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Phyllodes tumour of the breast: Clinical follow-up of 33 cases of this rare disease

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1. Introduction

The phyllodes tumour has a low incidence of 1 in 100,000 women and accounts for only 0.5% of all breast neoplasms [1]. It was first described by Johannes Mueller in 1838 and has been assigned various names, among them ''cystosarcoma phyllodes'', which is a confusing term [2]. The tumours are rarely cystic and the term ''sarcoma'' tends to overstate the malignant potential. Today, the suitable terminology ''phyllodes tumour'' given by the World Health Organisation (WHO) classifies it into benign, malignant and borderline tumours according to histopathological features. The etiology of this rare disease is still unknown. It appears mainly in women, only five case reports describe this rare breast neoplasm in men with pre-existing gynecomastia [3]. Its incidence is higher in whites in general, in Latina whites and East Asians in particular [4]. The tumour occurs usually in women of 35–55 years [5,6]. Clinically it appears as a round, mobile and painless mass. There are no pathognomonic mammographic or ultrasound features [7,8]. Therefore, it is impossible to distinguish it clearly from fibroadenomas, which are often treated with a non-operative

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management. Still, the optimal treatment remains unclear. Discussing our data including patient characteristics, tumour biology, rates of local recurrence, incidence of distant metastases and survival, we outline the clinical management of primary, recurrent and metastatic phyllodes tumour.

2. Patients and methods

The data of 5270 patients with primary breast neoplasms treated at the Department of Obstetrics and Gynecology of the Grosshadern Hospital of Munich University between 1984 and 2005 were retrospectively analysed for the histopathologic diagnosis of a cystosarcoma phyllodes. Only patients with a histologically proven phyllodes tumour of the breast were included, and 33 such cases could be identified. Medical records and the histopathologic report of each patient were reviewed retrospectively. In our histopathologic reports, the World Health Organisation (WHO) criteria [9] are routinely applied, including the extent of cellular atypia and pleomorphism, the number of mitoses, tumour margin, stromal pattern and differentiation. A detailed analysis was also included for resection margins. We defined three groups of patients according to the width of the narrowest resection margin given, i.e. patients with resection margins of less than 1 mm, between 1 and 20 mm and patients with resection margins of more than 20 mm. Rate of recurrence and metastasis were further analysed for each group.

Clinical data, demographic, diagnostic and treatment information were primarily collected from the patient charts, including history of previous breast neoplasms. Further follow-up was carried out by chart review including outpatient visits, contact with treating physicians outside the hospital and direct phone calls to the patients. The patients' data were further reviewed for the surgical procedure performed (breast conserving operation versus mastectomy), and tumours were subdivided into three groups according to their maximum diameter (<5 cm; 5–10 cm; >10 cm) given in the histopathological report.

The main outcomes assessed were local and distant recurrence and survival. Statistical analysis was performed using Mann–Whitney *U*-test for the determination of significance of differences between patient groups; p values less than 0.05 were considered significant. All values are given as mean ± standard deviation. For time to relapse and to metastatic spread, median values were calculated additionally.

3. Results

Thirty-three patients with histologically proven cystosarcoma phyllodes of the breast could be identified. In 24 cases the suspicion of a phyllodes tumour had been raised by core needle biopsy taken before surgery. Core needle biopsy had not been performed routinely before 1992, so that the diagnosis was confirmed after primary surgery in the other nine patients.

Table 1
Patient and tumour related characteristica by local recurrence and distant recurrence; NA: not applicable

	Total	Local recurrence	Distant recurrence
Total	33	8	3
Histology			
Benigne	12	1	0
Borderline	10	2	0
Malignant	8	4	3
NA	3	1	0
Tumour size			
<5cm	13	2	2
>5 cm < 10 cm	10	4	1
>10 cm	5	2	0
NA	5	0	0
Age at diagnosis			
<40 years	7	2	1
≥40 years	26	6	2
Laterality			
Left	14	4	2
Right	17	4	1
Bilateral	1	0	0
NA	1	0	0
Surgical approach			
Breast-conserving surgery	19	6	0
Mastectomy	13	2	3
NA	1	0	0
Resection margins			
1 mm and ≤20 mm	25	7	2
>20 mm	8	1	1
Axillary lymph-node dissection at primary diagnosis			
Done	10	2	2
Not done	21	6	1
NA	2	0	0

Mean age at diagnosis was 47 (47 ± 12) years, median also was 47 years. The youngest and eldest patients were 18 and 77 years old at diagnosis, respectively. Two patients showed a history of previous fibroadenoma, but none had been diagnosed with breast cancer. Median follow up was 87 months (range 1–222 months). Fourteen (45%) of the tumours occurred in the right, 17 (55%) in the left breast. There was one case of bilateral phyllodes tumour, and in one case the laterality was not evident in the records. The tumours were classified histologically into benign (40%), borderline (27%) and malignant tumours (33%) based on standardized criteria; three tumours were unclassified (cf. Table 1). Surgery was conducted as a breast conserving procedure (19/32, 59%) or mastectomy (13/32, 41%), and the surgical approach remained unclear in one file. Only one patient was treated with adjuvant radiotherapy after primary surgery. Mean tumour size was 6.9 ± 6.0 cm. The smallest tumour was 1.4 cm in size and the largest was a very large phyllodes tumour of 30 cm diameter (Fig. 1).

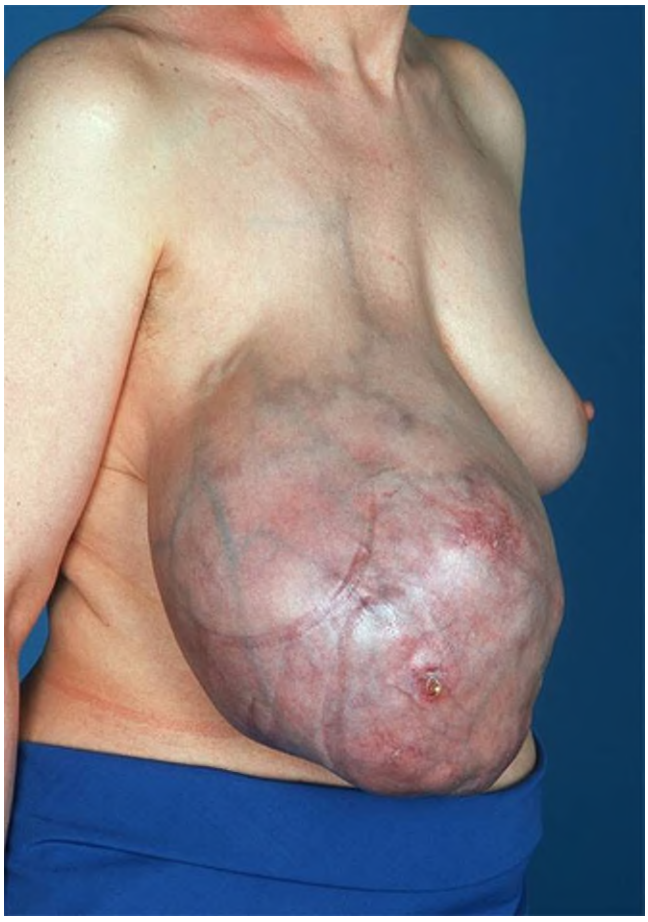

Fig. 1. Benign phyllodes tumour of the breast with a diameter of 30 cm in a 55-year-old patient. The visible vessels and the thinned skin are characteristic for large phyllodes tumours.

Forty-six percent of the (13 of 28) patients had a tumour of less than 5 cm diameter, 36% (10/28) had a tumour between 5 and 10 cm and 18% (5/28) had tumours of more than 10 cm diameter; exact total tumour diameters had not been recorded in the files of five patients. Surgical removal of lymph nodes was performed in 10 cases. Eight of these ten patients had the lymph node dissection at primary diagnosis, the two other at local relapse when reconstructive flaps (latissimus dorsi flaps) were performed simultaneously. All lymph node dissections except one were performed in histologically malignant or borderline tumours. The exception was the patient with the previously mentioned very large tumour. No lymph node infiltration was found in any of the patients who received axillary lymph node dissection.

Local recurrence occurred in 8 of 33 patients (26%) (Table 1). Seventy-five percent (6/8) of the patients with a local recurrence had been treated with breast conserving surgery. In patients with the diagnosis of a malignant phyllodes tumour we observed a recurrence rate of 50% (4/8), in those with borderline tumours of 20% (2/10), whereas those with benign phyllodes tumour had a local relapse rate of 8% (1/12). The time to relapse was 72 months in median and 83 on average (83 $\pm$ 48). Distant metastases were seen in three patients (9%) with a malignant phyllodes tumour (Table 1). The metastases were found in liver or lungs. They appeared in a median time of 40 (mean 30 $\pm$ 26) months. All patients with distant metastases in the follow up had been treated radically (mastectomy) at primary diagnosis. Two patients died during the follow up period: one had distant metastases at primary diagnosis and died 26 months later from liver insufficiency due to extensive metastatic spread. The other patient had a history of a malignant melanoma and cervix cancer and died with unknown cause 40 months after diagnosis of the malignant phyllodes tumour. Thus, accounting for the follow up time of the individual patient, we observe a 5-year survival rate of 89.5% and a 10-year survival rate of 84.6%.

One patient diagnosed with a metastasis was lost to follow up after 54 months. Neither regarding age at primary diagnosis nor in tumour size there was a significant difference between patients with local recurrence or metastasic spread and those without ($p = 0.28$ tumour size, $p = 0.74$ for age).

Altogether 75% (25/33) of the patients had resection margins between 1 and 20 mm width. In those cases a larger resection margin could not be achieved due to the tumour's proximity to the thoracic wall or the skin. Twenty-five percent (8/33) had a circular resection margin of more than 20 mm. Altogether, a local recurrence occurred in eight patients, with 7 (88%) of them with a resection margin of less than 20 mm width. Of the three patients with metastases, two had resection margins of less than 20 mm width.

The mean resection margin in our patient collective was 6.7 $\pm$ 7.9 mm. Patients with a local failure had an average tumour free resection margin of 4.1 $\pm$ 6.2 mm versus 7.5 $\pm$ 8.2 mm ($p = 0.20$) in patients without local recurrence. On average, there was no difference in the width of the resection margin for patients with metastases and those without (7.0 $\pm$ 11.3 vs. 6.7 $\pm$ 7.7; $p = 0.57$).

4. Discussion

The phyllodes tumour of the breast is a rare disease [1]. It occurs mainly in middle-aged women. Mean age ranges from 30 to 52 years in the literature [1,5,6,10,11], and our data show a mean age of 47 years at primary diagnosis. Patient age does not seem to be a prognostic factor [10,12,13].

The ratio of benign, borderline and malignant tumours found in this study compares well with some studies in literature [5,14] while other observers reported different ratios [15]. In the present study, malignant tumours accounted for 33% of the phyllodes tumours. The share of malignant phyllodes tumours described in literature varies from 8 to 45% [15]. One reason for this wide variation may be the low incidence of phyllodes tumours and the resulting small patient groups observed in the individual studies. But

also a lack of standardization in the interpretation of the histological features, which can be assumed regarding the different histological classification systems throughout the literature [5,6], may contribute to the inconsistency of the reported incidence of malignancy. Interestingly, two of our patients had a history of previous fibroadenoma, and Mangi et al. observed an 18% incidence of fibroadenomas in their study, suggesting a possible overlap and misdiagnosis between benign phyllodes tumour and fibroadenoma.

Surgical treatment is generally accepted as the most important and primary therapy for phyllodes tumours, regardless of its histological type. Yet, randomized studies comparing different operative procedures are lacking [10,16].

Most studies recommend a resection margin of more than 1–2 cm [5,6,16,17] based on the evidence that local recurrence occurs more frequently in patients with narrow surgical margins of less than 1–2 cm [6,14,15,18]. Our findings are in agreement with this data: In seven of the eight (87.5%) patients in whom a local recurrence occurred, the width of the resection margin had been less than 20 mm. This elucidates the importance of an adequate resection margin and confirms that a simple enucleation should be avoided [5,18]. However, an excision with the required margin is often impossible in huge phyllodes tumours because the surrounding normal breast tissue is too narrow. The fact that we could not achieve tumour free resection margins of 20 mm in 75% of our patients reflects the surgical limitations imposed by large tumour masses. Some studies claim an excision with a surgical margin of at least 1 cm to be the most important prognostic marker. In a meta-analysis by Barth et al. [19], 65% of all phyllodes tumour patients showed a local recurrence after local excision, compared to 36% after wide lumpectomy and 12% after mastectomy. Yet, there is no evidence that breast conserving therapy causes a reduced patient survival. Since local recurrence does not seem to be associated with systemic metastases, mastectomy is no longer considered to be the treatment of choice for malignant phyllodes tumour [5]. This data is in agreement with our findings as all patients with distant metastases had primarily received mastectomy. As radical mastectomy has not been shown to offer a benefit for overall survival, a breast conserving therapy with appropriate surgical margins can be regarded as adequate for all patients if the tumour-to-breast ratio is sufficient for a good cosmesis.

Based on our data, routine axillary lymph node dissection does not seem necessary. This is in agreement with the fact that lymph node involvement is rarely described in phyllodes tumours [6,11] and metastatic spread occurs mostly haematogenously. Axillary lymph node metastases are described in less than 10% of malignant phyllodes tumours [6]. Altogether, lymph node dissection seems only indicated in patients with palpable lymph node masses. Data regarding sentinel node biopsy in phyllodes tumours are lacking.

The organs most commonly affected by metastatic spread are the lungs, pleura and bones [6,16]. Seven percent of our patients were diagnosed with distant metastases (lung or liver). In literature, the incidence of metastatic spread of malignant phyllodes tumours varies from 25 to 40% [6,16,20] which is in the range of our data showing a rate of 30% in this patient group, in which only malignant tumours metastasized.

Prognostic markers like histopathologic features are discussed controversially. In our observation the histological tumour type seems to be most relevant for the clinical course of the disease. In literature, the incidence of local recurrence varies, probably mainly due to the small number of patients, between 9 and 29% [6,10]. Regarding our data, the variable follow-up of 86 months on average but less than one year in two of our patients may introduce a bias causing an underestimation of the incidence of recurrence or metastasis which occurred only after 83 and 30 months on average, respectively. Patients with a malignant tumour are at high risk for local recurrence (40%) and metastasic spread (30%). Therefore, the histopathologic classification seems to be the strongest prognostic factor in this disease. Our data showed a recurrence rate of 40% in malignant versus 25% in borderline tumours. Benign phyllodes tumours had a local relapse rate of 8%, and the small sample size can be assumed to be the main cause for the failure to reach statistical significance. De Roos et al. reported in a retrospective study that local recurrence was not significantly associated with tumour size, type of surgical procedure or patient's age [14]. This is in agreement with the results of this study in which we did not find a significant difference between patients with local recurrence or metastatic spread and those without, neither regarding age at primary diagnosis nor in tumour size ($p = 0.284$ for tumour size, $p = 0.739$ for age, Wilcoxon-W).

Neither radiotherapy nor chemotherapy play a dominant role for adjuvant therapy [21]. Yet, there are only few controlled studies addressing radiotherapy in phyllodes tumours patients which have a very limited statistical power due to their very small sample sizes [22]. Radiotherapy has been used with good results for local control of the disease [23]. There even is a study postulating adjuvant radiotherapy to improve the disease-free survival [24].

Different chemotherapy regimens have been applied in malignant phyllodes tumours. Doxorubicin and ifosfamide-based chemotherapies have shown some efficacy in women with metastatic spread of phyllodes tumours [13]. In one study of 101 patients, 4 patients were treated with chemotherapy [25] and a role for adjuvant chemotherapy in patients with stromal overgrowth was considered. This recommendation has so far not been confirmed in literature. Altogether, there is no clear indication for adjuvant chemotherapy for patients with phyllodes tumours [13,19,26–28]. None of our patients received adjuvant chemotherapy. Only in the metastasized stage one patient was treated with six cycles of CMF. This patient had had distant metastases at primary diagnosis and lived 26 months

after the beginning of treatment. In literature, the 5- and 10-year survival rates range from for 54 to 82% [25] and from 23 to 42% [6], respectively, for malignant phyllodes tumours. Looking at our data, we observe a 5-year survival rate of 89.5% and a 10-year survival rate of 84.3%, respectively.

5. Conclusion

Local excision with appropriate surgical margins seems adequate in all patients if the tumour-to-breast ratio is sufficient for good cosmesis. Based on our data, routine axillary lymph node dissection is not required, which is in agreement with the fact that lymph node involvement is rarely described in phyllodes tumours. Patients with a malignant tumour are at higher risk for local recurrence and metastatic spread. Therefore, the histopathological classification seems to be the strongest prognostic factor in this disease.

References

[1] Moffat CJ, Pinder SE, Dixon AR, Elston CW, Blamey RW, Ellis IO. Phyllodes tumours of the breast: a clinicopathological review of thirty-two cases. Histopathology 1995;27(3):205–18.

[2] Fiks A. Cystosarcoma phyllodes of the mammary gland—Muller's tumor. For the 180th birthday of Johannes Muller. Virchows Arch A: Pathol Anat Histol 1981;392(1):1–6.

[3] Pantoja E, Llobet RE, Lopez E. Gigantic cystosarcoma phyllodes in a man with gynecomastia. Arch Surg 1976;111(5):611.

[4] Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. Cancer 1993;71(10):3020–4.

[5] Salvadori B, Cusumano F, Del Bo R, et al. Surgical treatment of phyllodes tumors of the breast. Cancer 1989;63(12):2532–6.

[6] Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. Cancer 1996;77(5):910–6.

[7] Buchberger W, Strasser K, Heim K, Muller E, Schrocksnadel H. Phylloides tumor: findings on mammography, sonography, and aspiration cytology in 10 cases. AJR Am J Roentgenol 1991;157(4):715–9.

[8] Liberman L, Bonaccio E, Hamele-Bena D, Abramson AF, Cohen MA, Dershaw DD. Benign and malignant phyllodes tumors: mammographic and sonographic findings. Radiology 1996;198(1):121–4.

[9] Bellocq J, Magro G. Fibroepithelial tumors. In: Tavassoli F, Devilee P, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003. p. 99–103.

[10] Ciatto S, Bonardi R, Cataliotti L, Cardona G. Phyllodes tumor of the breast: a multicenter series of 59 cases. Coordinating Center and Writing Committee of FONCAM (National Task Force for Breast Cancer), Italy. Eur J Surg Oncol 1992;18(6):545–9.

[11] Holthouse DJ, Smith PA, Naunton-Morgan R, Minchin D. Cystosarcoma phyllodes: the Western Australian experience. Aust N Z J Surg 1999;69(9):635–8.

[12] Vorherr H, Vorherr UF, Kutvirt DM, Key CR. Cystosarcoma phyllodes: epidemiology, pathohistology, pathobiology, diagnosis, therapy, and survival. Arch Gynecol 1985;236(3):173–81.

[13] Hawkins RE, Schofield JB, Wiltshaw E, Fisher C, McKinna JA. Ifosfamide is an active drug for chemotherapy of metastatic cystosarcoma phyllodes. Cancer 1992;69(9):2271–5.

[14] de Roos WK, Kaye P, Dent DM. Factors leading to local recurrence or death after surgical resection of phyllodes tumours of the breast. Br J Surg 1999;86(3):396–9.

[15] Mangi AA, Smith BL, Gadd MA, Tanabe KK, Ott MJ, Souba WW. Surgical management of phyllodes tumors. Arch Surg 1999;134(5): 487–92 [discussion 492–3].

[16] Kapiris I, Nasiri N, A'Hern R, Healy V, Gui GP. Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. Eur J Surg Oncol 2001;27(8):723–30.

[17] Grimes MM. Cystosarcoma phyllodes of the breast: histologic features, flow cytometric analysis, and clinical correlations. Mod Pathol 1992;5(3):232–9.

[18] Rowell MD, Perry RR, Hsiu JG, Barranco SC. Phyllodes tumors. Am J Surg 1993;165(3):376–9.

[19] Barth Jr RJ. Histologic features predict local recurrence after breast conserving therapy of phyllodes tumors. Breast Cancer Res Treat 1999;57(3):291–5.

[20] Parker SJ, Harries SA. Phyllodes tumours. Postgrad Med J 2001;77(909):428–35.

[21] Sheen-Chen SM, Chou FF, Chen WJ. Cystosarcoma phylloides of the breast: a review of clinical, pathological and therapeutic option in 18 cases. Int Surg 1991;76(2):101–4.

[22] Hopkins ML, McGowan TS, Rawlings G, et al. Phylloides tumor of the breast: a report of 14 cases. J Surg Oncol 1994;56(2):108–12.

[23] Stockdale AD, Leader M. Phyllodes tumour of the breast: response to radiotherapy. Clin Radiol 1987;38(3):287.

[24] August DA, Kearney T. Cystosarcoma phyllodes: mastectomy, lumpectomy, or lumpectomy plus irradiation. Surg Oncol 2000;9(2): 49–52.

[25] Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer 2000;89(7):1502–11.

[26] Ward RM, Evans HL. Cystosarcoma phyllodes. A clinicopathologic study of 26 cases. Cancer 1986;58(10):2282–9.

[27] Burton GV, Hart LL, Leight Jr GS, Iglehart JD, McCarty Jr KS, Cox EB. Cystosarcoma phyllodes. Effective therapy with cisplatin and etoposide chemotherapy. Cancer 1989;63(11):2088–92.

[28] Guerrero MA, Ballard BR, Grau AM. Malignant phyllodes tumor of the breast: review of the literature and case report of stromal overgrowth. Surg Oncol 2003;12(1):27–37.