

Benign and borderline phyllodes tumors of the breast: Clinicopathologic analysis of 205 cases with emphasis on the surgical margin status and local recurrence rate

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ABSTRACT

Background: The management of benign and borderline phyllodes tumors of the breast with a positive surgical margin is still controversial. Our aim in this study was to evaluate the impact of surgical margin status on the local recurrence rate of benign and borderline phyllodes tumors.

Methods: We reviewed 205 phyllodes tumors (191 benign, 14 borderline) that were surgically excised at our hospital between 2005 and 2019. Follow-up information extending to at least 6 months after surgery was retrieved from the clinical, radiology, and pathology records.

Results: The initial surgical margin was negative in 54 (26%) cases, close (≤ 1 mm) in 29 (14%) cases, and positive in 122 (60%) cases. Approximately half of the cases with a close margin and two-third of the cases with a positive margin underwent re-excision to obtain negative margins. Three (2.3%) local recurrences were observed among 131 cases with follow-up information, all three with benign phyllodes tumor. Of these three patients, one had a positive final margin, and two had negative final margins. There was no significant difference in the rate of local recurrence between PT with a positive surgical margin versus a close and negative margin.

Conclusion: The study results suggest that close clinical and radiologic follow-up may provide a better course of management rather than re-excision when managing positive margins in benign and borderline phyllodes tumors.

1. Introduction

Phyllodes tumors (PT) are rare fibroepithelial neoplasms of the breast, accounting for 0.3–1% of breast tumors, with a range of benign to aggressive behavior [1]. Various schemes have been used to classify phyllodes tumors by histologic features associated with clinical behavior [2]. The World Health Organization (WHO) recommends a classification into three subtypes: benign, borderline, and malignant subtypes [3,4]. While the majority of PTs have benign behavior, all phyllodes tumors have risk of local recurrence (LR) [1]. Traditionally, the concern for LR leads to the recommendation of wide local excision with tumor-free margin of 1 cm or greater, regardless of subtype [3]. Lumpectomy or partial mastectomy is the preferred surgical therapy, with total mastectomy only necessary if negative margins cannot be obtained by breast

conservation therapy. Given that PT rarely metastasize to the axillary lymph nodes (10–15%), surgical axillary staging is not necessary unless the lymph nodes are palpable on clinical examination [5]. Recently, the optimal excision margin has been brought into question, with hypotheses that optimal excision margins may depend on tumor grade [6].

In the case of positive margins, the current practice is re-excision of margins, despite subtype. However, given the low risk of recurrence in benign and borderline PT compared to malignant PT [1], it is important to consider whether the risk of returning to surgery for re-excision outweighs the benefit of prevention of LR. Returning to surgery for re-excision of margins exposes the patient to risks universal to all surgical procedures, in addition to the risk of poor cosmesis, greatly affecting the quality of life. In contrast to the published literature in the past, recent studies suggest that re-excision to negative margins might not be

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needed for benign and borderline PT [7-17]. In this study, we evaluated the rate of LR and the impact of margin status on LR in benign and borderline phyllodes tumors within our institution.

2. Materials and methods

After the study was approved by the Institutional Review Board, the pathology database of our hospital was searched for breast surgical excision specimens with a diagnosis of benign or borderline PT between January 1, 2005 and December 30, 2019. The pathology history of all identified patients was reviewed to document the surgical margin status of the excised tumors, subsequent surgical re-excision, presence/absence of remaining tumor in re-excision specimens, and the final margin status. Follow-up information extending to at least 6 months after surgery was retrieved from the clinical, radiology and pathology records. The patients who had additional treatments other than surgery in the same breast for any pathology were excluded from the study.

The surgical margin status of the tumors was classified as “negative”, “close (≤ 1 mm)” and “positive”. Positive margins were reported when tumors were histologically observed to involve the inked surgical resection margin. The cases were considered as “local recurrence” when a new PT was identified in the same quadrant of the ipsilateral breast. The pathology slides were retrieved and reviewed for cases to document the tumor border (circumscribed or infiltrative), stromal overgrowth (present or absent), atypia (mild, moderate, or marked) and the number of mitosis per 10 high-power fields. The histologic grading of the tumors was done according to the WHO classification of tumors of the breast [4].

The statistical analyses were performed on SPSS, version 22 for Windows. Chi-square and Fisher's exact tests were used to compare the categorical variables, and the Mann-Whitney *U* test was performed to evaluate the continuous variables. The results were considered significant if $p < 0.05$.

3. Results

A total of 205 PT (191 benign, 14 borderline) were surgically excised at our hospital between 2005 and 2019. The median age of all patients was 36 years, ranging from 16 to 69 years. The median age of the patients with borderline PT was statistically significantly higher than the patients with benign PT (48 years vs. 36 years; $p = 0.04$). The median overall size of all PT was 23 mm (3–83 mm) with no significant difference between benign and borderline PT (23 mm vs. 32 mm, $p = 0.14$). Borderline PT was significantly more likely to have infiltrative borders ($p = 0.01$), moderate atypia ($p = 0.04$), and higher mitotic rate ($p < 0.001$) compared to benign PT.

The core needle biopsy (CNB) diagnosis was available in 80 PT, 74 of 191 benign PT and 6 of 14 borderline PT. For benign PT, CNB was reported as PT or favor PT in 20 (27%) cases, fibroepithelial lesion in 24 (32%) cases, FA or favor FA in 27 (37%) cases, stromal fibrosis in 2 (3%) cases and spindle cell lesion in 1 (1%) case. For borderline PT, CNB showed PT or favor PT in 3 (50%) cases, fibroepithelial lesion in 2 (33%) cases and FA or favor FA in 1 (17%) case (Table 1).

The initial surgical margin status was negative in 54 (26%) cases, close in 29 (14%) cases and positive in 122 (60%) cases. Among 151 cases with positive or close margin status, a re-excision was performed in 91 cases: 15 of 29 (52%) cases with close margin and 76 of 122 (62%) cases with a positive margin. Among these 91 cases, the re-excision specimen showed a remaining tumor in only 10 cases, all with benign PT. The final margin status was negative in 145 (70%) cases, close in 14 (7%) cases and positive in 46 (23%) cases (Fig. 1).

Follow-up information was available for 131 patients: 124 of 191 patients with benign PT and 7 of 14 patients with borderline PT. The median follow-up period was 27 months, ranging from 6 months to 170 months. Among these 131 cases, 3 (2.3%) locally recurred during the course of follow-up; one with a positive margin and two with negative

Table 1
Comparison of benign and borderline phyllodes tumors.

Characteristics	Total PT	Benign PT	Borderline PT	<i>p</i> value
	N (%)	N (%)	N (%)	
Age (years)				
Median (range)	36 (16–69)	36 (16–69)	48 (27–65)	0.04
<50 years old	186 (91)	179 (94)	7 (50)	<0.001
≥ 50 years old	19 (9)	12 (7)	7 (50)	
Laterality				
Left	97 (47)	93 (49)	4 (29)	0.15
Right	108 (53)	98 (51)	10 (71)	
CNB diagnosis				
PT or favor PT	23 (29)	20 (27)	3 (50)	0.45
Fibroepithelial lesion	26 (33)	24 (32)	2 (33)	
FA or favor FA	28 (34)	27 (37)	1 (17)	
Stromal fibrosis	2 (3)	2 (3)	0 (0)	
Spindle cell lesion	1 (1)	1 (1)	0 (0)	
Size (mm)				
Median (range)	23 (3–140)	23 (3–140)	32 (10–83)	0.14
Border ^a				
Circum./pushing	72 (73)	69 (77)	3 (33)	0.01
Infiltrative	27 (27)	21 (23)	6 (67)	
Stromal overgrowth ^a				
Present	19 (19)	17 (19)	2 (22)	0.81
Absent	80 (81)	73 (81)	7 (78)	
Atypia ^a				
Mild	80 (81)	75 (83)	5 (56)	0.04
Moderate	19 (19)	15 (17)	4 (44)	
Mitotic rate ^a				
Median (range)	1 (0–10)	1 (0–4)	6 (4–10)	<0.001
<5	94 (95)	90 (100)	4 (44)	<0.001
≥ 5	5 (5)	0 (0)	5 (56)	
Initial margin				
Negative	54 (26)	52 (27)	2 (14)	0.48
≤ 1 mm	29 (14)	26 (14)	3 (21)	
Positive	122 (60)	113 (59)	9 (65)	
Re-excision				
No	60 (40)	55 (40)	5 (42)	0.78
Yes	91 (60)	84 (60)	7 (58)	
Final surgical margin				
Negative	145 (70)	135 (71)	9 (65)	0.58
≤ 1 mm	14 (7)	13 (7)	2 (14)	
Positive	46 (23)	43 (22)	3 (21)	
Follow-up (months)				
Median (range)	27 (6–170)	26 (6–170)	42 (8–132)	0.21
Local recurrence				
Yes	3 (2)	3 (2)	0 (0)	1.00
No	128 (98)	121 (98)	7 (100)	

Italic numbers represent the percentage, range, or *p* value. The bolded *p* values are statistically significant values.

Abbreviations: Circum., circumscribed; CNB, core needle biopsy; PT, phyllodes tumor; FA, fibroadenoma.

^a The numbers are based on 99 cases that a slide re-review was performed to document the histologic features.

margins. All three LR were benign PT; no LR was observed in cases with borderline PT (Table 2). The time interval to LR was 7, 42, and 62 months. Overall, there was no significant difference in initial margin status, re-excision rate, final margin status and LR rate between benign and borderline PT. Comparing the cases with LR and without LR revealed no significant difference in clinical or pathologic features (Table 2).

4. Discussion

The current guidelines recommend surgical excision with negative margins, greater than 1 cm, for the treatment of all PT in order to prevent LR. However, recent studies have suggested that the LR rate of benign and borderline PT is very low, regardless of margin status, suggesting that these tumors might be managed with close clinical and radiological follow-up instead of re-excision [7-17]. Also, the recent consensus review for PT of the breast recommends that negative margins should be achieved for only recurrent and malignant PT [18]. Our

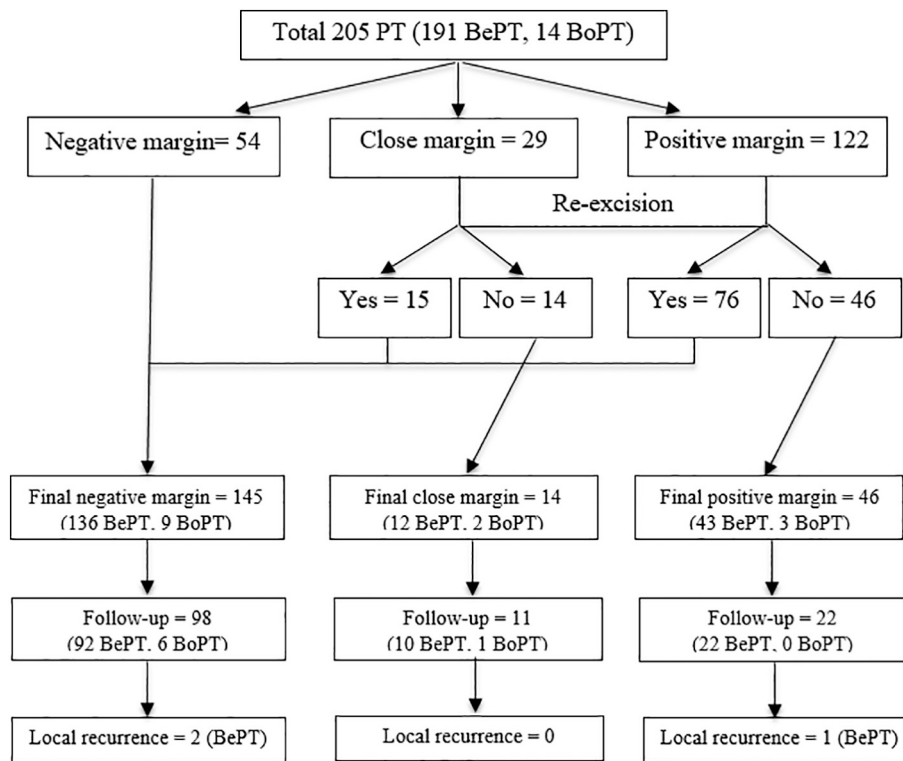


Fig. 1. Summary of cases according to surgical margin status and local recurrence. Abbreviations: BePT, Benign phyllodes tumor; BoPT, Borderline phyllodes tumor.

Table 2 Comparison of cases based on local recurrence status.

Characteristics	Total	Recurrence	No Recurrence	p value
	N (%)	N (%)	N (%)	
Age (years)				
Median (range)	37 (16–69)	33 (16–41)	37 (16–69)	0.26
<50 years old	119 (91)	3 (100)	116 (91)	1.00
≥50 years old	12 (9)	0 (0)	12 (9)	
Laterality				
Left	64 (49)	2 (67)	62 (48)	0.61
Right	67 (51)	1 (33)	66 (52)	
Grade				
Benign	124 (95)	3 (100)	121 (95)	1.00
Borderline	7 (5)	0 (0)	7 (5)	
Size (mm)				
Median (range)	40 (20–69)	25 (22–51)	40 (20–69)	0.87
Border ^a				
Circum./pushing	60 (71)	2 (67)	58 (71)	1.00
Infiltrative	25 (29)	1 (33)	24 (29)	
Stromal overgrowth ^a				
Present	11 (13)	0 (0)	11 (13)	1.00
Absent	74 (87)	3 (100)	71 (87)	
Atypia ^a				
Mild	69 (81)	2 (67)	67 (82)	0.47
Moderate	16 (19)	1 (33)	15 (18)	
Mitotic rate ^a				
Median (range)	1 (0–10)	0 (0–2)	1 (0–10)	0.89
Final surgical margin				
Negative + ≤ 1 mm	110 (84)	2 (67)	108 (84)	0.27
Positive	21 (16)	1 (33)	20 (16)	

Italic numbers represent the percentage, range, or p value.

Abbreviations: Circum., circumscribed.

^a The numbers are based on 85 cases that a slide re-review was performed to document the histologic features.

findings support the conclusions of the above-mentioned studies that the overall LR rate of benign and borderline PT is very low (2.3%) with no significant impact of surgical margin status on the local recurrence risk.

Among the recent studies, Moo et al. evaluated 216 benign PT in their study and found a LR rate of 1.9% (4/216), consistent with our study results [15]. Additionally, they found that LR rates in PT with positive surgical margins were not significantly different from those with negative surgical margins. Borhani-Khomani et al. reviewed 479 benign and borderline PT and found an overall LR rate of 6.3% with no significant difference between those with positive and negative margins [12]. A third study by Cowan et al. similarly reported a LR rate of 3% in 90 benign and borderline PT, finding no difference in LR rate between those with negative and those with positive margins [13]. Lastly, Yom et al. studied a collection of PT, including 252 classified as benign or borderline, and showed the LR rate for benign and borderline PT as 6% [16]. They also found that margin status was not significantly correlated with LR. Our study adds to this mounting body of evidence that calls into question the current assumption that negative margins are necessary to prevent LR in benign and borderline PT.

In a recent meta-analysis of 9234 benign, borderline and malignant PT from 54 studies, positive surgical margins were highly predictive of LR only in malignant PT [19]. The same relationship was not found in benign or borderline lesions. Their analysis identified several other significant clinicopathologic features predictive of LR, such as infiltrative borders, moderate/severe stromal cellularity, severe stromal overgrowth, and high mitotic count (≥10/10 HPF). A study by Chng et al. also reported that high mitotic count and stromal overgrowth are associated with LR [20]. A third study by Yom et al. further confirmed the association between LR and a high mitotic count [16]. While these studies identified several predictors of LR, they did not apply their analysis separately to only benign or borderline PT. In our study, none of the clinical, radiologic, or pathologic features were associated with LR, but further studies are needed to evaluate these features, particularly histopathologic features, as risk factors for LR of benign and borderline

PT.

The results of these studies may impact the current surgical management of benign and borderline PT. While the current treatment guideline is wide local excision for all PT regardless of subtype as well as re-excision for positive margins [3], the results of this study, along with others in the literature, suggest that re-excision for positive margins may not reduce LR. Wide local excision with margins of greater than 1 cm can prove to be challenging for multiple reasons. With respect to breast conservation surgery, there is a challenging balance between conserving as much healthy breast tissue as possible and removing all diseased tissue with required margin clearance in order to prevent LR. In the case of PT, it has been observed that microscopic projections of tumor often extend into the pseudocapsule of normal compressed breast tissue that surrounds the lesion, requiring the surgeon to remove more tissue than would be expected based on gross inspection [21]. This may lead to positive margins. In addition, in cases that re-excision of positive margins is attempted after lumpectomy, a simple mastectomy may be required to achieve the desired 1 cm margin [3,21]. The emotional and functional response of a patient to simple mastectomy compared to lumpectomy is highly individualized, however can have great negative effects. If repeat surgery for excision of margins is not necessary for reduction of LR, as the results of this study suggest, additional surgery puts the patient at great risk without any benefit.

Two of the key limitations of our study are its retrospective nature as well as the lack of follow-up information in approximately one-third of the study population, which could give rise to selection bias. This is particularly the case in our analysis of borderline PT, which is limited by the small sample size and relatively high number of patients lost to follow-up. Additionally, our definition of a close surgical margin was ≤ 1 mm rather than the ≤ 1 cm described guidelines, giving rise to the possibility of overcalling adequate margins. However, considering the very low LR rate in our study (a single PT with positive surgical margins went on to have LR), it is unlikely that this distinction had an effect on our results.

In conclusion, our study confirms recent literature that has demonstrated the very low rate of LR associated with benign and borderline PT regardless of their surgical margin status. With little evidence to support a difference in LR in benign and borderline PT despite margin status, re-excision for positive margin status seems to convey the risk of surgery to the patient without benefit. Based on these findings, close clinical and radiologic follow-up may provide a better course of management rather than re-excision when managing positive margins in benign and borderline phyllodes tumors.

Ethical approval

The study was approved and the requirement for obtaining informed consent was waived by the Northwell Health Institutional Review Board (19-0889-LHH). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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