

Is prediction of local recurrence possible in Paget's disease of the breast?

Sevim Turanli^{1*}

¹ SBU, Ankara Oncology Education and Research Hospital, Department of Surgical Oncology , Ankara, TR

* Corresponding Author: Sevim Turanli E-mail: turanlisevim@hotmail.com

ABSTRACT

Objective: Mammary Paget disease of the breast is a rare form of breast cancer. The study aimed to predict the patients prone to local recurrence, and to find out the answer to the question of who should be a candidate for breast conserving surgery.

Material and Methods: Between January 2007 and February 2022, 83 patients who underwent surgery and pathology report diagnosed as Paget's disease, were analyzed retrospectively. As factors that may affect local recurrence; age, presence of nipple symptoms, mass detection in radiological imaging, type of the surgery, stage, pathological findings of the tumor (histological type, multicentricity, ER, PR, HER2, Ki 67 proliferative index, molecular subtype) were evaluated.

Results: Among 83 patients, 32 (38.6%) had ductal carcinoma in situ, and 50 patients (60.2%) had invasive ductal carcinoma, and others had pure Paget disease. Number of the patients who underwent breast-conserving surgery and mastectomy was 19 and 64, respectively. Patients were followed-up for a median time of 73 months. Recurrence was developed in 12 patients (14.5%), 7 of them with local recurrence. Type of the surgery ($p=0.001$) and young age ($p=0.02$) were the factor influencing local recurrence. Subgroup analysis was performed among patients undergoing breast-conserving surgery, and age ($p=0.07$) and absence of nipple symptoms ($p=0.07$) were found to affect local recurrence.

Conclusion: Although the number of patients is small, it should be kept in mind that local recurrence may be high when breast-conserving surgery is performed in patients with young age

Keywords: Mammary Paget's disease, breast carcinoma, local recurrence, breast conserving surgery, Ki 67 proliferative index

INTRODUCTION

Paget's disease (PD) of the breast described by Sir James Paget's in 1874 is an uncommon entity associated with underlying breast cancer in most patients. Patients mostly have clinical symptoms such as itching, nipple discharge, erythema, eczematous changes, bleeding and ulceration with or without a lump. Also, Paget's disease can be diagnosed in patients who underwent mastectomy for breast cancer located outside the areola without nipple symptoms.

There are two hypotheses for the etiology of mammary PD; first one is called the epidermotropic theory, which involves the migration of cells from ductal carcinoma in situ (DCIS) to the overlying epidermis in the form of Paget cells. In the second theory, Toker cells migrate from nonneoplastic nipple ducts to become Paget cells (1).

If Paget's disease accompanies underlying breast carcinoma, the biological behavior of the tumor changes negatively due to this possible etiological difference. Additionally, lesions can be mammographically occult, multifocal or multicentric (2), and local recurrence rates are as high as 20-40% (3).

Although surgical procedure selection in breast cancer has already changed from mastectomy to breast-conserving surgery (BCS), BCS safety is still controversial in PD due to its different nature.

With this study, it is aimed to predict the patients who may develop local recurrence, and the answer to the question of who should be a candidate for BCS is sought.

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MATERIAL and METHODS

The study was performed according to the principles of the Helsinki Declaration. Approval was obtained from the ethics committee of our institution. Between January 2007 and February 2022, an institutional database search was done retrospectively to select patients with a diagnosis of mammary PD who underwent surgery in our hospital. Twelve patients with a synchronous other primary malignancy or who did not come to regular follow-up, were excluded. Eighty-three women operated for breast disease were enrolled in this cohort study. All of the patients were evaluated by physical examination, mammography and breast ultrasonography. Diagnosis of PD was made by breast discharge cytology, full thickness skin biopsy of involved nipple-areolar complex (NAC) or core biopsy from the retroareolar breast mass in patients with clinical suspicion of Paget's disease. Some patients without clinical manifestations of PD were diagnosed unexpectedly by pathological examination of their post-mastectomy specimen.

Demographic features of the patients, physical examination, radiological findings, type of surgery, pathological findings of the tumor [histological type, size, multicentricity, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki 67 proliferative index, molecular subtype according to gene expression profiles (4), lymph node status], postoperative treatments were analyzed. Multicentric tumor was defined as the presence of 2 or more invasive tumor foci in different area of the same breast. The staging was done according to the 8th edition of American Joint Committee on Cancer (AJCC) (5).

Ki-67 proliferative index was grouped as ≤ 14 , 15-30 and above 30 (6). Regardless of the condition of the axilla; either total mastectomy or BCS was performed on the patients. In BCS, the tumor was removed with a small amount of healthy surrounding tissue. A negative margin width of no ink of tumor for invasive breast cancer and a margin of 2 mm for women with DCIS and BCS was applied only to patients who will not have breast cancer foci behind. All of the patients, who underwent BCS, received standard whole-breast radiation therapy of 1.8 to 2.0 Gy daily fractions over 5 to 5.5 weeks (total dose, 45 to 50 Gy) and a 10 to 14 Gy boost to the tumor bed.

Axillary dissection was performed in patients with a preoperative fine needle aspiration biopsy (FNAB) pathology positive for malignancy, or a malignant sentinel lymph node biopsy (SLNB) result. These patients had axillary radiation therapy postoperatively. Chemotherapy and/or hormone therapy were added to the treatment of patients according to the medical oncologist's decision. Patients were followed up until May 2022.

The time between the date of diagnosis and the last control, and the time from the date of diagnosis to the recurrence were recorded. A local recurrence was defined as the first recurrence in the ipsilateral preserved breast or ipsilateral chest wall without distant disease and their pathology reports were similar to primary breast cancer pathology. If the features of the recurrent tumor were not similar to the primary tumor, it was considered as a second primary tumor. As factors that may affect local recurrence; age, presence of

nipple symptoms, mass detection in radiological imaging, the type of the surgery, stage, tumor pathological findings (histological type, multicentricity, ER, PR, HER2, Ki 67 proliferative index, molecular subtype) were evaluated.

Statistical analysis

Descriptive statistics (number, percentage) were used to analyze the parameters related to the patient demographic characteristics, tumor characteristics, and treatment. These categorical variables between patients without local recurrence and those with local recurrence were compared using Chi-square or Fisher's exact tests and continuous data was compared using a Student t test. In the evaluation of statistical analysis, confidence interval of 95% and p value of 0.05 were accepted. Data were evaluated using SPSS 18.0 program.

RESULTS

Among 83 patients, 32 patients (38.6%) had PD with DCIS and 50 patients (60.2%) had PD with invasive ductal carcinoma (IDC) and one patient with pure Paget's disease. Median age was 53 years (range; 31-89). Except one patient, Paget's disease affected only one breast in all patients. Fifty-three patients (63.9%) had NAC lesions and 52 patients (62.6%) had associated mass lesions in the breast, detected via radiologic imaging. Thirty patients (36.1%) without clinical manifestations of PD were diagnosed unexpectedly by pathological examination of their post-mastectomy specimen. Distribution of mammographic findings were microcalcifications in 23 patients (27.7%), mass in 37 patients (44.6%), mass lesion with microcalcifications in 15 patients (18.1%), asymmetrical density in 2 patients (2.4%) and no abnormality in 6 patients (7.2%).

The disease was diagnosed with breast discharge cytology in 1 patients (1.2%), full-thickness skin biopsy of involved NAC in 32 patients (38.6%), and core biopsy of the mass in 50 patients (60.2%). Initially, breast conserving surgery and total mastectomy were performed in 21 (25.3%) and 62 (74.7%) patients respectively. In 2 patients who underwent BCS, the operation was completed to total mastectomy since the tumor was continuous at the surgical margin in the pathology report.

In 6 patients nothing was done to the axilla, in 58 patients SLNB was done whereas the remaining 19 patients underwent directly axillary dissection. Among the SLNB group, lymph node metastases were detected in 17 patients and these patients underwent axillary dissection. Additional benign lesions were present in 42 (50.6%) of 83 patients. These were proliferative lesions in 21 patients, nonproliferative lesions in 11 patients, and atypia in 10 patients. When patients were grouped according to the breast cancer stage, 31 patients were stage 0, 14 patients were stage I, 30 patients were stage II and 7 patients were stage III. Tumor characteristics of the mammary Paget's disease was given in **Table 1**.

The molecular classification of the tumor was Luminal A in 2 patients (2.4%), Luminal B in 42 patients (50.6%), HER2-Enriched in 34 patients (41.0%) and basal-like in 5 patients (6.0%).

The multicentricity rate was 34.9% in the whole series (29 patients). Patients were followed-up for a median of 73 months (range; 3-177 months). Twelve (14.5%) out of 83 patients had recurrence and the median recurrence time was 46.0 months (range; 13-73 months). Of the recurrences, 6 were local, 5 were systemic disease, and 1 was both local and systemic disease. While median time of local recurrence development was 34 months (20-54 months), median time of systemic disease development was 31.5 months (10-54 months).

Among 6 patients only with local recurrence, 5 had previously underwent BCS for DCIS, and their disease recurred as Paget’s disease with DCIS in 4 of them, whereas one patient had invasive carcinoma. All of these patients had simple mastectomy for recurrent cancer. The other patient with local recurrence who formerly had central excision including nipple-areola complex for Paget’s disease with IDC, had recurrent IDC and finally treated with simple mastectomy. The only patient with both local and systemic recurrence was previously diagnosed as PD with IDC and treated with simple mastectomy, later on developed a local recurrence on the chest wall. Factors affecting local recurrence are given in **Table 2**. Type of the surgery (p=0.001) and age (p=0.02) were the factors influencing local recurrence. Subgroup analysis was performed among patients undergoing BCS, and their result was given **Table 3**. Age (p=0.07) and absence of nipple symptoms (p=0.07) were the factors affecting local recurrence.

Table I. Tumor characteristics of the Mammary Paget’s disease

		Patients No (%)
ER status	Positive	27(32.5%)
	Negative	56 (67.5%)
PR status	Positive	31(37.3%)
	Negative	52(62.7%)
HER2 expression	Positive	64(77.1%)
	Negative	10(12.0%)
	Unknown	9(10.9%)
Ki-67 proliferative index	≤14	5(6.0%)
	15-30	11(13.3%)
	>30	29(34.9%)
	Unknown	38(45.8%)
Molecular subtype	HR+HER2-	7(8.4%)
	HR+HER2+	30(36.2%)
	HR-HER2+	34(41.0%)
	HR-HER2- HR-HER2 unknown	3(3.6%) 9(10.8%)

ER estrogen receptor PR progesterone receptor
HER2 human epidermal growth factor receptor

Table II. Comparison factors for local recurrence in all patients

		Local recurrence		P values
		YES	NO	
		N: pts%	N: pts%	
Age (mean)		51.1±11.6	61.8±11.2	0.02
Nipple symptoms	Present	3(5.7%)	50(94.3%)	0.21
	Absent	4(13.3%)	26(86.7%)	
Breast mass (radiologic imaging)	Present	4(8.0%)	46(92.0%)	0.58
	Absent	3(9.1%)	30(90.9%)	
Breast operation	Breast-conserving surgery	6(31.6%)	13(68.4%)	0.001
	Total mastectomy	1(1.6)	63(98.4)	
Invasion depth	DCIS	5(12.6%)	27(84.4%)	0.78
	Invasive	2(4.0%)	48(96.0%)	
Stage	Stage 0	4(13.3%)	27(86.7%)	0.44
	Stage I	0(0.0%)	14(100.0%)	
	Stage II	3(10.0%)	27(90.0%)	
	Stage III	0(0.0%)	7(100.0%)	
Multicentricity	Present	3(10.3%)	26(89.7%)	0.46
	Absent	4(7.4%)	50(92.6%)	
ER status	Positive	3(11.1%)	24(88.9%)	0.41
	Negative	4(7.1%)	52(92.9%)	
PR status	Positive	4(12.9%)	27(87.1%)	0.23
	Negative	3(5.8%)	49(94.2%)	
HER2 expression	Positive	6(9.4%)	58(90.6%)	0.37
	Negative	0(0.0%)	10(100.0%)	
	Unknown	1(11.1%)	8(88.9%)	
Ki67 proliferative index	≤14	0(0.0%)	5(100.0%)	0.48
	15-30	1(9.1%)	10(90.9%)	
	>30	2(6.9%)	27(93.1%)	
	Unknown	1(10.5%)	34(89.5%)	
Molecular subtype	HR+HER2-	0(0.0%)	7(100.0%)	0.98
	HR+HER2+	4(13.3%)	26(86.7%)	
	HR-HER2+	2(5.9%)	32(94.1%)	
	HR-HER2-	0(0.0%)	3(100.0%)	
	HR-HER2 unknown	1(11.1%)	8(88.9%)	

ER estrogen receptor PR progesterone receptor
HER2 human epidermal growth factor receptor

Table 3. Comparison factors for local recurrence among patients undergoing BCS

		Local recurrence		P values
		YES N: pts%	NO N: pts%	
Age (mean)		60.7±11.7	49.7±11.2	0.07
Nipple symptoms	Present	3(20.0%)	12(80.0%)	0.07
	Absent	3(75.0%)	1(25.0%)	
Breast mass (radiologic imaging)	Present	3(30.0%)	7(70.0%)	0.63
	Absent	3(33.3%)	6(66.7%)	
Invasion depth	DCIS	5(35.7%)	9(64.3%)	0.48
	Invasive	1(20.0%)	4(80.0%)	
Stage	Stage 0	5(35.7%)	9(64.3%)	0.14
	Stage I	0(0.0%)	1(100.0%)	
	Stage II	1(25.0%)	3(75.0%)	
Multicentricity	Present	2(50.0%)	2(50.0%)	0.37
	Absent	4(26.7%)	11(73.3%)	
ER status	Positive	3(42.9%)	4(57.1%)	0.37
	Negative	3(25.0%)	9(75.0%)	
PR status	Positive	4(50.0%)	4(50.0%)	0.16
	Negative	2(18.2%)	9(81.8%)	
HER2 expression	Positive	5(31.3%)	11(68.7%)	0.40
	Negative	0(0.0%)	1(100.0%)	
	Unknown	1(50.0%)	1(50.0%)	
Ki67 proliferative index	≤14	0(0.0%)	1(100.0%)	0.89
	>30	2(50.0%)	2(50.0%)	
	Unknown	4(28.6%)	10(71.4%)	
Molecular subtype	HR+HER2-	0(0.0%)	1(100.0%)	0.83
	HR+HER2+	4(57.1%)	3(42.9%)	
	HR-HER2+	1(11.1%)	8(88.9%)	
	HR-HER2 unknown	1(50.0%)	1(50.0%)	

ER estrogen receptor PR progesterone receptor
HER2 human epidermal growth factor receptor

DISCUSSION

Paget's disease appears as pure PD, PD with DCIS and PD with IDC. Rate of Paget's disease with underlying breast cancer was found in different series as of 55% to 100% (7, 8). Since our hospital is a tertiary reference center; there was only one patients with pure Paget's disease in this series. According to Surveillance Epidemiology and end Results (SEER) data, consisting of 2631 patients, a decrease in the age-adjusted incidence of PD occurred from 2000 to 2011. Also, the overall rates of mastectomy in the PD only, PD with DCIS, and PD with IDC groups were 47, 69, and 88.9 %, respectively. Breast conserving surgery rate in patients with invasive cancer increased from 8.5% in 2000 to 15.7% in 2011 (8). Is PD incidence really decreasing? I think probably no.

In this series, half of the patients with local recurrence were not previously considered PD and tumor was detected in the non-areolar area, and BCS was performed. Paget's disease was diagnosed incidentally when mastectomy was performed after recurrence. If recurrence had not been developed in these patients and mastectomy had not been performed, the diagnosis of PD would not have been made or it would have been diagnosed when nipple symptoms had appeared. Therefore, as the BCS rate increases in patients without clinical findings of PD, the diagnosis of PD, which is overlooked, increases. Recent studies have suggested that a fraction of patients, between 15 % and 46 %, harbor clinically undetectable Paget's disease yet are incidentally diagnosed following microscopic examination of mastectomy specimens performed for another indication (9, 10).

Local recurrence rates in this group of patients were high, but it was not statistically significant. Whether or not PD is considered in physical examination, the lesion may not be visualized during imaging of breast with mammography and/or ultrasound. If mammography and ultrasound are negative in patients with PD, the extent of the disease can be better demonstrated by magnetic resonance imaging. However, since the disease tends to be multifocal or multicentric, and occult, extent of an underlying malignancy with radiological imaging may be overlooked (2, 11, 12). Although mammography, ultrasound and magnetic resonance imaging were negative in 6 patients in this series, cancer was detected in pathological examination incidentally.

What is the best treatment option for Paget's disease is controversial. I believe that two questions may be important in the decision of treatment: first, is Paget's disease accompanied by an underlying malignancy? Second, if the answer is yes, is the disease invasive or in situ? Since radiological imaging is more sensitive for invasive carcinoma than in situ carcinoma, local recurrence risk may be expected lower in patients with PD with invasive carcinoma. In this case, we can make BCS decision more confidently. However, since the number of patients is limited, it is difficult to find out a clear answer to these questions in studies comparing the results of the selected surgical method. In the series of Marshall et al, including 33 TisNOM0, 2 T1NOM0 and 1 T2NOM0 patients, partial or total nipple areola complex excision were done, followed by RT to the whole breast and tumor beds. Actuarial local control rates for the breast were 91% at 5 years, 87% at both 10 and 15 years.

While any local recurrence was not seen in 6 patients with pure Paget's disease, the rate was 20% among patients with Paget's disease with ductal carcinoma in situ (13). In another series of Bijker et al., the median follow-up was 6.4 years, local recurrence rates were 5.3% and 25.0% in Paget's disease with and without ductal carcinoma in situ, respectively (14). In the meta-analysis involving 685 patients by Li et al., local recurrence rate was 5.6% among women undergoing mastectomy and 13.2% among those treated with BCS (3). Their result concluded that BCS is not equivalent to mastectomy in the treatment of PD for local control. In our series, overall local recurrence rate was 8.4%, whereas it was 15.6% for PD with DCIS and 4.0% for PD with IDC patients. Literally local recurrence rate in invasive cases was low, but not significantly. In addition, local recurrence rate was 1.5% among women undergoing mastectomy and 31.7% among those treated with BCS. Age and BCS selection were a strong risk factors for local recurrence.

Multifocality and/or multicentricity were seen as another factor for local recurrence (15-17). In our series, recurrence was high in multicentric disease than unicentric disease, but this difference was not statistically significant. Breast cancer has different molecular features as well as different histological types. Major molecular subtypes have been identified according to gene expression profiles in breast cancer (18). The molecular subtypes can be reliably determined with immunohistochemical stain. Immunohistochemistry based panels, including ER, PR, HER2, Ki-67, and basal cytokeratins are used to reveal tumor features. When molecular subtypes are recognized, tumor biology is better established. In mammary PD, the frequency of molecular subtypes differs compared with invasive breast carcinoma, with HER2-amplified cases being overrepresented (19). Paget's disease associated carcinomas tend to have lower hormone receptor expression, higher HER2 expression. These cancers tend to have poor biological profiles (6, 20, 21). In a series covering 48 patients by Wachter et al, ER and/or PR positivity rate was 38.6% and Ki 67 index was found 20% or greater in 95.3% of the patients (19). In our series, ER and/or PR positivity rate was 44.6% and Ki-67 index was found 14 or greater in 88.8%. Ki 67 proliferative index was correlated with local recurrence; also, none of the patients with HER 2 negative tumor had local recurrence but this result was not significant. The limitation of this study is that it is a rare disease and the number of patients is low. Accordingly, the statistical power of the results is weak. However, I still think that the results of the treatment selection should be considered. In addition, this study included only one patients who had pure Paget's disease. Therefore, no conclusion can be made about the reliability of breast conserving surgery in this patient group.

CONCLUSION

As in other breast cancers, in Paget's disease, type of the surgery chosen seems to be a risk factor for local recurrence. Patients diagnosed with Mammary Paget's disease should be informed about surgical intervention options and their possible outcomes. Although the number of patients is small, it should be kept in mind that local recurrence may be high when BCS is performed in patients with young age.

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