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Original Article

How Similar are Molecular Characteristics of Mammary Paget's Disease to Underlying Ductal Carcinoma? Discussion of 42 Cases from a Tertiary Care Hospital

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Keywords: CerbB2; estrogen receptor; HER2-enriched; mammary; Paget's disease; survival.

ABSTRACT

Objective: It is aimed to evaluate the expression of estrogen receptor (ER), progesterone receptor (PR), CerbB2 status, and molecular subtypes in mammary Paget disease and concomitant ductal carcinoma and to discuss their concordance and their relation with other prognostic parameters.

Methods: This retrospective study evaluated the clinical and morphological data of the mammary Paget disease and underlying ductal carcinoma; immunohistochemical estrogen/PR and CerbB2 status; molecular subgroups and survival; and statistically compared all parameters.

Results: The study included 42 cases of mammary Paget's disease (PD) and concomitant ductal carcinoma. In breast specimens, 15 cases (36%) had *in situ*, 4 (9.5%) invasive, and 23 (54%) *in situ* + invasive ductal carcinoma. Axillary nodal involvement was seen in 13 cases (31%) and all had invasive components. Respectively, ER and PR expressions were detected in 16 (38%) and 8 (19%) of the ductal carcinomas and in 10 (23.8%) and 6 (14.2%) of the cases with PD. CerbB2 expression was 93% (39 cases) in ductal carcinoma and 100% in PD with a 93% concordance. The most frequent molecular subtype was HER2-enriched subtype for both mammary ductal carcinoma (62%, 26 cases) and PD (76%, 32 cases) and the concordance was 82% (p=0.03). The survival was 46.00±32.64 months in the exitus group (n=8), all of which had invasive ductal components (p=0.03).

Conclusion: ER and PR positivity were lower while CerbB2 was higher in Paget disease compared to concomitant ductal carcinoma. The most prominent molecular subtype was HER2-enriched subtype in both neoplasias. While hormonal and CerbB2 status of the tumors did not show any correlation with prognostic factors, existence of an invasive ductal component was the factor that correlated with survival.

INTRODUCTION

Mammary Paget's disease (PD) is an intraepithelial neoplasia that usually occurs at an advanced age and constitutes 0.5–5% of all breast cancers.[1–7] Histopathologically, infiltration of glandular neoplastic cells with clear cytoplasm and large nucleoli is observed in the epidermis of the nipple-areola complex.[2,4,7,8] Although 93–100% of PD is associated with underlying breast carcinoma,[2,3,5,7,9] about half of the breast tumors cannot be palpated, and 15% cannot be detected by mammography.[8] Ductal carcinomas associated with PD are more aggressive, present with axillary lymph node involvement,[4,8] and the 5-year survival is lower.[4,9,10] The treatment is planned according to the status of underlying mammary neoplasia.[4] It is an important issue to plan targeted therapies for this special type of tumors.

In this study, we aimed to compare the expression of estrogen receptor (ER), progesterone receptor (PR), and CerbB2 (HER2/neu) status and molecular subtypes in cases with coexisting mammary PD and ductal carcinoma. The results might contribute to the prognostic and individualized therapeutic approaches in this special patient group.

MATERIALS AND METHODS

This retrospective study included patients diagnosed with mammary PD together with ductal carcinoma in a tertiary

pathology clinic between 2009 and 2022. Paraffin blocks, hematoxylin-eosin (HE) stained slides, and final pathology reports of the cases were extracted from the archive and re-evaluated by two pathologists (SHK, AEG). Each patient's age, gender, tumor location, size, grade (modified Scarf-Bloom-Richardson) invasion status, and lymph node involvement were recorded. Immunohistochemically, ER, PR, and CerbB2 expressions were investigated for each case both in PD and ductal carcinoma. For immunohistochemical (IHC) analysis, a representative paraffin block that contained the tumor, as well as a normal tissue, was chosen in all cases. Immunostaining was performed on 3 micron deparaffinized sections using the standard avidin-biotin-peroxidase complex method with automated immunostainer (Ventana, Medical System BenchMark ULTRA/ISH Staining module). The Ultraview Universal DAB Detection Kit was used for detecting primary antibodies. CerbB2 examination was performed according to the American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline. Complete membranous staining within >10% of cells were considered three positive (+) staining; circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of tumor cells or complete and circumferential membrane staining that is intense and within ≤10% of tumor cells was considered 2+ staining and incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells was considered 1+ staining.[11] In ER and PR examination, staining in the nuclei of ≥1% tumor cells were accepted as positive. Positive and negative controls for antibodies were also run simultaneously. Mammary PD and concomitant breast carcinomas were molecularly classified as luminal A, B, HER2-enriched, and triple-negative subtypes, according to the decision of 2011 St. Gallen International Expert Consensus for Breast Cancer.[12]

Survival data were obtained from the death reporting system which was a part of the hospital information system for all cases.

Statistical analysis

Descriptive statistics in the study were given as mean, standard deviation, percentage, and frequency. Mann–Whitney U-test was used to examine the difference in survival times according to the groups. Chi-square analysis was applied to examine the survival status and the effect of nipple pathology on health, according to the groups. The significance value was 0.05 and the SPSS 25.00 package program was used for analysis.

Ethical approval Nr 514/189/6, November 11, 2020.

RESULTS

Totally, 42 cases (41 females and one male) with PD and concomitant ductal carcinomas were included in the study. The age range of the patients was 27–87 (mean age 57.98 for the female patients; 67 for the male patient). Histological diagnosis of breast tumors was mostly *in situ* + invasive ductal carcinoma (DCIS+IDC) (n=23; 54.7%); tumor size was between 0.2 and 10 cm (average 3.2 cm). Totally, 52% of the cases (n=22) were Grade 2 and 48% (n=20), Grade 3. Axillary nodal involvement was detected in 13/39 patients (33.3%), all with invasive components (Table 1).

ER positivity was 38% and PR positivity was 19% in total mammary ductal carcinomas, while, respectively, 24% and 14% in PD (Fig. 1a and b). Thus, ER positivity concordance was 63% and PR, 74%. In total, CerbB2 was positive (Fig. 1c and d) in 93% (39 cases) of mammary ductal carcinomas and in all PDs (100%); the concordance was 93%. The highest ER positivity concordance was between PD and DCIS (73%) while for PR concordance, between PD and IDC (56%); the lowest (87%) CerbB2 concordance was between PD and DCIS+IDC (Table 2).

In total, 26 (62%) mammary ductal carcinomas and 32 (76%) PD cases belonged to HER2-enriched molecular subtype; the concordance was 82%, and the highest was between DCIS and PD (88%). Luminal A subtype was found only in the mammary ductal carcinoma and no case with triple-negative subtype was detected (Table 2).

In terms of survival data, all of the PD+DCIS patients and 12 (52%) of the PD+IDC+DCIS patients were alive. All the PD+IDC cases (3 cases, 100%) died after 11–21 months and 5 (22%) PD+IDC+DCIS cases died after 26–94 months. The survival was 46.00±32.64 months in the exitus group (n=8) and was significantly shorter in invasive ductal carcinoma (p=0.03) (Table 3). Regarding the mammary PD, mortality was 33.3% in the luminal B group and 22.2% in HER2-enriched group (p=0.57).

Table 1. Clinicopathological characteristics of the patients and tumors

Clinicopathological characteristics	Number, n (%)
Gender	
Female	41 (97.6)
Male	1 (2.3)
Location	
Right breast	20 (47.6)
Left breast	22 (52.3)
Invasion status	
Invasive ductal carcinoma	4 (9.5)
In situ ductal carcinoma	15 (35.7)
Invasive and *in situ* ductal carcinoma	23 (54.7)
Histological grade	
Grade 2	22 (52.38)
Grade 3	20 (47.61)
Lymph node involvement	
Invasive ductal carcinoma	3/3 (100)
Invasive and *in situ* ductal carcinoma	10/23 (43.47)
Total	13/26 (50)
Survival status	
Alive	34 (80.95)
Exitus	8 (19)

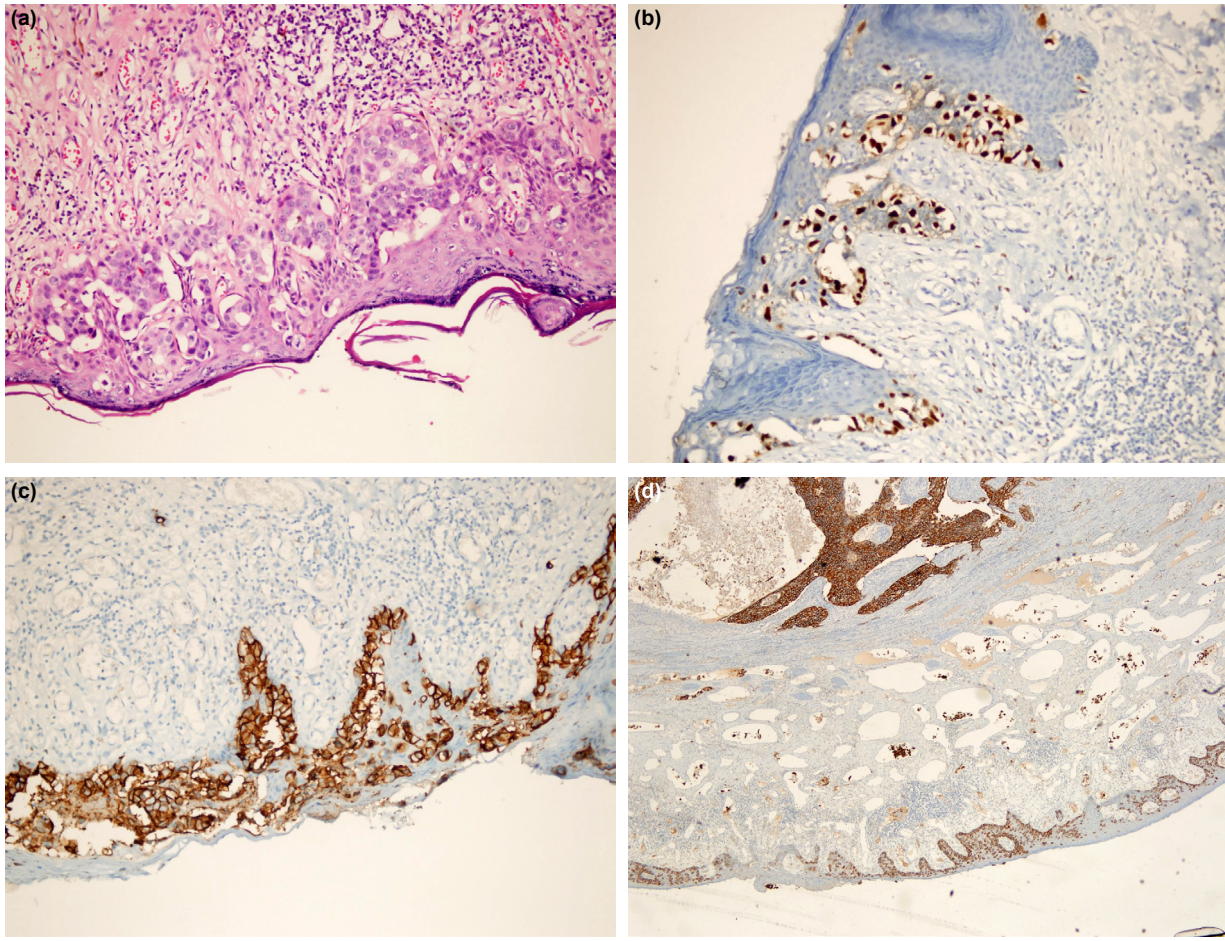

Figure 1. (a) Large, pale Paget cells with abundant clear cytoplasm and prominent nuclei infiltrating the epidermis of the nipple (hematoxylin-eosin ×200). **(b)** Positive nuclear estrogen receptor immunoreactivity in Paget cells (estrogen receptor ×200). **(c)** Complete membranous CerbB2 immunostaining in Paget cells (score 3) (CerbB2 ×200). **(d)** Complete membranous CerbB2 immunostaining (score 3) in mammary ductal carcinoma and Paget cells invading the nipple epidermis (CerbB2 ×40).

DISCUSSION

In the literature, ER immunoexpression was reported between 50 and 80% in breast carcinomas while if breast tumor coexisted with PD, the ER positivity was lower (11–30%). Meanwhile, mammary Paget cells showed 11–29% ER overexpression.[5,6,8,13,14] PR positivity was recorded as 60–70% in breast cancer while very low (4–25%), if coexisted with PD. Paget cells were found to be 0–29% positive for PR.[5,6,8,14] In our series, in mammary ductal cancer cells and Paget cells, ER (38% and 24%) and PR (19% and 14%) expression were within the limits of previous results.

HER2 (CerbB2) is a well-established transmembrane growth factor receptor gene encoded by the ERBB2 gene which regulates cell growth through phosphatidylinositol 3 kinase (PI3K/AKT) and mitogen-activated protein kinase (MAPK/ERK) pathways. CerbB2 overexpression rate in breast carcinoma is 13–30% and correlates with higher grade, larger size, and worse prognosis.[4] In breast tumors with PD, very high (60–80%,[6] 86%,[14] 93%,[15] and 97%[16]) CerbB2 positivity is reported in ductal cancer cells. CerbB2 expression in PD cells is also high as 84–93%.[5,9,14] Correspondingly, CerbB2 was positive in all (100%) of our PD cases and, we found a very high (93%) positivity in the concomitant breast tumor. The concordance in our series (93%) was higher than in literature (90%).[6]

Molecular subtypes in invasive breast tumors are associated with different risk factors, prognoses, and treatment responses; thus, are clinically significant. Hormone therapy agents and anti-HER2 treatments are valuable options. Of all breast tumors, 70% belong to luminal A or B, 15% to HER2-enriched, and 15% to triple-negative subtypes; the last two are associated with a more aggressive course. According to the previous studies, the prognosis of PD depends on the underlying ductal breast tumor, with the HER2-enriched subtype having the worst prognosis.[4,5,14] Paget cells are reported to be 50–71% HER2-enriched subtype.[4,5,14,17] A study by Wachter et al.[17] compared 48 cases of concomitant ductal carcinoma and PD in terms of molecular subtypes and found that HER2 enriched was the dominant subtype (66%) in PD, followed by luminal B (29%) and that only 2 cases (5%) were triple negative, while the underlying invasive tumor was usually luminal B followed by HER2-enriched and triple-negative subtypes.

Table 2. Concordance of estrogen/progesterone receptor positivity, CerbB2 immunoexpression, and molecular subtypes in mammary ductal carcinoma and Paget's disease

	Mammary Paget's disease (n=42) n (%)	Mammary ductal carcinoma				Concordance
		Total (n=42) n (%)	Invasive (n=4) n (%)	*In situ* (n=15) n (%)	Invasive+ *in situ* (n=23) n (%)	
Immunoexpression						
ER+	10 (23.8)	16 (38.09)	2 (50)	5 (33.33)	9 (39.13)	63.2% Invasive/PD; 48% *In situ*/PD; 72.7% Invasive+*in situ*/PD; 61.5%
PR+	6 (14.28)	8 (19.04)	1 (25)	1 (6.66)	6 (26.08)	73.6% Invasive/PD; 56% *In situ*/PD; 47.1% Invasive+*in situ*/PD; 53.8%
CerbB2+	42 (100)	39 (92.85)	4 (100)	15 (100)	20 (86.95)	92.85% Invasive/PD; 100% *In situ*/PD; 100% Invasive+*in situ*/PD; 87%
Molecular subtypes						
Luminal A	0	3 (7.14)	0	0	3 (13.04)	0
Luminal B	10 (23.8)	13 (30.95)	2 (50)	5 (33.33)	6 (26.08)	77.41% Invasive/PD; 65.78% *In situ*/PD; 48% Invasive+*in situ*/PD; 92.3%
HER2-enriched	32 (76.19)	26 (61.9)	2 (50)	10 (66.66)	14 (60.86)	81.57% Invasive/PD; 65.78% *In situ*/PD; 88.15% Invasive+*in situ*/PD; 80.26%

ER: Estrogen receptor; PR: Progesterone receptor; PD: Paget's disease.

Table 3. Survival status of the breast carcinoma groups

Mammary ductal carcinoma	n (%)	Survival±SD (month)
Invasive	3 (37.5)	16.00±5.00
Invasive+*In situ*	5 (62.5)	64.00±27.78
Total	8	46.00±32.64

p=0.03, SD: Standard deviation.

The majority of the PDs in our series were also HER2-enriched subtype and the rate was higher (76%). The underlying tumors were also mostly HER2-enriched subtype (62%), although the rate was lower than PD. In the literature, the concordance of molecular subtypes between PD and concomitant ductal carcinoma was between 71% and 90%;[6,17] our series showed a similar concordance rate (82%). According to the literature, incompatibility between the molecular subtypes of Paget disease and concomitant ductal carcinoma might be due to technical problems, tumor heterogeneity, or the presence of PD and IDC collision tumors. In addition, PD is probably composed of cells with different molecular characteristics and only one of these tumor cell clones might show invasion; or HER2 amplification in some tumor cells may facilitate pagetoid spread in the epidermis.[17] We think that, because of the differences between hormone receptor/CerbB2 status and molecular subtypes in PD and underlying tumor, identification of the IHC profile in both tumors might be useful and necessary.

Luminal A and HER2-enriched types are reportedly more common in DCIS cases.[17] Lester et al.[5] found that HER2-enriched DCIS cases were mostly accompanied by PD (88% of cases with and 29% of cases without); however, in luminal-type DCIS, the number of cases with and without PD was similar. In HER2-enriched type IDC, the ratio of cases with and without PD was close (40% vs. 37%); however, the PD rate was higher in the luminal B subtype of IDC (30% of cases are with and 7% without). Wachter et al.[17] found that the underlying invasive tumor in PD was usually luminal B (50% of cases) followed by HER2-enriched and triple-negative subtypes (40% and 10% of cases, respectively). Given these findings, researchers suggest that different mechanisms may be re-

sponsible for PD development depending on the invasiveness of the underlying lesion (DCIS, IDC, or both) and on the molecular subtype, with prognosis varying accordingly.[5,17] We also found HER2-enriched molecular subtype rate higher in PD+DCIS cases compared to the PD+DCIS+IDC group. We also think that PD with DCIS and PD with IDC might be considered different groups and that molecular differences between the groups should be taken into consideration for prognosis and therapeutic decisions.

Relationship between ER, PR, CerbB2 status, and the survival

Studies show that the prognosis is different among only PD, PD + IDC, and PD + DCIS.[1] According to the literature, cases of PD with underlying invasive breast cancer show worse tumor features, for example, higher grade.[1,9,18–20] In the Surveillance, Epidemiology, and End Results database, 5-year survival was 84% in PD-IDC cases and 98% in PD+DCIS cases.[1] In our series, in accordance with the literature, we found a significantly shorter survival in PD patients with ductal carcinoma with invasive components compared to PD+DCIS cases.

Chen et al.[18] thought that hormone receptor status, HER2 positivity, and molecular subtypes did not affect the prognosis in breast cancer patients with and without PD and researchers reported that, after adjusting for tumor characteristics and treatment approaches, only PD+DCIS was associated with poor prognosis rather than PD+IDC. Our findings that hormone receptor and CerbB2 expressions do not have prognostic significance support Chen et al.; however, because the prognosis was better in our PD+DCIS cases, our results show that invasiveness negatively affects survival. Furthermore, in accordance with the previous literature, 50% of our cases, all IDC, had positive lymph nodes; whereas no lymph node involvement existed in the PD+DCIS case. These results also make us think that PD+DCIS and PD+IDC should be considered different tumors regarding prognosis and treatment planning.

PD in men is rare and constitutes approximately 1.5% of male breast carcinomas. However, the prognosis is poor and the 5-year survival is 20–30%.[4,7,8] The male patient in our series was 67 years old with an *in situ* ductal carcinoma that was ER positive, while PR, and CerbB2 negative, without axillary nodal involvement at the time of diagnosis. He is alive at 5 years follow-up. The existence of an *in situ* tumor with CerbB2 negativity and ER positivity might explain the favorable prognosis. The tumor behavior and hormonal/CerbB2 status in male patients need to be further investigated.

One limitation of the study was a rather small sample group, although the study covered a long period. Incidence of PD is low and we could include only the cases that had concomitant PD and mammary ductal disease, not the cases with only PDs.

CONCLUSION

In this study, a lower ER and PR positivity and higher CerbB2 positivity were detected in PD compared to underlying mammary ductal carcinoma. However, invasion status was the primary factor determining prognosis in ductal carcinomas with PD, but not hormonal and CerbB2 status. The high CerbB2 rate observed in both PD and mammary ductal cancer might offer possible treatment benefits in concomitant cases. In cases presenting with only PD, an underlying undetected tumor might be considered to belong to the same molecular subtype due to a high concordance rate. We also consider this study valuable since it contributes to the epidemiological data on PD.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 11.11.2020, Decision No: 514/189/6).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Ş., Y.S.G., S.H.K.; Design: S.Ş., N.E., S.H.K., N.O.B., A.E.G.; Supervision: Y.S.G., N.E., N.O.B.; Materials: N.O.B., S.H.K., A.E.G.; Data: S.H.K., S.Ş., A.E.G., N.O.B.; Analysis: Y.S.G., S.H.K., S.Ş., A.E.G., N.E.; Literature search: S.Ş., Y.S.G., N.O.B., N.E.; Writing: S.Ş., S.H.K., A.E.G.; Critical revision: N.E., Y.S.G., N.O.B.

Conflict of Interest

None declared.

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Memenin Paget Hastalığının Moleküler Özellikleri Altta Yatan Duktal Karsinom ile Benzer mi? Üçüncü Basamak Bir Hastaneden Gelen 42 Olgunun Tartışılması

Amaç: Meme Paget hastalığı ve eşlik eden duktal karsinomda östrojen reseptörü, progesteron reseptörü, CerbB2 ekspresyonunu ve moleküler alt tipleri değerlendirmek, bunların uyumunu ve diğer prognostik parametrelerle ilişkisini tartışmak amaçlanmıştır.

Gereç ve Yöntem: Bu geriye dönük çalışmada Paget hastalığı ve beraberindeki meme karsinomunun klinik ve morfolojik verileri, östrojen/progesteron reseptörü ve CerbB2 immünekspresyonu, moleküler alt gruplar ve sağ kalım değerlendirilmiş olup tüm parametreler istatistiksel olarak karşılaştırılmıştır.

Bulgular: Çalışmaya, memenin Paget hastalığı ve eşlik eden duktal karsinomu olan 42 olgu alınmıştır. Meme örneklerinde 15 olguda (%36) *in situ*, 4 olguda (%9.5) invaziv ve 23 olguda (%54) *in situ*+invaziv duktal karsinom saptanmıştır. Aksiller lenf nodu tutulumu 13 olguda (%31) görülmüş olup tümünde invaziv komponent mevcuttur. Östrojen ve progesteron reseptörü ekspresyonu, sırasıyla, duktal karsinomların 16'sında (%38) ve 8'inde (%19) ve Paget hastalığı olgularının 10'unda (%23.8) ve 6'sında (%14.2) saptanmıştır. CerbB2 ekspresyonu, duktal karsinomda %93 (39 olgu) ve Paget hastalığında %100 olup %93'lük bir uyum göstermiştir. Hem meme duktal karsinomu (%62, 26 olgu) hem de Paget hastalığında (%76, 32 olgu) en sık HER2-baskın moleküler alt tip görülmüş olup %82 uyum saptanmıştır (p=0.03). Exitus grubunda (n=8) sağkalım 46.00 ± 32.64 aydır ve tümünde invaziv duktal komponent mevcuttur (p=0.03).

Sonuç: Paget hastalığında, eşlik eden duktal karsinoma göre östrojen/progesteron reseptör pozitifliği daha düşük, CerbB2 ekspresyonu ise daha yüksek bulunmuştur. Her iki neoplazide de en belirgin moleküler alt tip HER2-baskın alt tiptir. Tümörlerin hormonal ve CerbB2 immünpozitivitesi prognostik faktörlerle korelasyon göstermezken, invaziv duktal komponentin varlığı sağ kalım ile korelasyon göstermiştir.

Anahtar Sözcükler: CerbB2; HER2-baskın; meme; östrojen reseptörü; Paget hastalığı; sağ kalım.