Original Article

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The Clinical and Pathological Characteristics That Differentiate Cases With "Low Estrogen Receptor Expression" From Triple-Negative Breast Cancer

Cem Karaali[1], Mümin Emiroğlu[2], Mustafa Değirmenci[3], Murat Keser[3], Semra Salimoğlu[1], Canan Kelten Talu[2]

[1]Department of General Surgery, İzmir Faculty of Medicine, University of Health Sciences Turkey, İzmir, Turkey
[2]Department of Medical Pathology, İzmir Faculty of Medicine, University of Health Sciences Turkey, İzmir, Turkey
[3]Department of Medical Oncology, İzmir Faculty of Medicine, University of Health Sciences Turkey, İzmir, Turkey

ABSTRACT

Objective: Estrogen receptor (ER) expression is an immunohistochemical marker that is examined in all invasive breast cancers and has prognostic and predictive value. ER-positive breast cancers refer to those that show positivity for ER at 1% cellular expression or higher. The American Society of Clinical Oncology/College of American Pathologists guidelines suggest using the term "low ER-positive breast cancer" for tumors with ER expression between 1% and 10%. Low ER-positive breast cancers exhibit similarities, in terms of disease-free survival and overall survival rates, to triple-negative breast cancers (TNBCs) rather than ER-positive breast cancers. In this study, our aim was to compare the clinicopathological characteristics of low ER-positive breast cancer cases diagnosed and followed in our clinic with TNBCs.

Materials and Methods: A total of 26 cases of low ER-positive breast cancer diagnosed at University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital between 2010 and 2016 were retrieved from hospital records. The relevant histopathology slides and blocks were retrieved and re-evaluated retrospectively through microscopic examination. Thirteen cases that met the criteria were included in the study. Additionally, a consecutive series of 13 TNBC cases that did not receive neoadjuvant treatment within the same time period were identified.

Results: In the low ER-positive group, the presence of tumor necrosis, as well as histological grade, nuclear grade and Ki-67 proliferation index were significantly lower compared to the TNBC group. Ductal carcinoma *in situ* (DCIS) was significantly more common in the low ER-positive group compared to the TNBC group. There were no significant differences between the two groups in terms of tumor size, histological tumor type, axillary lymph node involvement, tumor margins, peritumoral and intratumoral inflammation, local recurrence, distant metastasis, survival, and other characteristics.

Conclusion: Although our study consisted of a small number of cases, some features showed significant differences between low ER-positive breast cancers and TNBCs. Histological and nuclear grades, as well as the presence of a DCIS component, were associated with low ER-positive breast cancer. In contrast, the presence of tumor necrosis, as well as Grade 3 features and a high Ki-67 proliferation index indicated TNBC.

Keywords: Low ER-positive breast carcinoma; triple-negative breast carcinoma; histopathological findings; clinicopathological features; survival

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Key Points

- Preanalytical and analytical processes play a crucial role in accurately molecular classification of tissue samples containing breast cancer and directing patients to appropriate treatment. Proper handling of samples such as needle biopsies or excision materials is essential.
- Low estrogen receptor (ER)-positive breast cancer has lower histological grade, nuclear grade, and Ki-67 proliferation index compared to triple-negative breast cancer (TNBC).
- Low ER-positive cancers are less likely to have tumor necrosis and more likely to have a higher percentage of intraductal carcinoma component compared to TNBC.

Corresponding Author:
Cem Karaali; cemkaraali@gmail.com

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Introduction

In 2018, approximately 2.1 million new cases of breast cancer were reported worldwide in women, accounting for a quarter of all female cancer cases (1). Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in more than 100 countries worldwide (1). The incidence of breast cancer and cancer-related deaths are increasing in developing countries, including Turkey. According to data from the Ministry of Health in Turkey, the incidence of breast cancer was reported as 48.5 per 100,000 in 2015 (2). In European Union countries, the incidence of breast cancer was 142.8 per 100,000 in 2020 (3).

Estrogen receptor (ER) expression is a marker that should be immunohistochemically examined in all invasive breast cancers due to its prognostic and predictive value. ER-positive breast cancers refer to tumors that show positive staining for ER at 1% or higher using immunohistochemistry. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend the term "low ER-positive breast cancer" for invasive breast cancers with ER expression between 1% and 10% (Figure 1) (3-7). The term low receptor-positive is applicable only to invasive breast tumors and the level of ER receptor expression. It is not valid for progesterone receptor (PR) expression levels or *in situ* carcinoma foci (7). Studies have shown that low ER-positive breast cancer cases constitute a heterogeneous group and share similarities with triple-negative breast cancer (TNBC) rather than ER-positive breast cancer in terms of clinical, histopathological, and molecular characteristics (4).

In this study, our aim was to re-evaluate cases diagnosed with invasive breast carcinoma at our center, which were initially classified as low ER-positive based on immunohistochemical (IHC) examination and compare them with cases of TNBC, in order to highlight the differences between the two diagnostic groups.

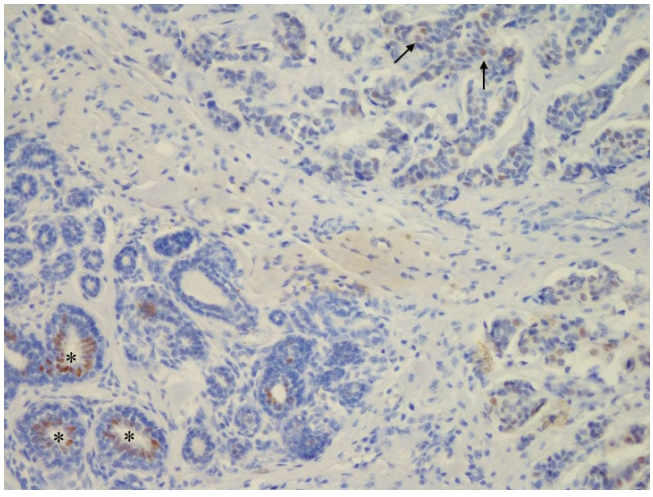

Figure 1. Low ER-positive breast cancer (ER immunohistochemistry, x200)

* Internal control: Presence of nuclear staining with ER in benign ductal luminal epithelial cells

→ Invasive tumor showing a small number of weakly intense nuclear staining with ER (between 1% and 10%)

ER: Estrogen receptor

Materials and Methods

Cases diagnosed with invasive breast carcinoma at University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pathology between 2010 and 2016 were identified. The ER and PR IHC staining profiles of these cases were checked, and a total of 26 cases that met the criteria for low ER positivity were identified. Hematoxylin and eosin (HE) and IHC stained slides (ER, PR, CerbB2, Ki-67) belonging to these cases were retrieved from the archive and re-evaluated. Histopathological features and clinical follow-up information from the cases were noted. During the re-evaluation, the ER expression level was assessed as <1% in 3 cases and >10% in 5 cases. HE-stained slides and paraffin blocks could not be retrieved from the archive for 3 cases, and 1 case was excluded due to receiving neoadjuvant chemotherapy, while 2 cases were excluded due to the absence of internal control in the ER and PR immunostains. Thus a total of 13 cases of low ER positivity were included in the study, all of which were Luminal-B molecular subtype. All cases with low ER positivity had breast-conserving surgery and adjuvant chemotherapy + radiotherapy + hormone therapy. For comparison, 13 consecutive TNBC cases, diagnosed within the same time period and without a history of neoadjuvant treatment, were identified. All TNBC cases had a history of breast-conserving surgery and adjuvant chemotherapy and radiotherapy. HE-stained slides and IHC stains of TNBC cases were retrieved from the archive and re-evaluated. Cases with negative ER and PR hormone expression in the invasive tumor, confirmed with internal control, were included in the study. Then, these two groups were compared in terms of tumor size, histological type, histological grade, nuclear grade, presence of lymph node metastasis, presence and severity of peritumoral/intratumoral inflammation, presence of extensive necrotic areas accompanying the tumor, presence of a ductal carcinoma *in situ* (DCIS) component, pattern of DCIS, percentage and intensity of ER staining, percentage and intensity of PR staining, CerbB2 staining score, Ki-67 proliferation index, local recurrence, distant metastasis, and survival parameters. The time from the initial diagnosis to death was evaluated as overall survival. The time from surgery to death or disease recurrence was evaluated as disease-free survival.

Statistical Analysis

Histopathological and clinical data were analyzed using SPSS, version 25 (IBM Inc., Armonk, NY, USA). Chi-square and Kaplan-Meier statistical methods were used for evaluation.

Results

Significant differences were observed between the two groups in terms of tumor necrosis, histological grade, nuclear grade, presence of DCIS component, and Ki-67 proliferation index (Table 1). In the low ER positive invasive breast carcinoma group, the presence of necrotic areas in the tumor was less common, and the histological grade and nuclear grade were lower (Grade 2). Although tumor metastasis in axillary lymph nodes was more common in the low ER positive group, this difference was not significant (p = 0.09).

There were no significant differences between the two groups in terms of patient age, tumor size, histological tumor type, presence and severity of peritumoral/intratumoral inflammation, pattern of DCIS, CerbB2 score, local recurrence, distant metastasis, overall survival, and disease-free survival.

Table 1. Clinicopathological features

	Low ER positive				**Triple negative**				***p*-value**
Age (Median)	53 (28-77 age)				49 (32-81 age)				
Tumor size (cm)	2.9				3.2				
Histological type	Ductal	Lobular	Ductal+lobular	Metaplastic	Ductal	Lobular	Ductal+lobular	Metaplastic	0.22
	12	0	1	0	10	0	0	3	
Nuclear grade	Grade 2		Grade 3		Grade 2		Grade 3		0.005
	7		6		0		13		
Histological grade	Grade 2		Grade 3		Grade 2		Grade 3		0.002
	8		5		0		13		
Peritumoral inflammation	Absent		Present		Absent		Present		1
	1		12		0		13		
Intensity of peritumoral inflammation	Absent	Mild	Moderate	Significant	Absent	Mild	Moderate	Significant	0.166
	1	5	5	2	0	2	4	7	
Intratumoral inflammation	Absent		Present		Absent		Present		0.48
	2		11		0		13		
Intensity of intratumoral inflammation	Absent	Mild	Moderate	Significant	Absent	Mild	Moderate	Significant	0.18
	2	5	5	1	0	4	4	5	
Necrosis	Absent		Present		Absent		Present		0.005
	10		3		2		11		
Presence of ductal carcinoma *in situ*	Absent		Present		Absent		Present		0.039
	8		5		12		1		
ER staining intensity	Negative	+	++	+++	Negative	+	++	+++	
	0	11	1	1	13	0	0	0	
PR staining intensity	Negative	+	++	+++	Negative	+	++	+++	
	9	2	1	1	13	0	0	0	
HER2 status*	Negative		Positive		Negative		Positive		
	7		6		13		0		
Ki-67 (mean)	36%				53%				0.036
Local recurrence	Absent		Present		Absent		Present		1
	12		1		13		0		
Lymph node metastasis	Absent		Present		Absent		Present		0.097
	2		11		7		6		
			N1: 8 N2: 0	N3: 3			N1: 5 N2: 0	N3: 1	
Distant metastasis	Absent		Present**		Absent		Present***		1

Table 1. Continued

	11	2	10	3	
Survive/exitus	Survive	Exitus	Survive	Exitus	
	9	4	10	3	
Disease-free survival	Mean	Median	Mean	Median	0.054
	96.6 month	101 month	78.7 month	97 month	
Overall survival	Mean	Median	Mean	Median	0.098
	104 month	102 month	83 month	98 month	

*HER2-negative group: Cases with an immunohistochemistry score of 0 or 1, and cases with a score of 2 but negative FISH result.
** Distant metastasis sites: One case in the liver and one case in the sacrum.
*** Distant metastasis sites: One case in the liver + brain; one case in the brain + lungs + abdominal wall; one case in bone + liver metastasis

Discussion and Conclusion

In this study, the group of patients with low ER-positive breast cancer was compared to a group of TNBC cases in terms of various clinicopathological features. It was found that the low ER-positive cases were associated with Grade 2 histological and nuclear characteristics, necrosis in the invasive tumor was less common, and there were lower levels of Ki-67 proliferation index. Although axillary lymph node metastasis, disease-free survival, and overall survival durations were higher in the low ER-positive group, these differences were not significant.

It is recommended to perform hormone receptor expression (ER, PR) and CerbB2 immunostaining in all newly diagnosed primary invasive breast carcinomas, as well as in recurrent or metastatic breast carcinomas (7, 8). In cases of multiple invasive breast tumors, immunostaining for ER, PR, and CerbB2 should be performed on the largest tumor. In the presence of multiple invasive tumor foci, if different histological types and higher grades are identified, these foci should also be separately evaluated for ER, PR, and CerbB2 staining. The aim of this practice is to identify possible expression differences among invasive tumors and determine the appropriate treatment regimen (7, 8). The ASCO and CAP guidelines highlight various pre-analytical and analytical factors that can affect the results of immunostaining in tissues (7). These factors include cold ischemia time, type of fixative, duration of tissue fixation, decalcification process, adequacy of tissue sample, and the clone of the primary antibody used (7, 9). Cold ischemia refers to the time from tissue removal to its placement in buffered formalin. If this time is unavoidably extended, the tissue sample can be stored in a refrigerator at +4 degrees Celsius for up to one hour (7, 9). The type of fixative is important in tissue fixation, and the use of buffered formalin is preferred. IHC stains should be evaluated in tumor foci that contain an adequate invasive tumor area. Foci with suspicious invasion or rare invasive tumor cells are not suitable for evaluation. In addition, if possible, FDA-approved and guideline-recommended clones of antibodies used for ER and PR immunostaining should be selected, and only nuclear staining should be considered. Epithelial cells in normal breast parenchyma carry ER and PR receptors, thus exhibiting varying degrees of nuclear staining. The presence of this staining in normal breast parenchyma serves as an "internal control" for evaluating staining in invasive tumor foci (7, 9). Factors that may lead to "false-negative" immunostaining results in tissues are briefly summarized in Table 2 (7). Knowing these factors and taking necessary precautions will ensure the accurate characterization of an invasive tumor as "ER-positive", "low ER-positive", or "ER-negative" and facilitate the correct guidance of treatment.

Table 2. Factors that may lead to "false ER negative" results in invasive breast carcinoma

Exposure of tumor cells to heat, such as during cautery
Prolonged cold ischemia time (causes a decrease in antigenic properties and reduces immunoreactivity)
Short or long fixation time (fixation time less than 6 hours or more than 72 hours reduces immunoreactivity)
Use of inappropriate fixatives (the use of buffered formalin is ideal. Acidic fixatives such as B5 or Bouin's solution are not suitable as they degrade ER)
Decalcification (reduces immunoreactivity)
Antibody clone used for ER (FDA-approved clones recommended by guidelines should be selected if possible)
Dark Hematoxylin background staining can obscure weak nuclear ER staining in tumor cells

ER: Estrogen receptor; FDA: Food and Drug Administration

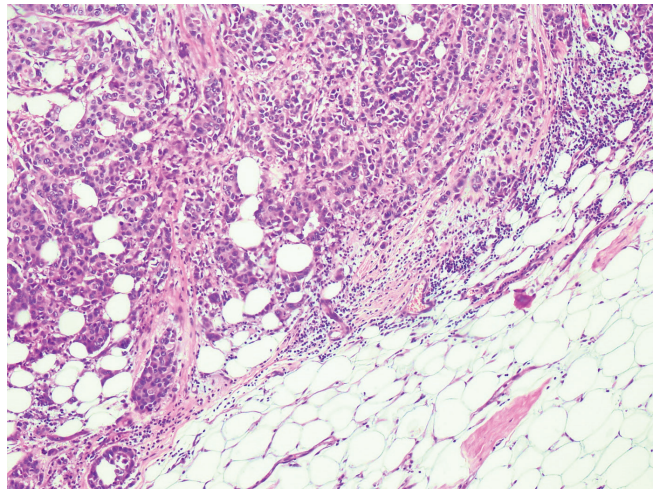

Figure 2. Invasive breast carcinoma (TNBC) showing a growth pattern characterized by solid islands of varying sizes, H&E x100

TNBC: Triple-negative breast cancer; H&E: Hematoxylin and eosin

Approximately 75–80% of invasive breast carcinomas are positive for ER and PR expression (7). Within this group, a small subset, around 2–3%, shows ER expression in 1 to 10% of tumor cells (9). The ASCO/CAP guidelines recommend reporting ER immunoreactivity between 1% and 10% as "low ER-positive". This suggested threshold represents the point at which patients derive clinical benefit from endocrine therapy. The success of hormone therapy in cases with weak nuclear staining intensity in the low ER-positive group remains controversial (6). Therefore, there is a need for studies investigating the relationship between ER staining intensity and hormone therapy.

Fei et al. (4) identified ER staining intensity as positive (+) in all 97 patients (100%) in their study on the low ER-positive group (3). In our study, we found ER staining intensity to be three positive (+++) in one case (7.7%), two positive (++) in one case (7.7%), and one positive (+) in the remaining eleven cases (84.6%) in the low ER-positive group. In the same study, Fei et al. (4) observed that the prognosis in the low ER-positive group was better than that in the TNBC group

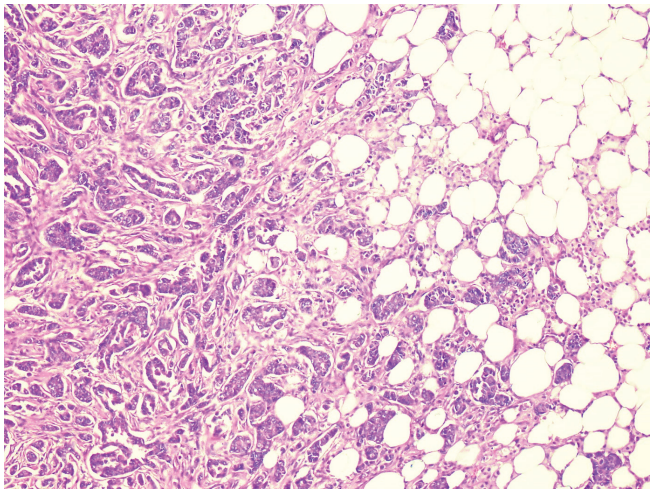

Figure 3. Invasive breast carcinoma (low-ER positive) displaying glandular structures, H&E x100

ER: Estrogen receptor; H&E: Hematoxylin and eosin

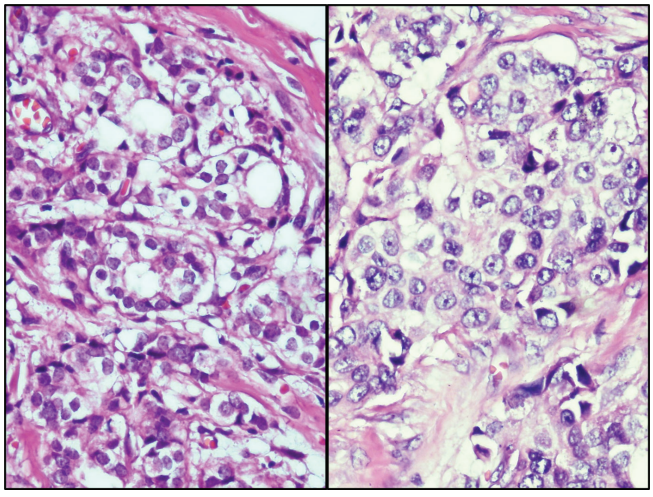

Figure 4. On the left side, tumor cells with round-oval nuclei and nuclear enlargement of moderate degree, showing nuclear grade 2 features (low ER-positive breast carcinoma); on the right side, tumor cells with large nuclei, prominent nucleoli, and nuclear grade 3 features (TNBC) (H&E x400)

TNBC: Triple-negative breast cancer; H&E: Hematoxylin and eosin

and emphasized the need for confirmation of this observation through larger cohort studies. In our study, although the difference between the two groups was not significant, disease-free survival and overall survival tended to be longer in the low ER-positive group compared to disease-free survival and overall survival in the TNBC group. In our cohort, we believe that the association between shorter survival and the TNBC group could be attributed to the higher histological and nuclear grades (Grade 3) (Figure 2), increased necrosis, and higher Ki-67 proliferation index in the TNBC group. Additionally, we observed a case of local recurrence in the low ER-positive group, while no recurrence was observed in the TNBC group. We speculate that the presence of extensive DCIS foci accompanying the invasive tumor in this recurrent case could be associated with local recurrence. Similarly, our more frequent detection of DCIS foci in the low ER-positive group may be associated with the lower Ki-67 proliferation exhibited by this group of tumors. In tumors with slower proliferation, it becomes easier to detect the tumor at the *in situ* stage. In our study, the mean Ki-67 proliferation index was 36% in low ER-positive breast carcinoma cases compared to 53% in the TNBC group (p = 0.036).

It has been reported that low ER-positive breast cancers show similarities with basal-like breast cancer or Human epidermal growth factor receptor 2-enriched breast carcinoma in molecular subtyping (3, 10). Low ER-positive breast cancers have been found to be less associated with Luminal B and Luminal A molecular subtypes (3).

In estrogen-positive tumors, the receptor activated by ER binds to target DNA and leads to changes in cellular gene expression, including PR. The expression levels of ER and PR determine the patient group that will receive endocrine therapy and are important predictors of the response to endocrine therapy. If the ER percentage threshold for deciding on treatment is lowered, more patients can receive the less toxic option of endocrine therapy. However, if patients in the low ER-positive group do not benefit from endocrine therapy, they may be exposed to unnecessary daily medication and the adverse effects of these treatments. Therefore, although the recommended threshold for hormone therapy in low ER-positive breast cancers is 1%, different clinics may choose different percentage levels (such as 5–10% and 20%) as the threshold for treatment (4). Molecular studies have suggested that chemotherapy may be more effective in these cases due to the small proportion of low ER-positive cases being luminal and the majority being basal-like molecular subtype (11). In a study by Gloyeske et al. (6), 90% of cases in the low ER-positive group were found to be negative for PR receptor. In our study, 69.2% of cases in the low ER-positive group were negative for PR receptor expression. The relationship between the response to hormone therapy in the low ER-positive group and PR levels may be suitable for further study.

Chen et al. (12) reported that in cases of low ER-positive breast carcinoma, the tumor size was smaller and the tumor was better differentiated compared to TNBC cases. Similarly, in the present study, the low ER-positive breast carcinoma group showed more nuclear and histological grade 2 characteristics, which were lower than those in the TNBC group (Figure 3). However, there was no significant difference in tumor size between the two groups. This could be due to the small number of cases in our study.

In a study conducted at MD Anderson Cancer Research Center, the incidence of *BRCA* germline mutations was investigated in 314 patients, and similar frequencies were found in the TNBC group (36.1%) and

the low ER-positive breast carcinoma group (39.5%) (13). In both groups, *BRCA1* germline mutation was reported more frequently than *BRCA2* mutation. Currently, the use of PARP inhibitors in treatment is determined by identifying the *BRCA1/2* germline mutation status in all recurrent or metastatic breast cancer cases (8). Therefore, the low ER-positive patient group should also be considered in terms of the frequency of *BRCA* germline mutations. In the present study, *BRCA1/2* mutation results were unavailable as the cases included in the study period have not yet been evaluated. Yoder et al. (14) compared the low ER-positive breast carcinoma group with the TNBC group and found no significant differences in clinical, demographic, germline *BRCA1/2* mutation prevalence, and chemotherapy use between the two groups. Additionally, they did not report any differences in disease-free survival and overall survival after a median follow-up period of 3 years. This study highlighted that although breast carcinomas showing low ER expression resemble TNBCs in terms of biological characteristics, they are deprived of current treatment options used in TNBC cases (such as immunotherapy) (14).

The predictive and prognostic characteristics of low ER-positive breast cancers have not yet been clearly defined. It is crucial to distinguish these patients from TNBC and obtain accurate clinicopathological data to select the appropriate patient group for hormone therapy. The importance of preanalytical processes, such as cold ischemia time, improper fixative use, or short or prolonged fixation, in determining the ER receptor expression level in breast cancer biopsy samples should be kept in mind. Factors that could negatively affect the process should be identified, and precautions should be taken. Additionally, correlation with tumor morphology should be established during IHC evaluation. In this study where we compared low ER-positive breast cancer cases with TNBC, we found that low ER-positive breast cancers were associated with histological and nuclear grade 2 features (Figure 4), less necrosis in invasive tumors, lower Ki-67 proliferation index, and more accompanying DCIS foci. The limitation of this study was the small number of cases. Further extensive case series are needed to identify low ER-positive breast cancers, which constitute a small proportion (2–3%) of invasive breast carcinomas and exhibit heterogeneous characteristics.

Ethics Committee Approval: Ethical approval has been obtained from the University of Health Sciences Turkey, Izmir Faculty of Medicine Tepecik Education and Research Hospital Ethics Committee (approval number: 2023/02-40, date: 08.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: C.K., S.S.; Design: C.K., C.K.T.; Data Collection and/or Processing: C.K., C.K.T.; Analysis and/or Interpretation: C.K., M.E., M.D., M.K., S.S., C.K.T.; Literature Search: C.K., M.D., M.K., C.K.T.; Writing: C.K., M.E., C.K.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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