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Prognostic factors in phyllodes tumours of the breast: retrospective study on 166 consecutive cases

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ABSTRACT

Background Phyllodes tumours (PTs) are rare fibroepithelial tumours accounting for <1% of all breast tumours. We assessed clinicopathological features and their prognostic effect in a single-institution patients' cohort.

Methods Patients diagnosed with PT between 2001 and 2018 at our institution were identified. Clinical, surgical and pathological features were collected. Phyllodes-related relapse was defined as locoregional or distant recurrence (contralateral excluded), whichever first.

Results A total of 166 patients were included: 115 with benign, 30 with borderline and 21 with malignant PTs. Features associated with malignant PT were younger age, larger T size, higher mitotic count, marked cytological atypia, stromal overgrowth, stromal hypercellularity, necrosis and heterologous differentiation (all p<0.01). The majority of patients with malignant PT underwent mastectomy (63.2% vs 3% of benign/borderline, p<0.001) and had negative surgical margins (83.3%). 4-year cumulative phyllodes-related relapse incidence was 7% for benign/borderline PT and 21.3% for malignant PT (p=0.107). In the entire cohort, marked cellular atypia and heterologous differentiation were associated with worse phyllodes-related relapse-free survival (HR 14.10, p=0.036 for marked vs mild atypia; HR 4.21, p=0.031 for heterologous differentiation present vs absent). For patients with benign PT, larger tumour size was associated with worse phyllodes-related relapse-free survival (HR 9.67, p=0.013 for T>5 cm vs T≤2 cm). Higher tumour-infiltrating lymphocytes (TILs) were associated with borderline and malignant PT (p=0.023); TILs were not associated with phyllodes-related relapse-free survival (HR 0.58, p=0.361 for TILs>2% vs≤2%). Overall, four patients died because of PT: three patients with malignant and one with borderline PT.

Conclusions Patients with malignant PT had increased rates of phyllodes-related relapse and phyllodes-related death. Cellular atypia and heterologous differentiation were poor prognostic factors in the entire cohort; large tumour size was associated with an increased risk of phyllodes-related relapse in benign PT.

Key questions

What is already known about this subject?

- Phyllodes tumours (PTs) of the breast are rare fibroepithelial tumours composed of a neoplastic mesenchymal proliferation associated with benign breast epithelium.
- The 2019 WHO classification of breast tumours classifies PT as benign, borderline and malignant according to five morphological parameters: stromal atypia, stromal cellularity, stromal overgrowth, mitotic count and tumour borders.
- PT may exhibit a heterogeneous clinical outcome, with both local and distant recurrence.

What does this study add?

- This study evaluated clinicopathological features and prognostic factors in a large cohort of PT with a long follow-up. We described a higher incidence of phyllodes-related relapse in malignant PT and reported marked cytological atypia and heterologous differentiation as prognostic factors affecting the cumulative incidence of phyllodes-related recurrence.
- We also analysed tumour-infiltrating lymphocytes (TILs) and observed generally low levels, with a significant association between higher TILs and worse PT classification (borderline or malignant).

How might it impact on clinical practice?

- This study identified prognostic factors in PT, which may help to properly stratify patients and therefore to define the optimal clinical management.

BACKGROUND

Phyllodes tumours (PTs) of the breast are rare fibroepithelial tumours accounting for 0.3%–1.0% of all breast tumours.[1] Clinically, PT presents as a large, well-limited, painless mass with rapid growth and without nodal involvement and typically affects women within the fourth or fifth decade of life.[2]

PTs are biphasic tumours composed of a neoplastic mesenchymal proliferation associated with benign breast epithelium. The 2019 WHO classification of breast tumours classifies PT as benign, borderline and malignant according to five morphological

parameters: stromal atypia, stromal cellularity, stromal overgrowth, mitotic count and tumour borders.[3] These three subsets of tumour represent 60%, 20% and 20% of all PTs, respectively.[4] This morphological risk assessment scheme has some limitations related to the subjectivity and operator dependence of the evaluation, the absence of standardised cut-off points for individual histological parameters and the possible presence of heterogeneous foci within the same neoplasm.[5]

The National Comprehensive Cancer Network Guidelines V.3.2020[6] recommends wide excision without axillary staging. The guidelines also specify that for malignant or borderline cases, wide excision means excision with the intention of obtaining margins of >1 cm. Narrow margins are associated with increased risk of local recurrence; however, they are not an absolute indication for mastectomy when partial mastectomy fails to achieve a margin width of ≥1 cm. No randomised trials have evaluated the role of neo/adjuvant chemotherapy and adjuvant radiotherapy in these patients.[7]

Although PTs usually have an indolent behaviour and a good prognosis, they may exhibit a heterogeneous clinical outcome. Local recurrences can occur in all cases of PT with an overall rate of 21%, within a range of 10%–17% for benign, 14%–25% for borderline and 23%–30% for malignant cases according to the fifth edition of WHO classification.[3] Distant recurrences are rarer and occur in borderline and malignant PT.[8]

Some clinical, pathological and surgical factors have been investigated to predict the risk of recurrence, with controversial results. The morphological risk assessment scheme generally correlates with prognosis; however, single histological features have not always been reported as predictive of recurrence and clinical outcome.[8 9] Thus, the determination of solid prognostic factors is still required to properly stratify patients and to better define the optimal clinical management of PT of the breast.

In the past years, the presence of high levels of lymphocytic infiltration has been consistently associated with a more favourable prognosis in patients with early-stage triple-negative and HER2-positive breast cancer.[10] Moreover, available evidence also support the favourable prognostic role of tertiary lymphoid structures (TLSs) in a variety of solid tumours.[11] The association between tumour infiltrating lymphocytes (TILs) and pathology features, as well as the clinical relevance of the immune system in biphasic tumours has not yet been assessed and no current data are available about distribution of TILs in PT.

In this work, we collected clinical, surgical and pathological features of a large retrospective series of patients with PT with the aim to assess their correlation with local and distant recurrence and survival.

METHODS

Patients cohort

We reported a retrospective observational monoinstitutional study of consecutive patients diagnosed with PT of the breast between July 2001 and April 2018 at our institution (Istituto Oncologico Veneto IRCCS, Padova, Italy). Demographic, clinicopathological and treatment data were collected from medical charts.

Pathology

Surgical margins were classified as negative (tumour at ≥1 mm from the inked tissue edge), close (tumour within 1 mm from the inked tissue edge) and positive (tumour at the inked tissue edge). Specific histological features were included: mitotic count, cytological atypia, stromal overgrowth, stromal hypercellularity, necrosis and heterologous differentiation. Whenever necessary, tissue samples were retrieved in order to evaluate histological features that were not described in the original pathology report. Tumours were classified as benign, borderline and malignant according to the 2019 WHO guidelines.[3] Cytological atypia was defined as mild with small, uniform nuclei and absent or inconspicuous nucleoli; marked with high variation on nuclear size and shape, irregular nuclear membrane and prominent nucleoli; or moderate with intermediated features between mild and marked. Stromal hypercellularity was defined as stromal cells in close contiguity with nuclei appearing to touch and overlap. Stromal overgrowth was defined as stromal proliferation without accompanying epithelial elements in at least one low-power field. Mitotic count was evaluated in more cellular areas, quantified per 10 high-power field (HPF), and the results were recorded as ≤4 mitotic figures/10 HPF, 5–9 mitotic figures/10 HPF or ≥10 mitotic figures/10 HPF. Heterologous differentiation was defined by the presence of heterologous sarcomatous elements; necrosis was described as absent or present.

Stromal TILs were evaluated on H&E-stained slides according to the International Guidelines on TIL Assessment in Breast Cancer.[12] We also evaluated TLS in the subset of malignant PT. For TLS evaluation, immunohistochemical staining for CD3 (clone LN10, Leica), CD20 (clone L26, Dako) and CD23 (clone 1B10, Cell Marque) was performed on tumour slides obtained from formalin-fixed paraffin-embedded tumour blocks. This staining allowed identification of follicles with B lymphocytes (CD20 positive) and dendritic follicular cells (CD23 positive) surrounded by parafollicular zone of T lymphocytes (CD3 positive). TLS were assessed in the tumour and its surrounding stroma area.

Statistical analysis

Statistical analysis was carried out using IBM SPSS V.25. Descriptive statistics were performed for patients' characteristics. The χ^2, the Kruskal-Wallis and the Mann-Whitney tests were used to study associations between variables.

Only patients with available follow-up data were included in clinical outcome analyses. Phyllodes-related relapse

was defined as local ipsilateral, axillary nodal or distant recurrence, whichever occurred first. We excluded from the analysis all the contralateral PTs. Phyllodes-related death was defined as death due to PT recurrence. Time to recurrence or death was calculated from the date of initial surgery. Cumulative incidence of phyllodes-related relapse was calculated using one minus the Kaplan-Meier estimate of phyllodes-related relapse-free survival. Cumulative incidence of phyllodes-related death was calculated using one minus the Kaplan-Meier estimate of phyllodes-related death-free survival. The log-rank test was used to compare between groups. Cox regression models were used to calculate HRs and their 95% CIs. All p values are two-sided, with significance level set at p<0.05.

RESULTS

Patients' characteristics

We included in the analysis 166 consecutive patients with diagnosis of PT of the breast from 2001 to 2018. Clinical, surgical and pathological characteristics are reported in table 1.

All patients were women and the median age at diagnosis was 41 years (range 16–85). A total of 115 patients (69.3%) had benign PT; 30 patients (18.1%) had borderline PT; and 21 patients (12.7%) had malignant PT. Presence of heterologous differentiation was reported in 12 patients; liposarcomatous differentiation was the most frequent (three patients).

Features associated with worse PT classification were older age (p<0.001), larger tumour size (p=0.001), higher mitotic count (p<0.001), marked cytological atypia (p<0.001), presence of stromal overgrowth (p<0.001), presence of stromal hypercellularity (p<0.001), presence of necrosis (p=0.001) and presence heterologous differentiation (p<0.001).

Overall, breast conservative surgery was performed in 146 (90.1%) patients. Mastectomy was performed more frequently in patients with malignant PT (63.2%) as compared with benign (1.8%) and borderline (6.7%) cases (p<0.001). The status of surgical margins was known for 126 patients and was negative in 47.6%, close in 15.9% and positive in 36.5% of the cases. Negative margin status was significantly more frequent in malignant tumours (83.3%, p=0.001).

An adjuvant treatment was administered to four patients only (all with malignant PT): three patients underwent adjuvant chemotherapy (anthracycline-based) and one patient underwent adjuvant radiotherapy.

Clinical outcome

A total of 149 patients with available follow-up data were included in the clinical outcome analyses (n=99, 66.4% with benign PT; n=30, 20.1% with borderline PT; n=20, 13.4% with malignant PT). At a median follow-up of 97.7 months (95% CI 82.5 to 113), 14 phyllodes-related relapses have occurred. The overall rate of recurrence was 9.4%. A numerically higher rate of phyllodes-related relapse was observed in patients with malignant PT: 8.1% in benign PT, 6.7% in borderline PT, 20.0% in malignant PT (p=0.212 for the comparison across the three categories; p=0.081 for the comparison between benign/borderline PT vs malignant PT) (table 2). Patients with benign and borderline PTs experienced only local recurrences (eight patients and two patients, respectively), whereas local and distant recurrences were observed in one and three patients with malignant PTs, respectively (table 2).

Three patients experienced multiple recurrences: a patient with benign PT presented three consecutive local recurrences; a patient with borderline PT presented two local recurrences and then one distant recurrence; a patient with malignant PT presented one distant and then one local recurrence. We observed morphological progression at recurrence in five patients: two from benign to borderline PT, one from borderline to malignant PT and two from benign to malignant PT. Lung was the most common site of distant recurrence followed by bone and lymph node; all relapsed patients experienced more than one site of recurrence.

The median time to recurrence, defined as the time from diagnosis to first phyllodes-related relapse, was 22.9 months (range 2.4–72.7 months). Cumulative incidence of phyllodes-related relapse according to PT classification is reported in figure 1A,B. The 5-year cumulative incidence rate of phyllodes-related relapse was 8.2% in benign PT, 6.8% in borderline PT and 21.3% in malignant PT (log rank p=0.273). When benign and borderline PTs were considered together, the 5-year cumulative incidence rates of phyllodes-related relapse were as follows: 8.1% in benign/borderline PT and 21.3% in malignant PT (log-rank p=0.107).

We observed four phyllodes-related deaths: three in malignant PT and one in borderline PT. All these patients experienced systemic progressive disease. In the patient with borderline PT, the distant recurrence followed the first local recurrence. Cumulative incidence of phyllodes-related death is reported in figure 1C. Cumulative incidence rate of phyllodes-related deaths at 5 years was 0% for benign PT, 0% for borderline PT and 16.4% for malignant PT (log rank p=0.001).

Prognostic factors

We performed univariate analysis of clinical, surgical and pathological factors related to phyllodes-related recurrence (table 3). Marked cytological atypia (HR 24.0, 95% CI 2.7 to 214.4, p=0.005 for marked vs mild cytological atypia) and heterologous differentiation (HR 4.2, 95% CI 1.1 to 15.6, p=0.031) were significantly correlated with phyllodes-related relapse-free survival. A multivariable model including these two variables (table 3) confirmed marked cytological atypia as an independent poor prognostic factor (HR 14.1, 95% CI 1.188 to 167.428, p=0.036 for marked vs mild cytological atypia). For those patients who had a recurrence tissue sample available, no difference in grade of atypia and heterologous differentiation between primary tumour and relapse was identified.

Table 1 Clinicopathological patients' characteristics of the entire cohort and according to phyllodes tumour grade

			Grade						
	Total (N=166)		Benign (n=115)		Borderline (n=30)		Malignant (n=21)		
Characteristics	n	%	n	%	n	%	n	%	P value
Age (years), mean±SD (range)	41.1±14.7 (15-84)		38.7±13.3 (15-82)		41.5±15.8 (16–84)		53.7±14.5 (16–79)		<0.001
Age (years)									<0.001
<35	49	29.7	39	34.2	9	30.0	1	4.8	
35–49	75	45.5	57	50.0	12	40.0	6	28.6	
≥50	42	24.8	19	15.8	9	30.0	14	66.7	
Final surgery									<0.001
Conservative	146	90.1	111	98.2	28	93.3	7	36.8	
Mastectomy	16	9.9	2	1.8	2	6.7	12	63.2	
Margins after final surgery									0.001
Negative	60	47.6	30	36.6	15	57.7	15	83.3	
Close	20	15.9	13	15.9	6	23.1	1	5.6	
Positive	46	36.5	39	47.6	5	19.2	2	11.1	
Adjuvant chemotherapy									
No	153	98.1	106	100	30	100	17	85.0	<0.001
Yes	3	1.9	0	0	0	0	3	15.0	
Adjuvant radiotherapy									
No	155	99.4	106	100	30	100	19	95.0	0.033
Yes	1	0.6	0	0	0	0	1	5.0	
T size (cm), mean±SD (range)	30.6±28.6 (4–250)		25.5±18.5 (4–130)		34.7±24.4 (10–110)		57.4±60.2 (18–250)		0.001
T size (cm)									0.009
≤2	76	48.4	61	55.0	11	37.9	4	23.5	
2–5	60	38.2	41	36.9	12	41.4	7	41.2	
>5	21	13.4	9	8.1	6	20.7	6	35.3	
Mitotic count (×10 HPF)									<0.001
≤4	120	76.4	108	97.3	12	42.9	0	0	
5–9	21	13.4	3	2.7	16	57.1	2	11.1	
≥10	16	10.2	0	0	0	0	16	88.9	
Cytological atypia									<0.001
Mild	79	58.1	64	71.1	15	51.7	0	0	
Moderate	43	31.6	24	26.7	12	41.4	7	41.2	
Marked	14	10.3	2	2.2	2	6.9	10	58.8	
Stromal overgrowth									
Absent	91	82.7	70	92.1	16	69.6	5	45.5	<0.001
Present	19	17.3	6	7.9	7	30.4	6	54.5	
Stromal hypercellularity									
Absent	56	36.8	53	49.1	3	10.7	0	0	<0.001
Present	96	63.2	55	50.9	25	89.3	16	100	
Necrosis									
Absent	130	87.8	94	90.4	25	96.2	11	61.1	0.001
Present	18	12.2	10	9.6	1	3.8	7	38.9	

Continued

Table 1 Continued

Characteristics	Total (N=166)		Grade						P value
			Benign (n=115)		Borderline (n=30)		Malignant (n=21)		
	n	%	n	%	n	%	n	%	
Heterologous differentiation									
Absent	142	92.2	106	98.1	27	96.4	9	50.0	<0.001
Present	12	7.8	2	1.9	1	3.6	9	50.0	
TIL (%), median (range)	2 (0–50)		2 (0–17)		5 (0–15)		5 (0–50)		0.023

HPF, high-power field; TIL, tumour-infiltrating lymphocyte.

When univariate Cox regression analysis was conducted in subgroups defined by PT classification, larger tumour size was associated with worse phyllodes-related relapse-free survival (HR 9.67, 95% CI 1.61 to 58.1, p=0.013 for T>5 cm vs T≤2 cm) in benign PT.

Immune variables

TILs were evaluable for 158 PT cases (for 8 cases, the TIL score was not assessable due to unavailability of archived tumour samples). Median stromal TILs level was 2% (range 0–50). We found that higher TILs were significantly associated with PT classification, being higher in borderline and malignant PT (p=0.023, table 4). No other significant association with clinicopathological features was observed (table 4). As a descriptive finding, we noted increased TILs when the epithelial counterpart of the biphasic lesion was highly represented. It should be noted that no standardised methodology is currently available for the evaluation of TILs specifically in PT. In this context, in our experience, we found it challenging to discriminate between TILs and picnotic nuclei on H&E-stained tumour sections. In addition, the identification of the proper denominator (area) to be used to determine the % of TILs may not be straightforward in case of biphasic tumours. In terms of prognosis, TILs were not associated in univariate analysis with phyllodes-related relapse-free survival (TILs as a continuous variable: HR 0.98, 95% CI 0.87 to 1.11, p=0.789; TILs>2% vs<2% vs HR 0.58, 95% CI 0.18 to 1.88, p=0.361).

We also looked at the presence of TLS, by focusing on malignant PT since this category showed the highest TILs levels. Among the 15 malignant PT cases with tissue available, 2 presented with TLS. They were both located in the tumour periphery, mostly in the mesenchymal component and not necessarily in the atypical zones. A representative picture of one case with TLS is shown in online supplemental figure S1.

DISCUSSION

PTs of the breast are rare, wide-spectrum fibroepithelial neoplasms. Considering the rarity of the disease, the sample size of our retrospective patients' cohort (n=166) is consistent with that of other published series.[13–15] Although wider patient cohorts have been published,[8 9 16] a strength of our work is the median follow-up of 97.7 months, longer than previously reported.[8 13 15 16]

We used the 2019 WHO criteria to classify PT and we found that the majority of patients harboured benign PT, followed by borderline and malignant PT. Despite the heterogeneity of previously reported series, the benign subset is largely the most frequent PT (65%–70% of all PTs), while borderline and malignant PTs occur less frequently.[7 13] In our series, the mean tumour size was 30.6 mm, smaller than what has been reported in other large cohorts: mean 60 mm in Mitus *et al* (n=340),[9] mean 62.4 mm in the work by Li *et al*[8] (n=290) and mean 38.9 mm in the French multicentric series by Adam *et al*

Table 2 Phyllodes-related relapse first events overall and according to phyllodes tumour grade

Phyllodes-related relapse	Grade								P value
	Benign		Borderline		Malignant		Total		
	n	%	n	%	n	%	n	%	
No	91	91.9	28	93.3	16	80.0	135	90.6	0.212*
Yes	8	8.1	2	6.7	4	20.0	14	9.4	0.081†
Local	8		2		1		11		
Distant	0		0		3		3		

*χ^2 test for the comparison across the three PT grade categories.
†χ^2 test for the comparison between benign/borderline PT versus malignant PT.
PT, phyllodes tumour.

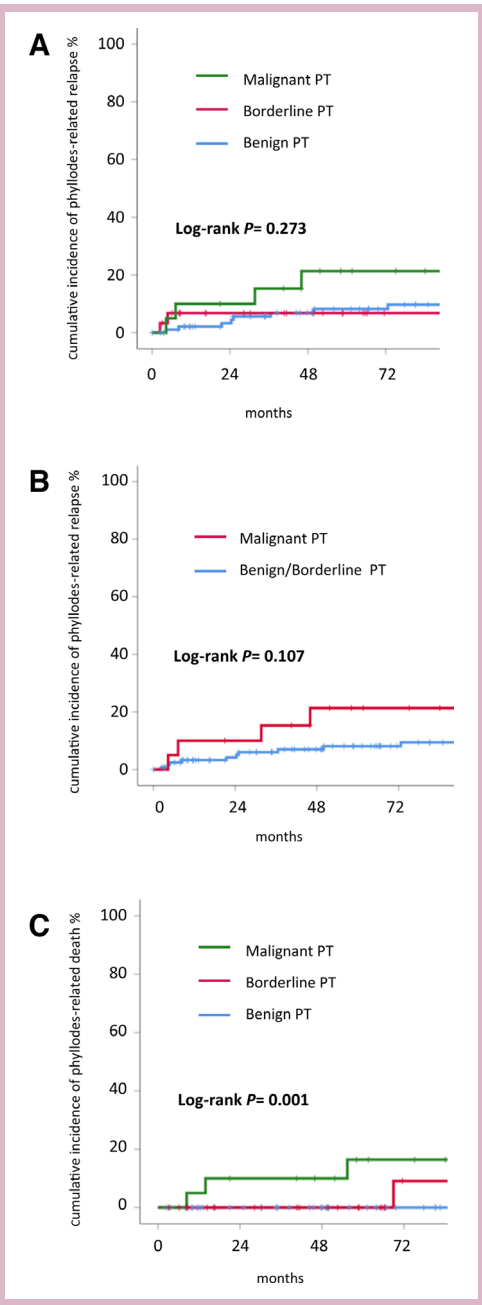

Figure 1 Cumulative incidence of phyllodes-related relapse according to PT grade: benign, borderline and malignant PT (A); benign/borderline and malignant (B); cumulative incidence of phyllodes-related death according to PT grade (C). PT, phyllodes tumour.

(n=230).[13] Moreover, Spitaleri *et al* (n=172) also reported lower rates of PT tumours of ≤2 cm as compared with our cohort (12% vs 48.4%).[15] Although a similar significant association between larger tumour size and increased PT malignancy was found in our series and in the works by Adam *et al*[13] and Spitaleri *et al*,[15] both studies reported a larger tumour size in each of the PT groups as compared with our data.

Consistent with the relatively smaller tumour size, less patients in our study underwent mastectomy as final surgical treatment as compared with other series. We reported a rate of mastectomy of 9.9%, whereas in other studies, the proportion of patients undergoing mastectomy as final surgery ranges from 13.4% to 40%.[8 9 13–15] However, another reason may have contributed to this different surgical pattern. Indeed, up to 36.5% (n=46) of patients in our cohort had positive margins after final surgery; the vast majority of them had a benign PT (n=39/46, 85%). This highlights that second surgery to achieve clean margins was not systematically performed for patients with benign PT. The proportion of patients with negative margins is variable across recently published works ranging from 1.8% to 24.8%.[8 9 13] Several studies reported an increased risk of local recurrence after positive margin surgery, although the impact of margin status and width appears to be more relevant in borderline/malignant PT rather than in benign PT.[7 9 13 16–20] What is consistent in our study and others is the high proportion of patients with malignant PT who achieved negative margins after final surgery: 83.3% in our cohort, 88.7% (close included) in Spitaleri *et al*,[15] 95.8% in Adam *et al*[13] and 84.9% in Ganesh *et al*.[14] According to these considerations, we observed an overall rate of phyllodes-related relapse of 9.4%, which is perfectly in line with recent literature data reporting rates of relapse of around 10%–14%.[8 9 13 15 16] Margin width was not associated with increased risk of phyllodes-related relapse in the overall cohort nor in subgroups defined by PT classification.

PT category is recognised as a main driver of the risk of relapse.[9 16 21 22] Indeed, we observed numerically higher rates of phyllodes-related relapse in malignant PT as compared with benign and borderline PT (with data in line with available literature[8 9 22]). However, cumulative incidence did not statistically differ according to PT categories due to limited sample size. We confirmed that distant relapses are rare, occurring with higher frequency in malignant PT.[8]

The prognostic value of the histological features used in the WHO classification has been evaluated in several studies with controversial results.[8 13 15 16 21–23] In our experience, marked cellular atypia and heterologous differentiation significantly correlated with increased cumulative incidence of phyllodes-related recurrence. Previous retrospective analysis reported the prognostic role of cytological atypia.[22 24] Recently, Tan *et al*[21] suggested the use of a nomogram based on atypia, mitoses, overgrowth and surgical margins to predict the clinical outcome of PT. Heterologous differentiation is rare and has been described only in case reports.[25] To our knowledge, this is the first study with evidence of correlation between heterologous differentiation and risk of recurrence. Koh *et al* recently reported a series of 83 cases of malignant PT showing that large tumours (≥90 mm) containing malignant heterologous elements disclosed significantly worse metastasis-free survival and a trend for poorer overall survival.[26] Multivariate analysis confirmed marked cytological atypia as an independent prognostic factor for cumulative incidence of phyllodes-related recurrence.

Table 3 Univariate and multivariate COX regression analysis for phyllodes-related relapse-free survival

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age (continuous)	1.01 (0.97 to 1.04)	0.686	–	–
Age (years) (categorical)				
<35	Ref			
35–49	3.7 (0.8 to 16.7)	0.094	–	–
≥50	1.2 (0.2 to 8.8)	0.832	–	–
Surgery margins				
Negative	Ref			
Close	0.7 (0.1 to 6.4)	0.764	–	–
Positive	1.7 (0.5 to 6.4)	0.426	–	–
Tumour size (cm)				
≤2	Ref			
2–5	1.4 (0.3 to 5.5)	0.661	–	–
>5	3.5 (0.9 to 14.2)	0.075	–	–
Mitotic count (×10 HPF)				
≤4	Ref			
5–9	2.9 (0.7 to 11.2)	0.132	–	–
≥10	3.0 (0.8 to 11.7)	0.109	–	–
Cytological atypia				
Mild	Ref		Ref	
Moderate	6.6 (0.7 to 59.1)	0.091	6.2 (0.7 to 55.9)	0.102
Marked	24.0 (2.7 to 214.4)	0.005	14.1 (1.2 to 167.4)	0.036
Stromal overgrowth				
Absent	Ref		–	–
Present	1.5 (0.3 to 7.4)	0.603	–	–
Stromal hypercellularity				
Absent	Ref			
Present	1.9 (0.5 to 6.9)	0.346	–	–
Necrosis				
Absent	Ref			
Present	0.0 (0.0 to 36.0)	0.351	–	–
Heterologous differentiation				
Absent	Ref		Ref	
Present	4.2 (1.1 to 15.6)	0.031	2.3 (0.4 to 14.3)	0.366
Tumour grade				
Benign	Ref			
Borderline	1.0 (0.2 to 4.6)	0.967	–	–
Malignant	2.5 (0.8 to 8.3)	0.136	–	–
Benign/borderline	Ref			
Malignant	2.5 (0.8 to 8.0)	0.120	–	–
TILs (continuous)	0.98 (0.87 to 1.11)	0.789	–	–
TILs (%) (categorical)				
≤2	Ref			
>2	0.58 (0.18 to 1.88)	0.361	–	–

HPF, high-power field; Ref, reference; TIL, tumour-infiltrating lymphocyte.

Table 4 Distribution of TILs according to clinicopathological variables

Characteristics	TIL (%), median (range)	P value
Total	2 (0–50)	–
Classification		
Benign	2 (0–17)	0.023
Borderline	5 (0–15)	
Malignant	5 (0–50)	
Age (years)		
<35	2 (0–12)	0.595
35–49	2 (0–17)	
≥50	2 (0–50)	
T size (cm)		
≤2	2 (0–10)	0.562
2–5	2 (0–50)	
>5	2 (0–20)	
Mitotic count (×10 HPF)		
≤4	2 (0–17)	0.164
5–9	5 (2–50)	
≥10	5 (0–20)	
Cytological atypia		
Mild	2 (0–12)	0.356
Moderate	2 (0–15)	
Marked	3.5 (0–50)	
Stromal overgrowth		
Absent	2 (0–50)	0.992
Present	3.5 (0–15)	
Stromal hypercellularity		
Absent	2 (0–15)	0.224
Present	2 (0–50)	
Necrosis		
Absent	2 (0–20)	0.667
Present	2 (0–50)	
Heterologous differentiation		
Absent	2 (0–50)	0.882
Present	2 (0–50)	

HPF, high-power field; TIL, tumour-infiltrating lymphocyte.

We described an upgrading of PT on recurrence. Histological transformation was seen in five cases and only in upgrading from benign to borderline, from borderline to malignant and from benign to malignant tumour. No cases of downgrading were observed. Although infrequent, this finding has been previously reported.[13 27] Additional molecular data are required for better understanding of the clinical significance of the histological change. We observed four phyllodes-related deaths concerning three malignant PTs and one borderline PT. All of these patients experienced distant recurrences. The rate of phyllodes-related death was significantly related with PT category.

Finally, we also provided a descriptive analysis of TILs in our cohort. We observed generally low levels of TILs, with malignant PT presenting with higher TILs. No association with phyllodes-related relapse-free survival was observed.

The major strengths of our work are the relatively large population as compared with other published series, the extensive availability of histopathological data and the long-term follow-up. The major limitations of this study are its retrospective nature, the lack of power for statistical analysis in patients' subgroups and the lack of information on tumour borders.

CONCLUSIONS

PTs of the breast are rare biphasic tumours with heterogeneous clinical outcome. In this study, we reported marked cytological atypia and heterologous differentiation as prognostic factors affecting the cumulative incidence of phyllodes-related recurrence. Further large prospective studies are required to identify clinical, pathological and molecular features in order to predict the aggressiveness of PTs and to assess the most appropriate surgical and clinical therapeutic strategies.

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Ethics approval All authors declare that the work has been carried out in accordance with The Code of Ethics of the World medical Association (Declaration of Helsinki). The study protocol has been approved by the Ethics Committee of Istituto Oncologico Veneto IRCCS of Padova.

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