Eur J Cancer, Vol. 29A, No. 9, pp. 1252–1256, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Malignant Phyllodes Tumours of the Breast. A Clinical and Pathological Analysis of 55 Cases

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55 cases of malignant phyllodes tumours of the breast are described. 36 patients (i.e. 65.5%) of the studied group survived 5 years with no evidence of disease after surgery. It was proved that a simple mastectomy is sufficient therapy for patients with tumour limited to the breast. Metastases to the axillary lymphatic nodes are very rare. The main reason for treatment failure is distant metastases in the lungs. The only prognostic factor in the studied group was the grade of histological malignancy, determined by such criteria as the ratio between the malignant sarcomatous tissue and that typical for phyllodes tumour, the degree of cell polymorphism, mitotic activity, and possible multidirectional differentiation (towards malignant neoplasms of soft tissue and bones).
Eur J Cancer, Vol. 29A, No. 9, pp. 1252–1256, 1993.

INTRODUCTION

PHYLLODES TUMOUR represents 0.3–4% of breast neoplasms in females [1–4]. In men it is very rare and only a few cases have been described [5, 6]. In females it occurs most frequently between the ages 30 and 50 [5, 7–9], yet there are reported cases of leaf-like projections in breast tumours in adolescents as well as in elderly women [7, 9–14]. In most patients the disease takes a slow and indolent course; tumours usually reach a large size and are incapsulated without infiltrating the surrounding tissues [15–18]. However, in some cases the tumour growth increases rapidly and the tumour becomes clinically malignant (biphasic growth). In other cases the growth of phyllodes tumour is rapid and malignant from the onset (monophasic growth). Generally, 10–40% of phyllodes tumours take a malignant course with a high tendency to local recurrence and general dissemination [1, 2, 5, 10, 14, 17, 19, 20]. There is not much correlation between the clinical picture of phyllodes tumour and its microscopic appearance [3, 7, 8, 13, 15, 16, 21, 22]. Most authors admit that microscopic features, such as considerable atypia of the cells, excessive proliferation of the stromal cells with an intensified pleomorphism, high mitotic activity, and increased vascularity, may suggest malignant clinical course of neoplasm [1, 16–19, 21, 23]. There is still controversy over whether these features are sufficient to designate a particular case as a malignant phyllodes tumour [5, 7, 8, 13, 22]. There is no doubt, however, that a phyllodes tumour can be diagnosed as malignant when the stromal component has a clear pattern of sarcoma [3–5, 16, 18, 24]. This article presents the pathological and clinical picture of malignant phyllodes tumour in a group of 55 patients.

PATIENTS AND METHODS

Between 1952 and 1985, 158 female patients with phyllodes tumours were seen at the Center of Oncology in Cracow. The subject of this study is the group of 55 (34.8%) patients with malignant phyllodes tumours.

All surgical specimens showed a characteristic phyllodes pattern with malignant mesenchymal tissue and poorly circumscribed microscopic margins of the tumour. Patients were divided into two groups according to the grade of malignancy. In the first group, consisting of 28 patients with high-grade malignancy, there were cases in which the tumour was characterised by the predominance of the sarcoma-type pattern over leaf-like projections, a high degree of cell polymorphism, considerable numbers of mitoses (three or more in 10 high-power fields), and possible multidirectional differentiation forming pictures resembling fibrosarcoma, leiosarcoma, liposarcoma, chondrosarcoma, or osteosarcoma (Fig. 1). The remaining 27 cases were rated as presenting a low degree of microscopic malignancy (Fig. 2). All histological slides were re-examined by a single pathologist according to WHO criteria.

The mean age of the patients was 51 years, ranging from 29 to 76 years. Duration of symptoms varied from 2 months to 30 years. In 31 (56.4%) cases we recorded a biphasic growth of the tumour. The first phase of a long, almost unnoticeable growth ranged from 2 to 30 years, the average being 10 years. The second, rather short phase, when a rapid increase in tumour size was noted, lasted from 2 to 13 months, with the average of 7 months. Monophasic rapid tumour growth lasting 2 to 14 months with the average time of 5 months occurred in 24 (43.6%) cases.

Tumour size was over 10 cm in diameter in 34 (61.8%) cases, over 20 cm in 3 patients and in 1 case it even exceeded 26 cm. In spite of this, in only 3 cases (5.5%) was there clinically recorded infiltration into the pectoralis major muscle and with limited mobility in relation to the chest wall. In 26 (47.3%) patients changes of breast skin were observed: thinning of the skin, bluish discoloration, prominent blood vessels and skin ulceration. In 2 cases these changes were classified histologically as neoplastic infiltration; in other cases they appeared to be trophic changes caused by the pressure exerted on the skin by an extensive tumour. At clinical examination there was a suspicion of axillary metastases in 11 (20%) patients.

In the group of patients with biphasic growth we found a statistically higher percentage of tumours greater than 10 cm in comparison to the group with monophasic growth ($P = 0.001$).

All 55 patients underwent surgery. Preoperative diagnostic procedures included a careful history and complete physical examination, routine biochemical analyses (renal and liver function tests), complete blood count, chest radiography and

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Revised 2 Sep. 1992; accepted 9 Dec. 1992.

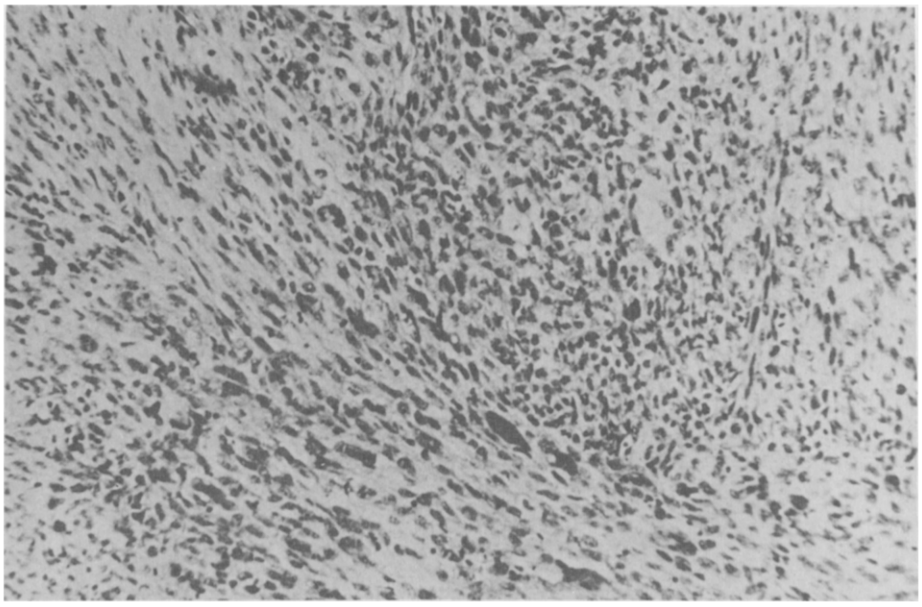

Fig. 1. Malignant phyllodes tumour—high microscopic malignancy (haematoxylin and eosin, × 160).

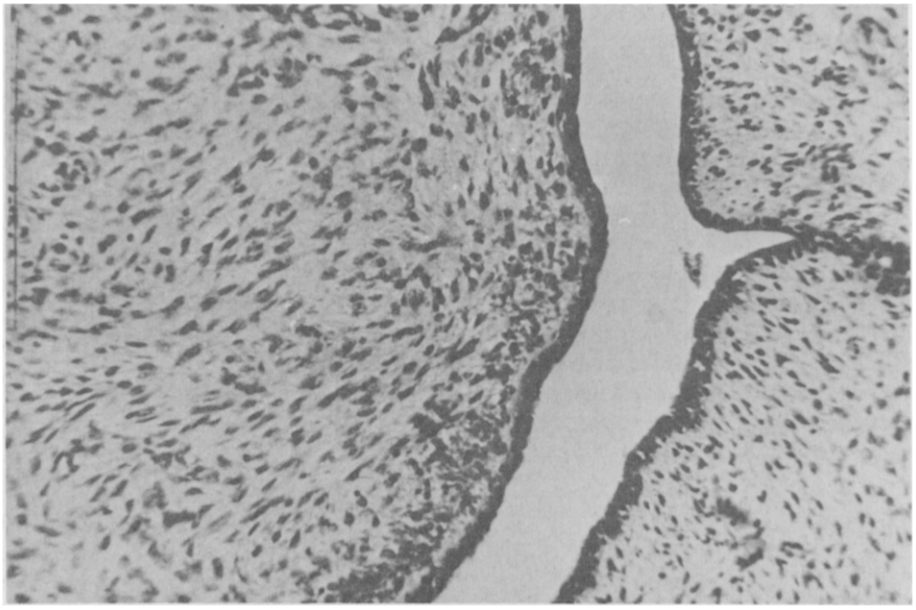

Fig. 2. Malignant phyllodes tumour—low microscopic malignancy (haematoxylin and eosin, × 160).

incisional biopsy of the tumour. 28 (50.9%) patients underwent simple mastectomy, 7 (12.7%) radical mastectomy (Patey), 20 (36.4%) radical mastectomy (Halsted). In all the 11 cases with clinically suspected axillary lymph nodes and in 3 cases with infiltration of pectoralis major muscle, the Halsted operation was performed. In the remaining cases the choice of the operation was left to the operating surgeon. 3 patients, with infiltration of pectoralis major muscle and limited mobility in relation to the chest wall, received postoperative irradiation because the Halsted operation was not microscopically complete. The dose of 5000 cGy in 25 fractions over 5 weeks was delivered to the chest wall and axillary nodes. Chemo- or hormonotherapy was applied in 6 patients who developed metastases to the lung: monochemotherapy (cyclophosphamide) in 2 cases, polychemotherapy (methotrexate, dactinomycin, cycloposphamide and vincristine) in 3 cases and hormonotherapy with testosterone in 1 case.

RESULTS

All the patients were followed for at least 5 years. They were examined every 3 months during the first 3 years, and every 6 months thereafter. Routine chest X-ray examination was performed every 6 months.

Five-year survival without evidence of disease (NED) was used as the end-point for analysis. The log-rank test was used in order to compare the survival curves, differences being

Table 1. Results of treatment of 55 patients with malignant phyllodes tumours

	No. of patients	Alive 5-year NED No.	%
Age			
≤ 40	13	8	61.5
> 40	42	28	66.7
Type of growth			
Monophasic	24	15	62.5
Biphasic	31	21	67.7
Size of tumour			
< 5 cm	6	4	66.7
5–10 cm	15	10	66.7
11–15 cm	15	9	60.0
> 15 cm	19	13	68.4
Changes in breast skin			
Yes	26	17	65.4
No	29	19	65.5
Axillary lymph nodes clinically			
Negative/No/	44	29	65.9
Positive/N+/	11	7	63.6
Grade of malignancy			
High	28	12	42.9
Low	27	24	88.9
Extent of surgical treatment			
Simple mastectomy	28	19	67.9
Radical mastectomy	27	17	63.0
Total	55	36	65.5

NED, No evidence of disease.

considered statistically significant if $P < 0.05$. Multivariate analysis was conducted by the Cox proportional hazard model to identify the onset of independent prognostic factors for 5-year NED survival.

Of the 55 treated patients, 36 (65.5%) survived 5 years NED. Table 1 shows the results according to the clinical features, grade of histological malignancy and extent of surgery. In the Cox multivariate analysis there was a significant correlation between the results of treatment and grade of malignancy only. Survival curves according to grade of malignancy are presented in Fig. 3, the difference is statistically significant (log-rank test, $P < 0.001$).

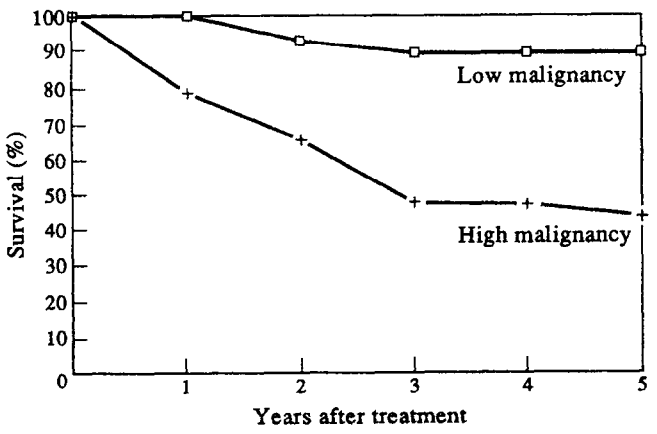

Fig. 3. Correlation between the results and microscopic malignancy.

In all 19 cases of failure of treatment, metastases to the lungs developed. 3 patients also had local recurrences of malignant phyllodes tumour along with pulmonary metastases. These patients were treated with the Halsted operation followed by postoperative radiotherapy which proved to be inefficient.

Chemo- and hormone-therapy were also inefficient in our 6 patients with dissemination. Distant metastases occurred after a mean period of 17 months (range 2–56). During the first 3 years after treatment, metastases were revealed in 94.7% of patients (18/19). Patients developing distant metastases survived from 2 to 9 months, with mean survival of 3 months; all these patients died within a 5-year follow-up.

Of the 27 patients undergoing radical mastectomy, metastases to axillary lymph nodes was found in only 1 case. This was a woman with locally highly advanced neoplasm (tumour 22 cm in diameter, clinical involvement of pectoralis major, and microscopic infiltration of the chest wall). Two of 17 lymph nodes were involved and the patient died due to pulmonary metastases. Of the group of 11 patients with clinically positive axillary nodes, she was the only one with nodal metastases. In the group of 44 women with no clinical evidence of metastases to axillary lymph nodes, 16 of whom had radical mastectomy, neither the operation nor frequent follow-up lasting for many years revealed metastases to axillary lymph nodes. No failure of treatment due to affected axillary lymph nodes was observed.

No servious treatment sequelae were discovered in any patients. 4 patients who underwent Halsted mastectomy had mild residual swelling of the arm.

DISCUSSION

In this group of patients with malignant phyllodes tumour surgical treatment proved to be highly effective, with 65.5% 5-year (NED) survivors. Similar results are reported by Contarini *et al.*, Khana *et al.*, Pietruszka and Barnes, West *et al.* and Lindquist *et al.* (50–58%); and are slightly improved in the report by Vorherr *et al.* (80%) [7–9, 18, 20, 22]. Of course it is very difficult to compare our results with those presented by other authors, because their references include joint reports on benign, borderline and malignant phyllodes tumours. The extent of surgery did not have a substantial influence on the results of treatment in our group, and simple mastectomy proved to be as efficient as radical mastectomy. The majority of other authors confirm this finding [7–9, 13, 16, 21–23, 25, 26]. It has been shown that widening of the operation has no influence on prognosis [7, 10, 13, 20, 21]. Only the spread of locally advanced neoplasm beyond the breast requires widening of the operation. The risk of metastases to axillary lymph nodes is very low, and in our group was seen in 1.8% of cases (1/55). This finding concurs with other authors [1, 8, 10, 13, 18–22, 25]. Local recurrences were found in 3 (5.5%) of our patients. In none of them was local relapse the direct cause of death, and all these 3 patients died of metastases to the lungs. Faraci and Schour, Hajdu *et al.* and West *et al.* confirm the correlation between local recurrences and the risk of distant metastases [9, 14, 17]. In the literature higher percentages of failures and local recurrences are often cited: from 19 to 50% [10, 13, 14, 16, 17, 21–23]. This is probably due to primary surgery being limited to local excision or quadrantectomy, while a simple mastectomy might be the preferred procedure [16, 23, 27, 28]. Radiotherapy is of little use and has a mainly palliative role [7, 10, 15, 20, 21, 29,30].

The main causes of treatment failure were distant metastases, mainly to the lungs, corresponding with the data in literature [1,

5, 7, 9, 13, 18–20, 22, 25]. In some reports partial regression was observed after chemotherapy [7, 10, 20, 22]. In our group chemotherapy was ineffective.

In our group of patients no clinical feature of prognostic importance was found. Some authors believe that the size of tumour does not correlate with the risk of recurrence, and our study also supports this opinion [10, 16, 20, 23, 27].

Significantly worse results were obtained in the group where we observed a high degree of histological malignancy, defined as predominance of the malignant sarcomatous tissue over the phyllodes pattern, high mitotic activity, high degree of cell polymorphism and possible multidirectional differentiation. In the literature the opinions on correlation between the histological appearance of tumours and the prognosis vary. Some authors question the existence of this correlation [7–9, 21, 22, 31], while the majority, who acknowledge it, do not agree as to which feature of the histological appearance is vital in prognosis. Some authors believe that these features are the mitotic activity, degree of stromal atypia, pleomorphism, vascularity, cellularity and differentiation of stromal components [5, 13, 18, 23]. Ward and Evans confirm that features such as tumour necrosis, mitotic rate, stromal cellularity, nuclear size and pleomorphism have no effect on the results of treatment. The prognostic factor in their group was stromal overgrowth understood as "a mesenchymal proliferation with complete absence of a ductal epithelial element in the area greater than one low-power (× 40) field" [16]. The importance of the presence of the stroma overgrowth is also emphasised by Oberman *et al.*, but according to these authors it is already sarcomatous stroma [32, 33]. Murad *et al.* emphasise the prognostic significance of microscopic features such as necrosis, infiltrating margins, the presence of more than one mesenchymal element, a high proliferative index and the presence of DNA aneuploidy by flow cytometric analysis [28]. Zahner and Bassler confirm that only high rates of mitosis (10 in 10 high-power fields) correlated well with a histopathological diagnosis of malignancy [34]. It should be noted that almost all the authors looked for a correlation between the histological appearance of the tumour and the clinical course in groups consisting of patients with benign, borderline and malignant phyllodes tumours [35]. Our study concerned only patients with malignant phyllodes tumours and thus it is difficult to compare it with the studies carried out by other authors.

A detailed analysis of our own clinical material consisting of 55 patients and a review of literature allows us to formulate the following conclusions regarding the clinical course, treatment and prognosis for patients with malignant phyllodes tumours:

— The growth of neoplasm can be relatively rapid (monophasic) or biphasic with the first phase one of slow growth for many years and the second phase of rapid violent growth. In the second type of growth the breast tumour usually becomes large.
— Metastases to axillary lymph nodes are very rare.
— Simple mastectomy is a sufficient treatment for patients with disease limited to the breast. Smaller tumours can be managed with breast conservation as long as adequate excision is obtained.
— The main cause of unsuccessful treatment is distant metastases, mainly to the lungs.
— None of the clinical features, including the breast tumour size are a prognostic factor.
— The prognostic factor in the studied group was the grade of microscopic malignancy, defined by such criteria as the ratio between the malignant, sarcomatous tissue and that typical for tumour phyllodes, the degree of cell polymorphism, mitotic activity and possible multidirectional differentiation (towards malignant neoplasms of soft tissue and bones).

A rare incidence of malignant phyllodes tumours makes it difficult to define the directions of further research which could be quickly developed. Nonetheless it seems necessary to collect and publish "pure" groups of patients consisting of separate cases of malignant and benign phyllodes tumours. Of course, it is necessary to define uniform criteria which would designate a particular case into a specific group. In such "pure" groups, fully convincing microscopic prognostic factors could be searched for. This article is an attempt at this type of research.

From the clinical point of view the main question is whether adjuvant chemotherapy can prevent distant metastases especially in patients with a high grade of microscopic malignancy. Since malignant phyllodes tumour is rare, it is very difficult to carry out controlled clinical studies. Close cooperation of many oncological centres is, therefore, necessary.

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Eur J Cancer, Vol. 29A, No. 9, pp. 1256–1260, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Zn-α_2-glycoprotein Levels in Breast Cancer Cytosols and Correlation with Clinical, Histological and Biochemical Parameters

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Zn-α_2-glycoprotein (Zn-α_2-gp), a protein present at high levels in breast cyst fluid, has been measured in 104 breast tumour cytosols by using an immunoenzymatic assay. Concentrations of Zn-α_2-gp ranged from 0 to 23.5 μg/mg of total soluble protein, with an average value of 2.4 μg/mg. There was no significant correlation between Zn-α_2-gp and menopausal status, tumour size or lymph node involvement, or between this protein and biochemical parameters such as oestrogen receptor, cathepsin D or pS2 levels. However, there was a significant association between Zn-α_2-gp and histological grade of tumours, with higher Zn-α_2-gp levels in well-differentiated tumours (mean 4.6 μg/mg) than in moderately (1.8 μg/mg) or poorly (0.9 μg/mg) differentiated tumours. On the basis of these results, we propose that Zn-α_2-gp may be considered as a biochemical marker of differentiation in breast cancer.
Eur J Cancer, Vol. 29A, No. 9, pp. 1256–1260, 1993.

INTRODUCTION

ZN-α_2-GLYCOPROTEIN (Zn-α_2-gp) is a human protein of unknown biological function, originally described in 1961 by Bürgi and Schmid [1]. The protein consists of a single polypeptide chain with a molecular mass of about 40 kD and displays a marked charge heterogeneity mainly due to variations in the composition of carbohydrate moiety [2].

This glycoprotein is present in high concentrations in cyst fluid from women with gross cystic breast disease [3], which has led to the proposal that Zn-α_2-gp and other major intracystic proteins like apolipoprotein D [4] may contribute to the pathogenesis of the disease. In addition, northern blot analysis of breast tissue specimens has revealed the existence of a certain subgroup of breast tumours which produce significant amounts of Zn-α_2-gp [5]. Similarly, immunohistochemical studies have demonstrated the presence of the protein in about 50% of invasive breast carcinomas [6], which is in good agreement with recent data from our laboratory indicating that Zn-α_2-gp is a major protein component in about 45% of breast secretions from

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Revised 20 July 1992; accepted 17 Nov. 1992.