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Current approaches to the management of neuroendocrine breast carcinoma (NEBC): a review

Mohsen S. Ali[1]

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Abstract

Neuroendocrine breast carcinoma (NEBC), an infrequent malignancy, accounts for 2–5% of all invasive breast cancer cases. The minimal occurrence of these tumours has resulted in knowledge primarily acquired from unique case reports or short retrospective studies. NEBC is diagnosed by identifying morphological characteristics related to gastrointestinal tracts and lung neuroendocrine tumors and neuroendocrine biomarkers. Recent investigations have revealed that NEBCs, despite being hormone receptor-positive and HER2-negative, may have adverse outcomes in comparison to invasive breast cancer lacking neuroendocrine differentiation. The primary approach for early NEBC is surgical intervention, which is identical to invasive non-special histological carcinoma treatment. Anthracycline-and-taxane protocols are commonly used for neoadjuvant, adjuvant, and metastatic diseases, whereas platinum substances and etoposide are widely utilized for small-cell histology and high-proliferation tumors. At present, NEBC is categorized as an unspecified form of invasive breast carcinoma, lacking a more precise classification, as there is insufficient evidence to inform treatment decisions due to its low incidence and absence of randomized data. This review outlines the WHO classification, pathology, immunohistochemistry, diagnosis, treatment, and prognosis of NEBC. Furthermore, it encapsulates the most recent research on the molecular characteristics of NEBC, intending to offer innovative therapeutic insights into the disease.

Key words neuroendocrine breast cancer, breast carcinoma, neuroendocrine tumor, small-cell breast cancer, breast

1. Department of Internal Medicine, Faculty of Medicine, Thamar University, Dhamar, Yemen.

Correspondence: Mohsen S. Ali (Department of Internal Medicine, Faculty of Medicine, Thamar University, Dhamar, Yemen; Email: Moh_aljumaini@hotmail.com).

Introduction

In Western nations, breast cancer stands as the foremost cause of female mortality [1]. It has emerged as the most commonly diagnosed malignancy globally, surpassing lung cancer. In 2020, the estimated incidence of new breast cancer cases reached over two million, representing 11.7% of all new cancer diagnoses, with 684,996 fatalities being caused by the disease [2]. The prevalence of breast cancer has shown an upward trajectory since the large-scale implementation of mammography screening and is expected to continue to rise as the general population advances [3].

Neuroendocrine neoplasms (NEN) possess characteristics that differentiate them from other solid tumors [4]. Distributed throughout the body, neuroendocrine cells possess dual characteristics: a morphology akin to nerve cells and biological functions resembling those of endocrine cells [5]. NEBC, alternatively termed breast carcinoma with neuroendocrine differentiation, is a heterogeneous group of relatively sporadic tumors that accounts for 2–5% of all invasive breast cancers [6]. The variation in reported statistics may be related to the absence of standardized histopathological and immunohistochemical diagnostic standards, as neuroendocrine biomarkers are rarely used in the diagnosis of breast tumor [7]. It is a rare and poorly differentiated form of breast cancer that is often underestimated [8, 9]. However, the prognostic significance of these markers remains unclear. Due to its low prevalence, there is also a lack of information regarding the most effective treatment of NEBC. This review highlights the existing knowledge regarding the histopathology and immunohistochemical characteristics, as well as the treatment and prognosis of NEBC.

WHO classification

The first description of NEBC was published in 1963. It was initially characterized as an invasive breast carcinoma that histologically resembles intestinal carcinoid tumors [10]. In 1977, the term breast primary carcinoid tumor was first used by Cubilla and Woodruff, who reported a rare subset of breast cancer cases with a carcinoid development pattern [11]. Eight years later, Bussolati et al. provided definitive evidence of neuroendocrine differentiation by demonstrating positive chromogranin A (CgA) expression in the typical mammary glandular tissue [12]. The original diagnostic criteria for NEBC were first proposed by Sapino et al. a few years later. They examined breast carcinomas that shared morphological traits with neuroendocrine tumors of the lungs and GI tract and showed high levels of neuroendocrine markers (over 50%, especially CgA and synaptophysin, or Syn).

Breast neuroendocrine tumors (NETs) were recognized as a separate breast component by the WHO Classification (3rd Edition) until 2003, when NEBC was identified by structural neuroendocrine characteristics resembling those of gastrointestinal/pulmonary NETs, exhibiting a neuroendocrine marker in a minimum of 50% of the total number of cells [13]. The most sensitive and specific histopathological markers of neuroendocrine tissue are CgA and Syn [14]. NEBC may also occasionally show a positive result for neuron-specific enolase (NSE) [15], whereas CD56 and other immunohistochemical indicators appear to be less sensitive and precise [16].

In 2012, the WHO raised concerns about the 2003 version, suggesting that a diagnosis may be established without a certain proportion of tumor cells manifesting neuroendocrine biomarkers. The 2012 WHO classification framework subdivides breast neoplasms exhibiting neuroendocrine properties into three distinct groups based on their morphological characteristics: (a) neuroendocrine tumor, well-differentiated (carcinoid-like), (b) poorly differentiated neuroendocrine carcinoma/small-cell carcinoma, and (c) invasive carcinoma exhibiting neuroendocrine differentiation. Well-differentiated neuroendocrine tumors are typically characterized by low to moderate nuclear-level invasive tumors. These tumors consist of spindle and plasmocytoid cellular elements, sometimes exhibiting apparent cell characteristics, and resemble carcinoid tumors originating in the gastrointestinal system and pulmonary tissues. Poorly differentiated/small-cell neuroendocrine carcinomas exhibit morphological characteristics indistinguishable from those of small-cell lung cancers. They feature a high nuclear/cytoplasmic ratio, condensed chromatin, a rapid mitotic activity, and localized necrotic zones. The third group includes various morphological variants of invasive breast carcinoma characterized by neuroendocrine differentiation, primarily exemplified by the hypercellular variants of mucinous carcinoma and the invasive type of solid papillary carcinoma [17-19].

The difficulties in differentiating between NEBC and breast tumor with neuroendocrine characteristics prompted the WHO in 2019 to reclassify breast neuroendocrine neoplasms (NENs) into well-differentiated neuroendocrine tumors (NET) and poorly differentiated NEBC, encompassing both small-cell neuroendocrine carcinoma (NEC) and large-cell NEC [20]. Breast NETs were assessed using the Nottingham scoring system, which assesses the extent of glandular tube formation, nuclear mutations, and mitotic activity in the infiltrating breast tissue. Mitotic count remains the fundamental parameter in classification systems [21]. In accordance with the Nottingham scoring system, breast NENs are classified into well-differentiated tumors (G1), intermediate-differentiated tumors (G2), or poorly differentiated carcinomas (G3). Specialized breast carcinomas (BCs) expressing neuroendocrine (NE) markers, including solid papillary carcinomas (SPCs) and mucinous carcinomas (MCs), were excluded from the neuroendocrine neoplasm (NEN) classification. **Table 1** provides an overview of the various classifications provided by the WHO.

Epidemiology

Accurate evaluation of the incidence of NEBC has been hindered by the lack of standardization in the terms and definition of neuroendocrine carcinomas resulting from the shift in categorization and varied morphological and immunohistochemical principles for the diagnosis of NEBC from 2003 to 2019. As a result, the reported morbidity varies dramatically, falling between 0.1 and 19.5% [22-24]. In a comprehensive study, Wang and colleagues examined 381,644 cases of breast carcinoma using data from the Surveillance, Epidemiology, and End Results (SEER) database. The results indicated that based on the WHO diagnostic criteria established in 2003, the prevalence of NEBC in breast cancer was only 0.1%, significantly lower than the 25% reported by the WHO in 2012 [22]. NEBC may be underestimated due to the lack of routine immunohistochemical examination for neuroendocrine biomarkers and the tendency of cytomorphological evaluation to underestimate neuroendocrine differentiation. Consequently, confirming the actual incidence of NEBC is challenging [25].

Pathology and immunohistochemistry

A precise method for the development of NEBC is currently unknown. Since neuroendocrine cells cannot be found in breast tissues, several researchers have proposed that NEBC develops from differentiation processes in breast cancer rather than from pre-existing and hyperplastic neuroendocrine cells [26]. Conversely, Tomonori et al. illustrated that noncancerous neuroendocrine cells manifest within the breast tissue accompanying NEBC and are

Table 1. Update on the latest WHO classification of NEBC.

Year	Terminology	Description	Subgroups	Neuroendocrine markers
2003	Neuroendocrine tumor	Histological characteristics analogous to those found in neuroendocrine tumors of the gastrointestinal tract and lung.	Solid neuroendocrine carcinoma Large cell carcinoma	Chromogranin (CG) Synaptophysin (SYN)
		50% of the cell population expresses the NE marker.	Small cell or oat cell carcinoma	Neuron-specific enolase (NSE)
		IBC-NOS with localized NED shown by NE markers in dispersed cells was removed.		
2012	Carcinoma exhibiting neuroendocrine characteristics	Structural features reminiscent of those exhibited by neuroendocrine neoplasms originating in the gastrointestinal and pulmonary regions.	Highly differentiated neuroendocrine tumor	Chromogranin
		Express NE marker to a higher or a lower extent.	Poorly differentiated neuroendocrine tumor/ small cell carcinoma	Synaptophysin
		IBC-NST and specific variants with NED were introduced.	IBC with neuroendocrine differentiation (mucinous and solid papillary carcinoma)	Neuron-specific enolase
2019	Neuroendocrine neoplasm	Tumour with over 90% NED.	Neuroendocrine tumor	Chromogranin
		Hypercellular mucinous carcinoma and solid papillary carcinoma were not included.	Neuroendocrine carcinoma (NEC) (Small cell NEC; Large cell NEC)	Synaptophysin CD56 PGP9.5
	NST with neuroendocrine features in invasive breast cancer	≤90% NE historical characteristics or NE marker expression.	-	-
		Mixed invasive NST and NET/NEC account for 10–90%.		
		<10% of invasive NSTs reported on the focused NE pattern.		

organized in confined, clustered, and circumferential designs, suggesting a potential correlation between neuroendocrine cell proliferation and precancerous conditions during the histogenesis of NEBC [27]. NEBC exhibits clinical and radiological features that make it challenging to differentiate it from prevalent breast cancer types [7, 28]. As a result, the diagnosis of NEBC is established through histological and immunostaining of neuroendocrine biomarkers, which is essential for enhancing the validation rate of NEBC. The histological subtypes of NEBC are small-cell NEC, large-cell NEC, and mixed neuroendocrine/non-neuroendocrine neoplasm of the breast (Br-MINEN) [29].

The most prevalent NEBC subtype is small-cell NEC, which comprises diffusely proliferating neoplastic cells with tiny, darker, hyperchromatic nuclei tightly packed together, scanty cytoplasm with poorly delineated boundaries, and a high nuclear/cytoplasmic ratio under a microscope [30]. There is a high mitotic count accompanied by apoptosis, and areas of necrosis may be present. Estrogen receptors (ER) and progesterone receptors (PR) are expressed in 30–50 percent of cases [31]. Although BCL2 is often described, HER2 is not. Despite the lack of evidence for TTF-1 expression in small-cell NEC, this gene can differentiate between small-cell NEC originating in the breast and those that have spread to the lungs [32-35]. Large NEC tumor cells exhibit highly pleomorphic nuclei characterized by coarse chromatin and an adequate cytoplasm. Diagnosing large-cell NEC presents challenges, particularly compared to lung or gastrointestinal cases, owing to their resemblance to high Nottingham histological grade invasive breast carcinoma of no particular type (IBC-NST) in H&E sections. Consequently, immunohistochemical staining for neuroendocrine markers may not be performed, resulting in inadequate reporting. Fewer than ten cases of large-cell NEC have been described in the literature, with diagnosis primarily based on the expression of neuroendocrine markers [36]. Information regarding Br-MiNEN is limited because most published cases, including those in the WHO classification, do not contain clinicopathological studies about this distinct entity. Consequently, the diagnostic criteria for Br-MiNENs were derived from those established for digestive MiNENs [37, 38].

The most reliable method for diagnosing NEBC is an immunohistochemical examination of neuroendocrine biomarkers

[39]. The development of immunohistochemical staining techniques allows for identifying neuroendocrine characteristics in groups of breast cancers by demonstrating their positivity for CD56, Syn, CgA, and (NSE). The neuroendocrine markers with the highest sensitivity and specificity were CgA and Syn, whereas NSE and CD56 showed lower levels of both markers. [40]. Insulinoma-associated protein 1 (INSM1) has been proposed as a reliable marker for neuroendocrine differentiation, aiding in diagnosing neuroendocrine neoplasms, particularly in cases of poor differentiation [41, 42]. Although these immunomarkers have potential utility, their application remains infrequent. Instead, they are typically reserved for instances where a highly skilled pathologist identifies or suspects neuroendocrine morphology on standard H&E-stained slides.

The majority of well-differentiated neuroendocrine tumours exhibit positive ER, PR, and AR markers. Additionally, these markers are present in more than half of poorly differentiated NEBC cases. Poorly differentiated neuroendocrine carcinomas of the breast frequently exhibit TTF1 expression, a marker typically associated with the lung lineage [43]. Additionally, up to 45% of these cases demonstrate androgen receptor (AR) expression, which is often expressed together with GCDFP15. Negative results were noted for basal markers (CK5/6, CK14, and p63) along with EGFR protein [44]. CDX2 uniformly demonstrates negative expression in primary breast neuroendocrine tumors, suggesting its potential utility in distinguishing these tumors from gastrointestinal tumors [45].

NEBCs are often positive for hormone receptors (HR) and negative for human epidermal growth factor receptor 2 (HER2) [6, 46]. They can be classified as either luminal A or luminal B molecular subtypes.

Approximately half of all NEBCs have a luminal B phenotype, an immunohistochemistry-defined HR-positive tumor with a high proliferation index (Ki67. 14%) [47]. Furthermore, there are cases of HER2-positive NEBC [48] and small-cell breast carcinoma with basal-like features [34]. Somatostatin receptors (SSTRs), a class of G-protein coupled receptors, are found in neuroendocrine tumor cells originating from pulmonary, prostatic, and gastrointestinal tissues. Additionally, these receptors are present in ductal breast carcinoma cells [49]. Five subtypes of SSTRs have been identified, ranging from SSTR1 to SSTR5. Among these, SSTR2A is the subtype most frequently expressed in breast cancer and shows the strongest association with luminal tumors [50].

Clinical presentation & diagnostic assessment

The low incidence of NEBC results in a lack of a comprehensive understanding of its specific clinical characteristics. Most information was from research papers, case studies, and reviews. Individuals diagnosed with NEBC predominantly fall within the 60–70-year age bracket, with a notable predominance of females [7, 51]. The clinical manifestation of NEBC is primarily defined as a solitary breast mass, potentially combined with cutaneous ulceration, bloody discharge from the nipple, skin retraction, clear axillary mass, and breast soreness [18]. Some individuals might experience problems such as bone pain, breathing problems, hepatic dysfunction, hematuria, and neuropathy resulting from metastasis [52]. Although specific individuals may remain asymptomatic, they sometimes reveal the presence of the disease through routine mammographic screening [53, 54]. Additionally, individuals may have elevated levels of hormones or carcinoid syndrome.

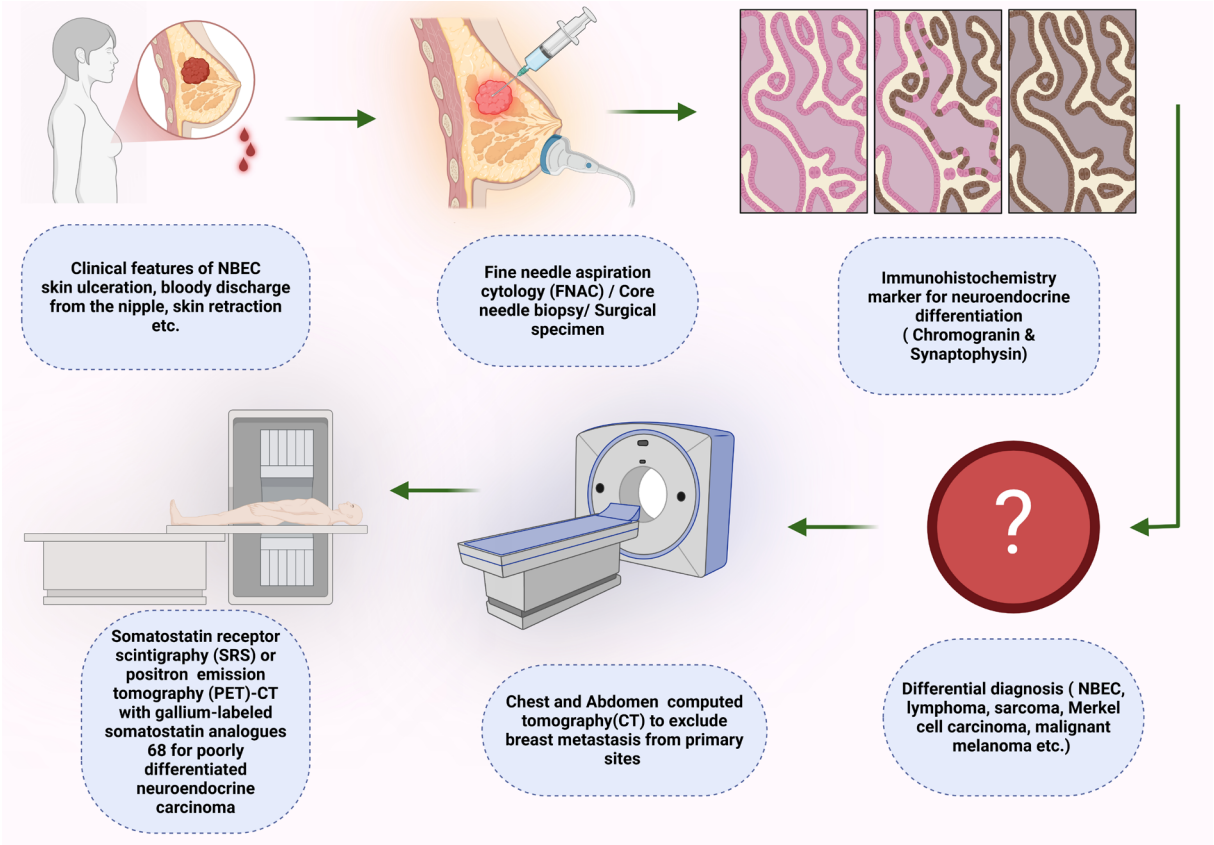

Figure 1. An illustration of the diagnostic process related to neuroendocrine breast cancer (NEBC).

A biopsy is required for a definitive diagnosis of NEBC based on morphological characteristics and neuroendocrine biomarkers [55]. Fine Needle Aspiration (FNA) is insufficient for diagnosing NEBC because of the overlapping cytological and morphological features present in other breast lumps, including invasive ductal carcinoma and intraductal papilloma [54, 56]. Consequently, performing an imaging-guided core needle biopsy accompanied by IHC staining for neuroendocrine markers is essential to achieve a conclusive diagnosis of NEBC. Since the majority of neuroendocrine tumors arise from pulmonary and gastrointestinal origins, it is necessary to rule out metastatic lesions from other primary neuroendocrine locations, as well as other differential diagnoses such as Merkel cell carcinoma or melanoma, prior to establishing a diagnosis of primary NEBC [57]. Consequently, thoracic, and abdominal computed tomography (CT) scans should be undertaken to elucidate potential primary neoplasms associated with breast metastasis. A positron emission tomography scan (PET-FDG18) offers further diagnostic insights when distinguishing between primary and secondary neuroendocrine tumors is uncertain [58, 59]. **Figure 1** illustrates the diagnostic processes associated with NEBC.

The radiological findings of NEBC are poorly understood and lack specificity. Numerous studies have indicated that NEBC typically presents with the following features: a circular, elliptical, or lobular mass with non-spiculated borders, a distinctly defined high-density lesion on a mammogram, a hypoechoic solid tumor with fuzzy boundaries, exhibiting increased vascularity, and the absence of posterior echo enhancement or a cystic component on breast scans. Magnetic resonance imaging reveals uniformly low levels of signals with heterogeneous quick initial augmentation on the T1-weighted view [60, 61]. In cases where the delineation between primary and secondary neuroendocrine tumours remains elusive, researchers have put forth various practical guidelines to facilitate differential diagnosis. Specifically, a giant tumor, the lack of an in-situ component, negative progesterone or estrogen receptor status, and no axillary nodal dissemination strongly indicate a secondary lesion rather than a primary one [62, 63].

Therapeutic intervention

Research has consistently shown that NEBC is associated with more intrusive behavior, a higher likelihood of distant metastasis and local recurrence, and a poorer prognosis when compared to IDC-NST [64]. Presently, a notable paucity of clinical investigations exists regarding NEBC, and surgical intervention continues to be the primary treatment, accompanied by adjunctive hormone therapy. Surgical excision stands as the optimal choice for localized disease, akin to ductal and lobular carcinoma of the breast. Surgeons must consider a range of important factors, including the patient's age, the overall state of health, the size and position of the tumor, and the ratio of tumor size to breast size [65, 66]. The existing literature primarily relies on classifications established before the WHO 2019 guidelines, which may introduce confusion and potentially result in inaccurate conclusions regarding mixed diagnostic variety [67]. Breast-conserving surgery (BCS), whether accompanied by adjuvant therapy or not, is increasingly selected; however, mastectomy remains the preferred surgical approach owing to the inherently aggressive behavior exhibited by neuroendocrine tumours during their early developmental stages [68]. To determine the optimal surgical approach, it is imperative to distinguish between primary and metastatic neuroendocrine neoplasms originating from other anatomical structures [69]. Despite its rarity, treatment options for NEBC lack standardization, with much of the evidence obtained from retrospective analysis and individual case studies (**Table 2**).

Radiotherapy

Currently, no dedicated studies have addressed adjuvant radiotherapy in NEBC, and its consideration should rely on the established protocols for several types of invasive breast cancer [9, 29]. Various factors, including the stage of the tumor, hormone receptor status, HER2 expression status, and the overall clinical condition of the patient influence the approach to managing NEBC through radiotherapy [70]. This method is commonly utilized after lumpectomy to reduce the chance of local recurrence and post-mastectomy when high-risk traits are identified, including significant tumour size, positive margins, or lymphatic node involvement [71, 72]. Hare et al. indicated that radiation therapy offers no advantage in small cell carcinoma of the breast [30].

Chemotherapy

Chemotherapy is an essential aspect of NEBC treatment, especially for high-grade tumors, advanced-stage disease, or metastatic dissemination. Currently, there is insufficient proof to determine the most efficient chemotherapeutic regimen. The histopathological features of NEBC may serve as a basis for the selection of appropriate chemotherapeutic agents. Typically, poorly differentiated small-cell NEC or large-cell NEC are managed using

Table 2. Information derived from case reports and retrospective studies for treatment of NEBC.

Stage	Subtype	Ki67 %	Hormonal status	Surgical Rx	Neoadjuvant chemotherapy	Adjuvant chemotherapy	Hormonal Therapy	Ref
IIIC	Small cell	Not reported	ER/PR/Her- 2(-)	Yes	No	Yes (CBDCA & VP-16)	No	[33]
IIIB	Not reported	>20%	ER(+) PR & Her-2(-)	Yes	Yes	Yes (CDDP/VP-16)	Yes	[69]
IIA	Small cell	50%	ER/ Her-2(-) PR(+)	Yes	No	Yes (CDDP/VP-16)+ FEC	No	[55]
IIIA	Large cell	75%	ER/PR/Her-2(-)	Yes	No	Yes (EC)	No	[36]
IIB	Not reported	90%	ER/PR/ (+) Her-2 (-)	Yes	No	Yes (FEC)	Yes	[70]

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; CBDCA, carboplatin; VP-16, Etoposide; CDDP, cisplatin; EC, Epirubicin/Cyclophosphamide; FEC, Fluorouracil/Epirubicin/Cyclophosphamide.

platinum and etoposide regimens [73, 74]. Other forms of NEBC are treated with taxane-based or anthracycline-based [75]. The available evidence concerning the management of NEBC through neoadjuvant chemotherapy is lacking. Sanguinetti et al. examined an aggressive NEBC by implementing neoadjuvant therapy with carboplatin and etoposide, leading to a stable condition [76, 77]. According to Wei et al., a patient with NEBC showed a significant improvement after four rounds of chemotherapy using TEC (docetaxel, epirubicin, and cyclophosphamide), which led to a substantial drop in the Ki-67 cell proliferation rate from a quarter to ten percent [75, 78]. However, a definitive suggestion could not be made because of the limited scope of knowledge.

Endocrine therapy has an apparent effect on the treatment of HR-positive breast cancer, suggesting that it could be a beneficial approach for managing NEBC. Several studies have indicated that hormonal treatment, especially when coupled with various other therapeutic strategies, is employed to treat NEBC in cases where the tumor exhibits relevant receptors [79]. Zhang et al. demonstrated that an adult NEBC patient who underwent treatment with goserelin and letrozole as neoadjuvant therapy experienced a remarkable response [80]. Neoadjuvant endocrine therapy may be employed for individuals with sizable tumors who wish to preserve the breast and oppose neoadjuvant chemotherapy. Shanks and colleagues reported a groundbreaking case involving a patient diagnosed with high-grade NEBC. This individual displayed resistance to conventional platinum-based chemotherapy and hormone therapy. However, the patient exhibited a remarkable response to a therapeutic regimen combining palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, with fulvestrant [81].

The most recent molecular research has identified PIK3CA mutations in 7–33% of NEBC cases, a proportion that falls below the incidence observed in HR-positive HER2-negative IBC-NSTs [82-84]. A standard treatment approach for HR-positive, HER2-negative IBC-NSTs involves targeting the PI3K/AKT/mTOR pathway by utilizing a PI3K inhibitor (such as alpelisib) alongside an mTOR inhibitor (such as everolimus) in various research studies [85-87]. Focusing on the PI3K/AKT/mTOR signalling cascade may be a viable and encouraging approach for managing HR-positive HER2-negative NEBC.

HER2 positivity is often associated with poorly differentiated breast tumors. Targeted therapy against HER2 may be applicable in occasional cases of NEBC, whether in the adjuvant phase or during metastatic progression with HER2 overexpression. Inga et al. documented a case involving a patient who received anti-HER2 therapy in the adjuvant context for HER-2-positive primary NEBC, resulting in 9-year disease-free survival [88]. Arpine managed a case involving a patient with recurrent bone NEBC exhibiting HER2 amplification who experienced an inadequate response to treatment with trastuzumab [89].

Somatostatin receptor (SSTR) ligands play a crucial role in the biological treatment of neuroendocrine neoplasms. Immunohistochemical analyses have revealed that mammary neuroendocrine tumours express somatostatin receptor subtypes 2, 2A, 2B, 3, and 5 [90]. Global standards support the use of these analogs as the primary treatment for well-differentiated G1/2 metastatic neuroendocrine tumors. Radiolabeled SSTR-targeted imaging and peptide receptor radionuclide therapy (PRRT) has shown significant advantages in treating SSTR-expressing neuroendocrine tumors, indicating that PRRT could be an effective option for NEBC. Furthermore, The potential for metastasis in

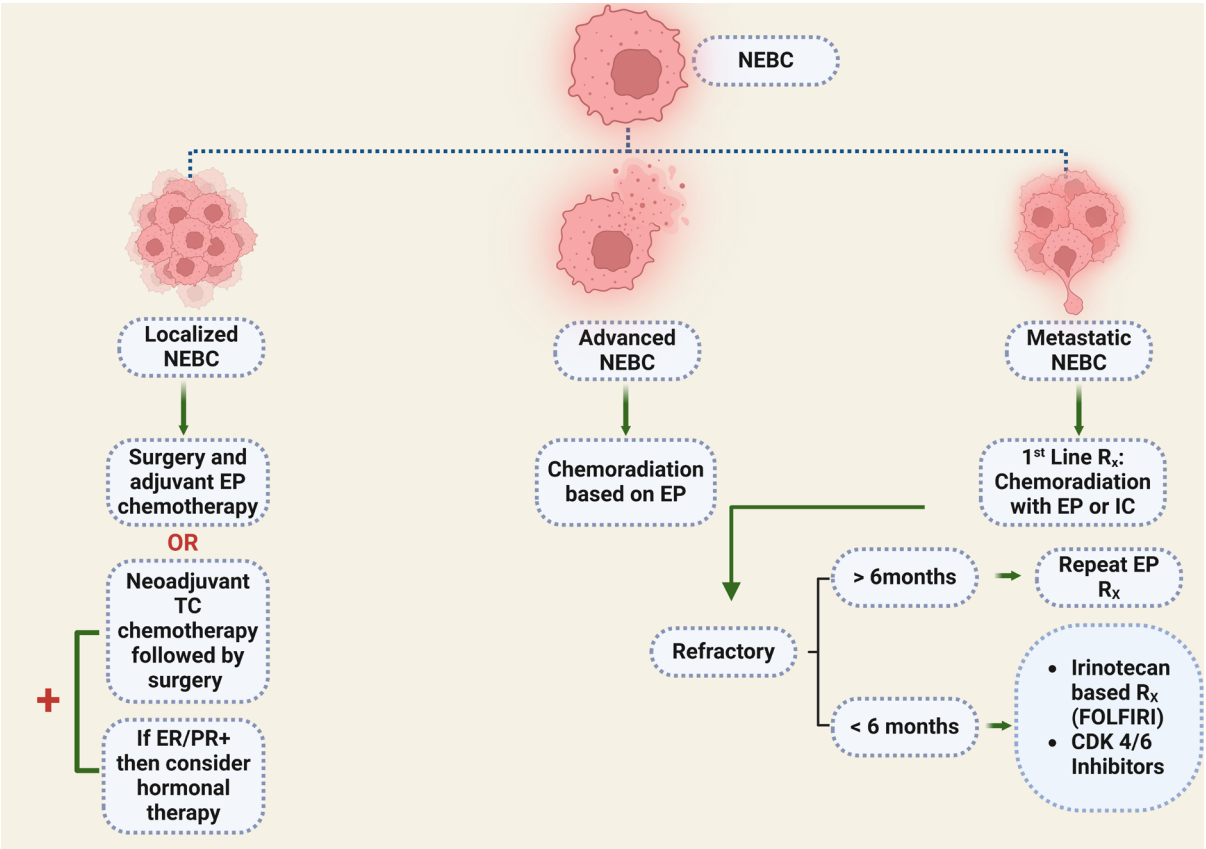

Figure 2. A protocol for the treatment of NEBC. EP, Etoposide plus platinum (cisplatin or carboplatin); TC, Taxotere and cyclophosphamide; IC, Irinotecan plus cisplatin; ER, Estrogen receptor; PR, Progesterone receptor.

NEBCs persists for years subsequent to primary tumour treatment. Thus, it is recommended that ongoing follow-ups be conducted [91]. An overview of NEBC treatment is presented in **Figure 2**.

Prognosis

The majority of studies available in the literature have collectively examined neuroendocrine breast neoplasms, failing to categorize them into distinct subtypes, as advised by the WHO. The current corpus of statistical evidence regarding the significance of neuroendocrine characteristics in mammary neoplasms is inadequate for formulating conclusive inferences [92, 93]. The vast majority of published studies indicate poor prognosis for neuroendocrine neoplasms, highlighting that neuroendocrine differentiation serves as an independent adverse prognostic factor for overall survival (OS) and disease-specific survival (DSS) in breast cancer (BC). This is associated with a higher incidence of both local and metastatic recurrence, even though some smaller-scale investigations have documented comparable or even improved results for neuroendocrine neoplasms in comparison to patients with non-specific breast cancer (BC-NST) [93, 94]. The prognosis is most severe when small-cell NEC are limited to specific histologic subgroups.

Additionally, cancer antigen 15-3 has been found to be considerably elevated in patients' baseline measurements and subsequently exhibited a substantial decrease following treatment, implying that CA15-3 could potentially serve as a prognostic marker [95]. Multiple investigations have demonstrated that patients presenting with tumours exceeding 20 mm in size, late-stage disease, Ki67 expression above 14%, and negative hormone receptor status are correlated with diminished OS [96]. When discussing the impact of therapeutic approaches on outcomes in NEBC, patients who did not undergo surgical intervention experienced unfavorable DSS and OS. In contrast, those treated with chemotherapy demonstrated improved DSS and OS in neuroendocrine neoplasms. According to Wei et al., radiation therapy and endocrine therapy tend to improve survival rates compared with traditional chemotherapy [97]. However, because of the small sample size and short follow-up period, none of the therapies achieved significant results in their analysis.

Conclusions

NEBC is an uncommon cancer, and its biological features, clinical manifestations, therapeutic modalities, and prognosis are not entirely comprehended. The identification of NEBC relies on observing morphological characteristics equivalent to those found in gastrointestinal and lung neuroendocrine tumors and detecting neuroendocrine markers. Given its infrequency and recent acknowledgment as a distinct category, existing diagnostic and treatment guidelines align closely with those for general invasive breast carcinomas. Therefore, additional research is essential to better pinpoint therapeutic targets and assist in developing more precise therapies that can enhance outcomes for individuals with NEBC.

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Availability of data and materials

Data and materials are available on request from the authors.

Ethical policy

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Author contributions

MSA contributed to draft, critical revision of the article, figure production and submitted the final version online.

Competing interests

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