Original article

Retrospective study of malignant phyllodes tumors of the breast: Younger age, prior fibroadenoma surgery, malignant heterologous elements and surgical margins may predict recurrence

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ABSTRACT

Purpose: The potential recurrence rate of malignant phyllodes tumors (MPTs) of the breast is high, and the prognostic factors are still unclear. We therefore aim to study the factors affecting the outcome of MPTs.
Methods: A retrospective review of MPT patients treated from 2006 to 2020 at our institution was conducted. Univariate and multivariate Cox proportional hazard models were used to examine the influence of different variables on RFS. Moreover, significant prognostic factors were combined to construct the nomogram to predict the probability of relapse occurring in MPT patients. The 5-year and 10-year RFS rates were estimated using the Kaplan−Meier method.
Results: During the study period, 188 MPT patients were identified. The presence of malignant heterologous elements was observed in 23 (12.2%) patients with MPT, and the patients with malignant heterologous elements who received chemotherapy had longer RFS, which could reduce the risk of recurrence (p = 0.022). Recurrence occurred in 56/188 (29.8%) patients, of whom 47 experienced local recurrence and 11 experienced distant metastases. The 5-year and 10-year cumulative RFS rates were 77.5% and 70.1%, respectively. Age (p = 0.041), fibroadenoma surgery history (p = 0.004), surgical margins (p = 0.001) and malignant heterologous elements (p < 0.001) were independent risk factors for postoperative RFS. Subsequently, a nomogram was built, with a C-index of 0.64 (95% CI: 0.629−0.661), to predict the risk of recurrence.
Conclusion: The results of this study showed that younger age, fibroadenoma surgery history, malignant heterologous elements and surgical margins <1 cm predict a higher incidence of recurrence in MPT patients. Patients with malignant heterologous elements treated with chemotherapy could have a reduced risk of recurrence.

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1. Introduction

Phyllodes tumors (PTs) of the breast are fibroepithelial tumors composed of two interdependent cellular compartments: epithelial and stromal tissue and subdivided into benign, borderline and malignant grades based on their histological features [1,2]. According to the 2012 WHO standard, malignant phyllodes tumors

(MPTs) are characterized by the presence of markedly increased stromal cellularity and atypia, 10 mitoses or more per 10 high-power fields, stromal overgrowth, and infiltrative tumor margins [2,3]. The average annual age-adjusted incidence rate of malignant phyllodes tumor (MPT) is 2.1 per million women [1]. The local recurrence rate in the published literature on MPTs is 23—30% [2]. Given the high incidence of recurrence, a summary of the behavior of the disease would be valuable.

Unfortunately, due to the scarcity of cases, there is no consensus on the risk factors of recurrence in MPT patients. The clinicopathologic factors correlated with prognosis based on previously published literature are inconsistent [4]. Surgical resection remains the cornerstone of treatment in MPTs, but the optimal width of tumor-free margins has been a matter of debate in recent years [5—13]. The National Comprehensive Cancer Network (NCCN) guidelines recommend obtaining at least a 1 cm surgical margin [14]. However, some authors have indicated that a previous tumor surgical margin (≥1 cm) is not necessary for MPTs [10—13]. Radiotherapy in the adjuvant setting also remains a matter of debate [4,10,15,16]. Furthermore, the role of chemotherapy has been analyzed only in small retrospective studies and case reports and needs to be further explored [10,16,17]. Further work in finding targeted agents against MPTs in the future to reduce the possibility of relapse is highly expected.

This paper is based on a large cohort of MPT patients to assess the risk factors and RFS, especially to explore the influence of clinical factors on the prognosis, with the hope of providing advice and guidance for clinicians and patients about appropriate treatment and management strategies.

2. Patients and methods

2.1. Patients

Data from MPT patients treated in our institute between 2006 and 2020 were retrospectively collected. The inclusion criteria were as follows: 1. all patients who had pathologically confirmed MPT and 2. patients without any other malignant tumor except MPT. The exclusion criteria included the following: 1. MPT patients with invasive ductal carcinoma elements; 2. a lack of clinicopathological information; and 3. patients with a history of borderline phyllodes tumor and MPT recurrence at the same site. A total of 188 MPT patients were ultimately included. The study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. The patients were not required to sign an informed consent form in the retrospective study.

3. Methods

The following clinicopathological characteristics and treatment modalities were recorded and analyzed. Clinicopathological characteristics at diagnosis included age, history of reproduction and lactation, family history of breast invasive carcinoma, fibroadenoma surgery history, clinical signs/symptoms at the initial visit, time interval between mass discovery and treatment, laterality, and malignant heterologous elements. Characteristics of initial treatment included core needle biopsy before lumpectomy, type of surgery, axillary procedure, surgical margins status, chemotherapy regimens, adjuvant radiotherapy and dosimetric parameters including fraction dose, total radiation dose and radiotherapy field. Histopathological slides for each case were reviewed by two pathologists from our institution. If the initial surgery was performed at other hospitals, the initial pathological sections were reviewed by our institute to confirm the diagnosis. The definite diagnoses of recurrence were based on the pathologic report from re-excision

lumpectomy specimens. All specimens were reassessed for diagnosis defined by the World Health Organization (WHO) criteria for the classification of breasts in 2012 [2]. Three patients with a previous diagnosis of MPT were reclassified and diagnosed with borderline phyllodes tumors and excluded from our cohort.

Descriptive statistics were performed to examine the baseline characteristics of all patients. The optimal cutoff value of the time interval between mass discovery and treatment was determined using a receiver operating characteristic (ROC) curve. We defined recurrence-free survival (RFS) as the time from surgery to the date of relapse from MPT or the date of last follow-up. Patients who did not experience the event of interest were censored at their last follow-up. The 5-year and 10-year RFS rates were estimated using the Kaplan−Meier method. We used univariate and multivariate Cox proportional hazard models to examine the influence of different variables on RFS. Hazard ratios and their associated 95% confidence intervals (95% CIs) were obtained from the Cox regression analysis. The nomogram was generated based on independent risk factors identified by Cox regression analysis using the rms package in R version 4.0.3. The nomogram was internally verified through discrimination and calibration curves [18]. Discrimination was estimated by Harrell's concordance index (C index = 0.5−1), where 0.5 and 1.0 mean the result was completely random and perfect discrimination, respectively. The calibration curve mainly reflected the consistency between the predicted risk of the model and the observed risk. These analyses used bootstrap analysis with 1000 resamples [19]. All statistical tests were two-sided in all results, and P values < 0.05 were considered statistically significant. Analyses were conducted using SPSS v22.0 (IBM SPSS, New York) and R software (version 4.0.3).

4. Results

4.1. Patient characteristics

The study cohort comprised 188 cases of MPT diagnosed at Tianjin Medical University Cancer Institute and Hospital from 2006 to 2020. The results of patient clinicopathologic features are summarized in Table 1. The median and mean age of the MPT cases at diagnosis were 48 and 46.5 years, respectively (ranging from 13 to 83 years old), and 54 (28.7%) patients were ≤40 years of age, while 134 (71.3%) were >40 years. Only 10 (5.3%) patients had a family history of breast carcinoma. A high proportion of MPT patients had previous child-bearing and lactation histories (87.2% and 77.7%, respectively). The median time interval between mass discovery and treatment was 5 months (range, 0−480 months). Only 50 (26.6%) patients had undergone prior breast adenofibroma resection. A pre-surgery core needle biopsy was performed in 55/188 (29.3%) patients, with 50.9% (28/55) having a presurgical malignant tumor diagnosis. A total of 80 patients (42.6%) had breast tumors measuring >5 cm in diameter, and 100 (53.2%) patients had tumors measuring ≤5 cm. The presence of malignant heterologous elements was observed in 23 (12.2%) cases of MPT. Of 23 patients with malignant heterologous elements, 8 (8/23, 34.8%) received postoperative chemotherapy compared with 13 (13/165, 7.9%) patients without malignant heterologous elements at our institution. Further analysis indicated that patients with malignant heterologous elements receiving chemotherapy had a reduced risk of recurrence (p = 0.022, Fig. 1). Thirteen (56.5%) patients who harbored malignant heterologous elements were found to relapse after surgery compared with the control group (26.1%) (p = 0.003).

4.2. Treatment

All patients in our research received surgery as their primary

treatment. As shown in Table 1, one hundred thirty-seven patients (71.8%) underwent breast-conserving surgery, of whom 92 (48.9%) underwent lumpectomy and 45 (23.9%) underwent wide excision. Mastectomy was the treatment used on 51 (27.1%) patients. Axillary lymph node dissection was performed in 28/188 (14.9%) patients, while sentinel lymph node biopsy was needed only in 1 (0.5%)

Table 1
Clinicopathologic features and management of malignant phyllodes tumors of the breast.

	N = 188	Percentage
Age(year)		
≤40	54	28.7
>40	134	71.3
Family history of breast invasive carcinoma		
Yes	10	5.3
No	176	93.6
Missing	2	1.1
Reproductive history		
Yes	164	87.2
No	22	11.7
Missing	2	1.1
History of lactation		
Yes	146	77.7
No	40	21.3
Missing	2	1.1
Presenting symptoms		
Breast mass	95	50.5
Tumor slow enlargement	37	19.7
Tumor rapid enlargement	11	5.9
Breast mass with pain	34	18.1
Skin dimpling	6	3.2
Nipple discharge	5	2.7
Time interval between mass discovery and treatment(month)		
≤3.5	76	40.4
>3.5	103	54.8
Missing	9	4.8
Fibroadenoma surgery history		
Yes	50	26.6
No	131	69.7
Missing	7	3.7
Tumor location		
Left breast	98	47.9
Right breast	90	52.1
Core needle biopsy		
Yes	55	29.3
No	133	70.7
Surgical methods		
Lumpectomy	92	48.9
Wide excision	45	23.9
Mastectomy	51	27.1
Axillary procedure		
Axillary lymph node dissection	28	14.9
Sentinel lymph node biopsy	1	0.5
None	159	84.6
Tumor size(cm)		
≤5	100	53.2
>5	80	42.6
Missing	8	4.3
Surgical margins(cm)		
<1	75	39.9
≥1	112	59.6
Missing	1	0.5
Malignant heterologous elements		
Absent	165	87.8
Present	23	12.2
Adjuvant chemotherapy		
Yes	21	11.2
No	164	87.2
Missing	3	1.6
Adjuvant radiation therapy		
Yes	5	2.7
No	178	94.7
Missing	5	2.7

patient. The postoperative pathological reports showed no lymph node metastasis in MPT patients. R0 resection at final surgery was achieved in the overall patient population as follows: 39.9% with <1 cm margin and 59.6% with ≥1 cm margin. Mastectomy was associated with wider surgical margins (P < 0.001). A total of 21/188 (11.2%) patients received adjuvant chemotherapy, of whom 12/21 (57.1%) had ifosfamide- and adriamycin-based induction regimens, 6 (28.6%) had taxane-based regimens, and 3 (14.3%) had unknown chemotherapy regimens. Age (p = 0.024), presenting symptoms (p < 0.001), presurgery core needle biopsy (p = 0.008), surgical methods (p < 0.001), surgical margins (p = 0.048), and malignant heterologous elements (p = 0.001) were associated with postoperative chemotherapy. Five (2.7%) of the 188 patients received adjuvant radiotherapy administration after surgery, namely, a 50-Gy dose in 25 fractions to the chest wall after mastectomy and a 50 Gy/25 F to the whole breast, followed by another tumor bed boost of 10 Gy/5 F after breast-conserving surgery. In the radiotherapy group, 60.0% had undergone a mastectomy, which was higher than that in the non-radiotherapy group (24.2%) (p < 0.001). Patients who were treated with radiotherapy were more frequently administered chemotherapy (60.0% vs 9.0%, p < 0.001). All 5 patients received adjuvant radiotherapy, and none experienced both local recurrence and distant metastasis.

4.3. Recurrence and patterns

The median follow-up period was 70 months (range, 1—173 months), and recurrence occurred in 56/188 (29.8%) patients, of whom 47 experienced local recurrence (LR) and 11 experienced distant metastases (DM) (Table 2). Of the cases of LR, 44 had ipsilateral breast tumor recurrence, and 3 had chest wall recurrence. The lung was the most common viscera of metastasis, and all patients with distant metastasis had at least pulmonary metastasis at presentation, followed by liver metastasis and bone metastasis (1 patient each). In ipsilateral breast tumor recurrence patients, 20/44 (45.5%) patients underwent total breast resection on the affected side, and 4/20 received chemotherapy. In patients with lung metastases, 5 received chemotherapy, 2 received immunotherapy (thymosinα1 or DC vaccine), and 3 received targeted therapy with lapatinib. In addition, in the relapsed population, 10 experienced a second relapse, and 2 experienced a third relapse. The second recurrence occurred on the same side of the chest wall or breast in all patients, and one of them had bone and lung metastases and
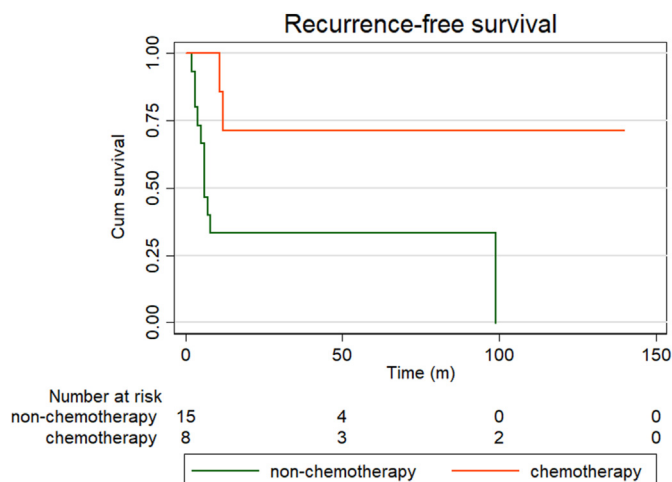

Fig. 1. Recurrence-free survival (RFS) in 23 patients with malignant heterologous elements.

received MAID (Mesna + ifosfamide + pirarubicin + dacarbazine) chemotherapy. Death occurred in 10/56 (17.8%) patients, all of whom had distant metastases.

4.4. Univariate and multivariate analyses

The univariate analysis revealed that recurrence was significantly associated with the following factors: age (p = 0.006), time interval between mass discovery and treatment (p = 0.013), fibroadenoma surgery history (p = 0.014), surgical methods (p = 0.004), surgical margins (p < 0.001), and malignant heterologous elements (p = 0.004) (Table 3). The significant parameters were subsequently involved in multivariate analysis and were summarized in Table 4. Age, fibroadenoma surgery history, surgical margins and malignant heterologous elements were independent risk factors for postoperative RFS. Specifically, age younger than 40 years (hazard ratio = 1.86, 95% CI: 1.03–3.37 p = 0.041), history of breast fibroadenoma excision (hazard ratio = 2.83, 95% CI: 1.51–5.32 p = 0.004) and presence of malignant heterologous elements (hazard ratio = 7.98, 95% CI: 3.74–17.03 p < 0.001) were more likely to relapse in MPT patients. The recurrence risk of the group with surgical margins ≥1 cm was lower than that of the group with surgical margins <1 cm (hazard ratio = 0.28, 95% CI: 0.13–0.61 p = 0.001). Moreover, the prognostic factors for overall survival were evaluated by univariate and multivariate analyses in 56 patients with recurrence, and the results showed that surgical margin was a prognostic factor for survival outcome but not an independent factor (Supplementary Table 1).

4.5. Recurrence-free survival

The 5-year cumulative RFS rate of the whole group was 77.5%, and the 10-year cumulative RFS rate was 70.1%. The median time interval between surgery and recurrence was 11.5 months (range, 1–107 months). Of the 56 cases experiencing recurrence, 31/56 (55.4%) developed within 1 year, 85.7% recurred within 3 years, and 92.9% recurred within 5 years. The overall RFS rates at 5 and 10 years in patients younger than 40 years were 55.8% and 46.6%, respectively, versus 76.9% and 72.4% in elderly patients (Fig. 2). Among those with a history of fibroadenoma excision and the presence of malignant heterologous elements, the 10-year cumulative RFS rates were 46.5% and 30.7%, respectively (Fig. 2). In the Kaplan-Meier analysis, women with surgical margins (<1 cm) had a poorer prognosis than those with surgical margins ≥1 cm (Fig. 2). The 10-year RFS rates of the no risk group, one risk factor group and two risk factor groups were 91.7%, 76.4% and 38.3%, respectively,

Table 2
Patterns of recurrence in malignant phyllodes tumors of the breast.

	N = 188	Percentage
Recurrence		
Yes	56	29.8
No	132	70.2
Local recurrence		
Yes	47	25.0
No	141	75.0
Sites of Local recurrence		
Breast	44	23.4
Chest wall	3	1.6
Distant metastasis		
Yes	11	5.9
No	177	94.1
Sites of metastasis		
Lung	9	4.8
Lung + bone	1	0.5
Lung + liver	1	0.5

while at the follow-up time of 70 months, all the cases with three or four risk factors experienced relapse, and the median RFS time of the group was 12 months (95% CI, 2–22 months) (Fig. 3).

4.6. Nomogram construction and validation

A nomogram model based on age, fibroadenoma surgery history, surgical margins and malignant heterologous elements was established to predict the risk of recurrence for MPT patients (Fig. 4A). In the current study, Harrell's C-index for relapse prediction was 0.64 (95% CI: 0.629–0.661), indicating a relatively good prediction model. The calibration plots showed good correlation between the observed and nomogram-predicted RFS (Fig. 4B–D).

5. Discussion

In this retrospective study, we assessed the risk factors and RFS in 188 patients with MPT. The results showed that age younger than 40 years (HR = 1.86), history of breast fibroadenoma resection (HR = 2.83) and MPT with the presence of malignant heterologous components (HR = 7.98) increased the risk of relapse. The risk of recurrence in patients with surgical margins ≥1 cm was lower than that in patients with surgical margins <1 cm (HR = 0.28). In addition, patients with malignant heterologous elements receiving chemotherapy had a reduced risk of recurrence (p = 0.022).

The overall RFS rates in MPT at 5 and 10 years were 77.5% and 70.1%, respectively. More than 90% of recurrences occurred within 5 years, and the median time to recurrence was 11.5 months before the 24-month mark, which was in line with previous studies [8,20,21]. Local recurrence and distant metastasis were 25% and 5.9%, respectively. A meta-analysis consisting of 54 studies reported that the LR rate for MPT was 18% (95% CI 14–21%), which was slightly lower than that in our data [4]. We found no evidence of metastasis in axillary lymph nodes [22,23], and the most commonly involved organ for distant failure was the lung (11,100%) [24,25], illustrating that MPTs appear to spread hematogenously, and metastases often manifested in distant viscera as opposed to locoregional lymph nodes.

The present study reveals that inadequate tumor surgical margins (<1 cm) increase the risk of recurrence and a poor prognosis for the patient. In recent years, close or tumor-positive margins for initial phyllodes tumors (BPTs) have been discussed, and "a watch-and-wait policy" of close follow-up could be adopted for BPTs [26,27]. A study summarizing breast phyllodes tumors reported from 1951 to 2012 showed that the average local recurrence rate of PT patients with positive surgical margins reached 31.5% (median 14.5%; range 1–67%) [28]. Therefore, we aim to demonstrate the feasibility of small margins for MPT patients to achieve both oncological safety and superior cosmetic outcomes. Lim et al. confirmed that patients with malignant phyllodes tumors who received only surgery had a high disease recurrence rate (57.4% at 5 years), and the surgical margin was the only parameter that affected disease-free survival and overall survival [29]. Previous literature has suggested that surgical excision with a margin no less than 1 cm was significantly associated with a decreased risk of recurrence in MPT patients [5–9,11]. However, some other articles showed that the prognosis of patients with resection margins <1 cm was not inferior to that of patients with resection margins of at least 1 cm [10–13]. We should note that these findings are based on small sample sizes, which prevents us from drawing firmer conclusions. Ogunbiyi et al., based on recent literature and retrospective research results of the center, believed that the NCCN guidelines of surgical treatment for phyllodes tumors with a 1 cm margin led to overtreatment [30]. A meta-analysis showed that, between margins of <1 cm and ≥1 cm, there was no statistically

Table 3
Prognostic factors for the univariate analysis of malignant phyllodes tumors (N = 188).

Clinicopathological parameters	Recurrence (n)	Crude HR	95%CI	p-value
Age(year)				**0.006**
≤40	24	2.55	1.31–4.97	
>40	32	–	–	
Family history of breast cancer				0.830
Yes	3	1.02	0.25–4.11	
No	52	–	–	
Reproductive history				0.806
Yes	48	0.89	0.34–2.31	
No	7	–	–	
History of lactation				0.581
Yes	41	0.73	0.35–1.53	
No	14	–	–	
Presenting symptoms				0.458
Breast mass	28	–	–	
Tumor slow enlargement	10	0.89	0.38–2.07	
Tumor rapid enlargement	3	0.90	0.22–3.63	
Breast mass with pain	10	1.00	0.42–2.36	
Skin dimpling	1	0.48	0.05–4.28	
Nipple discharge	4	9.57	1.02–89.48	
Time interval between mass discovery and treatment(month)				**0.013**
≤3.5	13	–	–	
>3.5	35	2.49	1.21–5.14	
Fibroadenoma surgery history				**0.014**
Yes	23	2.64	1.33–5.22	
No	32	–	–	
Tumor location				0.796
Left breast	30	1.09	0.58–2.03	
Right breast	26	–	–	
Core needle biopsy				0.238
Yes	13	–	–	
No	43	1.54	0.75–3.17	
Surgical methods				**0.004**
Lumpectomy	38	–	–	
Wide excision	8	0.31	0.13–0.73	
Mastectomy	10	0.35	0.16–0.78	
Axillary procedure				0.994
Axillary lymph node dissection	8	–	–	
Sentinel lymph node biopsy	1	NA	NA	
None	47	1.05	0.43–2.55	
Tumor size(cm)				0.327
≤5	27	–	–	
>5	27	1.38	0.73–2.61	
Surgical margins(cm)				**<0.001**
<1	38	–	–	
≥1	17	0.17	0.09–0.35	
Malignant heterologous elements				**0.004**
Absent	43	–	–	
Present	23	3.69	1.51–9.02	
Adjuvant chemotherapy				0.984
Yes	6	0.91	0.33–2.49	
No	50	–	–	
Adjuvant radiation therapy				0.876
Yes	55	NA	NA	
No	0	–	–	

significant difference between borderline and malignant PTs in terms of local recurrence, distant metastasis, and mortality. In addition, there was no significant difference in local recurrence among patients with borderline PT with margins of <1 cm and ≥1 cm[31]. Recently, Spanheimer et al. reported that margins within 1 mm were associated with an increased risk of locoregional recurrence compared with margins 1 mm or wider in the univariable analysis, but the small sample size of only 8 MPT patients with close/positive margins limited the reliability of the results [15]. In our research, a total of 188 patients with MPT were enrolled, of whom 75 had surgical resection margins <1 cm, and 38 experienced recurrence. Therefore, based on our larger sample size, we recommend wide resection with clear margins of at least 1 cm in MPT patients.

Younger age was an independent risk factor for poor prognosis in patients with MPT in our study. There have been relatively few reports in the literature on the effect of age on recurrence. In 1983, RM Briggs et al. reported that adolescents had a higher recurrence rate of phyllodes tumors than adults [32]. CL Chua et al. studied 106 phyllodes patients who underwent surgical treatment, indicating that in young patients (less than 20 years old), the recurrence rate of PT was higher [33]. Chen et al. and Wei et al. observed that younger patients were more likely to develop local recurrence, but no significant differences were observed with respect to DMFS and OS in PT [5,9]. Spitaleri et al. demonstrated that young age (<35 years) was associated with a significant increase in the risk of phyllodes-related events and remained the only significant prognostic factor in MPT [28]. However, some studies showed that young age did not have a statistically significant influence on LR for MPT [4,34]. Amerson reported the PT of 7 patients between the ages

Table 4
Prognostic factors for the multivariate analysis of malignant phyllodes tumors.

Clinicopathological parameters	Adjust HR	95%CI	p-value
Age(year)			**0.041**
≤40	1.86	1.03—3.37	
>40	—	—	
Time interval between mass discovery and treatment(month)			0.224
≤3.5	—	—	
>3.5	1.50	0.78—2.90	
Fibroadenoma surgery history			**0.004**
Yes	2.83	1.51—5.32	
No	—	—	
Surgical methods			0.303
Lumpectomy	—	—	
Wide excision	0.49	0.20—1.21	
Mastectomy	0.74	0.28—1.91	
Surgical margins(cm)			**0.001**
<1	—	—	
≥1	0.28	0.13—0.61	
Malignant heterologous elements			**<0.001**
Absent	—	—	
Present	7.98	3.74—17.03	
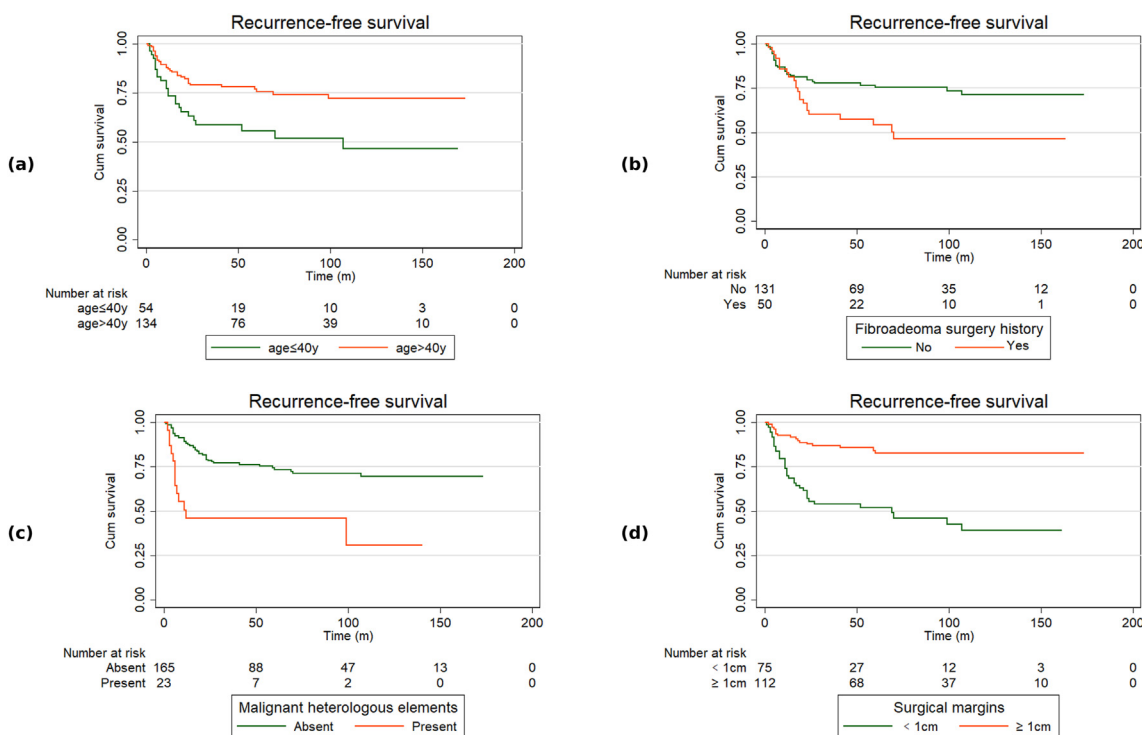
Fig. 2. Kaplan—Meier estimates of recurrence-free survival according to (a) age (b)fibroadenoma surgery history(c) surgical margins(d) malignant heterologous.

of 10 and 17 years, indicating that phyllodes tumors in adolescence were less aggressive [35]. Even though a study reported that older age (>50 years) was correlated with advanced tumor extension and poor cancer-specific survival, the author also pointed out that tumor extent and nodal status should be considered to explain the poor prognosis. Moreover, grade and LN status were not reported in more than 50% of patients in this article [36]. In agreement with previous reports [6,37], young age is an adverse prognostic factor for RFS in patients with MPT. Therefore, emphasis should be placed on improving the awareness of young patients on this disease.

The presence of malignant heterologous elements in our research was closely associated with the administration of chemotherapy and with a poor prognosis of patients with MPT, and

further analysis indicated that patients with malignant heterologous elements receiving chemotherapy could reduce the risk of recurrence (p = 0.022). Breast phyllodes tumors comprise benign epithelium and malignant stroma, and the stroma can exhibit heterologous sarcomatous differentiation [38]. The finding indicating that the presence of malignant stromal heterologous elements could predict a high risk of recurrence was in accordance with the published literature, mainly in small case series [8,39—41] and case reports [42,43]. Valerie et al. reported in 2017 that the presence of malignant heterologous elements alone was not associated with poor prognosis, but the combination of both tumor size and malignant heterologous elements was significantly correlated with distant metastasis, but this result was also limited by the small
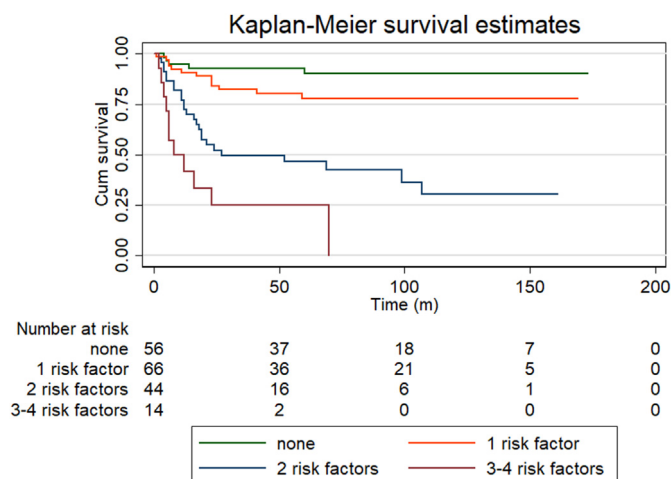
Fig. 3. Kaplan—Meier estimates of recurrence-free survival according to different risk factors.

number of studies [44]. The presence of malignant heterologous elements in PTs was classified as MPTs [40,45]. The work in this paper showed that adjuvant systemic chemotherapy had no exact efficacy for the outcome of MPTs, as has been reported previously [10,17]. However, we found that patients with malignant heterologous elements treated with chemotherapy had longer RFS. To the best of our knowledge, this is the first time that such an association has been reported.

Moreover, in this study, Cox regression analysis revealed that a previous history of breast fibromatosis excision (50/188, 26.6%) was an independent poor prognosis factor for relapse of MPT recurrence. Zhou et al. reported that a history of fibroadenoma surgery (59/236, 25%) was a high-risk prognostic factor for RFS in the univariate analysis but lost statistical significance in the multivariate analysis [34]. However, Abe et al. reported that the outcome of cases with a history of fibroadenoma (11/36, 30.6%) was significantly better than that of those without a history of fibroadenoma. The 36 malignant cases in the research were classified into two groups. One group comprising 11 cases was initially diagnosed with fibroadenoma, experienced recurrence during the follow-up period, and then was diagnosed with MPT. The other group was defined as cases without a history of fibroadenoma and in whom lesions initially occurred as MPT [46]. There was some evidence in the literature presenting the malignant transformation from fibroadenomas (FAs) to MPT, but the mechanism has not been definitively proven [46—49]. Tan et al. analyzed whether FAs might progress to MPTs in a linear fashion and suggested that the development of these tumors might not always follow a strict linear
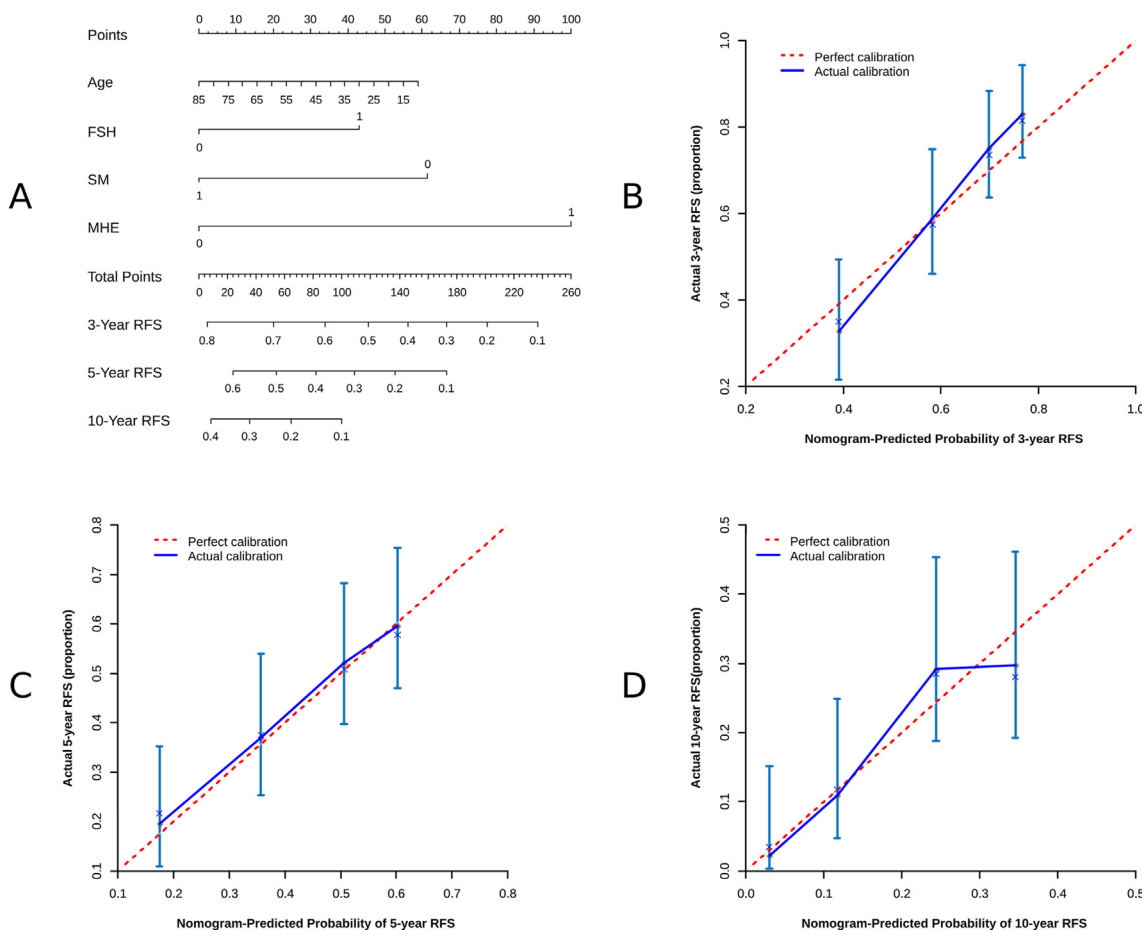

Fig. 4. Nomogram model and calibration curves. A Nomogram for predicting recurrence-free survival (RFS) of patients with MPTs. FSH: fibroadenoma surgery history 0: No,1: Yes. SM: surgical margins 0: surgical margins<1 cm, 1: surgical margins≥1 cm. MHE : malignant heterologous elements 0: Absent, 1: Present. B. 3-years RFS calibration curves; C. 5-years RFS calibration curves; D. 10-years RFS calibration curves; The x-axis shows the nomogram predicted probability, and the y-axis gives the actual survival as estimated by the Kaplan-Meier method. The deep blue line (Actual calibration) overlaps the red line (Perfect calibration) indicating near perfect calibration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

progression from FAs to phyllodes tumors and that MPTs might also arise de novo [49]. Piscuoglio et al. also showed that FAs harbored MED12 exon 2 somatic mutations significantly more frequently than MPTs and concluded that the majority of MPTs might be driven by other genetic/epigenetic alterations [50]. There was an obvious difference in the frequency of TERT mutations between MPTs and FAs, and TERT promoter hotspot mutations might play a role in the progression from the beginning to MPTs [51,52]. In our study, 23 (23/50, 54%) MPT patients had a history of FA relapse, and the high proportion of recurrences of these patients indicates that MPT patients with a history of FAs should be subject to periodic re-examinations.

Regarding radiotherapy, only five patients underwent radiotherapy in this retrospective analysis, which limited our ability to further study the effect of radiotherapy on local recurrence (LR). This treatment has been shown to reduce the risk of local recurrence but not distant metastases in malignant tumors [39,53—58]. Barth et al., in the first nonrandomized prospective trial of radiotherapy for 46 consecutive patients with MPTs, demonstrated that radiotherapy could reduce LR, although there were two cases of distant metastases [55]. Other studies reported that regardless of breast-conserving surgery or mastectomy, the local control rate of patients in the postoperative radiotherapy group was always higher than that of the control group [59].

There are some limitations to our research. First, this study has a retrospective design, so the potential of unmeasured patient-, disease-, and institution-associated confounding factors that may contribute to the prognosis must be considered. However, we should also realize the difficulty of conducting prospective research due to the rarity of MPT. It seems, for the time being, that large and rigorous retrospective studies are the best method to elucidate the whole course of MPT and to analyze the prognostic factors. Second, some parameters could be underpowered: (1) mastectomy was reported in only 51 cases, and the long-time span (14 years) for case collection might have affected the quality and type of treatment. (2) The role of chemotherapy in heterogeneous elements should be determined in a larger patient population. (3) In this study, only five patients were treated with radiotherapy, which needs to be verified in a larger group. Furthermore, regarding the nomogram, through the internal verification method, we could determine that the prediction model we established had certain feasibility, but further external verification is still needed. Finally, because it was difficult to obtain data from another outside cohort, external verification was impossible.

6. Conclusions

In the present study, we found that younger age, a history of fibroadenoma surgery, the presence of malignant heterologous elements and surgical margins <1 cm predicted a higher incidence of recurrence in MPT patients. In addition, patients with malignant heterologous elements treated with chemotherapy seemed to have an improved prognosis. Thus, we suggest adjuvant chemotherapy for MPT patients with malignant heterologous elements.

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Declaration of competing interest

The authors have stated that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.03.001.

References

[1] Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. Cancer 1993;71(10):3020—4.
[2] Lakhani SR, Ellis IO, Schnitt S, Tan PH, van de Vijver M. WHO classification of tumours of the breast. 2012.
[3] Chang J, Denham L, Dong EK, Malek K, Lum SS. Trends in the diagnosis of phyllodes tumors and fibroadenomas before and after release of WHO classification standards. Ann Surg Oncol 2018;25(10):3088—95.
[4] Lu Y, Chen Y, Zhu L, et al. Local recurrence of benign, borderline, and malignant phyllodes tumors of the breast: a systematic review and meta-analysis. Ann Surg Oncol 2019;26(5):1263—75.
[5] Wei J, Tan YT, Cai YC, et al. Predictive factors for the local recurrence and distant metastasis of phyllodes tumors of the breast: a retrospective analysis of 192 cases at a single center. Chin J Canc 2014;33(10):492—500.
[6] Choi N, Kim K, Shin KH, et al. The characteristics of local recurrence after breast-conserving surgery alone for malignant and borderline phyllodes tumors of the breast (KROG 16-08). Clin Breast Canc 2019;19(5):345—53. e342.
[7] Toussaint A, Piaget-Rossel R, Stormacq C, Mathevet P, Lepigeon K, Taffé P. Width of margins in phyllodes tumors of the breast: the controversy drags on?-a systematic review and meta-analysis. Breast cancer research and treatment; 2020.
[8] Chen WH, Cheng SP, Tzen CY, et al. Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. J Surg Oncol 2005;91(3):185—94.
[9] Bumpers HL, Tadros T, Gabram-Mendola S, et al. Phyllodes tumors in African American women. Am J Surg 2015;210(1):74—9.
[10] Neron M, Sajous C, Thezenas S, et al. Surgical margins and adjuvant therapies in malignant phyllodes tumors of the breast: a multicenter retrospective study. Ann Surg Oncol 2020;27(6):1818—27.
[11] Tremblay-LeMay R, Hogue JC, Provencher L, et al. How wide should margins Be for phyllodes tumors of the breast? Breast J 2017;23(3):315—22.
[12] Jang JH, Choi MY, Lee SK, et al. Clinicopathologic risk factors for the local recurrence of phyllodes tumors of the breast. Ann Surg Oncol 2012;19(8):2612—7.
[13] Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, Ballman KV, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. Ann Surg Oncol 2014;21(10):3304—9.
[14] Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw : JNCCN. 2020;18(4):452—78.
[15] Spanheimer PM, Murray MP, Zabor EC, et al. Long-Term outcomes after surgical treatment of malignant/borderline phyllodes tumors of the breast. Ann Surg Oncol 2019;26(7):2136—43.
[16] Gnerlich JL, Williams RT, Yao K, Jaskowiak N, Kulkarni SA. Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base, 1998-2009. Ann Surg Oncol 2014;21(4):1222—30.
[17] Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J 2007;13(6):551—6.
[18] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16(4):e173—180.
[19] Dai D, Jin H, Wang X. Nomogram for predicting survival in triple-negative breast cancer patients with histology of infiltrating duct carcinoma: a population-based study. Am J Cancer Res 2018;8(8):1576—85.
[20] Ganesh V, Drost L, Lee J, et al. A retrospective review of phyllodes tumours of the breast: a single institution experience. Breast 2018;38:52—7.
[21] Ruvalcaba-Limón E, Jiménez-López J, Bautista-Piña V, et al. Phyllodes tumor of the breast: 307 treated cases, the largest Mexican experience at a single breast disease institution. Iranian journal of pathology 2016;11(4):399—408.
[22] Liew KW, Siti Zubaidah S, Doreen L. Malignant phyllodes tumors of the breast: a single institution experience. Med J Malaysia 2018;73(5):297—300.
[23] Demian GA, Fayaz S, El-Sayed Eissa H, et al. Phyllodes tumors of the breast:

analysis of 35 cases from a single institution. J Egypt Natl Canc Inst 2016;28(4):243—8.

[24] Ditsatham C, Chongruksut W. Phyllodes tumor of the breast: diagnosis, management and outcome during a 10-year experience. Canc Manag Res 2019;11:7805—11.

[25] Asoglu O, Ugurlu MM, Blanchard K, et al. Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. Ann Surg Oncol 2004;11(11):1011—7.

[26] Noordman PCW, Klioueva NM, Weimann MN, Borgstein PJ, Vrouenraets BC. Phyllodes tumors of the breast: a retrospective analysis of 57 cases. Breast Canc Res Treat 2020;181(2):361—7.

[27] Mitus JW, Blecharz P, Jakubowicz J, Reinfuss M, Walasek T, Wysocki W. Phyllodes tumors of the breast. The treatment results for 340 patients from a single cancer centre. Breast 2019;43:85—90.

[28] Spitaleri G, Toesca A, Botteri E, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol-Hematol 2013;88(2):427—36.

[29] Lim SZ, Selvarajan S, Thike AA, et al. Breast sarcomas and malignant phyllodes tumours: comparison of clinicopathological features, treatment strategies, prognostic factors and outcomes. Breast Canc Res Treat 2016;159(2):229—44.

[30] Ogunbiyi S, Perry A, Jakate K, Simpson J, George R. Phyllodes tumour of the breast and margins: how much is enough. Canadian journal of surgery Journal canadien de chirurgie 2019;62(1):E19—e21.

[31] Thind A, Patel B, Thind K, et al. Surgical margins for borderline and malignant phyllodes tumours. Ann R Coll Surg Engl 2020;102(3):165—73.

[32] Briggs RM, Walters M, Rosenthal D. Cystosarcoma phylloides in adolescent female patients. Am J Surg 1983;146(6):712—4.

[33] Chua CL, Thomas A. Cystosarcoma phyllodes tumors. Surg Gynecol Obstet 1988;166(4):302—6.

[34] Zhou ZR, Wang CC, Sun XJ, et al. Prognostic factors in breast phyllodes tumors: a nomogram based on a retrospective cohort study of 404 patients. Cancer medicine 2018;7(4):1030—42.

[35] Amerson JR. Cystosarcoma phyllodes in adolescent females. A report of seven patients. Ann Surg 1970;171(6):849—56.

[36] Kim YJ, Kim K. Radiation therapy for malignant phyllodes tumor of the breast: an analysis of SEER data. Breast 2017;32:26—32.

[37] Slodkowska E, Nofech-Mozes S, Xu B, et al. Fibroepithelial lesions of the breast: a comprehensive morphological and outcome analysis of a large series. Mod Pathol : an official journal of the United States and Canadian Academy of Pathology, Inc. 2018;31(7):1073—84.

[38] Warrier S, Hwang SY, Gibbings K, Carmalt H, O'Toole S. Phyllodes tumour with heterologous sarcomatous differentiation: case series with literature review. International journal of surgery case reports 2015;11:91—4.

[39] Cohn-Cedermark G, Rutqvist LE, Rosendahl I, Silfverswärd C. Prognostic factors in cystosarcoma phyllodes. A clinicopathologic study of 77 patients. Cancer 1991;68(9):2017—22.

[40] McKenna AM, Pintilie M, Youngson B, Done SJ. Quantification of the morphologic features of fibroepithelial tumors of the breast. Arch Pathol Lab Med 2007;131(10):1568—73.

[41] Silver SA, Tavassoli FA. Osteosarcomatous differentiation in phyllodes tumors. Am J Surg Pathol 1999;23(7):815—21.

[42] Patil Okaly GV, Devadass CW, Metikurke SH. Malignant phyllodes tumor with heterologous differentiation: a rare case report. J Canc Res Therapeut 2015;11(3):651.

[43] Tsubochi H, Sato N, Kaimori M, Imai T. Osteosarcomatous differentiation in lung metastases from a malignant phyllodes tumour of the breast. J Clin Pathol 2004;57(4):432—4.

[44] Koh VCY, Thike AA, Nasir NDM, Yip GWC, Bay BH, Tan PH. Size and heterologous elements predict metastases in malignant phyllodes tumours of the breast. Virchows Arch : an international journal of pathology 2018;472(4):615—21.

[45] Adamson K, Chavez-MacGregor M, Caudle A, et al. Neoadjuvant chemotherapy does not increase complications in oncoplastic breast-conserving surgery. Ann Surg Oncol 2019;26(9):2730—7.

[46] Abe M, Miyata S, Nishimura S, et al. Malignant transformation of breast fibroadenoma to malignant phyllodes tumor: long-term outcome of 36 malignant phyllodes tumors. Breast Canc 2011;18(4):268—72.

[47] Kuijper A, Buerger H, Simon R, et al. Analysis of the progression of fibroepithelial tumours of the breast by PCR-based clonality assay. J Pathol 2002;197(5):575—81.

[48] Valdes EK, Boolbol SK, Cohen JM, Feldman SM. Malignant transformation of a breast fibroadenoma to cystosarcoma phyllodes: case report and review of the literature. Am Surg 2005;71(4):348—53.

[49] Tan J, Ong CK, Lim WK, et al. Genomic landscapes of breast fibroepithelial tumors. Nat Genet 2015;47(11):1341—5.

[50] Piscuoglio S, Murray M, Fusco N, et al. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. Histopathology 2015;67(5):719—29.

[51] Garcia-Dios DA, Levi D, Shah V, et al. MED12, TERT promoter and RBM15 mutations in primary and recurrent phyllodes tumours. Br J Canc 2018;118(2):277—84.

[52] Piscuoglio S, Ng CK, Murray M, et al. Massively parallel sequencing of phyllodes tumours of the breast reveals actionable mutations, and TERT promoter hotspot mutations and TERT gene amplification as likely drivers of progression. J Pathol 2016;238(4):508—18.

[53] Soumarová R, Seneklová Z, Horová H, et al. Retrospective analysis of 25 women with malignant cystosarcoma phyllodes–treatment results. Arch Gynecol Obstet 2004;269(4):278—81.

[54] Pandey M, Mathew A, Kattoor J, et al. Malignant phyllodes tumor. Breast J 2001;7(6):411—6.

[55] Barth Jr RJ, Wells WA, Mitchell SE, Cole BF. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Ann Surg Oncol 2009;16(8):2288—94.

[56] Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer 2000;89(7):1502—11.

[57] Bouhafa T, Masbah O, Bekkouch I, et al. [Phyllodes tumors of the breast: analysis of 53 patients]. Canc Radiother : journal de la Societe francaise de radiotherapie oncologique 2009;13(2):85—91.

[58] Christensen L, Schiødt T, Blichert-Toft M, Hansen JP, Hansen OH. Sarcomas of the breast: a clinico-pathological study of 67 patients with long term follow-up. Eur J Surg Oncol : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 1988;14(3):241—7.

[59] McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet (London, England) 2014;383(9935):2127—35.