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Predictors for axillary lymph node metastasis in primary neuroendocrine carcinomas of the breast and neuroendocrine differentiated breast cancers

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ABSTRACT

Aims: Primary neuroendocrine carcinomas of the breast (NEC) and neuroendocrine differentiated breast cancers are rare entities. The aim of this study was to investigate clinical and histopathological findings and predictors for axillary lymph node metastasis (ALNM) in primary neuroendocrine carcinomas of the breast (NEC) and neuroendocrine differentiated breast cancers (NEBC).

Methods: Patients with a diagnosis of breast cancer with histopathological neuroendocrine features between the years 2015 and 2022 were retrospectively screened. The patients were divided into two main groups, the NEC and NEBC groups. The two groups were evaluated in terms of their clinical and histopathological characteristics and predictive factors for axillary lymph node.

Results: A total of 35 patients [NEBC group: 24 patients, NEC group: 11 patients) were evaluated. At the time of diagnosis, the median age was 57 (NEC: 49 years, NEBC: 57.5). Of the 35 patients, 15 (57.1%) had ALNM, and lymphovascular invasion was detected in 16 (45.7%). When the whole patient population was evaluated for ALNM, it was found that lymphovascular invasion had an effect on ALNM (p=0.005). In the NEBC group, the rate of ALNM was associated with an increase in tumor diameter (p=0.035). Additionally, the tumor diameter was found to be predictive of ALNM in the ROC analysis (AUC: 0.753, 95% CI: 0.557-0.950, cut-off: 2.35 cm, p=0.035). Analyses of correlation revealed a low-level correlation between age and Ki-67 in the study cohort (ρ= -0.341, p=0.45).

Conclusion: NECs and NEBCs of the breast are uncommon tumors with a high ALNM potential. Patients with lymphovascular invasion and a large tumor diameter should be carefully evaluated for ALNM. Further research is required to determine the most appropriate treatment strategy for these rare subtypes of breast cancers.

Keywords: Neuroendocrine, breast cancer, axillary lymph node metastasis, nodal status

INTRODUCTION

Neuroendocrine tumors originates from submucosal neuroendocrine cells in the gastrointestinal tract and lungs. They are categorized as high-grade tumors with metastasis potential.[1,2]

Neuroendocrine breast tumors are rare tumors. Neuroendocrine breast tumors are detected by immunohistochemical staining with neuroendocrine markers (chromogranin A, synaptophysin, insulinoma-associated protein 1, neuron-specific enolase, and CD56). Neuroendocrine carcinoma of the breast (NEC) was first described in 1963. It was included in the World Health Organization (WHO) classification in 2003. Later, in 2012, WHO defined neuroendocrine neoplasms (NEN) into 3 subcategories: well-differentiated neuroendocrine tumor, poorly differentiated neuroendocrine carcinoma, and neuroendocrine differentiated breast cancer (NEBC).[3] WHO proposed a uniform classification including neuroendocrine neoplasms in different anatomical regions with breast NECs. According to this classification, breast cancers with >90% of tumor cells showing neuroendocrine differentiation were included in this group. Breast cancers with ≤90% of tumor cells showing neuroendocrine differentiation were considered as neuroendocrine differentiated breast cancer (NEBC) and were excluded it on the assumption that neuroendocrine differentiation in breast cancers has no therapeutic value.[4,5] In the National Comprehensive Cancer Network (NCCN) guidelines, NEBC is evaluated in the same category as invasive ductal carcinomas with non-specific types (BC-NST), and the same treatment strategies are recommended.[6]

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NECs represent 1% of all NECs and less than 5% of all breast tumors.[2,7-9] NEBC are more prevalent than NEC. The incidence rate of all invasive breast cancers varies between 0.1% and 30%, although the figures reported in the literature vary depending on the studies.[4,8,10-12] Due to frequent changes in diagnostic criteria and the lack of routine use of neuroendocrine markers, it is challenging to ascertain the true incidence.[4,7,10]

Axillary lymph node metastasis (ALNM) is a strong and independent negative prognostic factor in breast cancers.[13,14] The presence of axillary lymph node metastases is crucial for the management of breast cancer and the selection of surgical/neoadjuvant therapy. Determination of predictors for axillary lymph node metastasis of this rare tumor will guide surgeons and oncologists in determining prognosis and in treatment decision. This study aims to discuss the factors that influence the clinical, histopathological, and axillary lymph node metastasis of NEBCs and NECs through our case series analysis.

METHODS

The study was initiated with the approval of the Gazi University Non-interventional Clinical Researches Ethics Committee (Date: 08.05.2023, Decision No: 395). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

1002 patients who underwent surgical treatment for breast cancer at Gazi University Faculty of Medicine, Department of General Surgery, between 2015-2022 were evaluated retrospectively. The study included 35 patients with histopathologically confirmed cases of neuroendocrine breast cancer (NEC) and neuroendocrine differentiated breast cancer (NEBC). The inclusion criteria were: primary breast cancer with neuroendocrine differentiation; primary breast neuroendocrine carcinoma; and having undergone axillary lymph node sampling or dissection. The exclusion criteria were having distant metastases (M1) and receiving neoadjuvant therapy. Since the histopathological features of the tumors in patients with multifocal tumors were the same, they were not considered separate tumors, and the largest tumor diameter was used (TNM, 8th edition, 2018). Demographic, clinical, and histopathological data of patients who met the inclusion criteria were recorded. Next, factors affecting axillary lymph node metastasis in the NEC and NEBC subgroups of the entire patient population were evaluated.

Statistical Analysis

The data of our study was analyzed using the SPSS 21.0 program (IBM Inc, Chicago, IL, USA). The categorical data obtained were expressed as percentage and frequency (N), and the quantitative data as median (median) (IQR). Due to the small sample size and non-normal distribution of the data, non-parametric tests were used. A paired group (independent) comparison was performed using the Mann-Whitney U test. The relationship between binary categorical groups was examined using Pearson's chi-square test or Fisher's exact test. Spearman analyses revealed the correlations between the quantitative parameters. Diagnostic values, including predictive values, sensitivity, and specificity, were analyzed using ROC. In the study, an α (type-I error) value of 0.05 (5%) was used, and the p significance value was accepted as 0.05 for interpretation.

RESULTS

In this study, 35 patients who met the inclusion criteria were evaluated, 11 of whom had NEC and 24 of whom had NEBC. The clinical, histopathological features and performed surgical procedures of the study cohort are presented in **Tables 1**, **2** and **3**. The median age at diagnosis was 49 in the NEC group (min: 35, max: 80), 57.5 in the NEBC group (min: 32-max: 85), and 57 in the entire study cohort (min: 32, max: 85). Twelve patients (34.3%) had T1, 17 patients (48.6%) had T2, and 6 patients (17.1%) had T3 tumors. Of the 35 patients, 15 (57.1%) had ALNM, and lymphovascular invasion was detected in 16 (45.7%). The most common molecular subtype was Luminal B, detected in 16 patients (45.7%), followed by the Her-enriched subtype in 11 patients (31.4%) and 8 patients (22.9%) Twenty-one patients (60.0%) were positive for chromogranin A (CgA) (**Table 3**).

Analysis of quantitative and categorical parameters according to axillary lymph node metastasis status of the study cohort, NEC and NEBC group are presented in **Table 4**, **5** and **6**. When evaluating the study cohort for ALNM, it was found that lymphovascular invasion had an effect on ALNM (p=0.005) (**Table 4**). In the NEBC group, ALNM was associated with increased tumor size (p=0.035) (**Table 6**). ROC analysis data for quantitative parameters for axillary lymph node metastasis for the study cohort and NEBC group, tumor size was found to be predictive of ALNM (AUC: 0.753, 95% CI: 0.557-0.950, cut-off: 2.35 cm, p=0.035). Analyses of correlation revealed low-level correlation between age and Ki-67 in the study cohort (ρ= -0.341, p=0.45).

Table 1. Clinicopathological features in the study cohort.

Parameters	NEC group		NEBC group		Total	
	n	%	n	%	n	%
Age at diagnosis						
< 50	6	54.5	6	25.0	12	34.3
50-69	1	9.1	15	62.5	16	45.7
≥ 70	4	36.4	3	12.5	7	20.0
T-Stage						
T1	2	18.2	10	41.7	12	34.3
T2	7	63.6	10	41.7	17	48.6
T3	2	18.2	4	16.6	6	17.1
Tumor focality						
Unifocal	10	90.9	19	79.2	29	82.9
Multifocal	1	9.1	5	20.8	6	17.1
Tumor types						
Neuroendocrin carcinoma	11	100	-	-	11	31.4
Invasive ductal carcinoma	-	-	17	70.8	17	48.6
Mucinous carcinoma	-	-	5	20.8	5	14.3
Papillary carcinoma	-	-	2	8.4	2	5.7
Ductal carcinoma insitu component						
Yes	4	36.4	11	45.8	15	42.9
No	7	63.6	13	54.2	20	57.1
Ductal carcinoma insitu grade						
Grade 1	0	0.0	3	27.3	3	20.0
Grade 2	4	100	6	54.5	10	66.7
Grade 3	0	0	2	18.2	2	13.3
Axillary lymph node metastasis						
Positive	3	27.3	12	50.0	15	57.1
Negative	8	72.7	12	50.0	20	42.9
Grading						
Grade 1	4	36.4	2	8.3	6	17.1
Grade 2	5	45.4	17	70.9	22	62.9
Grade 3	2	18.2	5	20.8	7	20.0
Lymphovascular invasion						
Positive	5	45.4	11	45.8	16	45.7
Negative	6	54.6	13	54.2	19	54.3

DCIS: Ductal carcinoma insitu

Table 3. Distribution of histopathological, molecular, and receptor-related parameters in the study cohort

Parameters	NEC group	NEBC group	Total
			Frequency (%)
Chromogranin			
Positive (+)	7 (63.6%)	14 (58.3%)	21 (60.0%)
Negative (-)	4 (36.4%)	10 (41.7%)	14 (40.0%)
Snaptophysin			
Positive (+)	11 (100%)	24 (100%)	35 (100.0%)
Negative (-)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CD-56			
Positive (+)	0 (0.0%)	2 (8.3%)	2 (22.2%)
Negative (-)	3 (27.3%)	4 (16.7%)	7 (77.8%)
Unknown	9 (81.7%)	18 (75.0%)	
ER			
Positive (+)	11 (100%)	24 (100%)	35 (100.0%)
Negative (-)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR			
Positive (+)	11 (100%)	21 (87.5%)	32 (91.4%)
Negative (-)	0 (0.0%)	3 (12.5%)	3 (8.6%)
Cerb-b2			
Positive (+)	0 (0.0%)	11 (45.8%)	11 (31.4%)
Negative (-)	11 (100%)	13 (54.2%)	24 (68.6%)
Ki-67			
≤%14	5 (45.5%)	5 (20.8%)	10 (28.6%)
>%14	6 (54.5%)	19 (79.2%)	25 (71.4%)
Molecular Subtypes			
Luminal A	5 (45.5%)	3 (12.5%)	8 (22.9%)
Luminal B	6 (54.5%)	10 (41.7%)	16 (45.7%)
HER2-enriched	0 (0.0%)	11 (45.8%)	11 (31.4%)

ER: estrogen receptor, PR: progesterone receptor

Table 2. Surgical procedures performed in the study cohort

Surgical procedure	NEC Group		NEBC Group		Total	
	n	%	n	%	n	%
SM + SLNB	5	45.5	9	37.5	14	40
Modified radical mastectomy	2	18.2	8	33.3	10	28.6
BCS + SLNB	2	18.2	4	16.7	6	17.1
SM + ALND	1	9.1	2	8.4	3	8.6
BCS + ALND	1	9.1	1	4.2	2	5.7
Total:	11	100	24	100	35	100

SM: Simple mastectomy, BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

Table 4. Analysis of quantitative and categorical parameters according to axillary lymph node metastasis status of the study cohort

Median (min-max) [a]	Axillary Lymph Node Metastasis		p
	Negative (n=20, 57.1%)	Positive (n=15, 42.9%)	
Age (year)	51 (32-80)	58 (43-85)	0.142
Age at diagnosis			0.059 [b]
< 50	10 (83.3%)	2 (16.7%)	
50-69	6 (37.5%)	10 (62.5%)	
≥70	4 (57.1%)	3 (42.9%)	
Quadrants, n (%)			0.247 [b]
Upper-outer	7 (50.0%)	7 (50.0%)	
Upper-inner	3 (100%)	0 (0%)	
Lower-outer	8 (72.73%)	3 (27.27%)	
Lower-inner	1 (33.33%)	2 (66.67%)	
Central	1 (25.0%)	3 (75.0%)	
Focality, n (%)			0.481 [c]
Unifocal	16 (55.17%)	13 (44.83%)	
Multifocal	4 (66.67%)	2 (33.33%)	
Tumor size (cm)	2.35 (0.5-7.0%)	2.5 (0.7-11.0%)	0.359
Chromogranin, n (%)			0.486 [c]
Negative (-)	7 (50.0%)	7 (50.0%)	
Positive (+)	13 (61.9%)	8 (38.1%)	
Ki-67. n (%)			0.458 [b]
≤ %14	7 (70%)	3 (30%)	
> %14	13 (52%)	12 (48%)	
Ductal carcinoma insitu component n (%)			0.693 [c]
No	12 (60%)	8 (40%)	
Yes	8 (53.33%)	7 (46.67%)	
Cerb-b2. n (%)			0.99 [b]
Negative (-)	14 (58.33%)	10 (41.67%)	
Positive (+)	6 (54.55%)	5 (45.45%)	
Molecular subtypes, n (%)			0.611 [b]
Luminal A	6 (75.0%)	2 (25.0%)	
Luminal B	8 (50.0%)	8 (50.0%)	
HER2-enriched	6 (54.55%)	5 (45.45%)	
Lymphovascular invasion, n (%)			0.005 [b]
Negative	15 (78.95%)	4 (21.05%)	
Positive	5 (31.25%)	11 (68.75%)	
Grading, n (%)			0.89 [b]
Grade 1	4 (66.67%)	2 (33.33%)	
Grade 2	12 (54.55%)	10 (45.45%)	
Grade 3	4 (57.14%)	3 (42.86%)	
T-Stage, n (%)			0.99 [b]
T1	7 (58.33%)	5 (41.67%)	
T2	10 (58.82%)	7 (41.18%)	
T3	3 (50.0%)	3 (50.0%)	

a Mann Whitney U test; parameters (min-max), IQR= Interquartile Range, b Fisher's exact test, c Pearson chi-square analysis

Table 5. Analysis of quantitative and categorical parameters according to axillary lymph node metastasis status of the NEC group

Median (min-max) [a]	Axillary Lymph Node Metastasis		p
	Negative (n=8, %72.7)	Positive (n=3, %27.3)	
Age (year)	48.5 (35-80)	58 (43-72)	0.918
Age at diagnosis			0.41 [b]
< 50	5 (83.3%)	1 (16.7%)	
50-69	0 (0%)	1 (100.0%)	
≥70	3 (75.0%)	1 (25.0%)	
Quadrants, n (%)			0.121[b]
Upper-outer	1 (33.33%)	2 (66.67%)	
Upper-inner	1 (100%)	0 (0%)	
Lower-outer	5 (100%)	0 (0%)	
Lower-inner	0 (0%)	1 (100%)	
Central	1 (100%)	0 (0%)	
Focality, n (%)			0.99 [b]
Unifocal	7 (70.0%)	3 (30.0%)	
Multifocal	1 (100%)	0 (0%)	
Tumor size (cm)	2.95 (1.5-7%)	2.1 (1-2.8%)	0.153
Chromogranin, n (%)			0.491 [b]
Negative (-)	2 (50.0%)	2 (50.0%)	
Positive (+)	6 (85.71%)	1 (14.29%)	
Ki-67. n (%)			0.99 [b]
≤ %14	4 (80.0%)	1 (20.0%)	
> %14	4 (66.67%)	2 (33.33%)	
Ductal carcinoma insitu component n (%)			0.99 [b]
No	5 (71.43%)	2 (28.57%)	
Yes	3 (75.0%)	1 (25.0%)	
Cerb-b2. n (%)			
Negative (-)			
Positive (+)			
Molecular subtypes, n (%)			0.99 [b]
Luminal A	4 (80.0%)	1 (20.0%)	
Luminal B	4 (66.67%)	2 (33.33%)	
HER2-enriched	0 (0.0%)	0 (0.0%)	
Lymphovascular invasion, n (%)			0.424 [b]
Negative	5 (83.33%)	1 (16.67%)	
Positive	3 (60.0%)	2 (40.0%)	
Grading, n (%)			0.99 [b]
Grade 1	3 (75.0%)	1 (25.0%)	
Grade 2	3 (60.0%)	2 (40.0%)	
Grade 3	2 (100%)	0 (0%)	
T-Stage, n (%)			0.99 [b]
T1	1 (50.0%)	1 (50.0%)	
T2	5 (71.43%)	2 (28.57%)	
T3	2 (100%)	0 (0%)	

a Mann Whitney U test; parameters (min-max), IQR= Interquartile Range, b Fisher's exact test, c Pearson chi-square analysis

Table 6. Analysis of quantitative and categorical parameters according to axillary lymph node metastasis status of the NEBC group

Median (min-max) [a]	Axillary Lymph Node Metastasis		p
	Negative (n=12, %50.0)	Positive (n=12, %50.0)	
Age (year)	54.5 (32-80)	60.5 (47-85)	0.112
Age at diagnosis			0.188
< 50	5 (83.3%)	1 (16.7%)	
50-69	6 (40.0%)	9 (60.0%)	
≥70	1 (33.3%)	2 (66.7%)	
Quadrants, n (%)			0.34
Upper-outer	6 (54.55%)	5 (45.45%)	
Upper-inner	2 (100%)	0 (0%)	
Lower-outer	3 (50.0%)	3 (50.0%)	
Lower-inner	1 (50.0%)	1 (50.0%)	
Central	0 (0%)	3 (100%)	
Focality, n (%)			0.99 [b]
Unifocal	9 (47.37%)	10 (52.63%)	
Multifocal	3 (60.0%)	2 (40.0%)	
Tumor size (cm)	1.6 (0.5-5.0%)	3.25 (0.7-11.0%)	0.035
Chromogranin, n (%)			0.99 [c]
Negative (-)	5 (50.0%)	5 (50.0%)	
Positive (+)	7 (50.0%)	7 (50.0%)	
Ki-67. n (%)			0.99 [b]
≤ %14	3 (60%)	2 (40%)	
> %14	9 (47.37%)	10 (52.63%)	
Ductal carcinoma insitu component n (%)			0.68 [c]
No	7 (53.85%)	6 (46.15%)	
Yes	5 (45.45%)	6 (54.55%)	
Cerb-b2. n (%)			0.682 [c]
Negative (-)	6 (46.2%)	7 (53.8%)	
Positive (+)	6 (54.5%)	5 (45.5%)	
Molecular subtypes, n (%)			0.742 [b]
Luminal A	2 (66.67%)	1 (33.33%)	
Luminal B	4 (40.0%)	6 (60.0%)	
HER2-enriched	6 (54.55%)	5 (45.45%)	
Lymphovascular invasion, n (%)			0.004 [c]
Negative	10 (76.92%)	3 (23.08%)	
Positive	2 (18.18%)	9 (81.82%)	
Grading, n (%)			0.99 [b]
Grade 1	1 (50.0%)	1 (50.0%)	
Grade 2	9 (52.94%)	8 (47.06%)	
Grade 3	2 (40.0%)	3 (60.0%)	
T-Stage, n (%)			0.663 [b]
T1	6 (60.0%)	4 (40.0%)	
T2	5 (50.0%)	5 (50.0%)	
T3	1 (25.0%)	3 (75.0%)	

a Mann Whitney U test; parameters (min-max), IQR= Interquartile Range, b Fisher's exact test, c Pearson chi-square analysis

DISCUSSION

Despite neuroendocrine differentiation in breast cancers was initially described in 1963, it was not recognized as a distinct subtype by the WHO until 2003. Even though significant advances in breast cancer research and treatment in recent years, the exact prevalence, clinical behavior, and treatment standards for this rare subset of breast cancers have not been well established. This is likely a result of their low frequency and evolving definitions.[15]

All patients included in our study were diagnosed with neuroendocrine neoplasm in the breast according to WHO 2012 criteria. However, definitions of neuroendocrine neoplasms of the breast were changed again in 2012 and 2019. Lastly, WHO includes primary breast neuroendocrine tumors in the same classification as neuroendocrine tumors in other anatomical locations. They define neuroendocrine differentiated breast cancer as a non-specific subtype. Nonetheless, neuroendocrine differentiation in breast cancer has been associated with a number of distinct clinical characteristics.[9,11,12,16-24] Inclusion of breast neuroendocrine tumors in distinct classifications and the therapeutic value of neuroendocrine differentiation in breast cancers have not been adequately addressed as of yet. Debates regarding the WHO classification of neuroendocrine neoplasms of the breast are still ongoing and it is emphasized that it needs further adjustments regarding morphological and immunohistochemical criteria.[25] In particular, well-differentiated NECs of the breast are treated in the same way as invasive breast carcinoma. However, there is limited data on whether treatment modalities similar to this treatment for invasive breast carcinoma are effective for neuroendocrine neoplasm of the breast. Yang et al.[26] reported that current treatment protocols did not improve survival in breast NENs. Due to this confusion in diagnostic classification and treatment protocols, it is clear that new studies on the behavior of these tumors are necessary. Axillary lymph node metastasis is an important prognostic indicator of breast cancer. Therefore, the NEC and NECB subgroups of the patients included in our study were evaluated for axillary lymph node metastasis. Furthermore, it was intended to contribute to the body of knowledge with a large number of cases.

The median age at first diagnosis in our study cohort was 57, which was consistent with the median age at diagnosis of non-specific type breast cancers reported in the literature.[27] There are studies that do not indicate a difference in age at diagnosis between breast NEN and BC-NST.[16,21,23] Nevertheless, several studies conducted with large cohorts have reported that breast NENs are significantly older than BC-NST patients.[9,17,19,24] These different results may also be attributable to the non-standard diagnostic criteria employed in the studies. The majority of studies meeting WHO 2003 criteria indicate that breast NEN patients are significantly older than BC-NST patients.[9,17,19,24]

Most of the patients in our cohort (65.2%) had ≥T2 tumors. ALNM was present in 57.1% of our patients. Previous similar studies have also reported that neuroendocrine neoplasms of the breast have ALNM at the time of diagnosis. Wang et al.[9] showed in their study, which included 142 breast neuroendocrine neoplasms, that it had a higher rate of ALNM (28.8%) than other non-specific types. Krawczyk et al.[10] reported the ALNM rate as 37% in their series, in which they included 27 NEBCs. Cloyd et al.[20] reported the ALNM rate as 63.2% in breast NENs. In their series of 128 cases, Bogina et al.[23] reported the rate of ALNM as 33% in NEN patients and did not observe a significant difference with BC-NST. On the contrary, some studies have reported similar TNM stages at diagnosis in breast cancer cases with and without neuroendocrine differentiation.[16,17,21,28]

In our study, all of the patients were ER-positive, and 91.4% were PR-positive. Similar to previous studies, the majority (68.6%) had ER-positive, HER2-negative tumors.[9,16,18,22] However, when we classified them according to molecular subtypes, Luminal B (45.7%) was predominant due to high Ki-67 ratios. Previous research has demonstrated a significant association between neuroendocrine differentiation and the presence of positive hormone receptors and a negative HER2-status.[17,19,21,23,24]

ALNM is a strong and independent negative prognostic factor for breast cancers. Among women without metastatic disease, the five-year survival rate is 99 percent for those with a without ALNM and 85 percent for those with a with ALNM.[13] In addition, the presence of lymphovascular invasion appears to be a poor prognostic indicator, particularly in higher-grade tumors. In our study, we also showed that lymphovascular invasion has an effect on ALNM in breast NENs and NEBCs (p=0.005; p=0.004). Based on this result and in consideration of the high ALNM potential of breast NENs, we conclude that patients with lymphovascular invasion should be treated with caution when it comes to axillary lymph node management.

Tumor size was recognized early as an important prognostic factor in breast cancer. Tumor size is correlated with ALNM, but the prognostic value of the two factors is independent.[14] Interestingly, in our study, tumor size was found to be higher in ALNM-negative cases in the NEC group, although it was not statistically significant (2.95 cm vs 2.1 cm, p=0.153). This suggests that the NEC group exhibits a different biological behavior for ALNM than

other breast cancers. In our study, we also showed that increased tumor size in the NEBC group was associated with ALNM (AUC: 0.753, 95% CI: 0.557-0.950, cut-off: 2.35 cm, p=0.035). Hence, axillary lymph nodes should be carefully evaluated, especially in patients with NEBC tumors larger than 2 cm.

In our study, 62.9% of the patients had Grade-2 tumors, and in 71%, Ki-67 was higher than 14%. Similarly, Krawczyk et al.[10] reported that Grade-2 (78%) and Ki-67 >30% tumors were the most prevalent in their study. In other series in the literature, it has been shown that Grade-2 tumors are more prevalent among NEN patients than in BC-NST patients.[17,23] The relationship between Ki-67 and age is an issue that has not been clarified in the literature.[29] We also determined that increasing age was associated with lower Ki-67 rates in the cohort of our study (ρ=-0.341 p=0.45). Since Ki-67 is an important prognostic marker, we think that NECs and NEBCs diagnosed at younger ages may have a worse prognosis.

Study Limitations

Our study has some limitations. Patients were identified retrospectively through a review of clinical records. A retrospective analysis of 1002 cases resulted in the identification of 35 cases (3.49%). In our study, we found a prevalence that is consistent with the 2-5% estimated by WHO.30 Due to the lack of a systematic morphological and immunohistochemical reassessment and the lack of routine use of neuroendocrine markers, we believe that the true prevalence is higher. The prevalence of neuroendocrine differentiation ranges from 0.1% to 20% in published studies.[9,28] The reason for this is the variable diagnostic criteria on the one hand and the NEN definition criteria used in published studies on the other. In our study, breast neuroendocrine neoplasms were also divided into NEC and NEBC subgroups for analysis. The limited number of patients included in the study may have also prevented the achievement of statistical significance in certain analyses.

CONCLUSION

The importance of primary neuroendocrine tumors of the breast and neuroendocrine differentiation in breast cancers in determining treatment strategies is still not clearly clarified. This tumor group has a high incidence of axillary lymph node metastases, which play an important role in the treatment strategy for breast cancer. In patients with lymphovascular invasion and a large tumor size, extra attention should be paid to axillary lymph node metastases. As previous research has shown that breast NECs and NEBCs are associated with poor clinical outcomes, further research is required to determine the optimal treatment strategy for this subtype of breast cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Gazi University Non-interventional Clinical Researches Ethics Committee (Date: 08.05.2023, Decision No: 395).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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

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