의학석사 학위논문

A retrospective multicenter study on malignant and borderline phyllodes tumors of the breast

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Abstract

Purpose: Despite surgical resection of malignant and borderline phyllodes tumors (PT), 9–24% of patients show local recurrence (LR). Recent studies demonstrate increasing utilization of adjuvant radiation therapy (RT) after breast-conserving surgery (BCS) with improvements in local control (LC). This retrospective multicenter study aimed to evaluate the patterns of failure after surgical resection of malignant and borderline PT, identify factors associated with LC, and evaluate the site and histologic grade of locally recurrent tumors that occur after treatment by BCS alone.

Methods: From 1981 to 2014, 362 patients with malignant (n=235) and borderline PT (n=127) were treated by BCS or total mastectomy (TM) at 10 centers. Thirty-one patients received adjuvant RT and those who received adjuvant chemotherapy were excluded from the study. LR was defined as true recurrence (TR) if detected < 2 cm from the primary tumor bed or surgical clips, if available. Any LR presenting outside of this boundary was defined as an elsewhere failure (EF).

Results: Median follow-up was 5 years. LR developed in 60 (16.6%) patients. Regional recurrence occurred in 2 (0.6%) and distant metastasis developed in 19 (5.2%) patients. Patients receiving BCS (p=0.025) and those not undergoing adjuvant RT (p=0.041) showed higher LR rates. After BCS alone (n=247), TR and EF occurred in 44 (17.8%) and 6 (2.4%) patients. Patients with malignant PT were more likely to recur as malignant compared to those with borderline PT (p=0.019). However, 28.6% (6 of 21) of borderline PT recurred as malignant (p=0.008). Five-year LC rates for malignant PT treated by BCS alone, BCS with adjuvant RT, TM alone, and TM with adjuvant RT were 80.7%, 93.3%, 92.4%, and 100%, respectively (p=0.033). Multivariate analyses revealed BCS alone, tumor size ≥ 5 cm, and positive margins as independent risk factors for LR. Margin-positive BCS alone showed poorest LC regardless of tumor size (62.5%, p=0.007). For margin-negative BCS alone, 5-year LC rates for tumor size ≥ 5 cm vs. those < 5 cm were 71.8% vs. 89.5% (p=0.012). For borderline subtypes, only positive margins (p=0.044) independently increased the risk of LR. DM developed exclusively in

malignant subtypes. Prior LR after initial BCS alone increased the risk of DM by near 8-fold (95% CI 1.3-48.7, p=0.028).

Conclusions: Margin-positive BCS is inadequate therapy for both malignant and borderline PT, with dismal LC and high EF rates. Re-excision or adjuvant whole breast irradiation is advised. LR after BCS alone significantly increases the risk of developing DM, thus achieving LC is crucial for malignant PT. Though margin-negative BCS alone seem suitable for malignant PT < 5 cm, there is heightened risk of LR for larger tumors, suggesting the need of adjuvant RT.

Keywords: malignant phyllodes tumor; borderline phyllodes tumor; breast neoplasm; adjuvant therapy; recurrence; risk factor

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List of Abbreviations

BCS, breast-conserving surgery

CI, confidence interval

DFS, disease-free survival

DM, distant metastasis

DMFS, distant metastasis-free survival

EF, elsewhere failure

KROG, Korean Radiation Oncology Group

HR, hazard ratio

LC, local control

LR, local recurrence

PT, phyllodes tumor

RR, regional recurrence

RT, radiation therapy

TM, total mastectomy

TR, true recurrence

WHO, World Health Organization

Introduction

Phyllodes tumors (PT) are uncommon fibroepithelial lesions that account for 0.3–1% of primary breast neoplasms, characterized by increased stromal proliferation and a "leaf-like" tumor growth that show cystic spaces lined by epithelium [1-3]. Majority manifest in women in the fifth decade of life and tend to be large in size, reaching 5 cm at average and exceeding 30 cm in rare cases [4]. These tumors lie on a spectrum of varying morphologic features and can clinically resemble a range of disease entities, from benign fibroadenomas to more aggressive soft tissue sarcomas [5-7]. The 1981 World Health Organization (WHO) histologic grading system classifies PT into benign, borderline, and malignant subtypes based on semi-objective assessment of histopathologic parameters, of which approximately 60% are benign and 20% are malignant [8, 9]. Local recurrence (LR) is the predominant pattern of failure for all subtypes, but potential for distant metastasis (DM) increases towards the malignant end of the spectrum [3, 10-12].

The standard treatment is wide local excision with the intention of obtaining tumor-free margins ≥ 1 cm by means of either total mastectomy (TM) or breast-conserving surgery (BCS) [13]. Though TM was historically suggested for all subtypes—without definite documentation of survival benefits—the use of BCS has demonstrated comparable treatment outcomes and is now the more preferred approach [2, 3, 9, 12-15]. Based on data of recent reports of > 50 malignant and borderline PT cases, LR occurs in 9–24% of patients with median onset at 2 years after initial definitive surgery [7, 14, 16-21]. Due to the difficulty of distinguishing this disease entity on pre-surgical fine needle aspiration cytology or core needle biopsy, risk of underdiagnosis and undertreatment persists to be an issue [6, 10, 11, 22]. Wide margins are often unachieved and 15% of patients have residual microscopic tumor at resection margins [3, 5]. Positive margins are a strong predictor of LR for which re-excision is advised [23, 24]. Though PT generally has good prognosis, with 5-year cancer-specific survival rates reaching 80–92%, patients that develop DM suffer rapid progression and have high risk of mortality [19, 25, 26]. DM occurs in 2–24% and literature indicates that 60–85% of these patients have a history of prior LR. But whether LR increases the risk of

subsequent DM is uncertain [16, 27-32].

Contemporary literature indicates that up to 21% of patients treated by BCS as the sole therapeutic approach experience LR despite achieving negative margins [14, 21, 33, 34]. In light of the high rates of LR, the use of adjuvant radiation therapy (RT) has noticeably increased over the past 30 years and is becoming a widely accepted approach in patients suspected at risk [25, 26, 35, 36]. Several retrospective studies describe improved LC, with a rise of 10-year LC rates from 59% to 86% (p=0.02) [21, 37-39]. In the only prospective study published to date, Barth et al. demonstrated excellent LC after margin-negative BCS with adjuvant RT [14]. Reports show that adjuvant RT is generally prescribed for malignant PT, to the whole breast, and by following principles used for soft tissue sarcoma [13]. But with the absence of randomized controlled trials and literature limited to small numbers of malignant and borderline cases, existing data are inconclusive on how management of malignant and borderline PT should be approached. Thus, this study aimed to (1) evaluate the patterns of failure after surgical resection of malignant and borderline PT, (2) identify factors associated with LC, and (3) evaluate the site and histologic grade of locally recurrent tumors that occur after treatment by BCS alone.

Materials and Methods

Patients

This retrospective multicenter study was registered as a protocol of the Korean Radiation Oncology Group (KROG 16-08) and participated by 10 academic-based medical centers in Korea, as listed in the Appendix. Women diagnosed with primary malignant or borderline PT of the breast after the publication of the 1981 WHO classification guideline and treated with definitive surgery by means of BCS or TM between December 1981 and December 2014 were identified. Patient exclusion criteria included (1) presentation of DM at the time of diagnosis, (2) use of chemotherapy during initial treatment, (3) diagnosis of other malignancy before or after the diagnosis of PT, and (4) follow-up duration less than 2 years. A total of 362 patients were analyzed.

Review of medical records was approved by the KROG review committee and institutional review boards of each participating center in accord to the ethical standards of the Helsinki Declaration. Requirement to obtain written informed consent was exempted. Data pertaining to demographic, clinicopathologic, and follow-up variables were acquired from each participating center and collectively analyzed by a single physician. For patients with multiple events of LR, data for the site and histologic grade of each subsequent locally recurrent tumors were obtained for up to 3 events. Treatment center characteristics were weighed by diagnosis rate and capacity. Diagnosis rate was defined as the ratio of total patients diagnosed with malignant and borderline PT at each center to follow-up duration, calculated as the interval years between the first and last eligible patient enrolled. Capacity was measured as the number of total hospital beds.

Pathology

Histopathologic diagnosis and grading was based on evaluation of surgical specimens and performed by specialized breast pathologists according to the 1981 WHO classification guideline (Table 1) [8, 9]. PT was defined as malignant if all malignant features or heterologous sarcomatous elements were present. If some, but not all malignant features were satisfied, PT was defined as borderline. Though a central pathologic review was not attainable due to the multicenter retrospective

design of this study, available data pertaining to the WHO parameters were collectively reviewed by a single physician to confirm diagnostic agreement.

Table 1. WHO classification guideline for PT of the breast

Parameters	Benign features	Borderline features	Malignant features
Stromal cellularity	Minimal	Moderate	Marked
Stromal atypia	Minimal	Moderate	Marked
Mitosis (per 10 HPF)	0–4	5–9	≥ 10
Tumor margin	Pushing	Pushing or infiltrating	Infiltrating
Stromal overgrowth	Uniform	Heterogeneous	Marked

Abbreviations: WHO, World Health Organization; PT, phyllodes tumor; HPF, high-power field

Treatment

All patients received surgical resection without prior neoadjuvant treatment. BCS was defined as local tumor excision with a margin of normal breast tissue, including wide local excision, lumpectomy, quadrantectomy, and partial mastectomy. TM was defined as removal of the entire unilateral breast tissue, including simple mastectomy, radical mastectomy, and modified radical mastectomy. Pathologic tumor size was measured from the maximum diameter on gross evaluation of surgical specimens. In cases presenting with multiple synchronous tumors in the same breast, size was recorded as the summation of the maximum diameter of each separate tumor. Whether these tumors were multifocal or multicentric was not distinguished.

Data on resection margin status (negative or positive) and margin width (minimum margin clear of tumor cells) were collected. Positive margins were defined as microscopic presence of tumor cells “on ink”. Among negative margins, close margins were defined as those < 2 mm. For patients that received a subsequent surgery due to initially positive margins, the type of surgery and final status of resection margins were recorded according to the last surgical procedure.

Because nodal involvement is known to be rare in PT of the breast, routine surgical evaluation of sentinel or axillary lymph nodes was not done [13]. The selection of surgical procedures and utilization of adjuvant RT was made at the discretion of the breast surgeon and radiation oncologist based on clinically estimated tumor size, breast size, likelihood of achieving tumor-free resection margins, and patient preference.

Definition of recurrence

LR was defined as pathologically proven tumor recurrence involving the previously treated ipsilateral breast after BCS or chest wall after TM. The site of LR occurring in patients that received BCS were clinically evaluated according to the criteria described by Recht et al. [37]. A true recurrence (TR) was defined as LR detected within a radial distance < 2 cm from the primary tumor bed or surgical clips, if available. Any LR presenting outside of this boundary was defined as an elsewhere failure (EF).

Regional recurrence was defined as pathologically proven metastatic disease involving ipsilateral axillary, supraclavicular, or internal mammary nodes. Distant metastasis was defined as the recurrence of PT occurring anywhere outside of the ipsilateral breast or regional nodes.

Statistical analyses

Patient distribution was compared with independent samples t-test for continuous variables. Chi-squared test and Fisher's exact test for categorical variables. Means and medians were compared using the Mann-Whitney U test. Base of follow-up was defined as the date of surgical resection. LC probability, disease-free survival (DFS), and DM-free survival (DMFS) rates were estimated using the Kaplan-Meier method and log-rank tests. Clinicopathologic factors with no missing data were included for univariate analyses. Factors with $p < 0.1$ and those previously documented to have potential prognostic value were entered for multivariate analyses using Cox proportional hazards models. Hazard ratios (HR) and 95% confidence intervals (CI) were computed. All statistical analyses were performed in R version 3.4.2 (http://www.r-project.org). Statistical significance was defined as $p < 0.05$ with a two-tailed approach.

Results

All patients (n=362)

Patient and treatment characteristics

The histologic grade of PT was malignant in 235 (64.9%) and borderline in 127 (35.1%) patients. Follow-up was longer for malignant subtypes, at median 6 (range 2–31) years compared to 5 (range 2–20) years for borderline (p=0.003). Most patients were diagnosed in their thirties or forties (Table 2).

Table 2. Patient and treatment characteristics (n=362)

	All (n=362)		Malignant PT (n=235)		Borderline PT (n=127)		
Variables	n	(%)	n	(%)	n	(%)	p*
Age (years)							
Median (range)	43	(13–75)	43	(13–75)	45	(14–72)	0.095
Multiple lesions							
No	346	(95.6)	226	(96.2)	120	(94.5)	0.593
Yes	16	(4.4)	9	(3.8)	7	(5.5)	
Tumor size (cm)							
Median (range)	5.0	(0–38.0)	5.0	(0–32.0)	4.0	(1.0–38.0)	0.027
Surgery							
BCS	265	(73.2)	153	(65.1)	112	(88.2)	< 0.001
TM	97	(26.8)	82	(34.9)	15	(11.8)	
Adjuvant RT							
No	331	(91.4)	206	(87.7)	125	(98.4)	< 0.001
Yes	31	(8.6)	29	(12.3)	2	(1.6)	
Combined modality							
BCS	247	(68.2)	137	(58.3)	110	(86.6)	< 0.001
BCS+RT	18	(5.0)	16	(6.8)	2	(1.6)	
TM	84	(23.2)	69	(29.4)	15	(11.8)	
TM+RT	13	(3.6)	13	(5.5)	0	(0)	
Axillary evaluation							
None	294	(81.2)	176	(74.9)	118	(92.9)	< 0.001
SLNB	47	(13.0)	41	(17.4)	6	(4.7)	
ALND	21	(5.8)	18	(7.7)	3	(2.4)	
Initial RM							
Negative	307	(84.8)	209	(88.9)	98	(77.2)	0.005
Positive	55	(15.2)	26	(11.1)	29	(22.8)	
Final RM							
Negative	324	(89.5)	219	(93.2)	105	(82.7)	0.003
Positive	38	(10.5)	16	(6.8)	22	(17.3)	

* Chi-squared and Fisher's exact test

Abbreviations: PT, phyllodes tumor; BCS, breast-conserving surgery; TM, total mastectomy; RT, radiation therapy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RM, resection margin

All patients had unilateral disease and presentation as multiple lesions was uncommon. Among malignant PT, heterologous sarcomatous elements were observed in 6 (2.6%) patients, with differentiation resembling liposarcoma in 3 patients, fibrosarcoma in 2 patients, and leiomyosarcoma in 1 patient. The median pathologic size of tumors ranged from no residual after diagnostic biopsy to 38.0 cm. Malignant PT had significantly larger size (p=0.027).

BCS without nodal evaluation was the most common approach to definitive treatment. BCS was done in 265 (73.2%) patients. After initial surgery, 15.2% (55 of 362) had positive margins: 18.9% after BCS (50 of 265) and in 5.2% after TM (5 of 97). Of these, 17 patients underwent re-excision and achieved negative margins, 2 patients received adjuvant RT, and 36 patients were closely followed-up without further treatment. A final 10.5% (38 of 362) had positive margins on final pathologic evaluation: 13.2% after BCS (35 of 265) and 3.1% after TM (3 of 97).

Patients with malignant PT ($p < 0.001$) or with tumors ≥ 5 cm ($p < 0.001$) were more likely to receive TM over BCS. Among the 97 patients who received TM, 82 (84.5%) patients had malignant PT and 80 (82.5%) patients had tumors ≥ 5 cm. Sixty-eight (18.8%) patients received surgical nodal evaluation. A mean of 3 sentinel lymph nodes (range 1–9) and 12 axillary lymph nodes (range 1–42) were dissected: none had pathologic nodal disease.

Thirty-one patients received adjuvant RT with conventional fractionation: all but 2 patients had malignant PT. The 2 patients that received adjuvant RT for borderline PT both had tumors < 5 cm treated by margin-negative BCS and remained disease-free for > 10 years of follow-up. Among patients that received adjuvant RT, 18 (58.1%) patients had tumors ≥ 5 cm and 2 patients had positive margins (6.5%). After BCS (n=18), 16 patients received whole breast irradiation (median 50.4 Gy, range 50.4–60.4), of which 9 patients received a subsequent tumor bed boost (median 9 Gy, range 9–10 Gy). For 2 patients, partial breast irradiation to the tumor bed was given up to 60 Gy. Both patients had malignant PT treated by margin-negative BCS and were disease-free for > 5 years of follow-up. After TM (n=13), 13 patients received chest wall irradiation (median 50.4 Gy, range 50.4–60), of which 3 patients also received elective nodal irradiation.

Participating centers had a median diagnosis rate of 1.4 person-years (range 0.8–3.6) and a median capacity of 1220 total hospital beds (range 571–2700). When

capacity was dichotomized by the median, rounded to the nearest hundreds, larger centers with ≥ 1200 total hospital beds showed statistical correlation with higher diagnosis rates (p=0.001). Significantly more patients with malignant PT were treated at larger centers (p=0.001). Therapeutic approach did not vary by treatment center (Supplement Table 1). However, patients treated at smaller centers had significantly higher rates of initial positive margins of 23.0% vs. 11.6% (p=0.008). This difference was compensated by re-excision, reaching similar rates of final positive margins (p=0.813).

Patterns of failure

Seventy-one (19.6%) patients had tumor recurrence (Table 3). The overall 5-year DFS was 81.5% for malignant PT and 81.4% for borderline PT (p=0.974). Sixty (16.6%) patients had LR, invariably as the first pattern of failure. The median time to LR was approximately 2 years after initial definitive surgery. Eight of 60 (13.3%) patients presented with LR later than 5 years. Crude rates (p=0.557) and onset of LR (p=0.856) did not differ by histologic grade. Among patients that manifested heterologous sarcomatous elements, 1 patient with fibrosarcomatous differentiation experienced LR as the only pattern of failure. Patients treated at smaller centers had higher rates of LR with marginal significance (Supplement Table 1, p=0.078). The 5-year LC rates were 77.2% and 87.6% for patients treated at centers with total hospital beds < 1200 and ≥ 1200, respectively (p=0.048). Statistical significance was not retained when individually analyzed by malignant (p=0.151) and borderline PT (p=0.294).

Table 3. Patterns of failure (n=362)

	All (n=362)	Malignant PT (n=235)	Borderline PT (n=127)	
Variables	n (%)	n (%)	n (%)	p*
Failure				
Local	60 (16.6)	37 (15.7)	23 (18.1)	0.557
Regional	2 (0.6)	2 (0.9)	0 (0)	0.543
Distant	19 (5.2)	19 (8.1)	0 (0)	< 0.001
Death	10 (2.8)	10 (4.3)	0 (0)	0.017

* Chi-squared and Fisher's exact test
Abbreviations: PT, phyllodes tumor; LR, local recurrence

Association between LR rates and treatment type was assessed as individual factors of surgery and adjuvant RT and also conjunctively as a combined modality approach. Individually, treatment by BCS (p=0.025) and no adjuvant RT (p=0.041) showed higher rates of LR (Table 4). LR occurred in 16.1% (37 of 230) of patients after margin-negative BCS and in 40.0% (14 of 35) of patients after margin-positive BCS.

Width of negative margins after BCS was reported for 37.8% (87 of 230) of patients with malignant and borderline PT. The median width was 2.0 mm (range 0.5–20) and margins ≥ 1 cm was achieved in 5.7% (5 of 87). LR occurred in 17.2% (15 of 87): median width was 1.0 mm (range 0.5–5). Though no correlation was found between LR and decreasing margin width (p=0.726), BCS with close margins < 2 mm demonstrated poor LC parallel to that of positive margins (Supplement Figure 1, p=0.333) and marginally inferior to that of margins ≥ 2 mm (p=0.061).

Table 4. LR rates by treatment type (n=362)

	All (n=362)			Malignant PT (n=235)			Borderline PT (n=127)		
	LR			LR			LR		
Variables	n	(%)	p*	n	(%)	p*	n	(%)	p*
Surgery									
BCS	51/265	(19.2)	0.025	30/153	(19.6)	0.037	21/112	(18.8)	1.000
TM	9/97	(9.3)		7/82	(8.5)		2/15	(13.3)	
Adjuvant RT									
No	59/331	(17.8)	0.041	36/206	(17.5)	0.057	23/125	(18.4)	1.000
Yes	1/31	(3.2)		1/29	(3.4)		0/2	(0)	
Combined modality									
BCS	50/247	(20.2)	0.039	29/137	(21.2)	0.049	21/110	(19.1)	0.823
BCS+RT	1/18	(5.6)		1/16	(6.2)		0/2	(0)	
TM	9/84	(10.7)		7/69	(10.1)		2/15	(13.3)	
TM+RT	0/13	(0)		0/13	(0)		–		

n presented as recurred patients/all patients
* Chi-squared and Fisher's exact test
Abbreviations: LR, local recurrence; PT, phyllodes tumor; BCS, breast-conserving surgery; TM, total mastectomy; RT, radiation therapy

Of the 31 patients that received adjuvant RT, only 1 patient (3.2%) experienced LR. This patient was initially treated for malignant PT by margin-negative BCS and adjuvant RT of 50.4 Gy to the whole breast, followed by a tumor bed boost of 9 Gy. She presented with LR 3 years after surgery, again as malignant, and was

successfully salvaged by TM. A disease-free status was maintained for > 5 years of follow-up.

Among all types of combined modality approaches, treatment by BCS alone had highest rates of LR (p=0.039). Kaplan-Meier survival estimates for LC also demonstrated poorest outcomes in patients treated by BCS as the sole therapeutic approach (Figure 1a, p=0.017), while the addition of adjuvant RT after BCS showed a marginal trend towards improved LC (p=0.079) with non-inferiority to TM alone (p=0.490). Subgroup comparison by histologic grade revealed that the type of treatment only influenced outcomes of patients with malignant PT (Figure 1b, p=0.033). The 5-year LC rate for malignant PT treated by BCS alone was 80.7%, significantly worse compared to 93.3% for BCS with adjuvant RT, 92.4% for TM alone, and 100% for TM with adjuvant RT. For borderline subtypes, no statistical difference between treatment modality was observed (Figure 1c, p=0.610).

RR and DM were observed only with malignant PT. Two (0.6%) patients had RR, both with synchronous detection of pulmonary DM. The first patient had previously experienced LR 1 year after treatment by BCS alone and was salvaged by TM and adjuvant RT. After a disease-free interval of 4.5 years, metastatic disease was found in the ipsilateral axillary nodes and lungs. The second patient, without prior LR, showed simultaneous regional and distant failure 1 year after initial treatment with TM and adjuvant RT. Metastatic disease involved the ipsilateral supraclavicular and internal mammary nodes and lungs. After multi-regimen palliative chemotherapy, both patients expired 1–1.5 years from onset of systemic relapse.

DM developed in 19 (5.2%) patients at median 3 (range 1–11) years after surgery. The 5-year DMFS was 92.7% and in 11 (3.0%) patients, DM was the first and sole pattern of failure. Lungs were the most common site of DM (15 of 19), followed by the bones (5 of 19). Other rare sites included the brain, distant nodes, liver, and soft tissue. No contralateral breast tumor recurrence was noted. A successfully salvaged LR preceded DM in 42% (8 of 19). Median time from LR to DM was 3 (range 1–5) years.

Ten (2.8%) patients died at median 5 (range 2–11) years after surgery, of which 8 had DM: 5 patients with DM only, 2 patients with DM after a prior LR, and 1

patient with RR and DM after a prior LR. Median time from DM to death was 1 (range 0–4) year.

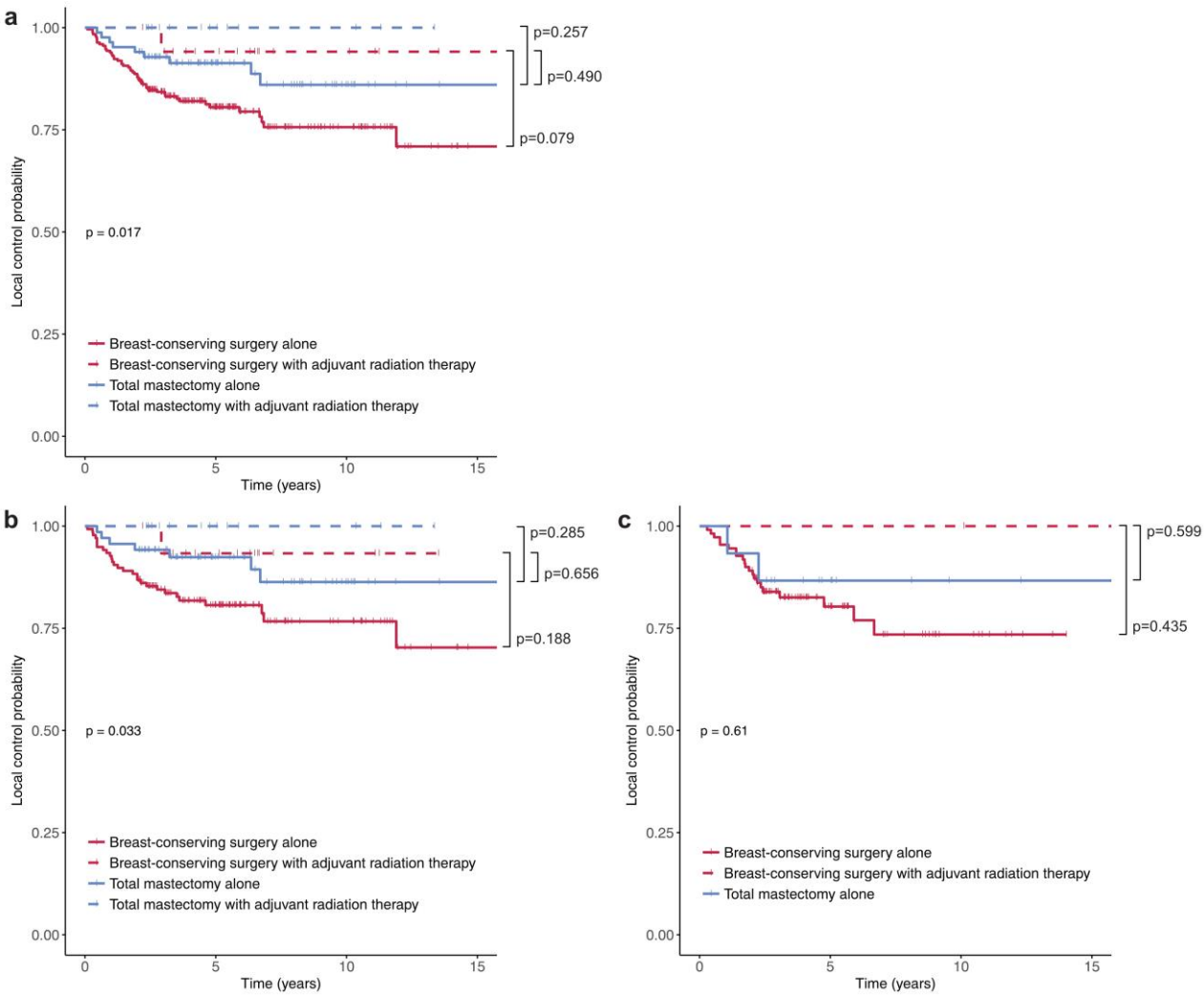

Figure 1. LC by treatment type

LC probability compared between the types of combined modality treatment for (a) malignant and borderline PT (n=362), (b) malignant PT only (n=235), and (c) borderline PT only (n=127).

Patients after surgery alone (n=331)

Risk factors for LC after BCS or TM alone (n=331)

Subgroup analyses were performed for 331 patients treated with surgery alone, by means of either BCS or TM, to identify potential prognostic factors (Table 5). Multivariate analysis for malignant PT (n=206) manifested significantly heightened risk of LR in BCS (p=0.023), tumor size ≥ 5 cm (p=0.024), and positive margins (p=0.044). Patients presenting with multiple lesions showed unsatisfactory LC rates, but without statistical significance (p=0.144). For borderline PT (n=125), only positive margins (p=0.044) was associated with increased LR risk.

Table 5. Risk factors of LC after BCS or TM alone (n=331)

	Malignant PT (n=206)				Borderline PT (n=125)			
	UVA		MVA		UVA		MVA	
Variables	5-year LC	p*	HR (95% CI)	$p^{\dagger}$	5-year LC	p*	HR (95% CI)	$p^{\dagger}$
Age (years)								
< 40	80.5%	0.204	Reference	0.592	74.9%	0.228	Reference	0.245
≥ 40	87.4%		0.8 (0.4-1.7)		83.5%		0.6 (0.3-1.4)	
Tumor size (cm)								
< 5	88.2%	0.103	Reference	0.024	81.2%	0.819	Reference	0.974
≥ 5	81.5%		2.3 (1.1-4.8)		81.0%		1.0 (0.4-2.4)	
Multiple lesions								
No	85.2%	0.117	Reference	0.144	82.1%	0.204	Reference	0.436
Yes	60.0%		3.0 (0.7-13.2)		60.0%		1.8 (0.4-8.3)	
Surgery								
TM	92.4%	0.027	Reference	0.023	86.7%	0.528	Reference	0.860
BCS	80.7%		2.7 (1.1-6.5)		80.3%		1.1 (0.2-5.3)	
Final RM								
Negative	85.6%	0.001	Reference	0.044	85.1%	0.017	Reference	0.044
Positive	67.3%		2.5 (1.0-6.2)		63.6%		2.5 (1.0-6.1)	

*Kaplan-Meier method and log-rank test

†Cox proportional hazards regression model

Abbreviations: LC, local control; BCS, breast-conserving surgery; TM, total mastectomy; PT, phyllodes tumor; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; RM, resection margin

The prognostic magnitude of factors associated with risk of LR was further stratified by surgery type. For malignant PT treated by BCS (n=137), positive margins (n=12) resulted in a 5-year LC rate of 62.5% (Figure 2, p=0.007), significantly the worst regardless of tumor size (p=0.518). For margin-negative BCS (n=125), patients with tumor size ≥ 5 cm had poorer 5-year LC rates of 71.8%

opposed to 89.5% for tumor size < 5 cm (p=0.012). Non-inferiority to TM was assessed with respect to tumor size. BCS for tumor size ≥ 5 cm manifested most unfavorable prognosis (Figure 3, p=0.004), whereas BCS for tumor size < 5 cm showed comparable outcomes to that of TM (p=0.660). Five-year LC rates were 71.8%, 89.5%, and 92.2%, respectively. In patients with borderline PT treated by BCS (n=110), positive margins was the single factor correlated with LC (p=0.020).

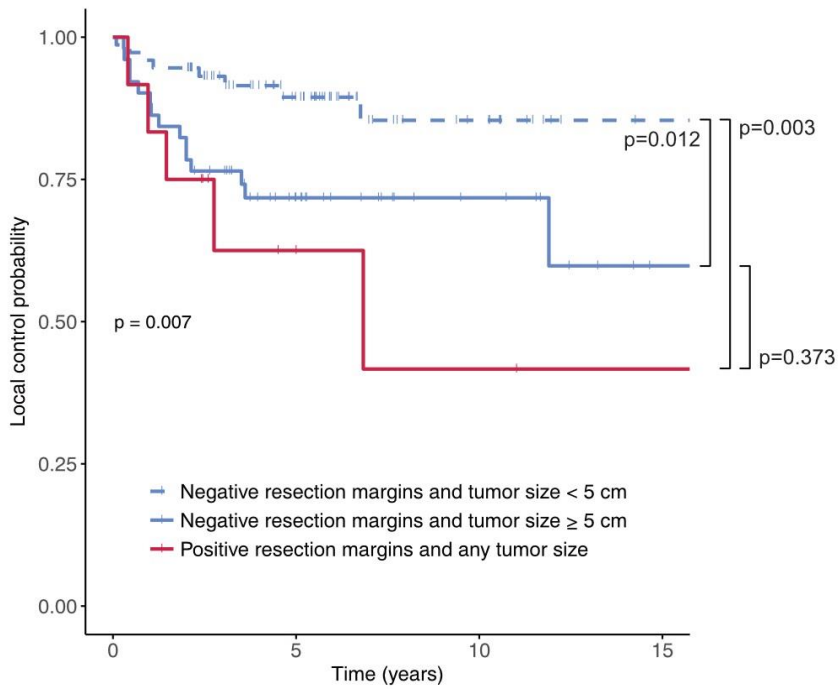

Figure 2. LC by margin status and tumor size

LC probability of malignant PT treated by BCS alone (n=137), stratified by resection margin status and tumor size.

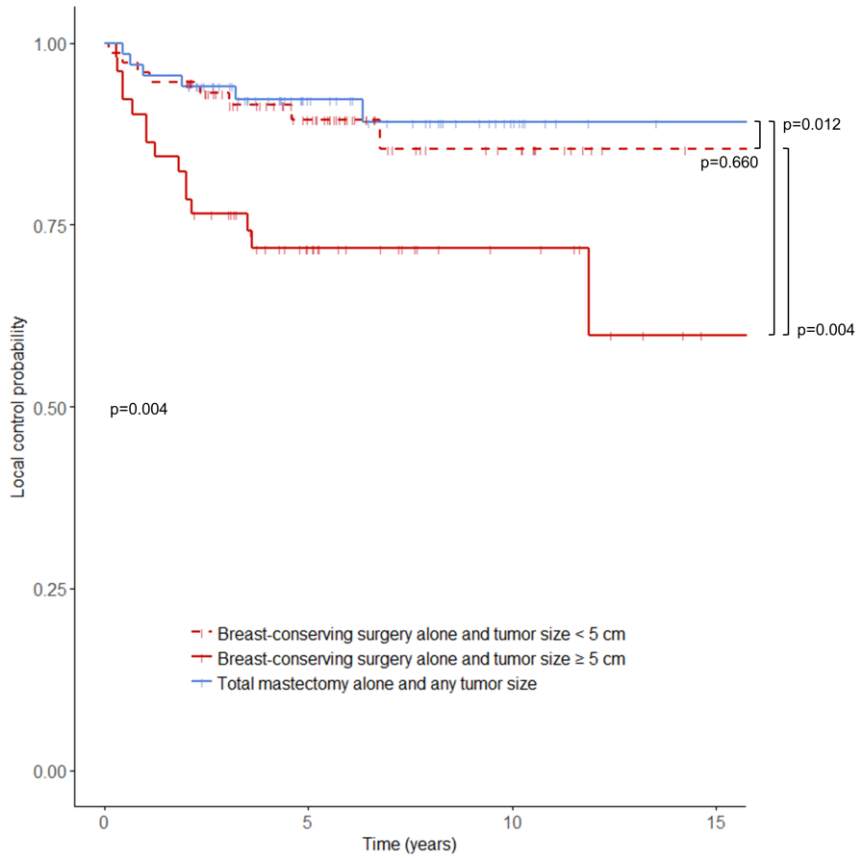

Figure 3. LC by surgery type and tumor size

LC probability for patients with malignant PT treated by margin-negative BCS or TM alone (n=192), stratified by surgery type and tumor size.

Site and grade of LR after BCS alone (n=247)

Fifty (20.2%) patients had LR after treatment by BCS alone (n=247), of which majority was TR (Figure 4). EF was generally rare, arising in 2.4% of patients. The median time to TR was 17 months (range 4–143), while the onset for EF was at median 38 months (range 21–201) after surgery. There was no statistical difference between the site of LR and initial histologic grade (p=0.882). TR and EF were respectively observed in 25 (18.2%) and 4 (2.9%) patients with malignant PT (n=137) and in 19 (17.3%) and 2 (1.8%) patients with borderline PT (n=110). Though presentation as multiple lesions resulted in higher TR rates (Table 6) and significantly worse 5-year TR-free survival of 55.6% (p=0.013), it was not identified as an independent prognostic factor. EF rates were significantly higher among patients with positive margins (p=0.004): 11.8% compared to 0.9% for

those with negative margins. No statistical difference of EF rates were seen with other factors.

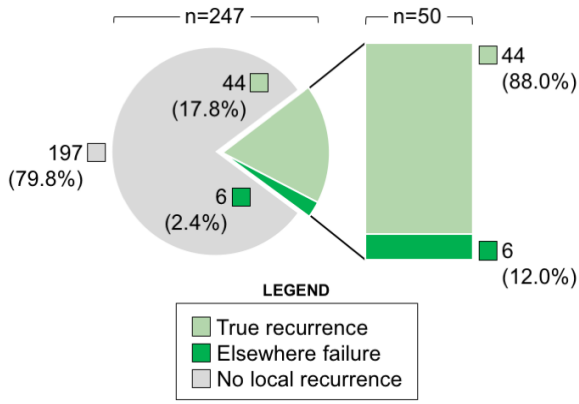

Figure 4. Site of locally recurrent tumors

Site of locally recurrent tumors (n=50) in patients with malignant and borderline PT treated by BCS alone (n=247).

Table 6. LR rates by site of recurrence after BCS alone (n=247)

	True recurrence (n=44)		Elsewhere failure (n=6)	
Variables	n (%)	*p**	n (%)	*p**
Initial histologic grade				
Malignant PT	25/137 (18.2)	0.869	4/137 (2.9)	0.695
Borderline PT	19/110 (17.3)		2/110 (1.8)	
Age (years)				
< 40	21/92 (22.8)	0.124	4/92 (4.3)	0.199
≥ 40	23/155 (14.8)		2/155 (1.3)	
Tumor size (cm)				
< 5	22/149 (14.8)	0.130	2/149 (1.3)	0.218
≥ 5	22/98 (22.4)		4/94 (4.1)	
Multiple lesions				
No	40/238 (16.8)	0.056	6/238 (2.5)	1.000
Yes	4/9 (44.4)		0/9 (0)	
Final RM				
Negative	34/213 (16.0)	0.087	2/213 (0.9)	0.004
Positive	10/34 (29.4)		4/34 (11.8)	

* Chi-squared and Fisher's exact test

Abbreviations: LR, local recurrence; BCS, breast-conserving surgery; PT, phyllodes tumor; RM, resection margin

For initially malignant PT, 69.0% (20 of 29) recurred again as malignant and 31.0% (9 of 29) recurred as borderline or benign. Patients with malignant PT at initial diagnosis were more likely to recur with malignant histologic grade compared to those with borderline PT (p=0.019). However, 28.6% (6 of 21) of borderline PT with LR show up-grading to malignant subtypes (p=0.008). Salvage

treatment for LR consisted of BCS alone for 35 (70.0%) patients, BCS followed by adjuvant RT for 5 (10.0%) patients, and TM alone for 10 (20.0%) patients. Data of subsequent second and third events of LR were compared to investigate changes of histologic grades with each event (Figure 5). After successful salvage of LR, 34.0% (17 of 50) experienced a second LR: 15 patients had been salvaged by BCS alone and 2 patients had previously been salvaged by TM alone. Despite another repeat salvage surgery, by means of local excision or, 88.2% (15 of 17) recurred a third time. The proportion of patients recurring as malignant subtypes increased with each subsequent event, reaching 100% and 77.8% at the third LR in patients with initially malignant and borderline PT, respectively.

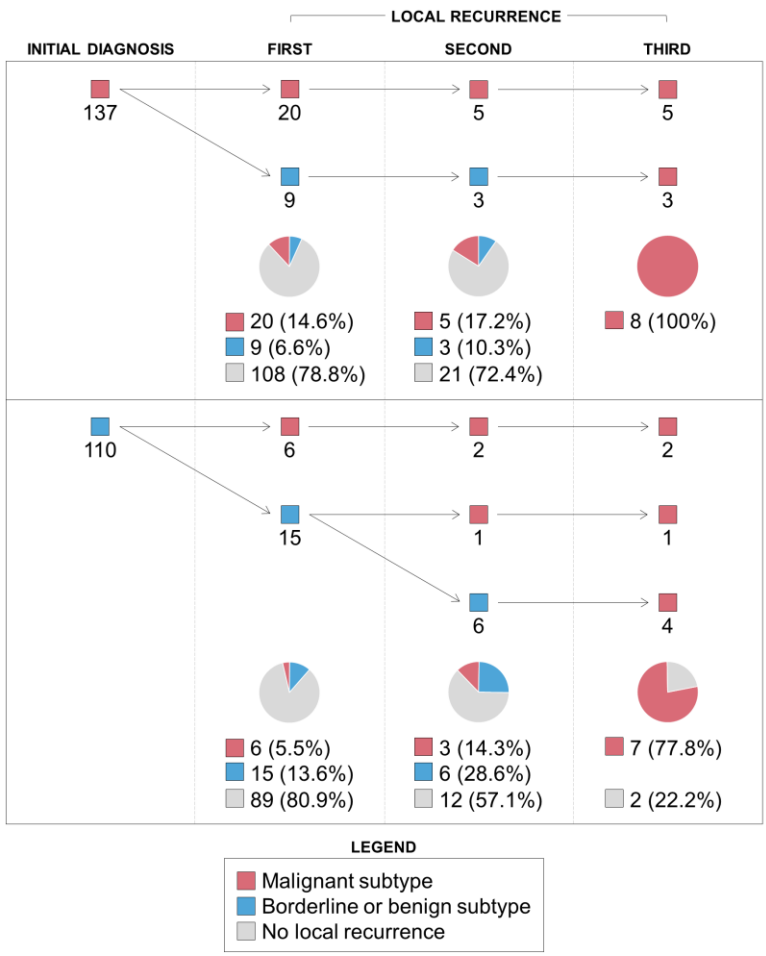

Figure 5. Change of histologic grade with multiple LR

Change of histologic grade with multiple events of LR in patients with malignant and borderline PT treated by BCS alone (n=247).

DM in malignant PT after BCS alone (n=137)

Clinicopathologic factors were investigated for association with risk of DM in patients with malignant PT treated by BCS alone (Table 7). DMFS rates were 92.7% at 5 years. On univariate analysis, presentation as multiple lesions demonstrated significantly worse DMFS (p=0.049), but did not retain significance on multivariate analysis. History of prior LR was the sole significant independent risk factor for DM after initial treatment by BCS alone, with a HR of 7.8 (95% CI 1.3-48.7, p=0.028).

Table 7. Risk factors of DMFS in malignant PT after BCS alone (n=137)

	UVA		MVA	
Variables	5-year DMFS	p*	HR (95% CI)	$p^{\dagger}$
Age (years)				
< 40	97.8%	0.162	Reference	0.084
≥ 40	91.9%		7.6 (0.8-76.3)	
Tumor size (cm)				
< 5	94.7%	0.683	Reference	0.638
≥ 5	94.3%		1.5 (0.3-8.9)	
Multiple lesions				
No	95.5%	0.049	Reference	0.338
Yes	66.7%		3.3 (0.3-38.0)	
Final RM				
Negative	95.1%	0.376	Reference	0.446
Positive	85.7%		2.5 (0.2-28.1)	
History of prior LR				
No	97.7%	0.005	Reference	0.028
Yes	81.2%		7.8 (1.3-48.7)	

* Kaplan-Meier method and log-rank test

† Cox proportional hazards regression model

Abbreviations: DMFS, distant metastasis-free survival; PT, phyllodes tumor, BCS, breast-conserving surgery; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; RM, resection margin; LR, local recurrence

Discussion

This study includes the largest number of malignant and borderline PT reported to date. As in literature, failures were predominantly local (16.6%) and did not differ by histologic grade [15, 20, 21, 34]. Median time to LR was 2 years and majority recurred within 5 years from surgery, comparable to the 2–5 years range of previous reports [14, 21, 25, 40, 41]. DM developed entirely in malignant subtypes only and demonstrated increased risk with prior history of LR after initial BCS alone.

Historically, TM was suggested for all PT regardless of histologic grade and without documented survival benefit [2, 3, 9, 12-15]. With demonstration of comparable treatment outcomes, preference for less radical approaches using BCS and adjuvant RT has noticeably increased [15, 26, 33, 34, 42]. In our analyses, treatment type affected LC outcomes of malignant PT, while no difference was seen for borderline PT. Among all types of combined modality approach for malignant PT, BCS alone demonstrated poorest LC rates (p=0.033), while the addition of adjuvant RT showed a marginal trend to LC improvement (p=0.079). LR occurred in 5.6% (1 of 18) after BCS with adjuvant RT, compared to 20.2% after BCS alone.

The need for adjuvant RT after BCS of malignant PT has been widely suggested in literature. Though adjuvant RT is standard therapy after BCS for early stage invasive breast carcinomas, its role for PT remains unclear and routine use is currently not recommended [13, 43]. Several studies describe favorable outcomes of adding RT, but results are limited to small numbers [37, 38]. Belkacémi et al. compared 159 patients with malignant and borderline PT, of whom 38 patients received adjuvant RT after BCS or TM. Adjuvant RT improved 10-year LC rates from 59% to 86% (p=0.02) and was the only favorable factor on multivariate analysis [21]. In the prospective study by Barth et al., 46 patients with malignant and borderline PT treated by margin-negative BCS were given adjuvant RT [14]. None had LR, but it should be noted that follow-up durations were generally short (median 56 months, range 12–129 months).

Several prognostic factors have been suggested for PT, of which resection margins is by far the strongest predictor of LR. Positive margins after BCS are

found in a considerably large proportion of patients with PT, which is in contrary to the low rates observed for invasive breast carcinomas [3, 10]. Reports show that up to 15.2% of patients with malignant and borderline PT are confirmed to have positive margins on final pathologic evaluation [20, 33, 40, 44]. Similarly, 13.2% of patients in this study were found to have positive margins after BCS. Resection margins is by far the most dominant prognostic marker for PT [3, 10, 13, 45] and re-excision of tumor-involved margins is advised [6, 14, 21, 37-39]. Decision for further management depended largely on patient preference: 30.9% (17 of 55) received re-excision and 3.6% (2 of 55) received adjuvant RT. LR developed in 41.6% (15 of 36) of patients who had positive margins with no further post-surgical management.

Positive margins after BCS demonstrated significantly increased risk of LR for both malignant and borderline PT. However, despite achieving negative margins, 16.9% (36 of 213) of patients had LR after BCS alone. In a review of patients with malignant and borderline PT treated by BCS alone, up to 21% of patients experienced LR despite achieving negative margins [14]. This rate is inadmissibly high, considering that LR is associated with risk of metastatic spread and increased mortality [15, 21, 27]. Cosmetic morbidity is also another concern, because patients with recurrent PT will require wide local re-excision or TM. Studies have shown heightened risk of LR with narrow negative margins, but failure to obtain 1 cm margins as recommended by NCCN guidelines is not an absolute indication for subsequent mastectomy [13]. Defining optimal negative margin width for minimizing LR risk has also been a topic of considerable controversy. Recent reports propose that the negative status of resection margins, no matter how narrow the width, has more clinical relevance [18, 19, 44, 46]. Tremblay-LeMay et al. investigated the risk of LR based on negative margin width and suggested that even margins $\leq$ 1 mm may be sufficient as long as it is tumor-free [46]. Based on available data for negative margin width after BCS alone, we found a marginally significant decline of LC when width was < 2 mm (p=0.061). No additional benefit was seen for wider negative margins (p=0.726).

Identifying patients who may have very low risk of LR after margin-negative BCS alone is important for deciding whether adjuvant RT can be dismissed. Aside from margin status, reports show association between larger tumor size and

increased risk of LR in malignant PT [12, 19, 21]. Kapiris et al. described adverse LC and survival for patients with large malignant PT, particularly when size exceeds 10 cm [27]. Likewise, we found malignant PT treated by BCS alone to have poor LC when tumor size ≥ 5 cm: 71.8% at 5-years (p=0.012). BCS alone for tumors < 5 cm showed LC non-inferior to that of TM alone (p=0.660): 5-year LC was 89.5% and 92.2% for these subsets of patients.

Guidelines for adjuvant RT in PT suggest following principles applied for soft tissue sarcomas [35, 47, 48]. The typical approach documented in literature is whole breast irradiation > 50 Gy with a tumor bed boost > 10 Gy in conventional fractionation [14, 15, 32, 39]. Randomized evidence of adjuvant partial breast irradiation, in properly selected invasive breast carcinoma patients, have shown LC outcomes similar to that of adjuvant whole breast irradiation [49-51]. Theoretically, there is concern of missing multicentric foci that may be present in other quadrants of the breast, a finding that is relatively common in invasive breast carcinomas [52]. In contrast, multicentric and even multifocal presentation of PT is rare: ranging from 0.9%–2.7% [7, 31, 40, 44]. In our series, 4.4% (16 of 362) presented with multiple lesions. Though this factor was not correlated with increased risk of LR after BCS alone, 44.4% (4 of 9) of patients that presented with multiple lesions recurred after treatment by BCS alone. Furthermore, LR after BCS is at most times found at or near the site of initial resection. Our data show that 88.0% of locally recurrent tumors are TR, suggesting that adjuvant partial breast irradiation could be a feasible option for select patients with malignant PT.

The metastatic potential of a locally recurrent borderline PT is not clear and adjuvant RT is infrequently advocated. Reports show that 2–4% show metastasis [21]. Malignant transformation, on the other hand, is well documented in literature. [7, 17, 28, 42, 53]. In our series, borderline PT transformed into malignant PT in 5.5% at first recurrence and in 14.3% at second recurrence. All borderline PT that recurred a third time were invariably malignant. Though borderline PT are only occasionally considered for adjuvant RT during definitive treatment, these patients may need more aggressive approach when presenting with locally recurrent tumors. Because these findings could also be a result of remnant malignant foci that may have been missed on initial pathologic examination, more accurate and precise diagnostic examinations of adequate amounts of stroma is mandatory. Another

interesting finding is the down-grading of malignant PT into borderline or benign subtypes. Based on histopathologic diversity and semi-objective assessment criteria for histologic grading, histologic down-grading due to insufficient sampling or discrepancies of pathologic evaluation cannot be excluded. Additional investigations are required for identifying the clinical significance and behavioral patterns of such histologic changes.

Though RR was rare for both histologic subtypes, malignant PT has incomparably greater risk of hematogenous spread to distant sites. As in reported documentation, lungs were the most common site of dissemination. Patients that develop DM are prone to carry dismal prognosis—these patients are often unresponsive to systemic chemotherapy and are at greater jeopardy of death due to disease progression [40, 45]. Patients that presented with DM, either as the first pattern of failure or after a prior LR, demonstrated rapid disease progression and eventual resistance to palliative chemotherapy. Precedent observations indicate 60–85% of patients with DM experience a preceding LR [27-29], but whether the event of a LR increases the risk of subsequent DM has been controversial. Of the 19 patients that developed DM, 42.1% (8 of 19) had a history of a prior event of LR and DM occurred at a median of 3 years after successful salvage of locally recurrent tumors. Results of this study reveal that patients who experience LR after initial treatment by BCS alone have a near 8-fold higher risk of DM compared to those with locally controlled primary tumors, indicating that local tumor control is a crucial step in the prognostic course of PT.

Due to the rarity of malignant and borderline PT, clinical experience and treatment outcomes can vary by treatment centers. Though approach to treatment did not prominently vary, patients being treated at smaller centers showed higher rates of having initially positive margins and experiencing LR. Such observations could be a consequence of underdiagnosis leading to undertreatment, perhaps due to differing levels of infrastructure availability for multidisciplinary treatment approaches. Larger centers also had significantly higher diagnosis rates and treated more cases of malignant PT. Because malignant PT can highly resemble soft tissue sarcomas, both clinically and pathologically, diagnosis is challenging and it is possible that such patients were referred to larger tertiary medical centers.

This study comprises the largest number of cases for malignant and borderline

PT among other retrospective studies published to date. Clinical outcomes after adjuvant RT were excellent, as in the limited data from literature. However, because relatively too few patients were treated with adjuvant RT in general, its role remains to be discussed in further large-scale investigations. The clinical value of other clinicopathologic factors that are known to influence treatment outcomes of invasive breast carcinomas, such as hormone receptors or Ki-67, remain uncertain for PT. The prognostic impact of molecular factors could not be defined due to the low rates of examination. Hormone receptor status and Ki-67 were reported in 7.5% and 14.9% of patients, respectively.

A major limitation of this study is the inevitable lack of a central pathologic review by a single pathologist. As a multicenter study with data collected from a span of 33-years, majority of pathologic specimens were not available. All pathology reports from each participating center were uniformly based on the WHO classification guidelines first reported in 1981. But because the criteria itself do not define objective cut-off values, grading of PT is prone to subjective differences [9, 11], thus the possibility of inter-observer discrepancy between pathologists of each participating center cannot be excluded. As an alternative, diagnostic agreement was confirmed by comparing pathology reports of patients with data available for all 5 histopathologic parameters used in the WHO classification guideline. Data for all 5 parameters were available for 172 (47.5%) patients. Parameters were reviewed by a single physician and compared to the final diagnosis reported by pathologist. Though all final diagnosis showed diagnostic agreement with review of histopathologic parameters, information was limited to less than half of the cohort. Another limitation is the lack of information for the width of negative margins, with most pathology reports only reporting the status of resection margins as either negative or positive. Detailed pathological or molecular data from surgical specimens, including tumor necrosis, hormone receptors, or Ki-67 were not available for many of the cases included for analyses.

In conclusion, results of this study support documented literature regarding margin-positive BCS as inadequate therapy for both malignant and borderline PT. These patients have dismal LC and high rates of EF, thus re-excision or adjuvant whole breast irradiation is advised. Because LR after BCS alone significantly increases the risk of developing DM, achieving LC is a crucial goal in the

therapeutic approach for malignant PT. Though margin-negative BCS alone seem suitable for malignant PT < 5 cm, with outcomes comparable to that of TM, there is heightened risk of LR for larger tumors, suggesting utilization of adjuvant RT. For select patients, adjuvant partial breast irradiation may be adapted, considering that majority of PT recur at the site of initial resection than elsewhere. As for borderline PT, malignant transformation more than doubles with each subsequent LR. Integration of adjuvant RT should be considered at the first event of LR.

Appendix

List of participating centers

- Seoul National University Hospital
  Seoul National University College of Medicine
  Seoul, Korea

- Samsung Medical Center, Sungkyunkwan University School of Medicine
  Seoul, Korea

- Asan Medical Center
  University of Ulsan College of Medicine
  Seoul, Korea

- National Cancer Center
  Goyang, Korea

- Yonsei Cancer Center
  Yonsei University College of Medicine
  Seoul, Korea

- Ajou University Hospital
  Ajou University School of Medicine
  Suwon, Korea

- Ewha Womans University Mokdong Hospital
  Ewha Womans University College of Medicine
  Seoul, Korea

- Seoul Metropolitan Government Boramae Medical Center
  Seoul National University College of Medicine
  Seoul, Korea

- Seoul St. Mary's Hospital
  The Catholic University of Korea College of Medicine
  Seoul, Korea

- Dongsan Medical Center
  Keimyung University School of Medicine
  Daegu, Korea

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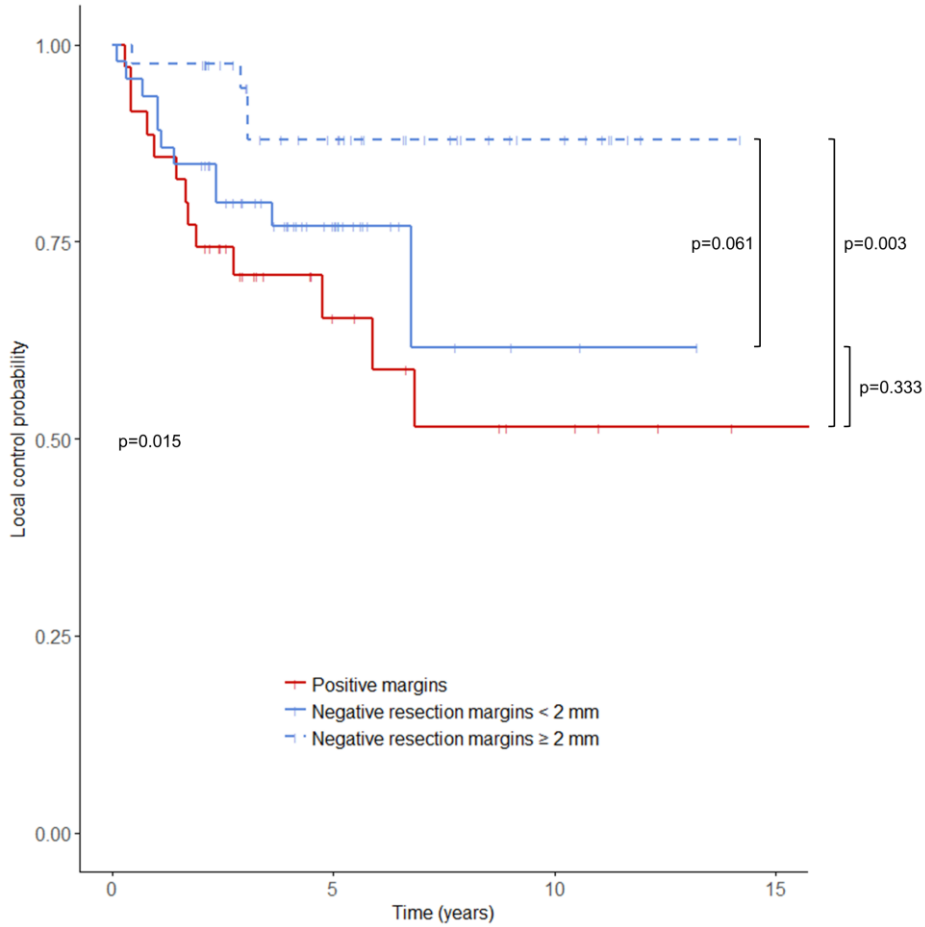
Supplements

Supplement Table 1. Comparison by center characteristics (n=362)

	Diagnosis rate (person-years)			Capacity (total hospital beds)		
	< 1.4 (n=91)	≥ 1.4 (n=271)		< 1200 (n=113)	≥ 1200 (n=249)	
Variables	n (%)	n (%)	*p**	n (%)	n (%)	*p**
Histologic grade						
Malignant	59 (64.8)	176 (64.9)	1.000	59 (52.2)	176 (70.7)	0.001
Borderline	32 (35.2)	95 (35.1)		32 (47.8)	95 (29.3)	
Combined modality						
BCS	60 (65.9)	187 (69.0)	0.133	85 (75.2)	162 (65.1)	0.299
BCS+RT	7 (7.7)	11 (4.1)		5 (4.4)	13 (5.2)	
TM	18 (19.8)	66 (24.4)		20 (17.7)	64 (25.7)	
TM+RT	6 (6.6)	7 (2.6)		3 (2.7)	10 (4.0)	
Initial RM						
Negative	81 (89.0)	226 (83.4)	0.262	87 (77.0)	220 (88.4)	0.008
Positive	10 (11.0)	45 (16.6)		26 (23.0)	29 (11.6)	
Final RM						
Negative	81 (89.0)	243 (89.7)	1.000	100 (88.5)	224 (90.0)	0.813
Positive	10 (11.0)	28 (10.3)		13 (11.5)	25 (10.0)	
LR						
No	73 (80.2)	229 (84.5)	0.431	88 (77.9)	214 (85.9)	0.078
Yes	18 (19.8)	42 (15.5)		25 (22.1)	35 (14.1)	

* Chi-squared and Fisher's exact test

Abbreviations: BCS, breast-conserving surgery; TM, total mastectomy; RT, radiation therapy; RM, resection margin; LR, local recurrence



Supplement Figure 1. LC by margin status and width

LC probability of patients with malignant and borderline PT with known margin width after BCS alone (n=122) compared by positive margins (n=35), close margins < 2 mm (n=46), and negative margins ≥ 2 mm (n=41).

국문초록

목적 : 유방엽상종양은 수술적 제거에도 불구하고 9-24%에서 국소재발을 보인다. 최근 발표된 연구들에 따르면 유방의 보존적 수술 후 보조적 방사선치료를 사용하는 빈도가 늘어나는 추세이며 이에 의한 국소제어율의 이득을 보이고 있다. 본 연구는 후향적 다기관 연구로써 악성 및 경계성 유방엽상종양으로 수술을 시행한 환자들의 치료 성적 및 재발 양상을 평가하고 국소제어율에 영향을 미치는 요인을 분석하고자 한다. 또한 보존적 수술 단독 치료 후 국소재발한 경우, 재발의 위치 및 조직학적 등급을 평가하고자 한다.

방법 : 1981 년부터 2014 년까지 10 개의 참여 기관에서 총 362 명의 환자가 악성 (n=235) 및 경계성 (n=127) 유방엽상종양으로 유방의 보존적 수술 또는 전절제를 받았다. 31 명이 보조적 방사선치료를 받았고 항암화학치료를 받은 환자는 분석에서 제외하였다. 보존적 수술 후 국소재발한 경우, 이전 수술 부위 또는 surgical clip 이 있는 경우 이로부터 2 cm 이내에서 발생한 국소재발을 true recurrence 라고 정의하였다. 이 범위를 벗어난 국소재발은 elsewhere failure 로 정의하였다.

결과 : 중앙 추적 관찰 기간 5 년(범위 2-31 년) 후 60 명(16.6%)의 환자에서 국소재발이 관찰되었다. 림프절 및 원격 전이는 각각 2 명(0.6%)과 19 명(5.2%)에서 나타났다. 보존적 수술을 받거나 (p=0.025) 보조적 방사선치료를 받지 않은 경우 (p=0.041) 국소재발율이 더 높았다. 보존적 수술 단독으로 치료 받은 경우 (n=247), true recurrence 와 elsewhere failure 는 각각 44 명 (17.8%)와 6 명(2.4%)에서 있었다. 악성 유방엽상종양이 경계성 유방엽상종양에 비하여 악성으로 재발할 확률이 더 높았다 (p=0.019). 그러나 경계성 유방엽상종양의 28.6% (21 명 중 6 명)이 악성으로 재발하였다 (p=0.008). 5 년 국소제어율은 보존적 수술 단독에서

80.7%로 가장 낮았으며 보존적 수술과 방사선치료에서 93.3%, 전절제 단독에서 92.4%, 그리고 전절제와 방사선치료에서 100%로 통계적으로 유의한 차이를 보였다(p=0.033). 보조적 방사선치료 없이 수술만 단독으로 시행 받은 악성 유방엽상종양 환자에서 보존적 수술 단독 치료(p=0.023), 5 cm 보다 크거나 같은 종양 크기(p=0.024), 그리고 양성 절제면(p=0.044)이 국소재발을 증가시키는 유의한 독립적 위험인자로 분석되었다. 이 환자들 중 보존적 수술 단독으로 치료받은 137 명의 환자를 추가 분석하였을 때 종양크기와 상관없이 절제면이 양성인 경우와 음성이지만 종양크기가 5 cm 보다 크거나 같은 경우 각각 62.5%와 71.8%로 불량한 5 년 국소제어율을 보였다 (p=0.007). 반면, 보조적 방사선치료 없이 수술만 단독으로 시행 받은 경계성 유방엽상종양 환자 125 명에서는 양성 절제면(p=0.044)이 국소재발의 유일한 위험인자로 관찰되었다. 보존적 수술 단독으로 치료 받은 이후 국소재발을 한 경우가 그렇지 않은 경우에 비하여 원격전이의 위험성이 8 배 더 높았다 (95% CI 1.3−48.7, p=0.028).

결론 : 보존적 수술 후 절제면이 양성인 경우 악성 및 경계성 유방엽상종양 모두에서 낮은 국소제어율과 높은 elsewhere failure 를 보이기 때문에 재절제 또는 전체 유방 방사선조사가 권장된다. 국소재발한 악성 유방엽상종양은 원격전이의 위험성이 높기 때문에 초기 효과적인 국소제어가 중요하다. 절제면이 음성인 경우 5 cm 이하 크기의 종양은 보존적 수술 단독 치료가 적합할 수 있겠으나 이보다 큰 종양에서는 국소재발율이 높아 보조적 방사선치료의 고려가 필요하다.

주요어 : 악성 유방엽상종양, 경계성 유방엽상종양, 유방종양, 보조요법, 국소재발, 위험인자

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