

Phyllodes tumor of the breast: case series of 40 patients

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Summary

Cystosarcoma phyllodes is a rare, uncommon fibroepithelial tumor of the breast. We analyzed the clinical situation in relation to the histopathologic findings.

Forty types of surgery, recurrences, histopathologic diagnosis and follow-up of patients were studied retrospectively. Histopathologic examination results were evaluated by logistic regression analysis.

Surgery was performed on all patients as the initial treatment. At the first examination 38 cases were evaluated as benign and the remaining two as malignant. Recurrent tumors were seen in nine (22.5%) cases during follow-up with a mean recurrence time of 30.1 months. Five of the recurrent cases were evaluated as malign. The total number of malignant cases reached seven (17.5%). In statistical analysis evidence of tumor necrosis, stromal atypism, stromal cellularity, number of mitoses and stromal overgrowth were found to be significantly correlated with malignancy ($p < 0.05$). Recurrences were also significantly correlated with stromal cellularity, stromal overgrowth, necrosis and malignancy ($p < 0.05$).

Cystosarcoma phyllodes recur with a high incidence and may transform to malignant disease. The patients should be followed strictly in order to detect recurrence earlier.

Key words: Cystosarcoma phyllodes; Malignant; Recurrence, Surgery.

Introduction

Cystosarcoma phyllodes are an uncommon tumor of the breast. It is a rare fibroepithelial tumor that accounts for 0.3% to 0.5% of all breast neoplasms [1]. The typical presentation of these tumors is a painless, well-circumscribed large mass with an average diameter of 3 to 5 cm [2-4]. The tumor is generally categorized as benign or malignant but in both categories it is accepted that it has an aggressive behavior. In several clinical studies it has been seen that the recurrence rate is very high and is independent of its benign or malignant nature [5, 6].

Cystosarcoma phyllodes still remains a challenge to pathologists. There are some difficulties including the histologic diagnosis, classification and correlation of clinical and histopathologic parameters.

It is composed of an epithelial and a cellular stromal component. The determination of the tumor as benign or malignant is mainly based on the histologic assessment such as: stromal overgrowth, hypercellularity and an increase in the mitotic rate [6]. It seems that this designation is independent of the size, presentation form and behavior. Therefore in this retrospective study we tried to analyze the clinical situation in relation to the histopathologic findings.

Materials and Methods

Between 1980 and 1997 at Ankara Oncology Hospital 40 patients with cystosarcoma phyllodes were enrolled in the study

and were retrospectively analyzed. The mean age of the patients was 37.5 (18-74). Localization of the tumor was left-sided in 17 and right-sided in 23 cases. In 20 cases the largest diameter of the tumor size was calculated as < 5 cm, $\geq 5 - < 10$ cm in 12 cases and ≥ 10 cm in eight cases with a mean of 6.8 cm (2-15 cm) (Table 1). All of these patients had undergone surgery. Types of surgery, recurrences, histopathologic diagnosis and follow-up of these patients were studied. With these clinical findings a histopathologic examination performed by a specialist pathologist and results were evaluated to find a correlation between these clinical and pathologic results. Stromal cellularity, stromal cellular atypia, number of mitosis, stromal overgrowth, tumor necrosis, components other than myxoid changes in stroma and border of the tumor were evaluated in a categorical manner (Table 2). A logistic regression analysis was also performed to find a significant correlation between malignant diagnosis and the mentioned histopathologic parameters, and which factors may have an effect on recurrences.

Results

As first-line treatment, surgery was performed in all patients: wide local excision in 30, simple mastectomy in eight, and simple mastectomy + axillary dissection in two cases. In the first examination 38 cases were evaluated as benign and the remaining two (5%) as malignant disease. In malignant cases after a diagnostic procedure with core biopsy, a simple mastectomy was performed with axillary dissection because of palpable axillary lymph nodes. Recurrent tumors were seen in nine (22.5%) cases at follow-up with a mean recurrence time of 30.1 months (5-110 mos.). In these nine cases 17 recurrences devel-

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Table 1. — Characteristics of patients.

No	Age	Side	Size (cm)	Surgery	Diagnoses	Recurrences	Follow-up	Status
1	74	L	13	SMAD	B	2 (Malign)	115	AED
2	45	R	3	TE	B	—	124	OF
3	27	R	4	TE	B	—	25	OF
4	23	R	2.5	TE	B	—	6	OF
5	40	R	12.5	SM	B	—	10	OF
6	45	L	8.5	TE	B	—	15	OF
7	44	L	3	TE	B	—	26	OF
8	52	L	11	TE	B	2 (Malign)	54	AED
9	22	L	2.5	TE	B	—	32	AED
10	30	R	4.5	TE	B	—	47	AED
11	56	R	6.5	TE	B	—	36	AED
12	35	L	5	TE	B	—	80	AED
13	32	L	10	TE	B	5 (Malign)	26	DDD
14	35	R	4	TE	B	—	11	OF
15	27	R	9	TE	B	1 (Benign)	81	OF
16	44	R	9.5	SM	B	—	27	OF
17	60	L	8	SMAD	M	2 (Malign)	28	DDD
18	47	R	2	TE	B	2 (Benign)	41	AED
19	29	R	3.5	TE	B	—	19	OF
20	24	R	7	TE	B	—	9	OF
21	38	R	4	TE	B	—	33	OF
22	48	R	12.5	SM	B	—	15	AED
23	35	R	15	SM	B	—	17	AED
24	46	R	4	TE	B	—	25	OF
25	19	L	11.5	SM	B	—	13	OF
26	21	L	3	TE	B	—	27	OF
27	40	L	4	TE	B	—	11	OF
28	39	R	9	TE	B	—	3	OF
29	31	R	4	TE	B	1 (Malign)	28	DDD
30	30	L	3.5	TE	B	—	21	OF
31	18	L	3	TE	B	—	15	OF
32	25	L	13	SM	B	—	21	OF
33	39	L	8	TE	B	—	13	OF
34	30	R	4	TE	B	1 (Benign)	19	OF
35	48	R	7.5	TE	B	1 (Malign)	35	AED
36	45	L	7.5	TE	B	—	1	OF
37	25	R	8	SM	M	—	1	OF
38	40	L	4.5	TE	B	—	16	AED
39	59	R	13.5	SM	B	—	33	AED
40	35	R	4.5	TE	B	—	25	AED

L: left, R: right, SMAD: simple mastectomy + axillary dissection, TE: total excision, SM: simple mastectomy, B: benign, M: malign, AED: alive without evidence of disease, OF: out of follow-up, DDD: death due to distant disease.

oped with five recurrences in one of the cases. All of the recurrent cases were treated with surgery (12 total excision, 4 simple mastectomy + axillary dissection and a simple mastectomy) (Table 1). Like the other two cases whose initial treatment was axillary dissection and simple mastectomy there were clinically palpable lymph nodes in four of the recurrent cases. At pathologic examination however, no axillary metastases were detected. The total number of malignant cases was seven (17.5%). Two were diagnosed at the first evaluation and the other five were regarded as malignant after recurrences occurred. The mean follow-up time for all patients was 29.4 months (1-124 mos.). There were 12 patients who were alive without disease at the time of this study was done, three patients were dead because of metastatic disease and the other 25 patients were out of follow-up at different times. In cases that had died because of metastatic disease it was observed that they were diagnosed as benign disease at the index operation. After recurrences their pathologies were

Table 2. — Histopathologic parameters and results.

	Benign	Malign
Stromal cellularity		
Slight to moderate	26	—
Prominent	10	9
Stromal cellular atypism		
None to moderate	29	2
Prominent	7	7
Mitotic activity (No of mitoses per 10 high power fields)		
0	1	1
≤ 3	26	4
4-9	4	1
10-20	2	2
Stromal overgrowth		
None	24	2
Evident	12	7
Tumor necrosis		
None	34	6
Evident	2	3
Components other than myxoid changes		
None	34	7
Evident	2	2
Border of the tumor		
Not evaluated	7	5
Pushing	25	2
Infiltrative	4	2

accepted as malignant and simple mastectomy + axillary dissection were performed as the definitive operation. Pulmonary metastases developed in follow-up. For all of these cases chemotherapy was applied after metastatic disease (FAC protocol: 5 fluorouracil, adriablastin, cyclophosphamide) but no response could be achieved.

At pathologic examinations specimens of 37 cases could be re-examined. There were 45 different tumor specimens including recurrences for examination. Microscopic slides were evaluated as mentioned in the previous section and the results are shown in Table 2.

At statistical analyses with linear regression evidence of tumor necrosis, stromal atypism, stromal cellularity, mitosis and stromal overgrowth were found to be significantly correlated with malignant diagnoses (Table 3). In the analyses of recurrence it was observed that stromal cellularity, stromal overgrowth, necrosis and malignant diagnoses were found to be significantly important for recurrences ($p < 0.05$) (Table 3).

Table 3. — Results of logistic regression analysis.

	Significance
Factors affecting malignancy	
Stromal cellularity	0.0041
Stromal atypism	0.046
Number of mitoses	0.019
Tumor necrosis	0.0016
Stromal overgrowth	0.015
Factors affecting recurrence	
Stromal cellularity	0.038
Stromal overgrowth	0.001
Tumor necrosis	0.007
Malignancy	0.000

Discussion

The appropriate surgical treatment for cystosarcoma is still debated. The reason for the choice of breast conserving therapy, wide local excision or simple mastectomy is unclear. There is not enough data on the best choice of therapy, risk of malignancy or recurrence. Recurrence rates of the tumor were given as between 17% and 28.1% in some series [1, 5-12], as was the case in our study. Salvadori *et al.* [8] mentioned in their study that the choice of surgery did not affect the prognosis. They added that all phyllodes tumors can recur regardless of their histology and the risk of local recurrence is very low for benign phyllodes and much higher for borderline and malignant tumors. Our findings were similar in this regard. Of 40 patients recurrences were seen in nine cases and in these nine patients malignant tumors developed in six of them. These cases were diagnosed as benign at previous pathologic examinations. It could be considered that a transformation developed from benign to malignant. Lu *et al.* [13] indicated that increased 1q copy number in chromosomes was associated with recurrence and might therefore be considered as an indicator of local aggressiveness requiring more radical treatment. We found that stromal cellularity, stromal overgrowth, necrosis and malignant diagnoses were significantly important for recurrences.

Biologically, all phyllodes tumors are considered to be potentially malignant. The reported incidence of malignant phyllodes tumors ranges from 12% to 54% [5, 6, 8-11, 14]. These rates are high for a tumor, which is considered as generally benign. These tumors could transform from benign to malignant over time with recurrences as shown before [1, 9, 14]. Several authors have analyzed the histopathologic factors, which are considered important in malignant diagnoses. Cedermark *et al.* [6] found that tumor necrosis and presence of stromal elements other than fibromyxoid tissue were important, while Kario *et al.* [7] and Ward and Evans [9] claimed that stromal overgrowth is an important factor for malignancy. Azzopardi [15] has established that mitoses exceeding 3 per 10 HPF is a potential indicator of malignancy. Kocova *et al.* [16] found a significant correlation with the expression of Ki-67 antigen and malignant disease. In our study we found tumor necrosis, stromal atypism, stromal cellularity number of mitoses and stromal overgrowth were significantly correlated with malignancy. We believe that to calculate a risk analysis to predict malignancy is quite difficult because of the small sample sizes of the studies previously done.

There is not enough data on the adjuvant treatment of cystosarcoma phyllodes. Only sporadic reports with a few cases that received radiotherapy can be found [17]. In metastatic cases chemotherapy has generally been found to be ineffective. In a study by Contarini *et al.* [18] one of 17 patients with metastatic disease responded to combination chemotherapy.

Conclusion

The choice of surgical treatment of phyllodes tumors depends on the size of the tumor and the breast. If an ade-

quate margin is achieved, wide local excision can be performed, otherwise total mastectomy should be the proper treatment modality and axillary dissection is not recommended [5, 8, 14, 19]. It should be remembered that these tumors could recur with a high incidence and transform to malignant disease. The patients should be strictly followed in order to detect recurrences earlier.

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