

Evaluation of the Immunohistochemical and Molecular Characteristics of Breast Cancers Exhibiting Fibrotic Scar Formation Following Neoadjuvant Chemotherapy

Neoadjuvan Kemoterapiye Fibröz SkarlaŒma ile Yanıt Veren Meme Kanserlerinin İmmunhistokimyasal ve Moleküler Özelliklerinin Deęerlendirilmesi

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Abstract

Objectives: Neoadjuvant chemotherapy (NACT) is widely used in breast cancer to reduce tumor burden and enable breast-conserving surgery. While pathological complete response is commonly used to assess efficacy, residual disease often shows heterogeneous morphological and biological patterns. Understanding this heterogeneity, particularly within fibrotic scar-dominant tumor beds, can provide insights into tumor biology, guide surgical planning, and optimize pathological sampling. This study aimed to examine the relationship between residual tumor distribution patterns and hormone receptor expression and discuss the clinical implications.

Material and Methods: We retrospectively analyzed 113 patients who underwent surgery following NACT between 2019 and 2025. Residual disease within the tumor bed was classified as either confined to the fibrotic scar or dispersed across a broader area. Immunohistochemical analyses included estrogen receptor (ER) and progesterone receptor (PR) expression. Morphological features were correlated with clinical and radiological findings, and ROC curves assessed the predictive capacity of receptor expression for residual patterns.

Results: In 87.6% of cases, residual tumor was confined within the fibrotic scar, while 12.4% exhibited a dispersed pattern. ER and PR expression levels were significantly higher in cases with a dispersed residual pattern (ER AUC=0.718; PR AUC=0.736), suggesting an association with hormone receptor-positive tumors. Ki-67 proliferation index did not differ significantly between patterns, indicating that proliferation alone does not explain the morphological spectrum. Clinically, dispersed patterns increased the risk of underestimating residual disease on imaging, highlighting the importance of comprehensive tumor bed evaluation.

Conclusion: These findings indicate that NACT response is not a uniform biological process and that residual tumor distribution may correlate with hormone receptor expression. The morphological and biological heterogeneity of residual disease is essential for guiding surgical planning and pathological sampling. In cases with likely dispersed patterns, ensuring margin safety and intensifying sampling may improve assessment of true residual extent. Recognizing these patterns can help anticipate discrepancies between imaging and actual disease, improve interpretation of treatment response, and support more personalized, biology-driven post-NACT management.

Keywords: Breast cancer, fibrotic scar, neoadjuvant chemotherapy, residual tumor, tumor heterogeneity



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Öz

Giriş / Amaç: Neoadjuvan kemoterapi (NAKT) meme kanseri tedavisinde tümör yükünü azaltmak ve meme koruyucu cerrahi mümkün kılmak amacıyla yaygın olarak kullanılmaktadır. Patolojik tam yanıt sıklıkla tedavi yanıtını değerlendirmek için kullanılsa da rezidü hastalık çoğu zaman heterojen morfolojik ve biyolojik özellikler sergiler. Özellikle tümör yatağı içindeki bu heterojenliğin anlaşılması tümör biyolojisi, cerrahi planlama ve patolojik örnekleme stratejilerinde kritik bilgiler sağlayabilir. Bu çalışmanın amacı NAKT sonrası fibrotik skar dokusu içinde kalan rezidü invaziv tümörün morfolojik olarak dağılım paternleri ile hormon reseptör ekspresyonu arasındaki ilişkiyi incelemek ve bulguların klinik önemini tartışmaktır.

Gereç ve Yöntem: 2019-2025 yılları arasında NAKT sonrası cerrahi tedavi uygulanmış 113 hasta retrospektif olarak analiz edildi. Rezidü hastalık paterni fibrotik skar içinde sınırlı veya daha geniş bir alana dağılmış olarak sınıflandırıldı. İmmünohistokimyasal analizlerde östrojen reseptörü (ER) ve progesteron reseptörü (PR) ekspresyonu değerlendirildi. Morfolojik özellikler klinik ve radyolojik bulgularla karşılaştırıldı, ROC eğrileri ile reseptör ekspresyonlarının dağılım paterni tahmin kapasitesi incelendi.

Bulgular: Olguların %87,6'sında rezidü tümör fibrotik skar içinde sınırlıyken, %12,4'ünde dağınık bir paterne rastlandı. Dağınık patern gösteren olgularda ER ve PR ekspresyonları anlamlı derecede yüksek bulundu (ER AUC=0,718; PR AUC=0,736). Ki-67 proliferasyon indeksi paternlere göre farklılık göstermedi; bu da proliferatif aktivitenin tek başına morfolojik spektrumu açıklamada yetersiz olabileceğini gösterdi. Klinik olarak dağınık patern görüntüleme ile rezidü hastalığın küçümsenme riskini artırdı ve tümör yatağının kapsamlı değerlendirilmesinin önemini vurguladı.

Tartışma / Sonuç: Elde edilen veriler NAKT'ye yanıtın tek tip bir biyolojik süreç olmadığını ve dağılım paterninin hormon reseptör ekspresyonlarıyla ilişkili olabileceğini göstermektedir. Rezidü hastalığın morfolojik ve biyolojik heterojenliği cerrahi planlama ve patolojik örnekleme stratejileri açısından önemlidir. Dağınık patern olasılığı bulunan olgularda cerrahi sınır güvenliğinin sağlanması ve patolojik örnekleminin yoğunlaştırılması gerçek rezidü yayılımının doğru değerlendirilmesini kolaylaştırabilir. Bulguların daha geniş hasta serilerinde ve prospektif çalışmalarda doğrulanması, rezidü hastalık değerlendirmesinde bütüncül ve biyoloji temelli stratejilerin geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Meme kanseri, fibrotik skar, neoadjuvan kemoterapi, rezidü tümör, tümör heterojenitesi

Introduction

The principal goals of neoadjuvant chemotherapy (NACT) in breast cancer include decreasing the size of the primary tumor to facilitate breast-conserving surgery; decreasing axillary tumor burden, thereby reducing the need for axillary dissection and its associated surgical morbidity; enabling early treatment of systemic micrometastases; allowing *in vivo* assessment of biological response to therapy; and supporting the planning of de-escalation or escalation strategies in adjuvant treatment. In addition, achievement of a pathological complete response (pCR) is a key prognostic indicator, especially among patients with triple-negative breast cancer (TNBC) or human epidermal growth factor-2 (HER2)-positive subtypes (1).

pCR refers to the complete absence of invasive tumor cells following NACT, indicating no residual invasive carcinoma is detectable. Attaining a pCR has been consistently associated with improved long-term survival, especially in individuals with TNBC or HER2-positive breast cancer (2). In contrast, residual disease exhibits considerable morphological heterogeneity, thereby obscuring the prognostic distinction between pCR and residual cancer burden. Consequently, numerous studies, including that of Symmans et al. (3) have proposed quantitative parameters ranging from primary tumor size to tumor bed cellularity to assess residual cancer burden. However, these scoring systems do not sufficiently incorporate the morphological patterns of

tumor regression, limiting their capacity to comprehensively characterize residual disease.

In clinical practice, a fragmented regression pattern is frequently observed following NACT, characterized by residual invasive tumor foci embedded within fibrotic scar tissue in the tumor bed. This pattern suggests that the therapeutic effect is mediated predominantly through stromal fibrosis and tissue remodeling. Importantly, it is biologically distinct from pCR, in which cytotoxic tumor cell eradication represents the dominant mechanism of response (4).

It is well established that breast cancers of the luminal molecular subtype exhibit relatively low pCR rates following NACT; however, they often demonstrate treatment responses characterized by prominent stromal alterations and partial tumor regression. These findings suggest that such responses may be closely related to the underlying biology of fibrotic scar formation and residual disease (5).

In this study, we aimed to elucidate the biological determinants underlying this distinct response pattern by analyzing the immunohistochemical and molecular characteristics of breast cancers that demonstrate residual invasive tumor foci within a fibrotic scar background and exhibit a fragmented regression pattern following NACT.

Materials and Methods

The study protocol received approval from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval no: E-50687469-799-302082838, date: 03.02.2026). All procedures were conducted in accordance with internationally recognized ethical standards, consistent with the principles set forth by the Declaration of Helsinki.

This retrospective, observational, single-center study evaluated the morphological and immunohistochemical characteristics of residual disease in patients with breast carcinoma who, following NACT, underwent definitive surgery—either mastectomy or breast-conserving surgery at the Department of Surgical Oncology, University of Health Sciences Türkiye, Gülhane Training and Research Hospital.

Between January 2019 and December 2025, 3358 patients with breast cancer who received surgical treatment were retrospectively screened from the hospital information system. Among them, 1119 patients who underwent surgery following NACT were identified, and their pathological specimens were re-evaluated in detail. The study included 113 female patients who demonstrated a fragmented regression pattern, characterized by residual invasive tumor foci within a fibrotic tumor bed, who did not meet the criteria for pCR.

Clinicopathological variables retrieved from hospital records included age; histological subtype; type of surgery and axillary management; number of excised and metastatic lymph nodes; presence of an *in situ* component; microcalcifications; multifocality (defined as the presence of two or more spatially separate invasive tumor foci within the breast parenchyma on pathological examination); lymphovascular invasion (LVI); tumor necrosis; fibrotic scar size; estrogen receptor (ER) and progesterone receptor (PR) expression; HER2 status; Ki-67 proliferation index; and response to NACT in both the breast and axillary lymph nodes.

The tumor bed was evaluated based on macroscopic and microscopic findings, with particular attention to treatment-related morphological changes. The size of the residual invasive tumor focus was determined based on the invasive component identified in the fibrotic tumor bed.

Within the study protocol, the distribution pattern of residual tumor foci and treatment-related stromal alterations following NACT was analyzed in two subgroups: group 1 (limited) and group 2 (dispersed). Group 1 (limited pattern) was defined by minimal treatment-related fibrosis, with either a single residual tumor focus or small clusters of tumor cells separated by limited fibrotic scarring, but confined to a well-demarcated area. Group 2 (dispersed pattern) was defined by the presence of three or

more spatially separated residual tumor foci within the fibrotic tumor bed, each separated by intervening fibrotic stroma. In these cases, isolated single tumor cells or very small clusters were irregularly distributed within the stroma, and treatment-related fibrosis represented the predominant morphological feature.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with ranges (minimum-maximum), and categorical variables as frequencies (percentages). The normality of distribution was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. Normally distributed variables were compared using the independent samples t-test, whereas non-normally distributed variables were analyzed with the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value. A p-value <0.05 was considered statistically significant.

Results

The study included 113 patients with a mean age of 48.08 ± 12.21 years (range, 26-86). Among cases with a fragmented regression pattern in a fibrotic tumor bed following NACT, invasive ductal carcinoma was the most common histological subtype (81.4%, n=92). This was followed by invasive lobular carcinoma (8.0%, n=9), papillary carcinoma (3.5%, n=4), and other less frequent histological subtypes. Regarding surgical management, 46 patients (40.7%) underwent breast-conserving surgery, while 67 patients (59.3%) underwent mastectomy.

In terms of axillary surgical management, sentinel lymph node biopsy (SLNB) was performed in 35 patients (31%), whereas 78 patients (69%) underwent axillary lymph node dissection (ALND). The mean number of dissected lymph nodes was 12.88 ± 7.36 (range, 1-30), and the mean number of metastatic lymph nodes was 3.42 ± 4.27 (range, 0-21). The clinicopathological characteristics of the study cohort are summarized in Table 1.

Following NACT, patients were categorized into two groups according to residual disease morphology: a limited residual pattern (group 1) and a dispersed residual pattern (group 2). Ninety-nine patients (87.6%) were classified as group 1, while 14 patients (12.4%) were classified as group 2 (Table 2). In group 1, residual invasive tumor foci were observed as solitary lesions or small clusters confined to limited fibrotic areas. In contrast, group 2 was characterized by scattered, irregularly distributed small clusters or single tumor cells within extensive fibrotic stromal areas. No statistically significant differences were identified between the two groups in terms of age, histological subtype, surgical approach, axillary management, number of dissected lymph nodes, or number of metastatic lymph nodes (all p>0.05).

Table 1. Demographic and histo-pathological distribution of all patients

Age, year, mean \pm SD, range	48.08 \pm 12.21 (26-86)
Tumor type, n (%)	
Ductal	92 (81.4%)
Lobular	9 (8%)
Mixed	2 (1.8%)
Papillary	4 (3.5%)
Neuroendocrine	3 (2.7%)
Metaplastic	1 (0.9%)
Mucinous	2 (1.8%)
Operation type, n (%)	
Breast-conserving surgery	46 (40.7%)
Mastectomy	67 (59.3%)
Axillary treatment, n (%)	
SLNB	35 (31%)
ALND	78 (69%)
Lymph node dissection, nb, mean \pm SD, range	12.88 \pm 7.36 (1-30)
Lymph node metastasis, nb, mean \pm SD, range	3.42 \pm 4.27 (0-21)
<i>In situ</i> component, n (%)	
Absent	39 (34.5%)
Present	74 (65.5%)
Microcalcification cluster, n (%)	
Absent	37 (32.7%)
Present	76 (67.3%)
Multifocality, n (%)	
Absent	10 (8.8%)
Present	103 (91.2%)
LVI, n (%)	
Absent	45 (39.8%)
Present	68 (60.2%)
Tumor necrosis, n (%)	
Absent	87 (77%)
Present	26 (23%)
ER, %, mean \pm SD, range	62.89 \pm 39.08 (0-100)
PR, %, mean \pm SD, range	29.43 \pm 35.87 (0-95)
HER2, n (%)	
0+	74 (65.5%)
1+	16 (14.2%)
2+	4 (3.5%)
3+	19 (16.8%)
Ki-67, %, mean \pm SD, range	20.22 \pm 19.35 (1-80)
Breast neoadjuvant response, n (%)	
Circumscribed (\leq 2 area)	99 (87.6%)
Scattered (\geq 3 area)	14 (12.4%)
Tumor fibrous area, mm ³ , mean \pm SD, range	95.29 \pm 498.93 (0.7-5292)
Lymph node neoadjuvant response, n (%)	
No response	30 (26.5%)
Partial response	68 (60.2%)
Partial-complete response	11 (9.7%)
Complete response	4 (3.5%)
SD: Standard deviation, ER: Estrogen receptor, PR: Progesterone receptor, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, LVI: Lymphovascular invasion, HER2: Human epidermal growth factor-2	

Similarly, no statistically significant differences were observed between the groups regarding the presence of an *in situ* component ($p=0.617$), microcalcification ($p=0.116$), multifocality ($p=0.077$), LVI ($p=0.804$), or tumor necrosis ($p=0.597$) (Table 2). In the overall study population, the mean ER expression was 62.89 \pm 39.08% (range, 0-100), and the mean PR expression was 29.43 \pm 35.87% (range, 0-95). HER2 overexpression (3+) was observed in 19 cases (16.8%).

A statistically significant difference in ER expression was observed among residual tumor distribution patterns ($p=0.008$). Median ER expression was higher in group 2 than in group 1. Similarly, PR expression differed significantly between the groups. The median PR level was 70% (range, 0-90) in group 2 and was 4% (range, 0-95) in group 1 ($p=0.004$). No statistically significant difference was observed in the Ki-67 proliferation index between the groups (group 1: median 12%; group 2: median 6.5%; $p=0.117$).

An *in situ* component was present in 74 patients (65.5%) and absent in 39 (34.5%). Microcalcifications were identified in 76 cases (67.3%). LVI was present in 68 patients (60.2%) and absent in 45 patients (39.8%). Tumor necrosis was observed in 26 cases (23%), while 87 cases (77%) showed no necrosis (Table 1). No statistically significant differences between the groups were observed for the Ki-67 proliferation index ($p=0.117$) or fibrotic tumor bed volume ($p=0.438$) (Table 2).

When axillary lymph node response to NACT was assessed, no statistically significant difference was observed between the groups ($p=0.065$) (Table 2). Partial-to-complete response rates were numerically higher in the dispersed residual pattern group.

ROC curve analysis was performed to evaluate the ability of ER and PR expression to distinguish residual tumor distribution patterns. The AUC for ER was 0.718 [95% confidence interval (CI): 0.578-0.858; $p=0.008$]. A cut-off value of 92.5 yielded 50% sensitivity and 76.8% specificity. The AUC for PR was 0.736 (95% CI: 0.610-0.862; $p=0.004$). A cut-off value of 45 yielded a sensitivity of 57.1% and a specificity of 69.7% (Figure 1).

Discussion

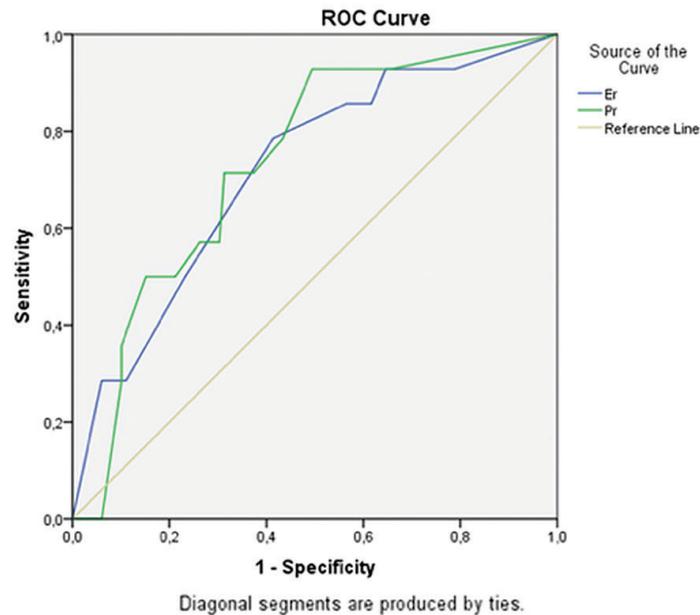
Although residual disease following NACT is generally regarded as an adverse prognostic indicator, the biological and clinical implications of its spatial distribution within the tumor bed and the accompanying stromal alterations remain insufficiently explored. Patients who do not achieve pCR exhibit marked morphological heterogeneity, which may reflect not only differences in residual tumor burden but also distinct patterns of tumor-stroma interaction and biological response to therapy.

In studies evaluating surgical approaches following NACT, Song et al. (6) reported that in appropriately selected patients, breast-

Table 2. Association between residual diseases groups and clinicopathological factors

Clinicopathological factors	No of patients (%)		p-value
	Limited residual group (99 patients 87.6%)	Dispersed residual group (14 patients 12.4%)	
Age, year, median, range	45 (26-86)	45 (32-65)	p=0.349 ^u
Tumor type, n (%)			p=0.097 ^{x2}
Ductal	80	12	
Lobular	9	0	
Mixed	2	0	
Papillary	4	0	
Neuroendocrine	1	2	
Metaplastic	1	0	
Mucinous	2	0	
Operation type, n (%)			p=0.323 ^{x2}
Breast-conserving surgery	42	4	
Mastectomy	57	10	
Axillary treatment, n (%)			p=0.682 ^{x2}
SLNB	30	5	
ALND	69	9	
Lymph node dissection, nb, median, range	13 (1-30)	13.5 (3-29)	p=0.986 ^u
Lymph node metastasis, nb, median, range	2 (0-21)	1 (0-9)	p=0.633 ^u
In situ component, n (%)			p=0.617 ^{x2}
Absent	35	4	
Present	64	10	
Microcalcification cluster, n (%)			p=0.11 ^{x2}
Absent	35	2	
Present	69	12	
Multifocality, n (%)			p=0.077 ^{x2}
Absent	7	3	
Present	92	11	
LVi, n (%)			p=0.804 ^{x2}
Absent	39	6	
Present	60	8	
Tumor necrosis, n (%)			p=0.597 ^{x2}
Absent	77	10	
Present	22	4	
ER, %, median, range	80 (0-100)	92.5 (0-100)	p=0.008 ^u
PR, %, median, range	4 (0-95)	70 (0-90)	p=0.004 ^u
HER2, n (%)			p=0.297 ^{x2}
0+	63	11	
1+	14	2	
2+	3	1	
3+	19	0	
Ki-67, %, median, range	12 (1-80)	6.5 (3-60)	p=0.117 ^u
Tumor fibrous area, mm ³ , median, range	23 (0.70-5292)	15 (1.79-200)	p=0.438 ^u
Lymph node neoadjuvant response, n (%)			p=0.065 ^{x2}
No response	26	4	
Partial response	62	6	
Partial-complete response	7	4	
Complete response	4	0	

SD: Standart deviation, ^{x2}: Pearson chi-square test, ^u: Mann-Whitney U test, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, HER2: Human epidermal growth factor-2



Variables	Sensitivity	Specificity	Area under curve	95% CI		Cut-off value	p-value
				Lower bound	Upper bound		
Estrogen receptor (ER)	50%	76.8%	0.718	0.578	0.858	92.5	0.008
Progesterone receptor (PR)	57.1%	69.7%	0.736	0.610	0.8.62	45	0.004

Figure 1. ROC curve analysis of ER and PR for neoadjuvant response residual diseases area
 ROC: Receiver operating characteristic, CI: Confidence interval

conserving surgery achieves oncologic outcomes and local control rates comparable to those after mastectomy. Patient preferences, however, tend to favor mastectomy, particularly in cases of locally advanced tumors prior to NACT. Despite significant reductions in tumor volume after NACT, factors such as initially large tumor size, multifocality, extent of residual disease, and the need for safe surgical margins frequently lead to choosing mastectomy over breast-conserving surgery. This pattern is also reflected in our data and consistently reported in the literature (6).

SLNB and ALND were performed in 31% (n=35) and 69% (n=78) of patients, respectively. This high rate of ALND may be associated with the prevalence of clinically node-positive disease and/or locally advanced tumors, and with the inclusion of patients treated through 2019.

In the OPBC-05/ICARO trial, following neoadjuvant therapy, the rate of additional axillary metastases in cases with isolated tumor cells during SLNB was approximately 11%, and routine ALND did not provide additional benefit in the presence of planned adjuvant radiotherapy (7). Similarly, in the MF18-02/MF18-03 NEOSENTITURK studies, selected patients achieving

clinical complete response after NACT with ypN+ status showed no significant differences in axillary or locoregional recurrence, or in 5-year disease-free survival and disease-specific survival, between SLNB and targeted axillary dissection groups (8). SLNB-based de-escalation strategies have been increasingly adopted in recent years, which partly explain the high ALND rates observed in our cohort. These findings should be interpreted in the context of evolving evidence and contemporary surgical practice.

Tumor response to NACT is not always reflected by a pCR; it is heterogeneous and cannot be fully captured by quantitative measures alone. The morphological features of treatment response provide additional insights into the underlying tumor biology. While the concept of residual cancer burden can partially quantify this heterogeneity, it does not capture the full spectrum of regression patterns as assessed morphologically (3).

In this study, we focused on a disease pattern frequently observed in clinical practice but less emphasized in the literature: residual invasive tumor foci within a fibrotic scar in the tumor bed. The morphology of residual disease may serve not only as an indicator of treatment response but also as a reflection of tumor biology. Notably, cases with a dispersed residual pattern showed

significantly higher expression of ER and PR (ER $p=0.008$; PR $p=0.004$); ER and PR values showed moderate discriminative performance in differentiating residual patterns (ER AUC=0.718; PR AUC=0.736). These findings suggest that the residual disease phenotype represents a biological trait in addition to its morphological characteristics. Due to the limited number and dispersion of cases, multivariable modeling was not performed to avoid overfitting.

It is well-established that hormone receptor-positive tumors generally have lower pCR rates following NACT, with responses often manifesting as partial regression accompanied by stromal remodeling or fibrosis. The lower pCR rates in luminal subtypes and the possibility of alternative biological mechanisms of response have been previously highlighted (5). In this context, a fibrotic scar-dominant response pattern-particularly observed in hormone receptor-positive tumors-may reflect a stromal remodeling process rather than purely cytotoxic eradication.

However, the lack of a statistically significant difference in Ki-67 proliferation index among the residual patterns suggests that proliferative activity alone may be insufficient to fully explain the spectrum of morphological responses. This observation indicates that treatment response is likely shaped by more intricate mechanisms, including stromal components, tumor microenvironment, immune infiltration, vascular alterations, and clonal selection of tumor cells. Therefore, our study underscores the need to consider not only receptor expression but also tumor microenvironment markers and stromal analyses in future translational research to achieve a comprehensive understanding.

An additional clinical implication of morphological heterogeneity is its role as a critical variable in assessing the extent of residual tumor, which is paramount to ensuring surgical margin safety and achieving effective local control. In their investigation of residual disease patterns following NACT, Pastorello and colleagues emphasized that response morphologies may be associated with distinct biological subtypes and highlighted the importance of these morphological features in surgical planning (4).

In our study, residual tumor was confined to a specific area within the fibrous scar substrate in 87.6% of cases, whereas 12.4% exhibited a more dispersed pattern. This heterogeneity represents a more challenging clinical scenario for assessing surgical margins and performing pathological sampling of the tumor bed. Another notable finding is the ROC performance of ER and PR expression for distinguishing residual patterns (ER AUC=0.718; PR AUC=0.736). Although these AUC values indicate only moderate discriminatory ability and the sensitivity of the proposed ER cut-off is limited, these findings should

be considered exploratory. They primarily suggest a potential association between hormone receptor expression and morphological response patterns, rather than establishing a clinically applicable predictive tool.

A dispersed pattern particularly increases the risk of discordance between post-neoadjuvant imaging and actual residual disease. Therefore, preoperative evaluation and surgical planning should interpret the tumor bed not only in terms of its overall size but also in terms of the distribution of treatment-induced structural changes. A more cautious approach is warranted to ensure safe surgical margins, and parameters that could guide the preoperative distribution of residual tumor should be incorporated into clinical decision-making.

Our study highlights that in cases exhibiting a residual response within a predominantly fibrotic scar matrix following NACT, the tumor's distribution pattern-not merely its volume-may independently influence surgical strategy. When a dispersed residual pattern is present, residual invasive tumor foci may be observed as small clusters or even single cells within extensive fibrotic areas. This can complicate clinical and radiological assessments, raising the possibility that, despite appearing "reduced" or "localized," residual disease may actually extend over a broader area than initially appreciated.

Consequently, preoperative assessment should adopt a comprehensive approach, incorporating not only the maximum tumor diameter but also the extent of fibrotic changes, the distribution pattern of microcalcifications, and detailed mapping of the tumor bed. In surgical planning, a more cautious approach-particularly in cases suspected to exhibit a dispersed pattern-may warrant wider excisions or enhanced margin control strategies to ensure complete removal. Similarly, in histopathological practice, meticulous and systematic sampling of the tumor bed is essential in cases with potential for a dispersed pattern, facilitating accurate evaluation of the true extent of residual invasive disease.

Study Limitations

The retrospective, single-center design of our study limits the generalizability of the results. Although the sample size represents a clinically meaningful cohort, the limited number of patients exhibiting a dispersed response pattern ($n=14$) may have diminished the statistical power of subgroup analyses and contributed to non-significant findings in some parameters. Nevertheless, the study's strengths include the large number of post-neoadjuvant therapy surgeries, the consistent application of criteria for identifying dispersed regression within fibrotic scar tissue, and the thorough re-examination of all pathological specimens.

Conclusion

This study elucidates that the fibrotic scar-dominant residual response observed within the tumor bed following NACT is not a uniform biological process and that the distribution pattern of residual invasive tumor may be associated with immunohistochemical characteristics. Notably, significantly higher expression of ER and PR in cases exhibiting a dispersed residual pattern suggests that this response modality may represent a distinct treatment phenotype linked to hormone receptor-positive biology.

These findings highlight the importance of evaluating not only the quantity of residual disease but also its distribution within the tumor bed and the associated stromal alterations. Such an approach is crucial for ensuring surgical margin safety, optimizing pathological sampling strategies, and accurately interpreting biological responses to therapy.

Validation of this integrative assessment-addressing both the morphological and biological heterogeneity of residual disease in larger patient cohorts and prospective studies could facilitate the development of more personalized, biology-driven decision-making frameworks in the post-neoadjuvant therapy setting.

Ethics

Ethics Committee Approval: The study protocol received approval from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval no: E-50687469-799-302082838, date: 03.02.2026).

Informed Consent: Retrospective, observational, single-center study.

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Footnotes

Authorship Contributions

Concept/Design: S.G., İ.B.B., Data Collection or Processing: S.G., Ö.K., Analysis or Interpretation: İ.B.B., M.T., M.A.G., Literature Review: Ö.K., M.T., M.A.G., Writing, Reviewing and Editing: S.G.

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