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Risk of Local Recurrence of Benign and Borderline Phyllodes Tumors: A Danish Population-Based Retrospective Study

Kaveh Borhani-Khomani, MS[1], Maj-Lis Møller Talman, MD[2], Niels Kroman, MD, DMSc[3], and Tove Filtenborg Tvedskov, MD, PhD[3]

[1]University of Copenhagen, København N, Denmark; [2]Department of Pathology, Copenhagen University Hospital, Rigshospitalet, København Ø, Denmark; [3]Department of Plastic Surgery, Breast Surgery and Burns Treatment, Copenhagen University Hospital, Rigshospitalet, København Ø, Denmark

ABSTRACT

Purpose. To determine the recurrence rate of benign and borderline phyllodes tumors (PTs) of the breast, the association between the size of resection margin and risk of recurrence and the risk of progression of histological grading at recurrence.

Methods. Nationwide retrospective study on Danish women aged 18 years or older, operated from 1999 to 2014, with resected benign or borderline PTs. Information on age, size of primary tumor and recurrence, histological grade, surgical treatment, margin size, and local recurrence were collected from the national Danish Pathology Register.

Results. A total of 479 cases were identified; 354 benign (74 %), 89 borderline (19 %), 6 uncertain histological grading (1.2 %), and 30 possibly PT (6 %). The mean age at presentation was 45.6 years (range 18–85), the mean tumor size was 3.5 cm (range 0.5–21), and the mean follow-up time was 98 months (range 1.1–192). We identified 30 local recurrences, i.e., a recurrence rate of 6.3 %. Twenty-three recurrences had similar or lower histological grading than the primary tumor, one primary benign PT recurred as a tumor with unclear diagnosis, and one primary borderline PT recurred as malignant. The number of recurrences was too low, and the information on the size of the closest resection margin was too sparse to estimate an adequate margin size for excision of nonmalignant PTs.

Conclusions. The recurrence rate of PTs was considerably lower than previously stated in literature. No apparent pattern of progression in histological grading was found. The results do not justify wide excision margins of nonmalignant phyllodes tumors of the breast.

Phyllodes tumors (PTs) of the breast comprise 0.3–1 % of all breast neoplasms and 2.5 % of fibroepithelial breast lesions and are classified as benign, borderline, or malignant according to the World Health Organization.[1–4]

Several studies have shown a considerable risk of local recurrence of PT.[5–8] As a result, most institutions, including the guidelines from the Danish Breast Cancer Cooperation Group, recommend PTs removed with margins of at least 1 cm regardless of histological subtype—an approach known as "wide local excision" (WLE).[9] Mastectomy can be performed if adequate margins cannot be accomplished or if conservative surgery will yield an unacceptable cosmetic outcome.[2,10]

According to existing literature, WLE reduces the recurrence rate from approximately 46 to 21 % for benign PTs and 29 to 8 % for borderline lesions compared with local excision.[8] However, a few recent studies do not find surgical margin status predictive of local recurrence, especially for benign tumors.[1,11]

It is uncertain if an initially benign or borderline PT will yield a malignant local recurrence. Few studies have investigated the potential progression of histological grading and found the rate of malignant recurrence from initially benign or borderline PTs to range between 4–18 % and 13–33 % respectively.[4,12–14] These studies, however, are based on small sample sizes, and further investigations are required to reach more definite conclusions.

This study was designed to determine the recurrence rate of benign and borderline PTs and to examine whether the size of the resection margins affected the risk of local

recurrence. Furthermore, we investigated whether a progression of histological grading of PTs occurred at the recurrences.

MATERIALS AND METHODS

Study Design

This was a nationwide retrospective study of Danish women aged 18 years or older who were diagnosed with benign or borderline PTs of the breast. Data on women, treated between 1999 and 2014, were retrieved from the national Danish Pathology Register (DPR) (est. 1997). All departments of pathology have recorded all pathology data online to the DPR from the Danish Pathology Data Bank (DPDB) since 1999. The DPR has been updated daily since 1999 from the DPDB, and the contents of the two registers are identical. It is mandatory to report to the DPR using the Danish version of the Systematized Nomenclature of Medicine (SNOMED).[15]

Records on age at diagnosis, primary tumor size and location, recurrence, histological grading of primary tumor and recurrence, and the size of resection margins were attained from the database. Recurrence was defined as repeated diagnosis of PTs. The size of the closest resection margin was classified as clear (unspecified), not clear (unspecified), <1 mm, 1–5 mm, 5–10 mm, ≥10 mm, and unknown. The type of surgery performed was categorized as lumpectomy (i.e., all surgeries termed resection, excision, excisional biopsy, tumorectomy, and lumpectomy), mastectomy, and unspecified. If reexcision or mastectomy was performed following the initial lumpectomy, the size of the resection margin was established from the most recent surgical procedure. Gross and microscopic descriptions on reexcisions were obtained from the original pathology files.

Patients with foreign ID numbers and those diagnosed with hybrid terms, such as "fibroadenoma with phyllodal features" or "fibroadenoma phyllodes," were excluded from this study. In addition, patients diagnosed with primary PTs before 1999 according to the original pathology files were likewise excluded. The study was approved by the Danish Data Protection Agency (journal no. 2014-41-3595).

Statistical Analysis

Differences in patient age and tumor size between benign and borderline PTs and respective recurrences were determined using two-sided Student's t tests. Pearson's χ^2 test was employed to investigate differences in the risk of local recurrence between benign and borderline PTs. A two-sided P value <0.05 was considered significant for all the tests.

RESULTS

In total, 479 patients were included in the study with a mean follow-up of 8.2 years (range 0.1–16). The majority (74 %) had benign phyllodes tumors. The distribution between tumor subtypes is shown in Table 1.

Six patients (1.3 %) had bilateral PTs and 13 patients had bifocal tumors. The mean age at presentation was 45.6 years (range 18–85) (Table 1). Patients with benign PTs were on average 8.8 years younger than those with borderline lesions ($P < 0.00001$). The mean tumor size was 3.5 cm (range 0.5–21) (Table 1). Benign PTs were significantly smaller than borderline tumors ($P < 0.00001$).

Five and three patients had concurrent ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), respectively, and one patient had mixed dysplastic changes of the breast. Two patients had invasive ductal carcinomas with ipsilateral concurrent benign PTs.

Thirty patients (6.3 %) experienced a local recurrence. Of these, eight patients (1.7 %) experienced local recurrence more than once. Characteristics of the recurrences are shown in Table 2. The mean duration from excision of the primary tumor to excision of the recurrence was overall 3.75 years. Borderline tumors tended to recur more rapidly than benign lesions, although the difference was not statistically significant ($P = 0.476$).

The recurrence rate was greater for borderline tumors (9.0 %) compared with benign tumors (6.2 %), although the difference was not statistically significant ($P = 0.35$). None of the patients in the other groups experienced local recurrences. The mean size of the recurrent lesions was 5.0 cm (range 0.5–21). The size of the borderline recurrence was significantly greater than the primary lesion ($P = 0.0022$; Table 2). The risk of recurrence for benign PTs was not associated with tumor size of the primary lesion, with a recurrence rate of 7.4 % for tumors ≤2 cm compared with 4.7 % for those >2 cm ($P = 0.375$). Similarly, there was no association between risk of recurrence and tumor size of the primary lesion for borderline PTs, with a recurrence rate of 0 % for tumors ≤2 cm compared with 11.3 % for those >2 cm ($P = 0.159$). Tumor size was unknown in 119 cases.

The majority of the recurrences had similar or lower grade compared with the primary tumor (Table 2). One of the benign PTs recurred as a tumor with unclear diagnosis in which fibroadenoma was the differential diagnosis. Overall, 20 % of the recurred PTs experienced a progression in histological grading compared to the primary tumor. Twenty-five percent of the primary borderline tumors showed

TABLE 1 Characteristics and management of 479 primary phyllodes tumors in Danish women operated between 1999 and 2014

Variables	Total	Benign	Borderline	Benign/borderline	Borderline/malignant	Possibly phyllodes
Cases (%)	479 (100)	354 (73.9)	89 (18.6)	2 (0.4)	4 (0.8)	30 (6.3)
Follow-up (months)						
Mean	98	103	84	115	81	94
Range	1.1–192	1.6–192	1.1–180	108–129	17–149	5.4–167
Age (years)						
Mean	45.6	44.2	53.0	46.5	55.7	38.6
Range	18–85	18–85	18–85	43–50	47–69	19–67
Tumor size (mm)						
Mean	34.9	31.5	47.1	27.6	51.7	30.2
Range	5–210	5–200	9–210	25–30	45–65	7–100
Type of surgery						
Lumpectomy (%)	424 (88.5)	316 (89.3)	79 (88.8)	1 (50)	3 (75)	25 (83.3)
Mastectomy (%)	10 (2.1)	6 (1.7)	4 (4.5)	0 (0)	0 (0)	0 (0)
Unspecified (%)	45 (20.9)	32 (9.0)	6 (6.7)	1 (50)	1 (25)	5 (16.7)
Reexcision after initial surgery						
Re-resection (%)	111 (23.2)	69 (19.5)	36 (40.4)	1 (50)	2 (50)	3 (10)
Mastectomy (%)	9 (1.9)	0 (0)	6 (6.7)	0 (0)	2 (50)	1 (3.3)
None (%)	359 (74.9)	285 (80.5)	47 (52.8)	1 (50)	0 (0)	26 (86.7)
No. of local recurrences	30	22	8	0	0	0
Recurrence rate (%)	6.3	6.2	9.0	0	0	0

TABLE 2 Characteristics of recurrent phyllodes tumors in relation to primary benign and borderline lesions

Histological grade of primary lesion	Total	Benign	Borderline
No. of recurrent lesions	30	22	8
Time from exc. of primary PT to recurrence (mo)			
Mean	45	48	38
Range	5.3–117	5.3–117	13–80
Size of recurrent lesion (mm)			
Mean	49.8	33.5	88.4
Range	5–210	5–210	22–140
Histological grading			
Benign	18	16	2
Borderline	10	5	5
Malignant	1	0	1
Possibly phyllodes	1	1	0

regression in histological grading in the recurred PTs. One of the primary borderline PTs with heterologous components (osseous metaplasia) recurred as a malignant lesion. None of the benign lesions recurred as malignant PTs.

The correlation between margin size and risk of local recurrence is presented in Table 3 for benign PTs and Table 4 for borderline lesions. We found no clear correlation between the size of the resection margin and the risk of recurrences for either type of tumor. Only 11.1 % of the PTs, i.e., 8.5 and 25.8 % for benign and borderline lesions,

respectively, were removed with certainty using WLE. Approximately 13 % of the PTs were not removed with clear margins. Still, less than 10 % of these patients with unclear margins experienced local recurrence (Tables 3 and 4). In a substantial number of the lesions (34.9 %), margins were described as clear but the margin size was not specified. Four percent of the tumors had no description on margin status at all.

DISCUSSION

This study found a local recurrence rate of benign and borderline tumors of 6.2–9.0 %, which is much lower than previously stated in literature.[8] Despite only 11 % of the patients in this study undergoing WLE with certainty, the recurrence rate is still remarkably low, suggesting that WLE may not be necessary to prevent local recurrence. This is further supported by the fact that less than 10 % of the patients with tumorous tissue present at the resection margin experienced local recurrence. However, the low number of patients with recurrence and the large percentage of patients without a quantified description of margin sizes prevent giving suggestions of an optimal margin size.

Generally, most patients underwent preoperative diagnosis with fine needle aspiration, core needle biopsy, or both prior to excisional biopsy. In some cases, preoperative biopsy indicated phyllodes tumors. Nevertheless, only

TABLE 3 Margin status of primary recurrent and nonrecurrent benign PTs

Benign							
Margin status							
	Clear, unspecified no (%)	Not clear, unspecified no (%)	<1 mm no (%)	1–5 mm no (%)	5–10 mm no (%)	≥10 mm no (%)	Unknown no (%)	Total no (%)
No recurrence	136 (41.1)	48 (14.5)	22 (6.6)	49 (14.8)	29 (8.8)	29 (8.8)	18 (5.4)	331 (93.5)
Recurrence	8 (36.4)	5 (22.7)	1 (4.5)	2 (9.0)	1 (4.5)	1 (4.5)	4 (18.2)	22 (6.2)
Total	144 (40.7)	53 (15.0)	23 (6.5)	51 (14.4)	30 (8.5)	30 (8.5)	22 (6.2)	354 (100)

Data are numbers with percentages in parentheses unless otherwise specified

TABLE 4 Margin status of primary recurrent and nonrecurrent borderline PTs

Borderline							
Margin status							
	Clear, unspecified no (%)	Not clear, unspecified no (%)	<1 mm no (%)	1–5 mm no (%)	5–10 mm no (%)	≥10 mm no (%)	Unknown no (%)	Total no (%)
No recurrence	18 (22.2)	8 (9.9)	6 (7.4)	13 (16.0)	13 (16.0)	23 (28.4)	0 (0)	81 (91)
Recurrence	5 (62.5)	1 (12.5)	1 (12.5)	1 (12.5)	0 (0)	0 (0)	0 (0)	8 (9)
Total	23 (25.8)	9 (10.1)	7 (7.9)	14 (15.7)	13 (14.6)	23 (25.8)	0 (100)	89 (100)

11 % of the patients underwent WLE and the reexcision rate was low, i.e., approximately 25 %. The low number of patients undergoing WLE and low number of reoperations are partly due to the inadequate data on the margin size but also may be explained by some patients choosing a "watch-and-wait" approach rather than undergoing additional surgery, or merely declining additional surgery and general anesthetics.

Size of margins for excision of PTs has been discussed in several studies. Barth et al. reviewed 20 small retrospective studies to evaluate the recurrence rate of PTs after WLE and local excision.[8] The study found overall recurrence rates of 8–29 and 21–46 % for benign and borderline tumors after WLE or local excision. However, the review is limited by the low number of patients in each study: a total number of only 39 patients in the borderline group and the lack of information on tumor involvement of margins in the lesions that were treated by local excision. Recent studies involving larger sample sizes have not been able to demonstrate similar recurrence rates nor a significant association between margin size and risk of recurrence.[1,11] Yom et al. found that clear margins <0.1 mm were not associated with a higher local recurrence rate compared with the ≥0.1 mm group.[11] Kim et al. similarly did not find surgical margin status predictive of local recurrence particularly for benign PTs.[1] These results are in line with those found this study.

We found no apparent pattern of progression in histological grading at recurrences. The majority of the recurrences had similar or even lower histological grading than the primary tumor. Only one recurrence was classified as malignant. However, this tumor showed heterologous elements as osseous components, which correlate with malignant PTs.[16] This implies that primary underdiagnosis could have been the case. The proportion of malignant recurrences among the total number of recurrent PTs was 0 and 12.5 % for benign and borderline PTs, respectively, which was much lower than the 4–18 and 13–33 % found in other studies.[4,12–14,17] The study by Akcakaya et al. found a proportion of malignant recurrences of approximately 14 % and stated that local recurrence is suggestive of an aggressive tumor or malignant transformation.[17] We found that only eight patients had local recurrence more than once, indicating that in a small number of patients, local recurrence may be suggestive of a locally aggressive tumor rather than malignant transformation with metastatic potential.

The risk of bilateral disease was very low. This is in line with the results from previous studies where the incidence of bilateral disease has been reported to range between 0 and 3.5 %, indicating that examination of contralateral breasts at follow-up of patients with PTs might not be needed.[18]

There was no significant association between risk of recurrence and tumor size for borderline PTs. However, a

trend was observed towards higher risk of recurrence in patients with tumor size >2 cm, where 11.3 % experienced a recurrence compared with none with tumor size ≤2 cm. It cannot be excluded that a larger sample size would have revealed a significant difference.

Only two patients (0.7 %) in this study had concurrent invasive breast carcinomas. This breast cancer incidence is of the same magnitude as breast cancers found at the first screening round.[19] Only case reports of breast carcinomas with concurrent PTs has been described in the literature, and an etiological relationship between PTs and carcinomas is not evident.[20]

The strengths of this study include its large sample size of 479 patients. Given the fact that PTs are uncommon, a population-based study like this, which includes patients during several years, is needed. Our datasets are based on the Danish population, which is mainly constituted of Caucasians. The frequency of PTs is higher among Asian women compared with women in western countries with a predominantly Caucasian population.[21].It is unknown whether the findings of our study also apply to a population with a different demographic than the Danish. The data from the DPR has almost 100 % coverage and approval of all diagnostic statements by pathologists ensures a high quality of the registry. In addition, all records are subjected to error tracing, such as missing mandatory data or incorrect ID number.[15]

The relatively long follow-up of 98 months (8.2 years) is an additional strength of the study. The duration from excision of the primary tumor to recurrence in our study was approximately 4 years, although it ranged considerably. Borderline PTs tended to recur faster than benign lesions. Due to large range in time to recurrence, it is important to have a sufficiently long follow-up period. Previous studies had shorter mean follow-up periods, ranging from 21 to 96 months.[1,2,5,6,11,17,18,22–26] Still, local recurrence occurred up to 10 years after excision of the primary lesion in our study, and it cannot be excluded that an even longer follow-up would have revealed additional recurrences.

This study does have some potential limitations. Apart from the limitation in terms of the retrospective nature of the study, misclassification could arise if pathologists employ different criteria for diagnosis of PTs. The DBCG guidelines recommend a semiquantitative method for diagnosis and histological grading of PTs, in which quantitative analysis such as Ki-67 immunohistochemistry may be useful.[27,28] However, only a small number of the pathology reports included the Ki-67 proliferation index and its significance in evaluating the risk of recurrence was not included in this study. In addition, no objective biomarker has been found to aid the diagnosis of PTs. Investigation of biomarkers, including epidermal growth factor receptor and c-kit, to determine their role in tumor progression from fibroadenoma to malignant PT has given inconsistent results.[18]

The distinction between PTs and various subtypes of fibroadenomas, and the determination of histological classification of PTs can be complicated, even after surgical excision. In this study, 6.3 % of the patients had uncertain diagnosis with both PTs and various subtypes of fibroadenomas being considered. In addition, 1.2 % of all the patients had unclear histological classification of PTs in the pathology reports. Similar difficulties in the diagnostics of PTs have been found in other studies. Khazai et al. found that a breast pathology second review identified clinically significant discrepancies in 11 % of patients.[29] One of the primary areas of difficulty was histological grading. Lawton et al. found that there were substantial interobserver variability by pathologist, impeding the establishment of firm diagnoses, especially between PTs and cellular fibroadenomas.[30] Overall, it indicates that the diagnostic criteria for PTs may be too weakly defined for pathologists to firmly diagnose PTs and ascertain the correct histological grading.

Another limitation of our study was the inadequate quantification of margin size in a substantial number of pathology reports, which prevented determining the optimal margin size. Further research on the association between margin size and risk of local recurrence is required to reach definite conclusions. Nevertheless, based on the low recurrence rate found in this study, along with the results from recent studies with similar large sample sizes, and the low risk of initially benign or borderline lesions recurring as malignant lesions, it is suggested that margins sizes >1 cm are overestimated for surgical excision of nonmalignant PTs.[1,11]

In conclusion, mammary PTs appear to have a much lower recurrence rate than previously stated in literature. Furthermore, no apparent pattern of progression in histological grading was observed at recurrence. The number of patients diagnosed with recurrence of PTs was too small to establish an optimal margin size. However, the resection margin size of at least 1 cm may be redundant and reexcision should only be considered when tumor tissue is observed "on ink."

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