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Management of malignant and borderline phyllodes tumors of the breast: our experience

Stefanos Zervoudis^{1,2,3}, Grigoris Xepapadakis¹, Nikos Psarros¹, Anastasia Bothou^{3,4}, Panagiotis Tsikouras⁴, Georgios Galazios⁴, Panagiota Kontogianni¹, Maria Papazian¹, Iordanis Navrozoglou², Georgios Iatrakis^{1,3}, Minas Paschopoulos²

¹Rea Hospital, Breast Clinic & Greek-French Breast Unit, Athens, Greece; ²Ioannina University Hospital, Ioannina University, Ioannina, Greece; ³University of West Attica, Athens, Greece; ⁴Alexandroupolis University Hospital, Alexandroupolis, Greece

Summary

Purpose: Phyllodes breast tumors (PT) range from benign lesions to malignant ones that may give distant metastasis. Preoperative diagnosis is difficult, while the treatment of borderline and malignant disease remains controversial.

Methods: Eighteen patients in 3 clinics were included in the study. Lumpectomy with large margins was performed in 15 patients, while mastectomy was performed in 3 patients. Lymph node excision was carried out in 3 patients with malignant tumors. Radiation therapy (RT) was delivered after a second lumpectomy in cases of local recurrence. Chemotherapy was used only in 2 patients with aggressive recurrent tumors.

Results: Borderline behavior was reported in 4 patients.

Lumpectomy was performed in these cases, with local recurrence in 2 of them. Malignant behavior was reported in 14 patients. Lumpectomy was performed in 10 patients and mastectomy in 3. Local recurrence was reported in 5 cases and in 2 patients recurrence after a 2^{nd} operation was also reported.

Conclusions: Borderline PT were treated conservatively and the prognosis was excellent, while malignant subtypes needed mastectomy in about 25% of the cases, The local recurrence rate was high, but the disease free survival (DFS) and the overall survival (OS) were also very high (94%).

Key words: breast cancer, borderline tumors, malignant tumors, Phyllodes tumors, breast tumors

Introduction

Phyllodes tumor (PT) of the breast is an unusual fibroepithelial neoplasm that accounts for less than 1% of breast tumors [1-10] (Figures 1 and 2). PT represents a range of neoplasms spanning from benign to malignant, capable of distant metastasis. Sixty-four percent of PTs are described as benign, while the remainder have been characterized as borderline and malignant subtypes [4]. The malignant subtype accounts for approximately 25% of the excised PTs [4]. However, only 5% of the malignant PTs, develop distant metastasis, most commonly in the lung, liver and bones [9]. Generally, PT is most common in patients during the fourth or fifth decade of life [4,10].

Clinically, most tumors appear as a smooth, multinodular, painless, palpable mass, while their size at presentation is variable [4,10]. However, their size is typically larger than fibroadenomas, although rapid increase in size has not been associated with malignancy [10]. In mammography, PTs present usually as smooth, polylobulated lesions, although only 20% of them give abnormal findings on screening mammography [10] (Figure 3). On ultrasound (US), they appear as solid, hy-

Corresponding author: Stefanos Zervoudis, MD, PhD. Rea Maternity Hospital, Andrea Siggrou 383 Ave, Paleo Faliro, Athens 175 64, Greece.

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Figure 1. Pathology of phyllodes tumor: Neoplasm includes bundles of striated muscle.

poechoic, well circumscribed masses that often include cystic areas (Figure 4). Wide excision with margins larger than 1 cm is the primary surgical approach and is suggested even in malignant cases [10] (Figure 5). For malignant tumors, the risk of local recurrence after wide excision is reported as 20–30%, which is higher than the rate of local recurrence when mastectomy is used as a primary treatment [4,5,10]. However, no impact on OS is reported [10].

Pre-operative diagnosis is difficult, while the treatment of both borderline and malignant types remains controversial [4,5]. Local recurrence in both benign and malignant disease is the main concern. The primary objective of the current study was to share our experience on PT regarding the effect of the wide excision on the local recurrence rate and on OS rate.



Figure 2. Pathology of phyllodes tumor: neoplasm infiltrated bundle muscle (immunohistochemical staining).



Figure 4. Phyllodes tumor in ultrasound: solid, hypoechoic, heterogenic, well-circumscribed masses.



Figure 3. Phyllodes tumor: digital mammography showing a tumor with irregular shape and microlobulated margins.



Figure 5. Surgical specimen of wide lumpectomy for malignant phyllodes tumor showing a tumor with irregular shape and microlobulated margins.

Methods

Eighteen patients in 3 breast clinics in Greece (Rea Hospital in Athens, Alexandroupolis University Hospital in Thrace, and Ioannina University Hospital, in Ioannina) were included in the study. The mean patient age was 49.8 years (range 32-71). The mean size of the tumor was 51.6mm (range 22-110). Diagnosis was based on the combination of mammography and US. Lumpectomy was performed with complete excision of the tumor with margins larger than 1 cm in 15 patients (83%) (Figure 5) and mastectomy was performed in 3 patients (17%).

Lymph node excision was applied in 3 patients (17%) with malignant tumors, although it is not classical. Extensive follow-up with physical examination, mammography (yearly) and CT-scan (thorax and abdomen) was performed in 100% of the patients. The cases of local recurrence were all treated by lumpectomy. Radiation therapy (RT) was administered in cases of local recurrence after a second lumpectomy. Moreover, chemotherapy was used only in 2 patients with an aggressive malignant recurrent PT. Further statistical analysis of the results was not employed, due to the small sample size.

Patients	Age, years	Tumor size, mm	Treatment	Recurrence, years	Recurrence after 2 nd surgery
1	32	40	Lumpectomy Margins>20mm	2	No recurrence
2	48	90	Lumpectomy Margins>10mm	1	No recurrence
3	48	25	Lumpectomy Margins>10mm	No recurrence	
4	52	32	Lumpectomy Margins>10,mm	No recurrence	

Table 1. Phyllodes borderline tumors

Table 2. Phyllodes malignant tumors

Patient	Age, years	Tumor size, mm	Treatment	Recurrence, years	Recurrence after 2 nd operation
5	43	35	Lumpectomy Margins>15mm	1	No recurrence
6	61	60	Lumpectomy Margins>10mm	2	After 3 years
7	62	110	Mastectomy	2	No recurrence
8	62	40	Lumpectomy Margins>10mm	1	No recurrence
9	36	45	Lumpectomy Margins>10mm	No recurrence	-
10	71	30	Lumpectomy Margins>10mm Lymph node biopsy Chemotherapy	No recurrence	-
11	38	90	Lumpectomy Margins>10mm	No recurrence	-
12	62	16	Mastectomy	No recurrence	-
13	57	31	Lumpectomy Margins>10mm	No recurrence	-
14	44	43	Lumpectomy Margins>10mm	No recurrence	-
15	55	65	Mastectomy	2	After 4 years
16	33	22	Lumpectomy Margins>10mm	No recurrence	-
17	41	54	Lumpectomy Margins>10mm	No recurrence	-
18	52	100	Mastectomy Lymph node biopsy	Recurrence Metastatic disease	-

Results

Borderline behavior was reported in 4 patients (22%) with a mean age 45.0 years and range 32-52 years (Tables 1 and 2). The mean size was 47.25mm (range 25-90mm). Lumpectomy was performed in 100% of the cases and local recurrence was observed in 2 of them (50%). Recurrent disease was treated with a second lumpectomy and the recurrence rate after the 2nd operation was 0%. The DFS and OS at 5 years was excellent (100%).

Malignant behavior was reported in 14 patients (78%) with a mean age 51.2 years (range 33-71). The mean tumor size was 57mm (range 16-110). Lumpectomy was performed in 10 (79%) patients, while mastectomy was needed in 4 (21%) patients. Local recurrence was reported in 5 cases overall (35%). The recurrence rate was 30% in patients that were initially treated with lumpectomy and 50% in patients that were initially treated with mastectomy and in 2 (14%) patients recurrence after 2nd operation was also reported. All recurrent cases were subsequently treated with lumpectomy, the recurrence rate after the 2^{nd} operation was 40% (observed in 2 patients) and the DFS and OS at 5 years was 100%. Metastatic disease (lung) was observed in one case (7% of the malignant cases) and resulted to the death of the patient in 2 years after the diagnosis.

Discussion

The general prognosis of the borderline PT that were treated conservatively was excellent. A second surgery was necessary later in 2 (50%) cases due to local recurrence, but the prognosis was 100% survival rate at 5 years. On the contrary, malignant PT needed mastectomy in 25% of the patients. The local recurrence rate associated with malignancy was high (reported in more than one third of the patients and in 50% of the patients treated with mastectomy), but the DFS and the OS rate was also very high 94%. Therefore, no significant disadvantage of breast conservative surgery compared to mastectomy was found. Unfortunately, our series does not allow to provide adequate information regarding the risk of local recurrence after excision with wide margins because of the small sample size. Recurrent tumors were treated with second lumpectomy and the recurrence rate after the second operation was 29%. Distant metastasis was detected in one of the 14 cases (7%). The site of the metastasis was in the lung (with multiple lesions). The rest of the imaging studies (abdominal CT etc.) was normal. Further management of this unique patient included chemotherapy. The patient died 2 years after diagnosis. Therefore, it would be possible to summarize the behavior of these rare breast tumors as neoplasms with frequent recurrence rate but very good prognosis.

Our results are in accordance with the relevant literature which recommends wide excision with a margin of at least 1 cm [3,5,10]. The reported mean age of occurrence varies from 41 to 44.9 years with no significant difference between borderline and malignant tumors [4], while the mean tumor size on presentation varies from 60 to 125mm for borderline cases and from 68 to 158mm for malignant ones [4,11]. Recurrence rates are reported to range between 14 and 21% with no significant difference between borderline and malignant cases [7,8,10]. The higher recurrence rate for borderline tumors in our series compared to previous references [12], may be explained by the small size of the sample (4 patients with borderline tumors) and the large size of the tumor in these cases. The risk of distant metastasis increases with the size of the tumor [9]. As in the unique case in ours series, the lung is one of the most common metastatic sites [9]. Other common locations include bones, liver and brain [9]. Finally, the role of RT and adjuvant therapies could not be adequately investigated, because of the small sample size and could be more carefully studied in future studies.

Conclusion

The management of the borderline and malignant phyllodes tumors is heterogeneous, depending on the histology and the primary surgical procedure. The initial surgery with wide margins is an important procedure to decrease the risk of recurrence.

Conflict of interests

The authors declare no conflict of interests.

References

1. Cimino-Mathews A, Hicks JL, Sharma R et al. A subset of malignant phyllodes tumors harbors alterations in the Rb/p16 pathway. Hum Pathol 2013;44:2494-500.

2. Kang YK, Guermah M, Yuan CX, Roeder RG. The TRAP/ Mediator coactivator complex interacts directly with estrogen receptors α and β through the TRAP220 subunit and directly enhances estrogen receptor function in 8. vitro. Proc Natl Acad Sci USA 2002;99:2642-7.

- Kim YJ, Kim K. Radiation therapy for malignant phyllodes tumor of the breast: an analysis of SEER data. Breast 2016;32:26-32.
- 4. Macdonald OK, Lee CM, Tward JD et al. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer 2006;107:2127-33.
- 5. Majeski J, Stroud J. Malignant Phyllodes Tumors of the Breast: A Study in Clinical Practice. Int Surg 2012;97:95-98.
- 6. Reinfuss M, Mituś J, Duda K et al. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. Cancer 1996;77:910.
- 7. Ross-Innes CS, Stark R, Holmes KA et al. Cooperative interaction between retinoic acid receptor-alpha and estrogen receptor in breast cancer. Genes Dev 2010;24:171-82.

- Stebbing F, Nash AG. Diagnosis and management of phyllodes tumour of the breast: experience of 33 cases at a specialist centre. Ann R Coll Surg Engl 1995;77:181-4.
- Oktar A, Mustafa M. Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. Ann Surg Oncol 2004;11:1011-7.
- 10. Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of malignant phyllodes tumors of the breast. The Breast 2017;33:91-6.
- 11. Wang H, Wang X, Wang CF. Comparison of clinical characteristics between benign borderline and malignant phyllodes tumors of the breast. Asian Pac J Cancer Prev 2014;15:10791-5.
- 12. Christensen L, Schiodt T, Bichert-Toft M. Sarcomatoid tumors of the breast in Denmark from 1977 to 1987. A clinicopathological and immunohistochemical study of 100 cases. Eur J Cancer 1993;29A:1824-31.