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Clinicopathological Characteristics of Breast Tumors with Neuroendocrine Features: A Retrospective Case Series

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Abbreviations:
WHO: World Health Organization;
CK7: Cytokeratin 7;
CK5/6: Cytokeratin 5/6;
TTF-1: Thyroid Transcription Factor-1;
CDX2: Caudal-type Homeobox 2;
HER2: Human Epidermal Growth Factor Receptor 2;
SEER: Surveillance, Epidemiology, and End Results.

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Rezumat

Caracteristicile clinicopatologice ale tumorilor mamare cu diferențiere neuroendocrină: o serie retrospectivă de cazuri

Introducere: Neoplasmele mamare cu diferențiere neuroendocrină constituie un grup rar şi heterogen de tumori, incluzând atât carcinoame invazive cu diferențiere neuroendocrină, cât şi neoplasme neuroendocrine primare ale sânului. Din cauza incidenței reduse, caracteristicile clinicopatologice şi comportamentul biologic ale acestor tumori rămân insuficient definite.
Material şi Metodă: A fost realizat un studiu retrospectiv care a inclus 22 de paciente diagnosticate cu neoplasme mamare cu diferențiere neuroendocrină, tratate în cadrul Clinicii I Chirurgie Oncologică a Institutului Regional de Oncologie Iaşi. Au fost analizate datele clinicopatologice, profilul imunohistochimic şi strategiile terapeutice.
Rezultate: Vârsta mediană la diagnostic a fost de 66,1 ani (interval: 35–83). Majoritatea cazurilor au fost reprezentate de carcinom invaziv de tip nespecific (NST) cu diferențiere neuroendocrină, în timp ce un număr redus de cazuri a îndeplinit criteriile pentru neoplasme neuroendocrine primare ale sânului. Profilul imunohistochimic a evidențiat un fenotip luminal predominant, caracterizat prin expresie intensă a receptorilor estrogenici şi absența supraexpresiei HER2. Indicele de proliferare Ki-67 mediu a fost de 40,3%. Metastazele ganglionare au fost identificate în 45,5% dintre cazuri. Toate pacientele au beneficiat de tratament conform ghidurilor standard pentru cancerul mamar, incluzând intervenție chirurgicală, chimioterapie, hormonoterapie şi radioterapie, în funcție de indicație. Durata mediană de urmărire a fost de 26 de luni. Analiza supraviețuirii a inclus 20 de paciente, 2 fiind pierdute din urmărire. În perioada de monitorizare au fost înregistrate 9 decese, corespunzând unei rate globale de mortalitate de aproximativ 45%.
Concluzii: Cancerele mamare cu diferențiere neuroendocrină au prezentat în principal un fenotip luminal şi nu au evidențiat un comportament clinic distinct față de carcinomul mamar convențional receptor hormonal pozitiv.

Aceste date susțin ipoteza conform căreia diferențierea neuroendocrină reprezintă mai degrabă o particularitate morfologică în cadrul spectrului tumoral luminal, decât o entitate biologică distinctă.

Cuvinte cheie: cancer mamar, diferențiere neuroendocrină, chirurgia sânului, management multidisciplinar

Abstract

Introduction: Breast neoplasms with neuroendocrine characteristics form a rare and heterogeneous group that includes both invasive carcinomas showing neuroendocrine differentiation and primary neuroendocrine tumors arising in the breast. Because these lesions are uncommon, their clinicopathological features and biological behavior are still not fully elucidated.
Methods: We conducted a retrospective analysis of 22 patients diagnosed with breast tumors showing neuro-endocrine features and treated in 1st Surgical Unit of Regional Institute of Oncology, Iasi. Clinicopathological characteristics, immunohistochemical profile and treatment patterns were analyzed.
Results: The median age at diagnosis was 66.1 years (range: 35–83). Most tumors corresponded to invasive carcinoma of no special type with neuroendocrine differentiation, while a smaller subset fulfilled the criteria for primary neuroendocrine neoplasms of the breast. Immunohistochemical analysis revealed a predominantly luminal immunophenotype, characterized by strong estrogen receptor expression and absence of HER2 overexpression. T0he median Ki-67 proliferation index was 40.3%. Lymph node involvement was observed in 45.5% of cases. All patients were treated according to standard breast cancer protocols, including surgery, chemotherapy, endocrine therapy and radiotherapy when indicated. The median follow-up was 26 months. Survival analysis included 20 patients with available follow-up data, while 2 patients were lost to follow-up. During the follow-up period, 9 deaths were recorded, corresponding to an overall mortality rate of approximately 45%.
Conclusions: In our study, breast tumors with neuroendocrine features exhibited a luminal immunophenotype and did not demonstrate a clearly distinct clinical behavior compared with conventional hormone receptor–positive breast cancer. Neuroendocrine differentiation may therefore represent a morphological feature within the luminal spectrum rather than a distinct biological entity.

Keywords: breast cancer, neuroendocrine differentiation, breast surgery, multidisciplinary management

Introduction

Primary neuroendocrine neoplasms (NENs) of the breast are rare entities. According to the current WHO classification (unchanged since 2019), they are divided into well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuro-endocrine carcinomas (NECs), including small-cell and large-cell types. However, most breast carcinomas showing neuroendocrine marker expression represent recognized morphological subtypes - most commonly invasive carcinoma of no special type (NST) - with neuroendocrine differentiation rather than true primary NENs (1).

The latest WHO classification introduced several key modifications in the classification of breast neuroendocrine neoplasms, including the use of the percentage of tumor cells showing neuroendocrine differentiation as a defining criterion, the exclusion of specific histologic types such as solid papillary carcinoma and hyper-cellular variants of mucinous carcinoma, and the addition of large-cell neuroendocrine carcinoma (LCNEC) as a recognized entity (*Table 1*) (2).

The true incidence of invasive breast carcinomas (IBCs) showing neuroendocrine differentiation remains difficult to determine. One of the main reasons is that immunohistochemical evaluation

Table 1. World Health Organization (WHO) classification of tumours of the breast with neuroendocrine 'features'. (Breast cancer with neuroendocrine differentiation: an update based on the latest WHO classification) (2)

Percentage of tumor cells showing neuroendocrine morphology	Recommended classification	Notes
>90%	Neuroendocrine neoplasm (NET or NEC)	Tumor classified as a primary neuroendocrine tumor of the breast
10%-90%	Mixed invasive carcinoma (NST or other type) and NET/NEC	The proportion of the neuroendocrine component should be reported
<10%	Invasive carcinoma of no special type (IBC-NST)	Neuroendocrine differentiation may be mentioned as a focal feature in the pathology report

for neuroendocrine markers is neither routinely performed nor currently recommended in standard breast cancer diagnostics. Consequently, reported prevalence rates vary widely in the literature, ranging from approximately 0.1% to 20% of breast cancers, with the World Health Organization estimating a prevalence of up to about 5% (3).

Tumour heterogeneity and sampling limitations may contribute to underestimation of the real incidence. Focal neuroendocrine differentiation can be present only in limited tumour areas and may therefore be missed if immunohistochemical studies are not performed or if the sampled tissue does not include these regions. Furthermore, many breast carcinomas with partial neuroendocrine differentiation are currently classified according to their predominant morphological subtype (such as invasive carcinoma of no special type), rather than as true neuroendocrine neoplasms (4,5). As a result, the actual frequency of breast tumours with neuro-endocrine features is likely underestimated, and the epidemiology of these lesions remains incompletely defined.

Classification is morphology-driven, and the diagnosis of primary breast NET or NEC should be reserved for tumours with distinct and uniform neuroendocrine features, after exclusion of metastatic disease. Clinically, these tumours are managed according to standard breast cancer parameters, and routine neuroendocrine marker testing is not recommended (1).

Breast neuroendocrine neoplasms share similar clinical characteristics with invasive breast carcinoma of no special type (IBC-NST). They are more commonly diagnosed in postmenopausal or elderly women, although rare cases have been reported in men. Importantly, they generally do not present with paraneoplastic manifestations related to ectopic hormone secretion, such as carcinoid syndrome (6).

Accurate diagnosis relies on comprehensive immunohistochemical analysis and appropriate imaging studies. Among immunohistochemical markers, chromogranin and synaptophysin demonstrate the highest sensitivity and specificity for neuroendocrine differentiation. Additional, less specific markers that may show positivity include neuron-specific enolase (NSE), CK7, and CK5/6. In contrast, TTF-1 and CDX2 are typically negative. Neuroendocrine carcinoma of the breast is frequently hormone receptor–positive (ER and PR), while HER2 is generally negative, although HER2-positive cases have been reported (7).

Two main theories have been proposed to explain the histogenesis of primary neuro-endocrine breast tumors. The first hypothesis suggests that these tumors arise from the neoplastic transformation of native neuro-endocrine cells within breast tissue. However, this theory remains controversial, as the presence of neuroendocrine cells in normal breast tissue has not been consistently confirmed. The more widely accepted hypothesis proposes that neuro-endocrine differentiation results from the divergent differentiation of a neoplastic epithelial progenitor or stem cell into both epithelial and neuroendocrine cell lineages during early carcinogenesis. This concept is supported by the absence of benign neuro-endocrine tumors of the breast and by evidence indicating that neuroendocrine tumor cells are clonally related to malignant epithelial cells (8-10).

The aim of this study was to investigate the clinicopathological features, immunohistochemical characteristics and therapeutic management of breast tumors with neuroendocrine features in a retrospective institutional cohort, with particular attention to the distribution of histological subtypes and their clinical behavior.

Materials and Methods

Study Design and Patient Selection

This retrospective study included patients diagnosed with breast tumors with neuro-endocrine features who underwent surgical treatment in First Oncological Surgical Unit of Regional Institute of Oncology, Iasi, between January 2014 and December 2025. A total of 22 patients were identified from the institutional pathology database. The diagnosis was established based on histopathological examination and confirmed by immunohistochemical expression of neuroendocrine markers.

Clinical and pathological data were retrieved from medical records and pathology reports. The collected variables included patient age at diagnosis, tumor size, histological type and grade, pathological stage, lymph node status, hormone receptor status, HER2 expression, proliferation index (Ki-67), treatment modalities and clinical outcomes.

Histopathological Evaluation

All surgical specimens were processed according to standard pathology protocols. Tumors were classified according to the current classification criteria of the World Health Organization (WHO) for breast tumors (1). Histological grading was performed using the Nottingham Grading System (NGS) (11). Breast tumors showing neuroendocrine features were classified according to the current WHO classification: invasive breast carcinoma of no special type with neuroendocrine differentiation and primary

neuro-endocrine neoplasms of the breast (including neuro-endocrine tumors and neuroendocrine carcinomas). Special histologic types showing neuroendocrine differentiation were not included in the present analysis; therefore, two cases of mucinous carcinoma with neuroendocrine differentiation were excluded from the study. Tumor staging was determined according to the TNM staging system of the American Joint Committee on Cancer (AJCC) based on pathological examination of the surgical specimens (pTNM staging) (12).

Immunohistochemistry

Immunohistochemical analysis was performed on representative tumor sections. Neuroendocrine differentiation was confirmed by the expression of at least one neuroendocrine marker, including chromogranin A, synaptophysin or CD56. Additional immunohistochemical markers were evaluated for breast cancer characterization, including estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 proliferation index. Hormone receptor positivity was defined according to established guidelines when ≥1% of tumor cells showed nuclear staining (13). HER2 status was assessed following current ASCO/CAP recommendations (14). The Ki-67 index was reported as the percentage of positively stained tumor cell nuclei (15). The Ki-67 proliferation index was assessed as the percentage of positively stained tumor cell nuclei in areas of highest labeling ("hot spots"), counting at least 500 tumor cells. Tumors with Ki-67 values ≥20% were considered to have a high proliferative index according to commonly used thresholds in the literature (16).

Treatment and Follow-Up

All patients underwent surgical treatment, consisting of either breast-conserving surgery or mastectomy with axillary lymph node dissection or sentinel lymph node biopsy. Adjuvant/neo-adjuvant treatment, including chemotherapy, radiotherapy, and endocrine therapy, was administered according to institutional protocols and current clinical guidelines based on tumor stage and biological profile. Treatment decisions were established within a multidisciplinary team setting, ensuring an individualized therapeutic approach for each patient.

Statistical Analysis

Descriptive statistical analysis was performed to summarize the clinical and pathological characteristics of the study population. Continuous variables were expressed as mean and range, while categorical variables were presented as frequencies and percentages. All analyses were performed using standard statistical methods to describe the distribution of variables within the cohort.

Results

During the study period, 4942 patients underwent surgery for breast cancer, among whom 22 were diagnosed with breast carcinoma with neuroendocrine differentiation, corresponding to an incidence of approximately 0.44%.

The mean age at diagnosis was 66.1 years (range: 35-83). Most patients were postmenopausal, accounting for 20 cases (90.9%), while only 2 patients (9.1%) were premenopausal. Clinicopathological characteristics of patients undergoing surgical interventions for breast carcinoma with neuroendocrine differentiation are presented in *Table 2*.

According to the AJCC anatomic staging system (12), most patients presented with stage II disease at diagnosis (63.6%). Stage IIA was the most frequent stage, observed in 8 patients (36.4%), followed by stage IIB in 6 patients (27.3%). Early-stage disease (stage IA) was identified in 2 patients (9.1 %). Locally advanced disease (stage III) was present in 6 patients (27.3%), including stage IIIA in 3 patients (13.6%), stage IIIB in 2 patients (9.1%), and stage IIIC in 1 patient (4.5%). The rate of lymph node involvement (45.5%) observed in our cohort appears relatively high (*Table 2*). This finding may be explained by the stage distribution, as a considerable proportion of patients were diagnosed with stage II and III disease.

Regarding molecular subtypes, the majority of tumors were classified as Luminal B, identified in 19 cases (86.4%), while Luminal A subtype was observed in 3 cases (13.6%). HER2 negativity was reported in all 22 cases (100%).

Histological grading according to the Nottingham Grading System (11) showed that intermediate-grade tumors (G2) were the most frequent, identified in 10 cases (45.5%), while low-grade tumors (G1) were present in 4 cases (18.2%), and high-grade tumors (G3) were observed in 8 cases (36.4%). From a histological perspective, the predominant subtype was invasive breast carcinoma of no special type with neuroendocrine differentiation, accounting for 17 cases (77.3%). Less frequent histological types included neuroendocrine tumors in 3 cases (13.6%), large-cell neuroendocrine carcinoma in 1 cases (4.5%), and small-cell neuro-endocrine carcinoma in 1 case (4.5%).

Neoadjuvant systemic therapy was administered in 10 patients (45.5%). Regarding surgical management, modified radical mastectomy (Madden procedure) was

Table 2. Clinicopathological characteristics of patients undergoing surgical treatment for breast carcinoma with neuroendocrine differentiation

	Value	Percentage
Age (mean age)	66.04	
Stage (AJCC Anatomic Stage Groups)		
IA	2	9.1
II A	8	36.4
II B	6	27.3
III A	3	13.6
III B	2	9.1
III C	1	4.5
Lymph node metastasis		
Yes	10	45.5
No	12	54.5
Menopausal status		
Premenopausal	2	9.1
Postmenopausal	20	90.9
Molecular typing		
Luminal A	3	13.6
Luminal B	19	86.4
Her 2 negative	22	100
Neoadjuvant treatment	10	45.45
Bloom-Richardson grade		
G1	4	18.2
G2	10	45.5
G3	8	36.4
Surgical treatment		
Madden	19	86.4
Breast conserving surgery	3	13.6
Histology		
IBC– NST with neuroendocrine differentiation	17	77.3
Large-cell neuroendocrine carcinoma	1	4.5
Small-cell neuroendocrine carcinoma	1	4.5
Neuroendocrine tumor	3	13.6
Chromogranin		
Positive	11	50
Negative	5	22.7
Unknown	6	27.3
Synaptophysin		
Positive	18	81.8
Negative	3	13.6
Unknown	1	4.5
CD56		
Positive	7	31.8
Negative	1	4.5
Unknown	14	63.6

the most commonly performed surgical treatment, carried out in 19 patients (86.4%), while breast-conserving surgery was performed in 3 patients (13.6%).

Immunohistochemical evaluation of neuro-endocrine markers revealed variable expression. Synaptophysin was the most frequently expressed marker, being positive in 18 cases (81.8%), negative in 3 cases (13.6%), and not available in 1 case (4.5%). Chromogranin expression was positive in 11 cases (50%), negative in 5 cases (22.7%), and unavailable in 6 cases (27.3%). CD56 positivity was observed in 7 cases (31.8%), while 1 case (4.5%) was negative and 14 cases (63.6%) lacked available data.

Adjuvant chemotherapy was administered to 8 patients (36.4%), while 15 patients (68.2%) received adjuvant radiotherapy. Adjuvant endocrine therapy was administered in 12 cases (54.5%) (*Table 3*). The median follow-up was 26 months. Survival analysis included 20 patients with available follow-up data, while 2 patients were lost to follow-up. During the follow-up period, 9 deaths were recorded, corresponding to an overall mortality rate of approximately 45%. No cases of local or regional recurrence were observed among the 22 patients included in the study during the follow-up period.

Table 3. Adjuvant treatment characteristics

Adjuvant therapy	No	Percentage
Chemotherapy		
Yes	8	36.4
No	14	63.4
Radiotherapy		
Yes	15	68.2
No	7	31.8
Endocrine therapy		
Yes	12	54.5
No	12	54.5

Five patients in our cohort were diagnosed with rare primary neuroendocrine neoplasms of the breast, representing pure neuroendocrine histo-logical subtypes. The patients were between 50 and 73 years old. Histologically, the tumors included one large cell neuroendocrine carcinoma, one well-differentiated neuroendocrine tumor (NET G1), two moderately differentiated neuroendocrine tumors (NET G2), and one poorly differentiated small cell neuroendocrine carcinoma. At diagnosis, the disease stage ranged from early stage IA to locally advanced disease, including stage IIB and stage IIIA-IIIB tumors, with most cases presenting with nodal involvement. Regarding molecular profile, tumors belonged to the luminal subtype, reflecting the frequent hormone receptor positivity reported in neuroendocrine breast tumors. During follow-up, four patients remained alive without disease progression, whereas one death occurred in the patient diagnosed with small cell neuro-endocrine carcinoma, suggesting a more aggressive biological behavior of poorly differentiated neuro-endocrine carcinomas compared with well-differentiated NETs (*Table 4*).

Overall, the cohort was characterized predominantly by postmenopausal patients (90.9%), Luminal B molecular subtype (86.4%), intermediate histological grade (45.5%), and stage II disease at diagnosis (63.6%), alongside a substantial proportion of cases exhibiting nodal involvement, with synaptophysin representing the most frequently expressed neuroendocrine marker (81.8%).

Discussion

Breast tumors with neuroendocrine features represent

Table 4. Rare Neuroendocrine Subtypes Identified in the Study Cohort

	Age (years)	Histological subtype	cTNM	AJCC stage	HER2neg/luminal	Neadjuvant Treatment	Outcome
Pt 1	72	LCNEC	cT1N0M0	IA	Luminal B	no	Alive,no progression
Pt 2	50	NET G1	cT2N1M0	IIB	Luminal A	no	Alive,no progression
Pt 3	72	NET G2	cT3N2M0	IIIA	Luminal B	yes	Alive,no progression
Pt 4	73	NET G2	cT4N1M0	IIIB	Luminal B	yes	Alive,no progression
Pt 5	69	SCNEC	cT3N2M0	IIIA	Luminal B	yes	deceased

a rare and heterogeneous spectrum of neoplasms, and their clinicopathological characteristics, biological behavior, and optimal management strategies remain incompletely defined. Because of their low incidence and the evolution of diagnostic criteria over time, the available evidence is mainly derived from small retrospective series, which has contributed to considerable heterogeneity in the literature.

In the present study, we analyzed a cohort of 22 patients diagnosed with neuroendocrine neoplasms of the breast, including invasive breast carcinoma with neuroendocrine differentiation as well as true neuroendocrine tumors and neuro-endocrine carcinomas. Our findings provide additional insight into the clinicopathological characteristics and immunohistochemical profile of these rare tumors.

In our cohort, the mean age at diagnosis was 66.1 years, and the vast majority of patients were postmenopausal (90.9%). These findings are consistent with previously reported data indicating that breast carcinomas with neuroendocrine differentiation occur predominantly in older women, most frequently during the sixth and seventh decades of life. For example, several clinicopathological series have reported mean ages ranging between 60 and 70 years at diagnosis, with a clear predominance of postmenopausal patients (3,17-20). In the present study, 16 of the 22 patients (72.7%) were aged ≥65 years at the time of diagnosis. This demographic pattern suggests that neuro-endocrine breast tumors share epidemiological characteristics with conventional luminal-type breast cancers.

Although some authors have proposed classifying neuroendocrine tumors of the breast as a distinct histologic entity, the practical value of this approach remains limited. In routine practice, most of these tumors can be adequately reported as invasive breast carcinoma of no special type with neuroendocrine differentiation, while still being distinguished from metastatic neuroendocrine tumors originating from other organs. Furthermore, the lack of clearly defined diagnostic criteria and the absence of consistent clinical or prognostic differences between these entities limit the usefulness of such a subclassification in routine clinical practice (9).

The majority of tumors in our cohort (77.3%) corresponded to IBC-NST with neuroendocrine differentiation, while true neuroendocrine neoplasms represented only a minority of cases. This distribution is consistent with previous reports indicating that most breast tumors showing neuro-endocrine features correspond to conventional invasive breast carcinomas exhibiting focal or diffuse neuroendocrine differentiation rather than true primary neuroendocrine neoplasms of the breast (21).

The expression of neuroendocrine markers in breast tumors is often variable, and no universally accepted threshold has been established for their clinical significance. In routine practice, neuro endocrine markers are typically evaluated when the tumor morphology suggests neuroendocrine differentiation, such as nested or solid growth patterns and granular cytoplasm. Usually, at least two markers, most commonly synaptophysin and chromogranin, are assessed to support the diagnosis. The coexpression of multiple markers may strengthen the diagnosis but is not strictly required (9,22).

In the present study, synaptophysin was the most frequently expressed neuroendocrine marker, showing positivity in 81.8% of cases, followed by chromogranin (50%) and CD56 (31.8%). These findings are consistent with previously published studies indicating that synaptophysin represents the most sensitive immunohistochemical marker for detecting neuroendocrine differentiation in breast tumors, whereas chromogranin expression is more variable and CD56 is less frequently expressed (7,8). In a retrospective study analyzing 14 cases of breast neuroendocrine neoplasms, synaptophysin positivity was observed in 100% of evaluated cases, while chromogranin expression was detected in 85.7% of cases (17).

Several clinicopathological studies have reported similar results, with synaptophysin positivity observed in the majority of cases of breast tumors with neuroendocrine differentiation. For example, Rosen and Gattuso reported that synaptophysin is the most consistently expressed neuroendocrine marker in these tumors, while chromogranin expression may be

focal or absent in a proportion of cases (8). Likewise, other studies have shown that CD56 expression is less common and is therefore considered a supportive rather than a primary diagnostic marker (6,17,23).

These observations support the use of synaptophysin as the most reliable marker for confirming neuroendocrine differentiation in breast tumors, while chromogranin and CD56 may provide additional diagnostic support when used as part of an immunohistochemical panel.

In our cohort, the majority of tumors were classified as Luminal B (86.4%), while Luminal A tumors accounted for only 13.6% of cases, and all tumors were HER2-negative. These findings confirm the strong predominance of hormone receptor–positive molecular subtypes among breast tumors with neuroendocrine differentiation. Hasbay et al. reported in a single-center study including 56 cases of breast neuroendocrine tumors that the majority of tumors exhibited a luminal molecular phenotype, with 78.6% classified as Luminal A and 21.4% as Luminal B (17). Although the distribution of luminal subtypes differs from that observed in our cohort, both studies emphasize the predominance of estrogen receptor - positive tumors among breast neoplasms with neuroendocrine differentiation.

Consistent with these findings, Qiu et al., in a retrospective analysis of 87 patients with breast carcinoma with neuroendocrine features, also reported a high proportion of hormone receptor – positive and HER2-negative tumors, with Luminal B representing the most common molecular subtype (71.26%) (23). Similarly, in our cohort, Luminal B tumors accounted for 86.4% of cases, further supporting the notion that neuroendocrine neoplasm of the breast are predominantly associated with the luminal molecular spectrum.

The Ki-67 proliferation index is widely used as a marker of tumor proliferative activity and plays an important role in the molecular classification of breast cancer. In our cohort, the mean Ki-67 proliferation index was 40.3% (range 2–75%), indicating a relatively high proliferative activity among tumors with neuroendocrine differentiation.

In our study, most patients were diagnosed with stage II disease, particularly stage IIA. Similar findings were reported by Qiu et al., who analyzed 87 patients with breast carcinoma with neuroendocrine features and observed that nearly half of the patients presented with stage II tumors (23), suggesting that breast neoplasms with neuro-endocrine differentiation are most frequently diagnosed at intermediate stages of the disease. Peng et al., in a series of 131 primary neuroendocrine breast carcinoma cases, reported that 78 patients had stage I or II disease, 22 had stage III or IV disease (18). The rates observed in our cohort likely reflect the characteristics of the study population.The relatively high frequency of lymph node involvement may be related not only to the stage distribution but also to the biological behavior of breast carcinomas with neuroendocrine differentiation, which have been suggested in some reports to exhibit a more aggressive pattern of spread (6).

In the present cohort, modified radical mastectomy represented the most frequently performed surgical intervention, accounting for 19 cases (86.4%), while breast-conserving surgery was performed in only 3 patients (13.6%). This relatively high proportion of mastectomies should be interpreted in the context of the study period, which began in 2014, when surgical management strategies and institutional practices differed from current trends.

Peng et al., in a study analyzing 131 cases of primary neuroendocrine breast carcinoma, reported that mastectomy was the most frequently performed surgical procedure. In their cohort, the majority of patients underwent mastectomy with axillary lymph node dissection, while a smaller proportion received mastectomy with sentinel lymph node biopsy. Breast-conserving approaches were less commonly performed, including lumpectomy combined with axillary lymph node dissection or sentinel lymph node biopsy (18). Roininen et al., in a retrospective study including 43 patients with primary neuroendocrine breast carcinoma, reported a heterogeneous distribution of surgical procedures. In their cohort, 19 patients (44.2%) underwent mastectomy with axillary lymph node dissection, 11 patients (25.6%) underwent breast-conserving surgery with sentinel lymph node biopsy and 6 patients (14.0%) received mastectomy with sentinel node biopsy (24).

In contrast, Püsküllüoğlu et al., in a series of patients with non-metastatic primary neuroendocrine neoplasms of the breast, reported that breast-conserving surgery was the most frequently performed procedure, often combined with sentinel lymph node biopsy, while mastectomy was required in a smaller proportion of cases. The authors also emphasized that surgical treatment remains essential. However, due to the rarity of these tumors, the optimal extent of surgical resection for early-stage disease remains insufficiently defined (25).

Although the number of mastectomies observed in our cohort was relatively high, several factors may account for this finding. First, a considerable number of patients presented with stage II or stage III disease, which may have favored more extensive surgical approaches. In addition, tumor size and the tumor-to-breast size ratio may have limited the feasibility of

breast-conserving surgery in certain cases. Patient preference may also have contributed to the choice of mastectomy, as some patients opt for a more radical surgical procedure due to concerns regarding local recurrence or for psychological reassurance. Furthermore, during the earlier years of the study period, the clinical behavior and prognosis of breast tumors with neuroendocrine differentiation were less well understood, which may have encouraged a more cautious surgical strategy.

However, as experience with these tumors has gradually increased and more data have become available, breast-conserving surgery has emerged as a feasible treatment option when oncologically appropriate, a trend that is also reflected in our cohort.

Surgery remains the cornerstone of treatment for breast tumors with neuroendocrine differentiation. However, due to the rarity of these tumors, the optimal extent of surgical resection has not been clearly established. Current evidence suggests that the choice between breast-conserving surgery and mastectomy should primarily depend on the tumor stage, localization, and accurate pathological diagnosis, in a manner similar to the management of conventional invasive breast carcinomas (10).

The interpretation of survival outcomes in our study should be made with caution. The relatively small sample size and the advanced age of the study population may influence mortality estimates. In addition, the cohort includes patients diagnosed over a long study period beginning in 2014, resulting in heterogeneous follow-up durations. For these reasons, our results should be interpreted primarily in a descriptive manner rather than as definitive survival estimates. The median follow-up was 26 months. Survival analysis included 20 patients with available follow-up data, while 2 patients were lost to follow-up. During the follow-up period, 9 deaths were recorded, corresponding to an overall mortality rate of approximately 45%. Although the stage distribution may appear relatively favorable, a substantial proportion of patients presented with stage II–III disease and lymph node involvement (45.5%), which may suggest a more aggressive disease profile.

Several studies have reported variable survival outcomes in breast tumors with neuroendocrine features. Yang et al., in an analysis of the National Cancer Database, observed inferior overall survival for neuroendocrine neoplasms compared with invasive carcinoma not otherwise specified (26). Similarly, Roininen et al., in a retrospective study including 43 patients with neuroendocrine breast carcinoma, reported significantly worse relapse-free survival and overall survival compared with conventional ductal carcinomas (24). Lavigne et al. also demonstrated shorter progression-free survival in patients with neuroendocrine carcinoma of the breast compared with matched controls with invasive carcinoma of no special type, although no significant differences in overall survival were observed (20).

In addition to the more common invasive breast carcinomas with neuroendocrine differentiation, several rare histological subtypes were identified in our cohort, including well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. These entities represent uncommon forms of primary neuroendocrine neoplasms of the breast and account for only a small proportion of breast tumors with neuro-endocrine features. Their recognition is important, as they reflect the biological heterogeneity of neuro-endocrine breast tumors and may be associated with different clinical behavior compared with conventional invasive breast carcinomas (27).

Platinum–etoposide regimens, commonly used for small cell neuroendocrine carcinomas in other organs, may also be considered in selected cases. Clinically, neuroendocrine breast carcinomas lack distinctive features and patients often present with stage II disease and regional lymph node involvement (21).

Adjuvant treatment for neuroendocrine carcinoma of the breast generally follows the same principles as for other types of invasive breast cancer, although accurate diagnosis becomes particularly important in metastatic disease, where multimodal strategies including targeted therapies such as peptide receptor radionuclide therapy may be considered (28). The role of radiotherapy in the locoregional management of breast neuroendocrine neoplasms remains controversial. An analysis of the SEER database did not demonstrate a clear survival benefit in patients with non-metastatic disease, although evidence is limited due to the rarity of these tumors (29). In our cohort, radiotherapy was administered according to the same indications used for invasive ductal carcinoma, being recommended after breast-conserving surgery and considered after mastectomy based on established risk factors such as tumor size and nodal involvement.

The present study has several limitations. First, the relatively small number of cases reflects the rarity of breast tumors with neuroendocrine differentiation and limits the statistical power of the analysis. Second, the retrospective design and the long study period may have introduced variability in diagnostic criteria and treatment strategies. Finally, the follow-up duration was heterogeneous, which may influence survival estimates

Despite these limitations, our findings contribute

additional data regarding the clinicopathological characteristics of these rare tumors and emphasize the importance of recognizing neuroendocrine differentiation in breast carcinomas. A multidisciplinary approach involving pathologists, surgeons, and oncologists remains essential for accurate diagnosis and optimal management.

An important strength of the present study is that it includes the entire spectrum of breast tumors showing neuroendocrine features. While many previously published series have focused either on invasive breast carcinoma with neuro-endocrine differentiation or on primary neuro-endocrine neoplasms alone, our cohort encompasses both entities as well as special histologic types exhibiting neuroendocrine differentiation. This approach reflects the heterogeneity of these tumors in routine pathological practice and provides a more comprehensive overview of their clinicopathological characteristics.

Conclusions

Breast carcinomas with neuroendocrine differentiation represent a rare and heterogeneous group of tumors, most frequently associated with luminal molecular subtypes. Despite their generally intermediate stage at diagnosis, their biological behavior remains variable. Further studies on larger cohorts are needed to better define their prognostic significance and optimize management strategies.

Conflicts of Interest

The authors declare that they have no conflict of interests.

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Informed Consent Statement

This study was conducted following the ethical principles of the latest version of the Declaration of Helsinki. Patient confidentiality was ensured.

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