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

ABSTRACT

Purpose

Mammary Paget disease of the breast is rare form of breast cancer. Recent trends in the management have changed from mastectomy to breast conserving surgery, its safety is still controversial. 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.

Methods

Between January 2007 and December 2017, 69 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 69 patients, 26 patients had ductal carcinoma in situ and others had invasive ductal carcinoma. Number of the patients underwent breast conserving surgery and mastectomy was 15 and 54 respectively. Patients were followed-up for a median time of 45 months. Recurrence was developed in 12 patients, half of them with local recurrence. Type of the surgery was the unique factor influencing local recurrence (p=0.001). Subgroup analysis was performed among patients undergoing breast conserving surgery, only Ki 67 proliferative index above 30 (p=0.002) was 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 BCS is performed in patients with the tumor's Ki 67 proliferative index is above 30.

Key words

Mammary Paget’s disease; Breast carcinoma; Local recurrence; Breast conserving surgery; Ki 67 proliferative index; Molecular subtype

WHAT’S KNOWN?

Mammary Paget’s disease can be mammographically occult, multifocal or multicentric, and local recurrence rates are as high. It is hard to decide what type of surgery should be done in Paget’s disease.

WHAT’S NEW?

We found that at median follow-up of 45 months, recurrence was developed in a median time of 26.5 months in 12 patients (17.4%), half of them with local recurrence. Type of the surgery was the unique factor influencing local recurrence. 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 the tumor's Ki 67 proliferative index is above 30.

INTRODUCTION

Paget's disease (PD) of the breast described by Sir James Paget's in 1874 is an uncommon entity that is associated with underlying breast cancer in the majority of 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 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.

MATERIALS 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 December 2017, an institutional database search was done retrospectively to select patients with a diagnosis of mammary PD and underwent surgery in our hospital. Eleven patients with a synchronous other primary malignancy or who did not come to regular follow-up, were

excluded. Sixty-nine women operated for a stage I to III breast cancer 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, lymph node status], postoperative treatments were recorded. Multicentric tumor was defined as the presence of 2 or more invasive tumor foci in different quadrants of the same breast. Staging was done according to the 8th edition of American Joint Committee on Cancer (AJCC) [4]. Ki-67 proliferative index was grouped as ≤14, 15-30 and above 30 [5]. 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 hormonotherapy were added to the treatment of patients according to the medical oncologist's decision. Patients were followed up until

August 2020. 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 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 69 patients, 26 patients (37.7%) had PD with DCIS and 43 patients (62.3%) had PD with invasive ductal carcinoma (IDC). There was no patient with pure Paget's disease. Median age was 53 years (range; 33-77). Paget's disease affected only one breast in all patients. Forty-eight patients (% 69.6) had NAC lesions and 51 patients (%73.9) had associated mass lesion in the breast, detected via radiologic imaging. Nine patients without clinical manifestations of PD were diagnosed unexpectedly by pathological examination of their post-mastectomy specimen. Distribution of mammographic findings were

microcalcifications in 13 patients (18.8%), mass in 41 patients (59.4%), mass lesion with microcalcifications in 10 patients (14.5%), asymmetrical density in 3 patients (4.3%) and no abnormality in 2 patients (2.9%). The disease was diagnosed with breast discharge cytology in 2 patients (2.9%), full thickness skin biopsy of involved NAC in 34 patients (49.3%), and core biopsy of the mass in 33 patients (47.8%). Breast conserving surgery and total mastectomy were performed in 17 (24.6%) and 52 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 3 patients nothing was done to the axilla, in 41 patients only SLNB was done whereas the remaining 25 patients underwent directly axillary dissection. Among the SLNB group, lymph node metastases were detected in 10 patients and these patients underwent axillary dissection. Additional benign lesions were present in 35 (50.7%) of 69 patients. These were proliferative lesions in 16 patients, nonproliferative lesions in 16 patients, and atypia in 3 patients. When patients were grouped according to the breast cancer stage, 26 patients (37.7%) were stage 0, 10 patients (14.5%) were stage I, 22 patients (31.9%) were stage II and 11 patients (15.9%) were stage III. The molecular characteristics of the tumor are given in Table 1. The multicentricity rate was 26.1% in the whole series (18 patients). Patients were followed-up for a median of 45 months (range; 5-136 months). Twelve (17.4%) out of 69 patients had recurrence and the median recurrence time was 26.5 months (range; 10-47 months). Half of the recurrences were local and the rest were distant metastases. While median time of local recurrence development was 31 months (21-41 months), median time of systemic disease development was 18.5 months (10-47 months). Three patients who previously underwent BCS for DCIS, had local recurrence with Paget's disease and DCIS, and simple mastectomy was performed. In 2 of the remaining 3 patients, central excision including nipple-areola complex was performed due to Paget's disease with IDC. Local recurrence was as IDC in one patient and in the second one as DCIS, total

mastectomy was performed in both. In all patients who developed local recurrence after BCS, the recurrence area was close to the first primary tumor location and the recurrence pathology was similar to the original pathology. The last patient of the recurrence group was diagnosed as PD with IDC previously, and developed a local recurrence in the chest wall after mastectomy. Factors affecting local recurrence are given in Table 2. Type of the surgery was the unique factor influencing local recurrence (p=0.001). Subgroup analysis was performed among patients undergoing BCS and their result was given Table 3. Only Ki 67 proliferative index above 30 (p=0.002) was the factor affecting local recurrence.

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% [6,7]. Since our hospital is a tertiary reference center; there were no 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 [7]. 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 [8,9]. Local recurrence rate in this group of patients was 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 [2,10,11]. Although mammography, ultrasound and magnetic resonance imaging were negative in 2 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 TisN0M0, 2 T1N0M0 and 1 T2N0M0 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 [12]. 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 [13]. 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 8.7%, whereas it was 11.5% for PD with DCIS and 7.0% for PD with IDC patients. Literally local recurrence rate in invasive cases was low, but not significantly. In addition, only BCS selection was a strong risk factor for local recurrence.

Multifocality and/or multicentricity were seen as another factor for local recurrence [14-16]. In our series, recurrence was high in multicentric disease than unicentric disease, but this difference was not significant. Breast cancer has different molecular features as well as different histological types. Major molecular subtypes have been identified according to gene expression profile in breast cancer [17]. 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 [18]. Paget's disease associated carcinomas tend to have lower hormone receptor expression, higher HER2 expression. These cancers tend to have poor biological profiles [8,19,20]. 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 [18]. In our series, ER and/or PR positivity rate was 43.4% and Ki-67 index was found 14 or greater in 91.3%. 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.

Limits of the study

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 does not include 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 the tumor's Ki 67 proliferative index is above 30.

Compliance with Ethical Standard

Disclosure of potential conflicts of interest

Sevim Turanli declares that she has no conflict of interest concerning the research, authorship, or publication of this article.

Research involving Human Participants and/or Animals

Research involves only human participants.

Institutional review board statement: Ethics committee approval was received for this study from the Ethics Committee of Ankara Oncology Education and Research Hospital (16.06.2016/ 20033663)

Informed consent statement: Informed consent was not received due to the retrospective nature of the study.

Funding: No funding support

DATA AVAILABILITY STATEMENT

The Author declare that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. Moreover, the Author ensure that their datasets are presented in the main manuscript.

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

		Patients No (%)
ER status	Positive	21(30.4%)
	Negative	48 (69.6%)
PR status	Positive	27(39.1%)

	Negative	42(60.9%)
HER2 expression	Positive	51(73.9%)
	Negative	10(14.5%)
	Unknown	8(11.6%)
Ki-67 proliferative index	≤14	6(8.7%)
	15-30	13(18.8%)
	>30	22(31.9%)
	Unknown	28(40.6%)
Molecular subtype	HR+HER2-	8(11.6%)
	HR+HER2+	22(31.9%)
	HR-HER2+	29(42.0%)
	HR-HER2-	2(2.9%)
	HR-HER2 unknown	8(11.6%)

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 N: pts%	NO N: pts%	
Age (mean)		54.8±6.3	51.5±1.4	0.50

Nipple symptoms	Present Absent	3(6.3%) 3(14.3%)	45(93.8%) 18(85.7%)	0.25
Breast mass (radiologic imaging)	Present Absent	5(9.8%) 1(5.6%)	46(90.2%) 17(94.4%)	0.50
Breast operation	Breast-conserving surgery Total mastectomy	5(33.3%) 1(1.9)	10(66.7%) 53(98.1)	**0,001**
Invasion depth	DCIS Invasive	3(11.5%) 3(7.0%)	23(88.5%) 40(93.0%)	0.40
Stage	Stage 0 Stage I Stage II Stage III	3(11.5%) 1(10.0%) 1(4.5%) 1(9.1%)	23(88.5%) 9(90.0%) 21(95.5%) 10(90.9%)	0.55
Multicentricity	Present Absent	3(16.7%) 3(5.9%)	15(83.3%) 48(94.1%)	0.18
ER status	Positive Negative	2(9.5%) 4(8.3%)	19(90.5%) 44(91.7%)	0.59
PR status	Positive Negative	3(11.1%) 3(7.1%)	24(88.9%) 39(92.9%)	0.56

HER2 expression	Positive	6(11.8%)	45(88.2%)	
	Negative	0(0.0%)	10(100.0%)	0.25
	Unknown	0(0.0%)	8(100.0%)	
	≤14	0(0.0%)	6(100.0%)	
Ki67 proliferative	15-30	1(7.7%)	12(92.3%)	0.18
index	>30	4(18.2%)	18(81.8%)	
	Unknown	1(3.6%)	27(96.4%)	
Molecular subtype	HR+HER2-	0(0.0%)	8(100.0%)	
	HR+HER2+	3(13.6%)	19(86.4%)	
	HR-HER2+	3(10.3%)	26(89.7%)	0.76
	HR-HER2-	0(0.0%)	2(100.0%)	
	HR-HER2 unknown	0(0.0%)	8(100.0%)	

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)		59.2±5.6	49.8±2.9	0.12
Nipple symptoms	Present	3(23.1%)	10(76.9%)	0.09

	Absent	2(100.0%)	0(0.0%)	
Breast mass (radiologic imaging)	Present Absent	4(57.1%) 1(12.5%)	3(42.9%) 7(87.5%)	0.10
Invasion depth	DCIS Invasive	3(25.0%) 2(66.7%)	9(75.0%) 1(33.3%)	0.24
Stage	Stage 0 Stage I	2(18.2%) 3(75.0%)	9(81.8%) 1(25.0%)	0.07
Multicentricity	Present Absent	2(100.0%) 3(23.1%)	0(0.0%) 10(76.9%)	0.09
ER status	Positive Negative	1(25.0%) 4(36.4%)	3(75.0%) 7(63.6%)	0.59
PR status	Positive Negative	2(40.0%) 3(30.0%)	3(60.0%) 7(70.0%)	0.56
HER2 expression	Positive Negative Unknown	4(33.3%) 0(0.0%) 1(50.0%)	8(66.7%) 1(100.0%) 1(50.0%))	0.42
Ki67 proliferative	≤14 >30	0(0.0%) 4(100.0%)	1(100.0%) 0(0.0%)	**0.002**

index	Unknown	1(10.0%)	9(90.0%)	
Molecular subtype	HR+HER2-	0(0.0%)	1(100.0%)	
	HR+HER2+	2(50.0%)	2(50.0%)	
	HR-HER2+	2(25.0%)	6(75.0%)	0.73
	HR-HER2 unknown	1(50.0%)	1(50.0%)	

ER estrogen receptor PR progesterone receptor

HER2 human epidermal growth factor receptor