Thieme

Invasive Breast Carcinoma with Neuroendocrine Differentiation: A Single-Center Analysis of Clinical Features and Prognosis

Invasives Mammakarzinom mit neuroendokriner Differenzierung: eine monozentrische Analyse der klinischen Merkmale und Prognose

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ABSTRACT

Introduction Invasive breast cancer with neuroendocrine differentiation is a rare subtype of breast malignancy. Due to frequent changes in the definition of these lesions, the correct diagnosis, estimation of exact prevalence, and clinical behaviour of this entity may be challenging. The aim of this study was to evaluate the prevalence, clinical features, and outcomes in a large cohort of patients with breast cancer with neuroendocrine differentiation.

Patients Twenty-seven cases of breast cancer with neuroendocrine differentiation have been included in this analysis. Twenty-one cases were identified by systematic immunohistochemical re-evaluation of 465 breast cancer specimens using the neuroendocrine markers chromogranin A and synaptophysin, resulting in a prevalence of 4.5%. A further six cases were identified by a review of clinical records.

Results Median age at the time of diagnosis was 61 years. 70% of patients had T2–4 tumors and 37% were node-positive. The most common immunohistochemical subtype was HR-positive/HER2-negative (85%). 93% were positive for synaptophysin and 48% for chromogranin A. Somatostatin receptor type 2A status was positive in 12 of 24 analyzed tumors

(50%). Neuroendocrine-specific treatment with somatostatin analogues was administered in two patients. The 5-year survival rate was 70%.

Conclusions Breast cancer with neuroendocrine differentiation is mostly HR-positive/HER2-negative and the diagnosis is made at a higher TNM stage than in patients with conventional invasive breast carcinoma. Moreover, breast cancer with neuroendocrine differentiation was found to be associated with impaired prognosis in several retrospective trials. Due to somatostatin receptor 2A expression, somatostatin receptor-based imaging can be used and somatostatin receptor-targeted therapy can be offered in selected cases.

ZUSAMMENFASSUNG

Einleitung Invasives Mammakarzinom mit neuroendokriner Differenzierung ist eine seltene Unterart von Brustkrebs. Da die Definition dieser Läsionen häufig geändert wurde, kann eine korrekte Diagnose sowie eine richtige Einschätzung der genauen Prävalenz und des klinischen Verhaltens dieser Entität Schwierigkeiten bereiten. Ziel dieser Studie war es, die Prävalenz, die klinischen Merkmale und das Outcome in einem großen Patientenkollektiv von Frauen mit Mammakarzinom und neuroendokriner Differenzierung zu evaluieren.

Patientinnen Die Daten von 27 Patientinnen mit Brustkrebs mit neuroendokriner Differenzierung wurden in diese Analyse aufgenommen. 21 Fälle wurden durch eine systematische immunohistochemische Reevaluierung von 465 Brustkrebsproben mit Verwendung der neuroendokrinen Basismarker Chromogranin A und Synaptophysin identifiziert, was einer Prävalenz von 4,5% entspricht. Sechs weitere Fälle wurden durch eine Überprüfung der klinischen Krankenakten indentifiziert.

Ergebnisse Das durchschnittliche Alter zum Zeitpunkt der Diagnose betrug 61 Jahre. 70% der Patientinnen hatten T2–4 Tumoren, und 37% hatten positive Lymphknotenbefunde. Die häufigste immunohistochemische Unterart war HR-positiv/HER2-negativ (85%). 93% waren für Synaptophysin und 48% für Chromogranin A positiv. Der Somatostatin-Rezeptor-2A-Status war in 12 von 24 analysierten Tumoren positiv (50%). Zwei Patientinnen erhielten eine neuroendokrin-spezifische Therapie mit Somatostatin-Analoga. Die 5-Jahres-Überlebensrate betrug 70%.

Schlussfolgerungen Brustkrebs mit neuroendokriner Differenzierung ist meist HR-positiv/HER2-negativ, und die Diagnose wird meist in einem höheren TNM-Stadium gestellt als bei Patientinnen mit herkömmlichen invasiven Mammakarzinom. Darüber hinaus war der Brustkrebs mit neuroendokriner Differenzierung in mehreren retrospektiven Studien mit einer schlechten Prognose assoziiert. Im Falle eines positiven SSTR2A-Status kann eine Somatostatin-Rezeptor-basierte Bildgebung eingesetzt werden, und in ausgewählten Fällen eine zielgerichtete Therapie mit Somatostatinanaloga angeboten werden.

Abbreviations

BC-NE   breast cancer with neuroendocrine differentiation
BC-NST   breast cancer no special type
LCNEC   large cell neuroendocrine cancer
NE   neuroendocrine
NET   neuroendocrine tumor
NEN   neuroendocrine neoplasia
SCNEC   small cell neuroendocrine cancer
SSA   somatostatin analogues
SSTR   somatostatin receptor

Background

Primary neuroendocrine neoplasia (NEN) of the breast is a rare subtype of breast cancer (BC) representing <1% of all NENs, which occur most commonly in the gastrointestinal tract and the lung [1, 2]. The prevalence of neuroendocrine differentiation among BC patients varies between 0.1 and 20% in the literature, with the World Health Organization (WHO) reporting a prevalence of up to 5% of BC cases [3]. This discrepancy is due to the fact that the diagnostic criteria and definition of this heterogeneous group of lesions have frequently changed in the last two decades, and neuroendocrine immunohistochemical markers are not routinely used in BC diagnostics [4]. The previous and current WHO classification of NEN of the breast are shown in ▶ **Table 1**.

Neuroendocrine differentiation in BC was first described by Feyrter and Hartmann in 1963; this was followed by a series of eight patients with "primary carcinoid tumor of the breast" reported by Cubilla and Woodruff in 1977 [5, 6]. Since then, many authors have tried to describe and characterize this heterogeneous entity until in 2000, Sapino et al. proposed a definition for NEN of the breast as a subset of tumors with specific morphological features and expression of the neuroendocrine markers chromogranin and/or synaptophysin in more than 50% of tumor cells [7]. This definition was later adopted by the WHO classification of NEN of the breast introduced in 2003 and last modified in 2019 [8 – 10].

While earlier classifications included a category comprising a subset of BC (no special or special type, e.g., mucinous, papillary etc.) with neuroendocrine differentiation as determined by morphological and immunohistochemical analysis, the latest version excludes BC-NE from the NEN group altogether (▶ **Table 1**). Through these changes, the WHO has attempted to develop a uniform classification framework for NENs at different anatomical sites to provide pathologists and clinicians with a consistent management strategy for NEN patients, since neuroendocrine differentiation in BC, with the exception of small cell carcinoma, is assumed to have no therapeutic significance [3].

However, there are certain diagnostic and therapeutic aspects of BC-NE that should be acknowledged, even if current guidelines recommend treatment based on the general principles of breast cancer therapy. The aims of this retrospective study were:

1. to analyze the clinical features and treatment strategies of BC-NE,
2. to assess the prognostic impact of BC-NE, and
3. to compare our results to previously published studies.

▶ **Table 1** Different classifications of NEN of the breast in the last two decades.

WHO 2003 [8]	WHO 2012 [9]	WHO 2019 [10]
Solid neuroendocrine carcinoma (NEC)*	Well differentiated neuroendocrine tumor (WD-NET)[2]	Neuroendocrine tumor (NET) • grade 1 • grade 2
	Invasive breast carcinoma with neuroendocrine differentiation** • special type • no special type	Invasive breast cancer with neuroendocrine differentiation overridden by morphological tumor type should not be classified as a true neuroendocrine neoplasia but as a morphological subtype (e.g., NST, mucinous, papillary) with neuroendocrine differentiation
Large cell neuroendocrine carcinoma (LCNEC)[1]		Large cell neuroendocrine carcinoma[1] (LCNEC)
Small cell/oat cell carcinoma (SCNEC)[1]	Poorly differentiated neuroendocrine carcinoma (PD-NEC)/small cell carcinoma[1]	Small cell neuroendocrine carcinoma[1] (SCNEC)

* Expression of neuroendocrine markers > 50% (particularly chromogranin A and/or synaptophysin), ** no threshold for the expression of the neuroendocrine markers, [1] analogous to small-cell or large-cell lung cancer, [2] low grade tumors morphologically similar to carcinoid tumors of other sites. NST: no special type.
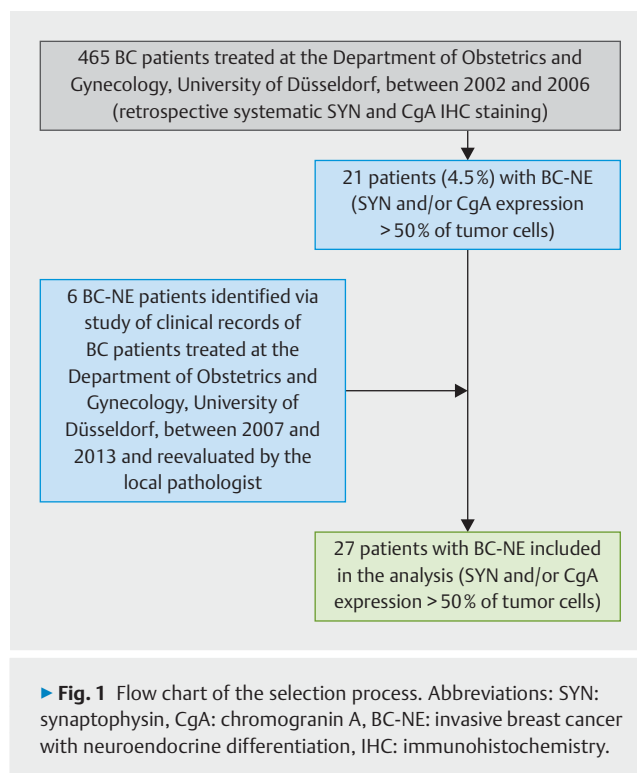
Materials and Methods

Patient material

A total of 27 patients with BC-NE treated at the Department of Obstetrics and Gynecology of the University of Duesseldorf, Germany, between 2002 and 2013 were included in this analysis. Surgically excised breast specimens from 465 BC patients treated between 2002 and 2006 were systematically re-evaluated in terms of neuroendocrine differentiation. Moreover, a review of the clinical records of BC patients treated at our department between 2007 and 2013 was performed to identify further BC-NE patients. Inclusion criteria were: primary breast cancer with neuroendocrine differentiation (T1–T4, N0–3, M0/M1) (TNM, 8th edition 2017) defined as > 50% positivity for the immunohistochemical neuroendocrine markers chromogranin A and/or synaptophysin according to the NEN definition from 2003 (▶ **Table 1**). Exclusion criteria were the following entities: poorly differentiated large or small cell neuroendocrine carcinoma and well differentiated neuroendocrine tumor (NET, G1). The flow chart showing patient selection for our analysis is presented in ▶ **Fig. 1**. The study was approved by the local Ethical Committee of the Heinrich Heine University of Duesseldorf (Study number 4524).

Immunohistochemistry staining

Tissue sections (2 μm) were deparaffinized and rehydrated. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide. Blocking non-specific protein-binding sites, normal mouse serum was applied. Neuroendocrine markers were detected with specific monoclonal mouse antibodies for synaptophysin (NCL-L-Synap 299, Novocastra, Berlin, Germany) and chromogranin A (MAB 5268, Chemikon, Schwalbach, Germany) at a dilution of 1:100 and 1:1000, respectively. Immunostaining was performed with anti-mouse IgG and Vectastain ABC, followed by chromogen detection. Finally, the slides were counterstained with hematoxylin and mounted for examination. SSTR 2A status was

465 BC patients treated at the Department of Obstetrics and Gynecology, University of Düsseldorf, between 2002 and 2006 (retrospective systematic SYN and CgA IHC staining)

21 patients (4.5%) with BC-NE (SYN and/or CgA expression > 50% of tumor cells)

6 BC-NE patients identified via study of clinical records of BC patients treated at the Department of Obstetrics and Gynecology, University of Düsseldorf, between 2007 and 2013 and reevaluated by the local pathologist

27 patients with BC-NE included in the analysis (SYN and/or CgA expression > 50% of tumor cells)

▶ **Fig. 1** Flow chart of the selection process. Abbreviations: SYN: synaptophysin, CgA: chromogranin A, BC-NE: invasive breast cancer with neuroendocrine differentiation, IHC: immunohistochemistry.

determined with monoclonal rabbit antibody (UMB1, Abcam, Cambridge, UK) at a dilution of 1:50. Membranous staining was scored as: 0: no staining; 1: weak staining (< 10%); 2+: moderate staining (10–80%); and 3+: strong staining (> 80% tumor cells).

Statistical analysis

Statistical analysis was performed using SPSS (version 25). Survival intervals were measured from the time of diagnosis until death or the first clinical, radiological or pathological diagnosis of relapse, whichever occurred first. Relapse was defined as either local

	n (%)
Total	27 (100)
Age at diagnosis	
▪ < 50	4 (15)
▪ 50–69	13 (48)
▪ ≥ 70	10 (37)
Menopausal status	
▪ Premenopausal	5 (18.5)
▪ Postmenopausal	22 (81.5)
Stage at diagnosis	
▪ I	6 (22)
▪ II	14 (52)
▪ III	3 (11)
▪ IV	3 (11)
▪ Unknown	1 (4)
Tumor stage	
▪ T1	7 (26)
▪ T2	16 (60)
▪ T3-4	3 (11)
▪ Unknown	1 (4)
Tumor focality	
▪ Unifocal	21 (78)
▪ Multifocal	5 (19)
▪ Unknown	1 (4)
DCIS component	
▪ Yes	12 (44
▪ No	15 (56)
Nodal status	
▪ Negative	15 (56)
▪ Positive	10 (37)
▪ Unknown	2 (7)
Lymphatic vessel infiltration	
▪ L0	11 (41)
▪ L1	8 (30)
▪ Unknown	8 (30)
Original histology	
▪ NST	16 (59)
▪ Lobular	1 (4)
▪ NST/lobular	1 (4)
▪ Mucinous	4 (15)
▪ NET*	5 (18)
Grading	
▪ II	21 (78)
▪ III	6 (22)

▶ **Table 2** Clinicopathological features and administered therapy in the study cohort. *(Continued)*

	n (%)
Ki-67 index	
▪ < 15	6 (22)
▪ 15–29	8 (30)
▪ ≥ 30	11 (41)
▪ Unknown	2 (7)
IHC subtype	
▪ HR+/HER2−	23 (85)
▪ HR+/HER2+	2 (7)
▪ HR−/HER2+	0 (0)
▪ TNBC	2 (7)
SSTR-based imaging performed	
▪ Yes	5 (19)
▪ No	22 (81)
Surgical procedure	
▪ Mastectomy	14 (52)
▪ Breast-conserving surgery	11 (41)
▪ None	2 (7)
AT-based Chemotherapy	
▪ Yes	14 (52)
▪ No	13 (48)
Endocrine therapy	
▪ Yes	24 (89)
▪ No	3 (11)
NE-specific therapy	
▪ Yes	2 (7)
▪ No	25 (93)

* Initially diagnosed as NET G2. TNBC: triple negative breast cancer, BCS: breast conserving surgery, NE: neuroendocrine, SSTR: somatostatin receptor, AT: anthracycline-taxane. Numbers in parentheses are percentages and do not add to 100 in some instances owing to rounding.

recurrence or distant metastasis. Survival was calculated using the Kaplan-Meier method. Primarily metastatic patients were excluded from the disease-free survival (DFS) analysis.

Results

Patients' characteristics

Clinical data from 27 patients with BC-NE were eligible for this study. Twenty-one of these patients were identified by a systematic immunohistochemical re-evaluation of 465 breast surgical specimens with regard to NE differentiation, resulting in a prevalence of 4.5%. A further six patients were identified through an analysis of the clinical records of BC patients treated between 2007 and 2013 and subsequent histological re-evaluation (▶ **Fig. 1**). Clinical features of the study cohort are presented in ▶ **Table 2**. The median age at the time of diagnosis was 61 years
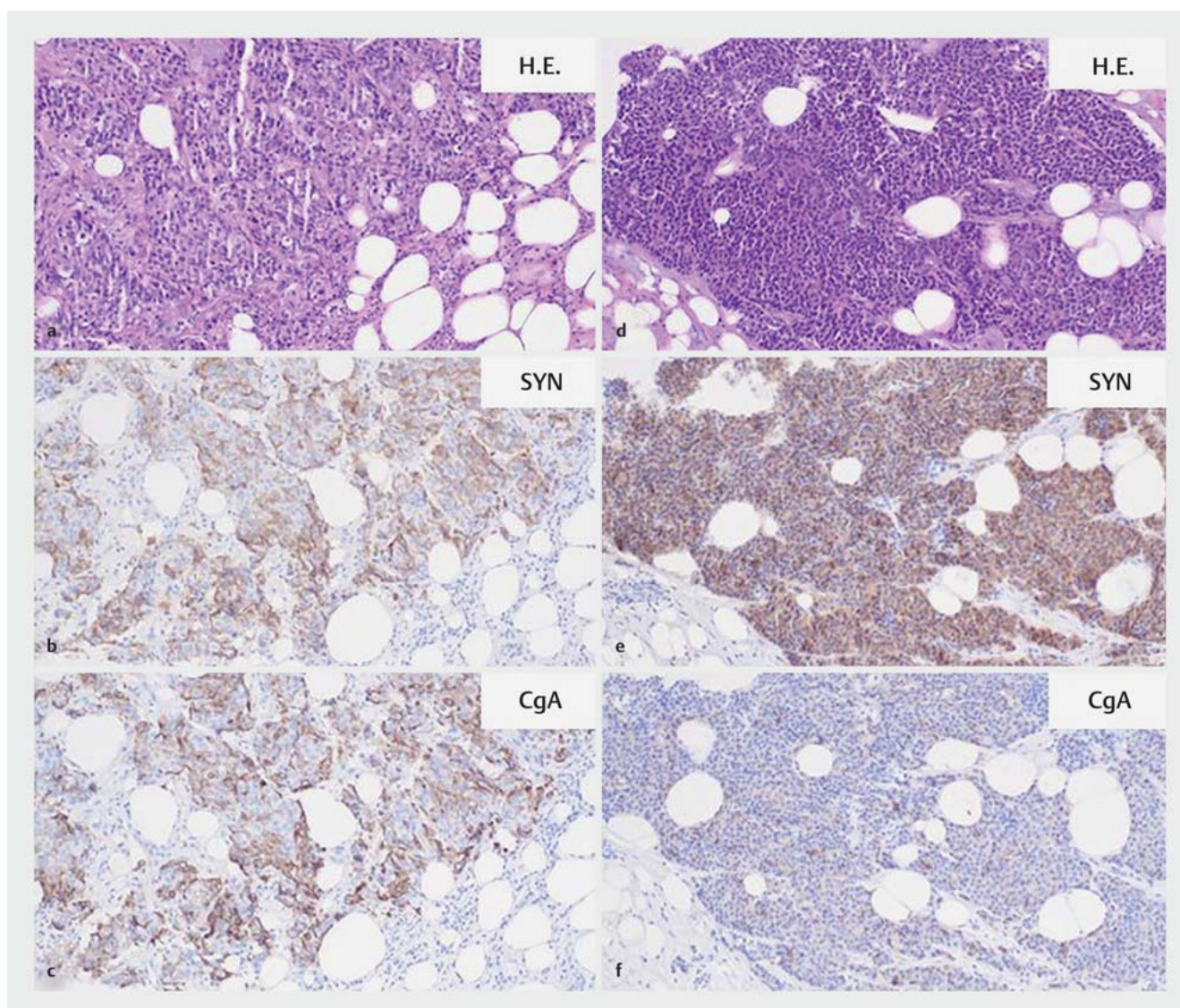
▶ **Fig. 2** Histopathology and expression of general neuroendocrine marker proteins in two different breast carcinomas with neuroendocrine differentiation. **a, d** Hematoxylin and eosin (H.E.) staining demonstrates a solid growth pattern and complete lack of tubular architecture in both carcinomas. Cytology of the tumor cells in **a** show an NST-like pattern, while cytology of the tumor cells in **d** is highly suggestive for a neuroendocrine phenotype. **b, e** Expression of the pan-neuroendocrine marker synaptophysin (SYN) in more than 50% of tumor cells in **b** and in 100% of tumor cells in **e**. **c, f** Expression of the large dense core neuroendocrine vesicle marker chromogranin A (CgA) in more than 50% of tumor cells in **c**, while tumor cells in **f** are positive in a minor subpopulation.

(range 38–84 years) and 22 out of 27 patients (82%) were postmenopausal. Nineteen patients (70%) had T2–4 tumors and 10 (37%) were node-positive with lymphatic vessel infiltration (L1) detected in 8 out of 27 cases (30%). The most common immunohistochemical tumor subtype was HR-positive/HER2-negative, diagnosed in 23 patients (85%), followed by HR-positive/HER2-positive and triple-negative BC in two patients each (7%). Thirteen tumors (48%) were positive for chromogranin A (CgA) and 25 (93%) were positive for synaptophysin (Syn), whereas 12 tumors (44%) expressed both markers in >50% of tumor cells (▶ **Fig. 2**, **Table 3**). Somatostatin receptor type 2A (SSTR 2A) was analyzed in 24 tumors and of which 12 (50%) showed a SSTR 2A-positive status (▶ **Fig. 3**, **Table 3**). None of the patients in our cohort present-

ed with specific clinical symptoms due to neuroendocrine tumor differentiation.

Clinical diagnosis and treatment

Standard thoracic and abdominal imaging (CT scan or ultrasound and X-ray according to the current recommendations and internal standards) as well as bone scans were performed in all patients at the time of diagnosis to exclude metastatic disease. Additional SSTR-based neuroendocrine imaging (octreoscan or 68Ga-DOTA-TOC PET/CT) was performed in five patients with known neuroendocrine differentiation of BC at the time of the diagnosis and a SSTR-positive score. Two primary metastatic patients received an octreotide scan to confirm the NE differentiation of the metastatic
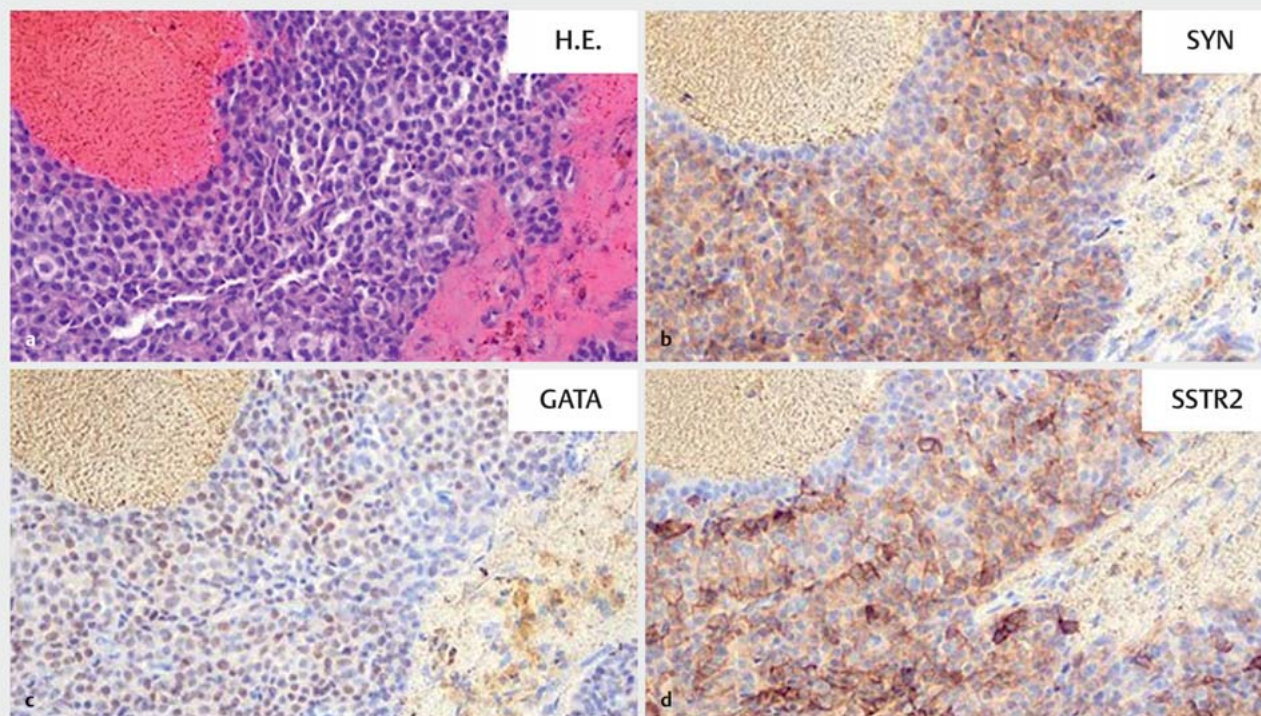
▶ **Fig. 3** Expression of the nuclear transcription factor GATA and the somatostatin receptor 2A in breast carcinoma with neuroendocrine differentiation. **a** Hematoxylin and eosin (H. E.) staining reveals a solid growth pattern, complete lack of tubular architecture and a cytology highly suggestive of neuroendocrine differentiation. **b** Expression of the pan-neuroendocrine marker synaptophysin (SYN) in approximately all tumor cells. **c** Nuclear expression of the breast-specific transcription factor GATA in the majority of tumor cells. **d** Circular membranous staining for the somatostatin receptor type 2A (SSTR 2) in a major subpopulation of tumor cells.

sites. In one patient with diffuse NE bone marrow infiltration and disease progress after chemotherapy with epirubicin weekly and endocrine therapy with fulvestrant, the octreotide scan was performed in order to evaluate the possibility of SSTR-specific radionuclide therapy. This therapy was not administered as the patient's condition worsened rapidly. In another primary metastatic patient (bones, lung), NE differentiation of the metastatic sites was confirmed and SSTR-targeted therapy with lanreotide was successfully administered for several months. Further octreotide scans and 68Ga-DOTATOC PET/CT were performed during follow-up in this patient to assess therapy response. Three other patients with unclear findings on conventional radiologic imaging received an octreotide scan to exclude metastatic lesions with NE differentiation.

Fourteen patients (52%) received a mastectomy, while breast conserving surgery was performed in 11 patients (41%). Two patients had no surgical procedure, one because of stage IV disease at the time of diagnosis and one due to her poor general condition (*advanced cardiovascular disease*). Fourteen patients (52%) were treated with chemotherapy (5 patients received anthracyclines, 2 patients were given taxanes, 7 patients had anthracyclines + taxanes) and 24 (90%) with endocrine therapy. Neuroendocrine-specific treatment with somatostatin analogues was administered in two patients, one diagnosed in stage IV and one diagnosed in stage II. The first patient with stage IV disease and metastases of the bone and lung (T3 N0 M1, G2, Ki-67 25%, HR+/HER2−, SSTR 2 + 70%) received endocrine therapy in combination with lanreotide (120 mg s. c. q4w) after 6 doses of paclitaxel weekly 80 mg/m² and achieved complete radiological remission with no evidence of disease at the follow-up of 66 months. At least 60 cycles of lanreotide were administered in combination with endocrine therapy until the last documented follow-up. No SSTR-analogue-specific side effects which altered the therapy regimen were reported. The other patient received the somatostatin analogue octreotide (2 × 50 µg s. c. per day) in stage II (T2 N1 M0, G2, Ki-67 5%, HR+/HER2+, SSTR 2+), after standard therapy was considered unsuitable due to the patient's poor general condition (cirrhosis of the liver (Child's C), thrombocytopenia). Octreotide treatment was administered for 3 months, however this patient died 5 months after diagnosis (no details regarding the exact cause of death or further symptoms and side effects available). ▶ **Table 4** shows the systemic treatment of study patients according to tumor stage and receptor status.

Survival analysis

Follow-up data were available for 26 out of 27 patients. The median follow-up was 63 months (range: 11–170 months). Nine patients died during follow-up and five of 22 initially non-metastatic and R0 operated patients were diagnosed with recurrence (local recurrence and/or distant metastasis). The mean overall survival

Overall survival

Disease-free survival
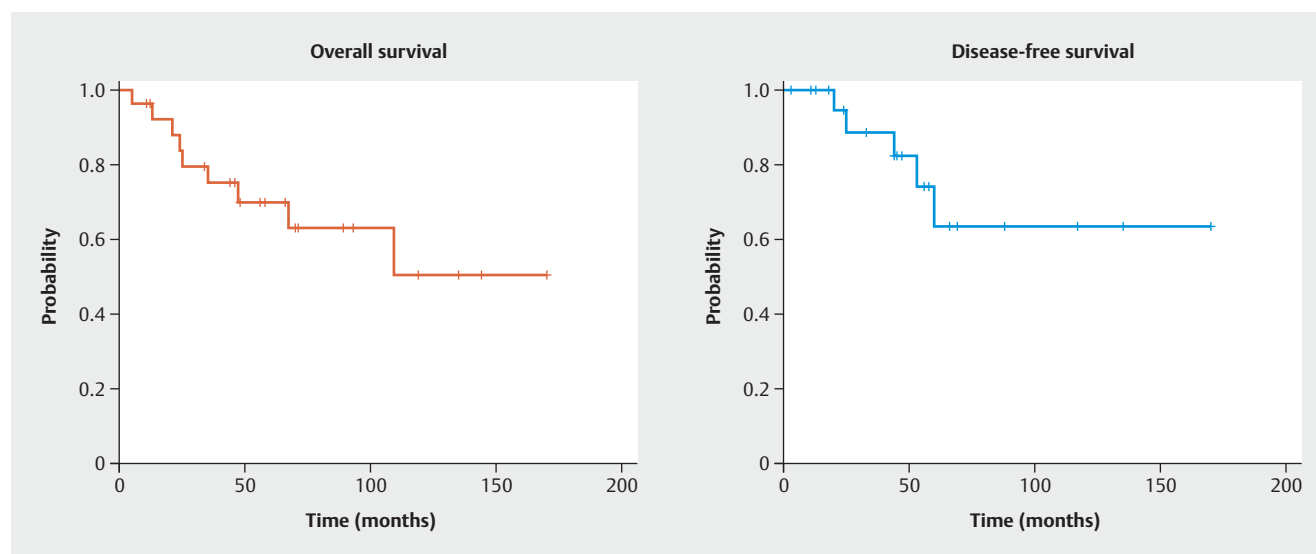
▶ **Fig. 4** Kaplan–Meier survival curves of BC-NE patients.

▶ **Table 3** Neuroendocrine-specific immunochemistry findings.

Marker/receptor	n (%)
Total n (%)	27 (100)
Chromogranin A	
▪ > 50% of tumor cells positive	13 (48)
▪ 1–50 of tumor cells positive	4 (15)
▪ Negative	10 (37)
Synaptophysin positivity	
▪ > 50% of tumor cells positive	25 (93)
▪ 1–50 of tumor cells positive	2 (7)
▪ Negative	0 (0)
CgA and Syn in > 50% of tumor cells positive	
▪ Yes	12 (44)
▪ No	15 (56)
SSTR 2A	
▪ Negative	12 (44)
▪ Score 1	2 (7)
▪ Score 2	7 (26)
▪ Score 3	3 (11)
▪ Not evaluated	3 (11)

NE: neuroendocrine, CgA: chromogranine A, Syn: synaptophysin, SSTR 2A: somatostatin receptor type 2A. Numbers in parentheses are percentages and do not add to 100 in some instances owing to rounding.

(OS) was 111 months (95% CI: 82–140 months), the mean DFS was 124 months (95% CI: 90–157 months). The 5-year OS rate was 70% (▶ **Fig. 4**).

For comparison, results from other studies published are summarized in ▶ **Table 5**. Only studies published after 2003 and including at least 20 patients with NEN were considered.

Discussion

Although neuroendocrine differentiation in BC is a long-known phenomenon, first described in 1963 [6], it was not until 2003 that NEN of the breast was defined by the WHO as a distinct subtype. Despite significant advances in the research and treatment of early and metastatic breast cancer over the last decades [11–15], the exact prevalence, clinical behaviour and effective therapy standards for this subset of BC have not been well established so far, possibly due to its low incidence and discrepant definitions.

All patients eligible for our analysis were diagnosed with a NEN of the breast according to WHO 2003 criteria (Syn and/or CgA > 50%). Poorly differentiated large or small cell neuroendocrine carcinoma and well differentiated neuroendocrine tumors (NET, G1) were excluded from this study (▶ **Table 1**). Since the definition of NEN of the breast has changed twice in the last two decades, the majority of cases described in our study would be currently defined as BC-NE (WHO 2012) and thus, in line with the latest NEN classification 2019, not be classified as a true NEN of the breast (▶ **Table 1**). However, diffuse neuroendocrine differentiation (Syn and/or CgA > 50%) in BC has been shown to be associated with certain specific clinical features, and several published studies on NEN of the breast report on these tumors as well (▶ **Table 5**). In particular, the question whether neuroendocrine differentiation in BC might have a diagnostic or therapeutic significance has not yet been sufficiently answered.

Here we report on a series of 27 cases of BC-NE and present their clinicopathological characteristics, survival analysis as well as NE-specific diagnostic and therapeutic aspects and compare it with other published studies on NEN of the breast.

► **Table 4** Systemic treatment of study patients according to tumor stage and receptor status.

PT	Age	TNM	G	ER	PR	HER2	SSTR 2A score (%)	CT	ET	SSTR therapy
1	61	T1 N0 M0	2	80%	80%	pos.*	2 (60)	No	AI	No
2	46	T4 N1 M1**	2	80%	40%	neg.	1 (<10)	7×E q1w	Ful	No
3	73	T2 N0 M0	2	80%	30%	neg.	0	No	AI	No
4	74	T2 N1 M0	2	40%	15%	neg.	0	3×Pac q1w	AI	No
5	84	T2 N0 M0	2	90%	90%	neg.	2 (60)	No	AI	No
6	62	T3 N0 M1	2	80%	90%	neg.	3 (90)	6×Pac q1w	AI	Lanreotide 120 mg q4w
7	53	T2 N1 M0	3	80%	0	neg.	1 (<10)	3×FEC – 3×DOC	AI	No
8	72	Tx Nx M0**	2	90%	90%	neg.	2 (70)	No	AI	No
9	51	T1 N0 M0	2	50%	80%	neg.	0	No	AI	No
10	50	T2 N0 M0	2	80%	90%	neg.	3 (90)	6×FEC q3w	Tam	No
11	42	T2 N3 M0	2	90%	90%	neg.	0	3×A – 3×C – 3×Pac q2w	Tam + GnRH	No
12	38	T2 N0 M0	3	0	0	neg.	0	6×FEC q3w	No	No
13	53	T2 N3 M1	2	0	0	neg.	n. d.	4×EC – 4×DOC	No	No
14	81	T4 Nx M0	2	90%	60%	neg.	3 (90)	No	AI	No
15	80	T2 N3 M0	2	80%	10%	neg.	0	no	AI	No
16	70	T1 N0 M0	2	80%	80%	neg.	0	No	Tam	No
17	56	T2 N0 M0	2	80%	80%	neg.	2 (60)	4×EC q3w	Tam-AI	No
18	48	T1 N0 M0	2	90%	90%	neg.	n. d.	6×FEC q3w	Tam	No
19	62	T2 N1 M0	2	80%	20%	neg.	0	3×;FEC – 3×DOC q3w	AI	No
20	84	T2 N0 M0	3	90%	0	neg.	0	No	AI	No
21	72	T1 N0 M0	2	80%	80%	neg.	2 (30)	No	Tam-AI	No
22	56	T1 N1 M0	2	90%	90%	neg.	0	3×FEC – 3×DOC q3w	Tam-AI	No
23	51	T2 N1 M0	2	80%	30%	neg.	0	3×FEC – 3×DOC q3w	Tam/AI	No
24	60	T1 N0 M0	2	90%	90%	neg.	n. d.	No	Tam/AI	No
25	81	T2 N0 M0	2	50%	<10%	neg.	0	No	Tam	No
26	56	T2 N0 M0	2	100%	10%	neg.	2 (30)	3×FEC – 3×DOC q3w	Tam/AI	No
27	69	T2 N1 M0	2	90%	90%	pos.*	2 (70)	No	No	Octreotide 50 µg 2/d

PT: patient, G: grading, ER: estrogen receptor, PR: progesterone receptor, SSTR 2A: somatostatin receptor type 2A, CT: chemotherapy, ET: endocrine therapy, AI: aromatase inhibitors, Ful: fulvestrant, E: epirubicin, Pac: paclitaxel, F: fluorouracil, C: cyclophosphamide, DOC: docetaxel, A: doxorubicin, d: day, n. d.: not done, q1w: weekly, q2w: every two weeks, q3w every three weeks, * no anti-HER2 therapy administered (PT 1 diagnosed in 2002, PT 27 not-suitable due to cirrhosis of the liver), ** no primary surgery performed (PT 2: stage IV with malignant bone marrow infiltration, PT 8: not suitable due to advanced cardiovascular disease).

Since some patients were identified through clinical records review and others through retrospective staining of neuroendocrine markers, we can only report on the actual prevalence in the collective of 465 patients. With 21 cases identified by a systematic morphological and immunohistochemical re-evaluation, we established a BC-NE prevalence to be 4.5%, which is in line with the 2–5% estimated by the WHO [16]. However, the prevalence of neuroendocrine differentiation in the published studies varies from less than 0.1% [17] to over 20% [18] (► **Table 5**). This is due to the variable diagnostic criteria on the one hand and the NEN identification process used in published trials on the other. Analyses that implement the 50% threshold for Syn or CgA according to the WHO 2003 definition generally report lower a NEN prevalence

comparing to those meeting WHO 2012 criteria without a threshold and/or using further neuroendocrine markers such as NSE or CD56 for NEN diagnosis [18–21] (► **Table 5**). Moreover, trials that identify NEN cases via a review of clinical records or databases report a generally lower and probably underestimated prevalence compared to those which performed a systematic re-evaluation of histology slides from BC patients, since neuroendocrine markers are not routinely used in BC diagnosis [17, 22–24].

The median age at initial diagnosis in our cohort was 61 years, which is in accordance with the median age at diagnosis of breast cancer of no special type without neuroendocrine differentiation (BC-NST) [25]. No differences between NEN of the breast and BC-NST in terms of age at diagnosis have been reported in other

▲ **Table 5** Prevalence, definitions, and clinical characteristics in important studies published on NEN of the breast*.

Study	No. of patients	NEN definition	NEN identification process	Prevalence	Age (range)	Morphology/ initial histology n (%)	IHC staining/ IHC subtype n (%)	Grading n (%)	Tumor size n (%)	N status n (%)	Outcome
Makretsov et al. 2004 [11]	65	Positivity of single NE marker (NSE, CgA or Syn), without threshold	Systematic histological re-evaluation of 334 surgical specimens from 1974–1995	19.5%	n.r.	n.r.	n.r.	n.r.	n.r	n.r.	No prognostic significance of CgA or Syn expression
	10	> 50% positivity of single NE marker (NSE, CgA or <Syn)	1974–1995	3%		IDC (NST) 5 (50), IDC/ILC 2 (20), IDC/MUC 2 (20), MUC 1 (10)	HR+/HER2− 7 (70), HR+/HER2+ 1 (10), HR−/HER2+ 0 (0), TNBC 2 (20)	G1 2(20), G2 7(70), G3 1(10)			n.r.
van Krimpen et al. 2004 [12]	40	Positivity of single NE marker (Syn and/or CgA), no treshold	Histological re-evaluation of 317 surgical specimens from 1983–1990	12,6	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	No prognostic significance of NE differentiation
Righi et al. 2010 [13]	89	WHO 2003	n.r	n.r.	Median 67 (43–92)	Solid cohesive 35 (39)	ER+ (83), HER2+ (0)	G1 (26), G2 (54), G3 (20)	T1 (62), T2 (31), T3–4 (7)	N0 (71), N+ (29)	n.r.
					Median 68 (54–84)	Alveolar 10 (11)	ER+ (55), HER2 0	G1 0 (0), G2 5 (50), G3 5 (50)	T1 (45), T2 (44), T3–4 (1)	N0 (72), N+ (28)	
					Median 62 (39–88)	Small cell 11 (12)	ER+ (67), HER2 0	G1 (0), G2 (18), G3 (82)	T1 (17), T2 (83)	N0 (40), N+ (60)	
					Median 71 (27–89)	Solid papillary 20 (22)	ER+ (100), HER2 0	G1 (45), G2 (45), G3 (10)	T1 (47), T2 (41), T3–4 (12)	N0 (53), N+ (47)	
					Median 66 (44–87)	Cellular mucinous 13 (15)	ER+ (92), HER2 0	G1 (31), G2 (69), G3 (0)	T1 (50), T2 (20), T3–4 (30)	N0 (75), N+ (25)	

▶ **Table 5** Prevalence, definitions, and clinical characteristics in important studies published on NEN of the breast*. *(Continued)*

Study	No. of patients	NEN definition	NEN identification process	Prevalence	Age (range)	Morphology/ initial histology n (%)	IHC staining/ IHC subtype n (%)	Grading n (%)	Tumor size n (%)	N status n (%)	Outcome
Wei et al. 2010 [14]	74	WHO 2003[1]	Review of clinical records	n.r.	Mean 61 (28–72) Median 63	Solid NE carcinoma Atypical carcinoid Large cell NE carcinoma	ER+ 70 (95) ER– 3 (4) Unknown 1 (1) ER+ 59 (80) ER– 14 (19) Unknown 1 (1) HER2+ 2 (3) HER2– 67 (91) Unknown 5 (6)	G1 2 (3) G2 57 (77) G3 15 (20)	T1 33 (45) T2 31 (42) T3 4 (5) T4 6 (8)	N0 41 (57) N1 31 (42) Unknown 2 (3)	Significantly worse clinical outcome than IDC NST LRFS (p = 0.001), DRFS (p < 0.0001), and OS (p = 0.002)
Riccardi et al. 2011 [15]	22	WHO 2003	Review of clinical records	n.r.	Median 63 (38–74)	n.r.	ER+ 18 (82) ER– 4 (18) PR+ 12 (54) PR– 10 (45) HER2 n.r.	n.r.	n.r.	n.r.	n.r.
Marton et al. 2012 [16]	31	WHO 2003	Review of clinical records; 3058 BC cases diagnosed 2001–2005	1,1 %	61.7 (44–86)	n.r.	ER+ 27 (87) ER– 4 (13) PR+ 23 (74) PR– 8 (26) HER2+ 1 (3) HER2– 30 (97)	G1 7 (23) G2 19 (61) G3 5 (16)	T1 12 (39) T2 18 (58) T3 1 (3) T4 0 (0)	N0 16 (52) N+ 15 (48)	Median follow-up 58.7 months (2–144), disease relapse in 25.8%, median time to relapse 34.3 months (14.5–54.1)
Rovera et al. 2013 [17]	96	WHO 2012	Review of clinical records, 2829 BC cases diagnosed 1992–2013	3.2 %	Median 70 (40–94)	Solid type 38 (62) MUC 14 (23) Microinvasive 6 (10) LCNEC 2 (3) SCNEC 1 (2)	ER+ (90) PR+ (75) HER2+ 0	G1 (34) G2 (64) G3 (2)	T1 35 (60) T2 20 (34) T3 1 (2) T4 2 (3)	N0 36 (77) N+ 11 (33)	Median follow-up 65 months (range 2–242); 10-year OS 87%[1]
	61	WHO 2003				n.r.	n.r.	n.r.	n.r.	n.r.	

▶ Table 5 Prevalence, definitions, and clinical characteristics in important studies published on NEN of the breast*. *(Continued)*

Study	No. of patients	NEN definition	NEN identification process	Prevalence	Age (range)	Morphology/ initial histology n (%)	IHC staining/ IHC subtype n (%)	Grading n (%)	Tumor size n (%)	N status n (%)	Outcome
Zhang et al. 2013 [18]	107	WHO 2003[1]	Review of clinical records, IHC confirmation	n.r.	Median 64 (25–95)	n.r.	ER+ 101 (94) ER– 6 (6) PR+ 91 (85) PR– 16 (15) HER2+ 3 (3) HER2– 104 (97)		T1 48 (45) T2 54 (50) T3 5 (5) T4 0 (0)	N0 81 (76) N+ 26 (24)	Median follow-up 27 months (3–134); OS 85.1 vs. 92.4% (NST) (p = 0.030) LRFS NEC (7.5%) vs. NST (2.8%) (p = 0.043) DRFS NEC (5%) vs. NST (8.3%) (p = 0.061)
Zhu et al. 2013 [19]	22	WHO 2003	Review of clinical records, 7542 BC cases diagnosed 2004–2010	0.29%	Mean 52.5 (29–77)	n.r.	ER+ 20 (91) ER– 2 (9) PR+ 21 (95) PR– 1 (5) HER2+ 5 (23) HER2– 17 (77)	n.r.	n.r.	n.r.	Mean follow-up 64.5 months (4–89), 95% of patients disease-free
Cloyd et al. 2014 [20]	284	WHO 2012	Review of SEER database (BC cases diagnosed between 2003 and 2010)	n.r.	n.r.	Well differentiated 148 (52.1) Small cell 73 (25.7) CA with NE features 42 (14.8) Large cell 14 (4.9) Carcinoid 7 (2.5)	ER+ 132 (46.5%) PR+ 101 (35.6%) HER2 n.r.	G1 28 (10) G2 56 (20) G3 127 (45) Unknown 73 (26)	T1 87 (31) T2 99 (35) T3–4 51 (18) Unknown 47 (16)	N0 145 (51) N+ 103 (36) Unknown 36 (13)	SCNEC: worse DSS (OR 6.46, 95% CI: 0.88–47.68, p = 0.07) and OS (1.97, 95% CI: 0.47–8.22, p = 0.36) compared to other neuroendocrine tumors of the breast
Kwon et al. 2014 [21]	32 / 59	WHO 2003 / WHO 2012	Histological re-evaluation of 1428 surgical specimens from 2012	2.2% / 4.1%	Median 49	IDC 54 (91.5) MUC 3 (5.1) Micropapillary 2 (3.4)	ER+ 55 (93) ER– 4 (7) PR+ 49 (83) PR– 10 (17) HER2+ 5 (8.5) HER2– 54 (91.5)	G1 8 (14) G2 19 (32) G3 32 (54)	T1 24 (41) T2 32 (54) T3 3 (5) T4 0 (0)	N0 24 (41) N+ 35 (59)	NE differentiation associated with impaired OS (p = 0.004) and DFS (p < 0.001)[3] No difference between focal and diffuse NE differentiation (OS, p = 0.986; DFS, p = 0.861), follow-up 56 months (1–122)

Table 5 Prevalence, definitions, and clinical characteristics in important studies published on NEN of the breast*. (Continued)

Study	No. of patients	NEN definition	NEN identification process	Prevalence	Age (range)	Morphology/initial histology n (%)	IHC staining/IHC subtype n (%)	Grading n (%)	Tumor size n (%)	N status n (%)	Outcome
Park et al. 2013 [22]	87	WHO 2003	Review of clinical records, 12945 BC cases diagnosed 1984–2011	1%	Mean 63 (28–89)	IDC 60 (69) IDC/MUC 17 (19.5) IDC/ILC 8 (9.2) Unknown 2 (2.3)	ER+ 86 (99) ER− 1 (1) PR+ 67 (77) PR− 19 (22) Unknown 1 (1) HER2+ 2 (2) HER2− 82 (94) Unknown 3 (3)	G1 8 (9) G2 67 (77) G3 10 (11) Unknown 2 (2)	n.r.	N0 44 (50) N+ 39 (45) Unknown 4 (5)	n.r.
Wang et al. 2014 [23]	142	WHO 2003	Review of SEER database (BC cases diagnosed between 2003 and 2009)	<0.1%	Mean 64 (26–99)	n.r.	ER+ 77 (54) ER− 37 (26) Unknown 28 (20) PR+ 53 (37) PR− 59 (42) Unknown 30 (21) HER2+ n.r.	G1 17 (12) G2 30 (21) G3 60 (42) Unknown 35 (25)		N0 52 (37) N+ 40 (28) Unknown 50 (35)	Impaired prognosis compared to BC-NST Median OS 26 months (12–48) 5-year OS 53.6% (95% CI: 42.2–63.7) NE differentiation (pos. vs. neg.) DSS 1.80 (95% CI: 1.36–2.37), p < 0.0001, OS 1.84 (95% CI: 1.50–2.26), p < 0.0001[3]
Bogina et al. 2016 [24]	84	WHO 2003[1]	Histological re-evaluation of 1232 surgical specimens from 2000–2012	6.8%		NST 58 (69) ILC 5 (6) MUC 6 (7) Solid papillary 15 (18)	ER+/HER2− (Ki-67 <14) 34 (41) ER+/HER2− (Ki-67 ≥14) 43 (51) ER+/HER2+ 4 (5) ER−/HER2+ 1 (1) TNBC 2 (2)	G1 3 (5) G2 41 (71) G3 14 (24)	T1 51 (61) T2 20 (24) T3–4 13 (15)	N0 38 (30) N+ 31 (37) Unknown 15 (18)	Worse DFS compared to BC-NST, no difference in CSS NE differentiation (pos. vs. neg.) DFS 3.12 (95% CI: 1.30–7.69), p = 0.011[3]
	128	WHO 2012[1]		10.4%		NST 95 (74) ILC 5 (4) MUC 7 (6) Solid papillary 21 (16)	ER+/HER2− (Ki-67 <14) 47 (37) ER+/HER2− (Ki-67 ≥14) 65 (51) ER+/HER2+ 9 (7) ER−/HER2+ 3 (2) TNBC 4 (3)	G1 6 (7) G2 65 (68) G3 24 (25)	T1 77 (60) T2 36 (28) T3–4 15 (12)	N0 64 (50) N+ 42 (33) Unknown 22 (17)	

▶ **Table 5** Prevalence, definitions, and clinical characteristics in important studies published on NEN of the breast*. *(Continued)*

Study	No. of patients	NEN definition	NEN identification process	Prevalence	Age (range)	Morphology/ initial histology n (%)	IHC staining/ IHC subtype n (%)	Grading n (%)	Tumor size n (%)	N status n (%)	Outcome
Roininen et al. 2017 [25]	43	WHO 2003	Review of clinical records, 12 945 BC cases diagnosed 2007–2015	n.r.	Median 66	n.r.	ER+ 41 (96) ER− 1 (2) Missing 1 (2) PR+ 37 (86) PR− 4 (9) Missing 2 (5) HER2+ 2 (5) HER2− 40 (93) Missing 1 (2)	n.r.	T1 29 (67) T2 11 (26) T3 2 (5) T4 1 (2)	N0 24 (56) N+ 17 (39) Missing 2 (5)	Worse DFS (p = 0.024) and OS (p = 0.0028) No difference in DDF, BCSS Mean follow-up of NEN 35.4 months (95% CI: 23.5–47.2 months)
Kelten Talu et al. 2018 [26]	36	WHO 2003[1]	Review of clinical records and IHC confirmation, BC cases 2007–2016	n.r.	Median 69.5, mean 67.4 (40–88)	IDC + NE differentiation 28 (78) Solid NEC 2 (5) IDC/MUC 2 (5) MUC 2 (5) IDC/ILC 1 (3) Solid papillary carcinoma 1 (3)	HR+/HER2− 33 (91.6) HR+/HER2+ 2 (5.6) TNBC 1 (2.7)	G1 0 (0) G2 31 (86) G3 5 (14)	T1 13/36 (36) ≥T2 21/36 (58)	n.r.	No conclusions
Lavigne et al. 2018 [27]	47	WHO 2003	Review of clinical records	n.r.	Median 67, mean 69 (33–91)	NST 37 (79) ILC 2 (4) Solid papillary carcinoma 5 (11) MUC 3 (6)	ER+ 47 (100) ER− 0 (0) PR+ 36 (77) PR− 10 (21) Unknown 1 (2) HER2+ 1 (2) HER2− 46 (98)	G1 3 (6) G2 29 (62) G3 15 (32)	T1 28 (60) T2 16 (34) T3 2 (4) T4 1 (2)	N0 22 (47) N+ 18 (38) Unknown 7 (15)	Impaired DFS, no difference in OS
Our study	27	WHO 2003[1]	Histological re-evaluation of 465 surgical specimens from 2002–2006, review of clinical records 2007–2013	4,5%	Median 61 (28–84)	NST 16 (59) ILC 1 (4) NST/ILC 1 (4) MUC 4 (15) NET 5 (18)	HR+/HER2− 23 (85) HR+/HER2+ 2 (7) HR−/HER2+ 0 (0) TNBC 2 (7)	G1 0 (0) G2 21 (78) G3 6 (22)	T1 7 (26) T2 16 (60) T3–4 3 (11) Unknown 1 (4)	N0 15 (56) N+ 10 (37) Unknown 2 (7)	Median follow-up 63 months (11–170), 5-year OS 70%

* Studies and case series published after 2003 with at least 20 patients have been listed. Numbers in parentheses are percentages and do not add to 100 in some instances owing to rounding. Abbreviations: NEN: neuroendocrine neoplasia, SCNEC: small cell neuroendocrine carcinoma, LCNEC: large cell neuroendocrine carcinoma, CSS: cancer specific survival, CgA/B: chromogranin A/B, Syn: synaptophysin, NSE: neuron-specific enolase, DRFS: distant recurrence-free survival, LRFS: local recurrence-free survival, DSS: disease-specific survival, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, MUC: mucinous, NST: no special type, BC-NST: breast cancer of no special type, DFS: disease free survival, OS: overall survival, n.r.: not reported. [1] No SCNEC and/or LCNEC included, [2] no cases with > 50 % positivity, [3] multivariate analysis

case series [19, 26, 27]. However, several trials with large cohorts reported NEN of the breast patients to be significantly older than BC-NST patients [17, 28–30], These discrepancies may also be due to nonuniform diagnostic criteria used in published series: most of the studies meeting WHO 2003 criteria report NEN of the breast patients being significantly older than BC-NST patients [17, 28–30] (▶ Table 5).

The majority (60%) of patients in our cohort were diagnosed with ≥ T2 tumors, and 37% of our analysed patients had lymph node metastases. This observation, i.e., NEN of the breast being diagnosed at a higher TNM stage than BC-NST, has also been reported by others. Wang et al. in their study of 142 NEN of the breast patients showed that those tumors were significantly larger, had higher stage disease and were significantly often node-positive compared to control cohorts with BC-NST [17]. In the study by Cloyd et al. of 284 patients, NEN of the breast was associated with relatively more advanced disease than BC-NST [31]. In their trial of 128 cases, Bogina et al. reported that NEN patients presented with larger tumors than BC-NST patients but no difference regarding node status was observed [19]. In contrast, some, mostly small series, reported similar TNM stages at diagnosis between BC with and without neuroendocrine differentiation [18, 26–28]. The proposed rationale for this phenomenon in NEN of other locations is their low grading and therefore slow growth, resulting in a lack of early symptoms. However, the association with higher TNM stages has been also reported in NEN cohorts with high rates of poorly differentiated tumors [17, 31].

Similar to previous studies, the majority of patients (85%) in our analysis presented with ER-positive HER2-negative tumors (▶ Fig. 5) [17, 22, 27, 32]. Previously, neuroendocrine differentiation has been shown to be significantly associated with positive HR-status [19, 26, 30] and negative HER2-status [28, 29]. Most tumors in our analysis were G2 tumors (78%) and Ki-67 was higher than 30% in 11 of 27 patients (41%). Similarly, NEN patients in other series were shown to have G2 tumors significantly more often than patients with BC-NST [19, 28], whereas some studies reported NEN being of a significantly higher histologic grade [17] and others found no association between neuroendocrine differentiation and grading [26, 27]. These discrepancies may be due to inconsistent NEN cohorts, since particular subtypes of NEN are associated with certain pathological features. In the trial by Cloyd et al., 45% NEN patients presented with poorly differentiated or undifferentiated tumors. However, 26% of NEN analyzed were SCNEC, well known for poor differentiation [33] and this entity has been excluded from several studies on NEN of the breast, including our analysis. In contrast, studies that analyzed primarily mucinous NEN demonstrated that the majority of these patients had well differentiated tumors [34, 35]. As mentioned above, due to different diagnostic criteria and the fact that specific subtypes within NEN have not been reported in most analyses (e.g., solid NEC vs. well differentiated NET vs. BC-NE vs. SCNEC/LCNEC), the comparison and interpretation of published data is difficult (▶ Tables 1 and 5).

The question whether neuroendocrine differentiation affects the prognosis of BC patients remains a very much debated issue. The 5-year OS rate of 70% in our cohort of patients with BC-NE is lower than the OS in patients with BC-NST [25]. Although some

smaller studies reported similar [18, 20, 21, 36] or even better [32, 37, 38] outcomes for NEN compared to BC-NST patients, the majority of published large series demonstrated an impaired prognosis for NEN [17, 19, 26–30] and most of these studies do not include any SCNEC cases, well known for having a very poor outcome [19, 26–29]. The association with poor clinical outcome was also present in multivariate analysis after adjusting for pathological stage [17, 26], histological grade, and ER and HER2 status [19, 26], showing that neuroendocrine differentiation is an independent prognostic factor in BC.

Expression of somatostatin receptor (SSTR) in NEN of the breast, similarly to NEN of other sites, is a long-known phenomenon [39], potentially allowing SSTR-targeted tumor imaging and treatment, even though it is not restricted to this subset of BC [40]. Among them, SSTR 2A is a subtype most commonly expressed in BC [41] and able to mediate the antiproliferative effect of somatostatin analogues (SSA) in the strongest manner [42]. However, the SSTR 2A positivity rate in BC-NE has, to the best of our knowledge, only been analyzed in one study so far [43]. This recently published retrospective analysis of 31 NEN cases reported a SSTR 2A positivity rate of 71% [43]. In our series, SSTR 2A was evaluated in 24 patients and 12 of them (50%) were SSTR 2A-positive. Based on this, five patients received SSTR-based imaging (octreoscan or ^{68}Ga-DOTATOC PET/CT) to confirm or exclude metastatic disease at the time of diagnosis or to evaluate therapy response over the course of disease. It is possible that the number of patients receiving SSTR-based imaging would have been much higher if neuroendocrine differentiation had been identified at diagnosis and not, as was the case in the majority of our BC-NE patients, retrospectively.

Beyond these specific diagnostic aspects, SSTR 2A can potentially be targeted with SSA such as octreotide or lanreotide. These substances, which have been a mainstay of antisecretory treatment in functional NEN for a long time, were also shown to have antiproliferative activity and to be associated with a clinical benefit in some NEN patients [44]. In NEN of other sites, which is much more common, this therapy is mainly being considered in well differentiated NET (G1/2, Ki-67 < 10%) [45]. Current recommendations for BC-NE therapy are based on general guidelines for breast cancer, and poorly differentiated SCNEC (▶ Table 1) is the only entity with specific recommendations (i.e., platinum/etoposide-based chemotherapy similar to small cell lung cancer). However, only a few case reports on the treatment of BC patients with this regimen have been published so far [46, 47]. Since this rare subtype of NEN of the breast known to have a very poor outcome has been excluded from our analysis, all patients in our study were treated with a standard anthracycline-taxane (AT)-based chemotherapy. In our series, two SSTR-positive BC-NE patients received SSA in combination with endocrine therapy and one of these patients, initially diagnosed at stage IV with metastasis to lung and bones, achieved complete remission showing no evidence of disease on radiological and SSTR-based imaging 66 months after the first diagnosis. This patient exhibited strong SSTR 2A-expressing BC-NE G2 with a Ki-67 of 25% and not a typical well differentiated NET. Indeed, SSA therapy has been evaluated in BC-NST in the past and showed response rates of up to 40% in a metastatic setting in phase I–II trials [48]. However, a phase III study comparing
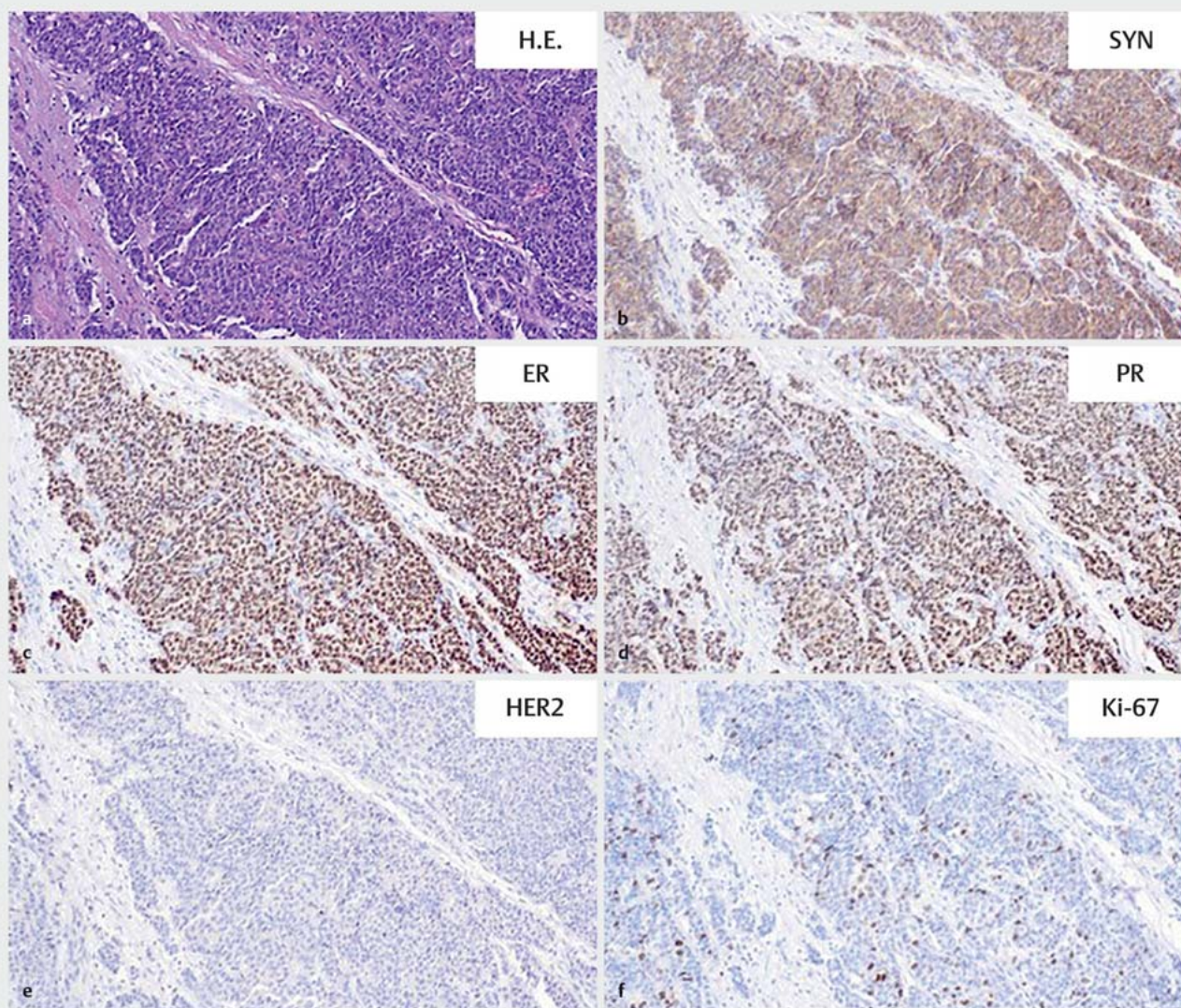
► **Fig. 5** Expression of receptors and proliferative activity in breast carcinoma with neuroendocrine differentiation. **a** Hematoxylin and eosin (H.E.) staining, demonstrating a solid growth pattern, complete lack of tubular architecture and a cytology of tumor cells highly suggestive of a neuro-endocrine phenotype. **b** Strong expression of the pan-neuroendocrine marker synaptophysin (SYN) in all tumor cells. **c** Strong nuclear expression of the estrogen receptor (ER) in > 90 % of tumor cells resulting in an ER score of 12 (scale 0–12). **d** Strong nuclear expression of the progesterone receptor (PR) in > 90 % of tumor cells resulting in an ER score of 12 (scale 0–12). **e** Complete lack of HER2 expression corresponding to a score of 0 (scale 0–3). **f** Analysis of Ki-67 protein expression reveals a proliferative activity of approximately 15 %.

endocrine therapy with or without octreotide in primary ER-posi-tive BC did not show a benefit of SSA treatment in this setting [49]. Nonetheless, none of these studies evaluated the SSTR sta-tus of tumor tissue prior to SSA-based therapy. Here we demon-strate that SSA therapy in SSTR 2A-positive BC-NE can be offered as an individual treatment option to selected patients, e.g., as combination therapy in a palliative setting or in the case of contra-indications to the standard treatment. Since neuroendocrine dif-ferentiation has been shown to be associated with impaired out-comes in several retrospective trials, further studies are needed to identify the most appropriate treatment strategy for this BC subtype.

Conclusion

Invasive breast cancer with neuroendocrine differentiation repre-sents mostly HR-positive and HER2-negative disease and the diag-nosis is made at a higher TNM stage than for BC-NST. Neuroendo-crine differentiation in BC has been shown to be associated with impaired prognosis in several retrospective trials. However, the clinical impact of NE features in BC is still a very much debated is-sue, since the diagnostic criteria of this entity differ in published studies, making an estimation of clinical behavior difficult. Cur-rent recommendations for BC-NE therapy are based on general guidelines for breast cancer. Nevertheless, a significant number of these cancers express SSTR 2A receptors, allowing SSTR-based

imaging and potentially SSTR-targeted therapy in selected cases. Moreover, platinum/etoposide-based chemotherapy may be an alternative to the standard AT-based treatment in poorly differentiated SCNEC of the breast.

Declarations Section

Ethics approval and consent to participate: The study was approved by the Ethical Committee of the Heinrich Heine University of Duesseldorf.

Consent to publish: This manuscript does not contain any details, images, or videos that might lead to the identification of any individual patient.

Availability of data and materials section: The data that support the findings of this study are available from the authors on reasonable request and with the permission of Tanja Fehm.

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Authors' contribution: NK performed the data analysis and drafted the manuscript. RR collected the data and helped to draft the manuscript. SO, KL helped to perform the IHC experiments. MA, and SB performed the IHC experiments, the morphological evaluation and helped to draft the manuscript, IE perform the IHC experiments and help to draft the manuscript, CM helped to draft the manuscript. MN designed and coordinated the study, TF designed the study, made substantial contribution to interpretation of the data and reviewed the manuscript. MBP, ER, SM, JH, TK, BJ were involved, in interpretation of the data, drafting of the manuscript or revising it. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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