International Journal of Surgery (2013) **11**(S1), S79–S83

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

ORIGINAL ARTICLE

Neuroendocrine breast cancer: retrospective analysis of 96 patients and review of literature

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ARTICLE INFO

Keywords:
Breast cancer
Neuroendocrine
Retrospective
Survival

ABSTRACT

Background and Purpose: Primary neuroendocrine breast carcinomas (NEBC) are uncommon lesions; they constitute approximately 1% of all breast cancers and mostly affect elderly patients. According to the most recent World Health Organization classification, it concerns almost exclusively the female population between the sixth and seventh decades. The aim of this retrospective study is to analyze the clinicopathological aspects of 96 NEBC patients who had undergone surgical resection at a single institute.
Methods: We retrospectively analyzed a series of 96 patients who underwent surgical resection for NEBC between January 1992 and August 2013.
Results: The 96 patients with NEBC were divided into two categories: 61 (63.5%) in whom the expression of a neuroendocrine marker was present in more than 50% of neoplastic cells and 35 (36.5%) with a minor neuroendocrine component. Our data show a mean age of the patients at diagnosis of 70 years (range 42–87 years); the 10-year survival of the 96 patients was 87%, moreover we report tumor location, type of surgical operation, tumor size (average 2.1 cm), hormone therapy, chemotherapy and radiotherapy if used, recurrence sites, overall and disease free survival times.
Conclusions: This study showed a better prognosis in patients with NEBC compared with breast carcinomas with a minor neuroendocrine component and with conventional invasive ductal or lobular cancers.

1. Introduction

Neuroendocrine breast carcinomas (NEBC) include an heterogeneous group of tumors, showing morphological features similar to those of neuroendocrine tumors of the gut and lung, and expressing one or more neuroendocrine markers in at least 50% of tumor cells. NEBC are rare lesions, representing about 1% of all breast cancers (BC), and according to World Health Organization (WHO) data mostly affect elderly patients. [1] Except for its small-cell variant, NEBC is characterized by less aggressiveness than the invasive ductal variant of BC.

In the international scientific literature the first description of BC morphologically similar to intestinal carcinoids dates back to 1963 and is attributed to Feyrter and Hartmann. [2] On the basis of argentic impregnation, Feyrter and Hartmann suggested the nature of endocrine "mucoid" carcinoma of the breast. However, it is commonly accepted that the first histopathological classification of NEBC, together with a clinical and prognostic analysis, is to be attributed to two American pathologists: Antonio Cubilla and James Woodruff in 1977. [3] They published a series of 8 cases sharing peculiar cytological characteristics, such as a microscopic appearance comparable to intestinal carcinoid, a positive staining for Grimelius coloration and a neurosecretory structure at the electron microscope.

Because of the work of Cubilla and Woodruff on NEBC, this cancer has been identified by some authors as "carcinoid of Cubilla and Woodruff". This name was progressively abandoned, until the definitive taxonomic proposal of neuroendocrine breast cancer. [1,4]

Since 2003, WHO defines NEBC as a separate entity, [1] consisting of a heterogeneous group of breast primitive tumors of epithelial origin and morphology, similar to gastrointestinal and pulmonary neuroendocrine tumors, expressing a neuroendocrine marker [1] in at least 50% of the total cell population. In fact, a focal neuroendocrine differentiation is observed in a large number of breast cancers: according to statistics, it may be represented in 10–18% of BC. [1,4–7] It can be found in many breast histotypes, such as ductal, NOS, lobular, [1,8] mucinous, tubular and papillary breast cancers. [9]

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The diagnosis of NEBC needs immunohistochemistry (HIC) positivity in at least 50% of the following markers in the tumor population:

- chromogranin (Cg): although their hormonal function is not precisely known, [10] Cgs are the most represented proteins in the granules of neurosecretion, where they can reach 80% of the total proteins. [11] Cgs were initially identified in the adrenal medulla, [12] after they had been found in endocrine tissues and in the brain. Their expression in neoplastic tissue, however, is related to the grading of the tumor, with less expression in poorly differentiated carcinomas. [13] CgA is the most sensitive neuroendocrine marker [14]: it consists of 439 amino acids and it is usually bound by the monoclonal antibody LK2H10, which confers high diagnostic reliability. The advent of immunohistochemical staining, thanks to the work of Bussolati et al. [15] in 1985, gave new support to the theory of the presence of cells belonging to the diffuse neuroendocrine system in the normal mammary epithelium. In fact, according to the authors, CgA can be present even in non-neoplastic tissue samples. CgB and secretogranin II are less specific than CgA for normal and neoplastic endocrine tissue;
- synaptophysin (Syn): this is a cytoplasmic glycoprotein composed of 313 amino acids, involved in synaptic transmission and expressed by almost all neuronal and neuroendocrine cells. It is one of the most reliable neuroendocrine tumor markers [6];
- neuron-specific enolase (NSE): this is an isoform of enolase, selectively expressed in neurons and endocrine cells. It is occasionally HIC positive in NEBC [16];
- CD56: this is a typical adhesion protein of neuronal cells; if detected by a specific monoclonal antibody, it can act as a neuroendocrine marker, but it is considered to be statistically less sensitive and less specific, thus playing a minor role compared to the markers mentioned above. [17]

Moreover, NEBC can be diagnosed by the presence of secretory granules by electron microscope, although this is an instrument rarely used in clinical practice. Ultrastructural analysis shows the NEBC differentiation [18] by the presence of electron-dense scattered intracytoplasmic granules. [19] These granules have a clear peripheral ring and a central electron-dense core, with a strong dimensional variability [20] (range 150–450 nm). Moreover, they appear in small vesicles, structures derived from the Golgi apparatus, positioning most of the time close to the nucleus.

In breast pathology no debate has reached such a high number of dissenting voices as the acceptance of NEBC being a primitive mammary tumor. One reason is the absence of endocrine cells in the normal breast tissue, [8] both fetal and adult, although in 1947 the German pathologist Vogler [21] demonstrated their presence along the ductal epithelium: an event, anyway, considered rare even by Volger and the subsequent supporters of this theory. [2,3,22–24] They based this pathogenic theory on the wide distribution of argyrophilic cells in the body. In fact, endocrine cells (APUD cells) were progressively identified in extra-intestinal sites such as the lungs, [25,26] thymus, [27] gallbladder, skin, [28] ovary and testis. [29,30] It would then be likely that they could also occur sporadically in the breast. In 1985, this theory found the first immunohistochemical confirmation: Bussolati et al. [15] demonstrated CgA-positive cells in normal breast ducts. However, other authors [8,23] have not confirmed the presence of this cell differentiation in the breast parenchyma, fueling the controversy about the origin of the NEBC.

In parallel with this theory, however, there is the belief that NEBC originates – like any other histological type – from a primitive stem cell that differs along a line of ductal type (standard or special) or lobular type. Among the first studies in this direction we remember the study of Capella et al. [20] in 1990, which highlights the simultaneous presence of exocrine granules (mucinous) and endocrine effects in the context of breast cancer – a feature highly indicative of a common stem cell between the neuroendocrine and mucinous carcinoma. The epithelial cells should acquire then, during the process of carcinogenesis, the ability of differentiation, focal or diffused, towards a different histological line.

Among the studies in support of this hypothesis, it is worth mentioning the work of Perou et al. [31] in 2000, that gave birth to a different analytical approach to BC. Perou has indeed shifted the attention to the molecular analysis, setting the stage for the biological classification (cancer subtypes Luminal A, Luminal B, HER2+, Basal-like) on which actual BC treatments are based. Developing Perou's studies, Weigelt et al. [32] have investigated gene expression analysis using DNA-microarrays on special histological types of BC. It is interesting to report the results obtained on NEBC, which show important similarities with the mucinous carcinoma. In fact, starting from a stem cell, the carcinogenic process determines transcriptional mutations, genetic and epigenetic, common to NEBC and mucinous carcinoma (in particular subtype B, or "hypercellular", originally classified by Capella et al. [33]) with respect to ductal carcinoma. These mutations cause an overproduction of protein, confirmed by immunohistochemical analysis, which gives a specific biological behavior to this cancer. In particular, in the case of NEBC, compared with the same grading of ductal BC with Luminal A phenotype, genes coding for the chromogranins, synaptophysin, CD56, bombesin, metalloproteases and collagenases are amplified. Similarly, the genes FOXA1, XBP1, ERBB4 are up-regulated; these genes determine the expression of estrogen receptors, progesterone, and in 45% of cases, androgen. Down-regulation, instead, appears for gene networks involved in migration, invasion and proliferation; similarly the expression of high molecular weight cytokeratins is also decreased.

To date only one case of NEBC demonstrating positivity for cytokeratins basal-type has been reported, and this was a small-cell variant. [34] These genetic characteristics are reflected in the biological and immunohistochemical NEBC characteristics; in fact it is classified within the Luminal biological subtype. [35]

Epidemiologically, the incidence of NEBC appears to be controversial. According to the most recent WHO classification, similar to the more frequent breast cancers, NEBC almost exclusively affects female patients aged between the sixth and seventh decade [1,36]; few cases are therefore diagnosed in the premenopausal period. [37] Currently approximately 200 cases have been described in the literature, in the form of small series [3,5,6,24,36–41] or as individual case reports, one of them in the bilateral type. [3,42] A few cases in males have also been reported. [43–46]

Data related to the incidence of NEBC showed different percentages: from rare observations (0.09%) in the review by Fisher et al. (1979) [24] in a series of 3,300 BC, to slightly higher according to Günhan-Bilgen et al. (2003) where they represent 0.27% of 1,845 BC cases, [47] to Lopez-Bonet et al. (2008) reporting 0.51% of 1,368 patients. [38] The WHO confirms the incidence of NEBC as <1%, while, as far as concerns a focal representation within invasive carcinomas, the percentage increases to 10–18%. [1] With regard to the rare anaplastic small-cell variant, the first case was reported in 1983, [48] and up to now about 40 cases have been described [49–52]; of these, the largest series published includes 9 patients. [49]

The clinical presentation of NEBC has features comparable to those of more common forms of BC. In fact, mammographically it is substantially similar to the other malignant lesions. In the literature, although NEBC is described in some small series and numerous case reports, only three publications [47,48,53] provide an analysis of NEBC imaging. They agree on its mammographic appearance; in fact it often appears as a dense mass, predominantly with

speculated or lobulated margins. According to some authors, [54,55] presurgery diagnosis of NEBC by fine-needle aspiration cytology (FNAC) is possible, though not without difficulty. May–Grünwald–Giemsa staining shows moderate cellularity, low cohesiveness, with elements of polygonal shape and plasmacytoid, with abundant cytoplasm, oval nuclei and small nucleoli. Also, there is poor dimensional variation between the cell elements, but the decisive factor in the FNAC diagnosis appears to be the presence of cytoplasmic azurophilic granules, in particular in the cell periphery. [56] More frequently, authors report histological identification of NEBC by aspiration core biopsy. [37,42,44,54,57] At present, however, such a diagnosis does not determine a treatment divergent from that of other histological types of BC. Compared to histologically different BCs, a peculiarity of NEBC is the occurrence of clinical conditions related to hormonal hypersecretion, although extremely rare. In fact, patients with symptoms related to ectopic secretion of ACTH, [58] parathyroid hormone, prolactin, norepinephrine and calcitonin are described. [59,60] These clinical presentations, however, are now considered exceptional and related to advanced tumor stages. These stages of diagnosis have decreased in the last decade, due to the diagnostic anticipation produced by the increasingly wide spread of mammographic screening. Peculiar is the case report of a patient in whom a carcinoid crisis is described, induced by compression during mammography of the mammary gland, site of metastasis from ileal carcinoid. [61]

2. Patients and methods

We retrospectively reviewed a series of 2829 BC patients who underwent surgery between January 1992 and August 2013. There were 96 patients with neuroendocrine breast cancer (NEBC) or a focally expressed neuroendocrine component in the context of a different histological type (NEF). Survival analysis of entire sample considered the following variables: age, gender, histology, tumor diameter, tumor grade, number of lymph nodes involved, expression of hormone receptors, c-erbB2, Ki-67 proliferation index, oncoprotein p53 and type of surgical treatment (conservative/mastectomy, lymph nodes). We finally conducted bivariate analysis to identify factors associated with histotype NE.

3. Results

We divided the 96 patients with NEBC components into two groups:
- 61 (63.5%) NEBC, in whom the expression of a neuroendocrine marker was present in more than 50% of neoplastic cells.
- 35 (36.5%) NEF, carcinomas in which the expression of neuroendocrine markers was found in less than 50% of the tumor cells.

The cohort under consideration consists of 95 female patients and 1 male patient (infiltrating ductal carcinoma [IDC] + focal expression NEBC). The average age at the time of diagnosis was 70.1 years (range 40–94 years) and the median follow up was 65 months (range 2–242 months).

These two groups were analyzed separately in order to decrease the histological heterogeneity.

3.1. Primary neuroendocrine carcinomas (NEBC)

NEBC constitute 63.5% of all neuroendocrine carcinomas analyzed (n = 61). According to histological examination they were divided into NEBC solid type (n = 29), NEBC solid aspects mucinous type B (n = 14), micro-invasive NEBC (n = 6), NEBC solid associated with a second nodule of IDC or DCIS (n = 5), NEBC solid with focal component of DCIS (n = 3), NEBC solid with focal component of IDC (n = 1), and finally, with respect to anaplastic variants, large-cell NEBC (n = 2) and small-cell NEBC (n = 1). In order to standardize the categories of NEBC analyzed, anaplastic carcinomas (n = 3) were evaluated separately from the remaining 58 NEBC (Fig. 1).

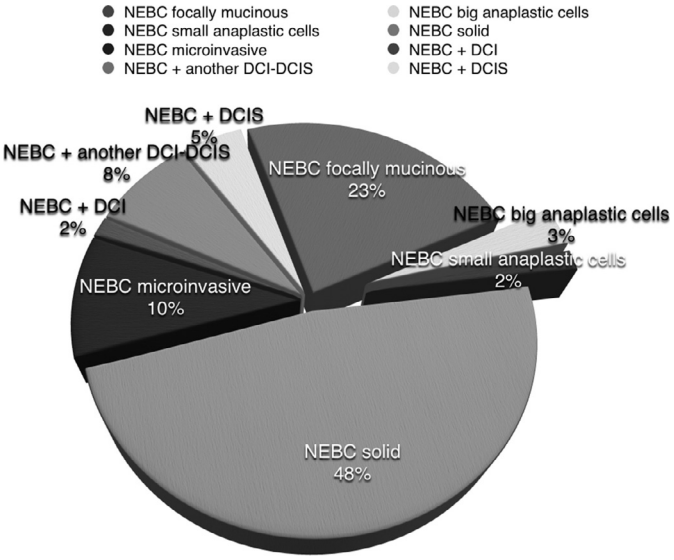

Fig. 1. Different histological types of NEBC present in our series.

The neuroendocrine carcinomas of solid type had the following clinical characteristics: the enrolled patients had a mean age at diagnosis of 70 years (range 42–87 years), mainly (90.5%) in patients in menopause (on average menarche has risen to 13 years and menopause to 48 years) with an average BMI of 26 kg/m^2. On average, they had 1.7 child per patient, with breast-feeding in 54% of cases. Some degree of family history of breast cancer was present in 27% of patients.

The laterality of the tumor was left breast in 50% of cases, right breast in 46.6%, and bilateral in 3.4% (n = 2, where histological examination of the contralateral nodule showed IDC in one case, and IDC with focal expression NE in the other).

Surgical therapy was performed as follows:
- 4 tumorectomies (including 1 followed by further lumpectomy, quadrantectomy and finally ipsilateral mastectomy, while in 1 case just quadrantectomy of completion);
- 26 quadrantectomies (including 1 for lumpectomy followed by recurrence, 1 contralateral quadrantectomy, 1 for contralateral cancer treated with medical therapy alone);
- 29 mastectomies (28 ab initio and 1 after quadrantectomy).

Furthermore, the surgical treatment of axilla we performed included:
- 16 patients who underwent sentinel lymph node biopsy (SLNB), followed in only 1 by axillary lymph node dissection due to the presence of metastasis in the SLN (3 levels of lymph nodes removed were found to be negative for neoplastic cells);
- 33 patients who underwent axillary lymph node dissection, without looking for the sentinel lymph node;
- 9 patients who did not receive any surgical treatment of the axilla (including 1 for previous ipsilateral axillary lymph node dissection).

Finally, related to the clinical presentation of the NEBC, in our series there was a high correspondence between the dimensional description of the echo-mammographic imaging (MRI was performed in only one case) and the subsequent definitive histological detection.

In just one patient the preoperative tumor markers were found to be significantly increased (CA 15-3 = 193 U/mL). Two patients had staging exams positive for distant metastases (bone metastases in

bone scintigraphy), but in these two cases the values of the pre-operative tumor markers are not available.

The pathological characteristics of the NE carcinomas analyzed can be summarized as follows:

- The focality was unifocal in 77% of cases (n = 47), bifocal in 14.7% (n = 9) and multifocal in 3.3% (n = 2).
- Histological grade reported was G1 in 34% of cases, G2 in 64% and G3 in 2%.
- Average tumor diameter was 2.05 cm (range 0.6–6 cm), determining a pT1a = 0%, pT1b = 17.2% (n = 10), pT1c = 43.1% (n = 25), overall pT1 = 60.3% (n = 35); pT2 = 34.5% (n = 20), pT3 = 1.7% (n = 1), pT4a = 0% and pT4b = 3.4% (n = 2).
- With regard to lymph node involvement, if axillary surgery performed, there were pN0 = 76.6% of cases (n = 36), pN1 = 21.3% (n = 10), pN2 = 0% and pN3 = 2.1% (n = 1).

Receptor expression can be summarized as follows:

- Estrogen receptor (ER) was present in 90% of carcinomas, with an expressiveness average of 87%, while the progesterone receptor (PgR) of 75%;
- The proliferation index Ki-67 average was overexpressed in 14% of cells, with a range of 0% to 39%;
- The growth factor receptor c-erbB2 was virtually absent (in only one case it was overexpressed in 15% of the cell population);
- The p53 tumor suppressor gene was overexpressed, on average, only in 2% of the neoplastic cells (range 0–20%).

As regards post-operative treatment, adjuvant chemotherapy was administered in 5% of cases (n = 6), radiotherapy in 48% (n = 27), and hormone therapy in 75% (n = 42), with some patients receiving multimodal treatment.

The median follow up of the NEBC patients was 88 months (range 4–242 months), with pathological findings (for neoplastic recurrence or any other neoplastic disease) in 19.7% of cases (n = 12). Specifically, local or systemic recurrence occurred in 14.8% of patients (n = 9) after a median time of 53.7 months (range 8–120 months), while the onset of a different cancer was recorded in 4.9% (n = 3), including a contralateral breast cancer and uterine cancer in one patient, and contralateral breast tumor in two patients.

Recurrences of the solid type of NEBC (n = 9) occurred in the same breast in 33% of cases (n = 3), as liver metastases in 44% (n = 4), as bone metastases in 66% (n = 6), with brain localization in 11% (n = 1) and with lymphnodal distant dissemination in 33% of cases (n = 3). Of these patients, 7 (78%) died from cancer cachexia, 1 (11%) died from liver metastases, and 1 (11%) is still alive after a lumpectomy of breast recurrence and subsequent hormone therapy.

3.2. Carcinomas with focal neuroendocrine component

These constitute 36.5% of neuroendocrine carcinomas analyzed (n = 35). Focal expression of neuroendocrine cancer was associated with mucinous carcinoma (n = 4), intraductal papillary carcinoma (n = 1), ductal-lobular carcinoma (n = 1), ductal carcinoma in situ (n = 1), and predominantly with infiltrating ductal carcinoma (n = 28).

3.3. Survival analysis

For survival analysis (OS and DFS) we assessed a cohort of 84 patients with neuroendocrine carcinomas for whom follow up was available: 52 patients with NEBC and 32 patients with solid carcinomas with NE component focally expressed. In the comparison of OS between the two groups, the curve for the focal NE is worse, although not statistically significantly ($p = 0.43$). Moreover we have compared patients with neuroendocrine tumors with a group of 2,745 control cases; NE patients had significantly larger tumor diameter ($p = 0.04$), increased expression of hormone receptors ($p << 0.001$), and a lower expression of the biomarkers erbB2 ($p = 0.002$), Ki-67 ($p < 0.001$) and p53 ($p = 0.005$).

At the molecular level, our data agree with recent gene expression profiling studies [62] that show NE as belonging to the Luminal A molecular type. Indeed, there was positivity for hormone receptors (in our experience, on average ER = 87% and PgR = 75%), low expression of Ki67 (14%) and c-erbB2 virtually absent (< 1%). Because of this, the prognosis for NEBC patients is reported to be good usually, in accordance with our data, collected in an average follow up of 89 months. The 10-year survival of our 96 patients (NE+NEF) was 87%.

4. Discussion

NEBC shows clinical and biological characteristics more favorable than the majority of breast cancers. This characteristic is observed even in their prognosis. Considering the incidence of NEBC, which nearly 1% of breast cancers, in our opinion it deserves the development of more specific therapies, like other subtypes of breast cancer.

5. Conclusion

A primary challenge for future treatment of patients will be to distinguish between genes and pathways that drive cancer proliferation and genes and pathways that have no primary role in the development of cancer. The identification of functional pathways that are enriched for mutated genes will select subpopulations of patients that will most likely be sensitive to chemotherapy or to biology-driven targeted agents. Also, loco-regional treatment might become personalized according to specific subtypes of breast cancer, in order to maximize efficacy while minimizing the extent of treatment. Anyway this aim requires tailored treatment investigations through international cooperation and should not just rely on information predominantly contributed by small retrospective analyses.

Funding
None.

Disclosure statement
The authors have no conflicts of interest to declare.

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