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Radiological and Histopathological Predictors of Survival in Neuroendocrine Differentiated Breast Cancer: A Comparative Analysis with NS-IDC

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Purpose: This study aims to compare the radiological and immunohistochemical (IHC) features of neuroendocrine differentiated breast cancer (NEBC) with those of non-specific invasive ductal carcinoma (NS-IDC) and to examine the prognostic relevance of these features, including their association with overall survival (OS).

Patients and Methods: Patients with histopathologically confirmed NEBC between 2015 and 2022 were retrospectively identified. Inclusion criteria were availability of preoperative mammography, ultrasonography, and magnetic resonance imaging (MRI), along with complete clinical records; patients with missing data were excluded. A randomly selected NS-IDC cohort from the same institutional database served as the comparison group. Histopathology was the reference standard. Imaging was reassessed by two breast radiologists, and pathological specimens were reviewed by an experienced breast pathologist. Statistical analyses were performed using IBM SPSS 26.0, with significance set at $p < 0.05$.

Results: Eighty-five patients (44 NEBC, 41 NS-IDC) were included. Compared with NS-IDC, NEBC more frequently demonstrated rapid initial enhancement and late washout on MRI (p=0.001 and p=0.009, respectively), and higher progesterone reseptor (PR) expression (p=0.037). Five-year OS did not differ significantly between groups ($p = 0.858$). Multivariate analysis revealed that the presence of ductal carcinoma in situ (DCIS), T stage, and T2 hyperintensity on MRI emerged as independent predictors of mortality ($p = 0.006$, $p = 0.003$, and $p = 0.028$, respectively).

Conclusion: Although NEBC exhibits distinct MRI characteristics and a predominantly hormone-positive IHC profile, survival outcomes were comparable to those of NS-IDC. Notably, T2 hyperintensity on MRI was the strongest imaging feature associated with poorer survival, suggesting a potential role in future prognostic stratification. The modest sample size, prognostic interpretations should be viewed as exploratory. Larger prospective studies are needed to validate these findings.

Keywords: neuroendocrine carcinoma, breast cancer, magnetic resonance imaging, mammography, ultrasound, BIRADS

Introduction

Breast cancer is one of the most commonly diagnosed malignancies worldwide and, according to the latest GLOBOCAN 2022 estimates, it remains the leading cancer type in women, representing a substantial global health burden.[1] Neuroendocrine neoplasms of the breast constitute a rare and heterogeneous subset within this broad spectrum. All other subtypes, such as nonspecific invasive breast carcinoma, solid papillary carcinoma, or mucinous carcinoma, may share neuroendocrine features.[2]

Neuroendocrine breast tumors are normally diagnosed by the microscopic detection of neuroendocrine architecture in cancer cells and immunohistochemical (IHC) staining with neuroendocrine markers such as chromogranin A and synaptophysin. In 2019, the World Health Organization (WHO) revised the classification of NEBC to be similar to the

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classification of neuroendocrine carcinoma (NEC) in other organs, grouping it into large cell NEC, small cell NEC, and primary NEC.[3] NEC accounts for less than 1% of all breast cancers.[4] Focal neuroendocrine differentiation is more common in breast cancer, with a reported incidence ranging from 1% to 20% in the literature.[5] One of the reasons for this wide range is the lack of routine use of neuroendocrine markers such as chromogranin A and synaptophysin in the pathological evaluation of breast cancer.[6]

The imaging characteristics of NEC of the breast were first described by Wade et al. Due to its rarity as a breast carcinoma, there have been few studies to date examining the imaging characteristics and prognosis of these tumors.[7,8] Recent studies emphasize the growing role of imaging modalities, particularly mammography, ultrasonography (USG), and magnetic resonance imaging (MRI), in the detection and characterization of NEBC. MRI techniques, including dynamic contrast-enhanced sequences and T2-weighted imaging, have shown promise in highlighting tumor heterogeneity and in differentiating malignant subtypes. However, the diagnostic performance of imaging for NEBC remains incompletely understood, and standardized radiologic criteria are lacking.[9,10] There is still no consensus on the effect of NEBC on prognosis. The prognostic significance of neuroendocrine differentiation in breast cancer remains highly controversial. Earlier small-scale studies suggested similar or even more favorable outcomes compared to conventional IDC, whereas more recent population-based analyses report worse long-term survival, higher recurrence rates, and more aggressive biological behavior. In a review, Adams et al showed that the prognosis is generally quite favorable in small tumors and in the absence of nodal involvement.[8] The heterogeneity of diagnostic criteria, inconsistent application of IHC markers, and limited sample sizes have contributed to these conflicting findings. Moreover, studies evaluating the radiological correlates of prognosis in NEBC are extremely scarce. The potential of imaging biomarkers, such as MRI enhancement kinetics, shape descriptors, margin characteristics, and T2 hyperintensity, which may reflect tumor cellularity or necrosis, has not been systematically explored.

Given these limitations, there is a clear gap in the literature regarding the combined use of multimodality imaging, histopathology, and survival analysis to better characterize NEBC and its clinical behavior. Therefore, the aim of this study is to provide a comparative evaluation of NEBC and NS-IDC using multimodality imaging and histopathological assessment, and to determine which radiological and pathological features are associated with prognosis.

Materials and Methods

Patient Selection

In this study, patients diagnosed with histopathologically confirmed breast cancer in our hospital database between 2015 and 2023 were retrospectively screened. Histopathological confirmation through core needle biopsy or surgical specimen was required for all patients and served as the reference standard. A total of 44 patients showing neuroendocrine features, including two with primary NEC, were included in the NEBC group. For comparison, 41 patients with non-specific invasive ductal carcinoma (NS-IDC) were randomly selected from the year 2018, chosen to ensure consistent imaging protocols and reporting formats used during that calendar year.

Inclusion Criteria

- histopathologically confirmed NEBC or NS-IDC
- availability of preoperative mammography, USG, and MRI
- complete clinical, radiological, and pathological records

Exclusion Criteria

- absence of any of the three required preoperative imaging modalities
- recurrent breast cancer
- incomplete pathological documentation
- cases lacking adequate follow-up information
- benign lesions detected during initial radiological screening

Prior to commencement of the study, this study was performed following approval from the Ethics Committee of Izmir City Hospital, Turkey (Approval date: 02/26/2025 and number: 2025/103) the requirement for written informed consent has been waived and in compliance with the Declaration of Helsinki.

All radiological images were blinded and reviewed for pathological findings by two specialist physicians with 9 and 30 years of experience in breast radiology. Findings were evaluated according to the Breast Imaging Reporting and Data System (BI-RADS) 5th edition and consensus was reached.

Data Collection and Variables

Demographic, clinical, pathological, and imaging data were extracted from the hospital electronic medical record system and PACS. All data were compiled and organized in Microsoft Excel (Microsoft Corp.) prior to statistical analysis.

Imaging Technique

Standard craniocaudal and mediolateral oblique mammograms were obtained in all patients (Mammomat Revelation, Siemens, Erlangen, Germany). Sonographic examination was performed using a linear probe (Samsung trademark) with a frequency of 2.0–14.0 MHz. The evaluation was performed based on the image outputs, reports, and images recorded in our hospital database.

MRI was performed with a 1.5 Tesla MRI (Magnetom Aera, Siemens, Germany) using a 4-channel breast coil. Axial T1-weighted pre-contrast images and fat-suppressed T2-weighted images were obtained on all MRI scans. Diffusion-weighted images (DWI) were also obtained at b-values of 0, 500, and 1000 s/mm^2. Apparent diffusion coefficient (ADC) maps were automatically generated on the operating console with all three images and b-values of 0, 500, and 1000 s/mm^2. After intravenous injection of 0. 1 mmol/kg body weight gadolinium contrast (Gadoteric acid, Dotarem, Guerbet), 5 dynamic postcontrast fat suppressed T1 weighted images were obtained.

Histopathological Evaluation

All pathology specimens were blinded and re-evaluated for final results by a breast pathologist with 20 years of experience. The histological subtype of the tumor, estrogen receptor (ER), progesterone receptor (PR), status of both receptors, staining status for synaptophysin and chromogranin, Ki-67 value, histological grade, lymphovascular invasion (LVI), perineural invasion (PNI), and the presence of accompanying ductal carcinoma insitu (DCIS) were evaluated. Tumor cells were considered ER and PR positive and immunohistochemically stained (+3) when at least 1% of the tumor cells were stained. Cases with Her2 (+2) were examined by fluorescent in situ hybridization. Those showing focal staining with synaptophysin or chromogranin were defined as NEBC, while those showing diffuse staining were defined as NEC.

Oncological Evaluation

Clinical and treatment-related data, including age, menopausal status, comorbidities, tumor stage, nodal involvement, distant metastasis, surgical technique, chemotherapy, and endocrine therapy, were recorded. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition TNM system. Overall Survival (OS) was defined as the interval between histopathological diagnosis and death from any cause. Clinical, pathological, and imaging characteristics associated with 5-year OS were analyzed. Parameters affecting survival between groups were also examined.

Statistical Analysis

The IBM SPSS Statistics 26.0 software (IBM Corp., Armonk, NY, USA) was used for data analysis. The comparative analysis employed a two-sample t-test or Wilcoxon rank-sum test for continuous variables and a chi-squared test or Fisher's exact test for categorical variables. Survival analyses were performed using the Kaplan-Meier method, and differences between groups were evaluated using the Log rank test. Cox proportional hazards regression analyses were performed to evaluate predictors of OS. Variables for the Cox model were selected based on clinical relevance and univariate results. Multiple comparison correction was not applied due to the exploratory nature of the study. In all tests, the level of statistical significance was set at $p < 0.05$.

Results

Histopathological Findings A total of 85 patients (NEBC: 44, NS-IDC: 41) were evaluated in two groups. The mean age of patients was 61 ± 14 in the NEBC group and 56 ± 14 in the NS-IDC group. The most common type in the NEBC group was invasive ductal carcinoma at a rate of 70%. Immunohistochemically, most patients in both groups were ER or PR positive (NEBC: 96%, NS-IDC: 83%), and both were Her 2 negative (NEBC: 84%, NS-IDC: 86%). However, the mean PR value was significantly higher in the NEBC group compared to NS-IDC (median 75% vs 60%; median difference: 15%, 95% CI: 2–28%, p=0.037). ER positivity was high in both groups but numerically lower in NS-IDC. Ki-67 index tended to be higher in NS-IDC, consistent with a more proliferative phenotype, though not statistically significant. Detailed analysis is shown in Table 1.

Table 1 Histopathological Findings of NEBC and NS-IDC Groups

		NEBC (n=44)		**NS-IDC (n=41)**		**P value**
Age	Mean (SD)	61 ± 14		56 ± 14		0.136
Histological subtype	Invasive ductal carcinoma	31	70%	41	100%	**0.001**
	Mixed carcinoma	1	2%	0	0%	
	Mucinous carcinoma	6	14%	0	0%	
	Medullary carcinoma	1	2%	0	0%	
	Solid papillary carcinoma	3	7%	0	0%	
	Neuroendocrine carcinoma	2	5%	0	0%	
DCIS	Present	31	70%	26	63%	0.646
	Absent	13	30%	15	37%	
ER expression	Median (IQR), %	90 (80–93)		90 (70–100)		0.849
PR expression	Median (IQR), %	75 (25–90)		60 (10–80)		**0.037**
Molecular subtype	ER (+) / PR (+)	35	80%	29	71%	0.197
	ER (+) / PR (-)	1	2%	0	0%	
	ER/PR (-), Her 2 (+)	1	2%	1	2%	
	ER/PR (+), Her 2 (+)	6	14%	5	12%	
	Triple negative	1	2%	6	15%	
Ki-67 ratio	≤14%	14	32%	13	32%	0.991
	>14%	30	68%	28	68%	
Ki-67 ratio	Median (IQR), %	20 (11–30)		25 (12–40)		0.317
Her 2	Positive	15	34%	11	27%	0.468
	Negative	29	66%	30	73%	
Chromogranin	Positive	23	52%	0	0%	**<0.001**
	Negative	21	48%	41	100%	

(*Continued*)

Table 1 (Continued).

		NEBC (n=44)		NS-IDC (n=41)		P value
Synaptophysin	Positive	41	93%	0	0%	**<0.001**
	Negative	3	7%	41	100%	
Perineural invasion	Present	9	20%	9	22%	0.866
	Absent	35	80%	32	78%	
Lymphovascular invasion	Present	16	36%	18	44%	0.478
	Absent	28	64%	23	56%	
Histological Grade	Grade I	3	7%	5	12%	0.541
	Grade II	30	68%	23	56%	
	Grade III	11	25%	13	32%	

Note: Bold text indicates statistical significance at p<0.05.
Abbreviations: ER, Estrogen receptor; PR, Progesterone receptor; DCIS, Ductal carcinoma in situ; NEBC, Neuroendocrine differentiated breast cancer; NS-IDC, Non-specific invasive ductal carcinoma; SD, Standard deviation; IQR, Interquartile range.

Radiological Findings

The full imaging modality sample size is 85. Tumor sizes measured by all three imaging methods did not show significant differences between groups. Median tumor size on MRI was comparable (NEBC: 21 mm [IQR: 18–33] vs NS-IDC: 23 mm [IQR: 18–30]; median difference: −2 mm, 95% CI: −7–3 mm).

The proportion of irregularly shaped masses was higher in NEBC in both mammography (75% vs 63%; OR = 1.74, 95% CI: 0.74–4.10) and ultrasound (77% vs 76%; OR = 1.05, 95% CI: 0.39–2.84). But the round shape feature was more common in NS-IDC (15%) than in NEBC (2%) (p=0.030). Microlobulated margins (50%) were more common in the NEBC group, while spiculated margins (59%) were more prevalent in the NS-IDC group. Complex cystic and solid echo-patterning with hyperechoic lesions were seen only in NEBC. Mammography and ultrasound findings are presented in Tables 2 and 3, respectively.

Table 2 Mammographic Findings of NEBC and NS-IDC Groups

		NEBC (n=44)		NS-IDC (n=41)		P value
Diameter (mm, max, IQR)		20 (17–30)		20 (16–28)		0.606
Side	Right	29	66%	19	46%	**0.044**
	Left	15	34%	22	54%	
Nipple	Effected	11	25%	11	27%	0.847
	Normal	33	75%	30	73%	
Pattern	A	10	23%	9	22%	0.630
	B	20	45%	14	34%	
	C	9	20%	13	32%	
	D	5	11%	5	12%	

(*Continued*)

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Table 2 (Continued).

		NEBC (n=44)		NS-IDC (n=41)		P value
Shape	Round	3	7%	8	20%	0.216
	Oval	8	18%	7	17%	
	Irregular	33	75%	26	63%	
Asymmetry	Present	17	39%	21	51%	0.244
	Absent	27	61%	20	49%	
Distortion	Present	9	20%	10	24%	0.663
	Absent	35	80%	31	76%	
Margin	Circumscribed	2	5%	0	0%	**0.043**
	Obscured	4	9%	6	15%	
	Microlobulated	20	45%	10	24%	
	Indistinct	7	16%	6	15%	
	Spiculated	11	25%	19	46%	
Density	Low density	2	5%	0	0%	0.627
	Equal density	17	39%	16	39%	
	High density	25	57%	25	61%	
Calcifications	Microcalsification	7	16%	13	32%	0.100
	Macrocalsification	0	0%	1	2%	
	Absent	37	84%	27	66%	

Note: Bold text indicates statistical significance at p<0.05.
Abbreviations: NEBC, Neuroendocrine differentiated breast cancer; NS-IDC, Non-specific invasive ductal carcinoma; IQR, Interquartile range.

Table 3 Ultrasonographic Findings of NEBC and NS-IDC Groups

		NEBC (n=44)		NS-IDC (n=41)		P value
Diameter (mm, max, IQR)		23 (17–30)		21 (17–31)		0.871
Tissue composition	Homogeneous-fat	10	23%	10	24%	0.972
	Homogeneous-fibroglandular	29	66%	26	63%	
	Heterogeneous	5	11%	5	12%	
Shape	Round	1	2%	6	15%	**0.030**
	Oval	9	20%	4	10%	
	Irregular	34	77%	31	76%	

(*Continued*)

Table 3 (Continued).

		NEBC (n=44)		NS-IDC (n=41)		P value
Margin	Circumscribed	1	2%	0	0%	0.105
	Indistinct	3	7%	4	10%	
	Microlobulated	22	50%	13	32%	
	Spiculated	16	36%	24	59%	
	Microlobulated- Spiculated	2	5%	0	0%	
Orientation	Parallel to skin	11	25%	14	34%	0.492
	Not parallel	33	75%	27	66%	
Echo Pattern	Complex cystic and solid	4	9%	0	0%	**0.003**
	Hypoechoic	21	48%	14	34%	
	Hyperechoic	3	7%	0	0%	
	Heterogeneous	14	32%	27	66%	
	Complex- Hypoechoic	2	5%	0	0%	
Posterior features	No posterior features	26	59%	20	49%	0.510
	Enhancement	1	2%	0	0%	
	Shadowing	8	18%	12	29%	
	Combined pattern	9	20%	9	22%	
Surrounding tissue changes	Present	16	36%	23	56%	**0.038**
	Absent	28	64%	18	44%	

Note: Bold text indicates statistical significance at p<0.05.
Abbreviations: NEBC, Neuroendocrine differentiated breast cancer; NS-IDC, Non-specific invasive ductal carcinoma; IQR, Interquartile range.

MRI features revealed some significant differences between groups. The irregular shape feature was statistically significantly more common in the NEBC group compared to the NS-IDC group (89% vs 68%; OR = 3.76, 95% CI: 1.23–11.45, p=0.041). Similar to USG, the round (17%) and oval (15%) shape features were more frequently observed in NS-IDC. Microlobulated margin (61% vs 22%; OR = 5.54, 95% CI: 2.16–14.26) was more common in NEBC, while spiculated borders (71%) were more prevalent in NS-IDC (Figures 1 and 2). Rapid initial enhancement (84% vs 41%; $p = 0.001$) and washout more common in NEBC (57% vs 27%; OR = 3.53, 95% CI: 1.44–8.67). MRI findings are presented in Table 4.

Oncological Findings and Survival Analysis

At diagnosis, 80% of the NEBC group and 61% of the NS-IDC group were stage 1–2 (AJCC 8th edition). No cases met diagnostic criteria for inflammatory breast cancer. During the five-year follow-up period, metastasis developed in 7 of 85 patients (8.2%). The median time to metastasis was 23.3 months, with the earliest metastasis occurring at 9 months and the latest at 46 months. A detailed analysis of the oncological evaluation is provided in Table 5.

During follow-up, 16% of patients (7/44) in the NEBC group and 15% (6/41) in the NS-IDC group died. The median survival was 54.6 (95% CI: 50.5–58.7) in the NEBC group and 54.9 (95% CI: 51.1–58.8) in the NS-IDC group. The hazard ratio (HR) in the NS-IDC group compared to the NEBC group was 0.91 (0.30–2.69) (95% CI: 0.30–2.69), indicating no statistically significant difference in risk between the groups (Figure 3).

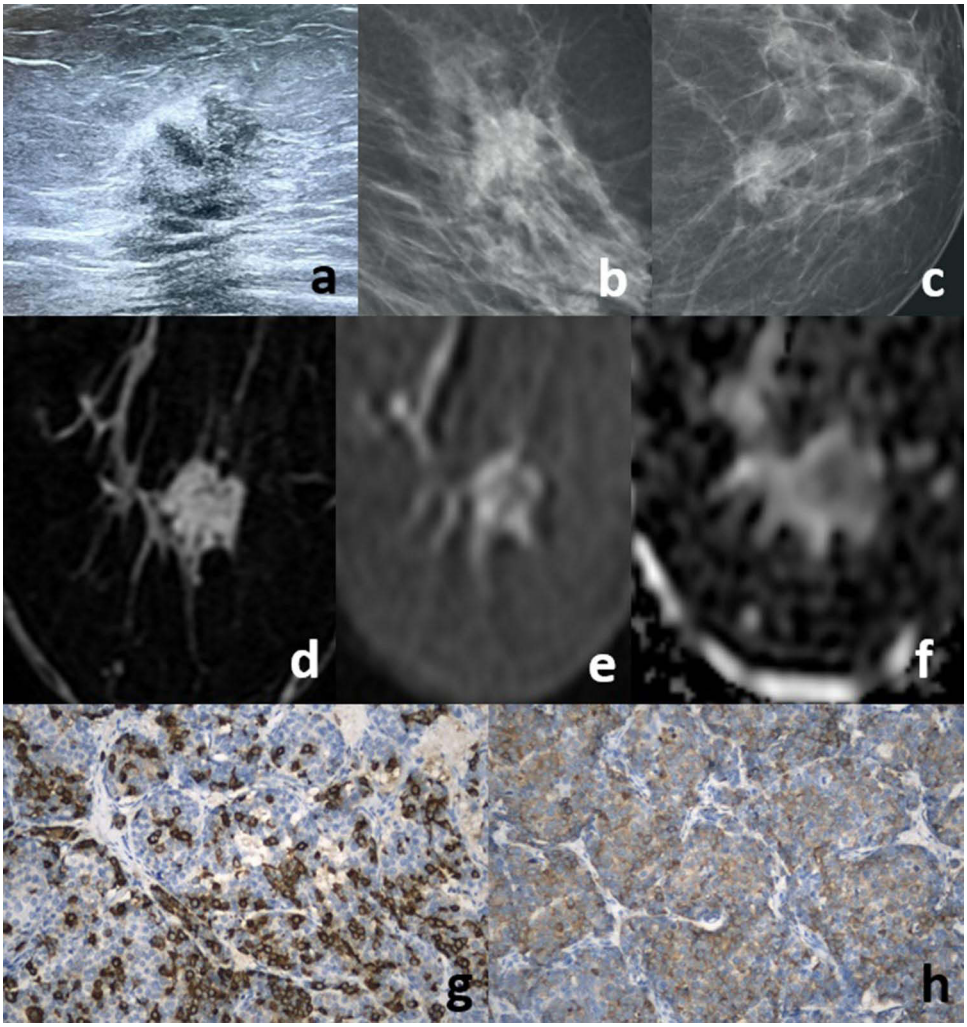

Figure 1 Please separate the text descriptions for panels b-c. Each panel should be described separately Histopathologically diagnosed as neuroendocrine-differentiated breast cancer, the lesion demonstrates an irregular shape, microlobulated margins, and posterior acoustic shadowing on ultrasound (**a**); and partially indistinct margins and microlobulated density on mammography in the mediolateral oblique view (**b**) and craniocaudal view (**c**). Magnetic resonance imaging (**d**) shows a microlobulated, heterogeneously enhanced mass on T1-weighted images and peripheral diffusion restriction on diffusion-weighted images (**e**) with low ADC values (**f**). Immunohistochemistry (IHC) demonstrated positivity for chromogranin (**g**) and synaptophysin (**h**) in tumor cells.

When comparing data from the deceased patients and the living patients, in NEBC cases, the ER expression percentage was found to be higher in the living patients (median=90, interquartile range [IQR]=80-97.5) than in the deceased patients (median=80, IQR=45-90) (U = 85.50, p = 0.036). The PR expression percentage was also higher in survivors (median=80, IQR=30-90) than in non-survivors (median=60, IQR=10-90) (U = 103.0, p = 0.042).

In NS-IDC cases, the maximum ultrasonographic tumor size was significantly larger in those who died (median = 38 mm, IQR=19.5–58.5) than in survivors (median = 20 mm, IQR=17-30) (U = 158.50, p = 0.047). ADC values were significantly higher in survivors (median = 748, IQR = 645–880) than in those who died (median = 635, IQR = 595–830) (U = 65.50, p = 0.048).

Cox Regression Analysis

Univariate Cox regression analyses were performed to evaluate factors associated with survival without group stratification. The type of surgery was found to have a significant effect on survival. In comparisons using BCS+ SLNB as the reference, mastectomy + SLNB, MRM, and non-operated patients were found to be significantly associated with a higher risk of mortality. The presence of DCIS was significantly associated with a higher risk of death compared to its absence (p = 0.028). In comparisons based on hormone receptor and Her-2 status, only triple-negative tumors showed a significantly higher risk

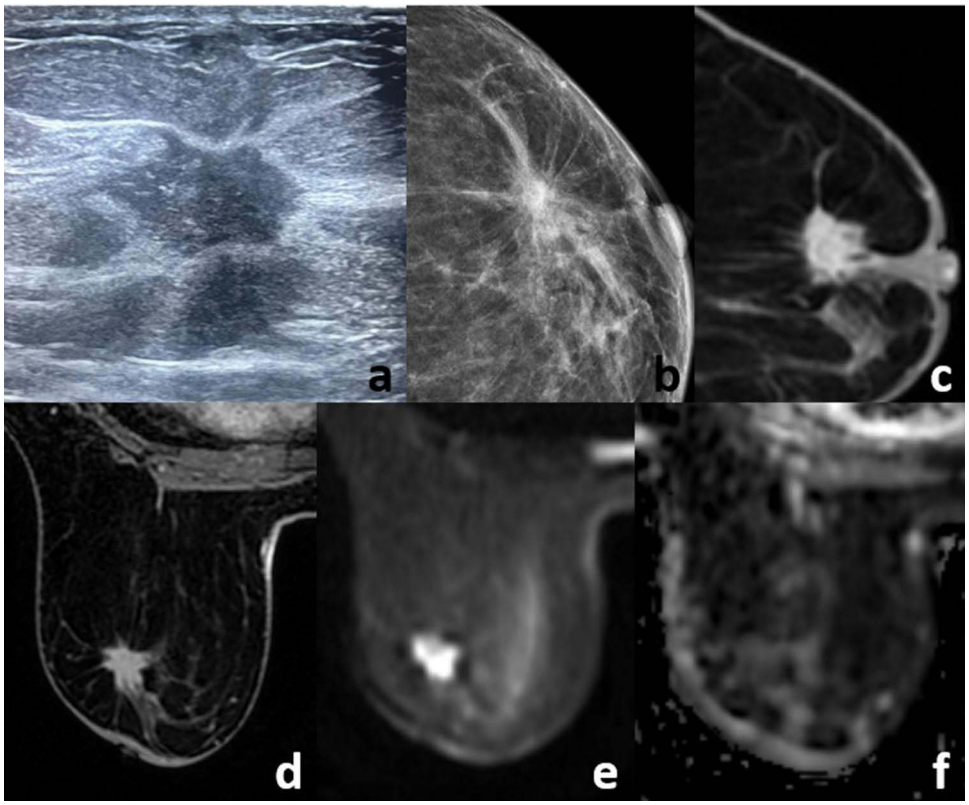

Figure 2 The lesion diagnosed histopathologically as invasive ductal breast cancer of nonspecific type shows a spiculated margin on ultrasound (**a**) and an irregularly shaped, spiculated density on mammography (**b**). Magnetic resonance imaging shows a spiculated, irregularly shaped, homogeneously enhanced mass on T1-weighted sagittal (**c**) and axial (**d**) images, and diffusion-weighted imaging reveals marked diffusion restriction (**e**) with low ADC values (**f**).

compared to the ER(+)/PR(+) group (p = 0.030). ER positivity also significantly reduced the risk of mortality (p = 0.022). In terms of T status, T1 tumors showed a significantly lower risk compared to others (p = 0.028). Among USG, mammography, and MRI features, only T2 signal was associated with survival, and T2 hyperintense lesions were found to be associated with a significantly increased risk of death (p = 0.010).

Table 4 Magnetic Resonance Imaging Findings of NEBC and NS-IDC Groups

		NEBC (n=44)		**NS-IDC (n=41)**		**P value**
Diameter (mm, max, IQR)		21 (18–33)		23 (18–30)		0.864
Shape	Round	1	2%	7	17%	**0.036**
	Oval	4	9%	6	15%	
	Irregular	39	89%	28	68%	
Margin	Circumscribed	2	5%	0	0%	**0.001**
	Microlobulated	27	61%	9	22%	
	Indistinct	4	9%	3	7%	
	Spiculated	11	25%	29	71%	

(*Continued*)

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Table 4 (Continued).

		NEBC (n=44)		NS-IDC (n=41)		P value
T1 Signal	Isointense	37	84%	35	85%	**0.027**
	Hypointense	6	14%	1	2%	
	Hyperintense	1	2%	5	12%	
T2 Signal	Isointense	17	39%	26	63%	**0.041**
	Hypointense	6	14%	3	7%	
	Hyperintense	21	48%	12	29%	
Enhancement pattern	Homogeneous	4	9%	1	2%	**0.040**
	Dark internal septations	4	9%	0	0%	
	Heterogeneous	36	82%	40	98%	
Initial Phase	Slow	1	2%	2	5%	**0.001**
	Medium	6	14%	22	54%	
	Rapid	37	84%	17	41%	
Late Phase	Persistent	0	0%	1	2%	**0.009**
	Plateau	19	43%	29	71%	
	Wash out	25	57%	11	27%	
Diffusion restriction	Present	42	95%	35	85%	0.222
	Absent	2	5%	6	15%	
BPE	Minimal	18	41%	16	39%	0.196
	Mild	16	36%	14	34%	
	Moderate	9	20%	5	12%	
	Marked	1	2%	6	15%	
Satellite	Present	18	41%	21	51%	0.340
	Absent	26	59%	20	49%	
Lymphadenopathy (Radiological)	Present	19	43%	20	49%	0.605
	Absent	25	57%	21	51%	
Multifocality	Present	11	25%	13	32%	0.492
	Absent	33	75%	28	68%	

Note: Bold text indicates statistical significance at p<0.05.
Abbreviations: BPE, Background parenchymal enhancement; NEBC, Neuroendocrine differentiated breast cancer; NS-IDC, Non-specific invasive ductal carcinoma; IQR, Interquartile range.

According to multivariate Cox analysis, the presence of DCIS, T status at diagnosis, and T2 characteristics on MRI significantly predicted survival (p = 0.006, p = 0.003, p = 0.028, respectively) (Table 6). T2 hyperintensity (HR 8.66) is highlighted as the strongest radiological predictor of OS.

Table 5 Clinical and Oncological Findings of NEBC and NS-IDC Groups. Categorized According to the TNM Classification American Joint Committee on Cancer (AJCC) 8th Edition

		NEBC (n=44)		NS-IDC (n=41)		P value
Comorbidity	Present	17	39%	15	37%	0.845
	Absent	27	61%	26	63%	
Menopausal status	Premenopause	12	27%	10	24%	**0.040**
	Perimenopause	2	5%	7	17%	
	Postmenopause	30	68%	24	59%	
T status (diagnosis)	T1	15	34%	13	32%	0.968
	T2	26	59%	26	63%	
	T3	2	5%	1	2%	
	T4	1	2%	1	2%	
N status (diagnosis)	N0	19	43%	12	29%	0.309
	N1	20	45%	21	51%	
	N2	2	5%	6	15%	
	N3	3	7%	2	5%	
Stage (diagnosis)	Stage I	9	20%	8	20%	**0.047**
	Stage II	26	59%	17	41%	
	Stage III	6	14%	15	37%	
	Stage IV	3	7%	1	2%	
M status (diagnosis)	M0	41	93%	39	95%	1.000
	M1	3	7%	2	5%	
Operation type	BCS+SLNB	24	55%	31	76%	**0.031**
	BCS+ALND	2	5%	0	0%	
	Mastectomy+ SLNB	6	14%	3	7%	
	MRM	8	18%	7	17%	
	Not operated	4	9%	0	0%	
Chemotherapy	Receive	30	68%	33	80%	0.196
	Not receive	14	32%	8	20%	
Endocrine therapy	Receive	40	91%	34	83%	0.273
	Not receive	4	9%	7	17%	
Metastasis	Present	3	7%	4	10%	0.922
	Absent	41	93%	37	90%	

(*Continued*)

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Table 5 (Continued).

		NEBC (n=44)		NS-IDC (n=41)		P value
Metastasis site	Bone	0	0%	3	75%	0.227
	Visceral	2	66%	1	25%	
	Cranial	1	33%	0	0%	
Survival	Alive	37	84%	35	85%	0.871
	Dead	7	16%	6	15%	

Note: Bold text indicates statistical significance at p<0.05.
Abbreviations: T, Tumour; N, Node; BCS, Breast conserving surgery; MRM, Modified radical mastectomy; SLNB, Sentinel lymph node biopsy; ALND, Axillary lymph node dissection.

Discussion

In our study, the radiological, pathological, and oncological data of breast tumors exhibiting neuroendocrine features were compared with those of non-specific type ductal carcinoma of the breast. Compared to NS-IDC, the NEBC group was found to have more irregularly shaped and microlobulated contours on MRI and showed rapidly contrast enhancement in the initial phase and washout in the late phase on dynamic imaging. Both groups were generally ER/PR positive, Her2 negative, and had tumors with a Ki-67 value greater than 14%, often accompanied by DCIS. In our study, the PR value was statistically significantly higher in the NEBC group (p=0.037). No significant differences were found between the groups in overall survival rates. In our study, among patients who were alive at follow-up, ER and PR were lower in the NEBC group compared to the NS-IDC group (p=0.061, p=0.042, respectively), and the size measured by ultrasound was larger and ADC values were lower in the NS-IDC group (p=0.047, p=0.042, respectively). Surgical type, presence of DCIS, molecular subtype, T status, and T2 hyperintensity on MRI were factors associated with overall survival regardless of group.

There are not many studies describing the radiological features of NEBC. In one of the largest series, a study of 87 patients with NEBC by Park et al,[11] mass lesions were generally irregular in shape and had indistinct borders, similar to

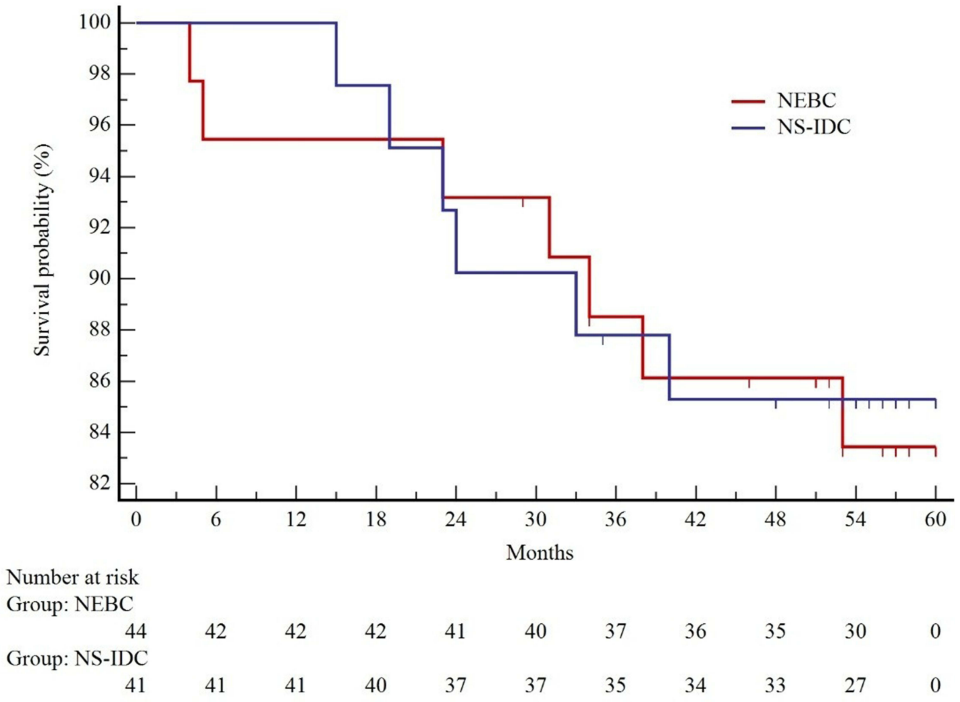

Figure 3 Overall survival analysis of NEBC and NS-IDC groups by Kaplan-Meier method. No statistically significant difference was observed (p = 0.858, Log rank test).

Table 6 Results of Univariate and Multivariate Cox Regression Analysis

	Univariate			Multivariate		
	HR (Exp(B))	**95% CI for HR**	**p**	**HR (Exp(B))**	**95% CI for HR**	**p**
ER positivity (%)	0.984	[0.971–0.998]	**0.022**	NS		
Ultrasonographic size (max, mm)	1.028	[1.001–1.057]	**0.043**	NS		
DCIS (Yes vs No)	3.494	1.142–10.692	**0.028**	13.973	[2.093–93.288]	**0.006**
Molecular subtype						
Triple negative vs ER(+)/PR(+)	4.381	[1.157–16.584]	**0.030**	NS		
ER(+)/PR(-) vs ER(+)/PR(+)	0.000	[0.000–00.000]	0.995	NS		
Her 2(+) vs ER(+)/PR(+)	1.537	[0.326–7.241]	0.587	NS		
Operation type						
BCS+SLNB	~0	—	0.987	NS		
BCS+ALND	6.812	1.374–33.778	**0.019**	NS		
Mastectomy+ SLNB	7.082	1.691–29.661	**0.007**	NS		
MRM	12.096	2.018–72.491	**0.006**	NS		
T stage (diagnosis)						**0.028**
• T1 vs T2	1.272	[0.329–4.921]	0.727	0.068	[0.001–0.935]	**0.044**
• T1 vs T3	10.713	[1.771–64.817]	**0.010**	0.237	[0.005–12.104]	0.473
• T1 vs T4	4.544	[0.472–43.750]	0.190	0.001	[0.001–0.127]	**0.010**
T2 signal				–	–	**0.003**
• Hypo vs isointense	2.531	[0.229–27.925]	0.448	0.001	[0.001–0.284]	**0.021**
• Hyper vs isointense	7.400	[1.620–33.794]	**0.010**	8.66	[1.39–54.01]	**0.021**

Note: Bold text indicates statistical significance at p<0.05.

Abbreviations: ER, Estrogen receptor; PR, Progesterone receptor; DCIS, Ductal carcinoma in situ; CI, Confidence Interval; HR, Hazard Ratio; BCS, Breast conserving surgery; MRM, Modified radical mastectomy; SLNB, Sentinel lymph node biopsy; ALND, Axillary lymph node dissection.

our study. Although the imaging findings of NEBC are not specific, similar to our study, they have been described as ill-defined, irregularly shaped, high-density masses on mammography and heterogeneous hypoechoic solid masses on ultrasound, rarely accompanied by cystic components.[7,11–13] The most common findings on MRI have been reported as a heterogeneous contrast pattern, early contrast enhancement in dynamic studies, washout in the late phase, and diffusion restriction.[2,11–14] Contrary to the literature, in a study by Kayadibi and colleagues[14] comparing neuroendocrine differentiated tumors with those without neuroendocrine differentiation, NEBCs were found to be more oval-round in shape and have better-defined contours. Similar to our study, this study also showed that NEBCs mostly exhibited diffusion restriction and washout in the late phase of dynamic imaging. Additionally, the rates of axillary lymph node metastasis vary in the literature and were found to be 43% in our study. Similarly, in the study by Park et al,[11] the rate was 47%, in the study by Krawczyk et al[15] it was 37%.

Among the imaging findings, T2 signal characteristics on MRI were the only parameter associated with survival. The finding that T2 hyperintense lesions were associated with a higher risk of death suggests that these tumors may correspond to biologically more aggressive subtypes. Previous studies have also reported that T2 hyperintensity is associated with tumor necrosis and high proliferative activity.[16,17] Due to the limited number of patients, these findings are exploratory and hypothesis-generating. This radiological signature warrants further investigation as a potential prognostic imaging biomarker in NEBC. These radiological

findings are corroborated by other studies in the literature we reviewed and support the reliability of our dataset despite the rarity of NEBC. The integration of three imaging modalities further strengthens the descriptive component of this study and contributes to the comparative data that is still scarce in the literature.

Although NEBC is most commonly associated with ductal carcinoma, it has also been reported in association with medullary, lobular carcinoma, signet ring cell carcinoma, and mixed breast carcinoma.[2,11,14–20] In our series, the most common association was with ductal carcinoma (70%), followed by mucinous carcinoma (14%). In the literature, which is similar to our study, most NEBCs are defined as ER/PR positive, Her2 negative, and Ki-67 values >14%.[2,7,14,15,20–22] Furthermore, in our study, the percentage of PR expression was statistically significantly higher in the NEBC group compared to NS-IDC (p=0.037). Although PR positivity is commonly reported in this patient group, a comparative analysis of its value has not been previously discussed in the literature. In our study, ER and PR percentages had an effect on OS in NEBC cases compared to NS-IDC cases. This suggests that tumors with hormone-positive characteristics may respond better to endocrine therapy.[18,23,24]

The radiological findings in NEBC appear to parallel its pathological profile. Irregular morphology and washout patterns may correspond to increased angiogenesis, while T2 hyperintensity may relate to microenvironmental changes driven by neuroendocrine differentiation. The higher PR expression observed in NEBC could partially explain the similar survival outcomes between NEBC and NS-IDC, despite imaging markers that may suggest aggressive behavior. Although our sample size limits deeper modeling, the convergence of radiologic and pathologic features offers a plausible biological interpretation that merits further study.

The presence of DCIS has been found to be an independent factor negatively affecting survival. Although DCIS is generally associated with a better prognosis,[25] its association with increased mortality risk in our study suggests that it may be related to the presence of an accompanying invasive component or high nuclear grade in the cases. This finding is noteworthy in that it demonstrates the biological heterogeneity of DCIS and that it does not always have a benign course.

There are some controversial studies regarding the effects of neuroendocrine differentiation on prognosis in breast cancer. Previous studies with smaller patient numbers have shown that lesions with neuroendocrine differentiation do not exhibit a significant difference in prognosis compared with other invasive breast cancers lacking this feature,[26–28] while some studies have shown a better prognosis.[27,29] However, more recent literature has found that these tumors have a poor prognosis on long-term follow-up and are prone to local and distant recurrences.[15,20,28–30] A population-based study by Wang et al, obtained from the SEER database, showed that overall survival and disease-specific survival are significantly shorter in NEBC compared with non-NEBCs of the same stage.[30] In our study, no significant difference was found in OS and metastasis intervals between the NEBC and NS-IDC patient groups, and their prognoses were found to be similar. It was noted that the NEBC group (80%) was more likely to be diagnosed at an early stage at diagnosis than the NS-IDC group (61%).

The effect of the surgical approach on survival was found to be significant, consistent with the literature. The observation of better survival in patients who underwent BCS+ SLNB supports the high oncological safety of BCS in appropriately selected patient groups.[31,32]

Our study has certain limitations; its single-center retrospective design limits its generalizability. The relatively small sample size limits the statistical robustness of survival analyses, particularly multivariate models. Therefore, prognostic relationships should be considered preliminary. While NEBC cases span several years, the NS-IDC comparison cohort was obtained from the same single year to ensure consistency in imaging protocols and reporting. Differences in technology or clinical practice may affect comparability. The lack of routine use of neuroendocrine markers in pathology practice may not accurately reflect the number of NEBC cases and may lead to bias in patient selection. Furthermore, as genomic profiling was not available, it was not possible to evaluate the molecular differences underlying imaging phenotypes or clinical outcomes.

Our study is the only one in the literature that retrospectively evaluates the imaging characteristics of all patients in both groups (with and without neuroendocrine differentiation) using three modalities and examines their treatments and 5-year OS status. Furthermore, there is no other study in the literature investigating imaging characteristics associated with survival in NEBC. In terms of lesion count, it is the third most comprehensive study after those by Park et al and Kayadibi et al.[11,14]

Conclusion

In conclusion, when evaluated using multiple imaging modalities, NEBCs are more irregularly shaped masses with microlobulated margins compared to NS-IDCs and show heterogeneous contrast enhancement on MRI; contrast enhancement is seen in the

early phase, while washout is seen in the late phase. Histologically, they are mostly ER/PR positive and Her-2 negative. Treatment is similar to that currently used for nonspecific breast cancers. Although overall survival is similar between groups, MR T2 hyperintensity has emerged as a discovery marker associated with poorer outcomes. Given the limited number of cases and the heterogeneity of NEBC, these findings should be interpreted as hypothesis-generating rather than definitive. The multimodality imaging approach used in this study provides valuable descriptive data for this rare tumor type and highlights the potential role of MR features in future prognostic research. More extensive, multicenter, and molecularly integrated studies are needed to validate these observations and clarify how imaging biomarkers can aid the clinical decision-making process in NEBC.

Abbreviations

IHC, Immunohistochemical; WHO, World Health Organisation; NEBC, Neuroendocrine differentiated breast carcinoma; NEC, Neuroendocrine carcinoma; NS-IDC, Non-specific type invasive ductal carcinoma; MRI, Magnetic resonance imaging; BI-RADS, Breast Imaging Reporting and Data System; DWI, Diffusion-weighted images; ADC, Apparent diffusion coefficient; LVI, Lymphovascular invasion; PNI, Perineural invasion; DCIS, ductal carcinoma in situ; ER, Estrogen receptor; PR, Progesterone receptor; AJCC, American Joint Committee on Cancer; OS, Overall survival; CI, Confidence intervals; USG, Ultrasonography; MRM, Modified radical mastectomy; SLNB, Sentinel lymph node biopsy; BCS, Breast-conserving surgery; HR, Hazard ratio; IQR, Interquartile range.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Declarations

The Ethics Committee of Izmir City Hospital waived the requirement for informed consent because the study was retrospective in nature, involved no direct patient contact, and used anonymized medical data that pose minimal risk to participants. All patient records were handled in compliance with institutional data-protection standards, and no identifiable information was included in the analysis. All procedures involving human participants in this study were performed in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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