The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08)

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Abstract

Despite margin-negative breast-conserving surgery, malignant and borderline phyllodes tumors show frequent local recurrence. In this large-scale multicenter study we analyzed the characteristics of locally recurrent tumors after initial treatment with breast-conserving surgery alone. Local recurrences almost always occur near the primary tumor bed. Multiple events are relatively common, with each subsequent event showing increasing risk of borderline-to-malignant transformation.

Background: Despite margin-negative breast-conserving surgery (BCS), phyllodes tumors (PT) of the breast show high local recurrence (LR) rates. In this study we aimed to assess the site and grade of LR to identify high-risk patients after initial treatment of malignant and borderline PT using BCS alone. **Patients and Methods:** From 1981 to 2014, 312 patients with malignant (n = 164) and borderline (n = 148) PT were treated using BCS alone at 10 centers. LR was defined as true recurrence (TR) if < 2 cm from the primary tumor bed and as elsewhere failure (EF) if otherwise. **Results:** At a median of 21 months, LR occurred in 17.6% (55 of 312), 18.9% (31 of 164) among malignant and 16.2% (24 of 148) among borderline PT (P = .636). Only 1.9% (6 of 312) had EF. Five-year cumulative LR rates were 14.7% and 35.9% after margin-negative and -positive BCS, respectively ($P < .001$). Positive margin was an independent risk factor for TR ($P = .002$) and EF ($P = .002$). In multivariable competing risk regression of patients with negative margins < 1 cm (n = 115), age < 35 years ($P = .001$), and tumor size ≥ 5 cm ($P = .008$) independently increased LR risk. Of patients who experienced a LR, 30.9% (17 of 55) had a second or third repeated event. Borderline-to-malignant transformation rates increased at each LR event: 4.1% (6 of 148), 12.5% (3 of 24), and 77.8% (7 of 9) at first, second, and third LR, respectively (P = .006). **Conclusion:** LRs almost always develop near the primary tumor bed.

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Many patients experience multiple events, with heightened risk of borderline-to-malignant transformation at each subsequent event. For patients with negative margins < 1 cm, younger age and larger tumor size are independent risk factors for increased LR.

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Introduction

Phyllodes tumors (PT) of the breast are rare fibroepithelial lesions that constitute < 1% of all breast neoplasms.[1] These tumors are classified as benign, borderline, and malignant on the basis of a 3-tiered histologic grading system proposed by the World Health Organization (WHO).[2] Malignant and borderline subtypes have high rates of local recurrence (LR) and are capable of metastasizing to distant sites.[1,3] On the basis of comparable local control (LC) without documented survival difference, the treatment paradigm has shifted from total mastectomy (TM) to breast-conserving surgery (BCS)—a less morbid and cosmetically more preferred approach.[4,5] Guidelines recommend obtaining tumor-free margins of at least 1 cm, but this is frequently unachieved.[6] Positive resection margins are reported in up to 15%, a strong predictor of LR for which re-excision is highly recommended.[7-12]

Despite achieving negative resection margins, 13% to 27% of patients treated with BCS alone experience LR.[10,13-18] In context, adjuvant radiotherapy (RT) is widely suggested in the literature and utilization has substantially increased over the past decades.[5,19-24] In the first and only prospective study conducted by Barth et al, 46 patients received BCS followed by adjuvant RT, of whom none had LR after a mean follow-up of 60 months.[21] A relatively large study of 159 cases collected from the Rare Cancer Network between 1971 and 2003 showed that adjuvant RT improved LC from 59% to 86% at 10 years ($P = .02$).[22] Although several studies describe encouraging outcomes, advocating the oncological effectiveness and safety of adjuvant RT, large-scale data are scarce and indication criteria remain vague.[5,9,16,21,22,25,26] In a precedent retrospective study of 362 cases, malignant and borderline PT treated with BCS alone showed the highest LR rates of 20.2% compared with 10.7% for TM alone, 5.6% for BCS with adjuvant RT, and none for TM with adjuvant RT ($P = .039$).[27] Thus, this study aimed to assess the characteristics of LR in terms of the site and grade of recurrent tumors in patients with malignant and borderline PT initially treated with BCS alone.

Patients and Methods

Patients

Data were extracted from the Korean Radiation Oncology Group (KROG) 16-08 protocol, a multicenter retrospective study that enrolled women who were surgically diagnosed with malignant or borderline PT after BCS or TM between December 1981 and December 2014 at 10 participating centers. Review of medical records was approved by KROG and institutional review boards of each center on the basis of ethical standards of the Declaration of Helsinki. The requirement to obtain written informed consent was waived on the basis of the retrospective design of the study. To assess potential interinstitutional differences in clinical experience and treatment outcomes, participating centers were weighed according to the diagnosis rate and hospital capacity. The diagnosis rate was defined as a ratio of the total number of patients diagnosed with malignant and borderline PT over the follow-up span of each center, calculated as the interval years between the diagnosis of the first and last eligible patient. Hospital capacity was measured as the total number of beds.

The present study included patients with malignant and borderline PT treated with BCS with no additional RT or chemotherapy. Patients with: (1) evidence of distant metastasis (DM) at the time of diagnosis; (2) other malignancy before or after the diagnosis of PT; (3) surgical pathology revealing no residual tumor after initial biopsy; or (4) insufficient follow-up < 1 year were excluded. Patient demographic characteristics, clinicopathologic data, and survival outcomes were recorded. For patients who presented with LR more than once, data regarding the site and grade of up to 3 subsequent recurrent tumors were collected. In total, 312 patients with malignant (n = 164) and borderline (n = 148) PT treated with BCS alone were analyzed.

Definitions

Breast-conserving surgery included excisional biopsy, local excision, lumpectomy, quadrantectomy, and partial mastectomy. Surgical decisions were made at the discretion of the breast surgeon on the basis of clinically estimated tumor size, breast size, the likelihood of obtaining negative margins, cosmesis, and patient preference.

Histologic grading was done by trained breast pathologists on the basis of the 1981 WHO guidelines.[2,4] PT were classified as malignant if the following features were present: marked stromal cellularity and overgrowth, increased nuclear atypia, infiltrative tumor borders, and high mitotic activity of ≥ 10 mitoses per 10 high-power fields. Any PT with heterologous sarcomatous elements were also deemed malignant. Borderline PT were defined as the presence of some, but not all malignant features. Because data spanning over 30 years were collected from multiple centers nationwide, a central pathologic review was not attainable.

Tumor size was measured as the maximum diameter in pathologic evaluation. For tumors with multiple foci in the same breast, size was recorded as the summation of the maximum diameter of each separate tumor. Multifocality and multicentricity were not distinguished. Resection margin was defined as positive if tumors were present "on ink" and as negative if absent. If a re-excision was performed, margin was on the basis of the last procedure.

Local recurrence was defined as pathologically proven tumor recurrence in the previously treated breast. The site of LR was assessed on the basis of the criteria described by Recht et al.[28] LR

was defined as true recurrence (TR) if detected <2 cm from the primary tumor bed and as elsewhere failure (EF) if otherwise. Regional recurrence (RR) was defined as metastasis involving ipsilateral axillary, supraclavicular, or internal mammary nodes. Recurrence outside the ipsilateral breast or regional nodes was defined as DM.

Statistics

We used χ^2 and Fisher exact tests for descriptive statistics. Base of follow-up was defined as the date of last surgery. Optimal cutoff values for dichotomizing continuous variables, such as age and tumor size, were determined by estimating maximally selected log rank statistics.[29] Disease-free survival (DFS) rates were calculated using the Kaplan–Meier method. The 5- and 10-year cumulative incidence rates for LR and TR were estimated using competing risks analysis, where RR, DM, and death were considered competing events.[30] The Gray test for equality was performed to assess the statistical significance of cumulative incidence curves stratified according to clinicopathologic factors. Factors with $P < .10$ were entered for multivariable competing risks regression on the basis of the Fine and Gray model. Because EF was a rare event, univariable and multivariable logistic regression models were adjusted by the Firth penalized likelihood method to reduce bias.[31] Adjusted subdistribution hazard ratios (SHR) and 95% confidence intervals (CIs) were calculated. Two-tailed $P < .05$ was considered to indicate statistically significant differences. All analyses were performed using R version 3.5.1 using the maxstat, cmprsk, and firthlogit packages (http://www.r-project.org) and the Comprehensive R Archive Network.

Results

General Characteristics and Patterns of Failure

The median age at diagnosis was 43 years (Table 1). All patients had unilateral disease, of which 10 patients (n = 312, 3.2%) presented with multiple tumors of 2 or 3 foci. Most tumors were < 5 cm and none of the patients had nodal involvement. Five patients (1.6%) had heterologous sarcomatous elements; liposarcomatous and fibrosarcomatous differentiation were most common. Tumor necrosis was noted in 13 patients (4.2%); all but 1 patient had malignant PT. Resection margin was initially positive in 65 patients (20.8%). Seventeen patients underwent repeat BCS and the remaining 48 patients (15.4%) reluctant to have a second surgery were followed-up without further treatment. In final, 264 patients (84.6%) were treated with margin-negative BCS alone. Data on the minimum negative margin width were available in 122 patients, of whom 7 patients (5.7%) achieved ≥ 1-cm margins. An increase in tumor size demonstrated significant association with inadequate resection margins, either positive or < 1 cm ($P = .010$). Participating centers had a mean diagnosis rate of 1.9 malignant and borderline PT cases per year and a mean capacity of 1395 total beds (see Supplemental Table 1 in the online version), with no statistically significant correlation ($P = 1.000$).

After median follow-up of 5 (range, 1-21) years, 60 patients (19.2%) had treatment failure. DFS rates at 5 and 10 years were 80.7% and 74.8%, respectively. LR occurred in 55 patients (17.6%) at a median 21 (range, 4-201) months after surgery, invariably as the first pattern of failure. Neither LR rates ($P = .636$) nor median time to LR ($P = .966$) differed according to histologic grade: 18.9% (31 of 164) at a median of 21 months for malignant PT and 16.2% (24 of 148) at a median of 21 months for borderline PT. Any LR manifesting later than 5 years was uncommon: 5 patients had TR after 6 to 12 years and 1 patient had EF after 17 years. No contralateral breast tumor recurrence was noted. Although all patients were successfully salvaged with surgery, 30.9% (17 of 55) experienced a second LR. BCS alone was the most common method for initial salvage. After receiving a repeat salvage surgery using local excision or TM, 88.2% (15 of 17) had a third LR. LR rates did not statistically differ according to hospital capacity ($P = 1.000$) or diagnosis rate ($P = 1.000$).

Only 1 patient (0.3%) had RR that occurred after repetitive events of LR. The patient had initially denied re-excision after margin-positive BCS of malignant PT. Eight patients (2.6%) developed DM, all in the lungs and clinically originating from a malignant subtype. DM was the first and sole pattern of failure in 5 patients (1.6%), whereas LR preceded DM in 4 patients (1.3%).

Table 1 Patient and Tumor Characteristics at Initial Diagnosis (n = 312)

Variable	n	Value
Age, Years		
Median	43	13-75
≥35	232	74.4
<35	80	25.6
Histologic Grade		
Malignant	164	52.6
Borderline	148	47.4
Number of Tumors		
Single	302	96.8
Multiple	10	3.2
Tumor Size, cm		
Median	4	0.4-16.0
<5	190	60.9
≥5	122	39.1
Nodal Evaluation		
No	294	94.2
Yes	18	5.8
High Mitotic Activity		
No	146	46.8
Yes	141	45.2
Not reported	25	8.0
Margin Status		
Negative	264	84.6
Positive	48	15.4
Negative Margin Width, cm (n = 264)		
>0 and <1	115	43.6
≥1	7	2.7
NR	142	53.8

Data are presented as % or range, except where otherwise stated.

The time between LR and DM ranged from 1 to 4 years. Three patients (1.0%) died because of disease progression.

Local Recurrence-Related Risk Factors

Although multiple tumors or necrosis were uncommon findings, patients who presented with such features had particularly high 5-year cumulative LR rates > 40% (Table 2). Positive margin was shown to be a critical risk factor, with nearly 50% experiencing LR at 10 years after surgery. None of the 7 patients who achieved the recommended ≥ 1 cm margins had tumor recurrence, whereas those with negative margin width < 1 cm showed cumulative LR rates of 15.9% at 5 years and 23.9% at 10 years. In multivariable competing risks regression, age < 35 years ($P = .028$), tumor size ≥ 5 cm ($P = .018$), necrosis ($P = .019$), and positive margin ($P < .001$) were independently significant risk factors for LR (Table 2).

LR risk was further stratified by comparing 115 patients with known negative margin width < 1 cm (see Supplemental Table 2 in the online version). DFS rates at 5 and 10 years in this subgroup were 81.4% and 73.0%, respectively. LR developed in 18.3% (21 of 115). Competing risk cumulative LR incidence curves showed statistical differences according to age (Figure 1A; $P = .007$) and tumor size (Figure 1B; $P = .036$). Significance was also retained in multivariable analysis, with SHRs of 4.6 for age < 35 years (95% CI, 1.8-11.5; $P = .001$) and 3.4 for tumor size ≥5 cm (95% CI, 1.4-8.3; $P = .008$).

True Recurrence and EF

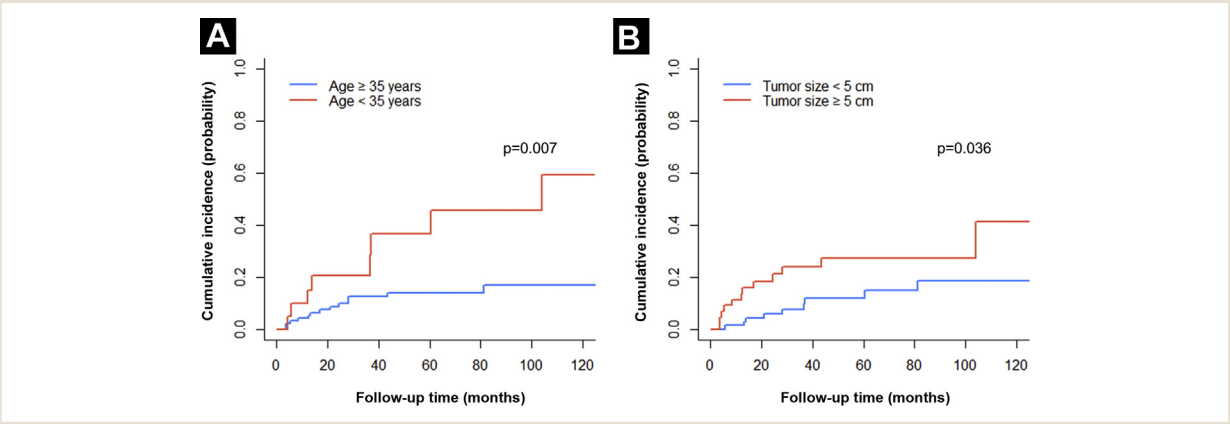
Approximately 90% (49 of 55) of all LRs developed within 2 cm from the primary tumor bed (Table 3). Competing risks analysis for TR was adjusted for competing events including EF, RR, DM, and death. In multivariable regression, age ($P = .044$), tumor size ($P = .027$), necrosis ($P = 15$), and positive margin ($P = .002$) were strongly associated with TR. For patients with negative margin width < 1 cm (n = 115), risk of TR independently increased with age < 35 years ($P = .001$), and tumor size ≥ 5 cm ($P = .008$).

Table 2 Factors Associated With LR Risk (n = 312)

	Crude LR Rates			Competing Risks Analysis				
				Cumulative LR Incidence Rates			Multivariable Analysis	
	n	%	P[a]	5 Years, %	10 Years, %	P[b]	SHR (95% CI)	P[c]
Age, Years								
≥35	34/232	14.7	.030	14.6	18.4	.013	1	.028
<35	21/80	26.2		27.8	39.6		1.9 (1.1-3.2)	
Histologic Grade								
Borderline	24/148	16.2	.636	17.9	25.4	.977	—	—
Malignant	31/164	18.9		17.7	22.9			
Number of Tumors								
Single	51/302	16.9	.080	16.9	23.1	.056	1	.321
Multiple	4/10	40.0		42.9	42.9		1.8 (0.6-5.3)	
Tumor Size, cm								
<5	23/190	12.1	.002	13.0	17.7	.003	1	.018
≥5	32/122	26.2		25.2	32.6		1.9 (1.1-3.3)	
Nodal Evaluation								
No	53/294	18.0	.749	18.2	24.5	.437	—	—
Yes	2/18	11.1		11.5	11.5			
High Mitotic Activity[d]								
No	21/146	14.4	.272	14.0	22.2	.418	—	—
Yes	28/141	19.9		19.8	24.8			
Necrosis								
No	50/299	16.7	.059	16.8	23.0	.043	1	.019
Yes	5/13	38.5		41.3	41.3		3.1 (1.2-7.9)	
Margin Status								
Negative	37/264	14.0	<.001	14.7	19.6	<.001	1	<.001
Positive	18/48	37.5		35.9	48.8		3.1 (1.7-5.6)	

Abbreviations: LR = local recurrence; SHR = subdistribution hazard ratio.
[a] χ^2 and Fisher exact tests.
[b] Gray test for equality.
[c] Competing risks regression using the Fine and Gray model.
[d] Analysis of available data.

Figure 1 Competing Risk Cumulative Incidence Curves for Local Recurrence in Patients With Negative Margins <1 cm (n = 115) Compared According to (A) Age and (B) Tumor Size



Elsewhere failure was observed in 6 patients (1.9%). Crude rates for EF were significantly high if margin status was positive (8.3%, 4 of 48 for positive margins vs. 0.7%, 2 of 264 for negative margins; P = .006). EF rates at 5 years were 10.7% for positive margin and 1.1% for negative margin ($P = .002$). All other clinicopathologic factors had no significant predictive value.

Malignant Transformation at Recurrence

Recurrent PT at first LR was significantly more likely to have the same grade as its initial form. Locally recurrent tumors showing malignant features were observed in 12.8% (21 of 164) and 4.1% (6 of 148) of initially malignant and borderline PT, respectively ($P = .006$). Among patients who experienced multiple events of LR, PT unvaryingly recurred as a malignant subtype if the previous LR had also been malignant, or if the event was a third LR. Although malignant transformation at first LR was relatively infrequent, the proportion of initially borderline PT showing histologic upgrading at recurrence increased at each subsequent event: 4.1% (6 of 148), 12.5% (3 of 24), and 77.8% (7 of 9) at first, second, and third LRs, respectively (Figure 2). Borderline-to-malignant transformation occurred in a total of 7.4% (11 of 148) during the follow-up duration, of which most had the aforementioned high-risk features of LR: younger age, larger tumor, or necrosis. These patients also had a shorter median time to first LR of 13.1 (range, 3.5-80.1) months compared with 21.9 (range, 4.3-70.8) months for those whose tumor recurred as borderline or benign PT ($P = .301$).

Discussion

The need for incorporating adjuvant RT after initial BCS in malignant and borderline PT is increasingly being emphasized. Several studies describe encouraging effects, but results are generally restricted to small numbers and indications for patient selection continue to be debated.[21,22,32] In this study we evaluated competing risk incidence rates of LR in patients initially treated with BCS alone to better define the potential need for adjuvant local therapy.

Positive margin is a strong predictor of LR, for which the literature widely recommends re-excision or adjuvant whole-breast RT because of potential risk of metastatic spread and tumor-related mortality.[22,23,33] Cosmetic morbidity is also another concern, because salvage therapy for LR demands repeat BCS or TM. In this study, 37.5% (18 of 48) had LR after margin-positive BCS alone, showing increased risk of TR ($P = .002$) and EF ($P = .002$). Although generally a rare event in PT, 8.3% (4 of 48) with positive margin experienced EF ($P = .006$).

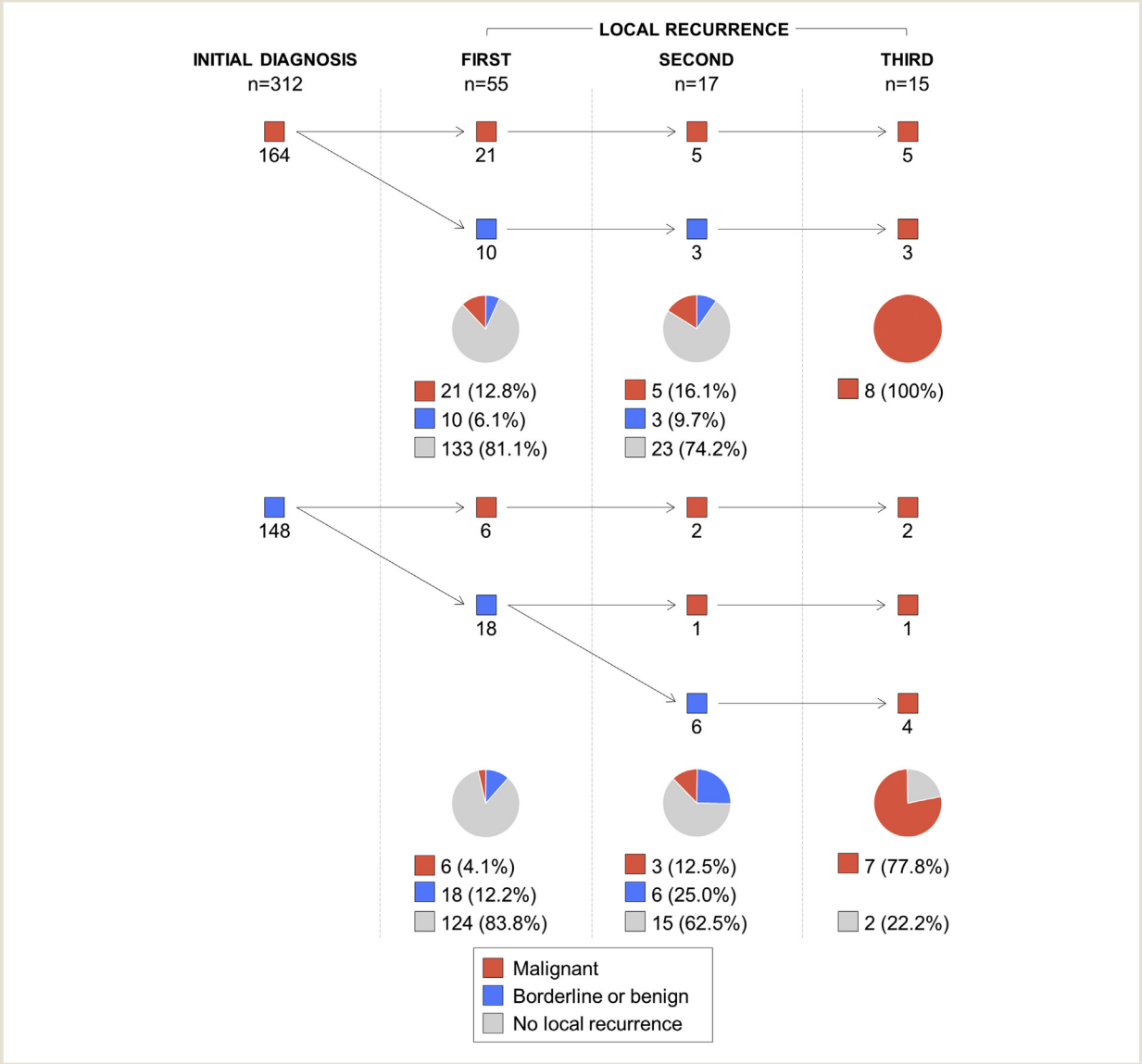
Several studies have reported that tumor-free margin status is most critical for decreasing LR risk and improving survival.[3,33-36] But despite margin-negative BCS, 14.7% experienced LR at 5 years after surgery. High LR rates were observed regardless of histologic grade ($P = .636$). Patients who achieved wide margins ≥1 cm, as recommended by treatment guidelines, showed excellent LC rates. If negative margins were <1 cm, LR risk significantly increased in patients with younger age (SHR, 4.6; $P = .001$) or large tumor size (SHR, 3.4; $P = .008$). In a retrospective study of 172 patients with

Table 3 Site of LR

Site of LR	Malignant PT (n = 164)		Borderline PT (n = 148)		P^a	All (n = 312)	
	n	%	n	%		n	%
TR	27	16.5	22	14.9	.756	49	15.7
EF	4	2.4	2	1.4	.687	6	1.9
No LR	133	81.1	124	83.8	.555	257	82.4

Abbreviations: EF = elsewhere failure; LR = local recurrence; PT = phyllodes tumor; TR = true recurrence.
[a] χ^2 test and Fisher exact test.

Figure 2 The Change of Histologic Grade at Each Subsequent Event of Local Recurrence



PT of any subtype, Spitaleri et al reported age <35 years, necrosis, and positive margin as independently significant predictors of any tumor-related recurrence. When limiting the analysis to malignant and borderline PT, only age remained significant.[37] Jang et al[36] showed increasing risk of LR with increasing tumor size and Kapiris et al[33] showed that tumors exceeding 10 cm had 7 times higher incidence of LR. Necrosis was an uncommon pathologic finding observed in 4.2% of all malignant and borderline PT, comparable with reports ranging from 3.9% to 6.0%, showing a negative prognostic effect (SHR, 3.1; $P = .019$) as supported by previous studies.[35,37,38] Although prognostic significance was not retained in analyses for negative margin width < 1 cm, it should be noted that only few cases had necrosis in this subgroup, causing limited statistical evaluation. The prognostic value of clinicopathologic factors aside from margin status has been inconsistently reported and defining an appropriate cutoff value for variables such as age or tumor size is a controversial issue.[14,36] Careful interpretation of results is warranted because most reports on PT include a large fraction of benign and small numbers of malignant PT.

In recent decades, BCS with adjuvant RT has become a widely accepted method for patients at risk of LR. Guidelines suggest following radiation principles for soft tissue sarcomas, but without detailed instructions.[6] Most studies report conventionally fractionated RT >50 Gy to the whole breast, followed by >10 Gy to the tumor bed.[9,10,18,21,39] Considering the low risk of EF, 1.1% at 5 years for margin-negative BCS alone ($P = .002$), whether irradiation of the whole breast is necessary is an issue to be contemplated. For properly selected patients with invasive breast carcinomas treated with BCS, randomized evidence has shown that accelerated partial breast RT results in LR rates comparable with that of whole-breast

Table 4 Local Recurrence of Malignant and Borderline PTs Reported During the Past 15 Years

Reference	Median Follow-up, Years	Positive Margin Rates, %	LR of Malignant and Borderline PT Definitively Treated With Surgery					Malignant Transformation of Initially Borderline PT					
			Any Margin BCS or TM		Margin-Negative BCS Alone		Site of LR After BCS	First LR[a]		Second LR[b]		Third LR[b]	
			n	%	n	%		n	%	n	%	n	%
Tan et al[38,c]	1.8	53	18/85	21[d]		–	–	3/54	6	1/11	9	1/3	33
Fou et al[13,c]	1.2	0	5/26	19[d]	4/17	24	–		–		–		–
Ben Hassouna et al[7]	3.6	13	10/44	23[d]		–	–	1/16	6		–		–
Lenhard et al[15]	6.0	0	8/32	25	4/16	25	–		–		–		–
Barrio et al[14,c]	2.0	11	12/90	13[d]	5/40	13	–		–		–		–
Karim et al[44,c]	5.3	–	6/31	19[d]		–	–	1/23	4		–		–
Kim et al[16,c]	5.4	15	13/48	27	9/36	25	–	3/33	9		–		–
McCarthy et al[45]	–	–	2/20	10[d]		–	Same quadrant (all)	1/16	6		–		–
Onkendi et al[17,c]	10.0	6	16/67	24	8/31	26	–		–		–		–
Xiao et al[24]	–	–	10/52	19[d]		–	Tumor bed (all) Other quadrant (1.6%)[e]	0/41	0		–		–
Borhani-Khomani et al[8]	8.2	13	8/89	9[d,f]		–	–	1/89	1		–		–
Tremblay-LeMay et al[46]	5.0, 5.4[g]	3	2/33	6		–	Tumor bed (all)	1/20	5	0/2	0	1/2	50
Rodrigues et al[10,c]	5.4	11	6/38	16[d]	4/15	27	–		–		–		–
Zhou et al[18,c]	3.8	2	47/226	21[d]	41/171	24	–	0/20	0		–		–
Sum			163/881	19	75/326	23		11/312	4	1/13	8	2/5	40
Present Study	4.2	15	55/312	18	37/264	14	TR (15.7%), EF (1.9%)	6/148	4	3/24	13	7/9	78
Total Sum, Including Present Study			218/1193	18	112/590	19		17/460	4	4/37	11	9/14	64

Abbreviations: BCS = breast-conserving surgery; EF = elsewhere failure; LR = local recurrence; PT = phyllodes tumor; TM = total mastectomy; TR = true recurrence.
[a]Per patients with initially borderline PT.
[b]Per patients with previous LR of an initially borderline PT.
[c]Pathologic review performed.
[d]Surgery alone.
[e]Simultaneous LR (includes benign PT).
[f]Borderline PT only.
[g]Median for malignant and borderline PT, respectively.

RT despite the theoretical concern of omitting tumors that might be present in other areas of the breast.[40-42] Compared with invasive breast carcinomas, PT rarely present as multiple tumors—3.2% in our series and 0.9% to 2.7% in literature—and almost always recur within 2 cm of the primary tumor bed.[10,38,43] Although therapeutic evaluation in a prospective and controlled manner is warranted, partial breast RT could be a feasible option in a carefully selected group of patients with low risk for LR.

Many reports have shown the potential risk for malignant transformation from previously low grade PT.[8,34,38] First LR from a borderline PT is likely to be nonmalignant ($P = .006$), but risk of upgrading was shown to increase with subsequent events: 4.1% (6 of 148), 12.5% (3 of 24), and 77.8% (7 of 9) at first, second, and third LRs, respectively. Although BCS alone for borderline PT is likely to be adequate as an initial definitive approach, integration of adjuvant RT as salvage therapy might be needed at the first LR event because of the risk of malignant transformation.

A literature review of data published in the past 15 years was done to compare LR rates of malignant and borderline PT graded according to the 1981 WHO guideline (Table 4).[7,8,10,13-18,24,38,44-46] Fourteen studies were identified, of which 23% (range, 13%-27%) among 326 pooled patients in 7 studies had LR after margin-negative BCS alone.[7,8,10,13-18,24,38,44-46] Three studies reported on the site of LR: all occurred at the primary tumor bed or previously treated quadrant.[24,45,46] Xiao et al reported 1.6% (2 of 127) to have synchronous LR in a different quadrant, but this study included mostly benign PT and lacked details on initial and recurrent histologic grade.[24] As in the present study, malignant transformation of initially borderline PT occurred in 4% (11 of 312). The histologic grade of subsequent locally recurrent tumors was rarely reported, but generally showed increasing rates of malignant transformation with each recurrence (from 8% to 40%).

This study was limited by the lack of a central pathologic review to validate diagnostic uniformity. The multicenter retrospective design and follow-up range spanning 30 years precluded the pooling of specimens. As an alternative, 40.4% (126 of 312) with report of all WHO parameters and 26.3% (82 of 312) with archived slides at the highest-contributing center were collectively reviewed. Hematoxylin and eosin-stained slides were reviewed by a trained breast pathologist and diagnostic agreement was confirmed by a single physician. In the context of histologic transformation upon recurrence, 6.1% (10 of 164) of initially malignant PT showed downgrading to borderline or benign subtypes. Thus, the possibility of diagnostic discrepancy because of the presence of multiple foci of mixed histopathologic features cannot be excluded. Another limitation was the inability to define an optimal margin width, a topic of considerable controversy. Most pathology reports lacked information on the width of negative margins. Among those with adequate data, only 5.7% (7 of 122) achieved $\geq$1 cm width. The literature shows similar rates ranging from 1.1% to 3.0%.[36,46] Although failure to obtain wide margins is not currently an absolute indication for further therapeutic intervention, the high rates of LR after BCS alone indicate a need for refining the association between margin width and recurrence risk.[6]

With acknowledgment of limitations, our study provides treatment outcomes of a large data set of malignant and borderline PT and, to our knowledge, is the first to specifically focus on the site and grade of locally recurrent tumors in a homogenously treated cohort. Although the literature widely suggests the need for adjuvant RT, there is a lack of prospective data and randomized evidence. The role of adjuvant chemotherapy or hormone therapy is questionable, with no clear benefit being described.[47,48] Future prospective studies will be needed to establish risk-adapted RT strategies, particularly to identify low-risk patients for whom irradiation fields might safely be reduced.

Conclusion

In summary, locally recurrent malignant and borderline PT almost always occur near the primary tumor bed and 2 or more repeated events is not uncommon. Although malignant transformation is infrequent at the first event, histologic upgrading increases with each subsequent LR. For patients with negative margins $<$ 1 cm, younger age and larger tumor size are independent risk factors for increased LR.

Clinical Practice Points

- Phyllodes tumors of the breast show high rates of LR despite BCS with tumor-free margins.
- Although guidelines suggest $\geq$1 cm margins, this is often unachieved.
- Our study provides treatment outcomes of a large data set of malignant and borderline PT and is, to our knowledge, the first to specifically focus on the site and grade of locally recurrent tumors in a homogenously treated cohort.
- Among patients treated with BCS with tumor-free margins $<$1 cm, those with younger age or larger tumor size have heightened risk of LR and should be considered for adjuvant RT.
- Patients with PT rarely present with multiple tumors and recurrence almost always occurs near the primary tumor bed.
- Elsewhere failure is rare, occurring in only 1.9% of all patients.
- Although evaluation in a prospective and controlled manner is warranted, partial breast RT could be a feasible option in carefully selected patients with low LR risk.
- When LR occurs, many patients experience 2 or more subsequent events.
- Although the first LR from a borderline PT is likely to be nonmalignant, risk of malignant transformation increases at each subsequent event.
- Breast-conserving surgery alone for borderline PT might be adequate as an initial definitive approach, but integration of adjuvant RT as salvage therapy might be needed after the onset of a LR.
- Future prospective studies will be needed to establish risk-adapted RT strategies, particularly to identify low-risk patients for whom irradiation fields might safely be reduced.

Disclosure

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

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.04.003.

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Supplemental Data

Supplemental Table 1 Comparison According to Participating Center (n = 312)

Center	Total Beds	Malignant and Borderline PT		Follow-up Span, Years[a]	Diagnosis Rate, Number Per Year	LR		DM	
		n	%			n	%	n	%
1	1792	82	26.3	22	3.7	10	12.2	3	3.7
2	1983	66	21.2	19	3.5	11	16.7	3	4.5
3	571	35	11.2	11	3.2	3	8.6	0	0.0
4	2700	28	9.0	15	1.8	8	28.6	0	0.0
5	1108	25	8.0	13	1.9	4	16.0	0	0.0
6	1332	18	5.8	15	1.2	3	16.7	0	0.0
7	2048	17	5.4	12	1.5	2	11.8	0	0.0
8	759	15	4.8	19	0.8	7	46.7	1	6.7
9	786	14	4.5	17	0.8	6	42.9	1	7.1
10	867	12	3.8	17	0.7	1	8.3	0	0.0

Abbreviations: DM = distant metastasis; LR = local recurrence; PT = phyllodes tumor.
[a]Years between the diagnosis date of the earliest and latest eligible patient enrolled at each center.

Supplemental Table 2 Factors Associated With LR Risk in Patients With Negative Margins < 1 cm (n = 115)

	Crude LR Rates			Competing Risks Analysis				
				Cumulative LR Incidence Rates			Multivariable Analysis	
	n	%	P[a]	5 Year, %	10 Year, %	P[b]	SHR (95% CI)	P[c]
Age, Years								
≥35	13/95	13.7	.010	14.0	17.0	.007	1	.001
<35	8/20	40.0		36.5	59.2		4.6 (1.8-11.5)	
Histologic Grade								
Borderline	7/55	12.7	.219	13.5	19.7	.292	—	—
Malignant	14/60	23.3		21.3	30.2			
Number of Tumors								
Single	20/113	17.7	.333	16.9	25.8	.417	—	—
Multiple	1/2	50.0		50.0	50.0			
Tumor Size, cm								
<5	6/71	12.7	.085	11.9	18.4	.036	1	.008
≥5	12/44	27.3		27.2	41.3		3.4 (1.4-8.3)	
Nodal Evaluation								
No	19/109	17.4	.301	16.7	25.3	.152	—	—
Yes	2/6	33.3		NA	NA			
High Mitotic Activity[d]								
No	9/60	15.0	.548	17.1	21.3	.616	—	—
Yes	11/52	21.2		17.7	28.3			
Necrosis								
No	19/110	17.3	.225	16.7	25.5	.181	—	—
Yes	2/5	40.0		40.0%	NA			

Abbreviations: LR = local recurrence; NA = not applicable; SHR = subdistribution hazard ratio.
[a] χ^2 and Fisher exact tests.
[b] Gray test for equality.
[c] Competing risks regression using the Fine and Gray model.
[d] Analysis of available data.