Original Article

Predicting the recurrence-free survival of phyllodes tumor of the breast: a nomogram based on clinicopathology features, treatment, and surgical margin

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Background: Grading based on histopathologic indicators cannot accurately assess the prognosis of phyllodes tumor (PT) of the breast. This article aimed to investigate the correlation between PT prognosis and clinicopathological features, treatment, and surgical margin.

Methods: The clinicopathological data of patients with pathologically confirmed PT at our institution were retrospectively collected. Univariate and multivariate Cox proportional risk models were employed to test the effects of different variables on the prognosis of PT. A nomogram to predict the 1-, 3-, 5-, and 10-year recurrence-free survival (RFS) of PT was proposed, and its discriminative ability and calibration were tested using the concordance index (C-index), area under the curve (AUC), and calibration plots. All statistical analyses were performed using R.

Results: A total of 342 PT patients were included, including 242 benign (70.8%), 75 borderline (21.9%) and 25 malignant (7.3%) cases. The median follow-up period was 64.5 months (range, 3–179 months), 66 PT patients had local recurrence (LR), and four patients had distant metastasis. The 1-, 3-, 5-, and 10-year RFS of the PT patients were 90.8%, 81.8%, 78%, and 76.7%, respectively. Age, fibroadenoma (FA) surgery history, treatment, mitotic activity, and surgical margin were selected as the independent factors for PT prognosis. The nomogram showed good discriminative ability and calibration, as indicated by the C-index [0.78, 95% confidence interval (CI): 0.75–0.11].

Conclusions: Independent predictors related to PT prognosis were selected to establish a nomogram for predicting the RFS of PT. This nomogram was able to objectively stratify PT patients into prognostic groups and performed well in the internal validation.

Keywords: Phyllodes tumor of the breast; recurrence; prediction model; nomogram

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Introduction

Phyllodes tumor (PT) of the breast is a rare fibroepithelial tumor (FEL) of the breast, accounting for 0.3–1% of all breast tumors (1). According to the World Health Organization (WHO), PTs can be divided into three pathological types based on their histological morphological characteristics: benign, borderline, and malignant. Studies have indicated that all pathologic types of PT have a possibility of local recurrence (LR), with recurrence rates of 10–17%, 14–25%, and 23–30%, respectively. Furthermore, some cases of recurrence may involve pathological grade upgrades (2). Pathological examination, as the only diagnostic and grading standard for PTs in clinical practice at present, is subjective and not completely consistent with the biological behavior of PT. Comprehensive consideration of the influence of clinicopathological indicators and surgical management in PT prognosis is very important for evaluating the prognosis of patients and prolonging their recurrence-free survival (RFS).

Several retrospective studies have explored the clinicopathological factors that affect the prognosis of PT patients, and have reported that age, tumor size, fibroadenoma (FA) surgery history, stromal overgrowth, mitotic activity, and margin status were related to the risk of LR (3-5). Margin status, as one of the most important factors among them, has also been confirmed in a meta-analysis conducted by our team (6). Moreover, studies have suggested that up to 20% of malignant PT may metastasize to the lung, bone, brain, etc., resulting in a poor prognosis (7). Slodkowska *et al.* showed that histological features, such as necrosis, may play important roles (8). However, no consistent conclusion has been reached regarding the prognostic factors of PT.

Clinical prediction models can combine multiple factors to achieve the individualized assessment of patient prognosis (9,10). Tan *et al.* reported on the use of a nomogram (stromal atypia, mitoses, overgrowth and surgical margins; AMOS) to predict the RFS of PT patients based on histopathological features (11). Furthermore, the AMOS nomogram was validated internally and externally in multiple subsequent cohorts (12-14). However, this nomogram only included histologically relevant indicators that were based on the subjective judgment of pathologists. Chao *et al.* established a nomogram combining margin width, mitotic activity, and tumor border (15). The National Comprehensive Cancer Network (NCCN) guidelines have revised the surgical management for benign PT, suggesting follow-up observation following excision rather than requiring at least a 1 cm margin. The correlation between the margin width and the prognosis of PT still needs to be further validated (16). Currently, there are no nomograms that integrate clinicopathological features, surgical treatment, and surgical margin. In this study, we sought to create and internally validate a nomogram to predict the individual risk of RFS in PT. We present the following article in accordance with the TRIPOD reporting checklist (https://gs.amegroups.com/article/view/10.21037/gs-22-542/rc).

Highlight box

Key findings

- A nomogram based on age, fibroadenoma surgery history, treatment, mitotic activity, and surgical margin of phyllodes tumor of the breast was established and performed well in the internal validation.

What is known and what is new?

- The prognosis of phyllodes tumor of the breast is known to be related to factors including clinicopathological features, treatment, surgical margin, etc.
- This manuscript analyzed the clinical statistics from our hospital, specified the prognosis factors, and established a nomogram to objectively and accurately predict the prognosis of the phyllodes tumor of the breast. Moreover, surgical management was further discussed and the results showed no significant prognostic difference between "re-resection" and observation, supporting the conclusion of the National Comprehensive Cancer Network (NCCN) guidelines.

What are the implications, and what should change now?

- Phyllodes tumor patients with high-risk scores require frequent follow-ups to prevent local recurrence.

Methods

Patient population and data collection

The data of all patients who visited the First Medical Center of PLA General Hospital from February 2006 to March 2022 and were pathologically diagnosed as PT were collected. Based on the inclusion and exclusion criteria, 342 patients were included in the analytic cohort. Among these, 238 patients were reported in our previous study (17). Only patients who underwent surgery in our hospital and were pathologically confirmed as PT were included. If the initial surgery was performed at a different hospital, the initial pathological sections were reviewed by our institute to confirm the diagnosis. The pathological diagnoses of all sections were jointly decided on by an attending physician

and chief physician. Recurrent cases needed to be confirmed by pathological diagnosis after surgical resection. Patients with a history of breast cancer or other malignant tumors, those with uncooperative follow-up, and those with missing important data were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese PLA General Hospital (No. S2022-319-01) and individual consent for this retrospective analysis was waived.

Clinicopathological data analysis

The patients' demographic and clinicopathological data were collected, including age, tumor size, location, FA surgery history, core needle biopsy (CNB), intraoperative frozen section diagnosis, pathological diagnosis, treatment, etc. Tumor size was defined as the maximal diameter of the tumor in the resected specimen; if this data was missing in the pathology report, ultrasound (US), mammography, and magnetic resonance imaging (MRI) examinations were referred to. The MRI results would be taken if differences between the imaging examinations existed. The tumor size grouping was divided into three cohorts according to the 8th edition of the American Cancer Society tumor node metastasis (TNM) classification of breast cancer. Pathological diagnosis was divided into benign, borderline, and malignant PT according to the 5th edition of the WHO guidelines (2). The characteristic manifestations of each pathological diagnostic criteria were shown in Figure S1.

Surgical treatment included US-guided vacuum-assisted breast biopsy (VABB), lumpectomy, wide local excision (WLE), and mastectomy. The 7-gauge EnCor® system (EnCor® MR, SenoRx, Allso Viejo, CA, USA) was used for the US-guided VABB to excise the target lesion until no residual disease was detected by US. Lumpectomy required surgical margins smaller than 1 cm, including excision and lumpectomy. WLE required surgical margins larger than or equal to 1 cm, including wide excision, partial mastectomy, and breast-conserving surgery. Mastectomy referred to the complete removal of breast tissue, including simple mastectomy, nipple-areola complex-sparing mastectomy (NSM), and modified radical mastectomy. The surgical margin of the tumors was classified as "negative", "positive", and "not available". Positive margins were reported when tumors were histologically observed to involve the inked surgical resection margin. The surgical margins of patients who were diagnosed with borderline PT and only underwent US-guided VABB were defined as "not available".

Survival outcomes and follow-up

All patients were asked to attend a subsequent visit 3 months after surgery. Regular follow-up results were obtained from the medical records and telephone interviews. RFS was defined as the time from surgery to the date of relapse or metastasis of PT or the last follow-up date for censored cases. The last follow-up was conducted in March 2022.

Statistical analysis

Categorical variables were reported as whole numbers and proportions, and continuous variables were reported as medians with interquartile ranges. The Chi-square test or Fisher's exact test was used for enumeration data, the Kaplan-Meier method was used to generate the RFS, and the log-rank test was used to test the difference in RFS between groups. Clinicopathological variables associated with the risk of LR were assessed as prior based on clinical significance, scientific knowledge, and predictors identified in previously published articles.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate the relationship between the clinicopathological factors and RFS. Factors included in the multivariate analysis were those associated with recurrence, as determined by univariate analysis or by previous literature. Backward stepwise selection of variables for a multivariate Cox proportional hazards regression model was performed using the Akaike Information Criterion (AIC) (18). The Schoenfeld residual test was applied to assess the proportional hazards assumption. Hazard ratios (HRs) and their associated 95% confidence intervals (95% CIs) were obtained by Cox regression analysis.

The selected variables were incorporated into nomograms to predict the probability of 1-, 3-, 5-, and 10-year RFS of PT using statistical software (rms in R, version 3.0.3; http://www.r-project.org). The discriminatory ability of the model was assessed using Harrell *et al.*'s C-index, which estimates the probability of rank-ordered agreement between predicted and observed outcomes (19). The 3- and 5-year receiver operating characteristic (ROC) curves and area under the curve (AUC) over time were plotted according to the method of Hung and Chiang, reflecting the predictive ability of the model at different time intervals (20). The

calibration performance of the model was assessed by 1-, 3-, 5-, and 10-year calibration curves comparing the predicted and actual probabilities. The 1,000 bootstrap sampling method was used to internally verify the validity of the model. Statistical analyses were performed using R (version 3.0.3; http://www.r-project.org). All trials were two-sided and P<0.05 was considered statistically significant.

Results

Clinicopathological characteristics

A total of 342 PT patients were included in this study, all of whom were female, including 242 (70.8%) benign, 75 borderline (21.9%) and 25 malignant (7.3%) cases. The median age of the patients was 41 years (range, 12–75 years), and the tumor size ranged between 0.3 and 26.5 cm, with a median size of 3 cm. The tumor was located in the left side in 172 cases (50.3%), the right side in 166 cases (48.5%), bilateral in 2 cases (0.6%), and the left accessory breast in 2 cases (0.6%). The two patients with bilateral tumors were both pathological graded as benign, with a similar histological morphology, and only differed in size. Additionally, for the convenience of statistical analysis, only the right tumor was selected for the subsequent analysis. The clinicopathological characteristics of patients stratified by pathological grade are shown in *Table 1*.

Patients with larger tumors and FA surgery history were more likely to have borderline or malignant PTs (P<0.05). A total of 51 patients underwent CNB, of whom only 47.1% (24/51) were diagnosed with PT and 21.6% (11/51) were diagnosed with FEL. Among the 127 patients who

Table 1 Clinicopathological characteristics of patients stratified according to histological grade

Variants	Benign	Borderline	Malignant	P
Age (years)				
≤40	115 (47.5)	35 (46.7)	10 (40.0)	0.773
>40	127 (52.5)	40 (53.3)	15 (60.0)	
Location				
Left	127 (52.5)	37 (49.3)	10 (40.0)	0.472
Right	115 (47.5)	38 (50.7)	15 (60.0)	
Size (cm)				
≤2	73 (30.2)	6 (8.0)	0 (0.0)	<0.001
>2, ≤5	145 (59.9)	48 (64.0)	12 (48.0)	
>5	24 (9.9)	21 (28.0)	13 (52.0)	
FA surgery history				
No	224 (92.6)	63 (84.0)	16 (64.0)	<0.001
Yes	18 (7.4)	12 (16.0)	9 (36.0)	
CNB				
No	217 (89.7)	54 (72.0)	20 (80.0)	0.001
Yes	25 (10.3)	21 (28.0)	5 (20.0)	
Treatment				
Lumpectomy	133 (55.0)	37 (49.3)	9 (36.0)	<0.001
WLE	47 (19.4)	19 (25.3)	7 (28.0)	
Mastectomy	8 (3.3)	14 (18.7)	9 (36.0)	
US-guided VABB	54 (22.3)	5 (6.7)	0 (0.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variants	Benign	Borderline	Malignant	P
Tumor border				
Well defined	195 (80.6)	44 (58.7)	12 (48.0)	<0.001
Permeative	47 (19.4)	31 (41.3)	13 (52.0)	
Stromal overgrowth				
Absent	214 (88.4)	44 (58.7)	11 (44.0)	<0.001
Present	28 (11.6)	31 (41.3)	14 (56.0)	
Stromal atypia				
Mild	236 (97.5)	49 (65.3)	10 (40.0)	<0.001
Moderate	6 (2.5)	18 (24.0)	5 (20.0)	
Marked	0 (0.0)	8 (10.7)	10 (40.0)	
Stromal cellularity				
Mild	185 (76.4)	46 (61.3)	14 (56.0)	<0.001
Moderate	44 (18.2)	20 (26.7)	0 (0.0)	
Marked	13 (5.4)	9 (12.0)	11 (44.0)	
Mitotic activity/10 HPF				
<5	240 (99.2)	20 (26.7)	0 (0.0)	<0.001
5–9	2 (0.8)	51 (68.0)	10 (40.0)	
≥10	0 (0.0)	4 (5.3)	15 (60.0)	
Surgical margin				
Negative	238 (98.3)	68 (90.7)	23 (92.0)	<0.001
Positive	4 (1.7)	2 (2.7)	2 (8.0)	
NA	0 (0.0)	5 (6.7)	0 (0.0)	
Chemotherapy				
No	242 (100.0)	75 (100.0)	22 (88.0)	<0.001
Yes	0 (0.0)	0 (0.0)	3 (12.0)	
Local recurrence				
No	210 (86.8)	52 (79.3)	14 (56.0)	<0.001
Yes	32 (13.2)	23 (20.7)	11 (44.0)	
Metastasis				
No	242 (100.0)	75 (100.0)	21 (84.0)	<0.001
Yes	0 (0.0)	0 (0.0)	4 (16.0)	

All variables are presented as n (%). FA, fibroadenoma; CNB, core needle biopsy; WLE, wide local excision; US, ultrasound; VABB, vacuum-assisted breast biopsy; HPF, high-power field; NA, not available.

received intraoperative frozen sectioning, 44.1% (56/127) were diagnosed as PT and 24.4% (31/127) were diagnosed as FA. No significant difference between CNB and the intraoperative frozen section in PT diagnosis was found (P=0.719).

Surgical treatment

The recurrence rates of lumpectomy, WLE, mastectomy and US-guided VABB were 24.0% (43/179), 12.3% (9/73), 12.9% (4/31), and 20.3% (12/59), respectively. For benign PT, there was no significant difference in RFS between the various surgical treatments (P=0.078). Marked differences in RFS between various the surgical approaches were observed in borderline and malignant PTs (P<0.001). For patients with benign PT after US-guided VABB or lumpectomy, re-resection (19/206) did not significantly improve the RFS compared with follow-up observation (187/206) (HR =0.265; 95% CI: 0.036–1.943; P=0.159). For borderline and malignant PTs patients after US-guided VABB or lumpectomy, re-resection (10/61) substantially improved the RFS (HR =0.119; 95% CI: 0.016–0.894; P<0.05).

Follow-up and prognosis

The median follow-up period was 64.5 months (range, 3–179 months), with a total of 66 cases of relapse. The recurrence rates among the different grades were 13.2% (32/242) in benign PT, 30.7% (23/75) in borderline PT, and 44% (11/25) in malignant PT, and the differences were statistically significant (P<0.001). Interestingly, six patients developed pathological grade upgrade after recurrence, among whom two were upgraded from benign to borderline PT, and four patients were upgraded from borderline to malignant PT. Also, four patients had metastasis; two had lung metastasis, one had chest wall metastasis, and one experienced multifocal metastases in the chest wall, axilla, lung, and pancreas. Only three patients received chemotherapy, including apatinib, epirubicin with ifosfamide and cisplatin, and cisplatin with doxorubicin, but all died due to tumor progression.

Univariate and multivariate analysis

The 1-, 3-, 5-, and 10-year RFS rates for the entire cohort were 90.8%, 81.8%, 78%, and 76.7%, respectively. The 5-year RFS rates for benign, borderline, and malignant PT were 85.5%, 63.4%, and 50.4%, respectively. The Kaplan-Meier curve showed that tumor size, FA surgery history, stromal atypia, mitotic activity, and surgical margin were related to poor prognosis and RFS (P<0.05) (*Figure 1*).

Established risk factors as well as demographic and tumor characteristics of clinical importance were selected as candidate variables for the prediction model. Backward stepwise selection using the AIC in the Cox proportional hazards regression model identified that age, FA surgery history, treatment, mitotic activity, and surgical margin were most strongly associated with RFS of PT (*Table 2*). Schoenfeld residual test results were shown in Figure S2.

Nomogram and model performance

Nomograms were created based on the five aforementioned independent factors (*Figure 2*). A higher total points score based on the sum of the assigned number of points for each factor in the nomogram was associated with a worse prognosis. The discriminative ability of the final model for RFS was assessed using the C-index (0.78, 95% CI: 0.75–0.11). The accuracy of the model was assessed by bootstrap validation with 1,000 replicates. The 1,000-sample bootstrapped calibration plots for the prediction of 1-, 3-, 5-, and 10-year RFS are shown in *Figure 3*. The nomogram-predicted RFS rate showed good agreement with the actual RFS rate, and all of the deviations were less than 10%. The 3- and 5-year ROC curves and AUC over time were plotted and indicated that the predictive ability of the model was considerable, with the AUC value at 3 years after surgery was 82.90 (95% CI: 79.42–86.38) (Figure S3).

Discussion

In this retrospective study, the risk factors and RFS in 342 patients with PTs were assessed. A nomogram was created based on the five following independent risk factors: age, FA surgery history, treatment, mitotic activity, and surgical margin. The discriminative ability and accuracy of the model revealed good predictive ability, and it performed well in the internal validation.

Pathological examination is currently the only diagnostic and classification criteria for PT. However, pathological grading based on morphological features is subjective and not completely consistent with the biological behavior of PT, and the indicators overlap. Tan *et al.* demonstrated that the AMOS score has good predictive ability (C-index, 0.79) and was better than histological scoring system (C-index, 0.65) (11). A comprehensive analysis of factors including

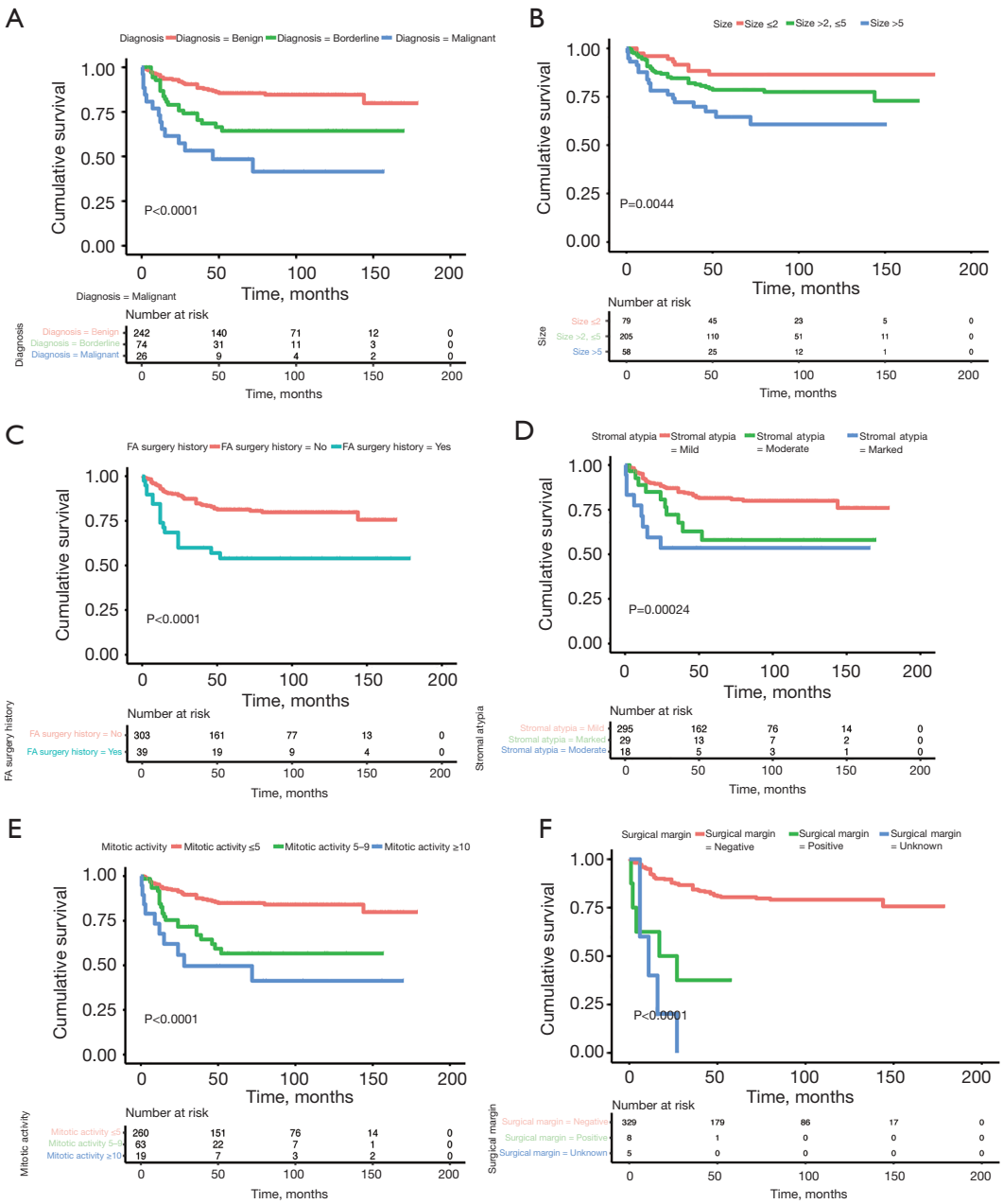

Figure 1 Kaplan-Meier estimates of RFS according to (A) diagnosis; (B) tumor size; (C) FA surgery history; (D) stromal atypia; (E) mitotic activity; (F) surgical margin. FA, fibroadenoma; RFS, recurrence-free survival.

the clinicopathological features and surgical treatment can more accurately assess the prognosis of PT. In addition, US-guided VABB, as a minimally invasive surgical method, has been widely applied for the resection of small breast lumps in China. The nomogram based on comprehensive variables in this study was more objective and suitable for the prognostic evaluation of PT patients in China.

Although factors related to the prognosis of PTs, such as stromal cellularity, mitotic activity, surgical margin etc., have been reported, there is currently not a consistent conclusion. Zhou *et al.* further divided PTs into low-risk (benign PTs) and high-risk (borderline and malignant PTs) groups, and explored the prognostic factors related to RFS in both groups. Stromal atypia was found to be an

Table 2 Univariate and multivariate analysis of RFS of PTs of the breast

Variants	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
≤40	Reference			
>40	0.63 (0.39–1.02)	0.058	0.55 (0.33–0.94)	0.029
Location				
Left	Reference			
Right	1.07 (0.67–1.72)	0.777	–	–
Size (cm)				
≤2	Reference			
>2, ≤5	1.80 (0.88–3.72)	0.110	1.53 (0.69–3.40)	0.291
>5	3.40 (1.54–7.52)	0.002	2.21 (0.84–5.80)	0.107
FA surgery history				
No	Reference			
Yes	2.94 (1.70–5.10)	<0.001	4.82 (2.47–9.43)	<0.001
CNB				
No	Reference			
Yes	1.14 (0.582–2.235)	0.701	–	–
Treatment				
Lumpectomy	Reference			
WLE	0.44 (0.22–0.91)	0.026	0.36 (0.17–0.75)	0.007
Mastectomy	0.46 (0.17–1.30)	0.143	0.13 (0.04–0.40)	<0.001
US-guided VABB	0.82 (0.43–1.55)	0.537	1.36 (0.55–3.35)	0.511
Tumor border				
Well defined	Reference			
Permeative	1.48 (0.88–2.48)	0.136	–	–
Stromal overgrowth				
Absent	Reference			
Present	1.29 (0.73–2.26)	0.381	–	–
Stromal atypia				
Mild	Reference			
Moderate	2.29 (1.16–4.52)	0.017	0.86 (0.38–1.95)	0.720
Marked	3.62 (1.72–7.64)	0.001	1.47 (0.57–3.80)	0.422

Table 2 (*continued*)

Table 2 (*continued*)

Variants	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Stromal cellularity				
Mild	Reference			
Moderate	1.17 (0.62–2.21)	0.636	0.78 (0.39–1.56)	0.477
Marked	2.02 (1.05–3.91)	0.036	0.87 (0.36–2.10)	0.752
Mitotic activity/10 HPF				
<5	Reference			
5–9	3.12 (1.83–5.32)	<0.001	3.29 (1.68–6.44)	<0.001
≥10	5.20 (2.58–10.49)	<0.001	7.19 (2.44–21.22)	<0.001
Surgical margin				
Negative	Reference			
Positive	6.09 (2.43–15.26)	<0.001	5.07 (1.66–15.48)	0.004
NA	14.33 (5.60–36.66)	<0.001	9.29 (2.46–35.13)	0.001

RFS, recurrence-free survival; PT, phyllodes tumor; HR, hazard ratio; CI, confidence interval; FA, fibroadenoma; CNB, core needle biopsy; WLE, wide local excision; US, ultrasound; VABB, vacuum-assisted breast biopsy; HPF, high-power field; NA, not available.

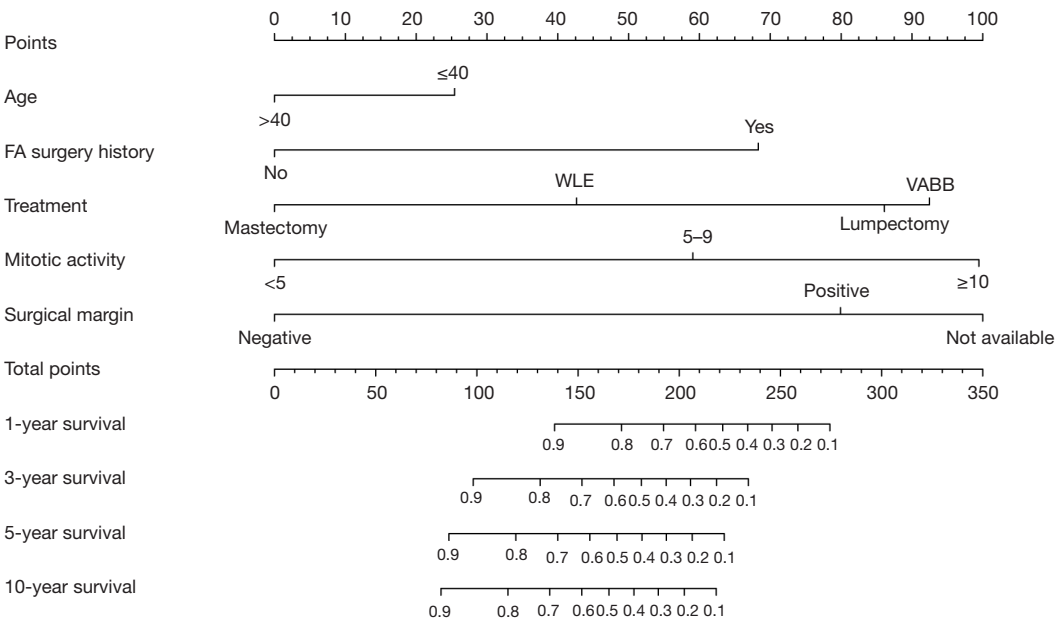

Figure 2 A nomogram for predicting the RFS of patients with PTs of the breast. Points were assigned for age, FA surgery history, treatment, mitotic activity and surgical margin, by drawing a line upward from the corresponding values to the "Points" line. The sum of these three points, plotted on the "Total points" line, corresponds to the prediction of probability of 1-, 3-, 5-, and 10-year RFS probabilities. FA, fibroadenoma; WLE, wide local excision; VABB, vacuum-assisted breast biopsy; RFS, recurrence-free survival; PT, phyllodes tumor.

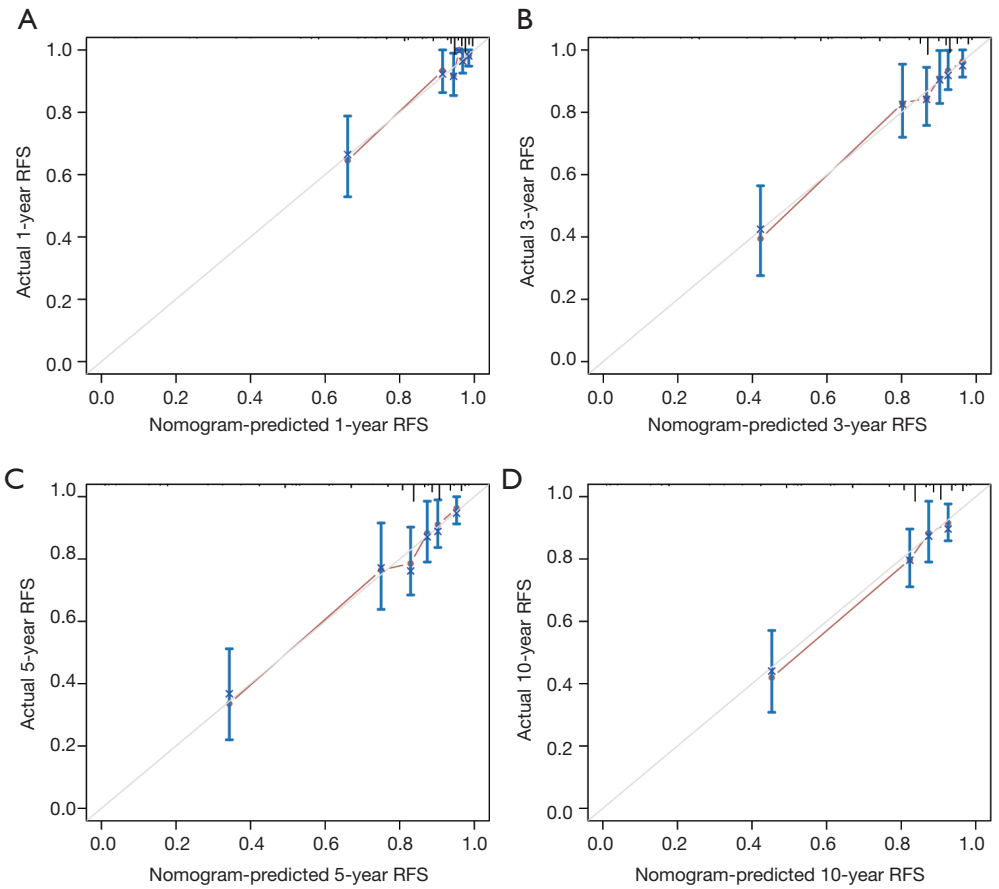

Figure 3 Bootstrapped estimates of calibration accuracy at (A) 1-year RFS; (B) 3-year RFS; (C) 5-year RFS; and (D) 10-year RFS. The x-axis shows the nomogram-predicted probability, and the y-axis displays the actual survival as estimated by the Kaplan-Meier method. This figure demonstrates how accurately the nomogram predictions at different risk levels conform to the observed outcomes. RFS, recurrence-free survival.

independent factor for RFS in the low-risk group, whereas surgical treatment and tumor border were identified in the high-risk group (21). Li *et al.* indicated that the recurrence risks of malignant PT patients with younger age, FA surgery history, malignant heterologous component, and surgical margin <1 cm were higher (22). In this study, age and FA surgery history, as clinically relevant factors, also proved to be independent prognostic factors.

Literature on the effect of age is limited. Spanheimer *et al.* suggested that age was significantly associated with the prognosis of borderline and malignant PTs (23). Wei *et al.* suggested that younger patients were more prone to LR but there was no significant difference in distant metastasis free survival (DMFS) and overall survival (OS) (24). The P value of age in this study was 0.058 in the univariate analysis. To avoid the bias of factor selection, we included it in the subsequent analysis. Genomics studies have found that PT and FA both had a MED12 gene hotspot mutation and may exhibit homology in development (25,26). Pareja *et al.* suggested that PT could be developed by FA-dependent MED12 mutation through progressive genetic alteration of oncogenes (27). For younger patients or patients with FA surgery history, regular follow-up should be performed for vigilant monitoring of recurrence; however, more studies are still needed to confirm this conclusion.

Surgical management has always been one of the most controversial issues in PTs, mainly in terms of margin status and margin width. Studies have shown that, regardless of PT grade, positive margin was significantly associated with LR risk, which is consistent with the results of a systematic review and meta-analysis conducted by our team (6,28-30). However, some studies have also suggested that margin

status was only associated with the prognosis of malignant PTs, and whether benign PTs with positive margins require further resection still remains controversial (31). In a systematic review of benign PTs, Shaaban *et al.* noted that patients with positive margins had an increased LR rate. However, given the low LR rate (12.9%), a "wait and see" strategy could also be adopted, and re-resection was only applicable to borderline and malignant PTs (32). In this study, margin status, as an independent prognostic factor for PTs, were significantly correlated with the LR risks. However, the number of patients with positive margins involved in this study was limited, and more evidence is needed.

The margin width was another important factor affecting the LR risk. Chao *et al.* defined the margin width surgically and incorporated it into a multivariate analysis to establish a nomogram based on margin width, mitotic activity, and tumor border (C-index, 0.71; 95% CI: 0.67–0.75). External validation was performed in the other two cohorts (cohort 1: C-index 0.67, 95% CI: 0.60–0.75; cohort 2: C-index 0.73, 95% CI: 0.60–0.83) (15). However, recent studies have shown that for benign PTs, ensuring a margin of at least 1 cm was not associated with a reduced risk of LR (33). The latest NCCN guideline recommended the "wait and watch" strategy following excision for benign PTs and a second extended resection for borderline and malignant PTs (16). The results of the present study showed that there was no significant difference in RFS between "re-resection" and observation, supporting the conclusion of the NCCN guidelines.

Previous studies have also found that other morphological features, including myxoid stroma, hemorrhage and necrosis, were also associated with PT prognosis (34,35). Slodkowska *et al.* demonstrated that factors including mucin-predominant stroma were independent factors for LR, while necrosis was one of the predictors of metastasis (8). Tan *et al.* indicated that tumor necrosis was associated with higher histological grades of PTs and poorer RFS, and the presence of tumor necrosis indicated a more active biologically performance (36). In our study, there were 11 cases with hemorrhagic or necrosis, five with LR, and two with metastasis. Notably, recurrences occurred in all patients with stromal myxoid degeneration (7/7) and FA-like areas (6/6). Nonetheless, more research is needed to supplement the correlation between the morphological features and PT prognosis.

This study also had some limitations that should be noted. Firstly, the nomogram constructed in this study was only validated internally, and thus, further validation is required with more follow-up cases and multicenter samples. Secondly, most of the cases included in this study were benign and borderline PTs, meaning that the nomogram may have limitations in predicting the prognosis of malignant PT. In addition, with the development of gene sequencing technology and the combined application of multi-omics, the exploration of prognosis-related biomarkers, radiomics features, and artificial intelligence were expected to be incorporated into clinical prediction models to further improve the predictive efficiency of PT prognosis.

Conclusions

Currently, pathological examination based on morphological indicators, as the only diagnostic and grading standard, is not completely consistent with the biological behavior of PT. In this study, a nomogram based on clinicopathology features, surgical treatment, and surgical margin was proposed to more objectively and accurately evaluate PT prognosis, prolong the RFS, and achieve individualized diagnosis and treatment.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-542/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-542/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-542/coif). XL serves as an Editor-in-Chief of *Gland Surgery* from May 2022 to April 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese PLA General Hospital (No. S2022-319-01) and individual consent for this retrospective analysis was waived.

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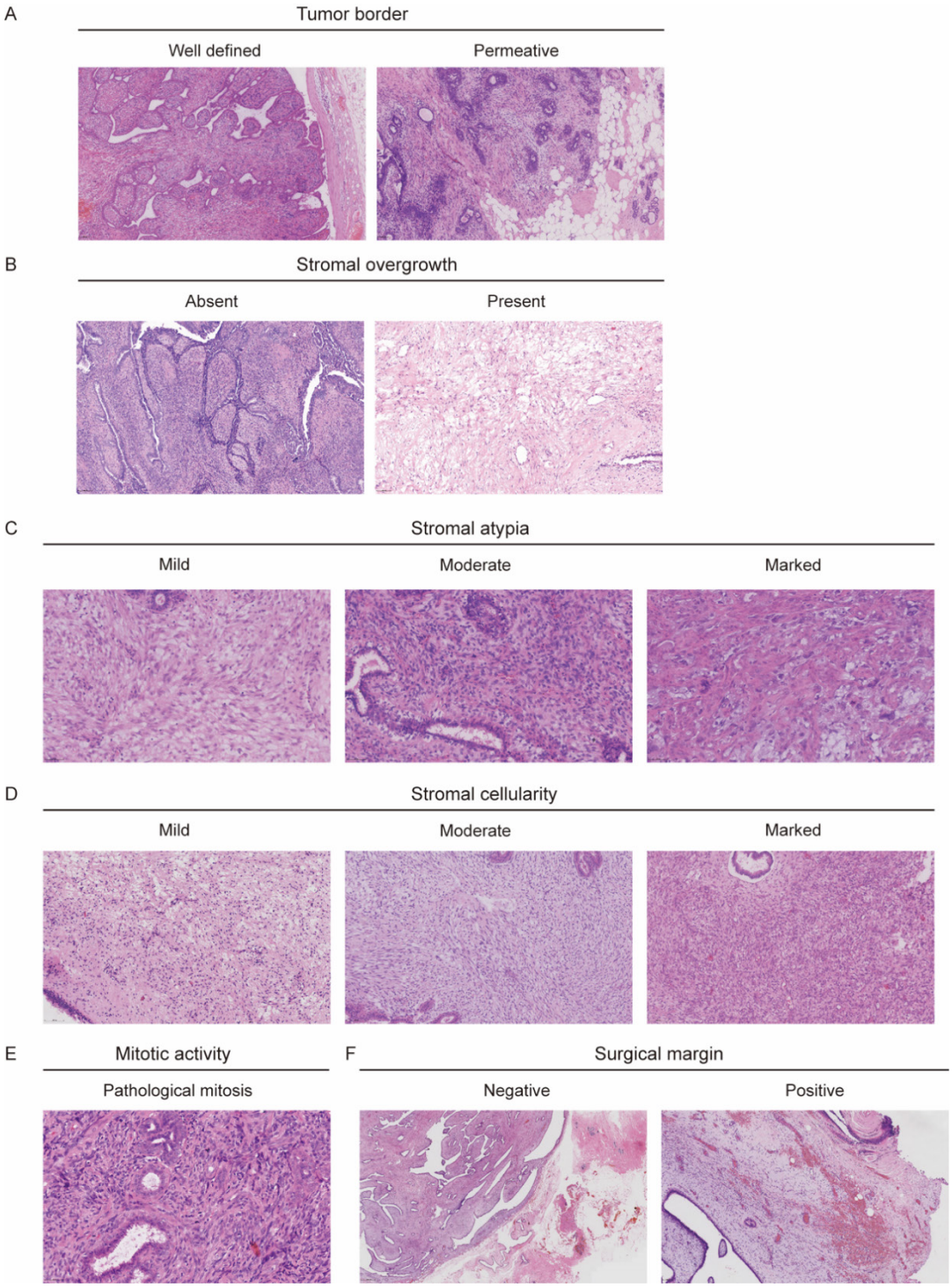

Figure S1 Histological features of PTs of the breast (HE staining). (A) Tumor border (×10, scale bar =100 μm); (B) stromal overgrowth (×10, scale bar =100 μm); (C) stromal atypia (×40, scale bar =50 μm); (D) stromal cellularity (×20, scale bar =100 μm); (E) mitotic activity (×40, scale bar =50 μm); (F) surgical margin: negative (×1.5, scale bar =1,000 μm) and positive (×10, scale bar =100 μm). PT, phyllodes tumor; HE, hematoxylin-erosin staining.

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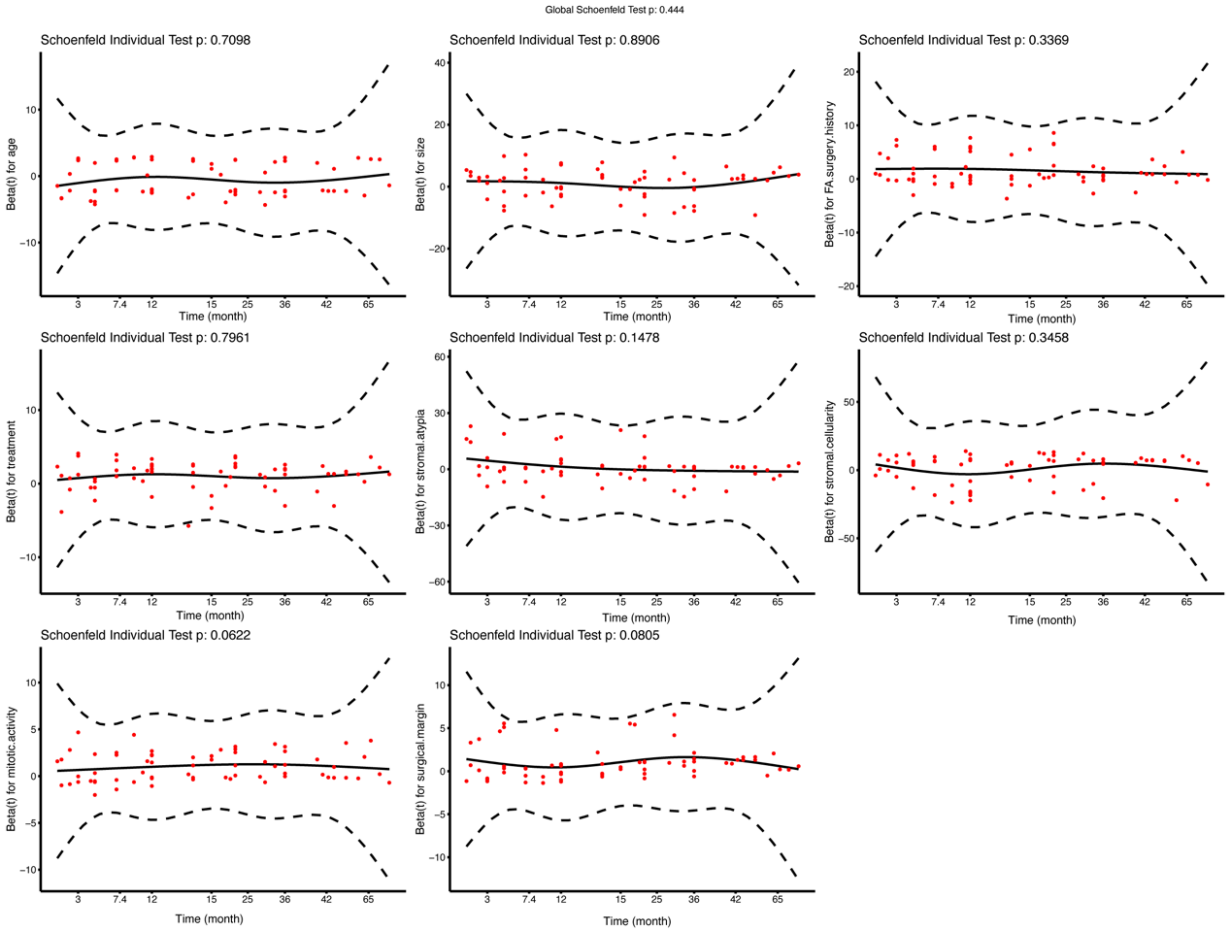

Figure S2 Schoenfeld individual test of Cox proportional hazards regression analysis with all factors meeting the results of the proportional test (P>0.05).

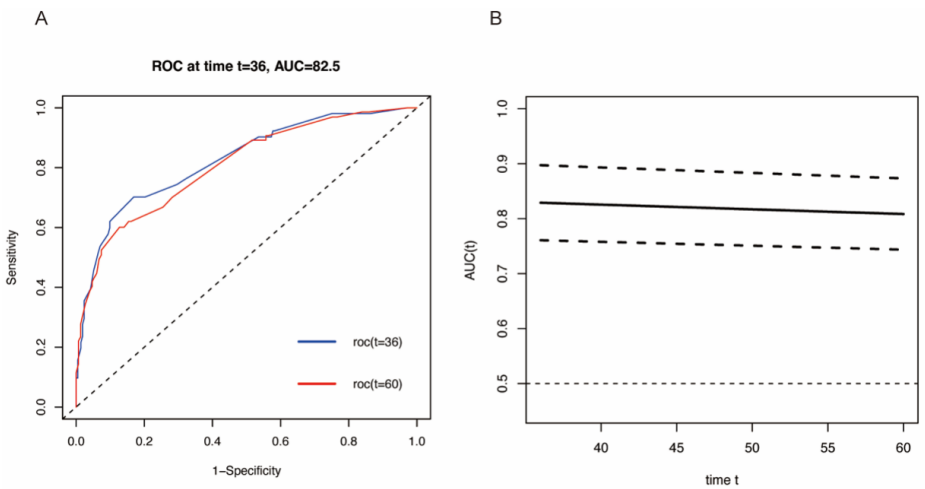

Figure S2 ROC curve and AUC change over time. The AUC value at 3 years after surgery was 82.90 (95% CI: 79.42–86.38). ROC, receiver operating characteristic; AUC, area under the curve.

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