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PRIMARY NEUROENDOCRINE CARCINOMA OF THE BREAST: A RARE ENTITY.

Oncology

KEYWORDS: Referrals, demand for dermatological care, Dermatologist's opinion

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ABSTRACT

Introduction

A neuroendocrine tumour is well described in the literature, but neuroendocrine carcinoma (NEC) of the breast is a very rare entity. NEC breast is not much reported in the literature so as to define the standard diagnostic, therapeutic and prognostic guidelines. It has almost similar clinical behavior; hence its diagnosis is based on histology and immunohistochemical markers.

Objective

Our aim is to determine the clinico-pathological features, treatment and prognostic features of primary neuroendocrine breast carcinoma.

Material and Methods

We searched the patient's records that were diagnosed with primary neuroendocrine carcinoma of the breast between 2008 and 2014 at a Regional Cancer Center in South India. We noted the demographic parameters, clinical features, diagnosis, treatment and follow-up of all the patients and we are presenting a case series study.

Results

Nineteen cases with diagnosis of primary NEC breast were admitted during this period. All the patients were females with median age of 57 (38-80) years. Ten patients were diagnosed preoperatively on core needle biopsy while remaining cases were diagnosed post-operatively on histopathology and immunohistochemichal markers. Fourteen patients presented with palpable lump in the breast with average size of 4.91cm and 13 patients had palpable axillary lymphadenopathy. Three patients presented with metastases at the time of diagnosis. On histopathology, 10/16 patients had metastatic axillary lymph nodes and most of them with N2 status. 15/19 patients were ER positive, 16/19 were PR positive and only one patient was HER2-neu positive and two were equivocal. The common neuroendocrine markers synatophysin, NSE and chromogranine were positive in almost all patients. Median follow up was 24 months (11 to 71 months). After completion of treatment, one patients had local at 18 months and 5 patients had distant recurrence. Positive lymph node status & negative ER/PR status was associated with poor prognostic factors.

Conclusion

The primary neuroendocrine carcinoma of the breast in comparison with other invasive breast cancer is rare and different in terms of hormone receptor status, staging, lymph node stage and risk of recurrence. Our study suggests that neuroendocrine carcinoma of the breast is a separate histological group and is not a less aggressive type of tumour.

INTRODUCTION

Neuroendocrine (NE) carcinoma originates from NE cells that are present throughout the body, but primary NE carcinoma of the breast is rare, comprising <1% of all breast carcinoma.[1] Initially, breast cancer with carcinoid type characteristics was named as primary neuroendocrine carcinoma of the breast. [2,3] It has been reported in literature since the time it was recognized first by Feyrter in 1963. First case series of 12 patients was published in 1977, by Cubilla and Woodruff. [3] It was diagnosed based on the neuroendocrine differentiation with neuroendocrine marker positivity, and estimated to be found in approximately 2% to 5% of all invasive breast cancers.[1] In 2003, the World Health Organisation (WHO) defined primary NE carcinoma of breast based on the report by Sapino et al, as expression of one or more NE markers (Synaptophysin, Chromogranin A, NSE, CK-7) in more than 50% of tumor cells, with histological presence of breast in situ component, and other primary sites ruled out.[4,5] Later in 2012, WHO divided breast NE carcinoma into three sub-types: 1) Neuroendocrine tumor, well differentiated; 2) Neuroendocrine carcinoma poorly differentiated/ small cell carcinoma, and 3) Invasive breast carcinoma with NE differentiation. [4,6]

The presence of scattered cells with neuroendocrine features in breast cancer is also found in 10-15% of all invasive cancers, which should be distinguished from differentiated neuroendocrine carcinoma with expression of specific apocrine phenotype and immune markers.[7,8] There are nine case series reported in the literature using the standard WHO criteria till 2014, with the largest retrospective series with a follow up data in only 135 patients based on SEER database.[9-13] The clinical outcome of these studies was variable, which may be due to inconsistent diagnostic criteria and non-standardized treatment. We are presenting a case series of 19 cases of primary neuroendocrine carcinoma breast (NEBC), diagnosed by strictly following the current WHO criteria. We weighed the clinico-pathological features and the immune-histochemical profile of primary NEBC in order to disclose the histopathological patterns and/or prognostic factors divergent from those of the conventional breast cancers.

Material and method

We retrospectively searched the prospectively maintained records of all patients with carcinoma of the breast treated in the Regional Cancer Centre between July 2006 and June 2014 to identify patients with primary NEC of breast. Patients were considered to have NE carcinoma of breast as per 2003 WHO criteria, pathological examination of their tumours revealed neuroendocrine differentiation with the presence of >50% of invasive tumour cells with cytoplasmic immunoreaction for one or more neuroendocrine markers. Patients with mixed tumour, focal neuroendocrine differentiation and metastatic neuroendocrine carcinoma to breast were excluded. Patients with evidence of neuroendocrine disease elsewhere in body were considered to have metastatic disease in breast with other primary organ, and excluded from the analysis. Patients with incomplete records were not included in the final analysis.

We noted the demographics, clinical features with clinical staging, histopathological diagnosis, immune markers, treatment either surgical or adjuvant, and clinical outcome with follow up of all patients with NEC breast. All patients were thoroughly investigated

to rule out metastatic NEC breast with primary other organs as lung and GIT. Immunohistochemical markers included synapthopyisin, chromogranin, estrogen receptor (ER), progesterone receptor (PR), HER2 (erbB-2). ER and PR were considered positive if >20% of nuclear invasive carcinoma cell staining was observed.

Statistical analysis
Outcome was recorded in terms of overall survival (OS), measured from the date of diagnosis to the date of death or the date last known to be alive, and disease free survival (DFS), measured from the date of diagnosis to the date of recurrence or death.

RESULTS
Incidence
We observed, retrospectively, a total number of 7880 patients with breast cancer presenting at our institute over the period of 2006 to 2014. Among all, 44 patients had neuroendocrine tumors including all types of neuroendocrine carcinoma breast as primary or metastatic and those with focal neuroendocrine differentiation and mixed carcinoma. Twenty patients had mixed or focal neuroendocrine differentiation, two cases pancreatic neuroendocrine tumor metastatic to breast, and one bronchial carcinoid metastatic to breast. Nineteen patients were diagnosed as primary neuroendocrine carcinoma breast according to WHO criteria, histological neuroendocrine differentiation with immune-reactivity for one or more immune markers in more than 50% of the tumour cells. The incidence of primary NEBC at our centre was estimated to be 0.24%. [Figure 1] The mean age in our series was 57 years (range 38 to 80).

Clinical presentation
The most common clinical presentation was breast lump in 14 (74%), followed by nipple discharge in 3 (16%), mastalgia in one patient, and one patient with back pain who was diagnosed incidentally during search for the primary tumour for skeletal metastasis. Majority of the patients had lesion in the upper-outer (n=6), followed by lower-outer (n=4), and central quadrant (n=2). The mean duration of symptoms in this series was 3.24 months. Majority of the women were post-menopausal, accounting for 68% (13) of the total. [Table 1]
Diagnosis and Clinical staging

Eleven patients were diagnosed initially as infiltrative ductal carcinoma on fine needle aspiration cytology, underwent further treatment according to stage, and were later diagnosed as primary NEBC. Core needle biopsy had a prominent role in pre-operative diagnosis with 71% sensitivity, rest of the patients were diagnosed with immune markers after mastectomy. The average size of the palpable lump was 4.91cm (range of 1.5 to 8cm). In two-thirds of patients (n=13; 68%), palpable axillary lymph nodes were found at the time of primary presentation. According to AJCC TNM staging system, majority of the patients were diagnosed in stage II (n=7; 37%) and III (n=8; 42%).[Table 1] Three patients were diagnosed with metastatic disease (stage IV).

Treatment
Twelve patients underwent modified radical mastectomy as upfront surgery. Among locally advanced disease, four patients received neoadjuvant chemotherapy, three patients received epirubucin with cyclophosphamide, and one of them received cisplatin with etoposide. After adequate response, these patients underwent MRM, followed by completion of chemotherapy. All women also received adjuvant radiation therapy, and one received hormone therapy as per receptor status. Among three patients with metastatic disease, only one patient with liver metastasis received palliative chemotherapy (cisplatin and etoposide), which did not respond well, and after three cycle it was abandoned in favour of best supportive care. One patient with liver and skeletal metastases, who initially presented with skeletal metastasis, underwent palliative mastectomy and received bisphosphonate and hormone therapy. Patient with lung metastasis were sent to palliative care unit for best supportive care. [Figure 1; Table 3]

Histopathology
On gross examination, lesions were found as firm, grey masses with or without infiltrating margins, with an average size of 3.96cms. On microscopic examination, small, uniform cancer cells growing in nests and alveolar-like structures, surrounded by delicate fibrovascular stroma and collagen that invaded ducts and ductules. It was seen as cellular monotony, nuclear palisading, pseudorosette formation, loss of cell cohesion, eosinophilic cytoplasm, and nuclei with stippled salt & pepper chromatin. [Figure 2] Cancer cells were polygonal, round, and oval shape, and had finely granular nuclear chromatin with uniform and vesicular nuclei and relatively eosinophilic cytoplasm. Most common types, the solid papillary and mixed type were found in 12/19 cases, followed by mucinous, small cell and apocrine type in 2 patients each, and poorly differentiated carcinoma in one patient. None of the patients had large cell carcinoma.[Table 4] Metastatic axillary lymph nodes were found in 10 out of 16 patients (63%) with an average yield of lymph nodes 13.37 (range 7 to 22) nodes and a median number of 13 nodes. Four patients had perinodal spread. Grades of differentiation were noted based on modified Scarff-Bloom-Richardson grading system, and most patient had grade II tumors (n=10/19; 53%) and III (7/19; 36%). [Table 4]

Hormone receptors and immunohistochemistry
Estrogen and progesterone receptor were defined as positive with a score of 2/8 or above. ER positivity in 15/19 (79%), PR positivity in16/19 (84%), and HER2-neu equivocal (score 2) in 2/19(10.5%) patients, with none of them positive. Chromogranin A was found diffuse positive in 16/19 (84%) patients, and Synaptophysin in 14/19 (74%) patients. CK-7, and E-cadherin were positive in 3, and 1 patients, respectively.[Table 4; Figure 3] Majority of patients had a high Ki-67 index (10-20% in 9, and ≥20% in 9).[Table 4]

Adjuvant treatment
12 patients received adjuvant chemotherapy, including epirubicin and cyclophosphamide ± 5-fluorouracil (n=11), sequential FAC + docetaxel (n=2), and etposide plus cisplatin (n=4). Nine patients received external beam radiotherapy to the chest wall, only four patient received EBRT to axilla. Twelve patients had received hormone therapy for a variable period of time.

Clinical outcome
Median duration of follow up was 24 months (range 11-71). After completion of the treatment in 16 patients, six patients had recurrence. Majority of the patients had recurrence at distant sites including bone (n=3) at 15, 22 and 25 months; liver (n=1) at 27 months; lung (n=1) at 19 months; and multiple organs (n=1). Only one patient had local chest wall recurrence. Recurrence free survival at two year was more than 80%, but at 3 years it was only 60%. Nine patients died during the follow up period, of these, five died with disease recurrence. Cancer specific mortality was estimated as 31%.[Table 5]

Prognostic factors
In view of small number of patients, on univariate analysis, positive metastatic axillary lymph nodes and negative steroid receptor status were found to be associated with poor prognosis.[Table 6]

Discussion
Neuroendocrine tumours are highly malignant but uncommon and slow growing tumors. These arise from neuroendocrine cells, which can be present in any organ of the body. It mainly arises in the bronchopulmonary and gastrointestinal systems. It has been reported to arise in different organs including the uterine cervix, pancreas, larynx, trachea, small intestine, stomach, prostate, and breast.[14,15]

Primary NEBC is very rare, and reported in only a few series and case reports, with less than 1000 cases reported in whole literature. The incidence as per WHO criteria, is reported within a range of 0.3% to 0.5% [16]. In our series, the incidence rate is estimated as 0.24%,

which is lower than the reported rates, and may be due to the strict adherence with the diagnostic criteria in this series. With changes in the definition and higher case fatality rates, the prevalence of the NEC is showing decreasing trends. [1,17-19].

Scattered neuroendocrine component on microscopic examination and focal marker positivity was not remarkable in our series, seen in only 2.5%, which is much lesser than reported previously as 10% to 17 %. [20,21] The metastatic neuroendocrine tumor in breast also reported, at our institute we found three cases of metastatic neuroendocrine tumor in breast, two had pancreatic neuroendocrine primary and one had bronchial carcinoid. [22]

It was classified into three subtypes including solid, small cell, and large cell carcinoma.[23] According to this definition, the actual incidence rates reported range from 0.3 to 0.5%, and SEER database 2003-2009 recognized much less incidence rate at 0.1% of all invasive breast cancers. [1,16,17]

NEBC has been seen to form a larger proportion of invasive breast cancers in males (2.1%) as compared to that in females (0.8%), but in the present series, no male patient was seen.[24,25] Women with NEBC are older than those with breast cancer NOS, and up to two-third women reported have age at the diagnosis ≥50 years.[26] In our series, mean age was 57 years, with a range of 38 to 80 years, and proportion of the patients aged ≥50 years was 66.67%. The presenting symptoms, duration of symptoms, and size of the lesion are usually similar as in other invasive carcinoma breast.[27] In our series, the most common presenting complaint was lump in the breast. Tumour stage at the time of diagnosis was not significantly different, with the same results seen in our series also.

The confirmation of the diagnosis of the PNEC breast is based on these two criteria: (1) other primary sites must be ruled out and (2) the tumour must show histological evidence of a breast in situ component.[28] The presence of intra-ductal component is the robust evidence to justify breast as the primary site of tumour origin.
Due to lack of adequate literature, the characteristic imaging features have not been described well.[10] Primary NEBC presents on sonography as an irregular and ill-defined solid lesion, with or without cystic component, with increased peripheral vascularity. It is a hypoechoic mass without posterior enhancement.[29] These features seem to be similar to other invasive carcinomas of breast. Breast NEC has also been reported in lesions with non-spiculated margins on mammography and absent posterior shadowing on sonography which might mimic fibroadenomas, cysts, or intramammary lymph nodes, leading to under-diagnosis in 1% to 3% of these cases.[30] Although, NEC breast has higher proliferative index compared to other invasive carcinoma breast, but diagnostic accuracy of fluorodeoxyglucose (FDG) PET is not satisfactory. The overlapping of radiological findings with other invasive types results in an under-diagnosis. Although the radiologic findings on mammography, sonography, and MRI could help differentiate these tumours from other malignancies, but still histological features with immunohistochemical markers remain the benchmark to confirm these tumours.[31] We did not find any specific imaging feature in this series also.

Breast cancer with microscopic neurosecretory granules on electron microscopy were defined as 'argyrophilic breast carcinoma' by Azzopardi.[32] With further development, neuro-immune marker positivity of these granules brought this new diagnosis into practice.[33]

The absence of neuroendocrine cells in normal breast decline the hypothesis of malignant transformation of naturally present neuroendocrine cells in the breast.[26,34] Several theories of primary NEBC development, proposed over time, are as follows: A) The argyrophilic cells of neural crest origin transformed into cancer cells initially that migrated to the mammary ducts.[3] B) At the time of early differentiation, neoplastic stem cell can divert into both epithelial and endocrine stream in breast.[27]

In the absence of other primary site with an in-situ element in the tumour tissue helps to confirm the breast as the primary site of origin of the tumor.[35] The characteristic microscopic features that help in diagnosis are cellular monotony, nuclear palisading pseudorosette formation, loss of cell cohesion, and abundant nuclei with stippled chromatin "salt and pepper" appearance, which are similar as in neuroendocrine tumors of lung and gastrointestinal tract.[36] The peculiar morphologic pattern, even with negative immune markers status, also suggestive NEBC.[21,37] Primary NEBC is classified into different histological variants with variable results including solid cohesive, alveolar, small cell, solid papillary and cellular mucinous.[38]

WHO also suggests groups of NEC breast including solid carcinoid like tumors, large cell type, and small or oat cell type similar to large and small cell neuroendocrine tumours of lung.[23,39,40] The common histological components are ductal or NOS, but lobular or medullary carcinomas can also be present. In our series, only two types of component were found, ductal and NOS. Although, the presence of mucinous and apocrine component is reported as a favourable feature associated with higher steroid receptor positivity, but results are variable in different series. [41] The most important prognostic factor is nuclear grade, similar to other histological types of breast cancer. Majority of the patients with NEBC are grade II, and in our series half the patients had grade II, but grade III also found in 45% cases. Even with advanced diagnostic modalities, there are a few pitfalls in the diagnosis of primary NEBC: 1) DCIS, intra-ductal atypical hyperplasia can be misdiagnosed with invasive component of primary NEBC [42]; 2) non-specific glandular patterns within the tumor may mimic IDC-NOS [21,42]; (3) cases with less common histology such as lobular, medullary or mucinous carcinoma may not be predictable as having neuroendocrine differentiation.[42]

The morphological features on microscopy and immunohistochemical pattern are the benchmark of the diagnosis. Therefore, FNAC has low sensitivity for primary NEBC, similar results were observed in the present series also. The common differential diagnoses include Merkel cell carcinoma, lymphoma, carcinoid tumor, and melanoma.[43] The positivity of steroid receptors also favours breast as the primary site of origin, but their expression varies within a wide range of 30-90%.

Most of the reports had higher percentage of the steroid receptor positivity (>80%).[14,44] In our series, ER expression was seen in 79%, and PR in 84% patients. Similar to previous studies, we confirmed the diagnosis of primary NEBC by using pathological criteria along with steroid receptor and neuronal immune markers.[7,8,17]

The primary NEBC are mainly luminal type A, followed by triple negative and basal type. In our series, most of these patients were luminal type A, accounting for 72%. Although, these patients with positive hormone receptor expression are expected to have a good prognosis and low recurrence, but the neuroendocrine differentiation has greater impact on prognosis and explains the poor survival compared to IDC-NOS.[39,45-47]

The proliferative index is an important factor to decide adjuvant treatment and prognosis in breast cancer NOS, similarly poor survival in primary NEBC is also explained with higher Ki-67 index.[48] The cut-off value of ≥10% of Ki-67 is an established prognostic factor in neuroendocrine tumors.[49] In our series, 18 out of 19 women had Ki-67 >10%, supporting the prognostic importance.
The standard surgical treatment of the primary NEBC breast is similar to any other invasive breast cancer. In our series, 16 patients underwent modified radical mastectomy, no one had conservative surgery. Conservative surgery is not studied in literature, because identifying the precise tumour margin status is challenging in NEC breast.[50]

The preoperative and postoperative chemotherapy was given as per standard protocol at our institute. It is challenging to decide the standard chemotherapy regimen for NEC breast for oncologists in view of low incidence and lack of randomized trials. Earlier, we used standard FAC regime similar to IDC-NOS in these cases. Later, we also used cisplatin plus etoposide, which is the standard regimen for common organ neuroendocrine carcinoma as GIT and lung due to its similar clinical behaviour.

Various regimens have been used in different reports without any definite conclusion on superior efficacy of one over another. In our series various regimens has been given i.e. epirubicin with cyclophosphamide plus 5-fluorouracil, sequential FAC and docetaxel, and cisplatin plus etoposide. However, chemotherapy as adjuvant treatment does not have a proved significance regarding disease specific survival and difference in various regimens. The role of adjuvant radiotherapy is yet not clear, and it is rarely used in a few cases in published reports. In our series, only twelves patients received adjuvant radiotherapy. In our series, the hormone receptor positivity was much higher, and hormone therapy was received by 12 out of 16 patients in the adjuvant setting.

Wei et al observed in their series that 25% patients had metastatic disease at the time of presentation. In our series, at the time of diagnosis, 3 out of 19 (16%) were with systemic metastasis. The recurrence rate was 37%, with the average time to recurrence 21.3 months. Wei et al reported a 15% 5-year local recurrence, and 34% 5-year distant recurrence, similarly, in our series 3-year disease free survival was 62%.[18]

The poor survival results might be owing to a higher tendency to be resistant to chemotherapy like NEC of other sites, and other therapeutic modalities including endocrine therapy, and radiation therapy. This is not revealed properly due to the small number of cases reported, and limited follow up.[51] Conversely, the best choice of treatment of the primary NEC breast appears to be mastectomy with axillary dissection, followed by a chemotherapy combining platinum compounds and etoposide with or without anthracycline.

In view of the lack of adequate number of cases and randomized or non-randomized trials, the prognostic factors in primary neuroendocrine carcinoma breast is not clear. The NEC differentiation, itself has a variable impact in various reports, ranging from better prognosis [17,52,53], no significance [18,54] to poor. [20,55] The results of our series support the reports that proposed it as a poor prognostic factor. Metastatic axillary lymph node and hormone receptor negativity has poor prognosis as in other invasive breast cancers.[49,56]

The prognostic impression of other factors including lesion size, and treatment modalities, which are proven factors in other invasive breast cancers, was not concluded due to the small size of study patients. In our series, 60% patients among recurrent disease had grade III tumour. On univariate analysis, the grade of tumour was found statistically significant for the recurrence (p=0.02). The impact of age at the time of diagnosis (>60 years) is also contradictory to IDC-NOS, and is associated with poor prognosis, similar trends were found in our series. In our series, positive lymph node status and negative hormone status were independent prognostic factors for DSS. Tian Z et al revealed that the overall survival differs according to lymph node status, tumor size, and Ki-67 index, but distant recurrence-free survival depends only on the nodal status.[54]

Conclusion

Primary NEBC are highly malignant but uncommon and slow growing neoplasms, which are more common in elderly women. NE carcinomas are significantly more likely to be ER/PR positive and HER-2 negative. The specific treatment guidelines are not in practice due to its low incidence. No chemotherapy regimen is superior to another in view of lack of randomized or non-randomized trials. Only positive lymph node status & negative ER/PR status was shown to be associated with poor prognosis.

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Author's contribution

RA and SA contributed in acquisition of data, design of study, analysis and drafting of manuscript. RA, SA and KVV searched literature and drafted manuscript. All authors read final manuscript and have given agreement for the publication.

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Tables

Table 1 Demographic profile

Age	**Mean**	**57**
	Range	**38-80 years**
Clinical presentation	**Lump**	**14**
	Nipple discharge	**4**
	Mastalgia	**1**
Mean duration of symptom		**3.25 months**
Size of lump	**Mean**	**4.91cm**
	Range	**1.5-8cm**
Axillary lymph adenopathy		**13/19 (68%)**
Staging (n=19)	**I**	**1 (5%)**
	II	**7 (37%)**
	III	**8 (42%)**
	IV	**3 (16%)**

Table 2 Pre operative diagnosis

FNAC (n=15)	**Duct carcinoma**	**9 (60%)**
	Poorly differentiated carcinoma	**4 (27%)**
	Inconclusive	**2 (13%)**
Core needle biopsy (n=14)	**NEC**	**10 (71%)**
	Poorly differentiated	**4 (29%)**

Table 3: Treatment.

SURGERY	**MRM**	**16**
	Mastectomy(Palliative)	**1**
CHEMOTHERAPY	**NACT**	**4**
	ADJUVANT	**12**
	FAC	**11**
	FAC + DOCETAXEL	**2**
	ETOPOSIDE + CISPLATIN	**4**
RADIOTHERAPY		**9**
HORMONAL THERAPY		**12**

Table 4: Histopathology & immunohistochemistry

Microscopic pattern (n=19)	**Solid**	**12 (63%)**
	Mucinous	**2 (11%)**
	Apocrine	**2 (11%)**
	Small cell	**2 (11%)**
	Poorly differentiated	**1 (4%)**
Grade	**I**	**2 (11%)**
	II	**10 (53%)**
	III	**7 (36%)**
Axillary lymph node (n=16)	**N0**	**6(37%)**
	N+	**10 (63%)**

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	Extranodal spread	4/10 (40%)
LVI (n=16)	Present	7 (44%)
	Absent	9 (56%)
Receptor status (n=19)	ER+	15(79%)
	PR+	16(84%)
	HER2-neu(equivocal)	2 (11%)
IHC	Chromogranin A	16 (84%)
	Synaptophysin	14 (74%)
	CK 7	3 (16%)
	NSE	1 (5%)
Ki67index(n=19)	<10	1 (6%)
	10-20	9(47%)
	>20	9 (47%)

Table 5: Clinical outcome

Follow up	No of patients on follow up	19
Duration of follow up	Median	24 months
	Range	11-71 months
Death(n=19)	Total	9
	Dead of disease	5
	Dead without disease	4
Recurrence(n=16)	Total	6
	Local	1
	Distant	5
	Bone mets	3
	Liver mets	1
	Lung mets	1
	Bone + Lung mets	1

Table 6: Univariate analysis

	RECURRENCE (n=6)	NO RECURRENCE (n=10)	p
STAGE			
I	0	1	
II	2	4	
III	4	5	
AXILARY LN			0.032
N0	1	5	
N+	6	4	
GRADING			
I	0	1	
II	2	7	0.02
III	4	2	
ER/PR POSITIVE	3	9	0.04
ER/PR NEGATIVE	3	1	

Figures

Figure 1: study population schema

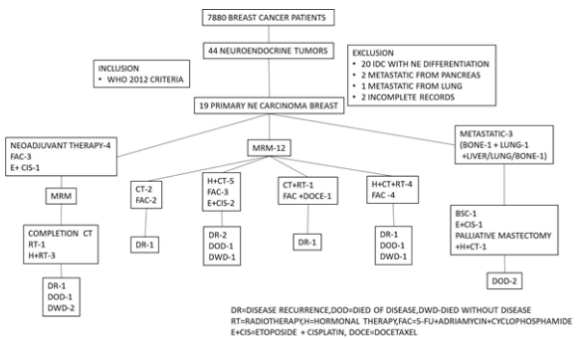
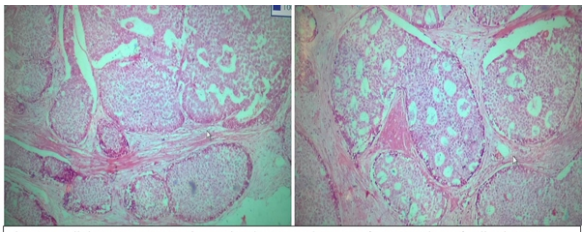
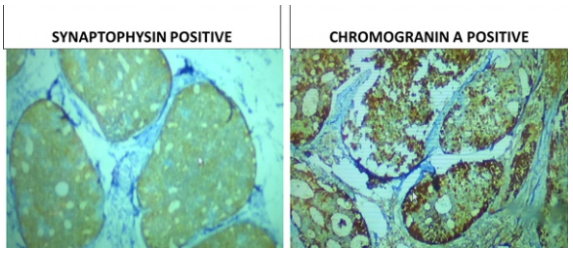


Figure 2: microscopic features of NEBC



Showing cellular monotony, nuclear palisading, pseudorosette formation,loss of cell cohesion and eosinophilic cytoplasm and nuclei with stippled salt & pepper chromatin.

Figure 3: Immmunohistochemistry of NEBC



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