Ann Surg Oncol
DOI 10.1245/s10434-015-4395-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Reappraisal of Conventional Risk Stratification for Local Recurrence Based on Clinical Outcomes in 285 Resected Phyllodes Tumors of the Breast

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ABSTRACT

Purpose. To ensure a surgical margin of ≥1 cm for the effective treatment of phyllodes tumors of the breast (PTB) a second resection has been recommended, but the outcomes of an extensive series of cases employing the aforementioned criterion cast doubt on this clinical approach. The aim of this study was to identify the local recurrence (LR) risk factors of PTB and determine future optimal surgical treatment according to verified risks.

Methods. All cases given a diagnosis of PTB, and resected between 1989 and 2008, were retrospectively evaluated. Clinicopathologic data and clinical outcomes were analyzed and stratified according to the risks for LR.

Results. All 285 cases were categorized as benign (191, 67.0 %), borderline (61, 21.4 %), or malignant (33, 11.6 %). Median follow-up was 6.7 years and there were 20 LRs during follow-up. All benign PTB recurred as benign PTB lesions. Mitoses ($p < 0.001$) and tumor size ($p = 0.021$) were independent prognostic factors for LR in multivariate analysis. Neither margin status ($p = 0.758$) nor type of surgery ($p = 0.922$) had any significance for LR. In the risk stratification for LR, PTB ≤5 cm in size with ≥10 mitoses/10 high-power fields (HPFs) had the highest LR rate (55.6 %) compared with all other subgroups ($p < 0.001$).

Conclusions. It is recommended a wide excision and clear margin of 1 cm be ascertained in only small PTB with frequent mitoses, if necessary by means of a second surgery, which could be considered in order to avoid the risk of LR in this distinct and limited group.

The primary concern in the management of phyllodes tumors of the breast (PTB) is to identify the risk of local recurrence (LR) and to provide optimal treatment for preventing LR. PTB have a diverse range of biologic behaviors, from benign forms to variants that metastasize distantly and sometimes dedifferentiate histologically into a sarcomatous lesion that lacks an epithelial component.[1]

The diagnosis of PTB prior to excisional biopsy or lumpectomy is uncommon because PTB are difficult to distinguish from fibroadenomas on both fine-needle aspiration and core biopsy.[2] Therefore, definitive diagnosis of PTB is based on pathologic examination of the completely resected tumor. In addition, the LR rate (LRR) of PTB has been reported to be approximately 20 %, regardless of classification as non-malignant or malignant.[3–5] Therefore, the mainstay of treatment of non-metastatic PTB is complete surgical resection with wide resection margins (at least 1 cm). The desired minimal 1 cm widths have been established based on retrospective analyses;[6–8] however, since negative surgical margins of any size are also known to be associated with good disease-free survival (DFS) and decreased LR, the question as to whether a secondary resection is essential to ensure a 1-cm tumor-free margin is increasingly being asked.

This large-series study therefore sought to gain insight into the clinical outcomes of PTB, to identify the risk

First Received: 14 October 2014

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Published online: 05 February 2015

factors that affect the LR of PTB, and objectively define the optimal treatment according to the retrospectively verified risks of LR.

METHODS

We retrospectively analyzed data on all 285 cases resected between June 1989 and December 2008 at the Department of Surgery of Seoul National University Hospital and affiliated hospitals. We excluded PTB co-presenting with breast cancer, including carcinoma in situ and invasive breast cancer, or a previous breast cancer history. Moreover, those who had a follow-up duration of less than 24 months were also excluded. Surgical treatment was categorized as the vacuum-assisted biopsy system (VABS), wide local excision (WLE), or mastectomy. All treated patients provided written informed consent in accordance with the Declaration of Helsinki, prior to surgery. The study was reviewed and approved by the local Institutional Review Committee (IRB No: B-1311/228-106) and registered in the Clinical Research Information Service (CRiS) [Registration Number KCT0000945].

Classification of PTB as benign, borderline, or malignant was recorded from the original pathology report issued at the time of diagnosis, using the morphologic criteria[9] of the World Health Organization (WHO). To collect and minimize missing data, two pathologists (SYPark and IAPark) reviewed all available archival slides stained with hematoxylin and eosin (H&E). They unified the diagnostic criteria prior to review and discussed special and difficult cases for diagnosis to minimize inconsistency between examiners and time period. The border between the tumor and the surrounding breast parenchyma was characterized as either well-circumscribed/pushing or infiltrative. The stromal pattern was categorized as uniform/expansive, or marked overgrowth. The surgical margin of the tumor was defined as positive if the tumor was present at or close to (<0.1 mm) the inked tissue edge on histopathologic evaluation. If a subsequent surgery was performed (re-excision or mastectomy), margin status was determined from the last surgical procedure.

Statistical analysis was performed using SPSS software, version 20.0 (IBM Corporation, Armonk, NY, USA). The Pearson χ^2 test was used to determine the correlations among the variables, and the Cox proportional regression hazard model was employed with several variables. Kaplan–Meier curves were plotted from survival data, and we used univariate and multivariate regression analysis with Cox proportional hazard models. *P* values were two-sided and were considered to indicate a statistically significant difference when they were less than 0.05.

RESULTS

Clinicopathologic Characteristics

A total of 325 cases of PTB were identified, of which 285 tumors, including three bilateral tumors and five multifocal lesions in 277 patients, were included in the study. All cases occurred in women, with 191 cases (67.0 %) categorized as benign, 61 cases (21.4 %) as borderline, and 33 cases (11.6 %) as malignant. The mean age of enrolled patients was 36.44 ± 10.76 (range 12–66) years of age. Patients with benign PTB ($p = 0.007$) were younger than those with borderline or malignant lesions (Table 1). Radiotherapy was undertaken in six malignant PTB, including two mastectomies and four WLEs in case of high mitoses (>20/10 high-power fields [HPF]) or larger tumors (>10 cm). Reoperation was performed in order to obtain a negative margin or to overcome discrepancies between initial and final diagnosis, depending on the surgeon's decision, in 22 cases, including 13 VABSs and in 9 WLEs. We obtained a clear margin in 18 of 22 cases. Finally, positive resection margins were seen in 15.8 % ($n = 45$) of cases, and were markedly frequent in benign PTB (17.3 % positivity; $p = 0.005$). The primary tumor size differed, with statistical significance, according to histologic type ($p < 0.001$). All pathologic features were significantly different according to histologic type (Table 2).

Clinical Outcomes

Median follow-up duration was 81.14 ± 27.98 (range 11.4–244.5) months. The 5-year overall survival (OS) rates for benign, borderline, and malignant tumors were 100.0, 98.3, and 84.7 %, respectively ($p < 0.001$) and 5-years LR-free survival rates were 95.0, 86.9, and 82.0 %, respectively ($p = 0.016$). During the study period, the 25 recurrent events (8.8 %) included 20 LRs (7.0 %), 1 contralateral breast recurrence, and 4 distant metastases (1.4 %). Recurrence ($p < 0.001$), LR ($p = 0.023$), and mortality ($p < 0.001$) were significantly more frequent in malignant PTB than in benign and borderline lesions (Table 1). The histologic type of recurrent lesions were diagnosed as nine malignant, seven borderline, and eight benign lesions. All locally recurrent lesions following resected cases of benign primary PTB of lesions were benign, and all distant metastases resulted from an initially malignant lesion. Mortality was reported to be 1.75 % ($n = 5$). One mortality case was due to the development of advanced gastric cancer, while the remaining four cases resulted from metastasis of PTB. There was no independent prognostic factor including LR for OS by multivariate analysis. Mitosis ($p < 0.001$) was the only independent

TABLE 1 Demographics and clinical characteristics of patients with 285 phyllodes tumors

Variables	Total		Benign		Borderline		Malignant		*p* value
	n	%	*n*	%	*n*	%	*n*	%	
Cases (%)	285	100.0	191	67.0	61	21.4	33	11.6	
Age (years)									0.007
Mean	36.44 ± 10.76		35.06 ± 10.80		38.87 ± 11.14		39.97 ± 8.21		
Range	12–66		12–60		13–66		20–56		
Follow-up (years)									0.077
Median	81.14 ± 27.98		81.22 ± 22.76		75.6 ± 26.30		77.53 ± 49.50		
Range	11.4–244.5		24.4–173.6		15.6–127.7		11.4–244.5		
Surgery									<0.001
VABS	25	8.8	23	12.0	1	1.6	1	3.0	
WLE	246	86.3	168	88.0	54	88.5	24	72.7	
Mastectomy	14	4.9	0	0.0	6	9.8	8	24.2	
AND									<0.001
No	275	96.5	190	99.5	60	98.4	25	75.8	
Yes	10	3.5	1	0.5	1	1.6	8	24.2	
Multicentricity									0.660
No	281	98.6	189	99.0	60	98.4	32	97.0	
Yes	4	1.4	2	1.0	1	1.6	1	3.0	
Radiotherapy									<0.001
No	279	97.9	191	100.0	60	100.0	27	81.8	
Yes	6	2.1	0	0.0	0	0.0	6	18.2	
Recurrence									<0.001
No	260	91.2	182	95.3	54	88.5	24	72.7	
Yes	25	8.8	9	4.7	7	11.5	9	27.3	
Local recurrence									0.023
No	265	93.0	183	95.8	54	88.5	28	84.8	
Yes	20	7.0	8	4.2	7	11.5	5	15.2	
Death									<0.001
No	280	98.2	191	100	60	98.4	29	87.9	
Yes	5	1.8	0	0.0	1	1.6	4	12.1	

VABS vacuum-assisted biopsy system, *WLE* wide local excision, *AND* axillary node dissection

prognostic factor in recurrence-free survival (RFS), although tumor size ($p = 0.051$) tended to be associated with recurrence, but without statistical significance.

Mitoses ($p < 0.001$) and primary tumor size ($p = 0.021$) were independent prognostic factors of LR on multivariate analysis (Table 3). Margin status ($p = 0.758$) and type of surgery ($p = 0.922$) did not have prognostic significance for local RFS, i.e. results with a margin of 0.1 mm were not inferior to a margin of 1 cm. Log-rank analysis for LR was significant in histology ($p = 0.016$) (Fig. 1a) and mitoses ($p = 0.007$) (Fig. 1b). In the subgroupings according to tumor size and mitoses, which were risk factors better reflecting the risk of LR rather than histology, although relatively uncommon, a tumor size of ≤5 cm with a high mitotic index showed a prominent LRR (55.6 %) compared with other groups ($p < 0.001$) (Table 4; Fig. 1c).

Distant failure ($n = 4$) was not associated with LR ($p = 1.000$), or margin status ($p = 0.761$), but with histologic type ($p < 0.001$), tumor size ($p = 0.006$), mitoses ($p < 0.001$), stromal pattern ($p < 0.001$), tumor border ($p = 0.037$), and cellular pleomorphism ($p < 0.001$).

DISCUSSION

We set out to determine the most appropriate surgical approach to PTB, especially with regard to aspects involving the question of eliminating the need for reoperation. Accurate preoperative pathologic diagnosis in many other diseases can allow optimal surgical planning and avoid reoperation[10–12] but accurate diagnosis of PTB prior to excisional biopsy or lumpectomy is uncommon. Moreover, LR of PTB appears to be related to lack of

TABLE 2 Pathologic features of phyllodes tumors

Characteristics	Total (%)	Benign (%)	Borderline (%)	Malignant (%)	*p* value
Cases (%)	285 (100.0)	191 (67.0)	61 (21.4)	33 (11.6)	
Tumor size (cm)					<0.001
≤2	78 (27.4)	71 (37.2)	5 (8.2)	2 (6.1)	
<2 and ≤5	153 (53.7)	103 (53.9)	39 (63.9)	11 (33.3)	
>5	52 (18.2)	16 (8.4)	17 (27.9)	19 (57.6)	
Unknown	2 (0.7)	1 (0.5)	0 (0.0)	1 (3.0)	
Margin status					0.005
Clear	217 (76.1)	135 (70.7)	52 (85.2)	30 (90.9)	
Close/involvement	45 (15.8)	33 (17.3)	9 (14.8)	3 (9.1)	
Unknown	23 (8.1)	23 (12.0)	0 (0.0)	0 (0.0)	
Borders					<0.001
Circumscribed/pushing	161 (56.5)	121 (63.4)	34 (55.7)	6 (18.2)	
Infiltrative	40 (14.0)	11 (5.8)	16 (26.2)	13 (39.4)	
Unknown	84 (29.5)	59 (30.9)	11 (18.0)	14 (42.4)	
Stromal pattern					<0.001
Uniform/expansive	167 (58.6)	127 (66.5)	36 (59.0)	4 (12.1)	
Marked overgrowth	21 (7.4)	1 (0.5)	4 (6.6)	16 (48.5)	
Unknown	97 (34.0)	63 (33.0)	21 (34.4)	13 (39.4)	
Cellular pleomorphism					<0.001
Minimal/modest	210 (73.7)	148 (77.5)	54 (88.5)	8 (24.2)	
Marked	16 (5.6)	0 (0.0)	1 (1.6)	15 (45.5)	
Unknown	59 (20.7)	43 (22.5)	6 (9.8)	10 (30.3)	
Stromal hypercellularity					0.001
Minimal/modest	140 (49.1)	96 (50.3)	38 (62.3)	6 (18.2)	
Marked	82 (28.8)	51 (26.7)	14 (23.0)	17 (51.5)	
Unknown	63 (22.1)	44 (20.3)	9 (14.8)	10 (30.3)	
Mitotic activity					<0.001
1–4/10 HPF	197 (69.1)	169 (88.5)	25 (41.0)	3 (9.1)	
5–9/10 HPF	43 (15.1)	3 (1.6)	35 (57.4)	5 (15.2)	
≥10/10 HPF	25 (8.8)	0 (0.0)	1 (1.6)	24 (72.7)	
Unknown	20 (7.0)	19 (9.9)	0 (0.0)	1 (3.0)	

HPF high-power fields

surgical margin of the initial surgery and is regarded as a failure of primary surgical treatment.[13] According to the National Comprehensive Cancer Network (NCCN) guidelines,[14] wide excision means excision with the intention of obtaining surgical margins ≥1 cm. Therefore, decisions regarding a second operation after initial surgery should depend on the final pathologic report.

However, the question remains, is it indispensable to obtain negative margins in all cases? PTB is still a problematic entity to identify those patients who need reoperation to obtain negative margins to avoid LR. In the current large-scale study, clear margins <0.1 mm were not associated with greater LR ($p = 0.773$ for LR-free survival compared with the ≥0.1 mm group), which justifies the clinical acceptability of a narrower margin and may alter our approach to the treatment of this entity. Emphasizing this point, 41 cases (65.1 %) among our 63 cases with a positive resection margin did not undergo reoperation. Among these 41 cases, there were only three recurrences, all of which were locally benign lesions. We obtained a clear margin in 18 cases of 22 re-excisions, and the remaining four cases still had a positive margin; one malignancy recurred as pulmonary metastasis. The recurrence rate of fibroadenoma is reported to be up to 15 %,[15,16] which is similar to that for benign phyllodes tumors.[17,18] While the overall recurrence rates of benign PTB are comparable with fibroadenoma, the critical difference is that a small percentage of PTB may recur as malignant lesions.[19] The NCCN guidelines[14] for PTB still recommend wide excision, even for benign PTB; therefore, if benign PTB is misdiagnosed as fibroadenoma by excisional biopsy at initial surgery, according to the NCCN, a

TABLE 3 Local recurrence-free survival by Cox-regression

Subgroup of patients	No recurrence		Recurrence		Univariate		Multivariate	
	n	%	*n*	%	HR	*p* value	HR	*p* value
Mitoses						0.012		<0.001
1–9/10 HPF	225	93.8	15	6.2				
≥10/10 HPF	20	80.0	5	20.0	3.647		10.282	
Size (cm)						0.160		0.021
≤5	212	87.9	19	12.1	4.237		12.500	
>5	51	98.1	1	1.9				
Operation						0.957		0.922
WLE	229	93.1	17	6.9				
VABS	23	92.0	2	8.0	1.247	0.768	1.230	0.865
Mastectomy	13	92.9	1	7.1	1.055	0.959	0.658	0.709
Margin						0.886		0.758
Clear	202	93.1	15	6.9				
Close/involvement	42	93.3	3	6.7	0.983	0.979	1.223	

HR hazard ratio, *HPF* high-power fields, *WLE* wide local excision, *VABS* vacuum-assisted biopsy system

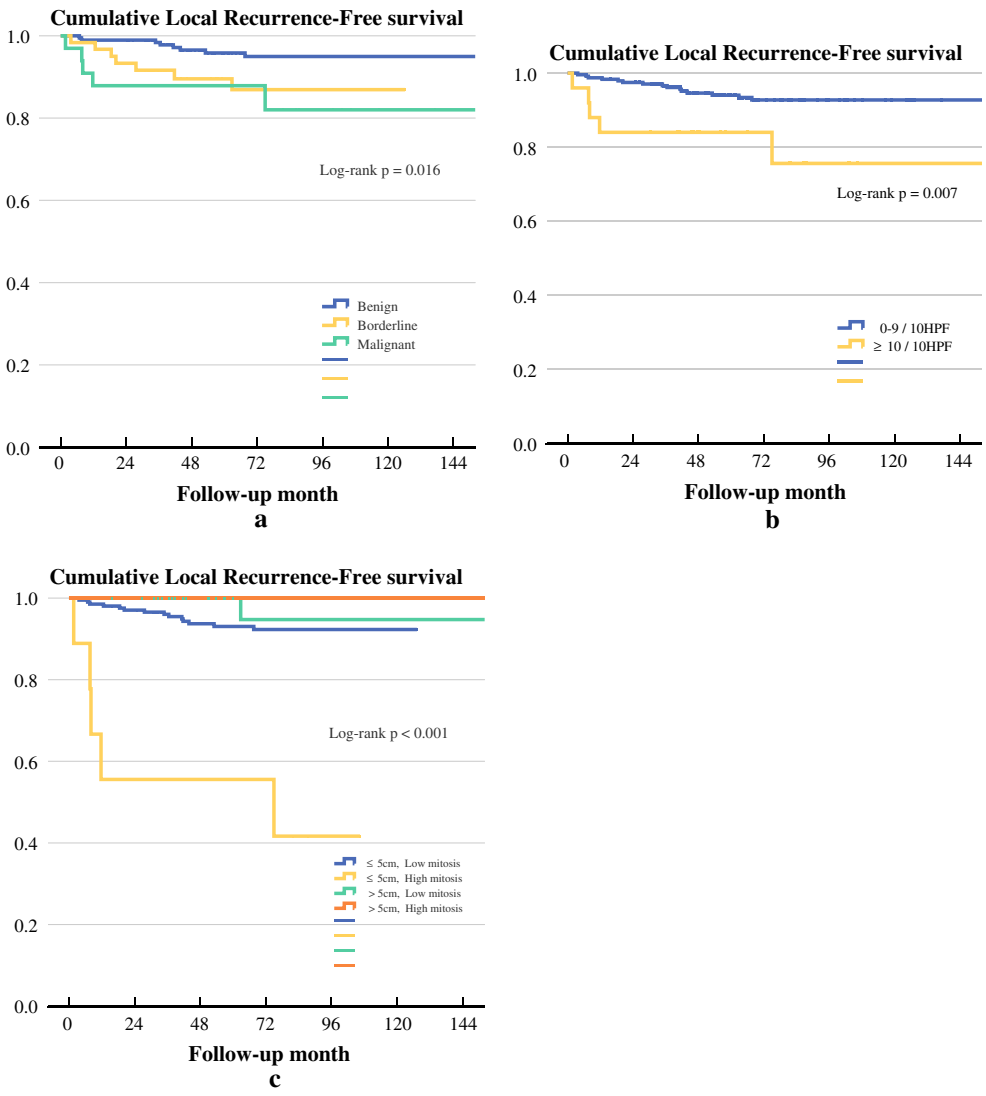

FIG. 1 Local recurrence-free survival by log-rank test in relation to **a** histological type ($n = 285$), **b** mitoses ($n = 265$), and **c** mitoses and tumor size ($n = 264$). *HPF* high-power fields

TABLE 4 Local recurrence rate according to subgrouping by tumor size and mitoses ($p < 0.001$)

Tumor size (cm)	Mitosis			
	0–9/10 HPF		≥10/10 HPF	
≤5	Group 1		Group 2	
	$N = 204$	LRR = 6.9 % (14/204)	$N = 9$	LRR = 55.6 % (5/9)
>5	Group 3		Group 4	
	$N = 36$	LRR = 2.8 % (1/36)	$N = 15$	LRR = 0.0 % (0/15)

HPF high-power fields, *LRR* local recurrence rate

second operation would be needed. However, in the present study, overall recurrence and LR of benign PTB were merely 4.7 and 4.2 %, respectively, and all benign PTB, without exception, recurred as benign PTB. Therefore, even for benign PTB that are extremely close to the resected margin or have positive margins, reoperation to obtain margin negativity is not absolutely necessary in all cases. This is, to some degree, supported by the MD Anderson Cancer Center clinical practice algorithm for phyllodes tumors,[20] in which it is recommend that if initial excision has a negative margin in benign PTB, further WLE is not required.

Interestingly, the significant prognostic factors for LR were mitoses (≥10/10 HPF; $p < 0.001$) and tumor size (≤5 cm; $p = 0.021$), as shown by multivariate analysis in this study (Table 3). The majority (81.1 %) of all PTB and 91.1 % of benign PTB were 5 cm or less. In addition, in this distinct size category, 95.0 % (19/20) of LRs also resulted from PTB. In addition, in multivariate analysis, a PTB ≤5 cm in size, with a high rate of mitosis (>10/10 HPF), showed relatively frequent LR. Therefore, we grouped the risks for LR according to tumor size and mitosis, which could be a more reliable standard to predict LR and provide optimal treatment for PTB. Stratification according to the new grouping indicated that tumors ≤5 cm in size with high mitotic activity (≥10/10 HPF) showed the poorest local RFS among all groups ($p < 0.001$) (Fig. 1c). In this group, although there are limitations of scale, it is worth noting that the LRR was 55.6 % (Table 4). Although we could evaluate the risk for LR with a given histologic grade of PTB ($p = 0.023$) (Table 1), new groupings might provide more predictable and reliable standards for judging LR. These results suggest that small PTB can be in the active proliferative phase with high numbers of mitotic figures and in a microenvironment with sufficient blood supply and nutrition more conducive to the promotion of tumor growth than large PTB.

This was a retrospective study and the results may reflect restrictions of ethnicity, especially in Korean women, which might be a limitation of this study. However, it was a representative population of the Seoul area, which constitutes approximately half of the population of Korea.

The clinicopathologic characteristics of repetitive LR cases more than twice (one, twice; one, three times; one, seven times) <5 cm in size and had clear resection margins with WLE in all cases. Apart from these two features, there was no point of similarity between them. This therefore requires further evaluation at the level of molecular biology, as mentioned above. If, on further study, molecular factors such as p53, Ki67, and CD117[13] are proven to be related to prognostic factors associated with recurrence, we could further optimize and specify the surgical treatment according to the size and histology of PTB.

CONCLUSIONS

PTB lesions ≤5 cm in size with frequent mitoses had the highest risk for LR; therefore, it is recommended that radical treatment be performed, including wide excision and close follow-up, to avoid LR in this group. However, our data from this extensive study group also distinctly indicate that a clear surgical margin of 0.1 mm is not inferior to a margin of 1 cm, and this could affect changes in the clinical treatment of PTB in the near future.

ACKNOWLEDGMENT The authors are indebted to J. Patrick Barron, Professor Emeritus, Tokyo Medical University, and Adjunct Professor, Seoul National University Bundang Hospital for his thorough editing of this article.

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