Primary neuroendocrine carcinoma of the breast

A single Center experience and review of the literature

Ann Ital Chir, 2017 88, 2: 116-121
pii: S0003469X16026580
free reading: www.annitalchir.com

Paolo Locurto, Angelo Danilo Antona, Antonietta Grillo, Antonio Ciulla, Stefania Martorana, Calogero Cipolla, Giuseppa Graceffa, Salvatore Vieni

A.O.U. Policlinico "Paolo Giaccone", Division of General and Oncological Surgery, University of Palermo, Palermo, Italy

Primary neuroendocrine carcinoma of the breast. A single Center experience and review of the literature

Neuroendocrine carcinoma of the breast is an extremely rare tumor. A standard treatment has yet to be established because only a few cases have been reported in literature. The authors report five cases observed from January 2007 to December 2014 and a review of literature. Four patients underwent quadrantectomy and in two cases axillary nodal dissection and only one to mastectomy with axillary nodal dissection. Tumor size was from T1 to T2 with N0 to N1, according TNM classification. Pathological specimens were stained with hematoxylin and eosin and an immunohistochemical panel of antibodies (Neuron-specific enolase, Chromogranin, Synaptophysin, Estrogen and Progesterone receptors, c-erb and Ki-67). All cases showed markers positivity to Neuron-specific enolase, Chromogranin, Synaptophysin and Estrogen and Progesterone receptors were found. Ki-67 was higher than 40% in four patients. Adjuvant chemotherapy was administrated in patients with Ki-67>10%; every patients were treated with radiotherapy and with hormonal therapy too. Although Neuroendocrine breast tumor is considered a distinct entity, the best treatment seems to be correlate to the size of tumor and to the lymph node status and to Ki-67 index like the common breast cancer.

KEY WORDS: Diagnosis, Neuroendocrine breast carcinoma

Introduction

Primary Neuroendocrine Breast Carcinomas (NEBC) are very rare malignant tumors.[1,2] They were first described in 1977 by Cubilla and Woodruff and since then only a limited number of studies have been reported in literature.[3] Primary NEBC representing about 0,1% of the total breast malignancies and they are very aggressive with tending to metastatize [4,5]. According to the WHO Classification, primary NEBC is defined as a group of breast cancer morphologically similar to neuroendocrine tumors from gastrointestinal tracts or lungs.[6] It was defined as an epithelial neoplasm with predominant neuroendocrine differentiation cells (50% or more of NE markers positivity).[7] The histogenesis of NEBC is unclear but they are thought to arise from endocrine differentiation of a breast carcinoma rather than from preexisting endocrine cells in the breast.[8,9,10] Much of the current limited knowledge of this disease is based on these small retrospective series and thus is subject to selection bias.[11] Therefore, very little is known about the disease incidence, age and sex predilection, race/ethnicity distribution, clinic and pathologic characteristics and survival. The limited number of cases and a few studies currently available in the literature make difficult to establish a standard approach to treating this tumor, since only a

Pervenuto in Redazione Ottobre 2016. Accettato per la pubblicazione Novembre 2016.
Correspondence to: Prof. Calogero Cipolla, MD, Division of General and Oncological Surgery, O.U. Policlinico Paolo Giaccone, Via del Vespro 129, 90127 Palermo, Italy. (e-mail:calogero.cipolla@unipa.it)

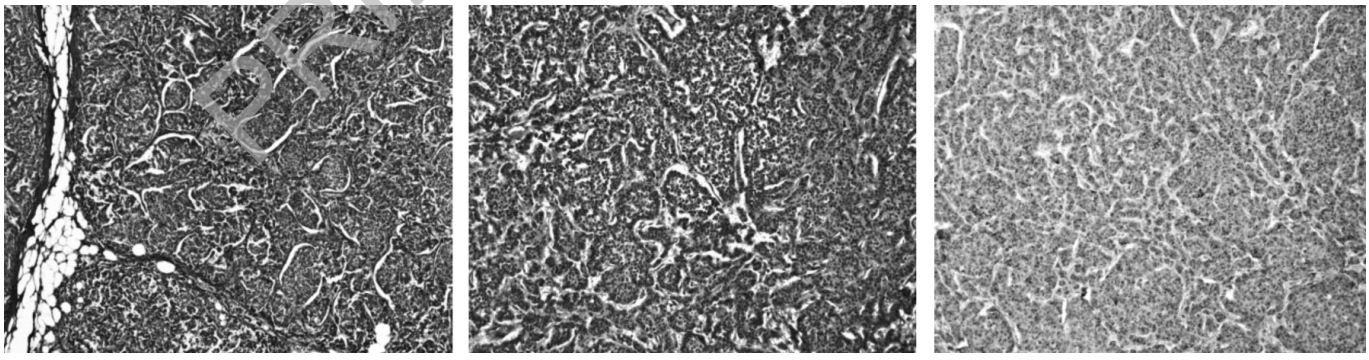
few case reports have indicated therapeutic options. The aim of this study was to apply pathological treatment modalities in clinical practice and to select the most appropriate treatment.

Material and Methods

Between 2007 and 2014, five women with primary NEBC were diagnosed and treated at the Policlinico Universirario "Paolo Giaccone" of Palermo, Department of Surgical Oncology. Four of these tumor were in the left breast, the other one in the right. The median age was 59.4 years (range 50-75). Patient characteristics are shown in Table I. Breast mass was evaluated by mammography and breast echotomography. All patients were submitted to core biopsy. Final diagnosis was made by pathological examination of surgical specimens obtained from the five patients. The specimens were fixed in formalin and routinely processed. The materials were stained with hematoxylin and eosin and later were examined using chromogranin, synaptophysin or neuron-specific enolase (NSE) antibodies (Fig. 1). A patient underwent mastectomy and four underwent quadrantectomy with biopsy of sentinel lymph node. The identification of sentinel lymph node was preoperative and intraoperative. In fact all patients, the day before surgery, underwent lymphoscintigraphy by means of a subareolar injection of tracer (Nanocoll). During surgery a gamma probe (Neoprobe 2000) was used in order to identify an remove the sentinel lymph node. In two case the sentinel lymph node was negative and in three cases axillary lymphadenectomy was performed. On the excised sentinel lymph node was first performed an intraoperative examination, then the definitive one. Moreover was performed an immunohistochemical analysis to define an eventually positivity to of steroid receptors, as well as, the expression of c-erbB2 and finally the grade of mitotic activity using the Ki-67 proliferative index. Following surgical treatment adjuvant chemotherapy and radiotherapy were administered to these patients. The Cisplatin and Etoposide combination was administered to all 4 patients with Ki 67 index > 40%. All patients were candidates for adjuvant radiotherapy with 6 MV photons, with a dose of 50 Gy (2Gy/fraction) to whole breast with tangential fields, and a subsequent additional dose of 10 Gy (2Gy/fraction) to the tumor bed. Each patient underwent a virtual CT-simulation, in supine position, using dedicated devices. The patient's arms were raised above the head using an arm support in carbon fiber. The three-dimensional treatment plan was set with the Pinnacle® TPS system, the target volumes were delineated according to the criteria of the Radiation Therapy Oncology Group (RTOG) contouring atlas. All patients with estrogen and progesterone receptors positivity received hormonal therapy (Tamoxifen). All patients received psychological support.

TABLE I - *Patients characteristics*

Patients	Age	Location	TNM	Surgical Treatment	Outcome
1	50	LEFT	T2N0M0	Quadrantectomy with biopsy of sentinel lymph node (-)	Alive, remission
2	65	LEFT	T2N1M0	Quadrantectomy and axillary lymphadenectomy	Alive, remission
3	55	LEFT	T2N1M0	Quadrantectomy and axillary lymphadenectomy	Alive, remission
4	75	LEFT	T2N1M0	Mastectomy and axillary lymphadenectomy	Dead
5	52	RIGHT	T2N0M0	Quadrantectomy with biopsy of sentinel lymph node (-)	Alive, remission



A B C

Fig. 1: Tumor staining.
A) NE50: Hematoxylin-Eosin, 50x; B) NE100: Hematoxylin-Eosin, 100x; C) NECromo: Chromogranin positivity, 100x.

TABLE II - *Pathological and immunohistochemical characteristics of the tumors.*

Patients	T	N	ER(%)	PR(%)	GRADE	C-erbB2	Chrom.	Synop.	NSE	Ki-67(%)
1	2.5	-	50	60	1	+	+	-	+	55
2	2.5	+	70	70	2	+	+	+	-	40
3	3	+	90	80	2	+	-	+	+	60
4	4.5	+	80	70	3	+	+	+	+	<10
5	2.3	+	100	0	3	+	-	+	+	80

Results

Tumor size range was from 2.3 to 4.5 cm in diameter. Surgery was well tolerated and in all of them was performed sentinel lymph node technique in order to find axillary metastatic disease. Lymph node metastasis was detected in three patients and in two case lymph node sentinel was found negative. Estrogen and Progesterone receptors expression was found in all patients. Chromogranin and Synaptophysin expression was found highly positive in all of them and the patients expressed c-erbB2 too. The pathological characteristics of the patient are shown in Table II. In the post-operative time none of them developed lymphedema of the arm or any sensibility disorders that are the most frequent collateral effect of this kind of surgery treatment. The patients were underwent four cycles of chemotherapy without collateral effects. Radiation therapy was feasible in all patients, no interruption of treatment was recorded in our experience. Heart and lung toxicity scoring was based on the common terminology criteria of adverse events (CTCAE). Scoring of breast/chest wall skin and subcutaneous toxicity used the Radiation Therapy Oncology Group (RTOG) acute (up to 1month post radiotherapy) and late (after 1month) morbidity scoring schemas. In our experience all five patients were treated with conventional treatment 3D CRT. At every week they were examined for acute toxicity at skin or others toxicity. Physical examination included also the evaluation of blood tests. The treatment was tolerated very well from all patients, with no acute toxicity. Then in all cases was administered Tamoxifen. Four patients are still alive and healthy, they are on a one year follow-up until they will reach the 5th year after surgery and then every 2 years. One patient dead.

Discussion

Neuroendocrine breast carcinomas (NEBC) include an heterogeneous group of tumors, showing morphological features similar to neuroendocrine tumors of the gut and lung, expressing one or more neuroendocrine markers in at least 50% of tumor cells [6,11]. NEBC are rare lesions, representing about 0,1% of all breast cancers (BC) and according to World Health Organization (WHO) data mostly affect elderly patients [1,2,12]. NEBC is characterized by less aggressiveness than the invasive ductal variant of BC, except for its small-cell variant. Epidemiologically, the incidence of NEBC appears to be controversial [3,7,11]. NEBC almost exclusively affects female patients aged between the sixth and seventh decade[13]; few cases are therefore diagnosed in the premenopausal period[14]. Currently approximately 200 cases have been described in the literature, in the form of small series or as individual case reports, one of them in the bilateral type [15-19]. A few cases in males have also been reported. Data related to the incidence of NEBC showed different percentages: from rare observations (0.09%) in the review by Fisher et al. [17] 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. [20] reporting 0.51% of 1,368 patients [20]. 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. On the basis of argentic impregnation, Feyrter and Hartmann suggested the nature of endocrine "mucoid" carcinoma of the breast[21]. 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 [3,22]. Since 2003, WHO defines NEBC as a separate entity, consisting of a varied group of breast primitive tumors of epithelial origin and morphology. In 2012, the last edition of World Health Organization (WHO) classification of breast and gynecologic tumors, described 4 main histologic types: solid (usually of low to intermediate grade), small/coat cell and large cell, that are both poorly differentiated variants and lately added atypical carcinoid tumor [6,2-27]. NEBC are considered to derive from divergent differentiation (exocrine and endocrine) of a neoplastic epithelial progenitor cell during carcinogenesis, as opposed to a preexisting neuroendocrine stem cell theory [8]. The diagnosis of NEBC needs immunohistochemistry positivity in at least 50% of the following markers in the tumor population [5,11] (Table III). According to some authors, pre-surgery diagnosis of NEBC by fine-needle aspiration cytology (FNAC) is possible, though not without difficulty [11,28].

TABLE III - *Tumor markers*

Chromogranin (Cg)	Cgs are the most represented proteins in the granules of neurosecretion, where they can reach 80% of the total proteins. Their expression in neoplastic tissue, however, is related to the grading of the tumor, with less expression in poorly differentiated carcinomas. CgA is the most sensitive neuroendocrine marker and confers high diagnostic reliability. 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;
Neuron-specific enolase (NSE)	This is an isoform of enolase, selectively expressed in neurons and endocrine cells. It is occasionally immunohistochemistry positive in NEBC;
CD56	This is a typical adhesion protein of neuronal cells; it is considered to be statistically less sensitive and less specific.

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. More frequently, authors report histological identification of NEBC by aspiration core biopsy [29-32]. 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, parathyroid hormone, prolactin, norepinephrine and calcitonin are described. 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 [33-35]. At diagnosis, most patients are in their 60s or 70s, and there are no remarkable differences in the clinical presentation compared with other breast carcinomas [22,36]. Tumor cells also show positivity for estrogen and progesterone receptors in well-differentiated tumors and in more than 50% of poorly differentiated small-cell carcinomas. However, the differential diagnosis of breast metastasis from neuroendocrine carcinoma of extra-mammary origin remains extremely challenging. Indeed, the rarity of these tumors does not allow large studies to be performed, and often such histologic entities are not included in large clinical trials of breast cancer treatment. The gold-standard treatment is substantially similar to that for ductal-type carcinoma. Moreover, no specific treatment has been standardized in the adjuvant or metastatic settings for NEBC, although theoretically hormonal therapy should be included in the strategy according to the cellular receptor pattern [22,37]. In terms of prognostic and predictive factors, HER-2 is almost always absent in NEBCs, while the vast majority express estrogen and/or progesterone receptors. The prognostic relevance of neuroendocrine differentiation is controversial, though most studies report a relatively poor prognosis based on the extent of the neuroendocrine component and the degree of its differentiation. The receptor status is most often of the Luminal A type: ER +, PR + and HER2 -, as described by Papotti, especially in non-small-cell subtypes [7,8,38]. Neuroendocrine carcinomas do not present any particular imaging finding and, in many cases, the findings are comparable to the ones of other types of breast tumors. On mammography, as described by Ogawa, such tumors may present as well circumscribed lesions, with no associated microcalcifications, mimicking benign lesions [4,38]. On ultrasonography, such tumors may present as either morphologically irregular solid lesions or lesions with a cystic component, with defined margins and increased vascularization. Also, in the present case, ultrasonography revealed the presence of a hypoechogenic mass with irregular morphology and defined contours, with no cystic component [39,40]. MRI demonstrated, like in other cases described in the literature, the presence of an irregular lesion with early, intense, ring-enhancement, with morphological and kinetic characteristics of contrast uptake consistent with malignancy. Thus, despite the rarity of neuroendocrine carcinomas, with nonspecific imaging findings, such tumors should be included in the differential diagnosis of a nodular lesion with no associated microcalcifications on mammography and sonographically corresponding to a hypoechogenic mass with microlobulated or irregular contours [41,42]. In our experience the subareolar injection of tracer to guide the accuracy of sentinel lymph node biopsy and the intraoperative frozen section examination of the node play an important role in the surgical management of the neuroendocrine breast carcinoma[43,44]. The extension of surgery could have an impact on the well-being of physicians apart from the stress induced by surgery-related complications, this effect can be added to the impact in the patient's quality of life and clinical management[45].

Conclusion

Neuroendocrine tumors of the breast are rare. Due to the lack of distinguishing features on presentation and imaging they can be misdiagnosed. The diagnosis of NEBC is exclusively immunohistological expressing neuroendocrine markers in ≥ 50% of the cancer cells.
In accord with other Authors, this trial shows that the gold-standard treatment is represented by surgical strategies, including breast-conserving surgery, as for usual-type breast cancers, associated to multidisciplinary approach with adjuvant chemotherapy and radiotherapy. However, because of the paucity of available literature on primary neuroendocrine carcinoma of the breast, their long-term prognosis and biologic behavior are not well known and the best treatment remains to be defined.

Riassunto

Il carcinoma neuroendocrino della mammella è un tumore estremamente raro. I casi riportati in letteratura sono molto pochi per cui la pianificazione del trattamento è ancora in discussione. Gli Autori riportano la loro esperienza su 5 casi osservati tra gennaio 2007 e dicembre 2014, insieme ad una revisione della letteratura. Quattro pazienti sono state sottoposte a quadrantectomia, in due delle quali è stata eseguita anche la linfadenectomia ascellare; in un solo caso è stata eseguita una mastectomia totale con linfadenectomia ascellare. In tutti i casi è stata utilizzata la colorazione con ematossilina-eosina ed è stata eseguita la valutazione immunoistochimica della enolasi neuronospecifica (NSE), cromogranina, sinaptofisina, recettori per estrogeni e per progesterone, c-erb e Ki-67. In tutti i casi è stata evidenziata una positività per enolasi neuronospecifica (NSE), cromogranina, sinaptofisina, recettori per estrogeni e per progesterone. In 4 pazienti il valore del Ki-67 era >40%. Una chemioterapia adiuvante è stata somministrata nei casi con Ki-67 >10%; tutte le pazienti sono state sottoposte a radioterapia sulla mammella operata ed hanno effettuato ormonoterapia. Nonostante il tumore neuroendocrino della mammella sia considerato una entità distinta, il trattamento più adeguato sembra essere correlato alle dimensioni del tumore, allo status linfonodali ed al Ki-67, come per gli altri istotipi di carcinoma della mammella.

References

1. López-Bonet E, Alonso-Ruano M, Barraza G, Vazquez-Martin A, Bernadó L, Menendez JA: *Solid neuroendocrine breast carcinomas: Incidence, clinico-pathological features and immunohistochemical profiling.* Oncol Rep, 2008; 20(6): 1369-374.

2. Maluf HM, Koerner FC: *Carcinomas of the breast with endocrine differentiation: A review.* Virchows Arch, 1994; 425(5):449-57.

3. Cubilla AL, Woodruff JM: *Primary carcinoid tumor of the breast. A report of 8 patients*. Am J Surg Pathol, 1977; 1:283-92.

4. Ogawa H, Nishio A, Satake H: *Neuroendocrine tumors in the breast*. Radiat Med, 2008; 26:28-32.

5. Wei X, Chen C, Xi D, Bai J, Huang W, Rong L, Wu M, Zhang G: *A case of primary neuroendocrine breast carcinoma that responded to neo-adjuvant chemotherapy*. Front Med, 2015, 9 (1): 112-16.

6. Valentim MH, Monteiro V, Marques JC: *Primary neuroendocrine breast carcinoma: A case report and literature review*. Radiol Bras 2014; 47(2):12-27.

7. Ellis IO, Schnitt SJ, Sastre-Garau X, et al.: *Tumours of the breast,neuroendocrine tumours.* In: Tavassoli FA, Devilee P, editors. *World Health Organization classification of tumours: pathology and genetics of tumours of the breast and female genital organs*. Lyon (France): International Agency for Research on Cancer (IARC); 2003; 32-4.

8. Adams RW, Dyson P, Barthelmes L: *Neuroendocrine breast tumours: Breast cancer or neuroendocrine cancer presenting in the breast?*. The Breast, 2014; 23:120-27.

9. Stita W, Trabelsi A, Gharbi O, Mokni M, Korbi S: *Primary solid neuroendocrine carcinoma of the breast*. Can J Surg, 2009; 289-90.

10. Ajisaka H, Maeda K, Miwa A, Yamamoto K: *Breast cancer with endocrine differentiation: Report of two cases showing different histologic patterns.* Surg Today, 2003; 33 (12):909-12.

11. Rovera F, Gavazza M, La Rosa S, Fachinetti A, Chiappa C, Marelli M, Sessa F, Giardina G, Gueli R, Dionigi G, Nausei S, Boni L, Dionigi R: *Neuroendocrine breast cancer: retrospective analysis of 96 patients and review of literature.* Int J Surg, 2013; 11: S79-S83.

12. Upalakalin JN, Collins LC, Tawa N, Parangi S: *Carcinoid tumors in the breast.* Am J Surg, 2006; 191:799-805.

13. Sapino A, Righi L, Cassoni P, Papotti M, Pietribiasi F, Bussolati G: *Expression of the neuroendocrine phenotype in carcinomas of the breast.* Semin Diagn Pathol, 2000; 17 (2):127-37.

14. Fujimoto Y, Yagyu R, Murase K, Kawajiri H, Ohtani H, Arimoto Y, Yamamura T, Inoue T, Moritani S: *A case of solid neuroendocrine carcinoma of the breast in a 40-year-old woman.* Breast Cancer, 2007; 14 (2):250-53.

15. Azzopardi JG, Muretto P, Goddeeris P, Eusebi V, Lauweryns JM: *'Carcinoid' tumours of the breast: the morphological spectrum of argyrophil carcinomas.* Histopathology 1982; 6 (5):549-69.

16. Papotti M, Macrì L, Finzi G, Capella C, Eusebi V, Bussolati G: *Neuroendocrine differentiation in carcinomas of the breast: A study of 51 cases.* Semin Diagn Pathol 1989; 6(2):174-88.

17. Fisher ER, Palekar AS: *Solid and mucinous varieties of so-called mammary carcinoid tumors.* Am J Clin Pathol, 1979; 72 (6): 909-16.

18. Saldamarco R, Pulcini A, Fabrizio G, Fazzi K, Feroci D, Gabatel R, Guerriero G, Mercurio C, Zimatore D, Giacomelli L: *Breast carcinoma with neuroendocrine differentiation. Clinical case and review of the literature.* Ann Ital Chir, 2002; 73 (4):377-79.

19. Wee A, Nilsson B, Chong SM, Raju GC: *Bilateral carcinoid tumor of the breast. Report of a case with diagnosis by fine needle aspiration cytology.* Acta Cytol 1992; 36 (1):55-9.

20. López-Bonet E, Alonso-Ruano M, Barraza G, Vazquez-Martin A, Bernadó L, Menendez JA: *Solid neuroendocrine breast carcinomas: Incidence, clinico-pathological features and immunohistochemical profiling.* Oncol Rep 2008; 20 (6): 1369-374.

21. Feyrter F, Hartmann G: *On the carcinoid growth from of the carcinoma mammae, especially the carcinoma solidum (gelatinosum) mammae.* Frankf Z Pathol, 1963; 73:24-39.

22. M Pagano, SNM Asensio, F Zanelli, F Lococo, A Cavazza, S Damiani, C Rapicetta, R Gnoni, C Boni: *Is There a role for hormonal therapy in neuroendocrine carcinoma of the breast? A Paradigmatic Case Report*. Clinical Breast Cancer, 2014;14 (5): e99-e101.

23. Menéndez P, García E, Rabadán L, Pardo R, Padilla D, Villarejo P: *Primary neuroendocrine breast carcinoma.* Clin Breast Cancer Epub 2012; 12:300-03.

24. Kim JW, Woo OH, Cho KR, Seo BK, Yong HS, Kim A, Kang EY: *Primary large cell neuroendocrine carcinoma of the breast: Radiologic and pathologic findings.* J Korean Med Sci, 2008; 23: 1118-120.

25. Manes K, Delis S, Papaspyrou N, Ghiconti I, Dervenis C: *Neuroendocrine breast carcinoma metastatic to the liver: Report of a case and review of the literature*. Int J Surg Case Rep, 2014; 5: 540-43.

26. Jiang J, Wang G, Lv L, Liu C, Liang X, Zhao H: *Primary small-cell neuroendocrine carcinoma of the male breast: a rare case report with review of the literature.* Onco Targets Ther, 2014; 7: 663-66.

27. Savelli G, Zaniboni A, Bertagna F, Bosio G, Nisa L, Rodella C, Biasiotto G, Bettinsoli G, Migliorati E, Peli A, Falchi R, Giuffrida F, Giubboni R: *Peptide Receptor Radionuclide Therapy (PRRT) in a patient affected by metastatic breast cancer with neuroendocrine differentiation*. Breast Care, 2012; 7:408-10.

28. Kawanishi N, Norimatsu Y, Funakoshi M, Kamei T, Sonobe H, Kawano R, Kobayashi TK: *Fine needle aspiration cytology of solid neuroendocrine carcinoma of the breast: A case report.* Diagn Cytopathol, 2011; 39 (7):527-30.

29. Yildirim Y, Elagoz S, Koyuncu A, Aydin C, Karadayi K: *Management of neuroendocrine carcinomas of the breast: A rare entity*. Oncol Lett, 2011; 2 (5):887-90.

30. Angarita FA, Rodríguez JL, Meek E, Sánchez JO, Tawil M, Torregrosa L: *Locally-advanced primary neuroendocrine carcinoma of the breast: Case report and review of the literature.* World J Surg Oncol, 2013; 11:128.

31. Watrowski R, Jager C, Mattern D, Horst C: *Neuroendocrine Carcinoma of the Breast. Diagnostic and clinical implications*. Anticancer Res, 2012; 32:5079-82.

32. Cipolla C, Fricano S, Vieni S, Amato C, Napoli L, Graceffa G, Latteri S, Latteri MA: *Validity of needle core biopsy in the histological characterisation of mammary lesions.* Breast, 2006; 15 (1): 76-80.

33. Woodard BH, Eisenbarth G, Wallace NR, Mossler JA, McCarty KS Jr.: *Adrenocorticotropin production by a mammary carcinoma.* Cancer, 1981; 47(7):1823-827.

34. Coombes RC, Easty GC, Detre SI, Hillyard CJ, Stevens U, Girgis SI, Galante LS, Heywood L, Macintyre I, Neville AM: *Secretion of immunoreactive calcitonin by human breast carcinomas.* Br Med J, 1975; 4:197-99.

35. Kaneko H, Hojo H, Ishikawa S, Yamanouchi H, Sumida T, Saito R: *Norepinephrine-producing tumors of bilateral breasts: A case report.* Cancer, 1978; 41(5):2002-07.

36. Zhang Y, Chen Z, Bao Y, Du Z, Li Q, Zhao Y, Tang F: *Invasive neuroendocrine carcinoma of the breast: a prognostic research of 107 Chinese patients.* Neoplasma, 2013; 60(2):215-22.

37. Suhani, Ali S, Desai G, Thomas S, Aggarwal L, Meena K, Kumar J, Jain M, Tudu SK: *Primary neuroendocrine carcinoma breast: Our experience.* Breast Dis, 2014; 34(3):95-9.

38. Kinoshita S, Hirano A, Komine K, Kobayashi S, Kyoda S, Takeyama H, Uchida K, Morikawa T, Nagase J, Sakamoto G: *Primary small-cell neuroendocrine carcinoma of the breast: Report of a case.* Surg Today, 2008; 38(8):734-38.

39. Wu J, Yang QX, Wu YP, Wang DL, Liu XW, Cui CY, Wang L, Chen Y, Xie CM, Zhang R: *Solid neuroendocrine breast carcinoma: mammographic and sonographic features in thirteen cases.* Chin J Cancer, 2012; 31 (11):549-56.

40. Chang ED, Kim MK, Kim JS, Whang IY: *Primary neuroendocrine tumor of the breast: imaging features.* Korean J Radiol, 2013; 14(3):395-99.

41. Park YM, Wu Y, Wei W, Yang WT: *Primary neuroendocrine carcinoma of the breast: Clinical, imaging, and histologic features.* AJR 2014; 203(2):221-30.

42. Yoon YS, Kim SY, Lee JH, Kim SY, Han SW: *Primary neuroendocrine carcinoma of the breast: Radiologic and pathologic correlation.* Clin Imaging, 2014; 38(5):734-38.

43. Cipolla C, Vieni S, Fricano S, Cabibi D, Graceffa G, Costa R, Latteri S, Latteri MA: *The accuracy of sentinel lymph node biopsy in the treatment of multicentric invasive breast cancer using a subareolar injection of tracer.* World J Surg, 2008; 32(11):2483-487.

44. Cipolla C, Cabibi D, Fricano S, Vieni S, Gentile I, Latteri MA: *The value of intraoperative frozen section examination of sentinel lymph nodes in surgical management of breast carcinoma.* Langenbecks Arch Sur, 2010; 395(6):685-91.

45. Russo A, De Luca R, Cicero G, Civilleri A, Bronte G, Dispenza J, Vieni S, Guarneri R, Cascio VL, Guadagna FP, Foddai E, Pace F: *Well-being among Italian medical oncologists: an exploratory study*. Oncology, 2014; 86(2):72-8.