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Does Tumor Laterality Influence Response to Neoadjuvant Chemotherapy in HER2-Positive Breast Cancer?

Tümör Lateralitesi, HER2-pozitif Meme Kanserinde Neoadjuvan Kemoterapiye Yanıtı Etkiler mi?

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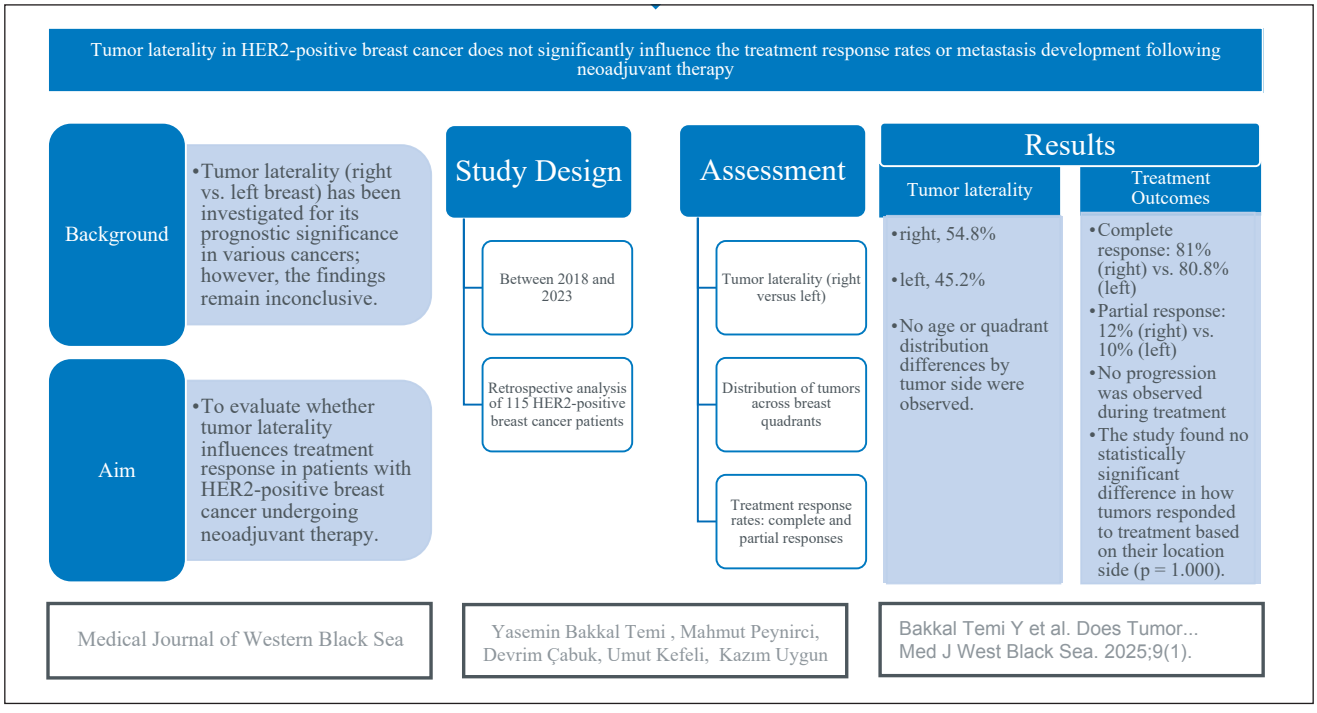
GRAPHICAL ABSTRACT



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ABSTRACT

Aim: The prognostic significance of tumor laterality has been explored in various solid malignancies, with varying findings across different cancer types. This study investigated the potential for predicting treatment response rates based on cancer laterality in patients with HER2-positive breast cancer undergoing neoadjuvant therapy.

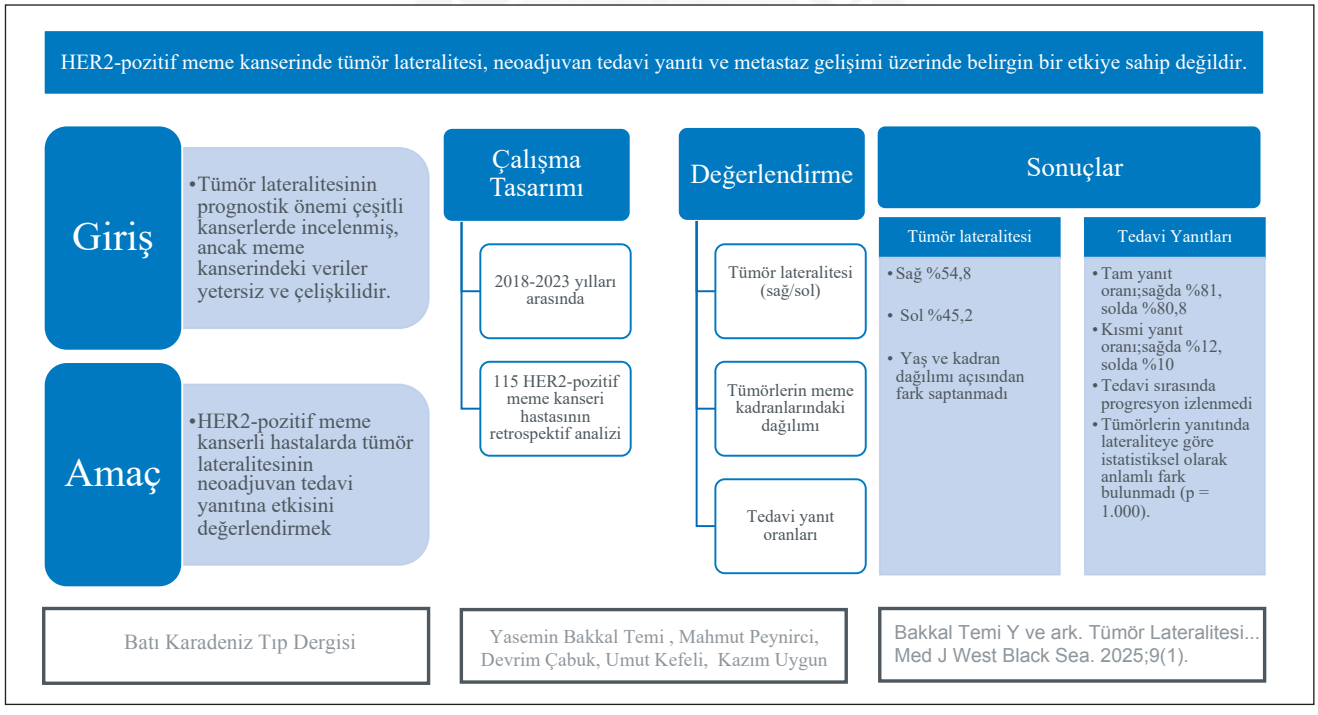
Material and Methods: A retrospective analysis was conducted on 115 patients diagnosed with HER2-positive breast cancer who underwent neoadjuvant therapy at the Department of Medical Oncology, Kocaeli University Hospital between January 2018 and March 2023.

Results: The median age of the patients was 49 years (range 41–59 years), with no significant difference in age distribution between the right and left breast tumors (p = 0.704). The study group was composed of 54.8% right breast tumor sand 45.2% left breast tumors. The distribution of primary tumors across quadrants in both breasts did not show a significant difference (p = 0.659). When examining the response to neoadjuvant therapy, no patient exhibited progression during treatment. Complete response rates were 81% and 80.8% for right-sided and left-sided breast tumors, respectively, and partial response rates were 12% and 10%, respectively. There was no statistical significance observed in treatment responses based on tumor location side (p = 1.000). During follow-up, 9.6% of patients developed metastasis.

Conclusion: This study highlights the lack of significant differences in treatment response rates and metastasis development based on tumor laterality in HER2-positive breast cancer patients receiving neoadjuvant therapy. Further research is needed to identify potential predictive factors for treatment response in this patient population.

Keywords: Breastcancer, HER2-positive, neoadjuvant therapy, laterality

GRAFİKSEL ÖZET



ÖZ

Amaç: Tümör lateralitesinin prognostik önemi, çeşitli solid malignitelerde farklı sonuçlar ortaya koymuştur. Bu çalışmada, neoadjuvan tedavi uygulanan HER2-pozitif meme kanseri hastalarında tümörün yerleşim tarafının tedavi yanıt oranlarını ön görmedeki rolü araştırılmıştır.

Gereç ve Yöntemler: Ocak 2018 ile Mart 2023 tarihleri arasında Kocaeli Üniversitesi Hastanesi Tıbbi Onkoloji Bölümü'nde neoadjuvan tedavi almış HER2-pozitif meme kanseri tanılı 115 hasta retrospektif olarak incelenmiştir.

Bulgular: Hastaların medyan yaşı 49 (41-59) idi ve sağ ve sol meme tümörleri arasında yaş dağılımında anlamlı bir fark bulunmadı (p=0,704). Çalışmaya dahil edilen hastaların %54,8'inde sağ, %45,2'sinde ise sol meme tümörleri saptandı. Her iki memede de primer tümörlerin kadranlara göre dağılımında anlamlı bir fark görülmedi (p = 0,659). Neoadjuvan tedavi sırasında hiçbir hastada progresyon izlenmezken, sağ meme tümörlerinde tam yanıt oranı %81, sol meme tümörlerinde ise %80,8 olarak bulundu; kısmi yanıt oranları sırasıyla %12 ve %10 idi. Tümörün yerleşim tarafına göre tedavi yanıtlarında istatistiksel olarak anlamlı bir fark bulunmadı (p = 1.000). Takip sürecinde hastaların %9,6'sında metastaz gelişti.

Sonuç: Neoadjuvan tedavi almış HER2-pozitif meme kanseri hastalarında tümörün lateralitesi, tedavi yanıt oranları ve metastaz gelişimi üzerinde belirleyici bir faktör olarak görülmemiştir. Bu hasta grubunda tedavi yanıtını öngörebilecek diğer potansiyel faktörlerin belirlenmesi için daha kapsamlı araştırmalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Meme kanseri, HER2- pozitif, neoadjuvan tedavi, lateralite

INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed malignancy in women and remains one of the leading causes of cancer-related mortality worldwide (1). Over the past three decades, mortality rates have consistently declined (2). This decline is primarily attributed to advancements in early detection through widespread mammography screening, increased public awareness, and significant progress in therapeutic strategies. BC is a heterogeneous disease. It is classified into four subtypes with distinct clinical characteristics: luminal A, luminal B, Human epidermal growth factor receptor 2 (HER2) positive (non-luminal) and basal tumours (3). HER2-positive breast cancer has attracted a lot of attention among these subtypes because of its unique molecular characteristics and potential therapeutic applications.

HER2 is a glycoprotein on the cell membrane that possesses intrinsic tyrosine kinase activity. It belongs to the epidermal growth factor receptor (EGFR) family. Approximately 15% of primary invasive breast cancers exhibit amplified or overexpressed HER2 oncogenes (4). HER2-positive tumors are associated with increased aggressiveness, higher recurrence rates, and reduced survival (5). Theuse of HER2-targeted therapies has resulted in improved survival outcomes in patients with the HER2-positive breast cancer subtype (6-9). In patients with HER2-positive breast cancer, neoadjuvant doublet anti-HER2 therapies have been administered to enhance the rate of pathological complete response (pCR) and improve over all survival outcomes (10-12). It is essential to recognize that patients receiving anti-HER2 therapy do not always exhibit a uniform response rate. The disparity in response rates can be ascribed to several factors, such as the unique biology of individual tumors and the specific clinical characteristics of patients.

Cancer laterality refers to the side of the body where a tumor develops, specifically in paired organs like breasts. In breast cancer, laterality distinguishes between left and right breast tumors. This concept has gained attention due to potential differences in prognosis and treatment outcomes based on tumor location (13,14). The role of breast cancer laterality in treatment decisions remains unclear, as factors like tumor stage, grade, and molecular subtype are generally considered more critical in determining treatment approaches and prognosis.

This study explored the potential for predicting treatment response rates based on cancer laterality in patients with HER2-positive breast cancer undergoing neoadjuvant therapy. Our analysis focused on the differences in breast cancer laterality and associated clinical and pathological features while also comparing our findings with those of previous studies.

MATERIALS and METHODS

This study included 115 individuals diagnosed with HER2-positive breast cancer. All participants were diagnosed and treated between January 2018 and March 2023. The following criteria were established for inclusion: primary, unilateral, non-metastatic invasive breast cancer, and trastuzumab-pertuzumab plus neoadjuvant chemotherapy (NACT). This study included patients whose neoadjuvant chemotherapy protocol adhered to the recommendations of the National Comprehensive Cancer Network (NCCN) Guidelines (Version 3. 2024) for HER2-positive breast cancer (15). Patients with invasive HER2-positive breast cancer confirmed through core needle biopsy were included in the study. HER2 status was evaluated using immunohistochemistry (IHC) in accordance with the guidelines of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (16). Specimens with an IHC score of 2+ underwent further evaluation using silver in situ hybridization (SISH) to confirm HER2 gene amplification. Biopsy samples were processed and analyzed at the Kocaeli University Hospital Pathology Laboratory in accordance with standardized protocols.

The patients received NACT before under going surgical intervention and completed the neoadjuvant therapy regimen before either lumpectomy or mastectomy. The study population did not include patients with phyllodes tumors, male sex, bilateral disease, ductal carcinoma in situ (DCIS), stage IV cancer, or those lacking stage data.Patients with bilateral disease and DCIS were excluded because of their significant differences in clinical management and prognosis compared with those with unilateral invasive breast cancer (17). Patients with stage IV cancer were excluded because neoadjuvant therapy is not the standard treatment for metastatic breast cancer and does not align with the study's objectives (15). Patients with missing stage data were excluded to ensure accuracy of the analysis and consistency in treatment evaluation.

Patient demographic and clinical data were retrieved from the medical records. The variables included age, body mass index (BMI), tumor localization, lymph node status,

stage at diagnosis, response to neoadjuvant therapy, metastasis, and mortality. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m²) and categorized according to the WHO classifications (18). Tumor localization was documented using laterality (right or left breast) and quadrant (upper outer, upper inner, lower outer, lower inner, or central). Lymph node status was determined through histopathological evaluation and staging was performed according to the 8th edition of the AJCC TNM classification and prognostic stage criteria (19). Response to neoadjuvant therapy was categorized as complete (ypT0/is N0), partial (tumor size reduction or decreased lymphnode involvement), or progressive (tumor growth). Distant metastases during follow-up and patient mortality, including the date and cause of death, were documented to evaluate disease progression, treatment efficacy, and overall survival.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA) and MedCalcversion 14 (MedCalc Software, Ostend, Belgium).Categorical variables are presented as frequencies and percentages, whereas continuous variables are reported as mean ± standard deviation or as median swith minimum–maximum values for non-normally distributed data. Descriptive statistics appropriate for each variable type were used to summarize patient demographics and clinical characteristics by side (left versus right). Comparisons between groups were performed using Mann–Whitney U tests for continuous variables and Pearson'schi-squaretests for categorical variables. To assess how the side influences different demographic and clinical subgroups, separate Cox regression models were customized, incorporating side, subgroup variables, and their interaction as predictive factors. Statistical significance was established at $p < 0.05$.

RESULTS

The study included 115 patients with a median age of 49 years (range 41–59 years). Patients with right-sided breast tumors had a median age of 49 years (range: 41–59 years), whereas those with left-sided tumors had a median age of 50 years (range: 42–59 years), showing no significant age difference (p = 0.704). Right breast tumors were present in 54.8% of the participants and left breast tumors were present in 45.2%. The tumor distribution across the breast quadrants was not significantly different (p = 0.659). The detailed cancer characteristics are provided in Table 1.

Table 1: Clinicopathological features of left and right breast cancer

Characteristic	Total (n= 115)	Right-Sided Breast (n=63)	Left-Sided Breast (n= 52)	p
Age (years)[a]	49 (41-59)	49 (41-59)	50 (42-59)	0.704
Age under 50 (years)[b]	59 (51.3)	34 (57.6)	25 (42.4)	0.577
BMI (kg/m)[a]	27.6 (24.6-32.0)	27.7 (24.6-32.3)	27 (24.6-31.4)	0.467
Tumor Location Side[b]	115	63 (54.8)	52 (45.2)	
Tumor Quadrant Localization[b]				
Upper outer	52 (45.2)	26 (41.3)	26 (50.0)	
Upper inner	14 (12.2)	7 (11.1)	7 (13.5)	0.659
Lower outer	17 (14.8)	9 (14.3)	8 (15.4)	
Lower inner	11 (9.6)	8 (12.7)	3 (5.8)	
Periareolar	21 (18.3)	13 (20.6)	8 (15.4)	
Lymph Node Status[b]				
cN0	61 (53.0)	36 (57.1)	25 (48.1)	
cN1	35 (30.4)	17 (27.0)	18 (34.6)	0.595
cN2	19 (16.5)	10 (15.9)	9 (17.3)	
Stage at Diagnosis[b]				
Stage 2	59 (51.3)	32 (50.8)	27 (51.9)	1.000
Stage 3	56 (48.7)	31 (49.2)	25 (48.1)	
Neoadjuvant Response[b]				
Complete	93 (80.9)	51 (81)	42 (80.8)	1.000
Partial	22 (19.1)	12 (19)	10 (19.2)	
Metastasis [b]				
Yes	11 (9.6)	7 (11.1)	4 (7.7)	0.752
Mortality[b]				
Death	3 (2.6)	2 (3.1)	1 (1.9)	

BMI: Body Mass Index, **a:** Median (IQR), **b:** n (%).

None of the patients with either right- or left-sided breast tumors exhibited disease progression during neoadjuvant therapy. Complete response was achieved in 51 (81%) patients with right-sided tumors and 42 (80.8%) with left-sided tumors. Partial responses were observed in 12% of right-sided tumors and 10% of left-sided tumors. The treatment response did not differ significantly based on the tumor location (p = 1.000).

During the follow-up period, 11 patients (9.6%) developed metastasis. Of these, seven (63.6%) had right breast tumors and four (36.4%) had left breast tumors (p = 0.752). Regarding neoadjuvant therapy, of the 93 patients with a complete response, 8 (8.6%) developed metastasis, whereas among the 22 patients with a partial response, 3 (16.6%) developed metastasis (p = 0.438). Among the 7 right breast metastasis cases, 71.4% involved bone metastasis, whereas none of the 4 left breast cases involved bone metastasis (p = 0.061). There were no statistically significant differences in the diagnostic stages or number of pathological lymph-nodes between the groups (Table 1).

The distribution of HER2 status among the patients, including the observed immunohistochemical and molecular subtypes, is presented in detail in Table 2. Regarding treatment response, 76 of 90 patients (84.4%) with HER2 3+ achieved a complete response, compared with 17 of 25 (68.0%) with HER2 IHC 2+/SISH+ (p = 0.085). Metastasis occurred in seven of the 90 HER2 3+ patients and in four of the 25 HER2 IHC 2+/SISH+ patients (p = 0.251). Tumor analysis based on pathological patterns, using data from 44 patients because of technical limitations, showed no significant differences in lymphovascular invasion (LVI) or perineural invasion (PNI). However, a significant association was found between DCIS (p = 0.016). Table 2 summarizes the tumor characteristics according to the pathological patterns for right- and left-sided tumors.

Table 2: Tumor Characteristics Based on Pathological Patterns for Right and Left Tumors

Characteristics*	Total (n=115)	Right-sided Breast (n=63)	Left-sided Breast (n=52)	P
ER %				
ER >50%	38 (33.0)	23 (36.5)	15 (28.8)	
ER 10-50%	15 (13.0)	6 (9.5)	9 (17.3)	
ER < 10%	8 (7.0)	6 (9.5)	2 (3.8)	
ER negative	54 (47.0)	28 (44.4)	26 (50)	0.354
PR %				
PR > 50%	16 (13.9)	63 (54.8)	8 (15.4)	
PR 10-50%	20 (17.4)	12 (19.0)	8 (15.4)	0.854
PR < 10%	16 (13.9)	10 (15.9)	6 (11.5)	
PR negative	63 (54.8)	33 (52.4)	30 (57.7)	
HER2				
3+	90 (78.3)	50 (79.4)	40 (76.9)	0.929
2+/ SISH +	25 (21.7)	13 (20.6)	12 (23.1)	
Grade				
Grade 1	8 (7.0)	5 (8.1)	3 (5.8)	
Grade 2	65 (56.5)	40 (64.5)	25 (48.1)	0.110
Grade 3	41 (35.7)	17 (27.4)	24 (46.2)	
Ki-67				
Ki-67 > 20%	64 (55.7)	32(69.6)	32 (72.7)	
Ki-67 10-20%	20 (17.4)	9 (19.6)	11 (25)	0.284
Ki-67 < 10%	6 (5.2)	5 (10.9)	1 (2.3)	
Not available	25 (21.0)	17 (26.9)	8 (15.3)	
LVI				
Negative	31 (70.5)	20 (76.9)	11 (61.1)	
Positive	13 (29.5)	6 (23.1)	7 (38.9)	0.427
Not available	71 (61.7)	37 (58.7)	34 (65.3)	
DCIS				
Negative	11 (25.0)	10 (38.5)	1 (5.6)	
Positive	33 (28.7)	16 (61.5)	17 (94.4)	0.016
Not available	71 (61.7)	37 (58.7)	34 (65.3)	

*Data were shown as n (%). **ER:** Estrogen receptor, **PR:** Progesterone receptor, **HER2:** Human Epidermal Growth Factor Receptor 2, **SISH:** Single-cell sequencing, **Ki-67:** Proliferation index, **LVI:** Lymphovascular invasion, **DCIS:** Ductal carcinoma in situ.

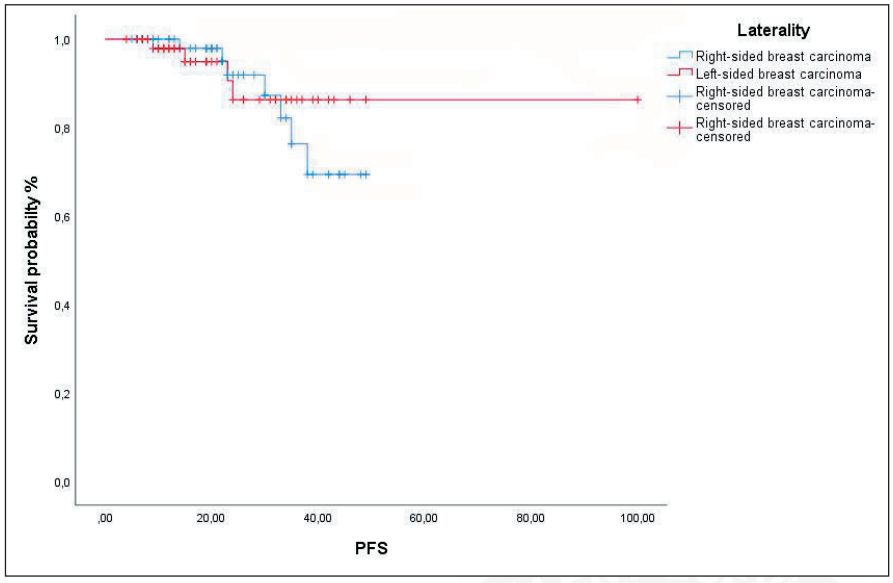


Figure 1: Kaplan-Meier curves of patients based on laterality

In our study, the median observation period was 22 months (IQR 12-34 months). According to the Kaplan–Meier analysis, the progression-free survival in right breast tumors was 43.3 ± 1.83 months, whereas it was 88.9 ± 5.2 months in left breast tumors (Figure 1). However, this observed disparity failed to attain statistical significance, yielding a p-value of 0.687.

DISCUSSION

In breast cancer characterized by over expression of the HER2 gene, patients who achieve pathological complete response after neoadjuvant therapy end to have beter overall survival rates than those who do not achieve it (20). The effectiveness of neoadjuvant therapy is influenced by a variety of histological, genetic, and molecular factors, which has led to the question of whether tumor location can serve as a simpler and quicker prognostic indicator. In the present study, we discovered that there was no detectable variation in the response to neoadjuvant therapy based on the laterality of the tumor, regardless of whether it was on the left or right side, among patients with HER2-positive breast cancer. Our results indicate that there was no difference in the incidence of metastasis between patients with breast cancers on the left or right side.

In contrast to the results of our study, Abdou et al. observed that left-sided tumors exhibited lower pCR than right-sided tumors (21). This difference may be due to various factors such as tumor characteristics, patient demographics, or treatment received. This disparity highlights the intricate nature of the factors that influence the response to neoadjuvant therapy in patients with HER2-positive breast cancer and under scores the necessity for further research to elucidate the underlying mechanisms driving tumor response based on tumor laterality.

Unlike the outcomes of an extensive investigation, which indicated a higher incidence of left-sided breast tumors, our research revealed a noticeable numerical predominance of right-sided tumors among the patient population (21,22). Several studies have indicated a minor deterioration in breast cancer-related death rates in the lower left iner quadrant; nonetheless, our research did not reveal any notable connection between laterality and the primary tumorsite (23,24). Consistent with our study, most previous studies have shown no disparity in survival outcomes based on breast cancer laterality (25,26).

After analyzing tumor characteristics based on the pathological patterns of right and left tumors, we found a notably higher incidence of DCIS in left-sided tumors. However, despite this observation, our data showed no disparity in neoadjuvant therapy response rates between tumors on the right and left sides. This finding contrasts with previous research, which has consistently shown that tumors with adjacent DCIS exhibit less aggressive behavior and enjoy significantly beter overall survival rates than those without DCIS (5-year OS, 89.3% vs. 85.5%, p<0.001)(27). Furthermore, patients achieving pCR, regardless of the presence or absence of DCIS, demonstrated significantly improved overall survival and disease-free survival compared with those with residual invasive cancer (28). No differences were observed in neoadjuvant treatment responsesbased on the HER2-positive subtype (HER2 IHC 3+ / IHC 2+/SISH+); no differences were noted between the right and left sides. Despite studies indicating that the overexpression of the HER2 protein could assist in predicting treatment response, our data did not reveal any differences in responses (29).

This study had certain limitations, primarily due to its retrospective design. Unfortunately, we failed to obtain patholog-

ical pattern data for all patients. Consequently, we could not definitively establish the influence of the higher incidence of DCIS in the left breast than in the right breast on neoadjuvant response rates. Instead, we could only identify these associations.

In conclusion, our findings indicate that there is no significant difference in the response to neoadjuvant chemotherapy between the right and left breast tumors. In addition, no disparity in metastasis development was observed during the follow-up period. Therefore, laterality is not considered a prognostic factor for breast cancer.

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None.

Author Contributions

Yasemin Bakkal Temi: Project development, desing, literature research, data analysis, manuscript writing. **Mahmut Peynirci:** Data collection, data analysis. **Devrim Çabuk:** Project development, management, manuscript editing. **Umut Kefeli:** Project development, manuscript editing. **Kazım Uygun:** Manuscript editing.

Conflicts of Interest

The authors declare that they have no competing interests relevant to the content of this article. We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal. Furthermore, the manuscript has not been presented at any conference.

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Ethical Approval

The Institutional Review Board of Kocaeli University approved the study and adhered to the principles of the Declaration of Helsinki. (Ethics Approval Code: KOÜ GOKAEK-2023/08.37, Project Identifier: 2023/131). Informed consent was not require dowing to the retrospective design of the study.

Review Process

Extremely and externally peer-reviewed.

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