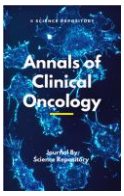

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Research Article

Diagnosis and Clinical Management of Neuroendocrine Tumor of the Breast: Report of Six Cases and Systematic Review of Existing Literature

Corrado Tinterri[1*], Giulia Puliani[2], Emilia Marrazzo[1], Andrea Sagona[1], Erika Barbieri[1], Wolfgang Gatzemeier[1], Giuseppe Canavese, Alberto Bottini, Alessandro De Luca[3] and Federico Frusone[3]

[1]Humanitas Research Hospital and Cancer Center, Breast Surgery Department, Milan, Rozzano, Italy
[2]Sapienza University of Rome, Department of Experimental Medicine
[3]Sapienza University of Rome, Department of Surgical Sciences

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ABSTRACT

Introduction: Neuroendocrine neoplasm of the breast (bNENs) are considered a rare disease, even if in WHO data they represent about 2-5 % of all breast cancer. The last WHO classification includes: well-differentiated neuroendocrine tumor (bNET), neuroendocrine carcinoma (NEC) and invasive carcinoma with neuroendocrine differentiation. The current knowledge on clinical management of bNENs is poor and patients are usually treated according to non-endocrine tumor components guidelines.

Materials and Methods: We presented our experience of six cases of bNENs. Moreover, we conducted a systematic review of published data on diagnosis, treatment and outcome of this kind of tumors.

Results: bNENS usually presented as palpable breast masses, classically appearing as irregular hypoechoic lesions at US examination and as hyperdense masses at mammography. Usually pre-operative tumor biopsy is not able to recognize the neuroendocrine components and the final diagnosis is performed only on definitive histopathological assessment. The most frequent subtype seems to be neuroendocrine carcinoma and synaptophysin is positive in most specimens. Treatment strategies, including surgical treatment, radiotherapy and medical treatment are nowadays based on current non-endocrine breast cancer guidelines, independently from neuroendocrine components, even if some studies have proposed the use of somatostatin analogues for bNET and cisplatin-etoposide for NEC. Prognosis of all bNENs, especially of poorly differentiated neoplasia, seems worse compared to non-neuroendocrine breast cancer and stage and morphology seem the best predictor of tumor outcome.

Conclusions: We provide an algorithm for clinical management of bNETs, basing on available data. More studies are necessary for confirming the best treatment strategy for these patients, in order to improve clinical outcome.

Introduction

The first description of a neuroendocrine tumor (NET) of the breast dates back to 1963: an invasive breast cancer morphologically similar to intestinal carcinoids [1]. World Health Organization (WHO) recognized neuroendocrine tumors of the breast as a separate entity of breast cancer only in 2003, defining them as primary neuroendocrine carcinomas exhibiting morphological features of gastrointestinal and pulmonary NETs in which more than 50% of the cells expresses neuroendocrine markers (chromogranin A and synaptophysin) [2]. In 2012 the cut-off of 50% of the cells expressing neuroendocrine markers was eliminated and bNENs were divided in groups according to morphology: well-differentiated (carcinoid-like) neuroendocrine tumor (bNET), poorly differentiated neuroendocrine carcinoma (NEC) small-cell neuroendocrine carcinoma (SCNC) and invasive carcinoma with neuroendocrine differentiation (ICNE) [3]. According to WHO data, bNENs represent about 2-5 % of all breast cancer [4]. In data from SEER database bNENs represent less than 0.1% of total invasive carcinomas of the breast [5]. Probably these frequencies may underestimate the real

**Correspondence to: Corrado Tinterri, Humanitas Research Hospital and Cancer Center, Breast Surgery Department, Milan, Rozzano, Italy; E-mail: corrado.tinterri@cancercenter.humanitas.it*

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incidence of bNENs: retrospective studies on breast tumor specimens showed high incidence of neuroendocrine cells with positive neuroendocrine markers [6, 7]. Nowadays, the impact of neuroendocrine differentiation of breast cancer on diagnosis, treatment and outcome is still unclear. Because of the low incidence of this kind of neoplasia, no clinical trials or guidelines are available on this topic. The aim of this systematic review is to summarize clinical presentation, diagnosis, treatment and outcomes of all available cases in Literature, adding our personal experience of six cases.

Materials and Methods

I Article Identification

We searched PubMed, Embase, Google Scholar and Cochrane databases for English language studies on neudoendocrine tumor of the breast. Search terms used were: "neuroendocrine tumor" AND breast, "neuroendocrine tumour" AND breast; "neuroendocrine cancer" AND breast; "neuroendocrine carcinoma" AND breast.

II Eligibility Criteria

We included English-language studies on humans with any of the following design: randomized clinical trials, prospective non-randomized trials, retrospective studies, case reports and case series. We selected cases classified by the pathologist as neuroendocrine breast tumor, according to WHO classification used at time of publication (2003 or 2012). For article published before 2003, we included cases defined as breast neuroendocrine tumors or carcinoids by the Authors. We included in the systematic reviews only articles with data on at least one of the following topics: clinical presentation, treatments and outcomes of neuroendocrine tumors of the breast. Last search date was February 2019.

III Article Selection

Each study was screened by abstract and title and potentially eligible studies were further assessed in detail by retrieving full-length articles. Each full-length article was independently reviewed by two separate Authors following inclusion criteria. Two authors independently extracted data from the articles that met the inclusion criteria. A standardized form was used to extract the following information: year of publication, type of study, number of patients included, age at diagnosis, sex, familiarity for breast tumors, other known risk factors for breast cancer, clinical presentation, palpability, diagnostic procedures (ultrasound, mammography, MRI, CT, PET, fine needle aspiration and biopsy), treatment strategy (surgery, medical treatment, radiotherapy), histopathological examination including immunohistochemistry, stadiation and outcomes.

Results

I Case Series

We present six cases of bNENs diagnosed in Humanitas Research Hospital of Milan from 2012 to 2018. All patients provided written informed consent to case publication. All cases were females, mean age 64.2 ± 13.7. All patients presented with breast lumps (in one case painful). When performed, breast ultrasound (US) always showed a mass (in three cases hypoechoic mass) and mammography showed 4 spiculated and 1 regular margin hyperdense lesion of 0.8-2.7 cm of maximum diameter. Breast magnetic resonance imaging (MRI) was not performed in all cases due to lack of indication. Biopsy showed in all cases infiltrating breast carcinoma but only in one case succeeded in identifying neuroendocrine differentiation. All patients underwent surgical intervention. Surgery on tumor mass was in 4 cases breast conservative surgery (BCS) and in 2 cases total mastectomy; axillary surgery consisted of 3 lymphadenectomies and 3 sentinel lymph node biopsies. Radiotherapy was performed in the 4 cases of BCS. Definitive histopathological evaluation confirmed in all cases the neuroendocrine differentiation: 2 bNET, 2 breast NEC and 2 ICNE. In our case series synaptophysin has been the most important neuroendocrine marker, been positive in 6/6 cases. Chromogranin was positive in 1/3 cases while NSE was never evaluated. 5/6 (83,3%) cases showed positivity for both oestrogen and progesterone receptors. Ki67 ranged from 10 to 90%.

After definitive diagnosis, all patients performed a total body scans (^{18}FDG PET/CT and contrast-enhanced total body CT scans) for excluding neuroendocrine neoplasm of other origin. After surgical removal, patients underwent chemotherapy or hormonal therapy according to associated non-endocrine breast tumor histotype guidelines (2 only hormone therapy, 1 chemotherapy, 3 hormone therapy associated to chemotherapy). One patient with NEC developed liver and bone metastasis after 6 months and is now alive with metastatic disease after one year of follow-up. Medium follow-up of other cases was 65 (35-120) months: 3 patients are today alive and disease free, two are alive with local recurrence. All data are summarized in Table 1A.

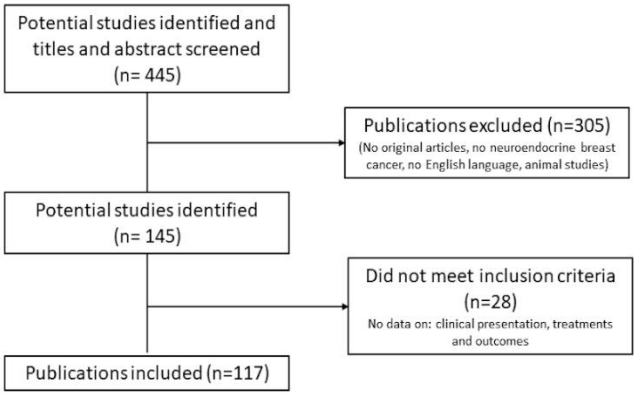

Figure 1: Flowchart of literature eligibility assessment process.

II Systematic Review

From the initial search we retrieved 445 articles. After screening for title and abstract we identified 140 potentially eligible articles. After full text examination a total of 117 articles were included in this systematic review (Figure 1). 102 articles were case reports on a total of 113 bNENs. Available data are summarized in Table 1B. 15 articles were retrospective studies or case series on a total number of 731 patients: data are summarized in Table 2.

Table 1A: Case series.

Preoperative diagnosis								Treatment				Tumor biology										Follow-up	
Case	Age	Clin pres	US	MX	CT	PET	Bio / Cit	Nadj treat	Surgery	Adj treat	Adj RT	pTNM	Tum size	LNs	Histo-type	CrA	Syn	ER	PR	Her2	Ki67	FUP (mo)	Alive status
1	66	BL	NA	NA	Neg	Neg	Bio	NO	BCS + ALND	ADR/CPA + DTX + Ana	Yes	T2N3aM0	2,3	12/14	ICNE	NA	+	70%	60%	0	10%	120	AWD
2	54	BL	HyBM	SBM	Neg	Neg	Bio	NO	Mast + SLNB	ADR/CPA + DTX + Ana	No	T2N0M0	2,7	0/1	NET	-	+	95%	29%	0	70%	60	NED
3	43	PBM	HyBM, N+	SBM	Neg	BoMet, LMet	Bio	Yes	Mast + ALND	CDDP + VP-16	Yes	T4bN3aM1	12	9/14	NEC	+	+	0	0	0	90%	12	AWD
4	66	BL	BM	HypBM	Neg	Neg	Bio	NO	BCS + ALND	ADR/CPA + DTX + Ana	Yes	T1N3aM0	0,8	13/15	ICNE	NA	+	80%	70%	0	12%	53	AWD
5	78	BL	HyBM	SBM	Neg	Neg	Bio	NO	BCS + SLNB	Ana	No	T1cN0M0	1,9	0/16	NET	-	+	95%	95%	1+	25%	76	NED
6	78	BL	BM	SBM	Neg	Neg	Bio	NO	BCS + SLNB	Ana	Yes	T1cN0M0	2	0/2	NEC	NA	+	95%	95%	0	20%	70	NED

HeadingS: NA = Not available data; Clin Pres = Clinical presentation; US = breast Ultrasound; MX = mammography; Bio = biopsy; Cit = citology; Ad treat = adjuvant treatment (chemotherapy and/or hormone therapy); Adj RT = adjuvant radiotherapy; Tum size = tumor size (centimeters); LNs = lymph nodes removed; CrA = Chromogranin A; Syn = Synaptophisin; ER = Estrogen receptor; PR = Progesterone receptor; Her2 = her2-neu receptor; FUP = follow-up (months).

Clinical and radiological findings: Pos = positive for malignancy; Neg = negative for malignancy; BM = Breast Mass; CM = carcinomatous mastitis; N+ = axillary adenopathy, PBM = Painful breast mass; BL = breast lump; SR = Skin retraction, NR = nipple retraction, PLM = Paget-like Mass; BND = Bloody nipple discharge; UBM = Ulcerated Breast Mass; MBM = Multilobulated breast mass; HyBM = Hypoechoic (US) / Hypodense (MX) breast mass; Hyp = Hyperechoic (US) / Hyperdense breast mass = HeBM = Heterogeneous breast mass, SBM = Spiculated breast mass, Mic = microcalcifications, BoMet = Bone Metastases; LMet = Lung metastasis; PAMet = Perianal metastases, PiMet = Pituitary metastases; PaMet = Pancreatic metastases; PE = Pleural effusion; MMet = Multiple metastases; IBM = Isoechoic breast mass
Neg = Negative; Sus = suspicious; LMet = lung metastasis.
Mast = Mastectomy; BCS = Breast Conservative Surgery; SLNB = Sentinel Lymph Node Biopsy; ALND = Axillary Lymph Node Dissection.

Chemotherapy: ChT = chemotherapy (not defined); HoT = hormone therapy (not defined); CDDP = Cisplatin, CBL = Carboplatin, VP-16 = Etoposide, CPT-11 = Irinotecan, 5-FU = Fluorouracil, EPI = Epirubicin, CAP = Capecitabine, DTX = Docetaxel, 5'-DFUR = 50 deoxy-5-fluorouridine, Tor = Toremifene, CPA = Cyclophosphamide, EPI = Epirubicin, Tam = Tamoxifen, Tor = Torenifene, Let = Letrozole, S = Streptozotocin, MTX = Methotrexate, Ana = Anastrazole, AI = Aromatase inhibitor, LHRH = Leutinising hormone releasing hormone analogue, UFT = Uracil & Tegafur, PTX = Paclitaxel, ADR = Adriamycin (Doxorubicin), Sando = Sandostatin, Som = Somatostatin; Ever = Everolimus, Bev = Bevacizumab, Erl = Erlotinib; Palb = Palbociclib; Oct = Octreotide.

Histology: SCNC = Small Cell Neuroendocrine Carcinoma, ICNE = Invasive carcinoma with neuroendocrine differentiation; NET = well-differentiated neuroendocrine tumor; NEC = poorly differentiated neuroendocrine carcinoma.

Follow-up: NED = No evidence of disease; AWD = Alive with disease; DOD = Died of disease; DUC = Died of Uncertain cause
†Median follow-up.

Table 1B: Case reports available in literature.

Author		Preoperative diagnosis							Treatment				Tumor biology										Follow-up	
Author (year)	Year	Age	Clin pres	US	MX	CT	PET	Bio / Cit	Nadj treat	Surgery	Adj treat	Adj RT	pTNM	Tum size	LNs	Histo-type	CrA	Syn	ER	PR	Her2	Ki67	FUP (mo)	Alive status
Wade[23]	1983	52	UBM N+	MBM	MBM	Neg	NO	Bio	NO	Mast + ALND	VP-16	NO	T4N1M0	10	25/25	SCNC	NA	NA	NA	NA	NA	NA	NA	NA
Jundt[24]	1984	52	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	TXN1M1	NA	+/?	NA	NA	NA	NA	NA	NA	NA	14	DOD
Francois[25]	1995	68	BM	HeBM	HBM	Neg	NO	Cit	NO	Mast + ALND	CPA/ADR/VP-16	Yes	T2N0M0	4	0/12	SCNC	NA	NA	-	NA	NA	NA	21	DUC
Chua[26]	1997	45	BM	NA	NA	NA	NA	Bio	NO	BCS	NA	NO	T2N0MX	4,5	NA	SCNC	-	+	-	-	NA	NA	<1	NED
Yalcin[27]	1997	63	BM	BM	BM	Neg	NA	Bio	NO	Mast + ALND	NO	NO	T2N0M0	5	0/?	NET	+	NA	NA	NA	NA	NA	18	NED
Fukunaga[28]	1998	51	BM	Neg	BM	Neg	NO	NA	NA	Mast + ALND	NA	NA	T2N0M0	2,5	0/29	NET	+	-	+	-	-	NA	16	NED
Fukunaga[29]	1998	38	BM	BM	BM	Neg	NO	NA	NO	Mast + ALND	NO	NO	T2N1M0	2,5	1/7	NEC	+	+	-	-	-	12%	72	NED
Sebenik[30]	1998	67	NA	NA	NA	NA	NA	NA	Yes	Mast + ALND	NA	NA	T2NXM0	4	NA	NA	NA	NA	NA	NA	NA	NA	33	NED
Samli[31]	2000	60	PBM	BM	BM	Neg	NO	Bio	Yes	Mast + ALND	CDDP/VP-16+ 5-FU/CPA/EPI	Yes	T4N1M0	4,5	10/11	SCNC	+	+	+	+	NA	NA	6	AWD
Yamasaki[32]	2000	41	BM	Neg	SBM	Neg	Sus	Cit	NO	Mast + ALND	CPA/MTX/5-FU	NO	T2N0M0	3,5	0/5	SCNC	+	-	-	-	NA	NA	16	NED
Hoang[33]	2001	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	T3NXMX	14,5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		51	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	T3NXMX	8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Salmo[34]	2001	46	NA	NA	NA	NA	NA	NA	NO	BCS	ChT	YES	T2N0M0	4	NA	NA	NA	NA	NA	NA	NA	NA	9	NED
Berruti[35]	2004	59	LMet	Neg	Neg	LMet	NO	NA	Yes	LMet resection	Tam	NO	TXNXM1	NA	NA	NEC	+	+	+	-	-	12	144	NED
Bigotti[36]	2004	56	CM	BM	BM	NA	Neg	Bio	Yes	NO	ChT + Som	NO	T3N1M0	18	2/9	SCNC	-	+	-	-	-	NA	15	DOD
Bergman[37]	2004	61	BL	BM	BM	Neg	Neg	Bio	NO	Mast + ALND	NO	NO	T2N1M0	2,5	2/5	SCNC	-	-	-	-	-	-	NA	NA
Jochems[38]	2004	71	BM	NA	BM	Neg	Neg	Bio	NO	Mast + ALND	Tam	NO	T2N0M0	3	0/10	NEC	+	+	+	+	-	NA	12	NED
Mariscal[39]	2004	53	BM, SR, N+	HyBM	BM, N+	Neg	Neg	Bio	Yes	BCS + ALND	HoT	NO	T3N1M0	5,5	1/?	SCNC	NA	+	NA	NA	NA	NA	6	NED
Sridhar[40]	2004	58	NA	NA	NA	NA	NA	NA	NO	BCS	ChT	YES	T2N1M0	2	NA	NA	NA	NA	NA	NA	NA	NA	18	NED
Yamamoto [41]	2004	53	NA	NA	NA	Neg	Neg	NA	NO	NA	NO	NO	T3N2M0	6,5	NA	NA	NA	NA	-	NA	NA	NA	34	NED
		75	NA	NA	NA	Neg	Neg	NA	NO	NA	CPA/MTX/5-FU + HoT	NO	T2N1M0	2,5	NA	NA	NA	NA	+	NA	NA	NA	43	NED
Adegbola[42]	2005	46	BL	NA	NA	Neg	NO	NO	NO	BCS	CDDP/VP-16+	Yes	T1NXM0	1	0	SCNC	+	+	-	NA	-	NA	48	NED
		60	BM	NA	NA	Neg	NO	NO	NO	BCS	CDDP/VP-16+	Yes	T1NxM0	1,7	0	SCNC	+	+	-	NA	-	NA	20	DOD
		61	BM, N+	NA	NA	Neg	NO	NO	NO	BCS	CDDP/VP-16+	Yes	T1NxM1	1,7	0	SCNC	+	-	-	NA	-	NA	6	AWD
Stein[43]	2005	54	BM, N+	NA	NA	NA	NA	Bio	Yes	Mast + ALND	NO	Yes	T1N1M0	1,5	5/15	SCNC	+	NA	-	NA	NA	NA	24	NED
Tsai[44]	2005	42	BM	NA	NA	Neg	NA	Bio	NA	Mast	NA	NA	NA	NA	NA	NEC	+	+	+	+	NA	NA	NA	NA
Fujimoto[45]	2007	40	BL, BND	HyBM	Neg	NO	NO	Bio	NO	Mast + SLNB	Ana	NO	T2(m)N0 M0	2	0/1	NEC	+	+	+	NA	+	NA	NA	NA
Hennessy[46]	2007	63	PAMet	Neg	Neg	BMet PAMet	NO	Bio	NO	Mast + SLNB	ChT/Tam	NO	TXNXM1	NA	NA	NEC	+	+	NA	NA	NA	NA	NA	AWD
Kitakata[47]	2007	44	BL	HyBM	BM	BM	Neg	Neg	NO	Mast + ALND	CPA/Epi + DTX	NO	T2N1M0	4,5	2/15	SCNC	-	+	-	+	-	NA	22	NED
La Rosa[48]	2007	49	BL	Pos	Pos	NO	NO	Cit	NO	Mast	ChT	NO	T2NXMX	2,5	NA	NEC	+	+	+	+	-	NA	NA	NA
Vidulich[49]	2007	76	BM, N+, PE	BM, N+	NA	LMet	MMet	Cit, Bio	NO	NO	Oct/Ever, Bev/Erl	NO	T4N1M1	5	NA	NEC	+	+	+	+	-	NA	NA	AWD

Yaren[50]	2007	76	NA	NA	NA	Neg	NA	NA	NO	Mast + ALND	HoT	NO	T2N0M0	5	0/13	NA	NA	NA	+	NA	NA	NA	12	NED
Jeong[51]	2008	39	BL	IBM	HypBM	NO	NO	NO	NO	Mast + ALND	ChT / Hot	Yes	T2N1M1	2,2	2/14	NEC	+	+	+	+	NA	NA	32	NED
Kim[52]	2008	27	BM	HeBM	BM	Neg	Neg	Bio	NO	BCS + ALND	ChT	Yes	T2NXM0	3,2	NA	NEC	+	+	-	NA	NA	NA	18	NED
Kinoshita[53]	2008	31	BL	HyBM	Neg	MMet	NO	Bio	Yes	Mast + ALND	CDDP/CPT-11	NO	T2N1M1	3,7	7/30	SCNC	+	+	-	+	-	NA	1	AWD
Lopez Garcia[54]	2008	31	NA	NA	NA	NA	Neg	NA	NO	Mast + ALND	NO	YES	T3N1MX	10	2/15	NA	NA	NA	-	NA	NA	NA	15	DOD
Mecca[55]	2008	70	PLM	NA	NA	NA	NO	NA	NO	BCS + SLNB	NO	NO	T4N1M0	1,9	2/2	NEC	NA	+	+	+	+	NA	12	NED
Ogawa[11]	2008	34	BM	HeBM	HypBM	Neg	NA	Bio	NA	BCS	NA	NA	T2NXM0	2,7	NA	NET	+	-	+	+	NA	NA	7	NED
Pagani[56]	2008	62	NA	NA	NA	NA	NA	NA	NA	BCS + ALND	NA	NA	T1N2MX	1,5	19/20	NA	NA	NA	+	NA	NA	NA	NA	NA
		41	NA	NA	NA	NA	NA	NA	NA	Mast + ALND	NA	NA	T2N1MX	4,1	1/18	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sadanaga[57]	2008	33	NA	NA	NA	NA	NA	NA	Yes	Mast ALND	ChT	YES	T2N0M0	4	0/?	NA	NA	NA	NA	NA	NA	NA	60	NED
Ulamec[58]	2008	60	Hematuria	BM	NA	NA	NA	NA	Yes	Mast + ALND	HoT	Yes	T4N2M1	4,5	9/9	NEC	-	+	+	+	+	5%	18	NED
Akhtar[59]	2009	40	BL, N+	NA	NA	NA	NA	Cit, Bio	NA	Mast + ALND	NA	NA	T3NXMX	8,5	NA	NEC	NA	+	NA	NA	NA	NA	NA	NA
Burckhardt[60]	2009	84	NA	NA	NA	NA	NA	NA	Yes	Mast + ALND	HoT	NO	T2N1M0	3	+/?	NA	NA	NA	+	NA	NA	NA	NA	NED
El Hassani[61]	2009	40	BM	NA	BM	Neg	NO	Bio	Yes	NO	VP16-CDDP	NA	T4NXMX	NA	NA	NEC	+	+	+	+	NA	NA	1	DOD
Ersahin[62]	2009	50	NA	NA	NA	NA	NA	NA	NA	BCS	NA	NA	T3NXM0	2,5	NA	NA	NA	NA	NA	NA	NA	NA	12	NED
Haji[63]	2009	68	NA	NA	NA	NA	NA	NA	YES	Mast + ALND	NO	NO	T3N1M0	5,8	NA	NA	NA	NA	NA	NA	NA	NA	6	DOD
Hojo[64]	2009	60	NA	NA	NA	NA	NA	NA	NO	Mast + ALND	NO	NO	T3N0M1	3	0/?	NA	NA	NA	NA	NA	NA	NA	26	AWD
Lee[65]	2009	65	BM	HyBM	HypBM	NO	Neg	Neg	NO	BCS + SLNB	HoT	NO	T1N0M0	1,6	0/1	NEC	NA	+	+	-	-	NA	NA	NED
Okoshi[66]	2009	63	BM	HyBM	HypBM	Neg	No	Cit	NO	BCS + ALND	ChT	Yes	T2N0M0	2	0/?	NET	-	+	-	-	+	NA	44	NED
Rivero[67]	2009	41	NA	NA	NA	NA	NA	NA	YES	BCS	NO	Yes	T3N0M0	6	0/?	NA	NA	NA	NA	NA	NA	NA	20	NED
Rineer[68]	2009	81	NA	NA	NA	NA	NA	NA	YES	BCS	NO	Yes	T3N1M0	5	NA	NA	NA	NA	NA	NA	NA	NA	26	AWD
Salama[69]	2009	48	BoMet	NA	NA	NA	NA	NA	YES	NO	NO	NO	T4NXMX	2,5	NA	NA	+	+	NA	NA	NA	NA	<1	AWD
Sartori[70]	2009	70	NA	NA	NA	NA	Neg	NA	NO	BCS + ALND	Som	Yes	T1N3M0	1,8	34/?	NA	NA	NA	+	NA	NA	NA	12	NED
Stita[71]	2009	64	BM	BM	BM	Neg	NO	NA	NO	Mast + ALND	ChT	NO	T2N0M0	3	0/?	NET	+	+	+	+	NA	NA	8	NED
Yamaguchi[72]	2009	51	BM	BM	BM	NA	Neg	Bio	NO	Mast + ALND	PTX	NO	T2N0M0	2,5	NA	SCNC	+	+	-	-	-	85%	12	AWD
Christie[73]	2010	61	NA	NA	NA	NA	NA	NA	NO	BCS	NO	NO	T3N2M0	3	NA	NA	NA	NA	NA	NA	NA	NA	3	DOD
Goucha[74]	2010	40	NA	NA	NA	NA	NA	NA	NO	BCS + ALND	NO	Yes	T1N0MX	1,8	0/15	NA	NA	NA	+	NA	NA	NA	12	NED
Honami[75]	2010	54	BND	HyBM	Neg	NO	No	Bio	NO	BCS	HoT	Yes	T1NXMX	1,5	NA	ICNE	+	+	+	NA	-	NA	18	NED
Huettemann [76]	2010	65	NA	NA	NA	Neg	Neg	NA	NO	Mast + ALND	DTX/Bev	NO	T3N1M1	9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Latif[77]	2010	53	BM	Neg	BM	NO	Neg	Cit, Bio	Yes	BCS + SLNB	Tam/Som	Yes	T3N0M0	1 cm	0/1	SCNC	+	+	-	NA	-	NA	NA	NA
Saglam[78]	2010	60	NA	NA	NA	NA	Neg	NA	NO	NO	NO	NO	T4N1M1	0,6	1/1	NA	NA	NA	+	NA	NA	NA	26	DOD
Salman[79]	2010	72	NA	NA	NA	Neg	Neg	NA	NO	Mast + ALND	Letr	NO	TXNXM1	NA	NA	NA	NA	NA	+	NA	NA	NA	12	NED
Buttar[80]	2011	63	Jaundice	NA	NA	Pos	NO	Bio	NO	NO	Tam/Ana	NO	T2N0M1	NA	0/1	NEC	-	+	+	NA	-	NA	12	NED
Cesaretti[81]	2011	68	BM, N+	BL	HypBM	NA	NA	Cit, Bio	NO	BCS + ALND	ADR/CPA + Ana	Yes	T1cN0Mx	1,1	0/19	NEC	+	+	+	+	-	7%	34	NED
Ghanem[82]	2011	64	BM, N+	BN	BN	Neg	NA	Bio	Yes	Mast + ALND	ADR/CPA + Ana	YES	T3N2M0	8	16/23	NA	+	NA	+	+	-	10%	32	AWD
Jach[83]	2011	28	BL	BN	NA	NA	NA	Bio	NO	BCS + ALND	ADR + Tam	YES	T1N0M0	1,1	0/4	ICNE	+	NA	+	+	NA	40%	NA	NA
Kavasaki[84]	2011	43	BND	BM	NA	NA	NA	NA	NO	BCS	NA	NA	T1N0M0	1,2	0/4	NEC	+	+	+	NA	+	NA	NA	NA
Kawanishi [85]	2011	67	UBM	HyBM	BM	NA	NA	Cit, Bio	NO	BCS + SLNB	Ana	NO	T1N0M0	0,8	0/1	NEC	+	+	+	NA	-	NA	12	NED

Navrozoglou[86]	2011	73	NO	BN	BN	NA	Neg	Bio	NO	Mast + ALND	NO	NO	T1N0M0	1,1	0/17	NET	+	+	NA	NA	NA	NA	48	NED
Nicoletti[87]	2011	40	BM	BN	BN	Neg	NO	Bio	NO	Mast + ALND	ADR/CPA + CBL/VP-16 + Tam/LHRH	NO	T2N1M0	3	1/16	SCNC	+	+	+	+	-	+	96	NED
Nozoe[88]	2011	57	BL	HyBM	BM	NA	NA	NA	NO	Mast + ALND	CMF + AI	NA	NA	3	0/?	NEC	NA	+	+	+	-	NA	NA	NA
Zhang[89]	2011	29	BND	BM	BM	NO	NO	Cit	NO	BCS + SLNB	CPA/EPI/5-FU + DTX + Tor	NA	T2N0M0	2	0/2	NET	+	+	+	+	-	1%	20	NED
Alkaied[90]	2012	83	Anorexia	Neg	Neg	NO	Pos	Bio	Yes	NO	Letr - Ana	NA	TXNXM1	NA	NA	SCNC	-	+	+	NA	NA	NA	12	NED
Flessas[91]	2012	59	NO	NA	Mic	NO	NO	Bio	NO	BCS +ALND	NA	NA	T2N1M0	2,8	1/?	ICNE	+	+	NA	NA	NA	NA	NA	NA
Graça[92]	2012	83	BM	BN	BM	Neg	Neg	Cit	NO	BCS + SLNB	HoT	NO	T2N0M0	2,4	0/1	NEC	NA	+	+	NA	NA	NA	NA	NED
Menéndez [93]	2012	44	NO	NA	BM	NA	NA	NA	NO	BCS + ALND	5-FU/EPI/CPA	Yes	T2N0M0	2	1/?	NEC	NA	NA	+	+	-	NA	48	NED
		68	NO	NA	BM	NA	NA	NA	NO	BCS + SLNB	5-FU/EPI/CPA + DTX + Ana	Yes		3,6	NA	NEC	+	NA	NA	NA	NA	NA	24	NED
		58	NO	NA	BM	NO	NO	Bio	NO	BCS + SLNB	5-FU/EPI/CPA	Yes	T1N0M0	1	0/1	NEC	NA	NA	+	-	-	NA	8	AWD
		69	NO	HyBM	BM	NA	NA	NA	NA	BCS + SLNB	NA	NA	T1N0M0	1,4	0/1	ICNE	+	+	+	+	-	10%	2	NED
Miura[94]	2012	72	NO	NA	NA	Neg	NA	Cit, Bio	NO	BCS + SLNB	NA	NA		1,5	0/1	NEC	+	+	+	+	-	1%	NA	NA
Psoma[95]	2012	46	BM	HyBM	HypBM	Neg	NO	NA	NO	Mast + ALND	CDDP/EPI/VP-16	Yes	T3N0M0	6,5	NA	NET	+	+	NA	NA	NA	NA	6	NED
Su[96]	2012	75	PBM	HyBM	HypBM	Neg	NA	Bio	NO	Mast + ALND	Let	NO	T2N0M0	4	0/?	ICNE	+	+	+	+	-	NA	20	NED
Watrowski [97]	2012	56	BM	HyBM	NA	NO	NO	Bio	NO	BCS + SLNB	CPA/EPI/5-FU + HoT	Yes	T1N0M0	1,7	0/1	NET	NA	+	-	-	-	46%	15	NED
Yavas[98]	2012	77	BM, N+	BM	HypBM	Neg	NO	NA	NO	Mast + ALND	NO	NO	T2N1M0	3	5/16	ICNE	NA	+	+	+	+	NA	15	NED
Abbasi[99]	2013	37	BL, N+	NA	NA	BoMet	NA	Bio	NO	Mast + ALND	5-FU/ADR/CPA + CDDP + VP-16	NO	T3N2M1	7,5	9/19	ICNE	+	+	NA	NA	NA	NA	6	NED
Angarita[100]	2013	51	BL	Neg	SBM	Neg	NO	Bio	Yes	BCS + ALND	CDDP/VP-16 + PTX	NA	T2N0M0	3,2	0/?	ICNE	+	+	-	NA	-	>20%	13	AWD
Chang[101]	2013	42	BL	MBM	HypBM	NO	Neg	Cit	No	NO	NA	NA	T2N1M0	NA	+/?	NEC	+	+	+	NA	-	NA	NA	NA
Hanna[102]	2013	60	PBM	Neg	Neg	Neg	NO	Bio	NO	BCS	CBL/VP-16	NO	T1N2M0	1,4	4/11	NEC	-	+	+	NA	-	NA	NA	NA
Senetta[103]	2013	82	Asthenia	BM	NA	PiMet	NO	Bio	NO	BCS + SLNB	HoT	NO	T1NXM1	2,3	NA	NEC	+	+	+	+	-	10	NA	NA
Yoon[8]	2013	44	BM	HyBM	HyBM	Neg	Neg	Bio	NA	Mast + ALND	CPA/ADR	NA	T2NXM0	2	NA	NEC	+	+	+	+	NA	NA	2	NED
Cinkir[104]	2014	75	BM	BM	BM	NA	NA	Bio	NO	Mast + ALND	CDDP/VP-16	Yes	T0N0M0	0	0/?	SCNC	+	+	+	+	-	5%	30%	NED
	2014	77	PBM	SBM	SBM	NA	NA	Bio	NO	Mast + ALND	AI	NO	T2NXM0	2,3	NA	NEC	+	+	+	+	-	10%	9%	NED
Pagano[105]	2014	51	BL, NR	NA	BM	Neg	NA	Bio	NO	Mast + ALND	CPA/MTX/5-FU + Tam	NA	T2N2M0	3,5	5/28	NET	+	+	+	+	-	30	126	AWD
Suhani[106]	2014	66	BL	NA	NA	Neg	NA	Bio	NO	Mast + ALND	CPA/ADR/5-FU + AI	Yes	T3N1M0	6,5	1/15	NET	+	-	+	+	-	NA	48	NED
		55	BL	NA	NA	Neg	NA	Bio	NO	Mast + ALND	CPA/ADR/5-FU + AI	Yes	T2N1M0	4,5	2/16	NET	+	-	+	-	-	NA	36	NED

		50	BL	NA	NA	Neg	NA	Bio	NO	Mast + ALND	CPA/ADR/5-FU + AI	Yes	T2N0M0	4	0/18	NET	+	+	+	+	-	NA	18	NED
		60	BL, BND	NA	NA	Neg	NA	Bio	NO	Mast + ALND	CPA/ADR/5-FU + AI	Yes	T3N1M0	5,5	1/16	NET	-	+	+	+	-	NA	9	NED
Janosky[107]	2015	34	BL	Neg	HypBM	NA	Neg	Bio	Yes	BCS + ALND	CBL/PTX	Yes	T2N0M0	3,5	0/?	NEC	+	+	-	NA	-	100%	2	AWD
Kawasaki[108]	2015	60	SR	HyBM	NA	Neg	NO	Bio	NO	BCS + ALND	Ana	NO	T1N0M0	1,2	0/4	NEC	+	-	+	NA	0	6.3%	48	AWD
Rana[109]	2015	65	BL	NA	NA	Neg	NO	Bio	NA	Mast + ALND	NA	NA	T3N2M0	6	4/20	NEC	+	+	+	+	-	NA	NA	NA
Santos-Juanez[110]	2015	80	BM	Neg	Neg	Pos	NO	Bio	Yes	NO	NO	Yes	T4NXM1	17	NA	NET	+	+	+	+	-	10%	5	NED
Sherwell-Cabello[111]	2015	60	BL, N+	NA	NA	NA	Neg	NA	NO	Mast + ALND	CBL/VP-16	Yes	T3N3M0	6	11/15	NET	-	+	-	-	-	70%	6	NED
Wei[112]	2015	43	BM	HyBM	MBM	NO	NO	Bio	Yes	Mast + ALND	NA	NA	T2N1M0	3	1/?	NET	+	+	+	-	+	10%	NA	NA
Alva[113]	2016	53	BL	Neg	SBM	Neg	NO	Cit	NO	Mast + ALND	NA	NA	T2N0M0	5	0/10	NEC	+	+	-	NA	-	NA		
Christensen [114]	2016	73	SR	BM	BM	PaMet	NA	NA	NA	BCS + ALND	NA	NA	T2N3M1	3,8	18/21	ICNE	-	+	NA	NA	NA		4,5	AWD
D'antonio [115]	2016	50	BL	BL	Neg	Neg	Neg	Bio	NO	BCS + ALND	NO	NO	T1N0M0	1,5	0/?	ICNE	+	+	-	+	-	<5%	12	NED
Mečiarová[116]	2016	42	BL	HyBM	HypBM, Mic	Neg	NA	NA	NO	BCS + SLNB	VP-16/CDDP	Yes	T2N1M0	3,2	1/1	NEC	+	+	-	-	-	50%	36	NED
Nakai[117]	2016	46	PBM	HyBM, N+	NA	Neg	NA	Bio	NO	Mast + ALND	CPA/EPI/5-FU	NA	T2N2M0	2,3	9/17	NET	+	+	+	+	+	61%	4	NED
Takanami [118]	2016	57	Neuralgia	NA	NA	Pos	NA	Bio	NA	Mast + ALND	NA	NA	T2N0M0	NA	NA	NET	NA	NA	NA	NA	NA	NA	180	AWD
Abou Dalle[119]	2017	47	NO	NA	BM	NO	Neg	Bio	NO	Mast + SLNB	CDDP/VP-16 + 5-FU/EPI/CPA + Tam	NO	T2N0M0	3	0/4	SCNC	+	+	+	NA	-	50%	10	NED
Maqsood [120]	2017	67	Neuralgia	HyBM	BM	MMet	MMet	Bio	Yes	NO	Let + Palb	NO	T1NXM1	1		NEC	-	+	+	NA	-	NA	3	AWD
Soe[121]	2017	57	BL	HyBM	HypBM	NA	BoMet	NA	NO	BCS	CDDP/VP-16 + Oct	NO	T2NXM1	4	NA	NET	+	+	+	+	NA	15%	18	NED

Headings: NA = Not available data; Clin Pres = Clinical presentation; US = breast Ultrasound; MX = mammography; Bio = biopsy; Cit = citology; Ad treat = adjuvant treatment (chemotherapy and/or hormone therapy); Adj RT = adjuvant radiotherapy; Tum size = tumor size (centimeters); LNs = lymph nodes removed; CrA = Chromogranin A; Syn = Synaptophisin; ER = Estrogen receptor; PR = Progesterone receptor; Her2 = her2-neu receptor; FUP = follow-up (months)

Clinical and radiological findings: Pos = positive for malignancy; Neg = negative for malignancy; BM = Breast Mass; CM = carcinomatous mastitis; N+ = axillary adenopathy, PBM = Painful breast mass; BL = breast lump; SR = Skin retraction, NR = nipple retraction, PLM = Paget-like Mass; BND = Bloody nipple discharge; UBM = Ulcerated Breast Mass; MBM = Multilobulated breast mass; HyBM = Hypoechoic (US) / Hypodense (MX) breast mass; Hyp = Hyperechoic (US) / Hyperdense breast mass = HeBM = Heterogeneous breast mass, SBM = Spiculated breast mass, Mic = microcalcifications, BoMet = Bone Metastases; LMet = Lung metastasis; PAMet = Perianal metastases, PiMet = Pituitary metastases; PaMet = Pancreatic metastases; PE = Pleural effusion; MMet = Multiple metastases; IBM = Isoechoic breast mass

Neg = Negative; Sus = suspicious; LMet = lung metastasis

Mast = Mastectomy; BCS = Breast Conservative Surgery; SLNB = Sentinel Lymph Node Biopsy; ALND = Axillary Lymph Node Dissection

Chemotherapy: ChT = chemotherapy (not defined); HoT = hormone therapy (not defined); CDDP = Cisplatin, CBL = Carboplatin, VP-16 = Etoposide, CPT-11 = Irinotecan, 5-FU = Fluorouracil, EPI = Epirubicin, CAP = Capecitabine, DTX = Docetaxel, 5'-DFUR = 50 deoxy-5-fluorouridine, Tor = Toremifene, CPA = Cyclophosphamide, EPI = Epirubicin, Tam = Tamoxifen, Tor = Torenifene, Let = Letrozole, S = Streptozotocin, MTX = Methotrexate, Ana = Anastrazole, AI = Aromatase inhibitor, LHRH = Leutinising hormone releasing hormone analogue, UFT = Uracil & Tegafur, PTX = Paclitaxel, ADR = Adriamycin (Doxorubicin), Sando = Sandostatin, Som = Somatostatin; Ever = Everolimus, Bev = Bevacizumab, Erl = Erlotinib; Palb = Palbociclib; Oct = Octreotide

Histology: SCNC = Small Cell Neuroendocrine Carcinoma, ICNE = Invasive carcinoma with neuroendocrine differentiation; NET = well-differentiated neuroendocrine tumor; NEC = poorly differentiated neuroendocrine carcinoma

Follow-Up: NED = No evidence of disease; AWD = Alive with disease; DOD = Died of disease; DUC = Died of Uncertain cause

†Median follow-up

Table 2: Case series and retrospective studies reported in literature.

Author	Year	Study type	N. patients	Mean age (range)	Only breast	N+ (%)	M1 (%)	ER+	PR+	Her2+	CrA+	Syn+	Mast	BCS	No surgery	Adj RT	Adj CHT	Adj OT	Mean FUP (range)
Papotti[122]	1992	CS*	4	56 (41-64)	25,00%	75,00%	50,00%	NA	NA	NA	NA	NA	100,00%	0,00%	0,00%	25,00%	25,00%	25,00%	20,5(9-44)
Shin[123]	2000	CS*	9	55,4 (43-70)	44,44%	55,56%	0,00%	66,67%	55,56%	0,00%	44,44%	44,44%	33,33%	66,67%	0,00%	44,44%	77,78%	0,00%	20,3(3-35)
Zekioglu[124]	2003	CS**	12	65,0 (43-49)	91,67%	8,33%	0,00%	91,67%	91,67%	16,67%	41,67%	91,67%	50,00%	50,00%	0,00%	NA	NA	NA	24,1(1-54)
Bonet[125]	2008	CS**	7	61,3 (35-88)	57,14%	42,86%	NA	100,00%	100,00%	14,29%	0%	100%	71,43%	14,29%	14,29%	28,57%	28,57%	100,00%	51,64(2, 7-115,5)
Tian[126]	2011	Ret**	74	61 (29-82)	52,70%	41,89%	8,11%	95,00%	80,00%	9,00%	NA	NA	40,54%	57,81%	17,27%	NA	NA	NA	46,92 (0-260)
Kanat[127]	2011	CS**	7	43,8 (29-56)	14,29%	85,71%	28,57%	28,57%	28,57%	0,00%	57,14%	100%	85,71%	14,29%	0,00%	71,43%	85,71%	28,57%	22,4(9-48)
Kawasaki[128]	2011	Ret**	27	47,8 (28-74)	95,83%	4,17%	0,00%	100,00%	100,00%	54,17%	NA	NA	37,50%	62,50%	0,00%	NA	NA	NA	83,7 (64-101)
Zhang[129]	2013	Ret**	107	65 (25-95)	NA	NA	NA	94,39%	85,05%	2,80%	NA	NA	NA	NA	NA	NA	NA	NA	27† (3-134)
Wu[130]	2012	Ret**	13	55,4 (36-78)	92,31%	7,69%	7,69%	100,00%	100,00%	0,00%	69,23%	30,77%	100,00%	0,00%	0,00%	NA	NA	100,00%	67,5 (41-89)
Rovera[131]	2013	Ret**	96	70,1 (40-94)	NA	NA	NA	90,00%	75,00%	1,04%	NA	NA	30,21%	31,25%	36,46%	48,00%	5,00%	75,00%	88† (4-242)
Zhu[132]	2013	Ret**	22	52,5 (29-77)	NA	NA	NA	90,91%	95,00%	25,00%	95,00%	14,29%	68,18%	31,82%	0,00%	0,00%	63,64%	90,91%	64,5 (4-89)
Charfi[133]	2013	Ret***	15	62,3 (37-78)	73,33%	26,67%	0,00%	80,00%	93,33%	0,00%	73,33%	6,67%	80,00%	20,00%	0,00%	86,67%	46,67%	60,00%	40,14 (3-125)
Cloyd[134]	2014	Ret***	284	NA	43,40%	36,20%	20,40%	46,5%	35,6%	NA	NA	NA	35,20%	36,60%	27,80%	41,50%	NA	NA	NA
Jeon[135]	2014	Ret***	11	54,7 (29-79)	NA	NA	NA	100,00%	100,00%	0,00%	54,55%	0,00%	36,36%	63,64%	0.00%	NA	NA	NA	38,6 (21-76)
Roininen[136]	2017	Ret***	43	66 (NA)	55,8%	39,53%	9,3%	97,70%	86,10%	4,70%	69,80%	0,00%	58,20%	39,60%	2,27%	74,40%	34,09%	75,00%	NA

Headings: Ret = retrospective; CS = Case Series;

*Previous to 2003 criteria, ** According to 2003 criteria, *** According to WHO 2012 criteria

†Median follow-up

Clinical Characteristics

From the analysis of 113 reported cases (Table 1), the most frequent clinical presentation was breast mass, which was present in 37 cases (in 7 cases also associated to axillary adenopathy and in 5 cases painful) followed by breast lump in 22 patients (of which 3 associated to axillary adenopathy, 2 to bloody nipple discharge, 1 to nipple retraction) and symptoms due to metastatic diffusion (1 jaundice, 1 haematuria, 1 bone pain, 1 respiratory symptoms, 1 perianal pain, 2 neuralgia). Less frequent clinical presentations were: isolated bloody nipple discharge (3 cases), only skin retraction (2 cases), anorexia (2 cases), locally advance disease in 3 cases (2 ulcerated breast masses, 1 carcinomatous mastitis, 1 Paget like mass). In 33 cases clinical presentation was not reported. Tumor was palpable in 58/77 cases (75%).

Radiological Findings

Radiological findings of bNENs were often similar to other breast cancer histotype, like ductal or lobular breast tumors. From available data, sonography was performed in 61 cases. In 11 cases US failed to detect breast lesions. In the other cases tumor appeared as irregular hypoechoic lesion. Data on mammographic finding was present in 61 cases and tumor always appeared as hyperdense mass. Notably, tumor was detected in all cases in which US and mammography were both performed. Only in 14 cases reported data on breast MRI: tumors appeared as irregular mass, hyperintense in T2-weighted sequences.

Histopathological Assessment

According to morphology, NEC was the most common histotype (36 cases), followed by bNET (20 cases), SCNC (20 cases), ICNE (10 cases). In 27 cases morphology was not described. Estrogen receptors was positive in 60/85 cases, progesterone receptors were positive in 37/53 cases, HER2 were positive in 8/59. Considering neuroendocrine markers, chromogranin was positive in 62/75 cases (83%), synaptophysin was positive 70/78 cases (90%). Considering data from case series and retrospective study (Table 2) chromogranin was positive in 41.67%- 95% of specimen, synaptophysin in 0%-100%.

Treatment

Most of the patients received surgical treatment (97/108 cases). The most frequent type of surgical intervention was total mastectomy, performed in 54/97 cases, followed by breast conservative surgery, in 43/97 cases. These data are concordant with retrospective studies and large case series available, in which mastectomy was performed in 30.21-100% of patients, breast conservative in 0-66.67% and no surgical treatment in 0-36.46% of patients. Considering case reports, radiotherapy was performed in 37/84 cases (44%), similarly to data from retrospective studies and large case series in which radiotherapy rate range from 25 to 86.67%.

Medical therapy was suggested in 79% of patients (73/92). Hormone therapy was indicated in 18/92 (19%), chemotherapy alone 36/92 (39%) and a combination of these two treatments were indicated in 38/92 cases (41%). Somatostatin analogue, the most used drugs in neuroendocrine tumors of other origin, was used only in three cases.

Outcome

Data on tumor outcome are available only for 91 patients: 18 patients were alive with active disease, 8 were dead of disease, 1 dead of uncertain causes and 63 were alive with no evidence of disease with a mean follow-up of 24.01 ± 29.8 months.

Discussion

bNENs are rare entities and no guidelines are available for the management of this kind of neoplasia. According to our systematic review, the most frequent clinical presentation is palpable breast mass, sometimes associated to axillary adenopathy or bloody nipple discharge. bNENs appears as hypervascular and irregular hypoechoic lesions at US examination and as hyperdense masses at mammography [8]. The detection rate of these two instrumental evaluations is high, even if is not possible to clearly differentiate this kind of tumor from another breast cancer histotype [9]. When performed, breast MRI shows irregular masses, usually hyperintense in T2-weighted sequences [8]. Before establishing treatment strategies, as recommended in all suspicious breast lesions, tumor biopsy should be performed, even if it is not always able to recognize a breast neuroendocrine tumor, which is often detected only by definitive histopathological assessment [10].

The contemporary presence of neuroendocrine cells with ductal carcinoma is usually considered a sign of the breast origin of the neuroendocrine lesions, even if a total body examination is mandatory for excluding neuroendocrine neoplasm of other origin [11]. Recommended imaging techniques are total body CT or PET/CT scan: ^{68}Gallium PET/CT in case of well-differentiated neuroendocrine tumors or ^{18}FDG PET/CT in case of poorly differentiated NEN (NEC, ICNE, SCNC) as commonly performed in other neuroendocrine neoplasia [12]. Considering available data, the most frequent subtype is NEC. Most all cases were positive for synaptophysin staining, followed by chromogranin; hormone receptors and Her2 expressions were heterogeneous but luminal type (estrogen and progesterone receptors positive and HER2 negative) was the most common, as previously published [13]. This finding is in accordance with the hypothesis that bNENs develop from breast stem cells which divides into neuroendocrine and epithelial cells [14].

Surgical treatment strategies are nowadays based on tumor size and lymph node status basing on current breast cancer guidelines, independently of neuroendocrine component. Likewise, radiotherapy is usually performed after BCS [10, 15]. Medical therapy depends on immunohistochemical analysis: in case of strong hormone receptors positivity, hormonal therapy is usually indicated [10]. In hormone-negative tumors, chemotherapy regimens, based on anthracyclines and or taxanes, is often used [10]. The possibility of using a cisplatin and etoposide regimen in breast NEC, as indicated for small cells carcinomas of other origin, has been evaluated only in small studies [16]. Specific treatment for well-differentiated neuroendocrine component is not routinely used. Only in 3 on 113 cases somatostatin analogues have been used as adjuvant therapy. Even if somatostatin analogues are considered first line therapy in the treatment of neuroendocrine tumors of other origin according to ENETS guidelines, this kind of drug is not approved for bNET, probably because of the paucity of data. Interestingly,

somatostatin receptors have been found in non-neuroendocrine breast tumors with high estrogen and progesterone receptor expression and low HER2 [17-20]. Moreover, somatostatin analogues are able to reduce breast cancer cells proliferation especially in case of low estrogen levels, providing the rationale for contemporary administration of hormonal therapy and somatostatin analogue therapy [21, 22]. In Figure 2, we propose a diagnostic and therapeutic algorithm for bNENs.

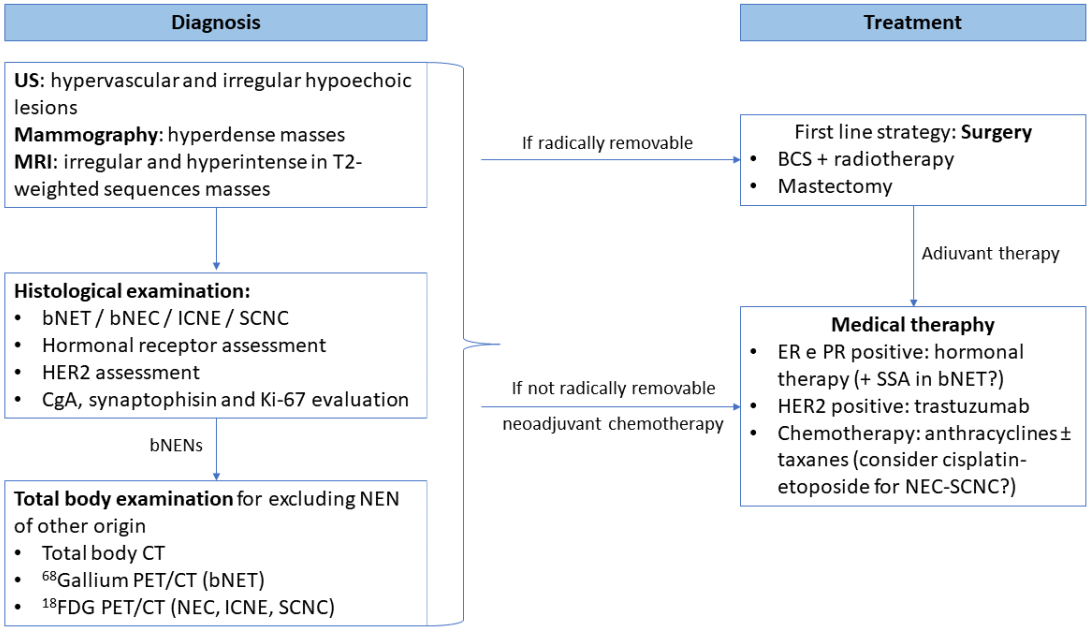

Figure 2: Proposal of diagnostic and therapeutic algorithm for NEN.

Finally, if the prognosis of all bNENs is different compared to non-neuroendocrine breast cancer is still debated. From the published cases, only 8 patients on a total of 91 deceased for the disease. When available, histotype of these neoplasms was NEC/SCNC. In the other 4 cases, tumor histology was not reported but tumor stage was advanced, implying that tumor stage and histology could be the main predictors of poor outcome. Data from the SEER database, comparing 142 breast NEC and non-neuroendocrine breast tumors, demonstrated a shorter overall survival and disease-specific survival of breast NEC and in a multivariate analysis neuroendocrine differentiation was an independent determinant of poorer prognosis [5]. Similarly, Bogina et al. have demonstrated a worse prognosis in 55 breast NEC patients compared to 115 matched non-neuroendocrine breast tumors patients [7].

Conclusions

bNENs are rare tumors, usually identified only during definitive histopathological examinations of surgical specimen. bNENs are nowadays treated similarly to non-neuroendocrine breast cancer, but they are very heterogeneous and not well understood. Similarly, to NEN of other origin, we should probably distinguish between well differentiated tumors, NET, and poorly differentiated tumors, NEC/small cells carcinomas regarding treatment and prognosis. Specific trials on adjuvant therapy, for example with somatostatin analogues for well differentiated form, bNET, or classical chemotherapy with cisplatin and etoposide in NEC and SCNC are necessary for establishing the best treatment strategy for these patients and improving clinical outcome.

Abbreviations

NET: neuroendocrine tumor
bNENs: breast neuroendocrine neoplasia
NEC: neuroendocrine carcinoma
ICNE: invasive breast tumor with endocrine differentiation
WHO: World Health Organization
US: ultrasound
MRI: magnetic resonance imaging
BCS: breast conservative surgery

Consent for Publication

All patients provided written informed consent to case publication.

Conflicts of Interests

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Author Contributions

Dr. Federico Frusone and Dr. Giulia Puliani cowrote this paper. Dr. Federico Frusone collected information of the case series from the database of Humanitas Research Hospital of Milan. Dr. Andrea Sagona,

Dr. Emilia Marrazzo and Dr. Erika Barbieri helped analysing the results of the case series. Dr. Giulia Puliani and Dr. Federico Frusone performed literature research and analysed the results. Dr. Alessandro De Luca helped analysing these results. Dr. Wolfgang Gatzemeier, Dr. Alberto Bottini and Dr. Corrado Tinterri reviewed the manuscript. All the authors read and approved the final manuscript.

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