437	11.937	**0.009**				
Border	9.689	2.397	39.159	**0.001**	10.935	1.703	70.233	**0.012**
Overgrowth	12.615	1.984	80.209	**0.007**				
Cellularity	1.594	0.559	4.543	NS				
Pleomorphism	4.162	1.226	14.132	**0.022**				
Mitosis	9.689	2.397	39.159	**0.001**				
Tumor size	1.011	1.001	1.021	**0.035**				
Age	1.050	0.990	1.115	NS				
PASH	20.568	2.395	176.669	**0.006**	55.328	3.302	927.187	**0.005**
Hyalinization	0.042	< 0.001	< 1000	NS				
Hemorrhage	3.691	0.431	31.615	NS				
Necrosis	16.334	2.988	89.285	**0.001**	15.311	2.080	112.714	**0.007**
Myxoid stroma	0.032	< 0.001	91.294	NS				

TABLE 2 continued

	Univariate				Multivariate			
	HR	Lower 95% CI	Upper 95% CI	*p* value	HR	Lower 95% CI	Upper 95% CI	*p* value
Cases with a clear surgical margin								
All recurrences								
Diagnosis	2.445	1.236	4.835	**0.010**				
Border	2.331	1.167	4.655	**0.016**				
Overgrowth	2.755	1.430	5.306	**0.002**	3.140	1.607	6.137	**0.001**
Cellularity	1.635	0.805	3.325	NS				
Pleomorphism	2.025	0.558	7.348	NS				
Mitosis	2.197	1.171	4.120	**0.014**				
Tumor size	1.005	0.996	1.013	NS				
Age	0.994	0.945	1.045	NS				
PASH	5.604	0.725	43.298	*0.098*	10.158	1.204	85.714	**0.033**
Hyalinization	0.714	0.093	5.496	NS				
Hemorrhage	1.627	0.211	12.521	NS				
Necrosis	4.231	0.937	19.096	*0.061*				
Myxoid stroma	0.543	0.120	2.452	NS				
Local recurrences								
Diagnosis	1.456	0.590	3.592	NS				
Border	0.794	0.250	2.524	NS				
Overgrowth	1.427	0.614	3.314	NS				
Cellularity	1.424	0.576	3.517	NS				
Pleomorphism	1.331	0.487	3.640	NS				
Mitosis	1.788	0.809	3.950	NS				
Tumor size	0.997	0.979	1.014	NS				
Age	0.952	0.895	1.012	NS				
PASH	0.049	< 0.001	> 1000	NS				
Hyalinization	1.262	0.155	10.628	NS				
Hemorrhage	0.046	< 0.001	> 1000	NS				
Necrosis	0.047	< 0.001	> 1000	NS				
Myxoid stroma	0.964	0.194	4.784	NS				
Metastases[a]								
Diagnosis	6.342	1.572	25.581	**0.009**				
Border	16.729	2.366	118.29	**0.005**				
Overgrowth	73.25	0.164	< 1000	NS				
Cellularity	2.043	0.641	6.516	NS				
Pleomorphism	7.253	1.523	34.538	**0.013**				
Mitosis	3.134	1.045	9.399	**0.041**				
Tumor size	1.011	1.001	1.021	**0.027**				
Age	1.052	0.966	1.122	NS				
PASH	18.918	2.105	170.017	**0.009**				
Hyalinization	0.042	< 0.001	> 1000	NS				
Hemorrhage	4.997	0.558	44.733	NS				
Necrosis	15.406	2.570	92.349	**0.003**				
Myxoid stroma	0.032	< 0.001	202.690	NS				

p values reaching statistical significance (> 0.05) are bolded, *p* values showing marginal correlations (> 0.1 and < 0.05) are italicized

In addition to age, all factors (except diagnosis) with a *p* value < 0.100 were included in the multivariate analysis

NS no statistical significance, *HR* hazard ratio, *CI* confidence interval, *PASH* pseudoangiomatous stromal hyperplasia

[a]There are too few cases with a clear margin of distant metastasis for multivariate analysis

TABLE 3 Details in treatment and margin status in relation to local recurrence and PT grade

	Margin status	Benign	Borderline	Malignant	Total
No recurrence					
Without RT					
BCS	Clear	97	37	11	145
	Involved	30	10	4	44
Mastectomy	Clear	6	5	2	13
	Involved	1	1	0	2
With RT					
BCS	Clear	3	6	3	12
	Involved	–	–	–	–
Mastectomy	Clear	2	2	10	14
	Involved	2	2	0	4
Recurrence					
Without RT					
BCS	Clear	3	2	1	6
	Involved	7	4	0	11
Mastectomy	Clear	0	2	0	2
	Involved	–	–	–	–
With RT					
BCS	Clear	–	–	–	–
	Involved	–	–	–	–
Mastectomy	Clear	–	–	–	–
	Involved	–	–	–	–

BCS breast-conserving surgery, *PT* phyllodes tumor, *RT* radiotherapy

surgical margin status have been variably reported as prognostic factors for local recurrences.[8–11,13] Among these, surgical margin status was the most consistent. This was further reaffirmed in the current series, where only surgical margin status was identified to be predictive of local recurrences, while histologic factors were not. Further works on novel genetic or biological markers, such as c-kit[24] and E-cadherin,[25] may be useful to elucidate other potential predictive factors for local recurrences.

In contrast, distant metastases were correlated with histologic parameters, but not surgical margin status. This indicated the inherent characteristic of PTs played a more important role in distant metastases, as confirmed by findings of other studies.[1,9,13,14] Other histologic features, such as PASH and necrosis, were related to distant metastasis, but none were correlated with local recurrences in the current series. Earlier smaller scaled studies suggested tumor necrosis may prognosticate outcome in PTs;[26,27] a recent study also demonstrated an association of tumor necrosis with higher histologic grade and diminished RFS.[2] The presence of tumor necrosis may indicate a biologically active tumor, thus a more aggressive clinical course. Currently, the grading of PTs is based on the evaluation of only five histologic features. Given the association of necrosis with metastasis, it may be prudent to report tumor necrosis as a 'soft sign' in the assessment of PTs. Like others, we found metastatic diseases mainly occurred in borderline/malignant primary PTs.[28] Nonetheless, there were sporadic reports indicating metastases following benign tumors.[1,29] We also observed a benign PT with four local recurrences with upgrade and a final recurrence as malignant metastatic tumors. This temporal heterogeneity of PTs suggested tumor evolution during recurrences.[30]

The role of postoperative adjuvant therapy for PTs has not been clearly established. Currently, there are clinical trials evaluating the efficacy of postoperative RT for PTs with a clear margin. Limited studies reported reduced local recurrence without any impact on overall survival in malignant PTs,[31] whereas others failed to demonstrate any benefits on recurrence prevention.[1,32–34] In all these reports, RT did not offer any advantages in metastases reduction. In the current series, all local recurrences were found in patients not receiving RT, regardless of surgical margin status. A probable contribution of RT towards local recurrence control could not be discounted.

TABLE 4 Details in treatment and margin distance in relation to local recurrence and PT grade

	Margin distance	Benign	Borderline	Malignant	Total
No recurrence					
Without RT					
BCS	Narrow	63	28	6	97
	Wide	5	4	4	13
Mastectomy	Narrow	5	2	2	9
	Wide	0	1	0	1
With RT					
BCS	Narrow	2	4	2	8
	Wide	0	2	0	2
Mastectomy	Narrow	2	2	9	13
	Wide	0	0	1	1
Recurrence					
Without RT					
BCS	Narrow	2	2	0	4
	Wide	–	–	–	–
Mastectomy	Narrow	–	–	–	–
	Wide	0	1	0	1
With RT					
BCS	Narrow	–	–	–	–
	Wide	–	–	–	–
Mastectomy	Narrow	–	–	–	–
	Wide	–	–	–	–

BCS breast-conserving surgery, *PT* phyllodes tumor, *RT* radiotherapy

Limitations of this study included the small number of recurrent and metastatic events and, in some cases, missing data.

CONCLUSIONS

Our data supported the requirement to achieve a negative surgical margin for effective control of local recurrence. A conservative surgical excision with a minimal margin clearance may be sufficient. Apart from tumor grading, stromal necrosis and PASH were identified as additional histologic parameters predicting distant metastases and poor outcome. As recurrences of PTs may show progression in histologic grade and acquisition of metastatic potential, it is prudent to ensure clear margins at recurrence excision. In the current series, adjuvant RT demonstrated a trend in local recurrence control and may be considered on a case-by-case basis.

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