Original Article
Middle East Journal of Cancer; July 2016; 7(3): 145-159

Paget's Disease of the Female Breast: Clinical Findings and Management in 53 Cases at a Single Institution

Hatem Bouzaiene*, Bassem Mezghani*♦, Maher Slimane*, Aida Goucha, Amir Ariane*, Lamia Naija*, Amor Gamoudi**, Tarek Dhieb*, Khaled Rahal***

**Department of Surgical Oncology, Salah Azaïz Institute, Tunis, Tunisia*
***Department of Pathology, Salah Azaïz Institute, Tunis, Tunisia*

Abstract

Background: Mammary Paget's disease is an uncommon form of primary breast cancer. The aim of this study is to assess our institution's experience in its management.

Methods: We retrospectively reviewed the medical records of 53 female patients with histologically confirmed Paget's disease, treated at the Salah Azaïz Institute between 2001 and 2010.

Results: There were palpable masses in 71.7% of cases, of which 90% revealed invasive carcinoma. Approximately 48% of underlying malignancies were multifocal/multicentric. Overall, invasive carcinoma accounted for 69.8% with a median tumor size of 40 mm, high grade in 62.2%, and negative hormone receptor in 47.6% of cases. There was only one case with direct dermis invasion among those with no underlying invasive carcinoma. After a median follow-up of 45 months, 49% of patients presented with relapse/progression and 47.1% died from their disease. Median overall survival was 67 months, whereas disease-free survival was 65 months. Tumor and node advanced clinical stages correlated with poor survival, as well as the presence of invasive carcinoma with additional negative impacts of large tumor size and lymph node involvement. Tumor stage was the only independent indicator on multivariate analysis.

Conclusion: The general trend for decreased incidence of Paget's disease is noted parallel to earlier breast cancer diagnosis. Paget's disease is at high risk of multifocal/multicentric underlying tumors. The presence of a palpable mass is almost pathognomonic of invasive neoplasm. The major challenge concerns aggressiveness of surgical procedures with breast and axilla preservation perspectives. Prognosis is mainly determined by that of an eventual underlying breast tumor.

Keywords: Breast neoplasms, Paget's disease, Mammary, Diagnosis, Therapy, Prognosis

♦Corresponding Author:
Bassem Mezghani, MD
5 Rue Lakhder de Hssine 2033
Megrine Tunis, Tunisie
Tel: 0021698958926
Fax: 0021671577863
Email: dr.bassem.mez@gmail.com

Middle East Journal of Cancer

Received: January 13, 2016; Accepted: April 26, 2016

Introduction

Mammary Paget's disease (PD) is an uncommon form of primary breast cancer that accounts for 1%-5% of cases.[1-6] Despite its prevalent typical clinical appearance, diagnosis is frequently delayed because of the neglect by patients and/or practitioners misled by the appearance of a benign dermatological lesion. The fortuitous finding of a clinically occult PD on mastectomy specimens remains a relatively frequent event.[1,7] Histological diagnosis is attested by the presence of nipple-areola complex (NAC) epidermis infiltration by Paget's cells. Regardless of their origin this is still debated.[3,5,7] Until recently, PD has not been incorporated in the American Joint Committee on Breast Cancer (AJCC) staging system despite its probable negative impact on prognosis.[8,9] The National Comprehensive Cancer Network (NCCN) guidelines include it in the "special considerations" breast cancer group.[10] Paget's disease is a heterogeneous entity depending on the invasiveness and extension of an almost constant underlying tumor in the breast parenchyma.[1,5,6,11] Difficulties in diagnosis and management are principally related to the subgroup of patients that have no clinical and radiological evidence of underlying tumor.[1,3] In the era of therapeutic de-escalation and esthetical requirements, mastectomy in patients with PD has become controversial whereas conservative management and use of sentinel lymph node biopsy (SNB) recently increased.[1] Debate concerning surgical management was recently revived by identification of cases with direct dermal invasion from the NAC epidermis. Clinical significance of the so-called invasive mammary PD remains to be determined.[12] The aim of this review is to assess our institution's experience in management of PD through a discussion of known data and recent improvements reported thus far.

Materials and Methods

The study retrospectively reviewed the records of all female patients with histologically confirmed PD treated at the Salah Azaïz Cancer Institute between January 2001 and December 2010. Excluded were patients with another concurrent malignancy and those with medical history of conservatively managed ipsilateral breast cancer. We collected data on clinical presentation, management, and follow-up. Typical signs of PD (TSPD) included NAC erythema, eczema, scaling, erosion, ulceration, and retraction. Areolar and subareolar underlying lesions were considered to be central tumor locations. Disease staging was performed according to the 6th edition of the AJCC-2002.[8] Classification of radiological images according to the Breast Imaging Reporting and Data System (BI-RADS) terminology was not always available.[13] Histologically, PD might either constitute an exclusive NAC disease (NACD) or be associated with underlying breast carcinomas such as ductal carcinoma *in situ* (DCIS), microinvasive carcinoma (MIC), and invasive carcinoma (IC). In this study, we divided the patients into 4 subgroups and compared their clinical features, therapeutic modalities, and prognoses. Tumors were graded according to the Van Nuys Prognostic Index (VN) in case of DCIS and the modified Scarff-Bloom-Richardson grading system (SBR) for IC. MIC were not graded.[14,15] Testing of hormone receptors (HR) and over-expression of human epidermal growth factor receptor oncoprotein (HER-2/neu) was introduced during the study period but its use was restricted to cases with underlying IC. Nipple-areola complex slides from patients with no underlying IC were reassessed for direct invasion of the dermis by Paget's cells. At the time of the study, endocrine therapy consisted almost exclusively of a selective estrogen receptor modulator (Tamoxifen). Use of aromatase inhibitors was restricted to cases with recurrent disease. We considered disease relapse or progression to be local/regional when it concerned the chest wall, axillary, and supraclavicular areas or eventually, the contralateral breast. According to the therapeutic response, cases with initially metastatic disease were considered either in remission or progression.

Statistical analyses were conducted using the

Statistical Package for the Social Sciences (SPSS 21) software. We compared subgroups according to chi-square and Fisher's exact test in case of categorical variables and the t-test for continuous variables. We calculated breast cancer specific overall survival (OS) from the date of surgery to the date of death or last follow-up visit according to the Kaplan-Meier method.[16] Reference remission date chosen for computing disease-free survival (DFS) matched variably to date of surgery or the end of systemic treatment. For patients lost to follow-up, duration was calculated from the date of first medical visit to that of postoperative discharge from hospital. The log-rank test compared survival according to univariate analysis, whereas the Cox regression method was used for multivariate analysis.[17] *P*-values less than 0.05 were considered statistically significant.

The Institute Research Board did not require any approval or consent for this study.

Results

Data analysis showed great disparities in the number of cases treated annually at our institution with peaks in the early 2000s. Cases associated with underlying IC decreased from 80% to 100% in the beginning to a maximum of 50% in the subsequent period. In parallel, less aggressive underlying tumors and cases with exclusive NACD increased. They accounted for at least 50% of annually recorded cases since 2004.

Epidemiology and clinical features

The median age at diagnosis was 55 years (range: 27-86). There were 33 (62.3%) menopausal patients. At least one risk factor for breast cancer was found in 18 (34%) patients, which included one patient with a history of contralateral breast cancer in remission for more than 5 years. The median delay from onset of symptoms to the first medical visit was 4 months (range: 1-240). Isolated nipple changes motivated medical consultation in 16 (30.2%) patients, however the main presenting symptom was a breast lump in 34 patients that included 7 with associated nipple changes and/or discharge. Other circumstances of diagnosis were breast pain (2 patients) and imaging screening (1 patient). On clinical examination, a palpable mass was found in 38 (71.7%) patients. These masses were isolated in 12 patients and associated either with TSPD (20 patients) or other cutaneous signs (6 patients). There were TSPD without palpable mass present in 15 (28.3%) patients, which included 3 that presented with erythema and/or scaling, 7 with eczema, and 3 with ulceration. In total, 35 (66%) presented with obvious signs of PD and 18 patients had occult disease. The median size of the palpable mass was 45 mm (range: 20-120) with peripheral locations more commonly observed in 26 (68.4%) patients. We found only one case with extended lesions. According to the AJCC staging system, patients were classified as follows: 15 (28.3%) T0, 18 (34%) T1-2, 5 (9.4%) T3, and15 (28.3%) T4 tumors, including 5 inflammatory breast cancers. Lymph node staging indicated 18 (34%) N0, 28 (52.8%) N1, and 7 (13.2%) N2-3c patients with clinically positive nodes. There were 20 (37.7%) patients that presented with locally advanced stages (T3-4 and/or N2-3c). A total of 5 cases initially presented with metastatic disease. The most common metastatic site was the bones; only one case had associated hepatic and bony lesions.

Imaging findings

All 53 patients had mammograms (MMG) and 38 (71.7%) underwent ultrasonography (US) studies. Results showed the presence of abnormalities on at least one imaging technique in 46 (86.8%) patients and normal results in 7 (13.2%), which included 3 patients that only underwent mammographic assessment. In 17 (32.1%) patients, MMG showed the presence of areolar and/or cutaneous modifications such as retraction or thickening. These lesions were the only finding in 2 cases and 15 patients they were associated with underlying parenchymal breast lesions. All told, 43 patients had parenchymal breast abnormalities located in depth. In 24 (45.3%) patients, the results indicated the presence of a mass of which included 9 patients with associated microcalcifications. An asymmetric focal density was noted in 10 (18.9%) patients. The

other 9 (17%) patients presented with microcalcifications, which included 3 with associated asymmetric focal density. Ultrasound findings showed a mass in 24 (63.2%) patients which included one case that presented with palpable mass and negative findings on MMG. Another case that presented with isolated TSPD, had an asymmetric focal density on MMG. Ultrasound results showed isolated skin thickening in 5 (13.1%) patients. In the entire imaging work-up, 15 (28.3%) had central abnormalities, 24 (45.3%) had peripheral abnormalities, and 7 (13.2%) had extended lesions. Median radiological size was 40 mm (range: 17-100). All 27 patients stratified according to BI-RADS classification were considered category 5. Data concerning axillary lymph nodes (ALN) assessment was not available and there was no recourse to MRI.

Surgical management

Preoperative biopsy for NAC and/or others breast lesions was performed in 26 (49.1%) patients. The NAC biopsy was performed in 12 of 15 (80%) patients who presented with TSPD and no palpable mass. Deep biopsies were performed in 14 of the 39 (35.9%) patients who presented with masses identified by clinical and/or radiological assessments. Corresponding pathology identified 13 IC and one DCIS. According to biopsy findings, 5 (9.4%) received preoperative chemotherapy because of locally advanced tumors in 3 patients and metastatic disease in 2. All were considered to have tumors that responded favorably to chemotherapy. Hence the decision was made to proceed with locoregional surgery, as for the other patients included in the study. In total, 4 (7.5%) patients twice underwent surgery. However, all 53 patients had definitive surgery that consisted of mastectomies with at least an ALN biopsy. In the 35 patients who presented with patent signs of PD, the first surgical procedure was breast conservation (lumpectomy with NAC removal) in 5 (14.3%) patients, of whom 3 presented with clinically and radiologically isolated TSPD and 2 with palpable mass. Conservative management was finally rejected because of positive margins/re-excision. Radical surgery was recommended either in the first or second procedure by the diagnosis of PD in 14 (26.4%) patients, the presence of diffuse microcalcifications in 5 (9.4%), locally advanced tumor stage and/or following preoperative chemotherapy in 18 (34%), and the presence of multifocality/multicentricity in 16 (30.2%) patients which included the 5 previously mentioned patients with positive margins/re-excision. In terms of ALN staging, 2 (3.8%) patients received SNB, 12 (22.6%) had level I dissection, and 39 (73.6%) had complete clearance.

Histological findings

The frozen section technique was used for 30 (56.6%) patients during the first surgical procedure. Proposed diagnoses agreed with final histological findings in 86.6% of these cases. In addition to Paget's cells, the pathology revealed an underlying tumor in 48 (90.6%) patients, which included 23 (47.9%) multifocal/multicentric lesions. Histological tumor locations agreed with radiological findings with the exception of 5 (10.5%) patients that included 3 overextended and 2 smaller lesions. Histological size was specified in 37 of 48 (79.2%) patients with underlying tumors and in 33 patients amongst the 38 that presented with palpable mass. The 39th case with a mass detected by US matched finally to an exclusive NACD. Size remained unspecified for 6 DCIS, 2 MIC, and 3 IC which included one case with diffuse lesions throughout the whole breast. Median size was 40 mm (range 1-90). The VN remained undetermined in 3 cases because of technical difficulties and 1 ALN status was missing because of clearance specimen's loss. HR testing was performed in 26 (49.1%) patients, whereas HER-2/neu was performed in 4 (7.55%) cases. All pathological features are summarized in Table 1.We reviewed the NAC section slides from 12 out of 16 patients that presented with no underlying IC. Only one patient that presented with an exclusive NACD had foci of direct dermis invasion that extended less than 1mm from the dermal-epidermal junction. According to immunohistochemistry (IHC)

findings, the tumor was positive for CK7 and HR, and negative for Her-2/neu.

Subgroups

A comparison of the epidemiological characteristics of patients in the histological subgroups showed no statistically significant differences in terms of mean age at diagnosis (P=0.14), menopausal status (P=0.882), duration of symptoms (P=0.167), and risk factors with the exception of a personal history of contralateral breast cancer in one case from the MIC subgroup (P=0.006). There were shorter, nonsignificant mean follow-up times (P>0.2) in the MIC (38.75 months) and IC (51.3 months) subgroups compared to the NACD and DCIS subgroups (approximately 65.8 months). The subgroups were assumed to be approximately similar in terms of epidemiological features and follow-up. We analyzed their clinical presentations, imaging features, histological findings, management and events, as summarized in Tables 2 and 3. In women younger than 35 years, PD was associated with underlying IC in 80% of cases. Less aggressive disease (NACD/DCIS/MIC) occurred mainly at a more advanced age (>35 years in 94% of cases). A palpable mass was found in 34 (91.9%) IC patients, 3 (75%) MIC patients, and one (14.3%) patient with DCIS (P<0.001). On the other hand, when clinical presentation included a palpable mass, an IC was found in approximately 90% of cases (Table 2). Tumors were classified as T0 according to the AJCC staging system in 15 (28.3%) patients, which included 13 with isolated TSPD and 2 patients with TSPD plus small cutaneous signs on presentation. Among these patients, 5 showed no abnormalities on imaging, 3 of whom had evidence of deeper tumors (2 IC and 1 DCIS) which corresponded to 60% of patients with no clinical and radiological evidence of underlying tumor. The sensitivity of combined MMG and US for detection of deeper breast lesions was 95.8%. It approximated 94.7% in the presence of a palpable mass versus 62.5% otherwise. There was only one case of exclusive NACD with false positive radiological investigations reported; the findings matched an extended asymmetric focal density. All 27 BIRADS-5 investigations revealed underlying tumors (DCIS in 7.4%, MIC in 11.1%, and IC in 81.5% of patients). There were palpable ALN in 31 (84%) patients from the IC subgroup, 50% in the MIC subgroup, and less than 20% in the other subgroups (P=0.004). ALN staging procedure consisted of level I dissection in 60% within the NACD subgroup and all patients with DCIS. In the IC subgroup, a complete clearance was realized in 92% of cases that included approximately 11% with no palpable lymph nodes. Sentinel lymph node biopsy twice showed negative results (Table 3). Overall, patients with positive axillary clearance had clinically palpable nodes in 90% of cases, of which all matched underlying IC except for 1 patient with MIC. On the other hand, there were palpable, positive ALN on histology in 74.1% of cases. In patients that presented with palpable masses, the positive clearance rate approximated 78% (29 patients). Peripheral tumors were the most common (50%) except in the DCIS subgroup, where central lesions predominated (85.7%). About 50% of tumors were multifocal/multicentric in the IC and MIC subgroups versus only 28.6% in the DCIS (P=0.54; Table 2). According to clinical presentation, the multifocality/multicentricity rate was approximately the same (about 50%) in the presence or absence of a palpable mass. Mean tumor size approximated 40 mm in the IC, 20 mm in the MIC, and 5mm DCIS subgroups but size was available in only one DCIS case (P=0.124). HR were negative in 47.6% (10 cases) of patients with underlying IC and 100% (2 cases) in the MIC subgroup (P=0.4; Table 2).

Postoperative course and prognosis

After surgery, 2 patients were lost to follow-up; one died as a result of this disease and did not receive postoperative treatment. The remaining patients received the total planned therapy, except for 4 cases of relapse/progression that occurred during the treatment phase. Altogether, 7 (13.7%) received no adjuvant treatment. These patients comprised 60% of the NACD, 42.9% DCIS, and 25% of the MIC subgroups. A total of 30 (58.8%)

Table 1. Clinicohistopathologic characteristics of the patients.

Histological type	Number (%)	
PD with exclusive NACD	5 (9.4)	
PD + underlying tumor	48 (90.6)	
IC	37 (69.8)	
DCIS	7 (13.2)	
MIC	4 (7.5)	
Total	**53**	
Tumor location	Number (%)	
Central	18 (37.5)	
Peripheral	24 (50)	
Extended	6 (12.5)	
Total	**48**	
Tumor size	Number (%)	
<20mm	7 (18.9)	
≥20 mm	30 (81.1)	
Total	**37**	
SBR	Number (%)	
SBR1	3 (8.1)	
SBR2	11 (29.7)	
SBR3	23 (62.2)	
Total	**37**	
VN	Number (%)	
Grade II	4 (57.1)	
Unspecified	3 (42.9)	
Total	**7**	
ALN staging	Median (range)	Number (%)
Number of ALN dissected	15 (3-25)	-
Patients with positive ALN	-	30 (57.7)
Number of positive ALN:	2 (0-22)	-
Total		**52**
HR status	Number (%)	
Negative	14 (26.4)	
Positive	12 (22.6)	
Unspecified	27 (50.9)	
Total	**53**	
HER-2/neu Score	Number	
1 +	1	
3+	3	
Total	**4**	

PD: Paget's disease;NACD: Nipple-areola complex disease; IC: Invasive carcinoma;DCIS: Ductal carcinoma in situ; MIC: Microinvasive carcinoma;SBR: Scarff-Bloom-Richardson grade score; VN: Van Nuys nuclear grade score; ALN: Axillary lymph nodes; HR: Hormone receptors; HER-2/neu: Human epidermal growth factor receptor oncoprotein.

patients received radiotherapy, which included 29 from the IC subgroup (82.9% within the IC subgroup). Irradiation was associated with systemic therapy in all of these cases (endocrine therapy alone in 13.3%; chemotherapy ± endocrine therapy in 86.7%). The remaining 13 (25.5%) received only systemic therapy which included 10 treated by endocrine therapy alone. This was the

case in 40% of NACD, 57.1% of DCIS, 50% of MIC, and less than 6% of the IC subgroups (Table3).By taking into consideration the entire postoperative treatment offered to patients, nonsignificant differences existed between subgroups (*P*=0.07).

Follow-up showed that 18 (approximately 34%) patients exceeded 60 months of monitoring and only 9 (17%) had 120 months of follow-up. Overall, 26 (51%) patients had no evidence of recurrence, relapse or disease progression during monitoring which corresponded to 100% within the NACD and DCIS subgroups, 50% among MIC patients, and 33.3% in the IC subgroup (*P*=0.009; Table 3). All were alive at the end of the study with the exception of 2 cases that died due to other reasons. The first 25 cases of recurrence, relapse or disease progression occurred in the IC subgroup, with the exception of one MIC patient. There were no cases of isolated local/regional recurrence or progression; all included distant metastasis (Table 3). One of the 25 patients with progressive disease was alive at the end of the study. All relapses occurred in patients who underwent complete axillary clearance. We found no events in cases that underwent SNB and level I dissection (*P*=0.004). The entire group had a mean OS of 82.3 months (95% CI: 65-99.5) and median survival of 67 months (95% CI: 0-147). The 5-year OS was 50%, whereas the 10-year OS was 42%. In cases of NACD and those with DCIS, both the 5- and 10-year OS were 100%. The MIC and IC subgroups had 5-years OS of 50% for MIC and 35% for the IC subgroup. At 10 years, OS was 28% for IC patients. Log rank test showed statistically significant differences among these subgroups (*P*=0.011). Median DFS was 65 months (95% CI: 13.45-116.55). The rate of DFS at 5 and 10 years in the overall group was 52% and 44%. Specifically, 5-year DFS was 67% in the MIC subgroup, 36% in the IC subgroup, and 100% in the NACD and DCIS subgroups. The 10-year DFS was available only in the IC subgroup (28%). Log rank test for DFS showed significant differences between subgroups (*P*=0.006). Kaplan-Meier plots for OS and DFS are shown in Figure 1.

We analyzed prognostic indicators for survival for overall patients according to univariate analysis. Select factors in the IC subgroup were analyzed by multivariate analysis because of statistical imperatives and incomplete data concerning prognostic factors in the other subgroups. Age at diagnosis, menopausal status, duration of symptoms, imaging findings, tumor localization and extension on pathology were not indicators of prognosis. Tumor and node staging according to the AJCC classification impacted OS and DFS according to univariate analysis, however only the T stage was identified as an independent indicator on multivariate analysis (Table 4).A correlation existed between clinical

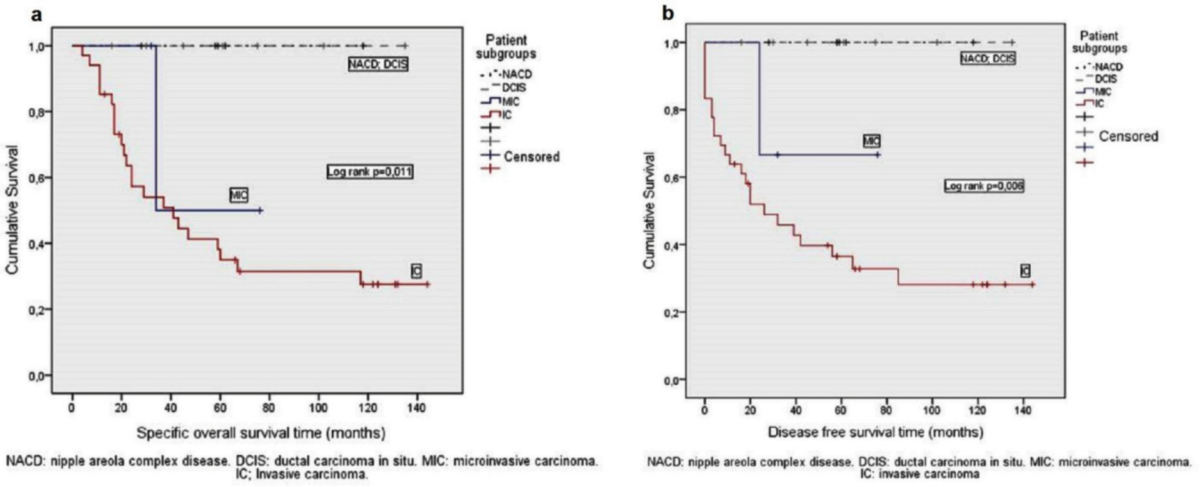

Figure 1. Illustration of Kaplan-Meier survival plots according to histological subgroups. A) Overall survival (OS). B) Disease-free survival (DFS).

Table 2. Summary of clinical features and pathology according to histological subgroups.

	NACD (n=5)	DCIS (n=7)	MIC (n=4)	IC (n=37)	Total (%) (n=53)	*P*-value
Clinical presentation						
Isolated TSPD	5	5	1	2	13 (24.5)	
Palpable mass ± CUTS	0	0	2	16	18 (34)	<0.001
Palpable mass + TSPD	0	1	1	18	20 (37.7)	
TSPD + CUTS	0	1	0	1	2 (3.8)	
TNM staging – T (Tumor) [a]						
T0	5	6	1	3	15 (28.3)	
T1	0	1	0	3	4 (7.5)	
T2	0	0	3	11	14 (26.4)	0.001
T3	0	0	0	5	5 (9.4)	
T4b	0	0	0	10	10 (18.9)	
T4d	0	0	0	5	5 (9.4)	
TNM staging – N (Node) [a]						
N0	4	6	2	6	18 (34)	
N1	1	1	2	24	28 (52.8)	0.02
N2/N3C	0	0	0	7	7 (13.2)	
Imaging features						
No abnormalities	2	1	0	4	7 (13.2)	
Central lesions	2	4	0	9	15 (28.3)	0.05
Peripheral lesions	0	0	3	21	25 (45.3)	
Extended lesions	1	2	1	3	7 (13.2)	
Histological tumor location						
Central	-	6	0	12	18 (37.5)	
Peripheral	-	1	3	20	24 (50)	0.04
Extended location	-	0	1	5	6 (12.5)	
Multifocality/multicentricity	-	2	2	19	23 (47.9)	0.54
ALN Status						
Positive clearance	0	0	1	29	30 (57.7)	<0.001
HR testing						
Realized	1	2	2	21	26 (49.1)	0.406
Positive status	0	1	0	11	12 (46.2)	
Her-2/neu testing						
Realized	-	2	1	1	4 (7.5)	0.513
Positive status	-	1	1	1	3 (75)	

NACD: Nipple-areola complex disease; DCIS: Ductal carcinoma in situ; MIC: Microinvasive carcinoma; IC: Invasive carcinoma; TSPD: Typical signs of Paget's disease (PD). CUTS: Cutaneous signs; ALN: Axillary lymph nodes; HR: Hormone receptors; HER-2/neu: Human epidermal growth factor receptor oncoprotein.
[a]TNM: Tumor node metastasis staging according to the 6th edition of the American Joint Committee on Cancer (AJCC).[8]

presentation, particularly the presence of a palpable mass, with poor OS and DFS. Its impact was significant only in univariate analysis for OS (*P*=0.036) and DFS (*P*<0.001). The presence of a mass at presentation resulted in an OS of 33%at 5 years and 25% at 10 years versus 100% in the presence of isolated TSPD (no palpable mass). Plot survivals are shown in Figure 2.The extent of the ALN dissection procedure negatively impacted OS (*P*=0.04) and DFS (*P*=0.001) according to univariate analysis. Analysis among the IC subgroup showed that tumor size and ALN status

were the only factors that impacted OS and DFS. We observed this finding only in the univariate model. There was a 5-year OS of 27% and 10-year OS of 22% for positive clearance versus 86% otherwise (P=0.001). Almost the same rates were noted for DFS (P<0.001). Scarff-Bloom-Richardson grade and HR status did not appear to be prognostic indicators.

We took into consideration the 38 patients with palpable mass according to the presence or absence of associated TSPD. There were 2 subgroups of 20 and 18 cases which we assumed to be similar in terms of epidemiological features (all P-values were >0.05). Survival analysis for these patients showed that 5- and 10-year OS in the presence of TSPD were not statistically worse compared with the occult PD group (P=0.08). Survival curves are shown in Figure 3.We found similar, nonstatistically significant results for DFS (P=0.09). However, there were significantly more advanced and extended tumors in the patent PD group compared with the occult PD group. A total of 55% of patent PD cases and 22.2% of occult PD cases had stage T4 disease (P=0.02). Lesions were histologically extended in 20% of patent PD cases and in 11.1% of occult PD cases (P=0.025).

Discussion

Epidemiological and clinical features

Paget's disease comprises 1%-5% of reported breast cancer cases.[1-6] A general trend of decreased incidence has been reported in the late 1990s, particularly in cases associated with underlying tumors. Those with exclusive NACD remained constant. Based on the "epidermotropic" theory for histogenesis, several authors explained this trend by the earlier diagnosis of breast cancer prior to pagetoid spread of malignant cells to overlying NAC. The subsequent rise in conservative management could also be implicated, which would explain the decrease number of cases with incidental histological findings.[11] The same tendency was observed in our study population with a lag of approximately 10 years that matched more recent improvements in breast cancer screening. The more accepted "epidermotropic" theory was sustained by the presence of an underlying carcinoma with most always the same IHC features compared to Paget's cells as seen in 65%-100% of cases.[5-7,9,11,18-20] The currently reported rate of approximately 90% has supported these data. The "intraepidermal *in situ* malignant transformation" theory is controversial and principally supported by the recording of additional cases with exclusive NACD.[1]

As we have reported in the current study, PD occurred mainly in post-menopausal women at a median age range of 50-66 years.[1-3,5,11,19,20] Generally, the median delay from onset of symptoms until the first medical visit is approximately 10 weeks and the 4 months reported

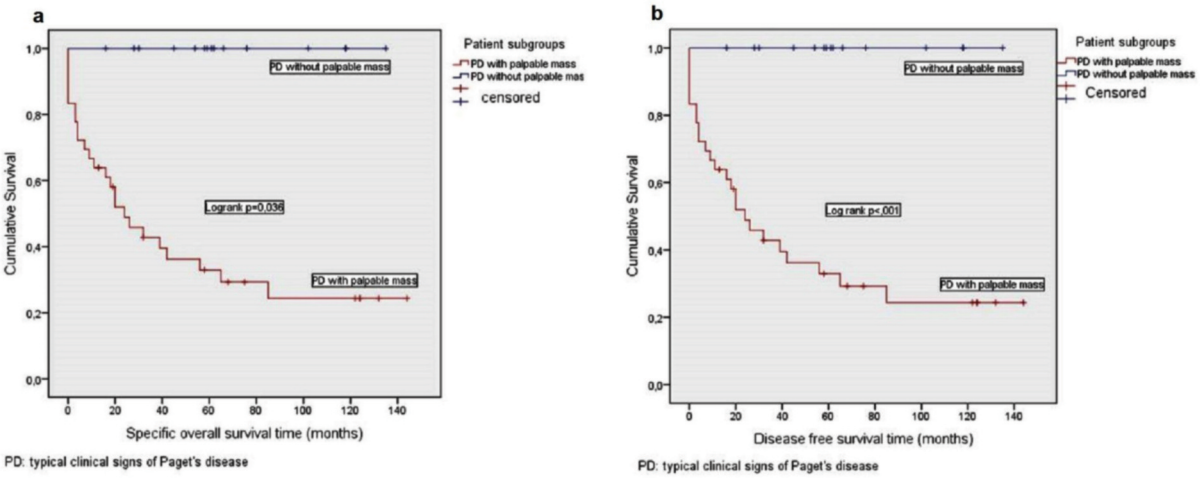

Figure 2. Illustration of Kaplan-Meier survival plots according to clinical presentation. A) Overall survival (OS). B) Disease-free survival (DFS).

Table 3. Summary of management and postoperative course according to histological subgroups.

	NACD n=5	DCIS n=7	MIC n=4	IC n=37	Total (%) n=53	*P*- value
AND procedure						
SNB	1	0	0	1	2 (3.8)	<0.001
AND level I	3	7	0	2	12 (22.6)	
AND level II/III	1	0	4	34	39 (73.6)	
Postoperative treatment [a]						
None	3	3	1	[b]	7 (13.7)	
Radiation	-	-	1	29	30 (58.8)	0.07
Systemic treatment	2	4	3	34	43 (84.3)	
CT	-	-	1	12[c]		
ET	2	4	2	6		
CT + ET	-	-	-	16		
Median follow-up (months) (range)	60	62	33.5	30	45 (1-144)	-
Events [a] [b]						
None	5	7	2	12	26 (51)	0.009
Metastatic R/P	-	-	1	14	15 (29.4)	
L/R + metastatic R/P	-	-	-	9	9 (17.7)	
Survival [a]						
Alive at the end of study	5	7	2	11	25 (49)	0.005
Disease specific death	-	-	1	23	24 (47)	
Death from other reasons	-	-	-	2	2	

NACD: Nipple-areola complex disease; DCIS: Ductal carcinoma in situ; MIC: Microinvasive carcinoma; IC: Invasive carcinoma; AND: Axillary node dissection; SNB: Sentinel lymph node biopsy; CT: Chemotherapy; ET: Endocrine therapy; R/P: Recurrence/progression; L/R: Local/regional.

[a]Missing data in 2 patients lost to follow-up.

[b]1 patient with initially progressive IC died from this disease prior to onset of postoperative treatment.

[c]1 patient received chemotherapy and trastuzumab.

reflects neglect of this condition.[19] Presenting symptoms consist mostly of TSPD that are present on clinical examination in 71%-98% of cases, whereas palpable masses are identified in 22%-50% of cases. Patients with occult PD are generally diagnosed at an advanced stage when taking into consideration their underlying breast cancer. These account for 10%-46% of patients. Overall, approximately 14% of PD patients have palpable ALN.[1-4,7,18,19,21] Clinical findings in the current study differ from the literature data with more advanced stages at diagnosis.

Imaging workup

Recommended first line imaging workup that includes MMG and US fails to identify underlying abnormalities in 40%-90% of cases and underestimates extending of identified lesions in up to 42% of cases. According to the literature, MMG sensitivity ranges from 34% to 78% with a particularly low performance in detection of DCIS. Reported rates for the US are slightly lower, from 48% to 70%.[1-3,5,19,22] Patients with isolated TSPD and no evidence of deeper lesions on classical imaging modalities have accounted for approximately 40% among PD cohorts and show underlying tumors in 73%-85% of cases, 60%-68% for DCIS and 5%-27% for IC cases.[4,20] These patients have benefitted tremendously from the high-sensitivity of MRI in detection and staging of underlying breast tumors, whereas additional findings on MRI for patients with previous positive MMG and/or US results do not modify subsequent management. MRI rectifies underestimation of MMG findings in 50%-70% of cases; however, its sensitivity range of 50%-

Table 4. Prognostic value of tumor and node staging for surviving patients in univariate and multivariate analyses.

	Overall survival (OS)			Disease-free survival (DFS)		
	Median (months)	UV [a]	MV [b]	Events[c] (%)	UV [a]	MV [b]
Tumor staging [d]			HR 1.945			HR 2.205
T0	135		CI (1.239-3.052)	0		CI (1.403-3.466)
T1/2/3	47.8	*P*<0.001	*P*=0.004	11 (52.4)	*P*<0.001	*P*<0.001
T4	21.5			14 (93.3)		
Node staging [d]			HR 1.245	1 (5.9)		HR 1.280
N0	135		CI (0.783-1.978)	17 (63)		CI (0.799-2.051)
N1	47.3	*P*<0.001	*P*=0.355	7 (100)	*P*<0.001	*P*=0.304
N2/3c	21.5					

UV: Univariate analysis; MV: Multivariate analysis; HR: Hazard ratio; CI: Confidence interval. [a]Log-rank test. [b]Cox regression model. [c]Cumulative events. [d]Stage according to the TNM-AJCC staging system.8

95% is impaired by misdiagnosis in DCIS. Despite the relatively high rate of false positive results, MRI ensures a reliable selection of patients for conservative management on the basis of the presence of unifocal and centrally located lesions. MRI is also efficient in detection of NAC involvement in cases of breast cancer with occult PD, as well as in their therapeutic planning, especially when breast preservation is considered.[2,5,22] Although MRI has been introduced in 2004 it was not used in any of the reported cases. Current findings supported with the relatively advanced clinical stage at diagnosis. The sensitivity of combined MMG and US was slightly lower in the DCIS subgroup and impaired in absence of a palpable mass with a misdiagnosis of deeper carcinoma in 60% of patients with no clinical and radiological evidence of underlying tumor.

Surgical management

Surgical management planning depends initially on the presence and extension of parenchymal breast lesions and secondly on the existence of preoperative evidence of NAC involvement.[2,3,5,7,22] Our team practice, based thus far on radical surgery, is currently undergoing several improvements since data have confirmed the reliability of MRI in detection and staging of tumors underlying to PD. Currently we comply with the NCCN algorithm for PD diagnosis and surgical management.[10] Historically, mastectomy has been used as the exclusive oncologically safe procedure for PD. Mastectomy does not necessarily improve prognosis regarding local control and survival rates compared to conservative management in rigorously selected patients. However, it remains largely used (60%-97% of PD patients), sustained by the high rate of multifocal and frequently occult underlying tumors that account for 20%-40% of mastectomy specimens. Radical surgery gives a local control rate (LCR) range of 90%-98%.[1,3,4,6,7,9,11,18-20] In the last decade, breast conservation surgery imperatively associated with radiotherapy has become a suitable therapeutic modality in selected patients that presented with no clinical and MRI findings of peripherally extended and/or multifocal

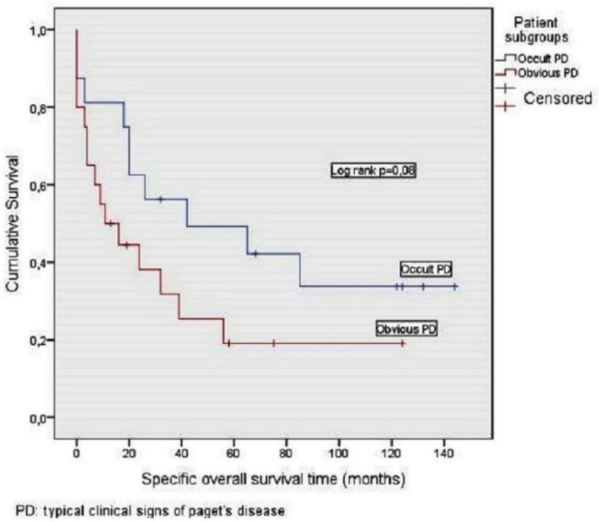

Figure 3. Illustration of Kaplan-Meier plots for overall survival (OS) of patients with palpable mass according to obvious or occult Paget's disease (PD) presentation.

underlying tumors who had sufficient breast volume to ensure successful cosmetic outcome. Conservative management is currently performed on approximately 25% of patients with underlying IC and up to 54% of the other cases despite the lack of randomized trials.[3,20] Considering the fact that recurrences in conservatively managed patients are frequently invasive and associated with poor prognosis, special care must be given to the complete removal of the NAC and underlying tumor, particularly in the presence of microcalcifications. Achievement of free histological margins must be verified before beginning radiotherapy, otherwise mastectomy should be performed.[2-4,6,7,20] Several, mostly retrospective studies assessed safety and cosmetic outcomes of conservative management. Most showed a moderate increase in the local recurrence rate compared with therapeutic modalities that included radical surgery in addition to the possible poor esthetical outcome reported in approximately 10% of cases.[5,6,18,20,23] The European Organization for Research and Treatment of Cancer (EORTC), in a prospective study of 61 patients without associated IC treated with conservative surgery and irradiation, reported a LCR of 94.8% at 5 years.[23] Other studies that compiled retrospectively entire cohorts of PD patients showed 10- and 15-year LCR that ranged from 84%-87%. Disease specific survivals reported at 15-years were >95%. In several of these studies, the authors noted that overall LCR and survival of patients with PD that received conservative management were similar to rates reported for patients who presented with DCIS without PD and received conservative management. They explained this finding by the fact that IC were frequently multifocal/multicentric or peripherally extended and these patients underwent mastectomies.[6,18,20] Until now, the suitable surgery in cases with no clinical and radiological evidence of breast lesions has remained controversial, particularly because of the frequent confinement of histological lesions to central locations, which suggested overtreatment by mastectomy.[5] In the current study, surgery for breast conservation was seen in only 14.3% of patients that presented with obvious signs of PD. This was consistent with our policy of radical surgeries in PD patients, however other criteria such as the presence of diffuse microcalcifications, locally advanced tumor stage, and preoperative chemotherapy motivated the decision for mastectomy. All patients received an ALN staging of mostly a complete clearance (73.6%) whereas SNB was performed in only few cases after its introduction to the team in 2006. Recently, on the basis of retrospective studies, SNB demonstrated its accuracy in axillary staging among clinically node-negative PD patients. According to the high rate of underlying breast carcinoma, frequently undetected preoperatively even after a suitable diagnosis strategy, several authors have recommended the SNB procedure when a mastectomy is the planned surgery and in cases where IC is present or a high suspicion of IC exists regardless of the planned surgery (conservative or mastectomy). Controversy persists about first line conservative procedures for presumed cases with exclusive NACD or DCIS. Nevertheless, when microinvasion is strongly suspected, SNB assessment seems to be adequate and may avoid a second surgery.[5,20,22,24]

Pathological features

Tumors underlying PD are reported to be centrally located in 25%-60% of cases and match principally to DCIS. Peripherally extended lesions are frequently multifocal/multicentric and consist mostly in IC. Overall, DCIS are the most common associated tumors and account for 39%-78% of associated tumors versus 30%-64% for IC. Specifically, the highest proportion of IC has been observed in women younger than 35 years whereas noninvasive disease occurred mainly at a more advanced age. MIC represented at most 5%-13% of reported cases. Exclusive NACD accounted for 5%-30% and was predominant in older patients.[1-7,9,11,19,20,22,24] These findings supported those reported in our study except for the higher rate of IC (70%) and less common DCIS (13.2%). Generally, in the literature, underlying IC appeared to be highly aggressive

with a grade 3 reported rate of 40%-65%, negative HR in 38%-75%, and overexpression of HER-2/neu in 70%-90% versus 20%-50% in the common form of breast cancer. The Ki67 index was >20% in up to 77% of cases.[3,4,9,11,19-21] Except for high grade and HR negativity rate, the lack of data in the current study impeded us from reaching additional conclusions. In the literature, the reported rates of positive axillary clearance ranged between 30% and 60% among patients with underlying IC and between 10%-31% in PD patients overall. In patients that presented with palpable masses, 86%-100% were IC. The positive clearance rate in the presence of a palpable mass ranged from 45%-60%. In the absence of a palpable mass, DCIS was the most frequent finding (66%-88%), however IC is present in 30%-43%. Regardless of the underlying tumor (DCIS/IC), clearance rates reportedly range between 0 and 20%.[3,5,7,11,20,21,24] In the current study, despite a consistent rate of IC found within patients with palpable mass, we found more frequent ALN involvement which supported the more advanced stage of disease at diagnosis. In the absence of a palpable mass, the findings were consistent with the data cited above which have reflected favorable features in the absence of a palpable mass and presence of only TSPD. Dermis invasion by Paget's cells is infrequent and probably an underreported phenomena (< 4%-8% among PD cohorts) since it is an unknown condition. Histological clear-cut distinction from an eventual underlying breast IC is mandatory in order to exclude direct skin invasion. Invasive mammary PD has been recently highlighted in a few case reports however its clinical significance, particularly in cases of exclusive NACD, is unclear. Recent reports suggest that the prognosis of PD is not modified in the presence of dermis invasion. If considering the fact that ALN invasion by isolated tumor clusters has been reported even in the absence of invasive underlying tumor, the value of SNB in cases of invasive PD is investigative.[2,12]

Postoperative management and prognosis

Recommendations for systemic treatment and irradiation match those of the common form of breast cancer. However, there is controversy concerning patients that receive breast sparing surgery for PD associated with DCIS since the rational and efficiency of different therapeutic modalities in prevention of recurrence is debatable.[9] When PD constitutes a local relapse after conservatively managed breast cancer or nipple-sparing mastectomy, no further conservative management is possible.[21] In the current study, 84.3% of patients have received postoperative treatment; 58.8% underwent radiation associated with systemic therapy. We believed that this intensive management was justified considering the 70% rate of associated IC, which was mostly diagnosed at an advanced stage. Because of the relapse risk, it has been recommended to extend follow-up for more than 10 years, particularly in cases of conservative management.[20] In our cohort, mean follow-up times were not significantly shorter in the presence of underlying IC. Presumably, this could be explained by a higher rate of cancer specific death and therefore of censored cases within those subgroups. Furthermore, follow-up showed significantly more frequent recurrence in patients that received complete axillary clearance. A possible explanation could be selection bias in surgical management where more aggressive axillary staging procedures are offered to patients with advance stage cancer to ensure local control.

The prognosis of PD is mainly determined by that of the eventual underlying tumor.[6,11] Classically, the presence of a palpable mass, along with underlying IC and ALN involvement are recognized as prognostic indicators for survival.[7] The literature review has shown 5-year OS rates of 69%-88% and 10-year OS rates of 75%-87%, which were considerably higher than those currently reported.[4,9] Specifically, in the presence of IC, 10-year OS ranged from 49%-62% versus 29%-50% for 10-year OS in our cohort (Figure 1).[11,21] According to the literature, 15-year OS in DCIS patients was approximately 88%; this

relatively poor prognosis suggested the possibility of undiagnosed foci of microinvasions within DCIS proliferations.[11,19] In the presence of a palpable mass, 5- and 10-year OS ranged between 30%-49%. In the absence of a palpable mass, the 5- and10-year OS ranged from 90%-100%. The ALN involvement correlated with a 10-year OS of 20%-47%, otherwise OS without ALN involvement ranged between 75%-93%.[1,7,11] We observed approximately the same rates. Data for DFS showed rates of approximately 82% at 5 years and 72% at 10 years.[4,9] The currently reported results were lower (Figure 1), impaired by the high rate of recurrence within the IC subgroup. Our statistical analysis concluded that the presence of IC, tumor and node staging according to the AJCC classification constituted prognostic indicators for OS and DFS. Specific analysis among the IC subgroup demonstrated additional prognostic impact of tumor size and ALN involvement. However, we have found the T stage to be the only independent factor for prediction of recurrence and mortality. We believe that inclusion of cases with locally advanced and initially metastatic disease negatively impacted prognosis and dispersed the presumed improvements related to radical surgery. In addition to a major delay in diagnosis, these cases could reflect the aggressiveness of breast cancer in the presence of PD compared with the common forms. The trend to worse prognosis in the presence of PD has been previously reported. The authors suggested that such differences could be explained by the aggressiveness of IC associated with PD with a strong presumption of HER-2/neu over-expression.[9,19,21] Another previously reported trend showed a not significant lower 5-year OS and DFS in the presence of occult PD compared to those with patent signs.[21] We observed an insignificant, inverse tendency in the current study (Figure 3). We believed that this tendency was distorted by selection bias related to significantly different extensions of underlying tumors.

In addition to retrospective design and small patient sample, another study limitation was the population heterogeneity with great disparities in epidemiological context and therapeutic modalities that changed considerably during the study period. Most studies that have dealt with this topic have been constrained by the limited number of cases reviewed. We believe that most likely there will not be a randomized trial for PD. Therefore, further improvements will be made on the basis of small population reports.

Conclusion

The general trend in decreased incidence of PD is noted parallel to earlier breast cancer diagnosis. Patients with PD have high risk of multifocal/multicentric underlying tumors. The presence of a palpable mass is almost pathognomonic of invasive neoplasm with substantial risk of ALN involvement. A reliable imaging workup that includes MRI, if necessary, is the key to management. The major challenge concerns aggressiveness of surgical procedures with perspectives of breast and axilla preservation. Due to the infrequency of this disease, oncological safety and prognostic impact of such management has not been evaluated in randomized trials. Prognosis is mainly determined by that of an almost constant underlying breast tumor where prognosis seems to be negatively impacted by the presence of PD. Clinical significance of invasive PD remains controversial and requires further assessment.

Conflict of Interest

No conflict of interest is declared.

References

1. Karakas C. Paget's disease of the breast. *J Carcinog.* 2011;10:31.
2. Trebska-McGowan K, Terracina KP, Takabe K. Update on the surgical management of Paget's disease. *Gland Surg.* 2013;2(3).
3. Dominici LS, Lester S, Liao GS, Guo L, Specht M, Smith BL, et al. Current surgical approach to Paget's disease. *Am J Surg.* 2012;204(1):18-22.
4. Onoe S, Kinoshita T, Tamura N, Nagao T, Kuno H, Hojo T, et al. Feasibility of breast conserving surgery for Paget's disease. *Breast.* 2011;20(6):515-8.
5. Morrogh M, Morris EA, Liberman L, Van Zee K,

Cody HS 3rd, King TA.MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. *J Am Coll Surg.* 2008;206(2):316-21.
6. Marshall JK, Griffith KA, Haffty BG, Solin LJ, Vicini FA, McCormick B, et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. *Cancer.* 2003;97(9):2142-9.
7. Kawase K, Dimaio DJ, Tucker SL, Buchholz TA, Ross MI, Feig BW, et al. Paget's disease of the breast: there is a role for breast-conserving therapy. *Ann Surg Oncol.* 2005;12(5):391-7.
8. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol.* 2002;20(17):3628-36.
9. Ortiz-Pagan S, Cunto-Amesty G, Narayan S, Crawford S, Derrick C, Larkin A, et al. Effect of Paget's disease on survival in breast cancer: an exploratory study. *Arch Surg.* 2011;146(11):1267-70.
10. National Comprehensive Cancer Network (2014). NCCN Clinical Practice Guidelines in oncology™: Paget's Disease [v.3.2014]. Retrieved February 09, 2015. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
11. Chen CY, Sun LM, and Anderson BO. Paget disease of the breast: Changing patterns of incidence, clinical presentation, and treatment in the U.S. Cancer. 2006; 107(7): 1448-58.
12. Lee HW, Kim TE, Cho SY, Kim SW, Kil WH, Lee JE, et al. Invasive Paget disease of the breast: 20 years of experience at a single institution. *Hum Pathol.* 2014;45(12):2480-7.
13. D'Orsi, CJ; Bassett, LW; Feig, SA, et al: Illustrated breast imaging reporting and data system: ACR BI-RADS. 3rd ed. Reston, VA: American College of Radiology; 1998.p.121-39.
14. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. *Am J Surg.* 2003;186(4):337-43.
15. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology.* 1991;19(5):403-10.
16. Kaplan E, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53(282): 457-81.
17. Grambsch P.M, Therneau T.M. Proportional hazard tests and diagnostics based on weighted residuals. *Biometrika.*1994; 81(3): 515-26.
18. Dalberg K, Hellborg H, Warnberg F. Paget's disease of the nipple in a population based cohort. *Breast Cancer Res Treat.* 2008;111(2):313-9.
19. Kothari AS, Beechey-Newman N, Hamed H, Fentiman IS, D'Arrigo C, Hanby AM, et al, Paget disease of the nipple: a multifocal manifestation of higher-risk disease. *Cancer.* 2002;95(1):1-7.
20. Caliskan M, Gatti G, Sosnovskikh I, Rotmensz N, Botteri E, Musmeci S, et al. Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat.* 2008;112(3):513-21.
21. Ling H, Hu X, Xu XL, Liu ZB, Shao ZM. Patients with nipple-areola Paget's disease and underlying invasive breast carcinoma have very poor survival: a matched cohort study. *PLoS One.* 2013;8(4):e61455.
22. Siponen E, Hukkinen K, Heikkilä P, Joensuu H, Leidenius M.Surgical treatment in Paget's disease of the breast. *Am J Surg.* 2010;200(2):241-6.
23. Bijker N, Rutgers EJ, Duchateau L, Peterse JL, Julien JP, Cataliotti L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer.* 2001;91(3):472-7.
24. Laronga C, Hasson D, Hoover S, Cox J, Cantor A, Cox C, et al. Paget's disease in the era of sentinel lymph node biopsy. *Am J Surg.* 2006;192(4):481-3.