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Primary Small Cell Neuroendocrine Carcinoma of the Breast in a 75-Year-Old Woman With Aggressive Recurrence Despite Multimodal Therapy: A Case Report and Literature Review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 75-year-old
Final Diagnosis: Small cell neuroendocrine breast carcinoma
Symptoms: Right breast mass
Clinical Procedure: —
Specialty: Surgery

Objective: Rare coexistence of disease or pathology

Background: Neuroendocrine breast tumors represent an uncommon subtype of breast cancer, accounting for less than 1% of all breast malignancies and fewer than 0.1% of all neuroendocrine tumors. Their histological and immunophenotypic features closely resemble neuroendocrine neoplasms of other organs, and diagnosis requires careful exclusion of extramammary primaries.

Case Report: We present the case of a 75-year-old woman diagnosed with primary small cell neuroendocrine breast carcinoma following an incidental detection of a right breast mass. She underwent a simple mastectomy with sentinel lymph node biopsy, followed by adjuvant carboplatin-etoposide chemotherapy. One year later, she developed a solitary hepatic metastasis, which was successfully treated with metastasectomy and repeat adjuvant chemotherapy. Despite initial responses, subsequent surveillance imaging demonstrated progressive hepatic metastatic disease. This case underscores the aggressive clinical behavior and diagnostic challenges associated with high-grade neuroendocrine breast tumors. The 2019 WHO classification highlights the importance of distinguishing neuroendocrine carcinoma subtypes due to differing prognostic and therapeutic implications. Although multiple treatment modalities exist, outcomes remain poor in high-grade or advanced disease.

Conclusions: Neuroendocrine breast tumors remain insufficiently understood because of their rarity. This report highlights the importance of thorough histopathological evaluation, meticulous exclusion of extramammary primaries, and close longitudinal follow-up. Additional research is needed to establish standardized diagnostic and therapeutic guidelines.

Keywords: Breast Diseases • Breast Neoplasms • Case Reports • Literature Review • Neuroendocrine Tumors • Oncology • Rare Diseases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/952443

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Introduction

Neuroendocrine breast tumors (NEBTs), also described as breast carcinomas with neuroendocrine differentiation, are considered a rare subset of breast cancers [1]. They most commonly arise from the gastroenteropancreatic tract (≈70%) and lungs (≈25%), but since neuroendocrine cells are present in various tissues, they can originate in diverse organs [2].

NEBTs account for less than 1% of all breast cancers and are most frequently identified in postmenopausal women [3,4].

Due to their rarity, the current understanding of NEBTs is limited and primarily based on retrospective data [1]. Earlier classification was largely determined by the extent of neuroendocrine marker expression. However, in the 2019 WHO classification, a new classification system was introduced, categorizing neuroendocrine neoplasms of the breast into (1) neuroendocrine tumors – typically well-differentiated; (2) neuroendocrine carcinomas (NECs) – poorly differentiated, including small cell carcinoma; and (3) invasive breast carcinoma of no special type with neuroendocrine differentiation [5,6].

Confirmatory diagnostic methods depend on histopathological assessment, immunohistochemical confirmation of neuroendocrine marker expression, and exclusion of an extramammary primary. While treatment is guided by stage, grade, and proliferative activity, no disease-specific treatment guidelines for neuroendocrine breast carcinoma (NEBC) have been established. Current management is guided from small cell lung cancer and gastrointestinal neuroendocrine carcinoma protocols, with platinum-etoposide regimens forming the backbone of systemic therapy for poorly differentiated subtypes [7,8]. Emerging approaches, including peptide receptor radionuclide therapy and immune checkpoint inhibitors remain unvalidated in this setting.

This report describes an aggressive case of primary small cell neuroendocrine carcinoma of the breast with subsequent hepatic metastases, illustrating the diagnostic complexities and clinical behavior of this rare entity.

Case Report

A 75-year-old woman came to the clinic with a lump in her right breast. Further examination revealed no significant past medical history for the patient and a negative familial history of breast, ovarian, or any other malignancies. Her main concern was a mass in her right breast that she found by accident while doing a routine self-exam. A core needle biopsy at the local hospital showed that the cancer was invasive duct carcinoma. Because there weren't enough resources in her area, she was sent to a third hospital for more tests and treatment.

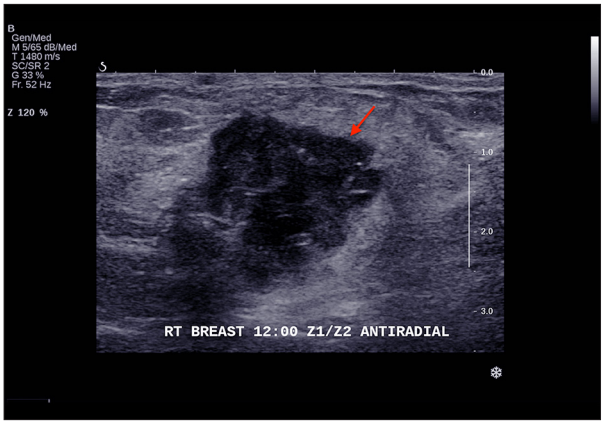

Figure 1. Breast ultrasound showing a single heterogeneous irregular hypoechoic mass (indicated by a red arrow) in the right breast, located at the 12 o'clock position, 1.5 cm from the nipple, and measuring 2.1×1.9×2.1 cm. The mass was associated with internal and peripheral vascularity with inner calcifications. It showed ductal extension with intraductal vascular components radiating and reaching the nipple, making it suspicious for nipple involvement. There was no axillary lymph node involvement.

Initially, at the oncology clinics, a full diagnostic workup was initiated. Moreover, the decision was made to present this case at the breast tumor board, where it was recommended to review her outside images (ultrasound and mammography), repeat the core needle biopsy for tumor grading, and refer the patient to the breast surgery clinic for further evaluation and definitive treatment. Bedside clinical breast examination revealed a mobile, firm mass measuring approximately 3×3 cm located at the 12 o'clock position near the upper areolar margin of the right breast. There was no peau' d'orange, skin changes, or nipple discharge. In addition, there was no axillary or supraclavicular or cervical lymphadenopathy, and the left breast examination was normal.

Subsequently, right breast ultrasound revealed a single, irregular, heterogeneous hypoechoic lesion at the same location, measuring 2.1×1.9×2.1 cm. There was internal and peripheral vascularity, and internal calcifications. The mass was located approximately 1.5 cm from the nipple. It showed ductal extension with an intraductal vascular component radiating and reaching the nipple. There were no suspicious axillary lymph nodes (**Figure 1**). This was further evaluated with a diagnostic right breast mammogram, including tomosynthesis with contrast which confirmed the presence of a heterogeneously enhancing, dense, spiculated mass measuring 2.7×2.6×2.4 cm located in the upper central mid-third of the right breast (**Figure 2**).

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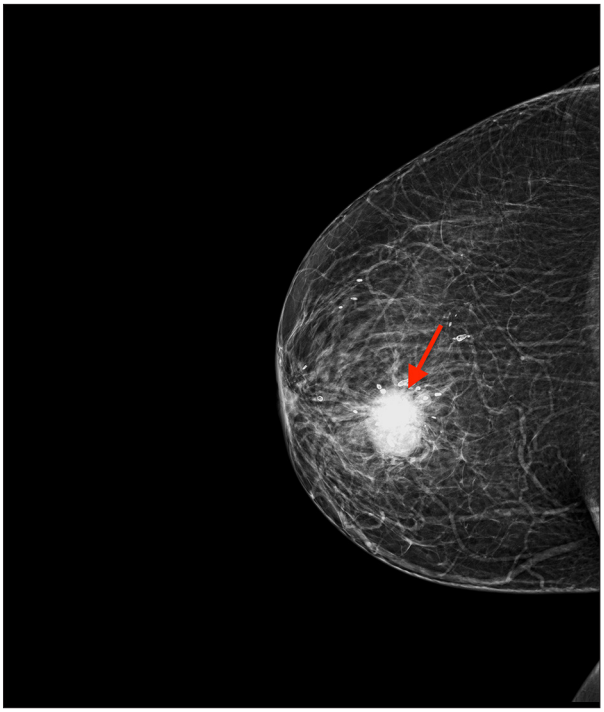

Figure 2. Contrast-enhanced bilateral digital breast tomosynthesis mammogram showing scattered fibroglandular densities with mild background parenchymal enhancement. There was a heterogeneously enhancing dense spiculated mass in the upper central mid-third of the breast with ductal extension/spicules towards the nipple (indicated by a red arrow). The mass measured 2.7×2.6×2.4 cm. There was a faint enhancing right breast retro-areolar lesion which may have been an extension from the index mass. Additionally, there was a non-enhancing circumscribed isodense nodule in the outer anterior to middle third measuring 0.6 cm.

Repeat histopathological examination of the specimen revealed neuroendocrine carcinoma of small cell type. Immunohistochemistry demonstrated diffuse positivity for chromogranin and synaptophysin, confirming neuroendocrine differentiation. E-cadherin was positive, excluding lobular carcinoma. GATA-3 was focally positive and estrogen receptor (ER) was positive (40%, strong), supporting a primary breast origin. Progesterone receptor (PR) was negative, HER2 was negative (score 0), and Ki-67 was 95%. p53 was negative, possibly indicating a mutant-type pattern.

Further staging investigations were conducted, including a computed tomography (CT) scan of the chest, abdomen, and pelvis (CT-CAP), abdominal magnetic resonance imaging (MRI), as well as a bone scan, according to our institution's guidelines. Subsequent findings from the abdominal MRI and CT-CAP along with bone scintigraphy revealed no evidence of metastatic disease.

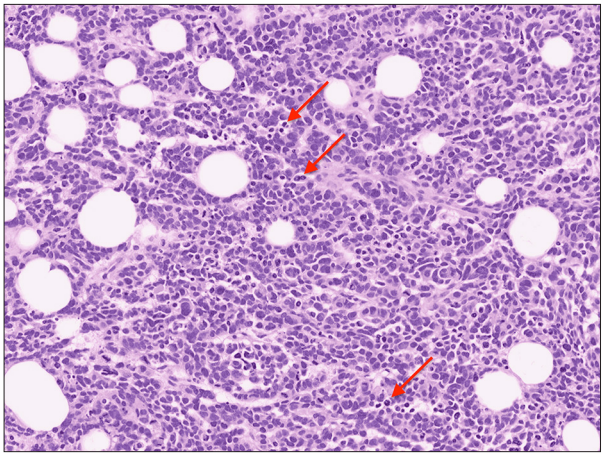

Figure 3. Hematoxylin and eosin (H&E) staining of the right breast mastectomy specimen (original magnification ×200). Diffuse sheets and nests of densely packed small tumor cells with scant cytoplasm and hyperchromatic nuclei (indicated by red arrows) are seen within a fibrotic stroma. The morphological features are consistent with poorly differentiated neuroendocrine carcinoma, small cell type (Nottingham grade 3/3).

Subsequently, after investigation, in January 2022, the patient underwent a right simple mastectomy with sentinel lymph node biopsy. The histopathology report of the excised mastectomy revealed a 4.6 cm small cell neuroendocrine carcinoma located in the center (**Figure 3**), with Nottingham histologic grade 3 (glandular differentiation score 3, nuclear pleomorphism score 3, mitotic rate score 3). Further, it was associated with high-grade ductal carcinoma in situ (solid pattern, comprising 5% of the tumor) with lymphovascular invasion.

The surgical margins were negative and uninvolved, with the invasive carcinoma being 1.9 cm from the deep margin. A sentinel lymph node biopsy showed metastatic carcinoma in 1 of the 2 lymph nodes that were looked at. The metastatic focus was 1.2 mm in size and did not extend outside of the lymph node. Immunohistochemistry on the mastectomy specimen indicated ER positivity (40%, strong) (**Figure 4**); PR positivity (40%, moderate); HER2 negativity (score 1+); GATA-3 positivity (**Figure 5**); chromogranin positivity (**Figure 6**); and a Ki-67 index of 95%. The pathologic stage was pT2, pN1mi(sn).

After appropriate postoperative care was achieved, adjuvant therapy and follow-up was started. She finished 4 cycles of carboplatin and etoposide with granulocyte colony-stimulating factor (G-CSF) support between March and May 2022. As part of the hospital's protocol, G-CSF was given to prevent chemotherapy-induced neutropenia and its associated complications, including febrile neutropenia. She remained under surveillance with CT-CAP and MRI every 4 months.

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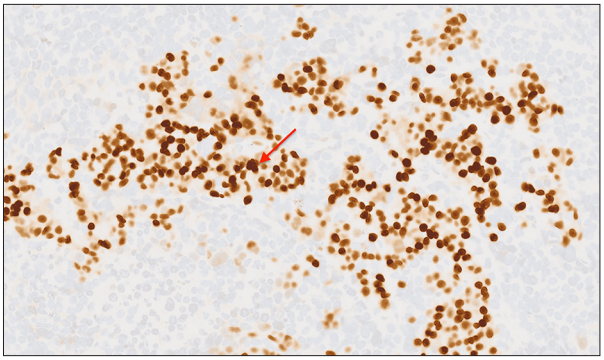

Figure 4. Immunohistochemical staining for estrogen receptor (ER) (indicated by a red arrow) on the mastectomy specimen (original magnification ×200). Tumor cells demonstrated positive nuclear staining of variable intensity, scored at 40%.

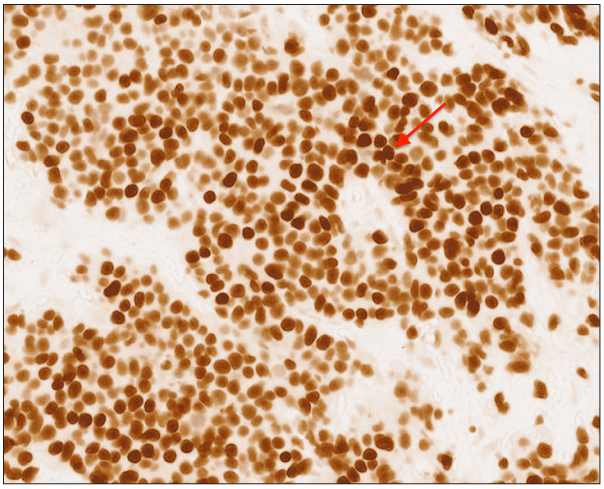

Figure 5. Immunohistochemical staining for GATA-3 on the mastectomy specimen (original magnification ×200). Diffuse strong nuclear positivity (indicated by a red arrow) was observed in tumor cells, supporting a primary breast origin.

However, in March 2023, surveillance MRI detected a new solitary hepatic lesion measuring 0.6 cm, which enlarged to 2.5 cm by July 2023. A positron emission tomography (PET)-CT in August 2023 confirmed a fluorodeoxyglucose-avid hepatic lesion consistent with metastasis. She underwent metastasectomy involving hepatic segments 7 and 8 with cholecystectomy. Pathology confirmed metastatic poorly differentiated neuroendocrine carcinoma (4 cm), ER/PR positive, GATA-3 positive, Ki-67 85-90%, with negative margins. Thereafter, she received another 4 cycles of carboplatin-etoposide with a 20% dose reduction, completed in March 2024. Initial post-treatment imaging showed no suspicious liver lesions.

Unfortunately, in July 2024, CT-CAP demonstrated new multiple subcentimeter hypodense hepatic lesions. In September 2024,

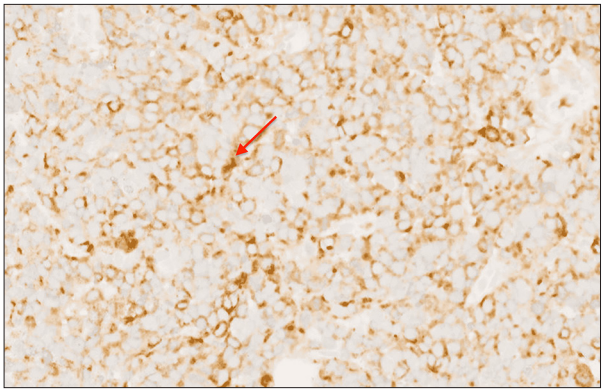

Figure 6. Immunohistochemical staining for chromogranin A (indicated by a red arrow) on the mastectomy specimen (original magnification ×200), confirming neuroendocrine origin.

subsequent imaging showed an increase in the size and number of liver lesions. She was started on dose-reduced carboplatin and etoposide, and finished in December 2024, at which time she initially showed treatment response radiologically.

Sadly, by May 2025, long-term follow-up imaging showed new hepatic lesions and extension to abdominal lymph nodes. After discussion in the tumor board, the decision was made to start systemic therapy with capecitabine and temozolomide because of the aggressiveness of the disease.

Discussion

Primary neuroendocrine tumors of the breast are rare, comprising fewer than 1% of all breast cancers [9]. Neuroendocrine tumors most commonly arise from the gastroenteropancreatic tract and lungs; small cell type has also been reported in other rare anatomical locations, such as paranasal sinuses, emphasizing the diagnostic complexity of these tumors [10]. Patients are typically older women, and presentation commonly includes a palpable breast mass, similar to other invasive breast carcinomas. Imaging findings are nonspecific and often indistinguishable from invasive breast carcinoma of no special type with neuroendocrine differentiation [5,9].

The 2003 and 2012 WHO classifications relied heavily on neuroendocrine marker expression (>50% of tumor cells) [11,12]. The 2019 WHO revision refined the categorization, emphasizing cell morphology and the degree of neuroendocrine differentiation [6]. In this framework, small cell carcinoma is classified as a NEC, reflecting its high-grade behavior.

Currently, no NEBC-specific treatment regimen exists from any guideline committee. The National Comprehensive Cancer Network addresses neuroendocrine carcinomas under its

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Neuroendocrine and Adrenal Tumors guidelines (v3.2025), recommending platinum-etoposide regimens for extrapulmonary poorly differentiated NECs, and under its breast cancer guidelines (v5.2025) for surgical and locoregional management [7,8]. All available evidence derives from case reports, small retrospective series, and extrapolation from small cell lung cancer and gastrointestinal NEC data. Mohamed et al proposed a treatment algorithm recommending etoposide-platinum as first-line therapy for poorly differentiated subtypes, with consideration of endocrine therapy for hormone receptor-positive tumors [13]. The absence of standardized treatment protocols underscores the need for prospective registries and collaborative studies [14].

Prognosis varies significantly between subtypes. High-grade NECs, particularly small cell variants, exhibit the poorest outcomes, with reported associations between elevated Ki-67 index, larger tumor size, nodal involvement, and reduced survival [15]. Our patient's tumor demonstrated several high-risk features: large size, grade 3 histology, lymphovascular invasion, nodal positivity, and extremely high Ki-67 (85-95%).

The choice of simple mastectomy with sentinel lymph node biopsy rather than modified radical mastectomy was consistent with the patient's clinically node-negative axilla. However, sentinel lymph node biopsy revealed a 1.2 mm micrometastasis in 1 of the 2 nodes examined, with no extranodal extension. Completion of axillary lymph node dissection was omitted based on evidence from the International Breast Cancer Study Group 23-01 trial, which demonstrated equivalent disease-free and overall survival at 10-year follow-up when axillary lymph node dissection was omitted in patients with sentinel lymph node micrometastases [16].

This management recommendation parallels treatment paradigms for small cell carcinomas in other organs, with carboplatin-etoposide commonly used for systemic therapy [14,17]. Localized hepatic metastases may be amenable to resection, as demonstrated in this case, though recurrence is frequent. Reported metastatic sites include the liver, bone, lungs, pancreas, brain, and soft tissues [18].

Management of recurrent or metastatic NEBC remains poorly defined. For poorly differentiated NECs, first-line systemic therapy consists of platinum-etoposide regimens, extrapolated from small cell lung cancer treatment paradigms [13,14]. The NORDIC NEC study reported a response rate of 31% to first-line platinum-based chemotherapy in 305 patients, with a median overall survival of 11 months [18,19]. Evidence for second-line therapy is extremely limited. Capecitabine and temozolomide treatment has demonstrated activity in well-to-moderately differentiated neuroendocrine tumors and has shown a disease control rate of approximately 77% in an analysis of 1818 patients with advanced neuroendocrine neoplasms, although data on poorly differentiated NECs and specifically on NEBC are scarce [20]. In our patient, the initial response to carboplatin-etoposide was followed by hepatic recurrence within 1 year, and successive re-challenges with the same regimen yielded progressively shorter durations of disease control. Metastasectomy for solitary hepatic metastases may offer temporary disease control, as demonstrated in this case, though recurrence remains the rule in high-grade disease [18].

The role of endocrine therapy in NEBC warrants consideration. Most NEBCs show ER and PR positivity, which is associated with a luminal molecular subtype [1,14]. Analysis of retrospective data showed that patients with NEBC who received endocrine therapy had longer overall survival and disease-free survival compared with those who did not [1]. The recurrent and progressive hepatic metastases in this patient highlight the aggressive nature of small cell NEC of the breast and the need for extended, vigilant follow-up. This case adds to the limited body of literature on primary small cell NEBC and reinforces the importance of thorough histopathological evaluation, multidisciplinary management, and close longitudinal surveillance.

Conclusions

To conclude, this case presents a 75-year-old woman with primary small cell neuroendocrine carcinoma of the breast, an uncommon and poorly understood tumor. Despite multiple therapy approaches, including surgery, repeated courses of chemotherapy, and metastasectomy, the patient experienced progressive deterioration.

Institution Where Work Was Done

King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

Patient Consent

Patient consent was obtained.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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References:

1. Trevisi E, La Salvia A, Daniele L, et al. Neuroendocrine breast carcinoma: A rare but challenging entity. Med Oncol. 2020;37(8):70
2. Ozaki Y, Miura S, Oki R, Morikawa T, Uchino K. Neuroendocrine neoplasms of the breast: The latest WHO classification and review of the literature. Cancers (Basel). 2022;14(1):101
3. Singh S, Aggarwal G, Kataria S, et al. Primary neuroendocrine carcinoma of breast. J Cytol. 2011;28(2):91-92
4. Baldelli R, Franco M, Renzelli V, et al. Neuroendocrine neoplasms of the breast: A multicenter retrospective Italian study. Minerva Endocrinol (Torino). 2025;50(4):408-14
5. Rosen LE, Gattuso P. Neuroendocrine tumors of the breast. Arch Pathol Lab Med. 2017;141(11):1577-81
6. Tan PH, Ellis I, Allison K, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathology. 2020;77(2):181-85
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors (v3.2025) [Internet]. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2025. Available from: https://www.nccn.org/guidelines/guidelines-detail?id=1448
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (v5.2025)[Internet]. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2025. Available from: https://www.nccn.org/guidelines/guidelines-detail?id=1419
9. Upalakalin JN, Collins LC, Tawa N, Parangi S. Carcinoid tumors in the breast. Am J Surg. 2006;191(6):799-805
10. Tankere P, Zanetta S, Kaderbhai CG, et al. Small cell neuroendocrine carcinoma of the paranasal sinuses with unexpected location and clinical presentation and occupational exposure: A case report. Am J Case Rep. 2022;23:e934980
11. Hanby AM, Walker C. Pathology and genetics: Tumours of the breast and female genital organs. Breast Cancer Res. 2004;6(3):133-36
12. Lakhani SR, Ellis IO, Schnitt SJ, et al, editors. WHO classification of tumours of the breast. 4th ed. Lyon (France): IARC Press; 2012
13. Mohamed A, Zeidalkilani J, Asa SL, et al. Management of neuroendocrine breast carcinoma (NEBC): Review of literature. Oncol Rev. 2024;18:12114
14. Inno A, Bogina G, Turazza M, et al. Neuroendocrine carcinoma of the breast: Current evidence and future perspectives. Oncologist. 2016;21(1):28-32
15. Wang J, Wei B, Albarracin CT, et al. Invasive neuroendocrine carcinoma of the breast: A population-based study from the SEER database. BMC Cancer. 2014;14:147
16. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297-305
17. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol. 2001;12(Suppl. 2):S99-S102
18. Manes K, Delis S, Papaspyrou N, et al. Neuroendocrine breast carcinoma metastatic to the liver: Report of a case and review of the literature. Int J Surg Case Rep. 2014;5(8):540-43
19. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol. 2013;24(1):152-60
20. Arrivi G, Verrico M, Roberto M, et al. Capecitabine and temozolomide (CAPTEM) in advanced neuroendocrine neoplasms (NENs): A systematic review and pooled analysis. Cancer Manag Res. 2022;14:3507-23

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