ORIGINAL ARTICLE

Effect of Paget's Disease on Survival in Breast Cancer

An Exploratory Study

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Objective: To explore whether Paget's disease (PD) has an effect on outcome in patients with breast cancer.

Design: Retrospective analysis of comprehensive pathology database, medical records, and slides of samples showing pathologic features.

Setting: UMass Memorial Health Care.

Patients: All patients with breast cancer and PD with records in a prospectively maintained database between January 1, 1990, and December 31, 2008, were identified. Each participant was matched (criteria: age within 5 years, year of treatment, and stage of breast cancer) with 2 controls (1:2 ratio).

Main Outcome Measures: Overall and disease-free survival were analyzed using Kaplan-Meier statistics and Cox proportional hazards modeling, accounting for matching in the latter analyses by using robust standard error estimates.

Results: Mean (SD) follow-up was 47 (33) months. Treatment involved mastectomy in 29 (91%) PD vs 16 (25%) non-PD patients ($P<.001$), radiotherapy in 14 (44%) PD vs 53 (83%) non-PD patients ($P<.001$), and hormonal therapy in 14 (44%) PD vs 33 (52%) non-PD patients ($P=.004$). Biological markers were not significantly different except for *ERBB2* (formerly *HER2* or *HER2/neu*) overexpression in 14 (44%) PD vs 16 (25%) non-PD patients ($P=.008$). The PD group had an overall 5-year survival of 81.2% vs 93.8% of the non-PD group (Kaplan-Meier log-rank, $P=.03$). The unadjusted hazard ratio for the PD vs non-PD group was 5.31 (95% CI, 1.74-16.27; $P=.003$). The corresponding hazard ratio after adjusting for local and systemic treatment was 2.26 (95% CI, 0.46-11.06; $P=.32$).

Conclusions: These exploratory data show that PD may have a negative effect on breast cancer survival. This finding needs to be substantiated in larger data sets.

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PAGET'S DISEASE (PD) OF THE breast is rarely present in breast cancer, with a reported incidence ranging from 0.5% to 2.8% (mean, 1.3%) of breast cancers.[1] The disease was first described by Velpeau in 1856.[2] This was followed by the description by Sir James Paget[3] in 1874 as nipple ulceration with an associated cancer. Paget's disease of the breast is characterized by a nipple or areolar eczematous lesion. The diagnosis is often delayed for months because it is commonly treated initially as a benign dermatologic condition.[1] Two theories about the pathogenesis of this disease have been proposed. The in situ transformation theory proposes that the Paget's cells arise as malignant cells in the nipple epidermis independent of any other pathologic process within the breast parenchyma. This theory would explain cases in which there is no underlying carcinoma or when there is a carcinoma remote from the nipple-areola complex.[2] However, the epidermotropic theory, which is currently the most accepted theory, states that Paget's cells are ductal carcinoma cells that have migrated from the underlying ducts to the epidermis.[4] This theory is supported by the presence of an underlying cancer in up to 90% of patients with PD.

See Invited Critique at end of article

Some series[5] have concluded that an underlying breast tumor is present in 96% to 100% of these patients and can be associated with a noninvasive (ie, ductal carcinoma in situ) or invasive cancer. However, in a few cases, PD of the breast is not associated with breast malignant tumors. Although prognosis is dictated by the underlying breast cancer, the presence of PD of the breast currently has no bearing on the American Joint Committee on Cancer[4] staging of breast cancer.

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Table. Baseline and Treatment Characteristics[a]

Characteristic	No. (%) PD Group (n=32)	No. (%) Control Group (n=64)	*P* Value[b]
Age, mean (SD), y	53.9 (15.0)	52.5 (12.9)	.63
Follow-up, mean (SD), mo	47.2 (32.9)	53.1 (30.2)	.38
Diagnosis			
DCIS	11 (34)	24 (38)	.45
IDC	18 (56)	38 (59)	
ILC	2 (6)	2 (3)	
No tumor	1 (3)	0	
Cancer stage			
0	12 (38)	24 (38)	>.99
I	8 (25)	16 (25)	
II	4 (13)	8 (13)	
III	6 (19)	12 (19)	
IV	2 (6)	4 (6)	
Local treatment			
Lumpectomy, no radiotherapy	0	3 (5)	<.001
Lumpectomy, radiotherapy	2 (6)	42 (66)	
Mastectomy, no radiotherapy	18 (56)	8 (13)	
Mastectomy, radiotherapy	11 (34)	8 (13)	
Radiotherapy, no surgery	1 (3)	3 (5)	
Systemic treatment			
None	11 (34)	7 (11)	.02
Chemotherapy only	7 (22)	24 (38)	
Hormonal therapy only	8 (25)	11 (17)	
Both	6 (19)	22 (34)	
Disease status at last follow-up			
Alive, disease free	25 (78)	55 (86)	.10
Alive, with disease	2 (6)	7 (11)	
Died, disease free	2 (6)	0	
Died, with disease	3 (9)	2 (3)	
Receptor status			
ER-positive (PD, 27 patients; non-PD, 53)	16 (59)	44 (83)	.03
PR-positive (PD, 27 patients; non-PD, 53)	16 (59)	41 (77)	.12
ERBB2-positive (PD, 17 patients; non-PD, 39)	14 (82)	16 (41)	.008

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PD, Paget's disease; PR, progesterone receptor.

[a] Data are given as number (percentage) unless otherwise indicated.

[b] *t* Test was performed for continuous variables, and Fisher exact test was performed for categorical variables.

For many years, retrospective studies have attempted to determine the best treatment for PD. Several of these studies[5] have demonstrated that breast conservation therapy is as effective as mastectomy. However, no study has addressed whether the presence of PD of the breast alters prognosis in patients with breast cancer. This is a challenging area to examine because of 2 interrelated problems: (1) it is a rare manifestation of breast cancer, and most institutions do not have enough volume to carry out survival comparisons, and (2) the criteria for diagnosis of PD may not be uniform, and there is the potential for a T4 lesion to be labeled as PD, which would require pathological reevaluation in each case for accuracy. Whereas larger data sets, such as the Surveillance Epidemiology and End Results (SEER) registry,[6] may provide the necessary volume of patients to study the survival differences, they do not render themselves to the scrutiny of pathologic findings that is necessary. Therefore, we have undertaken a 2-step approach to this problem. First, we planned a single-institution study to compare clinical outcomes in a contemporary cohort of age- and stage-matched patients with breast cancer with and without PD (confirmed with reevaluation of pathologic findings) of the breast. Second, we will explore these findings in a larger data set. The present report focuses on the single-institution trends that were delineated. We plan to publish the SEER data set results as a follow-up.

METHODS

After approval by the institutional review board, data were obtained from a prospectively maintained database that included records on patients with breast cancer treated at the Comprehensive Breast Center at UMass Memorial Health Care, a university-based tertiary care center in Worcester, Massachusetts. The database included 32 patients with cancer and PD of the breast treated from January 1, 1990, through December 31, 2008. Each patient with PD of the breast (case patients) was matched for stage (0-IV), age at diagnosis (within 5 years), and the year of treatment to 2 patients with breast cancer but without PD (control patients; 1:2 ratio). Slides of pathologic samples were reviewed in the departmental consensus pathology conference to ensure correct assignment of PD or non-PD status. Paget's disease was defined as the presence of adenocarcinoma cells within the epidermis of the nipple as opposed to a retroareolar invasive cancer directly eroding the dermal and epidermal layers of the skin (T4 lesion). The primary outcome measure was the disease-free status at last follow-up. Disease-free survival was defined as the interval between diagnosis and recurrence of local and/or distant cancer or death from any cause. Overall survival was also determined on the basis of the time between diagnosis and death from any cause, regardless of disease status.

Patients with PD and those without PD were compared regarding clinical characteristics using 2-tailed *t* tests for continuous variables and the Fisher exact test for categorical variables. Differences between groups in overall and disease-free survival were assessed using Kaplan-Meier survival curves with the log-rank test and Cox proportional hazards models. The latter analyses used robust ("sandwich") standard error estimates to account for clustering due to matching[7,8] and adjusted for local treatment (lumpectomy with and without radiotherapy, mastectomy with and without radiotherapy, and radiotherapy with no surgery) and systemic treatment (chemotherapy and hormonal therapy alone or together, and none). Supplemental analyses were adjusted for biological markers in the subset of patients with available measurements. $P < .05$ was used to indicate statistical significance.

RESULTS

Thirty-two patients with PD and 64 patients without PD were included in the study. Of the 32 patients with PD, 20 had received a diagnosis of invasive cancer and 11 of ductal carcinoma in situ; 1 patient had no underlying tumor (**Table**). The patient with no underlying tumor was matched with 2 patients in the control group with ductal carcinoma in situ. The mean (SD) follow-up was 47.2 (32.9) months in the PD group and 53.1 (30.2) months in the non-PD group ($P = .38$). Twenty-five (78%) of patients in the PD group were alive and disease free com-

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pared with 55 (86%) of those in the control group; this difference was not statistically significant ($P=.10$).

RECEPTOR STATUS AND PD

Paget's disease was associated with less favorable estrogen receptor (ER), progesterone receptor (PR), and *ERBB2* (OMIM *164870) (formerly *HER* or *HER2/neu*) receptor status. Patients with PD were significantly less likely to have ER-positive cancer (16 [59%] vs 44 [83%]; $P=.03$) but more likely to have *ERBB2*-positive cancer (14 [82%] vs 16 [41%]; $P=.008$). Although the finding was not statistically significant, patients with PD were also less likely to have PR-positive cancer (16 [59%] vs 41 [77%]; $P=.12$) (Table).

TREATMENT

The local treatment differed significantly between the 2 groups. The PD group was more likely to receive mastectomy (29 [91%] vs 16 [25%]; $P<.001$), whereas the non-PD group was more likely to receive lumpectomy and radiotherapy (42 [66%] vs 2 [6%]; $P<.001$). The difference in systemic treatment between the 2 groups was not statistically significant (Table).

OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL

The 5-year overall survival was lower in the PD group (26 of 32 [81%]) vs the non-PD group (60 of 64 [94%]) (log-rank, $P=.03$) (**Figure**, A). Before adjustment for confounding variables, the hazard ratio (HR) from Cox proportional hazards modeling for PD was 5.31 (95% CI, 1.74-16.27; $P=.003$). On adjustment for local and systemic treatment, the HR was attenuated at 2.26 (95% CI, 0.46-11.06; $P=.32$). In the subset of patients with available biomarker data (n=80), adjustment for ER and PR status did not reduce the HR for PD; the unadjusted HR was 8.54 (95% CI, 1.56-46.93; $P=.01$) and the adjusted HR was 10.62 (2.07-54.54; $P=.005$). Additional adjustment in this subset of patients for local and systemic treatment reduced the HR to 3.46 (95% CI, 0.22-55.10; $P=.38$). Similarly, in the subset of patients with available data on *ERBB2* receptor status (n=56), the unadjusted HR was 10.26 (95% CI, 1.95-54.02; $P=.006$) and the adjusted HR was 8.97 (2.41-33.42; $P=.001$); small sample sizes precluded additional adjustment for local and systemic treatment.

The 5-year disease-free survival was similar in the PD and non-PD groups (Figure, B; 80.2% vs 79.8%; log-rank, $P=.30$). The unadjusted HR for PD from Cox proportional hazards modeling was 1.69 (95% CI, 0.95-3.00; $P=.08$) and the corresponding adjusted HR was 0.88 (0.35-2.21; $P=.78$). In the subset of patients with available biomarker data (n=80), adjustment for ER and PR status had little effect on the HR for PD; the unadjusted HR was 1.67 (95% CI, 0.97-2.88; $P=.07$) and the adjusted HR was 1.59 (0.68-3.75; $P=.29$). Additional adjustment in this subset of patients for local and systemic treatment reduced the HR to 0.93 (95% CI, 0.42-2.08; $P=.86$). In similar analyses in the subset with data available on *ERBB2* receptor status (n=56), the unadjusted HR was 2.08 (95% CI, 1.10-3.93; $P=.02$) vs an HR adjusting for *ERBB2* receptor status of 2.35 (1.18-4.70; $P=.02$); small sample sizes again precluded additional adjustment for local and systemic treatment.

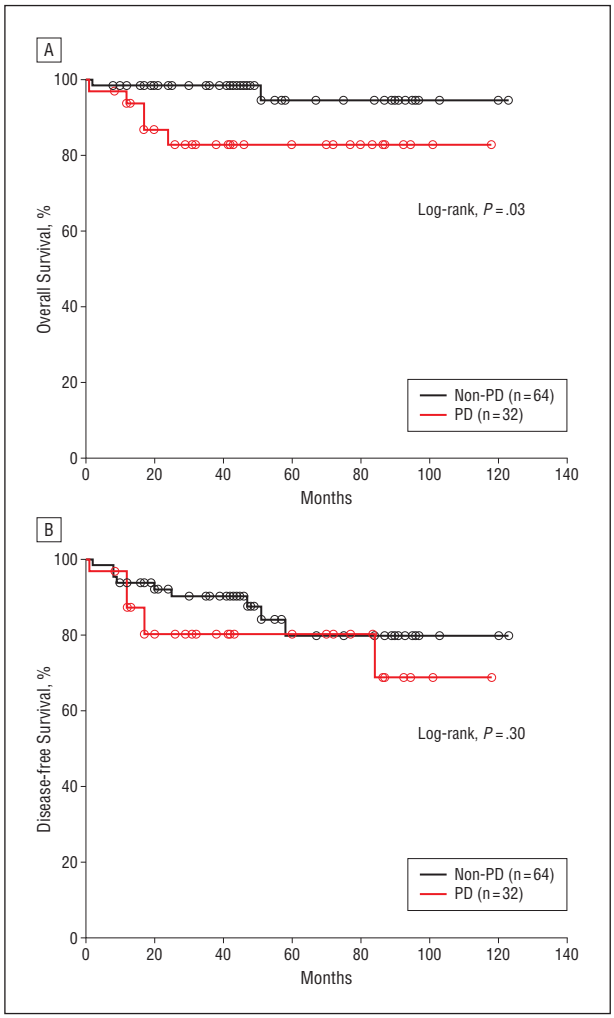

Figure. Comparison of survival between the Paget's disease (PD) and non-PD groups. A, Overall survival. B, Disease-free survival.

COMMENT

The presence of PD in patients with breast cancer has no prognostic significance in the current American Joint Committee on Cancer staging system.[9] At this time, the prognosis in this population is considered to be dictated by the underlying breast tumor. There is a dearth of knowledge regarding the biological relevance of PD owing to the rarity of this process. To our knowledge, this is the first, albeit exploratory, report of a possible negative effect of PD on breast cancer survival. In our study, patients with PD had an overall 5-year survival of 81.2% vs 93.8% in patients without PD. The 5-year overall survival in the PD group seen in our study was lower than that previously observed in the United States (88%)[10] and Canada (86%).[11]

In our study, at a mean follow-up of 47 months, 25 (78%) of the patients in the PD group were alive and disease free vs 55 (86%) in the non-PD group. The small number of patients with each stage of cancer precluded stage-specific analyses of survival, but the stage-matched outcome trend in our

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study points to the possibility that the presence of PD may independently confer a poorer prognosis, as suggested by the adjusted HR (2.26) for the overall 5-year survival. The HR for poorer survival was still seen in the stage/age/treatment year–matched patients with PD despite adjustment for known confounding factors, such as biological markers. Some of these trends were not statistically significant because of small sample sizes, although a negative influence was observed consistently. Interestingly, the HRs dropped closer to unity when adjustments for local treatments were made. Because large prospective trials have documented that treatment of breast conservation and radiotherapy vs mastectomy do not differ in survival, we believe that our study demonstrates this trend only because PD was more likely to have been treated with mastectomy in this cohort. Our study demonstrates an interesting trend. Because of the small numbers, it is impossible to suggest any changes in current management guidelines; however, these data are hypothesis generating: does the presence of PD alter prognosis in breast cancer stage for stage? Considering significant advances in systemic treatment of breast cancer and enhanced survival over the past few decades, this impact should be studied in a large data set with a long follow-up. Should this trend be confirmed in large data sets, a case for prospective registry at the multi-institutional level could be made for further study. The strength of the present report is that each case was managed at a single institution, ensuring that all pathological assessment and treatment could be accurately reported.

Fu et al[12] reported that patients with PD of the breast showed c-molecular markers commonly associated with more aggressive tumor behavior (*Ki-67*, *cyclin D1*, and *ERBB2*) and poorer survival in patients with breast cancer. Few of these tumors expressed *Bcl-2* or ER and PR, which are generally associated with better prognosis in breast cancer. Invasive cancer associated with PD of the breast is usually ER and PR negative, with high pathological grade.[13] In our study, most cases of PD of the breast were associated with an invasive cancer and were ER and PR positive; adjustment for ER and PR status had no effect on survival in the PD group. Because ER and PR information was not available for 17% of the patients, the adjustment for receptor status in multivariate hazard modeling was somewhat limited in this sample, and the results are suggestive but not definitive. It is noteworthy, though, that the impact of adjustment was consistent for overall and disease-free survival.

In the group of 20 patients with PD and invasive cancer, 17 patients (85%) were tested for *ERBB2*; results were positive in 14 patients (82%) and negative in 3 patients (18%). This information correlates with the high positivity for *ERBB2* in PD of the breast reported in several studies.[14] The presence of *ERBB2* is associated with a worse prognosis in breast cancer.[15] Overexpression of ERBB2 protein has been a consistent feature of both mammary and extramammary PD[16]; however, it is difficult to determine whether the effect of ERBB2 protein overexpression would offset the effect of PD on the prognosis. Given the small number of patients with data on *ERBB2* status in our sample, the results from these analyses are exploratory, suggesting that *ERBB2* does not explain much of the observed poorer overall survival in the patients with PD.

In conclusion, PD of the breast is a rare manifestation of breast cancer. These patients appear to have poorer overall survival in this exploratory study compared with stage- and age-matched patients with breast cancer without PD of the breast. This trend was seen even in cases of ER-positive, PR-positive, and *ERBB2*-negative malignant tumors. A high proportion of ERBB2 protein overexpression was seen, as previously reported. All these findings support further investigation of the possible negative impact of PD in breast cancer.

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