Surgical Management of Benign and Borderline Phyllodes Tumors of the Breast

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Abstract: Phyllodes tumors (PT) are uncommon fibroepithelial breast neoplasms and there is currently no clear consensual treatment for these tumors. The aim of our study was to evaluate the surgical management and outcome of benign and borderline PT. We retrospectively assessed 76 cases of benign or borderline PT managed at the Leon Berard comprehensive cancer center in Lyon, France between July 2003 and December 2013. The mean age at diagnosis was 37.9 years and the median follow-up was 58 months. Seventy-five patients (99%), with a mean tumor size of 27 mm, underwent a breast-conserving procedure. The tumor margins were considered positive (when the tumor was present at the inked surgical section) in seven of 76 cases (9%) and negative in 65 out of 76 cases (86%). We observed the presence of small negative surgical margins <10 mm in 89% and <1 mm in 71% of the patients. Although no re-excision was performed to increase these margins, we did not see any increase in the local recurrence rate (4%) when compared to recurrence rates reported in the literature. We thus suggest that systematic revision surgery for close or positive surgical margins for benign PT should not be systematically performed. However, as recurrences occur within 2 years of initial excision, we recommend a regular clinical and imaging follow-up especially during this period for which patient’s compliance is essential.

Key Words: benign phyllode tumor, borderline phyllode tumor, surgical margins

Phyllodes tumors (PT) are uncommon fibroepithelial tumors that account for 0.5 percent of all breast malignancies. They can affect women of all ages with a median age at presentation of 45 years. Only a few cases have been reported in men (1). Since Johannes Mueller first described “cystosarcoma phylloides” in 1838, many synonyms and histologic classification systems have been used. Currently, according to The World Health Organization (WHO) (2) the suitable terminology is “phyllodes tumors.” Their classification into benign, borderline, or malignant tumor is based on histologic parameters such as stromal cell atypia, mitotic activity, stromal overgrowth, stromal necrosis, stromal heterologous component, and infiltration of normal breast tissue.

Clinically, PT appear as mobile painless palpable mass in the breast (3). Their detection by imaging is not pathognomonic and their histologic distinction from fibroadenomas is not easy, particularly for benign PT (4,5). Consequently, accurate preoperative histologic diagnosis on core needle biopsy and especially distinction from fibroadenoma is difficult due to insufficient sampling. The underestimation rate in these conditions is up to 50%, which makes the surgical planning complicated. In fact, a nonoperative management or a simple enucleation is widely adopted for fibroadenomas, whereas the mainstay of treatment for PT is wide surgical excision irrespective of tumor grade or good cosmetic outcome.

Given their rarity, epidemiologic data and consensual clinical practice recommendations for treatment of PT are insufficient. Still, extent of initial resection and need of revision surgery to have “adequate” margins are controversial.

The aim of this retrospective study was to examine the clinicopathological features and clinical outcome of 76 benign and borderline PT and discuss
their therapeutic aspects. The terminology “Phyllode Tumor” represents a heterogeneous group of tumors including benign and borderline PT as well as malignant PT that have a more aggressive behavior and an increased propensity for rapid growth and metastatic spread. To have a homogeneous series, we voluntarily excluded the malignant PT of this study.

MATERIALS AND METHODS

Between July 2003 and December 2013, the medical records of 76 cases of benign or borderline PT, managed at the Leon Berard comprehensive cancer center in Lyon and prospectively saved in a dedicated data base, were reviewed retrospectively. Malignant PT were excluded.

The histotype of PT was assessed on the basis of the WHO criteria including the extent of cellular atypia, mitotic activity, tumor margin (circumscribed or infiltrative), stromal pattern, and differentiation.

Clinical and pathologic features were reviewed from medical records: age at diagnosis, circumstances leading to diagnosis (palpation or imagery), preoperative diagnosis on biopsy and its accordance with the final diagnosis, type of surgery, tumor size (determined from a pathologic measurement when available). Surgical margins were analyzed in detail.

We defined two groups of patients according to the thickness of the nearest resection margin given: (i) positive excision margin when the PT was present at the inked surgical section; (ii) negative excision margin when the PT was not present at the inked surgical section even when this margin was <1 mm. Each time the excision margin was negative, the thickness of the resection was recorded. Follow-up was obtained by outpatient’s visits to the hospital, interviews with patients (direct phone calls) or contact with treating physicians outside of the hospital.

Nature of follow-up (clinical or by imaging), time to recurrence, nature of recurrence, and outcome were reviewed. New primary phyllode tumor was defined as a recurrence located in a different site of the primary tumor (other quadrant in the same breast). Local recurrence was defined as a recurrence near the initial tumor bed within the same quadrant.

Categorical variables were expressed as percentages and continuous variables as means, standard deviation and range. Progression-free survival rates were estimated using the Kaplan–Meier method. Statistical analysis was performed using the statistical packages SPSS 12.0 (Chicago, IL).

RESULTS

Clinical Features

From 2003 to 2013, we identified 76 cases of breast benign or borderline PT (Table 1). All cases occurred in female patients. Clinical presentation was as usual nonspecific with palpable, mobile and painless mass in the breast. A total of 80% of patients underwent core needle biopsy before surgery. The underestimation rate was 15% (fibroadenoma) and the results were undetermined (between fibroadenoma and benign PT) in 49% of the biopsies. (Table 2).

Mean age at diagnosis was 37.9 years (range 15–65, ±11.9 SD). 99% of patients underwent a breast-conserving procedure. Wire-guided surgery was used in 36% of the cases. Only one patient underwent mastectomy as primary surgery for a 130 mm borderline PT on histopathological analysis. No patient had lymph node dissection. None of them was treated with adjuvant therapy.

Histopathologic Features

On histopathological analysis (Table 3), 67 (88%) of tumors were benign PT and 9 (12%) borderline PT. The mean tumor size was 27 mm (range 7–130, ±19.2 SD). Tumor size was unknown in four cases.

Surgical margins were available for 95% (n = 72) of patients.

Only seven patients had positive surgical margins.

Among patients with negative surgical margins (90%; n = 65):

| Table 1. Patient’s Characteristics (N = 76 Patients) |
|-----------------------------------------------|
| Mean ± SD (range) | n (%) |
| Age mean (years) | 37.9 ± 11.9 (15–65) | 76 (100) |
| Diagnosis | | |
| By palpation | 50 (66) |
| By ultrasound | 26 (34) |
| Preoperative biopsy | 61 (80) |
| In accordance with final diagnosis | 22 (29) |
| Type of surgery | | |
| Breast conserving | 75 (99) |
| Wire-guided | 26 (34) |
Table 2. Comparative Histopathological Diagnosis on Core Needle Biopsy and Final Analysis (N = 61)

| Final diagnosis | Biopsy | Benign PT | Borderline PT | Undetermined (FA or PT) |
|-----------------|--------|-----------|---------------|------------------------|
| FA              | 0      | 0         | 0             | 0                      |
| Benign PT       | 8      | 21        | 0             | 24                     |
| Borderline PT   | 1      | 1         | 0             | 6                      |
| Total           | 9 (15%)| 22 (36%)  | 0 (0%)        | 30 (49%)               |

FA, Fibroadenoma; PT, Phylloide tumor.

Table 3. Histopathological Characteristics (N = 76)

|                      | Benign (n = 67) | Borderline (n = 9) | Total (N = 76) |
|----------------------|-----------------|--------------------|----------------|
| Size, mean SD (range)| 35 ± 15.1 (7-70) | 29 ± 37.6 (8-130)   | 26.9 ± 19.2 (7-130) |
| Surgical margins, n (%)|                 |                    |                |
| Negative             | 58 (87)         | 7 (78)             | 65 (86)        |
| Positive             | 6 (9)           | 1 (11)             | 7 (9)          |
| Unknown              | 3 (4)           | 1 (11)             | 4 (5)          |
| Recurrence           | 6 (9)           | 1 (11)             | 7 (9)          |

- 71% (n = 46) of patients had margins <1 mm (93%; n = 43 of patients with benign PT and 7%; n = 3 of patients with borderline PT)
- 18% (n = 12) of patients had margins ≥1 mm and <10 mm
- 11% (n = 7) of patients had margins ≥10 mm

All patients initially diagnosed on core needle biopsy as fibroadenoma had negative surgical margins.

Follow-Up/Recurrent Disease

Median follow-up was 58 ± 37.2 months (range 0–126 months). A total of 89% of patients had an imaging follow-up and 88% a clinical follow-up visit (physical examination).

We observed three local recurrences (4%) and three recurrences in a different quadrant of the same breast, which we called “new primary PT” (4%).

Five of these six recurrences were discovered by systematic ultrasound follow-up and one by physical examination.

Local Recurrence (Three Cases) The primary tumor was a benign PT in two cases (with positive surgical margins) and borderline PT in one case (with negative surgical margin – thickness 2 mm). They all relapsed as benign PT. For one of the two patients with primary benign PT with positive margins, the relapse was discovered by physical palpation. For the two others patients, the relapse was discovered by systematic ultrasound follow-up.

For local recurrence, the 5-year disease-free survival rate was 95.1% and the mean time to relapse was 11.3 ± 1.5 months (range 10–13 months).

New Primary PT (Three Cases) (in a Different Quadrant of the Same Breast) In all cases, the primary tumor was a benign PT. One had positive excision margin and relapsed as benign PT. One patient had nonavailable surgical excision margin and relapsed as benign PT. One patient had a primary benign PT of 25 mm with negative excision margin (thickness 7 mm) in the upper inner quadrant of the left breast and relapsed with a 65 mm borderline PT in the lower outer quadrant of the same breast. This patient then underwent a mastectomy with sentinel lymph node dissection.

All these recurrences were discovered by systematic ultrasound follow-up. For new primary tumor, the 5-year disease-free survival rate was 94.9% and the mean time to relapse was 12.7 ± 8.1 months (range 4–20 months). All patients with local recurrence or new primary PT in a different quadrant of the same breast had a new conservative surgical treatment.

Tumors with Positive Surgical Margins Seven patients had positive surgical margins. Among these seven cases, three relapsed (two with local recurrence and one with new primary PT in the same breast). Patients underwent a new complete surgical excision with breast conservation.

No re-excision was performed on the four other patients with positive margins. All of them had a regular follow-up by physical examination and imaging.

DISCUSSION

Phyllodes tumors account for 0.5% of all breast neoplasms. These tumors are classified as benign, borderline, and malignant according to the WHO histotypes criterias (2). Their prognosis and clinical course are poorly understood. Nevertheless, malignant PT are considered as cystosarcoma and tend to have a more aggressive behavior, both locally and distantly (6,7). Current studies on PT are based on the analysis of benign, borderline and malignant PT together resulting in a very heterogeneous group. Due to the very different behavior and outcome of malignant PT compared to benign and borderline PT, we voluntarily
excluded malignant PT to have a more homogeneous series.

Preoperative diagnosis of PT is difficult because clinical and ultrasound examinations are no specific (3,4,8). PT are often first identified during clinical examination as a painless palpable mobile mass in the breast (66% in our series), especially in young patient not considered for systematic radiological breast cancer screening programs. They can also be suspected from abnormalities detected during imaging analyses (34% in our series). PT appear on mammography as round or lobulated benign-appearing opacity (4,5). On ultrasonography, PT look like solid hypoechoic well-circumscribed mass with no significant posterior shadowing. Therefore, PT are difficult to distinguish from fibroadenomas by imaging (5). Moreover, distinction between fibroadenomas and benign PT is almost impossible on preoperative core needle biopsies. As PT are part of a continuum, histopathological diagnosis is difficult and still somehow subjective (9). In fact, core needle biopsies have a poor correlation with postoperative pathologic report, as rates of false-negative as high as 30% have been reported in the literature (10,11). In our study, 80% of patients underwent core needle biopsies before surgery. The false-negative rate was 15% (with a preoperative diagnosis of fibroadenoma) and the diagnosis was unclear (between fibroadenoma and benign PT) in 49% of the cases.

The uncertainty of the preoperative diagnosis makes surgical procedures for fibroepithelial tumors difficult to plan. Indeed, recommended treatment of PT is a complete surgical excision with free margins containing normal breast tissue, whereas fibroadenoma could only be enucleated offering better cosmetic outcomes. The extent of resection and the thickness of margins for PT are still controversial. Some authors are in favor of a complete surgical resection with histologic negative margins (12), others recommend more than 1 mm margin (7,13,14), but most of the authors agree on a margin of more than 10 mm (7,15–17), resulting in difficulties to achieve a good cosmetic outcome. In the large study of Tan et al. (18) including 605 PT cases, the surgical margin status (positive or negative) appears to be an independent predictive factor of recurrence-free survival. Nevertheless, as it was a retrospective study, they were unable to establish a clearance margin distance. On the basis of these data and our series, we recommend a complete surgical resection with safe margins (and no enucleation), when benign PT or undetermined tumor (between fibroadenoma and benign PT) are suspected on core needle biopsy. Centimetric surgical margin should not be necessary for benign PT. Enucleation must be reserved for preoperative diagnosis of fibroadenoma, when an excision with narrow margin does not allow to keep good cosmetic results.

Indication of revision surgery is also ambiguous. In our series, 90% of patients had negative surgical margins and for 71% of them close surgical margin of less than 1 mm. None of them had revision surgery to increase margin. In the literature, there is no clear consensus about revision surgery in case of negative margins of less than 10 mm. In the study of the Institut Curie (17) including 165 PT, 28% of patients were in this situation (explained by false-negative preoperative diagnosis of fibroadenoma with treatment as simple enucleation); half of these patients had revision surgery and the other half had biannual follow-ups. There was no difference concerning the recurrence rate between these two groups. In accordance with these results and despite the very close surgical margins (71%, <1 mm) in our study, our local recurrence rate was not higher than what has been reported in the literature. Our local recurrence rate was less than 5% whereas local recurrence rate in other series varies from 8% to 13% (13,15,18,19). This low local recurrence rate could not be explained by missing information about patient’s outcome since all our patients have a regular radiological and clinical follow-up. This may be due to the exclusion of malignant PT in our series. In fact, most of the series reported heterogeneous population of PT, including malignant PT, which are associated with higher recurrence rates. Based on our data, revision surgery for benign PT does not seem mandatory. In addition, revision surgery is complex because the initial surgery often uses a periareolar incision distant of the initial tumor bed to achieve a better cosmetic result. And, contrary to infiltrative or in situ breast cancer, clips are not left on the tumor bed for fibroadenoma or PT. As a consequence, the possibility to achieve local disease control by re-excision appears uncertain, due to difficulty to accurately target the tumor bed.

When preoperative diagnosis of PT is made, surgeons try to remove a clear and safe margin around the tumor and to obtain a good cosmetic result looking at the tumor-to-breast ratio. However, it is not
CONCLUSION

Given their rarity, clinical behavior and prognosis of PT remain poorly understood. Nevertheless, benign and borderline PT have a less aggressive disease course than malignant PT. Due to their similarities on clinical, radiological and histologic examinations, these PT are often preoperatively misdiagnosed as fibroadenomas. As a consequence, if the mainstay of treatment for PT is surgery with a clear margin, enucleation without focusing on margins is often performed. We suggest that systematic revision surgery for close or positive surgical margins for benign PT should not be performed on carefully selected compliant patients. We also recommend surveillance with regular clinical and imaging follow-ups particularly during the first 2 years after therapy. Together, our study provides new insights for the surgical management of patients with benign or borderline PT, which should improve patients’ well-being and prevent tumor recurrence efficiently.

Acknowledgment

The authors would like to thank Dr Baptiste N. Jaeger for editing assistance.

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