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Association of Tumor Distribution Pattern with Stage at Diagnosis and Presentation Pattern in Patients with Invasive Breast Cancer

İnvaziv Meme Kanserli Hastalarda Tümör Dağılım Paterni ile Tanı Anındaki Evre ve Başvuru Şekli Arasındaki İlişki

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Abstract

Objective: Breast cancer remains the most frequently diagnosed malignancy among women worldwide. Although the prognostic significance of tumor location has been extensively investigated, its association with stage at diagnosis and presentation pattern has been less well characterized. This study aimed to evaluate the association of tumor distribution pattern with stage at diagnosis and presentation pattern in women with invasive breast cancer.

Method: This retrospective single-center study included 238 women diagnosed with invasive breast cancer between January 2015 and January 2025. Clinicopathological data were obtained from institutional medical records. Associations between tumor distribution pattern and both stage at diagnosis and presentation pattern were evaluated using Pearson's chi-square test. Multivariable binary logistic regression analyses were performed to identify factors independently associated with advanced-stage disease (Stage III-IV) and symptomatic presentation.

Results: A total of 238 patients were included (mean age, 49.2±12.0 years), of whom 79.8% presented symptomatically. The upper outer quadrant was the most common tumor distribution pattern (47.5%). Tumor distribution pattern was significantly associated with both stage at diagnosis (χ^2=28.756, p=0.017; Cramér's V=0.20) and presentation pattern (χ^2=12.236, p=0.032; Cramér's V=0.23), although both associations were modest in magnitude. In multivariable analysis, tumors located in the upper inner quadrant [odds ratio (OR) 0.33, 95% confidence interval (CI) 0.14-0.82; p=0.017] and lower outer quadrant (OR 0.36, 95% CI 0.14-0.96; p=0.041) were

Öz

Amaç: Meme kanseri, dünya genelinde kadınlarda en sık tanı alan malignite olmaya devam etmektedir. Tümör yerleşiminin prognostik önemi kapsamlı olarak araştırılmış olmakla birlikte, tanı anındaki evre ve başvuru şekli ile ilişkisi daha az incelenmiştir. Bu çalışma, invaziv meme kanserli kadınlarda tümör dağılım paterni ile tanı anındaki evre ve başvuru şekli arasındaki ilişkiyi değerlendirmeyi amaçlamıştır.

Yöntem: Bu retrospektif, tek merkezli çalışmaya Ocak 2015 ile Ocak 2025 tarihleri arasında invaziv meme kanseri tanısı alan 238 kadın hasta dahil edildi. Klinikopatolojik veriler kurumsal tıbbi kayıtlardan elde edildi. Tümör dağılım paterni ile hem tanı anındaki evre hem de başvuru şekli arasındaki ilişkiler Pearson ki-kare testi kullanılarak değerlendirildi. İleri evre hastalık (Evre III-IV) ve semptomatik başvuru ile bağımsız olarak ilişkili faktörleri belirlemek amacıyla çok değişkenli ikili lojistik regresyon analizleri gerçekleştirildi.

Bulgular: Toplam 238 hasta çalışmaya dahil edildi (ortalama yaş, 49,2±12,0 yıl) ve hastaların %79,8'i semptomatik olarak başvurdu. Üst dış kadran en sık görülen tümör dağılım paterniydi (%47,5). Tümör dağılım paterni hem tanı anındaki evre (χ^2=28,756; p=0,017; Cramér's V=0,20) hem de başvuru şekli (χ^2=12,236; p=0,032; Cramér's V=0,23) ile anlamlı olarak ilişkiliydi; ancak her iki ilişkinin büyüklüğü de mütevazı düzeydeydi. Çok değişkenli analizde, üst iç kadran [olasılık oranı (OR)=0,33; %95 güven aralığı (GA): 0,14-0,82; p=0,017] ve alt dış kadran yerleşimli tümörler (OO=0,36; %95 GA: 0,14-0,96; p=0,041) ileri evre hastalık olasılığının daha düşük olmasıyla bağımsız olarak ilişkiliyken, HER2-zengin moleküler alt tip daha yüksek olasılıkla

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Abstract

independently associated with lower odds of advanced-stage disease, whereas the HER2-enriched molecular subtype was independently associated with higher odds (OR 8.16, 95% CI 1.75-38.02; p=0.008). For symptomatic presentation, T2-T4 tumors were the factor most strongly associated with symptomatic presentation (OR 5.98, 95% CI 2.48-14.40; p<0.001), whereas lower inner quadrant tumors remained independently associated with lower odds of symptomatic presentation (OR 0.16, 95% CI 0.04-0.62; p=0.008).

Conclusion: Tumor distribution pattern was independently associated with stage at diagnosis and presentation pattern; however, the observed associations were modest. After adjustment for established clinicopathological variables, specific tumor distribution patterns remained independently associated with advanced-stage disease and symptomatic presentation. Tumor burden, represented by T-stage, was the factor most strongly associated with symptomatic presentation. Overall, tumor distribution pattern may provide complementary clinicopathological information during the initial evaluation of invasive breast cancer but should be interpreted alongside established clinicopathological factors.

Keywords: Breast neoplasms, early detection of cancer, multicentric tumor, neoplasm staging, tumor localization

Öz

bağımsız olarak ilişkiliydi (OR=8,16; %95 GA: 1,75-38,02; p=0,008). Semptomatik başvuru açısından, T2-T4 tümörler semptomatik başvuru ile en güçlü ilişkili faktördü (OR=5,98; %95 GA: 2,48-14,40; p<0,001); alt iç kadran yerleşimli tümörler ise semptomatik başvuru olasılığının daha düşük olmasıyla bağımsız olarak ilişkili olmaya devam etti (OR=0,16; %95 GA: 0,04-0,62; p=0,008).

Sonuç: Tümör dağılım paterni tanı anındaki evre ve başvuru şekli ile bağımsız olarak ilişkiliydi; ancak gözlenen ilişkiler mütevazı düzeydeydi. Yerleşik klinikopatolojik değişkenlere göre düzeltme yapıldıktan sonra, belirli tümör dağılım paternleri ileri evre hastalık ve semptomatik başvuru ile bağımsız olarak ilişkili olmaya devam etti. Tümör yükünü yansıtan T-evresi, semptomatik başvuru ile en güçlü ilişkili faktördü. Genel olarak, tümör dağılım paterni invaziv meme kanserinin ilk değerlendirilmesi sırasında tamamlayıcı klinikopatolojik bilgi sağlayabilir; ancak yerleşik klinikopatolojik faktörlerle birlikte yorumlanmalıdır.

Anahtar kelimeler: Kanserin erken tanısı, meme neoplazmları, multisentrik tümör, neoplazi evrelemesi, tümör lokalizasyonu

Introduction

Breast cancer continues to pose a major global health challenge and remains the leading malignancy among women worldwide. Despite considerable progress in screening programs and therapeutic approaches, it still contributes substantially to cancer-related morbidity and mortality (1). In Turkey, breast cancer similarly represents the leading malignancy among women, and patients are frequently diagnosed at younger ages compared with many Western populations (2).

The biological behavior and clinical outcomes of breast cancer are influenced by numerous established clinicopathological factors, including tumor size, nodal involvement, histological subtype, tumor grade, molecular characteristics, and metastatic burden at diagnosis. Invasive ductal carcinoma constitutes the predominant histological subtype in routine clinical practice (3). Although many patients are identified at earlier stages, a considerable proportion still present with locally advanced or metastatic disease, particularly in regions where participation in screening programs remains limited or delays in medical evaluation are common (4).

Tumor distribution pattern within the breast, including both anatomical tumor location and multicentric disease, has increasingly attracted attention as a potential factor associated with tumor behavior and clinical outcomes. Among different anatomical regions, the upper outer quadrant is reported as the most frequent site of tumor development, which may be related to the relatively greater concentration of glandular breast tissue in this area (5). Beyond differences in incidence, several studies have suggested that tumor distribution pattern may also be associated with disease progression, stage at diagnosis, and prognosis. Particular interest has focused on tumors arising in the inner quadrants of the breast, as these lesions may demonstrate distinct lymphatic drainage characteristics involving the internal mammary chain (6-8). In addition, tumors involving the central breast region or multicentric disease have been associated with unique clinicopathological features and potentially different patterns of dissemination (9-11).

The mode of presentation at diagnosis also represents an important clinical issue in breast cancer management. In countries with widespread screening implementation, a greater proportion of tumors are detected before symptom onset. However, symptomatic presentation continues to predominate in many developing and middle-income regions and is frequently associated with more advanced disease at diagnosis (4,12). Delayed medical evaluation may therefore contribute to unfavorable stage distribution and poorer clinical outcomes (12,13).

Although the prognostic significance of breast tumor location has been extensively investigated, relatively few studies have evaluated whether tumor distribution pattern is independently associated with stage at diagnosis and presentation pattern after adjustment for important clinicopathological variables. Most previous studies have primarily focused on survival outcomes, whereas evidence regarding diagnostic pathways and stage distribution in real-world patient cohorts remains limited.

Accordingly, the present study was designed to investigate the association of tumor distribution pattern with stage at diagnosis and presentation pattern in patients with invasive breast cancer treated in a real-world clinical setting. In addition, multivariable logistic regression analyses were performed to determine whether these associations remained independent after adjustment for established clinicopathological factors, including tumor burden and intrinsic tumor biology. A better understanding of these relationships may contribute to improved interpretation of tumor distribution pattern as a clinically relevant characteristic during the diagnostic evaluation of invasive breast cancer.

Materials and Methods

Study Design and Participants

This retrospective observational study was conducted at a tertiary oncology center and included female patients diagnosed with invasive breast cancer between January 2015 and January 2025. The study was designed to evaluate the association of tumor distribution pattern with stage at diagnosis and presentation pattern. A total of 238 patients were eligible for inclusion. Women aged 18 years or older with histopathologically confirmed invasive breast cancer and complete clinicopathological records were included in the analysis. Patients with missing essential data or without histological confirmation of invasive disease were excluded. Sex was determined according to institutional medical records, and all participants were female.

Data Collection and Definitions

Clinical and pathological variables were extracted from institutional databases and archived medical records. Variables collected for analysis included age, menopausal status, tumor distribution pattern, histological subtype, histological grade, molecular subtype, TNM stage, and mode of presentation at diagnosis.

Tumor distribution pattern was categorized as upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, central region, or multicentric disease. Multifocal tumors confined to a single breast quadrant were classified according to the corresponding anatomical quadrant, whereas tumors involving more than one breast quadrant were categorized as multicentric disease. Tumors located at the boundary between two adjacent quadrants were assigned to the quadrant containing the tumor epicenter, as determined from available imaging findings and pathological reports.

Disease stage was assigned according to the American Joint Committee on Cancer (AJCC) 8th edition TNM classification and categorized as stage I, II, III, or IV. For patients who received neoadjuvant therapy or presented with metastatic disease at diagnosis, stage was determined on the basis of clinical staging findings. For patients who underwent upfront surgery, pathological stage was used when available. Accordingly, throughout the manuscript, the term “stage at diagnosis” refers to the stage used for analysis based on this combined clinical-pathological staging approach.

Screening-detected cases were defined as asymptomatic tumors identified through routine mammographic screening, regardless of whether screening was performed within the national screening program or through individual opportunistic screening. Patients presenting with breast-related symptoms were classified as having symptomatic presentation.

Ethical Approval

Approval for the present study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Van Training and Research Hospital (date: 16.01.2026; decision no: GOKAEK/2026-01-15). The study was carried out in compliance with the ethical principles of the Declaration of Helsinki. Given the retrospective design and use of existing medical records, informed consent was not required and was formally waived by the ethics committee.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation or median (minimum-maximum), whereas categorical variables are summarized as frequencies and percentages.

Associations between tumor distribution pattern and stage at diagnosis, as well as presentation pattern, were initially evaluated using Pearson’s chi-square test. Monte Carlo

simulation was applied when appropriate to improve the reliability of probability estimation in contingency tables containing cells with low expected frequencies. The strength of statistically significant associations was quantified using Cramér's V coefficient. In addition, a sensitivity analysis excluding patients with multicentric disease was performed to evaluate whether the observed unadjusted associations between anatomical tumor distribution and both stage at diagnosis and presentation pattern persisted after removal of the multicentric subgroup.

To determine whether tumor distribution pattern was independently associated with advanced-stage disease and symptomatic presentation, two separate multivariable binary logistic regression models were constructed. The first model evaluated factors associated with advanced-stage disease (Stage III-IV vs. Stage I-II) and included age, menopausal status, tumor distribution pattern, histological grade, and molecular subtype. T and N stage were not included in this model because they are constituent components of the AJCC stage classification and their inclusion would have resulted in circular adjustment. The second model evaluated factors associated with symptomatic presentation (symptomatic vs. screening-detected) and included age, menopausal status, tumor distribution pattern, T-stage category (T2-T4 vs. T1), histological grade, histological subtype histological subtype [invasive ductal carcinoma (IDC) vs. non-IDC] and grouped molecular subtype. For the second model, molecular subtypes were grouped into hormone receptor-positive/HER2-negative (Luminal A and Luminal B/HER2-negative), HER2-positive (Luminal B/HER2-positive and HER2-enriched), and triple-negative categories to improve model stability and reduce sparse-data bias. Variables entered into both multivariable models were selected a priori based on their established clinical relevance rather than solely on univariable statistical significance.

Histological grade was unavailable for four patients; therefore, complete-case analysis was applied for multivariable regression. For the symptomatic-presentation model, patients with multicentric tumors were excluded because all multicentric tumors presented symptomatically, resulting in complete separation. In addition, two patients with Tx disease were excluded from this model because T-stage was included as an adjustment variable.

Adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Model fit was assessed using likelihood ratio chi-square statistics. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. The methodology and reporting structure of the present study were developed in accordance with the STROBE Statement for observational studies.

Results

Patient Characteristics

A total of 238 women with histopathologically confirmed invasive breast cancer were included in the study. The mean age at diagnosis was 49.2±12.0 years (median, 46.5 years; range, 28-93 years). Premenopausal women constituted 49.2% of the cohort, while 43.7% were postmenopausal and 7.1% were perimenopausal. Most patients (79.8%) presented with breast-related symptoms, whereas 20.2% were diagnosed through screening.

The upper outer quadrant was the most common tumor distribution pattern (47.5%), followed by the upper inner quadrant (16.8%), lower outer quadrant (13.0%), lower inner quadrant (8.4%), central region (8.0%), and multicentric disease (6.3%). Invasive ductal carcinoma was the predominant histological subtype (67.6%). Histological grade was available for 234 patients, with grade 2 tumors representing the largest subgroup (50.9%). According to stage at diagnosis, 26.5% of patients had stage I disease, 33.6% stage II, 21.8% stage III, and 18.1% stage IV. Detailed demographic and clinicopathological characteristics are summarized in Table 1.

Association Between Tumor Distribution Pattern and Stage at Diagnosis

The distribution of stage at diagnosis differed significantly according to tumor distribution pattern (χ^2=28.756, p=0.017) (Table 2). However, the strength of this association was modest (Cramér's V=0.20). Patients with multicentric disease demonstrated the highest proportion of stage IV disease (53.3%), whereas tumors located in the upper inner and lower outer quadrants were more frequently diagnosed at earlier stages. The remaining tumor distribution patterns showed relatively balanced stage distributions across the four stage categories.

Association Between Tumor Distribution Pattern and Presentation Pattern

Tumor distribution pattern was also significantly associated with presentation pattern (χ^2=12.236, p=0.032) (Table 3). The strength of this association was modest (Cramér's V=0.23). All patients with multicentric disease

Table 1. Demographic and clinicopathological characteristics of the study population

Variable	Category	Value
Age at diagnosis (years)	Mean ± SD	49.2±12.0
	Median (range)	46.5 (28-93)
Menopausal status	Premenopausal	117 (49.2)
	Postmenopausal	104 (43.7)
	Perimenopausal	17 (7.1)
Presentation pattern	Screening-detected	48 (20.2)
	Symptomatic	190 (79.8)
Tumor distribution pattern	Upper outer quadrant	113 (47.5)
	Upper inner quadrant	40 (16.8)
	Lower outer quadrant	31 (13.0)
	Lower inner quadrant	20 (8.4)
	Central region	19 (8.0)
	Multicentric	15 (6.3)
Histological subtype	Invasive ductal carcinoma	161 (67.6)
	Invasive lobular carcinoma	20 (8.4)
	Mixed invasive carcinoma	14 (5.9)
	Other invasive carcinoma	27 (11.3)
	Other histological types	16 (6.7)
Histological grade*	Grade 1	20 (8.5)
	Grade 2	119 (50.9)
	Grade 3	95 (40.6)
Molecular subtype	Luminal A	50 (21.0)
	Luminal B/HER2-negative	90 (37.8)
	Luminal B/HER2-positive	44 (18.5)
	HER2-enriched	15 (6.3)
	Triple-negative	39 (16.4)
Tumor (T) stage	T1	97 (40.8)
	T2	105 (44.1)
	T3	20 (8.4)
	T4	14 (5.9)
	Tx	2 (0.8)
Nodal (N) stage	N0	104 (43.7)
	N1	64 (26.9)
	N2	42 (17.6)
	N3	28 (11.8)
Stage at diagnosis	Stage I	63 (26.5)
	Stage II	80 (33.6)
	Stage III	52 (21.8)
	Stage IV	43 (18.1)

Data are presented as mean ± standard deviation, median (range), or n (%). SD: Standard deviation, HER2: Human epidermal growth factor receptor 2. Other invasive carcinoma and other histological types represent distinct histopathological categories that were analyzed separately because of their different pathological characteristics.
*: Grade information was unavailable for four patients; percentages for histological grade were calculated based on the available data (n=234)

presented symptomatically. Among the anatomical tumor distribution patterns, lower inner quadrant tumors showed the highest proportion of screening-detected cases (40.0%), whereas symptomatic presentation remained the predominant mode of diagnosis across all other tumor distribution patterns. Sensitivity analyses excluding patients with multicentric disease demonstrated that the association between anatomical tumor distribution and stage at diagnosis was attenuated and no longer statistically significant (χ^2=14.56, df=12, p=0.266). Similarly, the association between anatomical tumor distribution and presentation pattern was also attenuated and did not remain statistically significant (χ^2=7.81, df=4, p=0.099). These findings indicate that the statistically significant unadjusted associations observed in the overall cohort were largely influenced by the multicentric subgroup.

Multivariable Analysis of Factors Associated with Advanced Stage at Diagnosis

To determine whether tumor distribution pattern remained independently associated with advanced-stage disease, a multivariable logistic regression model was constructed (Table 4). Compared with tumors located in the upper outer quadrant, tumors arising in the upper inner quadrant (OR, 0.33; 95% CI, 0.14-0.82; p=0.017) and lower outer quadrant (OR, 0.36; 95% CI, 0.14-0.96; p=0.041) were associated with significantly lower odds of presenting with stage III-IV disease.

Among molecular subtypes, HER2-enriched tumors demonstrated significantly higher odds of advanced-stage disease than Luminal A tumors (OR, 8.16; 95% CI, 1.75-38.02; p=0.008). Although multicentric disease was associated with increased odds of advanced-stage presentation (OR, 3.30; 95% CI, 0.93-11.73), this association did not reach statistical significance (p=0.066). Age, menopausal status, histological grade, and the remaining molecular subtypes were not independently associated with advanced-stage disease after adjustment. The overall regression model was statistically significant (Likelihood ratio χ^2=35.96, p=0.001). These findings indicate that selected anatomical tumor distribution patterns and tumor biology were independently associated with the odds of presenting with advanced-stage disease.

Multivariable Analysis of Factors Associated with Symptomatic Presentation

A second multivariable logistic regression model was performed to identify factors independently associated with symptomatic presentation (Table 5). Increasing age was

Table 2. Association between tumor distribution pattern and stage at diagnosis

Tumor distribution pattern	Stage I, n (%)	Stage II, n (%)	Stage III, n (%)	Stage IV, n (%)	Overall p-value
Upper outer quadrant	26 (23.0)	37 (32.7)	32 (28.3)	18 (15.9)	**0.017**
Upper inner quadrant	17 (42.5)	13 (32.5)	3 (7.5)	7 (17.5)	
Lower outer quadrant	7 (22.6)	15 (48.4)	6 (19.4)	3 (9.7)	
Lower inner quadrant	5 (25.0)	8 (40.0)	3 (15.0)	4 (20.0)	
Central region	6 (31.6)	5 (26.3)	5 (26.3)	3 (15.8)	
Multicentric disease	2 (13.3)	2 (13.3)	3 (20.0)	8 (53.3)	

Values are presented as n (row %). The association between tumor distribution pattern and stage at diagnosis was evaluated using Pearson's chi-square test (χ^2=28.756, degrees of freedom =15, p=0.017). The magnitude of the association was modest (Cramér's V=0.20)

Table 3. Association between tumor distribution pattern and mode of clinical presentation

Tumor distribution pattern	Screening-detected, n (%)	Symptomatic presentation, n (%)	Overall p-value
Upper outer quadrant	20 (17.7)	93 (82.3)	**0.032**
Upper inner quadrant	10 (25.0)	30 (75.0)	
Lower outer quadrant	4 (12.9)	27 (87.1)	
Lower inner quadrant	8 (40.0)	12 (60.0)	
Central region	6 (31.6)	13 (68.4)	
Multicentric disease	0 (0.0)	15 (100.0)	

Values are presented as n (row %). The association between tumor distribution pattern and mode of clinical presentation was evaluated using Pearson's chi-square test (χ^2=12.236, degrees of freedom =5, p=0.032). The magnitude of the association was modest (Cramér's V=0.23)

Table 4. Multivariable logistic regression analysis for factors associated with advanced stage at diagnosis

Variable	Adjusted OR	95% CI	p-value
Age at diagnosis, per year increase	0.98	0.94-1.02	0.301
Menopausal status			
Postmenopausal vs. Premenopausal	1.60	0.63-4.04	0.322
Perimenopausal vs. Premenopausal	1.02	0.32-3.22	0.979
Tumor distribution pattern			
Upper inner quadrant vs. Upper outer quadrant	**0.33**	**0.14-0.82**	**0.017**
Lower outer quadrant vs. Upper outer quadrant	**0.36**	**0.14-0.96**	**0.041**
Lower inner quadrant vs. Upper outer quadrant	0.64	0.21-1.98	0.441
Central region vs. Upper outer quadrant	0.82	0.27-2.48	0.730
Multicentric disease vs. Upper outer quadrant	3.30	0.93-11.73	0.066
Histological grade			
Grade 2 vs. Grade 1	1.62	0.46-5.68	0.454
Grade 3 vs. Grade 1	2.85	0.72-11.24	0.136
Molecular subtype			
Luminal B/HER2- vs. Luminal A	1.17	0.47-2.89	0.741
Luminal B/HER2+ vs. Luminal A	1.92	0.68-5.44	0.217
HER2-enriched vs. Luminal A	**8.16**	**1.75-38.02**	**0.008**
Triple-negative vs. Luminal A	0.63	0.19-2.08	0.445

Dependent variable: advanced stage at diagnosis (Stage III-IV vs. Stage I-II). Odds ratios (ORs) were estimated using multivariable logistic regression. Odds ratios were adjusted simultaneously for all variables included in the model. Reference categories were premenopausal status, upper outer quadrant location, Grade 1 histological grade and Luminal A subtype. Overall model fit: likelihood ratio χ^2=35.96, p=0.001. Four patients with missing histological grade were excluded; therefore, the analysis included 234 patients, CI: Confidence interval

Table 5. Multivariable logistic regression analysis for factors associated with symptomatic presentation

Variable	Adjusted OR	95% CI	p-value
Age at diagnosis, per year increase	**0.94**	**0.89-0.998**	**0.036**
Menopausal status			
Postmenopausal vs. Premenopausal	1.38	0.35-5.40	0.642
Perimenopausal vs. Premenopausal	**0.19**	**0.05-0.79**	**0.022**
Tumor distribution pattern			
Upper inner quadrant vs. Upper outer quadrant	0.75	0.25-2.24	0.609
Lower outer quadrant vs. Upper outer quadrant	1.28	0.33-4.98	0.719
Lower inner quadrant vs. Upper outer quadrant	**0.16**	**0.04-0.62**	**0.008**
Central region vs. Upper outer quadrant	0.46	0.11-1.88	0.278
T-stage category			
T2-T4 vs. T1	**5.98**	**2.48-14.40**	**<0.001**
Histological grade			
Grade 2 vs. Grade 1	1.84	0.52-6.53	0.345
Grade 3 vs. Grade 1	**4.68**	**1.04-21.00**	**0.044**
Histological subtype			
Non-IDC vs. IDC	0.70	0.29-1.68	0.424
Molecular subtype			
HER2-positive vs. HR-positive/HER2-negative	2.71	0.91-8.07	0.073
Triple-negative vs. HR-positive/HER2-negative	1.64	0.41-6.53	0.483

The dependent variable was symptomatic presentation versus screening-detected presentation. Odds ratios were estimated using multivariable binary logistic regression and were adjusted simultaneously for all variables included in the model. For multivariable analysis, molecular subtypes were grouped as hormone receptor-positive/HER2-negative (Luminal A and Luminal B/HER2-negative), HER2-positive (Luminal B/HER2-positive and HER2-enriched), and triple-negative. Histological subtype was categorized as invasive ductal carcinoma (IDC) versus non-IDC. Reference categories were premenopausal status, upper outer quadrant location, T1 stage, Grade 1, IDC, and HR-positive/HER2-negative molecular subtype. Multicentric tumors were excluded because all multicentric cases presented symptomatically, resulting in complete separation. Patients with missing histological grade or Tx disease were also excluded; therefore, the analysis included 217 patients. Overall model fit: likelihood ratio χ^2=67.05, p<0.001. OR: Odds ratio, CI: Confidence interval, HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2

independently associated with lower odds of symptomatic presentation (OR, 0.94 per year; 95% CI, 0.89-1.00; p=0.036). Compared with premenopausal women, perimenopausal patients also had significantly lower odds of symptomatic presentation (OR, 0.19; 95% CI, 0.05-0.79; p=0.022), whereas postmenopausal status was not significantly associated with presentation pattern.

After adjustment for clinicopathological factors, patients with T2-T4 tumors had substantially higher odds of symptomatic presentation than those with T1 tumors (OR, 5.98; 95% CI, 2.48-14.40; p<0.001). Among tumor distribution patterns, lower inner quadrant tumors remained independently associated with lower odds of symptomatic presentation compared with upper outer quadrant tumors (OR, 0.16; 95% CI, 0.04-0.62; p=0.008). Grade 3 tumors were also independently associated with higher odds of symptomatic presentation than Grade 1 tumors (OR, 4.68; 95% CI, 1.04-21.00; p=0.044).

Neither histological subtype nor molecular subtype demonstrated statistically significant independent associations with symptomatic presentation after adjustment, although the HER2-positive group showed a trend toward higher odds of symptomatic presentation compared with the HR-positive/HER2-negative group (OR, 2.71; 95% CI, 0.91-8.07; p=0.073).

Patients with multicentric disease were excluded because all multicentric tumors presented symptomatically, resulting in complete separation. Patients with Tx disease were also excluded because T-stage was included in the multivariable model. The overall regression model was statistically significant (Likelihood ratio χ^2=67.05, p<0.001), indicating a statistically significant improvement over the intercept-only model.

Discussion

This retrospective study investigated the association of tumor distribution pattern with stage at diagnosis and presentation pattern in a real-world cohort of women with invasive breast cancer. The principal findings can be summarized as follows. First, tumor distribution pattern

was significantly associated with both stage at diagnosis and presentation pattern; however, the magnitude of these associations was modest. Second, after adjustment for relevant clinicopathological variables, tumors located in the upper inner and lower outer quadrants remained independently associated with lower odds of advanced-stage disease, whereas the HER2-enriched molecular subtype was independently associated with higher odds of presenting with stage III-IV disease. Third, T2-T4 tumors emerged as the strongest independent factor associated with symptomatic presentation. In addition, lower inner quadrant tumors remained independently associated with lower odds of symptomatic presentation after adjustment for T-stage and other clinicopathological variables, whereas Grade 3 tumors were associated with higher odds of symptomatic presentation. Collectively, these findings suggest that tumor distribution pattern may provide complementary clinicopathological information during the initial clinical assessment of patients with invasive breast cancer. Nevertheless, the observed effect sizes were modest, indicating that tumor distribution pattern should be interpreted alongside established clinicopathological factors rather than as an isolated determinant.

The association between breast tumor location and stage at diagnosis has been investigated in several previous studies; however, the reported findings have been inconsistent (14). Anatomically, the upper outer quadrant is the most common site of breast cancer development because of its relatively greater volume of glandular tissue, a finding that was also confirmed in our cohort (5). Beyond differences in tumor frequency, several studies have suggested that tumors arising in the inner quadrants may be associated with less favorable outcomes because of their lymphatic drainage to the internal mammary chain and the potential for occult nodal involvement (6-8,15). Other studies have reported distinct clinicopathological characteristics for centrally located and multicentric tumors, although their independent clinical significance remains uncertain (9-11,16,17). Consistent with these observations, our sensitivity analyses demonstrated that exclusion of multicentric tumors attenuated the associations between anatomical tumor distribution and both stage at diagnosis and presentation pattern. These findings suggest that the multicentric subgroup substantially influenced the statistically significant unadjusted associations observed in the overall cohort.

In the present study, tumor distribution pattern was significantly associated with stage at diagnosis; however, the magnitude of this association was modest. Furthermore, multivariable analysis demonstrated that tumors located in the upper inner and lower outer quadrants were independently associated with lower odds of advanced-stage disease compared with tumors in the upper outer quadrant, whereas multicentric disease showed only a non-significant trend toward higher odds of advanced-stage presentation after adjustment. These findings suggest that the relationship between tumor distribution pattern and stage at diagnosis is influenced by multiple clinicopathological factors rather than anatomical distribution alone (18). Although certain anatomical tumor distribution patterns remained independently associated with advanced-stage disease after adjustment, the modest effect sizes observed in the present study indicate that tumor distribution pattern should be interpreted as complementary to, rather than a substitute for, established clinicopathological factors.

An additional finding of the present study was the independent association between the HER2-enriched molecular subtype and advanced-stage disease at diagnosis. This finding is biologically plausible and is consistent with previous studies demonstrating the more aggressive clinical behavior of HER2-enriched tumors in the absence of HER2-targeted therapy, including higher proliferative activity and a greater likelihood of presenting with advanced disease. Although the introduction of contemporary anti-HER2 therapies has substantially improved clinical outcomes, our results suggest that intrinsic tumor biology remains an important factor associated with disease extent at diagnosis, independent of tumor distribution pattern. Therefore, assessment of molecular subtype together with anatomical tumor distribution may provide a more comprehensive characterization of disease at the time of diagnosis.

The relationship between tumor distribution pattern and presentation pattern has received considerably less attention than its association with survival outcomes. In general, breast cancers detected through organized screening programs are more likely to be diagnosed at earlier stages, whereas symptomatic presentation is commonly associated with greater tumor burden and more advanced disease (4,12,13). Consequently, factors associated with the timing or mode of detection may indirectly influence stage at diagnosis and subsequent treatment strategies.

In the present study, tumor distribution pattern was significantly associated with presentation pattern; however, the strength of this association was modest. After adjustment for relevant clinicopathological variables, T2-

T4 tumors emerged as the strongest factor independently associated with symptomatic presentation, emphasizing the predominant role of tumor burden in determining clinical detection. Nevertheless, lower inner quadrant tumors remained independently associated with lower odds of symptomatic presentation even after adjustment for T-stage, suggesting that this association cannot be fully explained by differences in tumor size at diagnosis alone. Grade 3 tumors were also independently associated with higher odds of symptomatic presentation, supporting the contribution of more aggressive tumor biology to clinically apparent disease.

The mechanisms underlying the observed association between lower inner quadrant tumors and presentation pattern remain uncertain. Given the modest effect size observed in the present study, this finding should be interpreted with caution and requires confirmation in larger prospective multicenter cohorts. Several explanations may account for this observation. Differences in healthcare utilization, participation in screening programs, breast anatomy, or other unmeasured clinicopathological characteristics may have contributed to the observed association. Because of the retrospective design and the possibility of residual confounding, the present findings should be considered hypothesis-generating rather than evidence of a causal relationship.

From a clinical perspective, the present findings suggest that tumor distribution pattern may provide complementary information during the initial evaluation of patients with invasive breast cancer (19). In the present study, tumor burden, represented by T-stage, emerged as the factor most strongly associated with symptomatic presentation, whereas tumor distribution pattern demonstrated additional independent associations beyond established clinicopathological variables. The persistence of the association between lower inner quadrant tumors and presentation pattern after adjustment for T-stage suggests that anatomical tumor distribution may be associated with clinical presentation independently of tumor size. However, given the modest effect sizes observed, tumor distribution pattern should be interpreted as a complementary clinicopathological characteristic rather than an independent determinant of clinical behavior.

Study Limitations

The present study has several strengths. It included a relatively large real-world cohort of patients with invasive breast cancer treated at a tertiary referral center over a 10-year period. Comprehensive clinicopathological data were available for most patients, allowing adjustment for important potential confounding factors using multivariable logistic regression analyses. In addition, the study evaluated both stage at diagnosis and presentation pattern, providing a broader assessment of the potential clinical relevance of tumor distribution pattern.

Nevertheless, several limitations should be acknowledged. First, the retrospective single-center design may have introduced selection bias and limits the generalizability of the findings. Second, residual confounding from unmeasured variables cannot be completely excluded despite multivariable adjustment. Detailed information regarding the regularity and frequency of screening mammography before diagnosis was not consistently available because of the retrospective design of the study. Therefore, the potential influence of prior screening adherence on presentation pattern could not be evaluated. Third, histological grade data were unavailable for a small number of patients, resulting in complete-case analysis for the multivariable regression models. In addition, stage at diagnosis was based on a combined clinical-pathological staging approach, which may have introduced some degree of classification heterogeneity between patients receiving neoadjuvant therapy and those undergoing upfront surgery.

The relatively limited number of screening-detected cases, together with the number of covariates included in the symptomatic-presentation model, may have reduced the precision of some adjusted estimates, as reflected by the wide CIs. Accordingly, some degree of model overfitting cannot be excluded. Furthermore, external validation of the present findings was not available, and survival outcomes were beyond the scope of this study; therefore, the prognostic implications of tumor distribution pattern could not be evaluated.

Finally, some tumor distribution subgroups, particularly multicentric, lower inner quadrant, and central tumors, contained relatively few patients. Consequently, subgroup-specific estimates should be considered exploratory and interpreted with caution. Moreover, the observed associations were modest in magnitude and therefore require confirmation in larger prospective multicenter studies before firm clinical conclusions can be drawn.

Conclusion

In conclusion, tumor distribution pattern was significantly associated with both stage at diagnosis and presentation

pattern in this real-world cohort of women with invasive breast cancer, although the observed associations were modest in magnitude. After adjustment for established clinicopathological variables, tumors located in the upper inner and lower outer quadrants remained independently associated with lower odds of advanced-stage disease, whereas lower inner quadrant tumors remained independently associated with lower odds of symptomatic presentation. Tumor burden, represented by T-stage, was the factor most strongly associated with symptomatic presentation. Overall, these findings suggest that tumor distribution pattern may provide complementary clinicopathological information during the initial evaluation of invasive breast cancer but should be interpreted together with established clinicopathological factors rather than as an independent determinant of clinical behavior. Further prospective multicenter studies incorporating survival outcomes are warranted to validate these findings and to further clarify the mechanisms underlying the observed associations.

Ethics

Ethics Committee Approval: Approval for the present study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Van Training and Research Hospital (date: 16.01.2026; decision no: GOKAEK/2026-01-15).

Informed Consent: Given the retrospective design and use of existing medical records, informed consent was not required and was formally waived by the ethics committee.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ş., A.G., Concept: E.Ş., A.G., Design: E.Ş., Data Collection or Processing: E.Ş., Analysis or Interpretation: E.Ş., A.G., Literature Search: E.Ş., A.G., Writing: E.Ş.

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