

## Risk Factors for Recurrence of Malignant Phyllodes Tumors of the Breast

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**Abstract.** *Background/Aim:* In this study, the treatment outcome and risk factors for recurrence in patients undergoing surgery with or without adjuvant radiotherapy (RT) for malignant phyllodes tumors of the breast (MPTB) were analyzed. *Patients and Methods:* Forty-three patients (61.4%) underwent breast-conserving surgery (BCS) and 27 (38.6%) underwent mastectomy. Fifteen patients (21.4%) received adjuvant RT. *Results:* With a median follow-up of 76 months, the 7-year local control (LC), distant metastasis-free survival (DMFS), disease-free survival (DFS), and cause-specific survival (CSS) rates were 90.7%, 85.2%, 80.3%, and 87.1%, respectively. Either the extent of surgery or treatment with adjuvant RT did not affect the outcomes. On multivariate analysis, the presence of tumor necrosis was associated with inferior DFS ( $p=0.017$ ), while infiltrative tumor border showed a marginal significance ( $p=0.078$ ). When stratified using these two adverse pathological features, the 7-year DFS rates were 100%, 54.9%, and 55.6% in patients with 0, 1, and 2 risk factors, respectively

( $p=0.002$ ). *Conclusion:* MPTB patients undergoing surgery with or without adjuvant RT had a favorable outcome. Although there was no local recurrence in patients treated with adjuvant RT, the effect of adjuvant RT failed to reach a statistical significance. Risk-grouping based on pathological features might help design a clinical trial for MPTB.

Phyllodes tumors are rare fibroepithelial lesions that account for less than 1% of all primary breast neoplasms (1, 2). In 1981, the World Health Organization (WHO) adopted the term phyllodes tumors and subclassified them into benign, borderline, or malignant tumors according to histopathological characteristics such as stromal cellularity, cellular atypia, mitotic activity, stromal overgrowth, and tumor border (3, 4). The majority of these tumors are benign (35-64%), and the rest are divided into borderline and malignant subtypes (5, 6). Although this classification has been helpful in predicting biological behavior, specific parameters that can define the likelihood of recurrence are not universally accepted (4). Certain studies have suggested the aforementioned histopathological features as prognostic factors (6, 7). On the other hand, other studies have reported that tumor size, necrosis, and adequacy of surgical margins are more important prognosticators (8-11).

Malignant phyllodes tumors of the breast (MPTB), on the contrary to the benign/borderline counterpart, are characterized by aggressive clinical features, propensity for local recurrence and capacity for distant metastasis (2). Given the high rate of local recurrence (LR) and their large tumor size, mastectomy has been the preferred surgical option for MPTB (12-15). Although breast-conserving surgery (BCS) +/- adjuvant radiotherapy (RT) is being frequently performed, there are only limited data on the effect of surgical extent or the benefit of adjuvant RT. In addition, most of the available studies analyzed all subtypes of phyllodes tumors altogether (8-10, 16) or borderline/malignant tumors combined (7, 17, 18). Also, more importantly, there was no randomized trial for

This article is freely accessible online.

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**Key Words:** Breast neoplasm, malignant phyllodes tumor, pathological feature, radiotherapy.

MPTB mainly due to its rarity. A few population-based studies and retrospective ones with a limited number of patients have reported the outcomes of MPTB exclusively (9, 15, 19, 20).

In this study, we analyzed the treatment outcomes of MPTB patients after surgical resection with or without adjuvant RT, and identified the risk factors of recurrence in these patients.

## Patients and Methods

After Institutional Review Board approval, the medical records of patients with phyllodes tumor of the breast who underwent surgical resection at Seoul National University Hospital between December 1991 and January 2014 were retrospectively reviewed. Among them, pathologically diagnosed malignant subtypes were classified according to the WHO classification. Patients with coexisting breast cancer, either invasive carcinoma or carcinoma *in situ*, or with a previous breast cancer history were excluded from the analysis. A total of 70 patients were eligible for this study.

Clinico-pathological information was collected; it included age at diagnosis, tumor size, type of surgery, nodal examination, adjuvant RT, and pathologic features such as resection margin status, tumor necrosis, stromal cellularity, nuclear atypia, mitotic activity, and tumor border. Tumor on inked margin was defined as R1 resection. All available slides were re-evaluated by a single pathologist who was blind to the clinical data, according to WHO guidelines (21).

The primary outcome of interest was LR, defined as tumor recurrence in the ipsilateral breast or chest wall. Distant metastasis (DM), any recurrence (LR or DM), and death from MPTB were second outcomes of interest. These events (LR, DM, any recurrence, and death from MPTB) were used for survival analysis. Time to event was calculated as the date of surgical resection to the occurrence of each event. Actuarial local control (LC), distant metastasis-free survival (DMFS), disease-free survival (DFS), and cause-specific survival (CSS) rates were calculated according to the Kaplan–Meier method, and comparisons between groups were performed using log-rank tests. A Cox proportional hazards model with backward stepwise method was used to identify correlations between outcomes and risk variables. *p*-Values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (release 12.0.1. SPSS Inc., Chicago, IL, USA).

## Results

**Characteristics.** The patient and tumor characteristics of all patients are summarized in Table I. The median age was 42 years (range=19-70 years). The median tumor size was 5.8 cm (range=1.3-25 cm). Forty-three patients (61.4%) underwent BCS and 27 patients (38.6%) underwent mastectomy. Seventeen patients had axillary nodal examination, and one showed nodal metastasis. Fifteen patients (21.4%) were given adjuvant RT; 9 patients (20.1%) after BCS and 6 patients (22.2%) after mastectomy. The median radiation dose was 54.9 Gy (range=50.4-60 Gy). Three patients were treated with adjuvant chemotherapy, including one patient with nodal metastasis. Six patients had involved resection margin after BCS, and one of them was given adjuvant RT.

Table I. Patient, tumor, and treatment characteristics.

Variables	No. of patients	%
Age, years		
≤40	29	41%
>40	41	59%
Tumor size		
≤2 cm	6	9%
2< to ≤5 cm	22	31%
5< to ≤10 cm	26	37%
10< to ≤20 cm	11	16%
> 20 cm	2	3%
Unknown	3	4%
Type of surgery		
BCS	43	61%
Mastectomy	27	39%
Nodal examination		
Yes	17	24%
No	53	76%
Increased cellularity		
Mild-moderate	35	50%
Marked	21	30%
Unknown	14	20%
No. of mitoses		
≤5/HPF	7	10%
>5/HPF	56	80%
Unknown	7	10%
Nuclear atypia		
Mild-moderate	31	44%
Marked	26	37%
Unknown	13	19%
Tumor border		
Pushing	24	34%
Infiltrative	26	37%
Unknown	20	29%
Stromal overgrowth		
Absent	17	24%
Present	36	51%
Unknown	17	24%
Tumor Necrosis		
Absent	33	47%
Present	15	21%
Unknown	22	31%
Resection margin		
Negative	34	49%
Close (≤2mm)	27	39%
Positive	6	9%
Unknown	3	4%
Adjuvant RT		
Yes	15	21%
No	55	79%

BCS: Breast-conserving surgery; HPF: high-power field; RT: radiotherapy.

**Treatment outcomes and patterns of failure.** With a median follow-up of 76 months (range=7-216 months), the 7-year LC, DMFS, DFS, and CSS rates were 90.7%, 85.2%, 80.3%, and 87.1%, respectively. There were 6 LR's; 5 in BCS group and one in mastectomy group. The median time to LR was

Table II. Univariate analyses for local control, distant metastasis-free survival, disease-free survival, and cause-specific survival.

Variables	No. of pts	7-yr LC (%)	p-Value	7-yr DMFS (%)	p-Value	7-yr DFS (%)	p-Value	7-yr CSS (%)	p-Value
Age (yr)			0.218		0.601		0.767		0.819
≤40	29	85.4		88.4		79.3		88.2	
>40	41	95.1		82.7		81.2		86.1	
Tumor size			0.057		0.532		0.681		0.699
≤5 cm	28	100		90.4		75.5		91.1	
>5 cm	39	78.9		86.1		86.1		88.9	
Type of surgery			0.209		0.265		0.629		0.128
BCS	43	90.0		88.7		85.2		91.8	
Mastectomy	27	90.9		79.5		72.3		79.9	
Increased cellularity			0.037		0.030		0.008		0.084
Mild-moderate	35	94.1		94.1		88.6		94.1	
Marked	21	81.8		68.6		63.7		85.7	
No. of mitoses			0.946		0.998		0.484		0.909
≤5	7	85.7		80.0		85.7		80.0	
>5	56	89.7		83.7		76.8		86.0	
Nuclear atypia			0.532		0.395		0.613		0.250
Mild-moderate	31	86.4		89.1		80.2		92.2	
Marked	26	92.9		84.0		78.0		84.6	
Tumor border			0.014		0.196		0.025		0.072
Pushing	24	100		91.3		91.3		95.8	
Infiltrative	26	63.7		75.6		52.8		77.2	
Stromal overgrowth			0.781		0.217		0.303		0.266
Absent	17	91.7		94.1		86.3		93.8	
Present	36	87.5		76.6		69.9		80.1	
Tumor necrosis			0.977		0.007		0.012		0.027
Absent	33	85.6		92.1		82.7		92.7	
Present	15	93.3		65.2		59.3		72.0	
Resection margin			0.000		0.141		0.003		0.074
Uninvolved	61	94.1		87.4		82.1		89.4	
Involved	6	50.0		50.0		50.0		50.0	
Adjuvant RT			0.237		0.865		0.684		0.603
Yes	15	100		86.2		86.2		86.0	
No	55	88.3		85.5		79.1		92.9	

\*Patients with unknown information were not included on univariate analyses. LC: Local control; DMFS: distant metastasis-free survival; DFS: disease-free survival; CSS: cause-specific survival; BCS: breast-conserving surgery; RT: radiotherapy.

25 months (range=5-201 months). All LR's developed in patients not receiving adjuvant RT. Among 6 patients with involved resection margin, 4 experienced LR. One patient treated with adjuvant RT after R1 resection remained disease-free at the time of analysis (80 months from the date of surgical resection). DM occurred in 9 patients, and the site of metastasis was lung in 7 patients, brain in two, bone in one, and soft tissue in one. Two patients experienced LR and subsequent DM, which occurred 37 and 45 months apart. A total of 9 patients were dead at the time of analysis, and 8 of them died of DM of MPTB. The median time from the date of surgical resection to cause-specific death was 28 months. *Prognostic factors affecting recurrences.* The results of univariate analyses of LC, DMFS, DFS, and CSS rates are presented in Table II. The extent of surgery (BCS vs. mastectomy) did not affect LC ( $p=0.209$ , Figure 1A), DMFS

( $p=0.265$ ), DFS ( $p=0.629$ ), and CSS ( $p=0.128$ ). Of note, there was no LR in patients treated with adjuvant RT (Figure 1B). Nevertheless, adjuvant RT did not show improvement in terms of LC ( $p=0.237$ ), DMFS ( $p=0.865$ ), DFS ( $p=0.684$ ), and CSS ( $p=0.603$ ). Univariate analyses of pathologic variables for LC revealed that increased cellularity, infiltrative tumor border, and involved surgical margin were significantly associated with inferior LC ( $p=0.037$ , 0.014, and 0.001, respectively). A tumor size >5 cm was marginally associated with inferior LC ( $p=0.057$ ). Univariate analyses for DMFS revealed that increased cellularity and the presence of tumor necrosis were independent risk factors for inferior DMFS ( $p=0.030$  and 0.007, respectively). As for DFS, increased cellularity, infiltrative tumor border, the presence of tumor necrosis, and involved surgical margin were significantly associated with inferior DFS ( $p=0.008$ , 0.025, 0.012, and

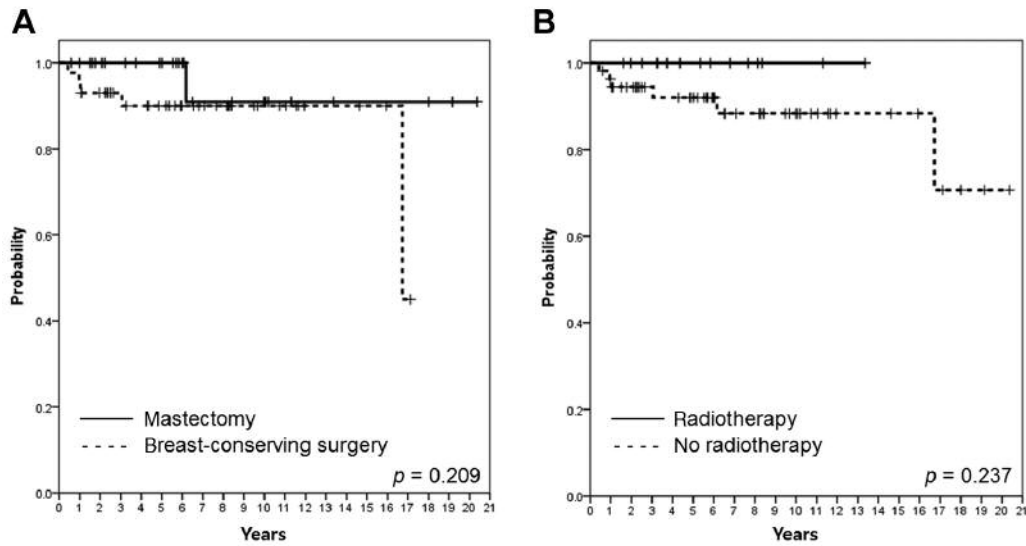


Figure 1. Probability of local control according to (A) type of surgery and (B) adjuvant radiotherapy.

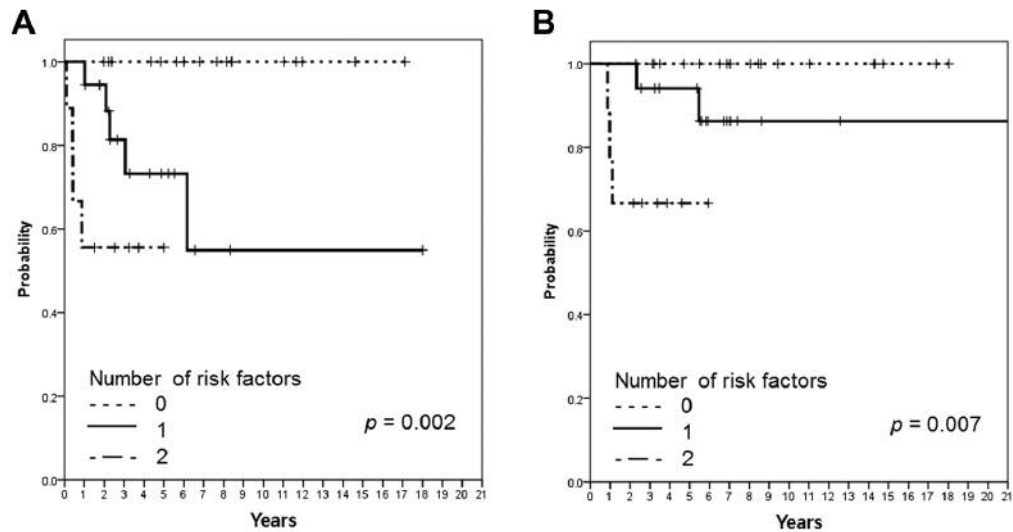


Figure 2. Disease-free survival (A), and cause-specific survival curves (B) according to increasing number of risk factors.

0.003, respectively). Also, the presence of tumor necrosis was the only risk factor for inferior CSS ( $p=0.027$ ), although increased cellularity, infiltrative tumor border, and involved surgical margin were marginally significant ( $p=0.084$ ,  $0.072$ , and  $0.074$ , respectively).

Multivariate analyses were performed incorporating variables with  $p$ -values  $\leq 0.25$  on univariate analyses (22). The presence of tumor necrosis was found to be correlated significantly with inferior DMFS, DFS, and CSS ( $p=0.006$ ,

Table III. Survival rates at 7-year according to increasing number of risk factors.

No. of risk factors	No. of patients	7-yr DFS ( $p=0.002$ )	7-yr CSS ( $p=0.007$ )
0	18	100%	100%
1	18	54.9%	86.3%
2	9	55.6%	66.7%

DFS: Disease-free survival; CSS: cause-specific survival.

Table IV. Reported risk factors predicting inferior local control, distant metastasis-free survival, disease-free survival, and cause-specific survival.

Study	No. of pts	Database	% of RT	LC	DMFS	DFS	CSS
Kapris <i>et al.</i> (23)	34 (48 <sup>a</sup> )	A single institution	6.2% (3/48)	Larger tumor, involved resection margin	Larger tumor, involved resection margin	–	–
Asoglu <i>et al.</i> (24)	50	A single institution	0.04% (2/50)	Stromal overgrowth, larger tumor, margin <1cm	Stromal overgrowth	–	Stromal overgrowth <sup>b</sup>
Macdonald <i>et al.</i> (15)	821	SEER database	9.2% (76/821)	–	–	–	Older age, adjuvant RT
Pezner <i>et al.</i> (11)	478	National Oncology Database	0%	Larger tumor (>2 cm for BCS; >10 cm for mastectomy)	–	–	Older age, larger tumor <sup>b</sup>
Onkendi <i>et al.</i> (7)	52 (67 <sup>a</sup> )	A single institution	6.0% (4/67)	–	–	Larger tumor, high cellularity, mitosis ≥10/10 HPFs, stromal overgrowth	Mitosis ≥10/10 HPFs, stromal overgrowth, high cellularity
Mitus <i>et al.</i> (9)	70	A single institution	8.6% (6/70)	–	–	None	–
This study	70	A single institution	21.4% (15/70)	–	Tumor necrosis, infiltrative tumor border <sup>c</sup>	Tumor necrosis	Tumor necrosis

<sup>a</sup>Sum of borderline and malignant subtype; <sup>b</sup>for overall survival; <sup>c</sup>marginally significant. LC: Local control; DMFS: distant metastasis-free survival; DFS: disease-free survival; CSS: cause-specific survival; BCS: breast-conserving surgery; HPF: high-power field; RT: radiotherapy.

0.017, and 0.030, respectively). Infiltrative tumor border was marginally associated with DFS ( $p=0.078$ ). Any of these variables was not associated with LC.

To identify patients at a higher risk of recurrence, risk stratification was performed according to the number of adverse clinicopathologic features associated with either local or distant recurrence. The presence of tumor necrosis ( $p=0.017$ ) and infiltrative tumor border ( $p=0.078$ ) were selected based on multivariate analyses for DFS. The DFS and CSS rates were significantly different among the three groups ( $p=0.002$  and  $0.007$ , respectively) (Table III and Figure 2).

## Discussion

The optimal local treatment for MPTB is controversial. Given the large tumor size and the high LR rate, a significant number of patients have been treated with mastectomy. However, according to the recent Surveillance, Epidemiology, and End Results (SEER) analysis (20), 58% of patients are treated with BCS, and adjuvant RT is offered in 16% of patients after mastectomy and 11% after BCS. In the current study, 61.4% of patients underwent BCS, and in 22.2% of patients adjuvant RT was given after mastectomy and in 20.1% after BCS. The present study showed that no LR occurred in patients treated with adjuvant RT regardless

of the type of surgery (BCS or mastectomy). Even though statistical significance was not reached, possible benefit from adjuvant RT might be expected because this result may have been influenced by the different treatments the few patients received. Regarding the benefit of adjuvant RT in MPTB, Gnerlich *et al.* noted that adjuvant RT reduced LR (hazard ratio=0.43) via the National Cancer Data Base analysis (19). Belkacemi *et al.* also noted that adjuvant RT increased LC rate in borderline/malignant phyllodes tumors (15). A recent meta-analysis by Zeng *et al.* observed a similar reduction in LR by adjuvant RT (hazard ratio=0.43) in borderline/malignant phyllodes tumors. However, according to the type of surgery, the improved LC was mainly seen in patients treated with BCS, not with mastectomy (17). Although there was no randomized trial on the benefit of adjuvant RT in MPTB, a multicenter prospective trial was conducted, evaluating the efficacy of adjuvant RT after BCS in borderline/malignant phyllodes tumors, and no LR was identified at a median follow-up of 56 months (18).

The capacity for DM as well as LR is a distinguishable feature of MPTB from benign/borderline phyllodes tumors. The reported DM rates of MPTB ranged from 14.3 to 27.0% (9), and the most frequent metastatic site was the lung. The results of our study were consistent with these observations; 9 out of 70 patients (12.9%) developed DM, and 7 had lung

metastasis. Whether LR is associated with DM or instigates DM is not clear. Kapiris *et al.* showed that 11 of 13 patients with DM had developed LR before the diagnosis of DM (23), and Asoglu *et al.* also showed that 8 of 13 patients with DM had a preceding LR (24). On the other hand, Mitus *et al.* reported DM in 10 of 70 patients, but no LR occurred among them (9). Similarly, only 2 patients experienced LR and subsequent DM in the present study.

The widely known risk factors predicting LR includes resection margin involvement, larger tumor size, and pathologic features (Table IV). Two studies, focused on MPTB, reported that involved resection margin was the predictor of LR; Kapiris *et al.* found that tumor size and resection margin were associated with LR (23), and Asoglu *et al.* found that stromal overgrowth, tumor size, and resection margin were significant prognosticators for LR (24). However, the number of MPTB patients was only 34 in the former and 50 in the latter, respectively. The current study included 70 MPTB patients from a single institution, and available pathological slides were reviewed by a single pathologist although some information was still unavailable. On univariate analysis of LC, cellularity, tumor border, and resection margin status were significantly associated with LR, and the statistical significance of tumor size was marginal. As for DM, the aforementioned studies analyzing MPTB showed inconsistent results. The present study showed that the presence of tumor necrosis was the only independent risk factor for inferior DMFS. On the other hand, Kapiris *et al.* reported that tumor size and resection margin were the principal determinants of LR as well as DM (23), and Asoglu *et al.* reported stromal overgrowth as the only significant predictor for DM (24). As for DFS, our study showed that the presence of tumor necrosis was an independent factor predicting inferior DFS, while infiltrative tumor border showed marginal significance. Meanwhile, Onkendi *et al.* conducted a retrospective analysis for borderline/malignant phyllodes tumors and noted that tumor size, mitosis, stromal overgrowth, and cellularity were predictive of DFS (7). Belkacemi *et al.* noted that mitosis, cellular atypia, stromal overgrowth, and tumor necrosis were predictive of DFS on univariate analysis, but the significance disappeared on multivariate analysis for all types of phyllodes tumors.

Although the current study showed an overall favorable LC (90.7% at 7-year) and DMFS (85.2% at 7-year), there might be a certain group of patients at higher risk of recurrence. We performed risk stratification according to 2 prognostic factors associated with either local or distant recurrences: presence of tumor necrosis and infiltrative tumor border. Patients with 2 risk factors showed a 7-year DFS rate of 55.6% and a 7-year CSS rate of 66.7%, whereas all patients with no risk factors survived without recurrence at 7-year. Therefore, high-risk patients might need more intensified treatment, but the

benefit of either adjuvant RT or systemic chemotherapy has not yet been demonstrated in the MPTB. Further studies are needed to elucidate the optimal treatment strategy for these patients, and the risk-grouping suggested here might be helpful in the design of clinical trials in the future.

The present study was retrospectively designed, and therefore, findings from this study should be interpreted with caution. Follow-up period was also relatively short considering the long natural history of phyllodes tumor of the breast. In addition, although all available slides were reviewed by a single pathologist, unknown pathologic features were still common. This might hamper an accurate analysis. Despite these limitations, the strength of our study is that it included exclusively an MPTB cohort, and not benign or borderline subtypes.

In conclusion, this study presented a favorable outcome in MPTB patients treated with surgical resection with or without adjuvant RT. Although there was no LR in patients receiving adjuvant RT, its benefit is still uncertain. Risk stratification was done based on adverse pathological features, and DFS and CSS were well separated according to the number of risk factors. This risk-grouping might help design a clinical trial for MPTB in the future.

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*Received October 20, 2018*

*Revised October 30, 2018*

*Accepted October 31, 2018*