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Clinical Outcome of Patients with Breast Phyllodes Tumors: A Retrospective Analysis of 129 Cases in Shiraz, Southern Iran

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Abstract

Background: Phyllodes tumors are uncommon neoplasms of the breast. Data about their outcome is limited. This study aims to evaluate patients diagnosed with phyllodes tumors in terms of local recurrence, distant metastasis and overall survival.

Methods: We retrospectively reviewed the medical records of 129 women with phyllodes tumors who referred to our center from 1999 to 2013. Clinical and pathological features, local and regional recurrence, distant metastasis and overall survival were determined. SPSS 15.0 statistical software was used for analysis.

Results: Mean patient age was 39 years (17-67 years). Mean size of the tumor was 5.38 cm. There were 105 (81.4%) benign, 8 (6.2%) borderline and 16 (12.4%) malignant tumors. The mean follow-up period of patients was 28 months (6 to 128 months). The rate of local recurrence among benign tumors was 3.8% (4 cases); in borderline cases the rate was 12.5% (1 case) and for malignant cases, it was 18.7% (3 cases). Three patients each recurred twice and one patient had local recurrence for a third time. Two patients died of malignant tumor-related disease - one due to advanced regional recurrence and lung metastasis, and the other to wide-spread metastasis. Another patient died from an unrelated cause (myocardial infarction) one year after surgery. For those with malignant phyllodes tumors, the five-year overall survival was 77.8% and disease-free survival rate was 85.7%.

Conclusion: Although, the prognosis for phyllodes tumors is good, the malignancy rate is higher in older patients and those with larger tumors. A higher local recurrence rate in malignant phyllodes tumors suggests the importance for adequate resection of margins in surgical management of these tumors.

Keywords: Breast, Phyllodes tumors, Outcome, Recurrence

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Introduction

Phyllodes tumors are uncommon fibroepithelial breast lesions classified as benign, borderline and malignant based on the degree of cellular atypia, stromal overgrowth and mitotic activity.[1] Borderline and malignant tumors appear to have higher potential for local recurrence.[2] These tumors have been initially described in 1774 but first fully classified in 1838 by Johannes Muller as cystosarcoma phyllodes.[3] There are no obvious differences in clinical characteristics and mammographic findings between phyllodes tumors and fibroadenomas. In contrast with breast carcinomas, phyllodes tumors arise from outside the ducts and lobules in breast stromal tissues. Stroma contains adipose tissue and ligaments that surround ducts, lobules, blood and lymphatic vessels. Phyllodes tumors consist of gelatinous solid and cystic sites that contain infarct and necrotic regions. These changes cause the specific leaf-like tumor shape (phyllode).[2] The first metastatic case has been discussed in an article in the American Journal of Cancer by Lee and Pack in 1931.[4]

One study reports that both epithelial and stromal cells are polyclonal in fibroadenomas. However, in phyllodes tumors, the epithelial cells are polyclonal and stromal cells are monoclonal.[5] These results demonstrate that fibroadenoma is a hyperplastic lesion rather than a neoplasm, and that phyllodes tumor is a neoplasm of the stromal cells.

Attention to clinical presentation is the first step for tumor diagnosis. Phyllodes tumor incidence age is 35 to 55 years in women.[5-7] A rapidly growing, benign appearing tumor is seen in most cases.[6,7] Although the median tumor size is 4 cm, there are reports of giant tumors 40 to 50 cm in size.[8,9] Diagnostic methods such as mammography, ultrasonography, MRI and Doppler sonography lack specificity for the diagnosis of phyllodes tumors. Fine needle aspiration (FNA) and core needle biopsy are other tests which may confirm phyllodes tumors with high cellular stroma and epithelial elements.

In order to manage phyllodes tumors, the National Comprehensive Cancer Network (NCCN) guideline suggests wide excisions with a margin of 1 cm or more. Narrower surgical margins may cause local recurrence. An absolute indication for mastectomy is not confirmed. Currently, the role of adjuvant radiotherapy and chemotherapy remain unclear although they are efficient as treatment for sarcomas.[8-12]

The rarity of phyllodes tumors, lack of patients and research about its pathology, clinical diagnostic tests and management methods, as well as the difficulty with differentiation between phyllodes tumor and fibroadenomas, even after pictorial tests and FNA, necessitate additional research in order to obtain an agreement for diagnosis and therapeutic options for these tumors.

In this retrospective study, we reviewed the clinic database of patients referred to Motahhari Breast Clinic from 1999 to 2013 with pathologically proven phyllodes tumors. The purpose of this study was to identify the most effective treatment and prognosis of patients with phyllodes tumors.

Materials and Methods

A total of 3156 breast cancer patients were admitted to the Shiraz Breast Clinic (affiliated with Shiraz University of Medical Sciences). We retrospectively reviewed the medical records of a series of 129 patients diagnosed with phyllodes tumors of the breast during a 14-year period, from 1999 to 2013. The extracted data included age, marital status, number of children, age at

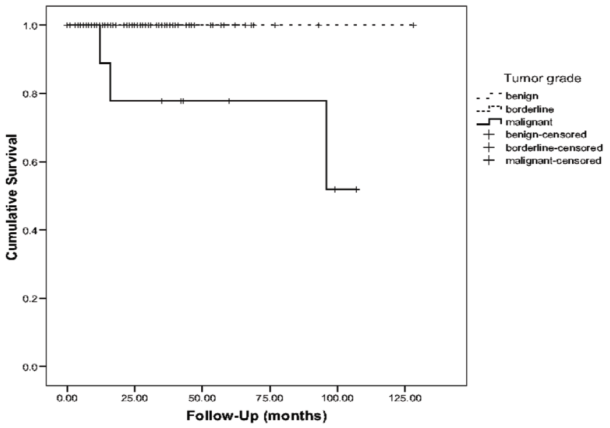

Figure 1. Patients' overall survival according to tumor grade.

marriage, age at first pregnancy, age at menarche, body mass index (BMI), history of oral contraceptive use, history of cancer, family history of breast cancer, FNA result, biopsy status, tumor size, tumor grade, type of surgery, history of other therapies, hormone receptor status, recurrence rate, type of recurrence and survival. Kaplan-Meier survival analysis was carried out for disease-free survival (DFS) and overall survival. The overall survival time was calculated as the date of surgery till the last follow up visit or death. Disease-free survival was defined as the date of surgery until the time of any first locoregional or distant metastasis. Local and regional recurrence, distant metastasis and DFS were determined. Statistical analysis was carried out using SPSS for Windows, version 15.

Results

Patient's ranged in age from 17 to 67 years with a mean age of 39 years. Of these, 6 (4.6%) were less than 20 years of age. There were 58.5% of patients who had children and 27.7% with no children. Data about the other patients (13.8%) was inadequate.

Patients' BMI ranged from 15 to 37.4 kg/m^2 with a mean patient BMI of 25.5 kg/m^2. In 54% of patients, the tumor was located in their left breasts, whereas it was present in the right breasts in 46% of cases. Tumors were benign in 105 (81.4%) patients, borderline in 8 (6.2%), and 16 (12.4%) had malignant tumors (Table 1). The mean follow-up period of patients was 28 months (6 months to 128 months).

Fine needle aspiration was performed in 59.8% of patients. The pathological report from these patients showed that 60% had fibroadenomas and 5.7% had phyllodes tumors. The FNA report was not phyllodes in 94.4% (sensitivity: 5.7%).

The mean tumor diameter was 5.38 cm, with a range from 1.5 to 34 cm. The tumor size was less than 2 cm in 3.8%, 2-5 cm in 52.8% and more than 5 cm in 39.8% of cases.

A considerable finding was the correlation between tumor size and tumor grade. The mean tumor size was 4.8 cm in benign and 7.7 cm in malignant tumors, which was statistically significant ($P \leq 0.001$). There was a correlation between patients' age and tumor grade such that older patients had higher rates of malignancy ($P=0.048$) (Table 1).

Primary surgical treatment was partial mastectomy in 90.4% and total mastectomy in 9.6% of cases. Axillary node staging was not routinely performed. Sentinel lymph node biopsy (SLNB) was performed in 6 (4.6%) cases and 8 (6.2%) underwent axillary lymph node dissection (AND). There were no positive lymph nodes reported for any patient. Totally, 64 lymph nodes were removed from the axilla, of which none had tumor involvement.

Local recurrence occurred in 8 (6.2%) patients. Of these, 3 patients had local recurrence for a second time and one patient had a third local recurrence. The rate of recurrence was 3.8% for benign, 12.5% for borderline and 18.7% for malignant tumors (Table 1). The treatment for local recurrence was mastectomy in two patients and partial mastectomy in the other.

Two patients died due to malignant tumor-related disease, one from developed advanced regional recurrence and lung metastasis; the other from wide-spread metastases. Another patient died due to unrelated causes (myocardial

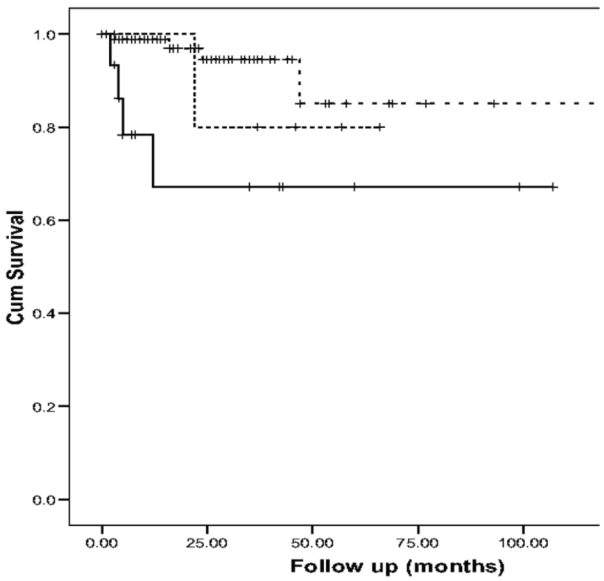

Figure 2. Patients' disease-free survival (DFS) according to tumor grade.

Table 1. Variables related to phyllodes tumors.

Characteristics	Benign	Borderline	Malignant
No. of patients	105	8	16
Age (yrs)			
(mean, range)	37.5 (18-63)	45.7 (32-67)	43.9 (17-64)
Tumor size (cm)			
(mean, range)	4.8 (1.5-18)	7.2 (2.5-19)	7.7 (3-15)
FNA results			
Fibroadenoma	48	2	2
Phyllodes	2	2	1
Positive for malignancy	5	0	1
Suspicious for malignancy	1	0	3
Fibrocystic	2	1	1
No malignant cells	6	0	3
Inadequate	3	0	0
Other	3	0	1
Missed data	35	0	4
Method of tissue sampling			
Incisional biopsy	2	0	1
Excisional biopsy	85	6	5
Missed data	18	2	9
Surgical approach			
Breast conservation	98	7	3
Simple mastectomy	7	1	3
Axillary management			
SLNB	5	0	1
AND	2	1	5
None	98	7	10
Chemotherapy			
Yes	0	0	2
No	105	8	14
Radiotherapy			
Yes	0	0	5
No	105	8	10
Recurrence	4	1	3
Mortality (disease-related)	0	0	2

*FNA: Fine needle aspiration; SLNB: Sentinel lymph node biopsy; AND: Axillary lymph node dissection

infarction) one year after surgery.

The mean overall survival (Figure 1) was 116 months and mean DFS (Figure 2) was 126 months. There were 120 DFS patients at a mean follow-up of 126 months (range: 123-129 months). The five-year overall survival rate was 97.1%. However, the five-year overall survival rates for benign and borderline tumors were both 100%, whereas for those with malignant phyllodes tumor, it was 77.8%.

Discussion

This retrospective study has analyzed 129 histopathologically proven phyllodes breast tumor cases to evaluate their outcome and response to standard treatment. Phyllodes tumors of the breast are uncommon neoplasms that represent less than 1% of all breast tumors.

There was no significant difference observed in the frequency of tumors between the right and left breasts. Among 129 cases, there were no cases of bilateral tumors observed. However, in a study of 13 cases by Macdonald et al., there were four cases of bilateral tumors reported.[13]

The majority of cases (79.6%) ranged from 20 to 50 years of age with a peak incidence between 40 and 45 years. Velázquez-Dohorn et al. reported a mean patient age of 42 years.[14] In a

study by Mishra et al., women from 35 to 55 years of age had the most involvement.[15]

Sawalhi and Al-Shatti reported a mean age of 39.8 years.[16]

In phyllodes tumors there is notable variation in tumor size. In the current study, we have observed that 52.3% of tumors were 2-5 cm and 39.8% were greater than 5 cm which correlated with data in the literature.[13,17,18] Kumar et al. reported the largest tumor (50 cm in greatest diameter).[8] In the current study, the largest tumor was 30 cm excised from a 36-year-old woman.[19]

In the current study, as with most studies, FNA had a low sensitivity for diagnosis of phyllodes tumors. In the majority of cases the biopsy method for definite diagnosis was exisional. The final histopathological results were benign phyllodes tumor in 81.4% of cases, borderline in 6.2% and malignant in 12.4%. Ramakant et al. reported that fine needle aspiration cytology (FNAC) was not beneficial.[20] In our series of patients with phyllodes tumors, only 24% could be correctly diagnosed with benign phyllodes tumors. The accuracy of FNAC in diagnosing phyllodes tumors was higher in malignant phyllodes tumors (63%) compared to benign tumors (24%). In a study by Foxcroft et al., FNAC had a low sensitivity of up to 60% in correctly diagnosing Phyllodes tumor.[21] Bandyopadhyay et al. reported that FNAC did not clearly help in differentiating fibroadenomas from phyllodes tumors.[22]

In the current study, 90.4% of patients underwent breast conservation and 9.6% were treated with simple mastectomy. A study by Kim et al. reported that 94.4% of patients underwent local and wide excisions, whereas 5.7% underwent mastectomy.[23] Blanco et al. reported that 6 out of 15 patients underwent mastectomy and the remaining 9 cases had local excision performed.[24]

There were no positive lymph nodes reported in any patients in the current study. Staren et al. reported axillary lymph node involvement in one out of 26 patients.[25] Minkowitz et al. described a single case of phyllodes with involvement of an axillary lymph node.[26] A study by Muttarak et al. reported that fewer than 1% of malignant phyllodes tumors spread to axillary lymph nodes and Macdonald et al. found lymph node involvement in 8 of 498 (1%) patients.[13,27]

Macdonald et al. reported that 76 out of 821 (9%) patients received radiation therapy.[13] In our study, 6 patients underwent radiotherapy and 2 received chemotherapy. Onkendi et al. reported that 2 patients received radiotherapy after wide local excision and 2 after mastectomy.[28] In a study by Mitus et al., adjuvant radiotherapy might be considered if tumor-free margins were <1 cm.[29] Mouna and Rhizlane reported that systemic chemotherapy must be explored for patients with metastatic malignant phyllodes tumors.[30]

Akin et al. reported that one out of 10 patients died due to lung metastasis one year after surgery.[17] A study by Bay et al. reported that 7 of 335 phyllodes tumor patients died of disease during the follow-up period.[31] Macdonald et al. reported that 81% (664 of 821) of patients survived and 19% (157 of 821) died. From these, 46% (72 of 157) died because of phyllodes tumors.[13] In our study, 3 patients died - 2 were attributed to tumor-related complications and one because of myocardial infarction.

Spitaleri et al., in a recent study that included 83 articles and 5530 patients, reported that local recurrence of phyllodes tumors were independent of histology.[32] However, this finding contrasted our study results. In the current research, the local recurrence rate among benign tumors was 3.8%, but 12.5% had borderline tumors, and 18.7% had malignant tumors.

In terms of distant metastasis, our result was similar to the literature where the overall metastasis rate for malignant tumors was higher than benign tumors.

In the current study, the five-year overall rate for malignant phyllodes tumors was 77.8%, whereas the DFS rate was 85.7%. Abdalla and Sakr[33] reported a five-year survival with no evidence of disease at 90% for patients with benign tumors compared to 69% for borderline and 61% for malignant phyllodes tumors.

Conclusion

In phyllodes tumor, the malignancy rate is higher in older patients and those with larger tumors. Malignant phyllodes tumors have higher local recurrence and distant metastasis rates than benign tumors. The low local recurrence rate and lack of distant metastasis in benign tumors allows for local excision as a therapeutic option when wide excision results in notable cosmetic disturbances, although the necessity of this strategy is careful follow up.

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Conflict of interest

No conflict of interest is declared.

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