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Changes in the clinical characteristics, treatment options, and therapy outcomes in patients with phyllodes tumor of the breast during 55 years of experience

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Background: Data from the literature suggests that the clinical picture of phyllodes tumor (PT) of the breast, as well as treatment options and perhaps therapy outcomes, have significantly changed. The aim of this work was to review these changes by analysis of consecutive patients with PT over a 55-year period at a single institution.

Material/Methods: From 1952 to 2007, 280 women with PT were treated surgically at the Maria Skłodowska-Curie Memorial Institute of Oncology, Cancer Center in Cracow. Age, size of breast tumor, microscopic type, extent of surgery, and therapy outcomes were compared between 2 groups: 190 patients treated from 1952 to 1991 vs 90 patients treated from 1992 to 2007.

Results: The results show that the 1992–2007 group compared to the 1952–1991 included more patients <50 years of age, with tumor <5 cm in diameter, undergoing breast-conserving therapy, as well as no evidence of disease at 5-year survival had increased and this change was statistically significant. In addition, malignant PT cases had decreased in frequency.

Conclusions: The results of this study show that patients with PT are increasingly younger, the breast tumors at diagnosis are smaller, malignant PT is becoming less frequent, and BCT is now the treatment of choice. Most importantly, the general treatment outcomes are significantly better.

Key words: **breast phyllodes tumor • clinical picture • outcomes • treatment**

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Background

Phyllodes tumor (PT) of the breast is a rare neoplasm that constitutes 0.2–2.0% of all breast tumors in women [1–6]. PT arises most often in women 35–55 years of age, and rarely is bilateral or multifocal [1,4,7–10]. These tumors usually clinically present as an oval-shaped breast tumor that is elastic and well-separated from the surrounding glandular tissue. PTs are frequently large and can occasionally reach up to 30–40 cm in diameter. Metastases to the axillary lymph nodes are found in less than 3% of patients [1–4,7–12]. PT is composed of epithelial elements and hypercellular mesenchymal stroma; the latter forms an essential microscopic feature of this neoplasm. The World Health Organization (WHO) distinguishes 3 microscopic types of PT: benign, borderline, and malignant. This classification is based on the microscopic evaluation of the following features: the tumor margin (infiltrated, pushing, and sharp [clearly separated tumors have better outcomes]), stromal overgrowth (in malignant PT, stromal cellularity is very high), mitotic activity (≥ 5 –10 mitoses indicates tumor malignancy), and stromal cell atypia (high atypia suggests a malignant type, but low atypia does not exclude malignancy) [13]. The majority of previous reports on PT stress that the appropriate differential diagnosis of microscopic PT can be difficult and the diagnosis is often made arbitrarily. The clinical course of this disease is frequently unpredictable [2–4,7,12,14,15]. However, the microscopic type of PT is commonly accepted as the only independent prognostic factor [2–4,7,15–17].

The primary treatment of choice in patients with PT is surgery. However, the optimal extent of the surgical excision is still a matter of debate, particularly for cases of borderline and malignant PT. Over the most recent decades, breast-conserving therapy (BCT) has been increasingly offered to patients with PT; the role of adjuvant radiotherapy has also been discussed [1–7,10–12,17–21]. Most investigators have indicated that the treatment efficacy of PT has constantly improved despite reduction of the extent of the surgical excision [2,16,20–23].

The aim of this study was to analyze changes in the clinical characteristics, treatment options, and therapy outcomes of patients with PT during 55 years at a single institution in Poland.

Material and Methods

From 1952 to 2007, 280 women diagnosed with PT were treated surgically at the Maria Skłodowska-Curie Memorial Institute of Oncology, Cancer Center in Cracow, Poland. All clinical details were acquired by the review of patients' charts. The diagnosis and specific microscopic type of neoplasm were confirmed according to the WHO classification (the definitions of different PT types are conservative over the analyzed period)

[13]. The clinical characteristics, treatment options, and therapy outcomes were compared between 2 groups: patients treated from 1952 to 1991 (190 patients) vs. patients treated from 1992 to 2007 (90 patients). The separation of the 2 groups was based on changes in routine surgical treatment: before 1992 a radical or simple mastectomy was the treatment of choice; from 1992 BCT was increasingly used.

Statistical analysis

Log rank test by Peto et al. was used for evaluation of significance [24]. As level of statistical significance, $p \leq 0.05$ was accepted. Treatment efficacy was measured by the 5-year no evidence of disease (NED) survival rate (from the date of surgery). The 5-year-NED was chosen as the primary end-point because it reflects local tumor control better than other commonly used outcome measures. All patients were followed up for at least 5 years (or until death). Mean time of follow-up was 11 years. A multivariate Cox proportional hazard model was applied to analyze influence of evaluated factors on the adjusted survival.

Patients

The ages ranged from 19 to 88 years of age; the mean age was 51 years; 161 (57.5%) patients were <50 years of age, and 119 (42.5%) were ≥ 50 years. Table 1 compares both age groups during the 2 periods of time analyzed (1952–1991 and 1992–2007).

Among the 190 patients treated from 1952 to 1991, 99 (52.1%) were <50 years of age and among the 90 patients treated from 1992 to 2007, 62 were <50 (68.9%); this difference was statistically significant (log rank test, $p=0.0080$). The mean age in the 1952–1991 group was 53 and it was 48 years of age in the 1992–2007 group.

Among all patients, 115 (41.1%) had breast tumors measuring <5 cm in diameter, 112 (40.0%) had tumors 5–10 cm, and 53 (18.9%) had tumors measuring >10 cm. Table 1 shows a comparison of breast tumor diameters during the 2 periods of time analyzed (1952–1991 and 1992–2007).

Among the 190 patients treated during 1952–1991, a breast tumor measuring <5 cm in diameter was noted in 70 (36.8%) cases. Among the 90 patients treated during 1992–2007, the number of tumors <5 cm in diameter was 45 (50.0%); the difference between these groups was significant (log rank test, $p=0.0370$). The mean tumor diameter in the respective groups was 8 and 6 cm.

Among all patients, 152 (54.3%) were diagnosed with benign PT, 35 (12.5%) with borderline PT, and 93 (33.2%) with malignant PT. Table 1 shows a comparison of the incidence of

Table 1. Age, breast tumor diameter, incidence of PT* microscopic types and extent of surgery during the two periods of time analyzed (1952–1991 and 1992–2007).

		Period of treatment		
		1952–1991	1992–2007	1952–2007
		No. (%)	No. (%)	No. (%)
Age (years)	<50	99 (52.1%)	62 (68.9%)	161 (57.5%)
	≥50	91 (47.9%)	28 (31.1%)	119 (42.5%)
Breast tumor diameter (cm)	<5	70 (36.8%)	45 (50%)	115 (41.1%)
	≥5	120 (63.2%)	45 (50%)	165 (58.9%)
PT* microscopic type	Benign	97 (51.1%)	55 (61.1%)	152 (54.3%)
	Borderline	20 (10.5%)	15 (16.7%)	35 (12.5%)
	Malignant	73 (38.4%)	20 (22.2%)	93 (33.2%)
Extent of surgery	BCT**	116 (61.0%)	76 (84.4%)	192 (68.6%)
	Simple mastectomy	45 (23.7%)	13 (14.4%)	58 (20.7%)
	Radical mastectomy	29 (15.3%)	1 (1.2%)	30 (10.7%)

* Phyllodes tumor; ** BCT – breast conserving therapy.

Table 2. Extent of surgery in patients with benign/borderline or malignant PT* during the two periods analyzed (1952–1991 and 1992–2007).

		Period of treatment		
		1952–1991	1992–2007	1952–2007
		No. (%)	No. (%)	No. (%)
Benign PT*	BCT**	82 (84.5%)	49 (89.1%)	131 (86.2%)
	Simple mastectomy	15 (15.5%)	6 (10.9%)	21 (13.8%)
Borderline PT*	BCT**	16 (80.0%)	15 (100.0%)	31 (88.6%)
	Simple mastectomy	4 (20.0%)	0 (0.0%)	4 (11.4%)
Malignant PT*	BCT**	18 (24.7%)	12 (60.0%)	30 (32.2%)
	Simple mastectomy	26 (35.6%)	7 (35.0%)	33 (35.6%)
	Radical mastectomy	29 (39.7%)	1 (5.0%)	30 (32.2%)

* Phyllodes tumor; ** BCT – breast conserving therapy.

the particular PT types during the 2 periods of time analyzed (1952–1991 and 1992–2007).

Among 190 patients treated during 1952–1991, 73 (38.4%) were diagnosed with malignant PT and among 90 patients treated during 1992–2007, the number of malignant cases was 20 (22.2%). This difference was significant (log rank test, $p=0.0072$).

Treatment

All 280 women received primary treatment with surgery; 192 (68.6%) patients underwent BCT, 58 (20.7%) underwent

simple mastectomy, and 30 (10.7%) were scheduled for radical mastectomy. Table 1 shows a comparison of the extent of surgery during the 2 periods of time analyzed (1952–1991 and 1992–2007).

During the first period of time analyzed (1952–1991), BCT was performed in 116 (61.0%) patients. During the second period of time analyzed (1992–2007), it was performed in 76 (84.4%) patients. This difference was statistically significant (log rank test, $p=0.0001$). Table 2 show a comparison of the extent of surgery in relationship to the PT type during the 2 periods of time analyzed (1952–1991 and 1992–2007).

Table 3. Overview of the treatment outcomes of 280 patients with PT* during the two periods analyzed (1952–1991 and 1992–2007) in relationship to the PT* type.

	Period of treatment		
	1952–1991	1992–2007	1952–2007
	No. (5-year NED** survival,%)	No. (5-year NED** survival,%)	No. (5-year NED** survival,%)
Benign	93 (95.9%)	54 (98.2%)	147 (96.7%)
Borderline	15 (75.0%)	14 (93.3%)	29 (82.9%)
Malignant	50 (68.5%)	17 (85.0%)	67 (72.0%)
Total	158 (83.2%)	85 (94.5%)	243 (86.9%)

* Phyllodes tumor; ** NED – no evidence of disease.

Among 117 patients with benign and borderline PT treated from 1952 to 1991, 98 (83.8%) underwent BCT. Among 70 patients diagnosed with the same PT types and treated from 1992 to 2007, BCT was performed in 64 (91.4%) patients. This difference was not significant (log rank test, $p=0.1359$).

Among 73 patients with malignant PT treated from 1952 to 1991, 18 (24.7%) underwent BCT. Among 20 patients treated for malignant PT from 1992 to 2007, BCT was performed in 12 (60.0%) cases. This difference was significant (log rank test, $p=0.0027$).

Results

In all 280 patients, 243 (86.8%) survived 5 years with no evidence of disease (NED). For the 190 patients treated from 1952 to 1991, there were 158 (83.2%) patients that survived 5 years with NED; among 90 patients treated from 1992 to 2007, there were 85 (94.5%) that survived 5 years with NED. The difference in the 5-year survival with NED was significant (log rank test, $p=0.0157$). Importantly (see Table 1), the rate of malignant PT observed during the first period (1952–1991) significantly decreased from 38.4% to 22.2% when compared to the second period (1992–2007). This observation could explain the better outcomes observed over the last several years. Table 3 shows the outcomes of the 2 time periods analyzed with reference to the PT type.

Among 93 patients with borderline or malignant PT treated from 1952 to 1991, 65 (69.9%) survived 5 years with NED. Among the 35 patients treated for borderline or malignant PT from 1992 to 2007, 31 (88.6%) survived 5 years with NED. This difference in the 5-year survival with NED was statistically significant (log rank test, $p=0.0313$).

Discussion

This study included 280 patients with PT treated over a period of 55 years. Two treatment periods (1992–2007 vs. 1952–1991) were compared and statistically significant differences related to the following factors were noted. In the study group, the frequency of younger (<50 years) patients increased from 52.1% to 68.9% and the mean age decreased from 53 to 48 years. Data from the medical literature confirm that the mean age of patients with PT continues to decrease, and currently is around 45 years of age [1,18,25]. According to Bouhafa et al., among the 53 cases of PT treated during 1998–2006 in Morocco, the mean age at diagnosis was 37 years [21]. The number of patients with PT <5 cm in diameter increased from 36.8% to 50.0%. The mean tumor diameter decreased from 8 to 6 cm. Younger age at diagnosis and smaller tumors could explain the rise in breast-conserving therapy and better treatment outcomes in the latter period. Cheng et al. compared 2 groups of patients with PT treated during 1985–1996 ($n=91$) and during 1997–2004 ($n=101$), and noted that the mean tumor diameter decreased from 7.7 to 4.6 cm [26]. In the study group, the number of patients with malignant PT decreased from 38.4% to 22.2%. There has been no similar finding reported in the available medical literature to date. The number of patients treated with BCT increased from 61% to 84.4% (for patients with malignant PT, this change was from 24.7% to 60.0%). It has been unequivocally shown recently that the number of patients treated for PT with BCT significantly increased [1–7,11,12,16–20,25–27]. According to SEER data, about half of the patients with malignant PT have been treated with BCT [28]. Data from the Institut Curie in Paris showed that from 1994 to 2009, 97% of women with PT underwent BCT (including 46 patients with borderline and malignant types) [19]. Studies performed recently have convincingly shown that excision of a PT with at least 1 cm of

free margin (ie, BCT) was the preferred treatment for all patients. Simple mastectomy should be performed only if the tumor diameter/breast size ratio prevents cosmetically satisfactory postoperative appearance of the preserved breast [2–4,7,9,17–20,26]. For all patients, the 5-year NED survival rate increased from 83.2% to 94.5% (it also increased in patients with borderline and malignant PT (Table 3)). Abdalla and Sakr confirmed this observation in their report of an 82.3% 5-year NED survival rate in patients with PT, as did Taira et al. (85.0%) and Karima et al. (81.0% in malignant PT patients only) [23,27,29].

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Conclusions

The results of this study show that when comparing current to past trends over 55 years, patients with PT are increasingly younger, the breast tumors at diagnosis are smaller, the malignant PT type is becoming less frequent, and BCT is now the treatment of choice. Finally, and most importantly, the general treatment outcomes are significantly better.

Statement

Conflict of interest statement: none declared.

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