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Non-epithelial malignant breast tumors: a retrospective study of 29 patients treated exclusively by surgery

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Introduction. The aim of the study was to perform a retrospective assessment of the outcome of patients with non-epithelial malignant breast tumors, treated exclusively by surgery.
Material and methods. We collected the survival data of 29 women with breast sarcoma or malignant cystosarcoma phyllodes, treated surgically between 1977 and 2001. The median size of the tumor was 10 cm (range: 3-30 cm).
Results. Recurrence of the disease was observed in 11 patients (38%), and 8 patients died during follow-up (28%). The probability of disease-free survival was 0.55 at 5 years and 0.44 at 10 years. The overall survival probability was 0.69 at 5 years and 0.61 at 10 years. A majority of the patients with recurrence (10/11; 91%) and all patients who had died had tumors larger than 5 cm.
Conclusion. The probability of disease relapse in patients with non-epithelial malignant breast tumors treated surgically is high in patients with tumors larger than 5 cm.

Nienabłonkowe złośliwe nowotwory piersi: retrospektywne badanie obejmujące 29 chorych leczonych tylko chirurgicznie

Wprowadzenie. Celem badania była retrospektywna ocena wyników leczenia chirurgicznego chorych na nienabłonkowe, złośliwe nowotwory piersi.
Materiał i metody. Dane na temat przeżyć wszystkich 29 kobiet chorych na mięsaki piersi i złośliwe guzy liściaste, leczonych w Klinice w latach 1977-2001, uzyskano z historii chorób. Mediana średnicy guza wynosiła 10 cm (zakres: 3-30 cm).
Wyniki. W okresie obserwacji nawrót choroby stwierdzono u 11 chorych (38%), a 8 chorych zmarło (28%). Prawdopodobieństwo przeżycia 5 lat bez choroby wynosiło 0,55, a przeżycia 10 lat wynosiło 0,44. Całkowite prawdopodobieństwo przeżycia wynosiło 0,69 po upływie 5 lat i 0,61 po upływie 10 lat. U większości chorych, u których doszło do nawrotu choroby (10/11; 91%), oraz u wszystkich chorych, które zmarły, guz pierwotny był większy niż 5 cm.
Wniosek. Prawdopodobieństwo nawrotu choroby u leczonych chirurgicznie chorych na nienabłonkowe złośliwe nowotwory piersi, których średnica jest większa od 5 cm, jest duże.

Key words: breast sarcoma, non-epithelial breast tumor, surgery, prognosis, treatment
Słowa kluczowe: mięsak piersi, nienabłonkowy nowotwór piersi, chirurgia, rokowanie, leczenie

Introduction

Non-epithelial malignant breast tumors compose a rare and heterogenic group of malignancies. They represent less than 1% of primary mammary malignant tumors [1-3]. Breast sarcomas and malignant cystosarcoma phyllodes tumors are of special interest. Many aspects of their clinical course are similar [3]. Clinical similarities and the rarity of these clinical entities are the main reasons due to which many authors studied these malignancies together [3-7]. Moreover, some authors rate malignant cystosarcoma phyllodes tumors among breast sarcomas [4-7].

Surgical resection is the primary treatment of such malignancies, however, further details concerning best treatment options remain unknown [8].

First, the extent of the surgical procedure is controversial. Some authors have claimed that mastectomy should be a standard procedure in such patients [2, 4, 9-11] having found that the incidence of relapses was lower among patients treated with mastectomy than among those treated with limited surgery. Other authors have recommended wide local excision as a good alternative for mastectomy, reporting no differences in disease free and overall survival between the compared treatment groups [3, 5, 6, 8, 12]. It is difficult to resolve this controversy as no prospective study has been conducted on the

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influence of the extent of surgical treatment on patient survival. All conclusions base on retrospective studies results.

Second, the role of adjuvant therapy has not been established [5, 13, 14]. It has been stated that adjuvant radiotherapy is not likely to be beneficial [9, 13, 15], however has also been advised cautiously to consider such a treatment option [13, 14]. Other authors have reported the excellent efficacy of postoperative radiotherapy [6, 16]. Chemotherapy is believed not to be useful in the treatment of the disease [13]. It is difficult to obtain a univocal opinion from published reports, and as in the case of the extent of surgery, there is no prospective data on the effectiveness of combined treatment in such patients [8].

Authors generally agree in two aspects of treatment. First, that ipsilateral axillary lymph nodes are rarely involved in such patients and that there is no need to remove them when they are not palpable [6-9, 14, 15]. Second, that the presence of negative resection margins is of a crucial importance for patient survival. It has been suggested that the results of treatment are influenced mainly by the adequacy, not by the extent, of the surgical procedure. The difference in the survival of patients operated with tumor-negative and with tumor-positive resection margins was considerable [3, 6, 13, 14, 17].

As the survival of non-epithelial malignant breast tumor patients treated exclusively by surgery was not evaluated in our setting we decided to perform a retrospective analysis of the files of such patients treated in our center to assess the long-term results of treatment: 5-year disease-free and overall survival, 10-year disease-free and overall survival and median length of disease-free and overall survival.

Material and methods

Our study comprised women treated exclusively by surgery for breast sarcoma or malignant cystosarcoma phyllodes, between January 1977 and December 2001 in the Clinical Department of Surgical Oncology of the Medical University of Lodz, Poland. All patients in case of whom resection margins were positive clinically and histologically, or in case of whom adjuvant radiotherapy and/or chemotherapy was introduced, were excluded from the study. We also disqualified all patients with axillary lymph nodes and/or distant metastases. Therefore, all patients in our study group were in the local stage of the disease.

A retrospective review of the files provided complete clinical and pathological data for 29 patients. These files were examined for details of physical findings, treatment, results of pathological examinations, disease recurrence and patient survival.

Patient characteristics

The median age at diagnosis was 53.0 years (range: 27-86 years; mean: 54.2 years). Eleven women (38%) were of premenopausal age (≤50) and 18 were of postmeopausal age (62%). The median duration of symptoms (presence of tumor in the breast) was 6 months (range: 1 week – 16 years). The tumors were located in the left breast in 11 cases (11/29; 38%) and in the right in 18 cases (18/29; 62%). The median diameter of the breast tumor was 10 cm (range, 3-30 cm; mean, 10.4 cm). The diameter of breast tumor exceeded 5 cm in 22/29 cases (76%). In 7 cases the axillary lymph nodes were palpable (7/29; 24%).

Treatment and results of pathologic examination

Twenty eight (97%) patients underwent mastectomy: 19 (66%) – simple mastectomy and 9 (31%) – modified radical mastectomy (Madden procedure). In one case (3%) wide local excision of the tumor was performed. Diagnoses of breast sarcoma or malignant cystosarcoma phyllodes were confirmed postoperatively in the course of the histological analysis. The distribution of the histological types of malignancies is presented in Table I. In all cases the surgical procedure was radical, i.e. no residual microscopic disease was found histologically at the excision margins. Metastases in the axillary lymph nodes were not discerned in the post-lymphadenectomy specimens.

Table I. Histological types of malignancy in 29 patients with non-epithelial malignant breast tumors

Histologic type of malignancy	Number of patients	Number of deaths
Cystosarcoma phyllodes	14	3
Sarcoma stromale	6	3
Fibrosarcoma	5	0
Haemangiosarcoma	2	1
Liposarcoma	2	1
Total	29	8

Statistics

Mean and median disease-free survival times were calculated by the product-limit estimate method. Disease-free and overall survival probabilities were calculated according to the Kaplan-Meier method for the estimation of survival functions. To compare the survival distributions the log-rank test was applied. P-value$<$0.05 was considered significant. All analyses were performed with Statistica software.

Results

Recurrence of disease, deaths

Five of the 29 patients (17%) developed local recurrence. Two patients (7%) developed recurrence in the ipsilateral axillary lymph nodes. Nine patients (31%) developed symptoms of distant metastases, predominantly pulmonary (7/9 cases). Altogether, relapse of the disease was observed in 11 patients (38%). Ten of these 11 patients had tumors bigger than 5 cm. Eight patients died during follow-up (28%). All patients who died had tumors bigger than 5 cm.

Disease-free survival

The 5-year disease-free survival probability for the entire group was 0.55. The 10-year disease-free survival

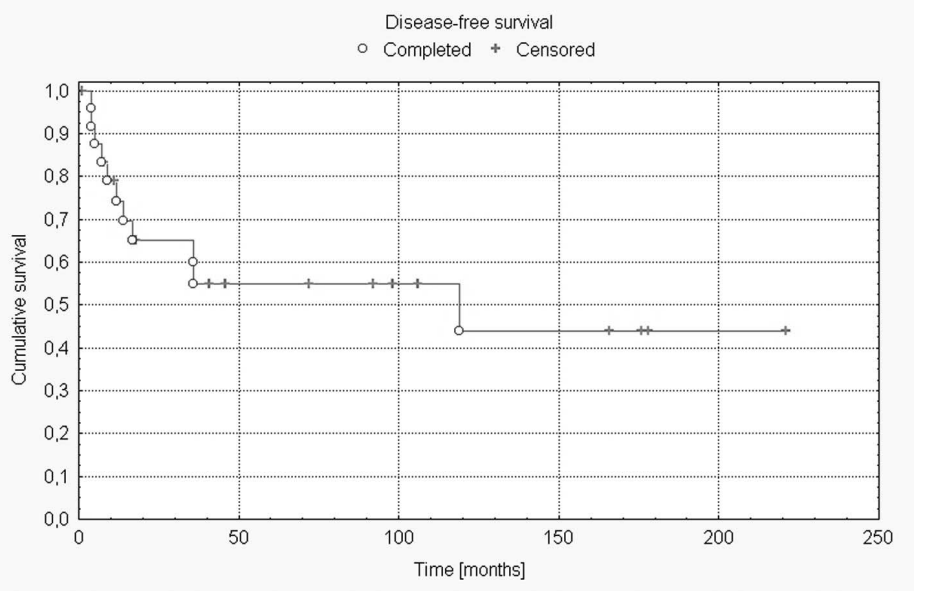

Figure 1. Disease-free survival of patients with non-epithelial malignant breast tumors

probability was 0.44 (Figure 1). The median disease-free survival was 119.0 months (mean: 117.2 months).

The probability of disease-free survival for patients with tumors not exceeding 5 cm was 0.75 at 5 years and 0.75 at 10 years (Figure 3). The mean disease-free survival for these patients was 133.5 months. It was impossible to calculate a median value of disease-free survival for these patients.

The 5-year disease-free survival probability for patients with tumors exceeding 5 cm was 0.48. The 10-year disease-free survival probability in this subgroup was 0.36 (Figure 3). The median disease-free survival was 36.0 months (mean: 99.9 months).

The difference between disease-free survival curves for tumor sizes was statistically not significant (log rank test statistic 2.09; df=1; p=0.15)

The probability of disease-free survival for patients with malignant cystosarcoma phyllodes was 0.71 at 5 years and 0.36 at 10 years (Figure 5). The mean disease-free survival for these patients was 123.5 months. The median disease-free survival was 119.0 months.

The 5-year disease-free survival probability for patients with breast sarcoma was 0.43. The 10-year disease-free survival probability in this subgroup was also 0.43 (Figure 5). The mean disease-free survival for these patients was 90.1 months. The median disease-free survival was 36.0 months.

The difference between disease-free survival curves (malignant cystosarcoma phyllodes vs. breast sarcoma) was statistically not significant (log rank test statistic 0.67; df=1; p=0.41)

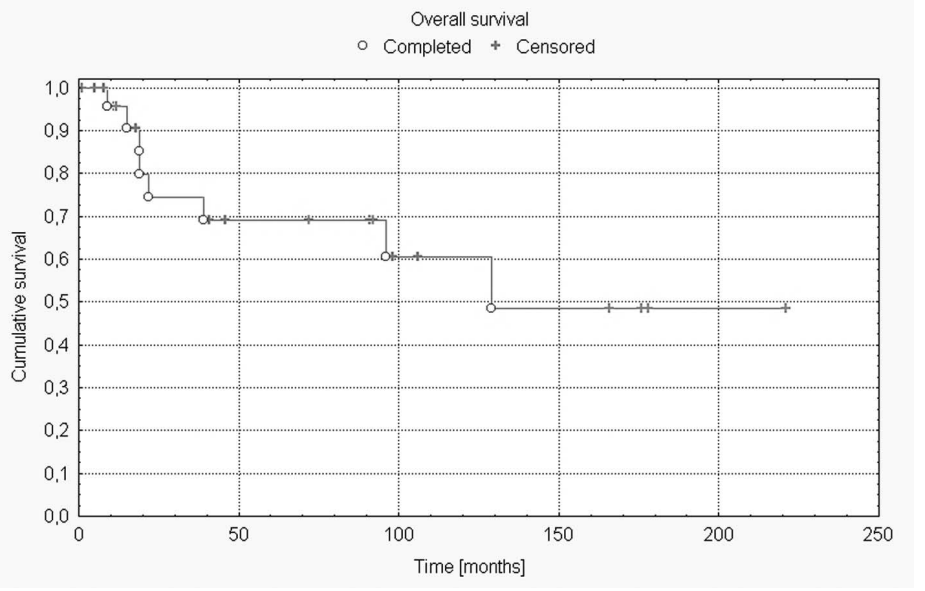

Figure 2. Overall survival of patients with non-epithelial malignant breast tumors

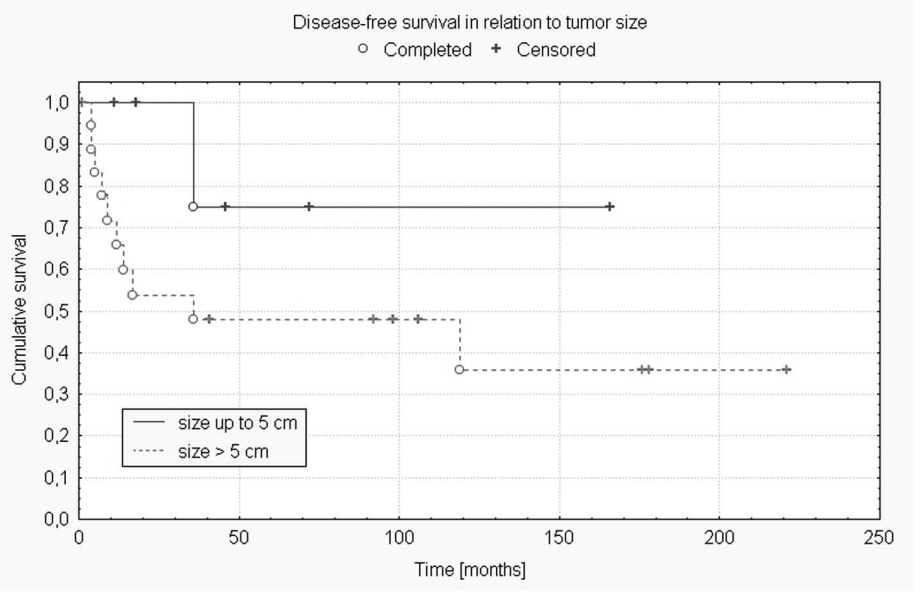

Figure 3. Disease-free survival of patients with non-epithelial malignant breast tumors in relation to tumor size

Overall survival

The 5-year overall survival probability was 0.69. The 10-year overall survival probability was 0.61 (Figure 2). The median overall survival was 129.0 months (mean: 137.3 months).

For patients with tumors not exceeding 5 cm the 5-year overall survival probability was 1.00 and the 10-year overall survival probability was 1.00 (Figure 4). Survival estimates could not be computed for these patients since all observations were censored.

For patients with tumors exceeding 5 cm the 5-year overall survival probability was 0.60 and the 10-year overall survival probability was 0.52 (Figure 4); the median overall survival was 129.0 months (mean: 118.7 months).

The difference between overall survival curves for tumor sizes was statistically not significant (log rank test statistic 2.54; df=1; p=0.11)

For patients with malignant cystosarcoma phyllodes the 5-year overall survival probability was 0.91, the 10-year overall survival probability was 0.68 (Figure 6); the median overall survival was 142.0 months (mean: 129.0 months).

For patients with breast sarcoma the 5-year overall survival probability was 0.54; the 10-year overall survival probability was 0.54 (Figure 6). The mean overall survival for these patients was 113.5 months. It was impossible to calculate a median value of overall survival for these patients.

The difference between overall survival curves (malignant cystosarcoma phyllodes vs. breast sarcoma)

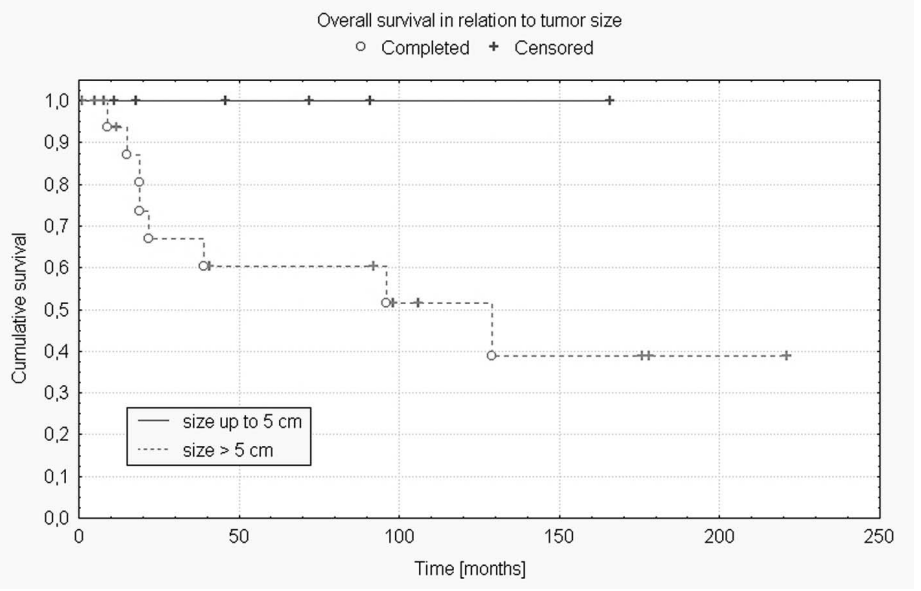

Figure 4. Overall survival of patients with non-epithelial malignant breast tumors in relation to tumor size

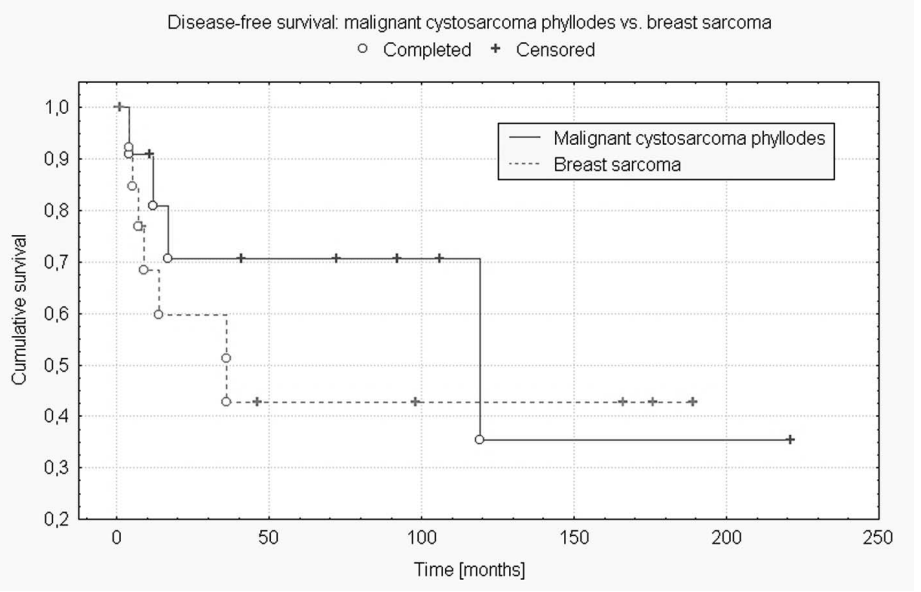

Figure 5. Disease-free survival of patients: malignant cystosarcoma phyllodes vs. breast sarcoma

was statistically not significant (log rank test statistic 0.28; df=1; p=0.59).

Discussion

The results of our study indicate that 5-year disease-free survival probability is very low. The calculated value is close to 0.5, despite achieving histologically confirmed tumor-negative resection margins during surgery. The probability of 5-year overall survival is somewhat better and close to 0.7. During the next five years after surgery (from the 6th to the 10th year of follow-up) both probabilities drop slightly by about 0.1 each. This is caused by the fact, that the majority of relapses and deaths took place during the first two years of follow-up (Figure 1 and 2).

Disease-free survival probabilities, as well as overall survival probabilities calculated for our patients, are within the ranges of values reported in medical literature [4, 6, 7, 9, 12, 16, 19]. However, it should be stressed that any comparison of treatment results of non-epithelial malignant breast tumor patients is very difficult. The studied groups of patients differ significantly from each other in the distribution of histologic types of malignancies, the grade and size of the primary tumors at presentation, the number of studied patients and the percentage of patients operated with positive resection margins. Moreover, many authors mix the treatment results of patients treated solely by surgery with those treated also with postoperative adjuvant therapy, creating therapeutically non-homogenous study group. Therefore

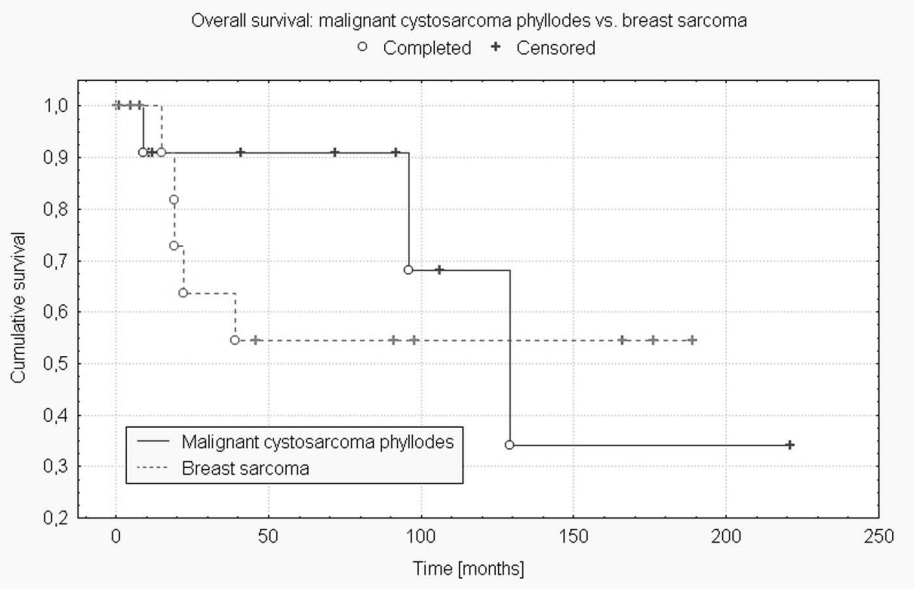

Figure 6. Overall survival of patients: malignant cystosarcoma phyllodes vs. breast sarcoma

comparisons of treatment results should be performed with due caution.

Our observations concerning the time distributions of relapses and deaths are similar to published data. No matter what treatment option is used, the shapes of the survival curves of non-epithelial malignant breast tumor patients are similar [3, 8, 16]. The majority of relapses are observed during the first two and five years of follow-up. After five years they are rare or are not encountered at all [5, 8, 9, 16, 17].

In a majority of our patients (10/11; 91%) in whom relapse was observed, the size of the primary tumor exceeded 5 cm. Similarly, all patients who had died due to disease progression during follow-up had presented with primary tumors exceeding 5 cm. Although the disease-free and overall survival curves are apparently different in patients with tumors larger and smaller than 5 cm, the differences do not reach the significance level. The phenomenon was probably caused by the small numbers of patients in the two compared subgroups.

Patients from our study group had huge breast tumors (mean size: 10.4 cm; median size: 10 cm). The majority of the primary tumors in the studied group exceeded 5 cm (22/29; 76%). The biggest tumor was 30 cm in diameter. It was probably related to the long duration of symptoms before presentation (median: 6 months) in the studied group. It also means that the majority of our patients were at a high risk of recurrence. We had no doubts concerning the extent of surgery. The size of the primary tumors was such, that in order to achieve wide (2-3 cm) tumor-negative resection margins around the primary tumor we had to perform mastectomies in 28 out of 29 of our patients (97%). Only one patient underwent a limited surgical procedure. This woman did not develop recurrence. Axillary lymphadenectomy was performed in the case of enlarged lymph nodes and when we suspected metastases, or in those cases where the lymphadenectomy was necessary to achieve proper surgical margins around the primary tumor. We cannot discuss the necessity of axillary lymph node dissection as patients with metastases in the axillary lymph nodes were considered to have disseminated disease at presentation, and were excluded from the study group.

Our observations are in concordance with other reports – that the larger the primary tumor, the higher is the risk of relapse [8, 13, 18] and that the incidence of recurrence is increased in patients with tumors exceeding 5 cm [8, 13, 18]. However, we believe that our study is unique as the mean and median sizes of tumors are unusually large. There are few reports in modern medical literature concerning such huge non-epithelial malignant breast tumors [19].

A comparison of the survival of patients with malignant cystosarcoma phyllodes and with breast sarcoma did not reveal significant differences. However, breast sarcoma patients presented with failures earlier during the course of the disease. The same observation is also reported in literature [3].

In the studied group no adjuvant radiotherapy was used. As the role of postoperative radiotherapy has not been confirmed, we cannot consider our therapeutical decisions as mistakes. However, one may find more and more suggestions that adjuvant therapy may be beneficial in such patients [8, 17] especially in case of large tumors [8]. Therefore we believe that adjuvant radiotherapy should be considered in patients who present with tumours exceeding 5 cm. We also stress the necessity of staging a multicenter prospective study on the treatment of patients with non-epithelial malignant breast tumors.

Conclusions

The probability of disease relapse in patients with non-epithelial malignant breast tumor treated surgically is high in patients with tumors exceeding 5 cm.

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