Invasive neuroendocrine carcinoma of the breast: A prognostic research of 107 Chinese patients

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Neuroendocrine carcinoma (NEC) of the breast, a distinct type of mammary carcinoma whose terminology was not proposed until 2003, has not been well recognized or studied. The aim of our study is to evaluate the clinicopathological features and outcomes of this type of tumor. We conducted a comparative study on 107 NEC patients and 475 invasive ductal carcinoma, not otherwise specified(IDC, NOS) patients from the Department of Pathology, Huashan Hospital, Fudan University, to determine the demographic, pathological, and clinical features at presentation, along with patient outcomes and prognostic factors. With an older age at presentation, NECs are more likely to be estrogen receptor(ER)/ progesterone receptor (PR) positive and human epidermal growth factor receptor 2 (HER-2) negative, and have a higher propensity for local recurrence and poorer overall survival(OS). Higher T classification, M classification, TNM stage, the expression of Ki67, and the absence of PR expression are prognostically of poorer OS and distant recurrence-free survival(DRFS). Distant metastasis is also a dependent prognostic factor. NEC of the breast is a distinct type of neoplasm with higher malignancy. Novel therapies such as the endocrine therapy should be explored and studies with larger case number and longer follow-up will be needed.

Key words: neuroendocrine, breast cancer, prognosis

Primary invasive breast carcinoma with neuroendocrine (NE) differentiation is an uncommon tumor, which accounts for 2-5% in all breast malignancies. In 1963 Feyrter and Hartmann described a carcinoid growth pattern in some cases of invasive breast carcinoma [1]. Since then it had been sporadically reported [2,3,4,5]. Immunohistochemical staining for the neuroendocrine markers synaptophysin, chromogranin and neuron-specific enolase (NSE) subsequently became the standard method of confirming neuroendocrine differentiation. In 2003, WHO histologic classification of tumors of the breast and female genital organs defined it as mammary carcinoma with more than 50% of neoplastic cells expressing NE markers by immunohistochemistry[6].

Most of the studies on NEC of the breast were conducted prior to the 2003 WHO criteria [7, 8, 9, 28]. Before that time, there was no consensus on whether the diagnosis of NEC of the breast should be based on morphology alone or in conjunction with immunohistochemical studies or the amount of NE differentiation required for the diagnosis. Due to lack of a precise definition of mammary NEC, it was difficult to compare the clinicopathological features and outcome data between mammary NEC and invasive ductal carcinoma, not otherwise specified (IDC, NOS). Since 2003, when the WHO criteria demanded immunohistochemical confirmation of neuroendocrine differentiation in >50% of NEC tumor cells, limited studies have been conducted [6, 10, 11, 25, 27].

In this paper, we carried out a comparative study on 116 Chinese NEC patients who were treated from 2000 to 2011 at the Department of Pathology, Huashan Hospital, Fudan University (Shanghai, China). Most of the patients were initially diagnosed as IDC,NOS. Immunochemistry on NE markers was performed retrospectively to confirm NEC. Clinical treatment and follow-up information were available in 107 of the 116. We show that NEC is a malignant tumor with a higher tendency for local recurrence and a poorer overall survival than IDC, NOS. Therefore, further investigations on the clinicalpathological features, novel treatments, and prognosis-influencing factors are of high significance.
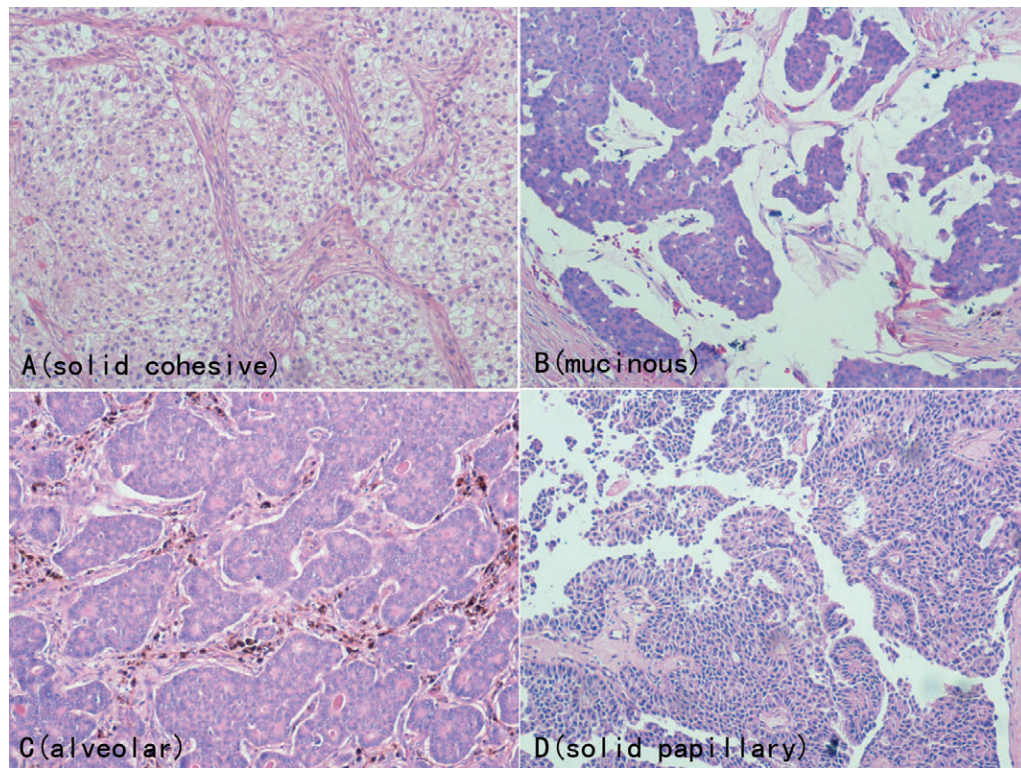
Figure 1. Photomicrographs of NEC subtypes of the breast, solid cohesive(A), mucinous(B), alveolar(C), and solid papillary(D).

Materials and methods

Study group. A total of 116 NEC patients were identified from 2000 to 2011 at the Department of Pathology, Huashan Hospital, Fudan University. 107 of them have complete clinicalpathological information and outcome data. All 107 cases were confirmed to be NEC by immunohistochemical staining for NE markers (ie, >50% of the invasive tumor cells expressing synaptophysin(Sy) and/or chromograninA(CgA) based on the 2003 WHO criteria). Photomicrographs of NEC of the breast and immunohistochemical results are shown in *Fig1* and *Fig2*. Demographics, clinicopathological factors, treatments and outcome data were retrospectively reviewed.

Cases that fulfill the current 2003 WHO diagnostic criteria were included in this group: ① with histologic features similar to NE tumors in the gastrointestinal tract and lung and ② with more than 50% of tumor cells expressing NE markers by immunohistochemistry. Cases are excluded if: ① <50% tumor cells expressed NE markers, ② metastatic NECs from other organs based on clinical medical records and pathological features(since we basically focused on primary neuroendocrine carcinoma of the breast) ③ tumor fulfilled the criteria of a small cell carcinoma(since the clinicopathologic features and poor clinical outcome of small cell carcinoma have been well documented [12, 13]).

All 107 cases were Chinese and female, and were treated at Huashan Hospital, Fudan University from 2000 to 2011. Four (3.7%) patients were first diagnosed with invasive breast carcinoma before 2003 WHO NEC diagnostic criteria, the remaining 103(96.3%) in or after 2003. Diagnoses of those 4 patients before 2003 were retrospectively rendered based on the pathological review of their materials and immunohistochemical staining on NE markers(ie, Sy and CgA).

Comparative group. A total of 602 patients with IDC,NOS were treated at Huashan Hospital, Fudan University between January 1999 and December 2003. 475 cases with complete follow-up information were used as a control cohort to compare the clinicopathological features and outcome with the NEC group. All cases were confirmed by thorough review of medical records, hematoxylin and eosin–stained histological and immunohistochemical slides. The remaining 127 patients were excluded because we couldn't obtain complete follow-up information from our medical records.

Histopathologic examination. The histopathology of each case was re-reviewed and the diagnoses were confirmed by positive immunohistochemical staining for Sy(27G12, DAKO, Shanghai) and/or CgA (LK2H101+PHE5,DAKO, Shanghai) in >50% of the invasive tumor cells. Immunohistochemical studies were manually performed on one representative block, using the avidin–biotin complex (ABC) horseradish-peroxidase method.
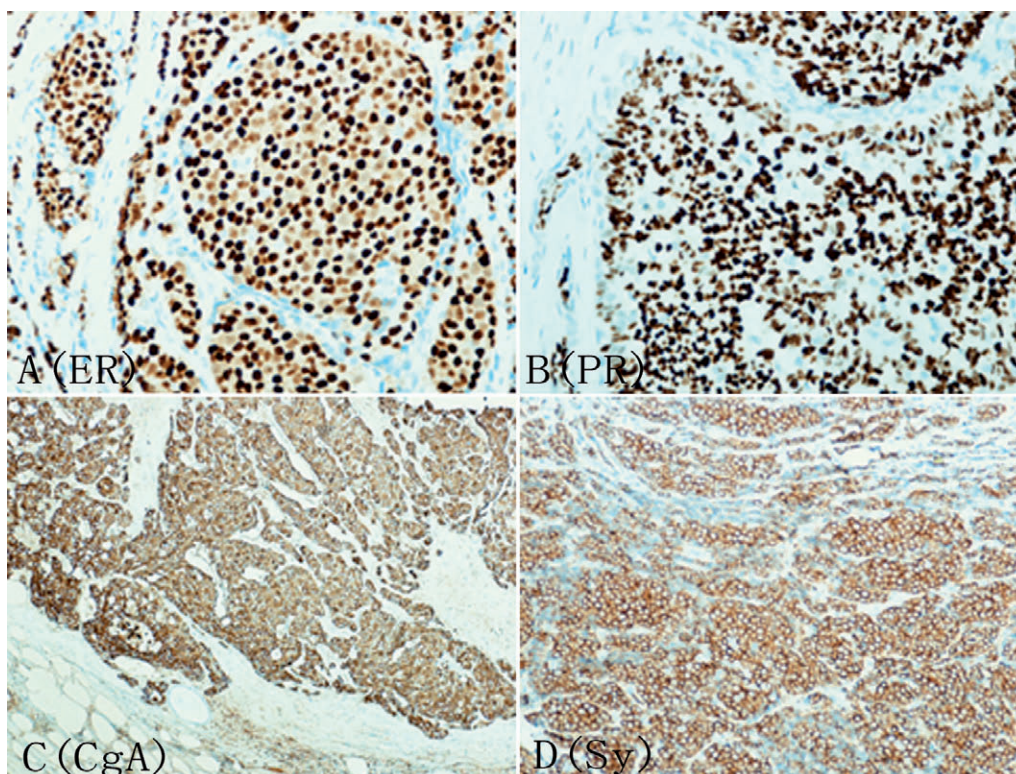
Figure 2. Immunohistochemistry of NEC of the breast showing positivity for estrogen receptor (A), progesterone receptor (B), chromogranin (C) and synaptophysin (D).

Primary antibodies against the following antigens were applied according to the manufacturer's guidelines (Dako): ER, PR, HER-2, Ki67, Sy, and CgA. ER/PR/HER-2 results were obtained from the original histo-pathology reports. Nuclear staining in 10% of tumor cells was the threshold for ER and PR positivity. HER-2 positivity was referred to as +++ (>30% tumour cells were strongly positive). Tumors was determined as having low (<14% Ki67 positive cells) and high (>14% Ki67 positive cells) proliferative activity [14]. The same methods and scoring system were used in NEC and IDC,NOS group. The antibodies used in this study were listed in *Table 1*.

Statistical analysis. Descriptive statistics were calculated for demographic and clinicopathological factors. Differences in these factors between NEC and IDC, NOS of the breast were compared using chi-square or Fisher exact test, where appropriate.

Survival data were analyzed based on 3 endpoints from the time of diagnosis. Overall survival was measured from the date of diagnosis to the time to death. Local recurrence-free survival (LRFS) was defined as the time to local disease recurrence or death as a result of NEC or IDC NOS. Likewise, distant recurrence-free survival (DRFS) referred to as the time to distant disease recurrence or death from NEC or IDC NOS. Survival curves were constructed using the Kaplan–Meier method, and differences between curves were analyzed using the Log-rank

Table1. The list of antibodies.

Antibody(clone)	Company	Antigen Retrieval	Dilution
Sy(27G12)	DAKO	Citrate	1:100
CgA(LK2H101+PHE5)	DAKO	Citrate	1:100
ER(1D5)	DAKO	Citrate	1:100
PR(1A6)	DAKO	Citrate	1:100
HER-2(e2-4001+3B5)	DAKO	Citrate	1:100
Ki67(SP6)	DAKO	Citrate	1:100

test. Multivariate analysis for survival time was performed using the Cox proportional hazards model. Qualitative variables were analyzed using the Pearson X^2 test or the Fisher's exact test, when appropriate. All calculations were performed with Stata software (Stata/SE 15.0 for Windows; StataCorp, College Station, Tex).Two-tailed P values.05 were considered statistically significant.

Results

Clinicopathological features and outcomes of IDC,NOS and NEC of the breast

Clinical presentation at diagnosis. The clinicopathological characteristics of the 107 patients with NEC of the breast and
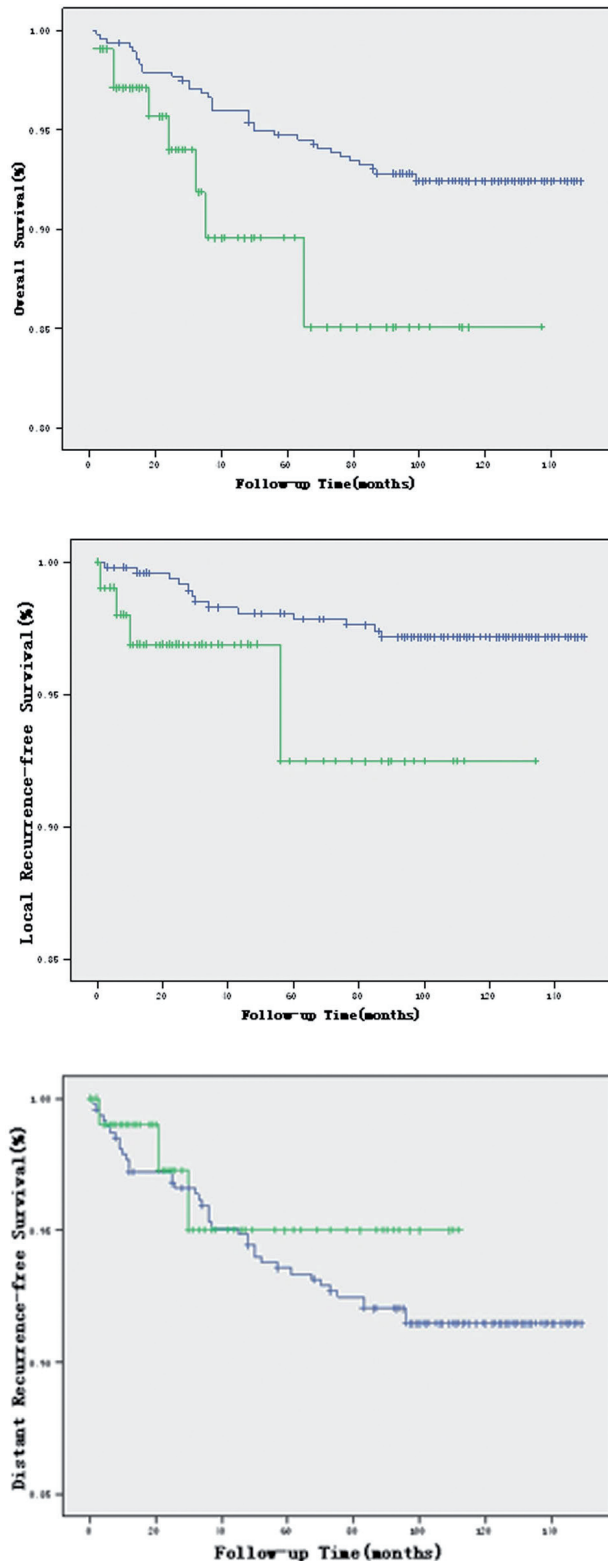
Figure 3. Overall survival, local recurrence-free survival and distant recurrence-free survival comparison between 107 patients with neuroendocrine carcinoma and 475 controls with invasive ductal carcinoma, not otherwise specified are shown.

the group of 475 patients with IDC,NOS from Huashan Hospital, Fudan University are summarized in *Table 2.*

Age at diagnosis. The mean age of patients at presentation in NEC group was 65 years (range, 25-95 years; median, 64years). Patients with NEC were significantly older (P<.0001) than the 475 patients with IDC, NOS (range, 28-95 years, median, 54 years).

Menstrual status. 78 of 107 (72.90%) patients with NEC of the breast were postmenopausal, 29(27.10%)were premenopausal, while in the IDC, NOS group, 227 (47.79%) were postmenopausal and 248 (52,21%) premenopausal. There were significantly more postmenopausal patients in the NEC group than in the IDC, NOS group (P<0.0001). This was consistent with the higher presenting age at diagnosis in NEC patients.

Stage at diagnosis

Tumor stage (Tumor size.) The diameter of tumors ranged from 0.8 to 5.0cm in the NEC group, and 0.6 to 8.0cm in the IDC, NOS group. Most tumors in patients with NEC were stage T2 (54, 50.47%), compared with a large number of tumors in IDC, NOS patients being stage T1 (281, 59.16%). Tumor stage in NEC patients were significantly higher than that in IDC, NOS patients (P=0.014).

Regional lymph node metastasis (N classification). Among the 107 NEC patients, 81 (75.70%) were stage N0, 18 (16.82%) were stage N1, 2 (1.87%) were stage N2, and 6 (5.61%) were stage N3. N classification of NEC tumors was significantly lower than that in IDC, NOS (P=0.026)

Distant metastasis (M classification.) There was no obvious difference between the two cohorts as to distant metastasis in tumors.

AJCC TNM stage. Based on the AJCC staging system (version6) of tumors [15], 39 (36.45%) NEC patients were stage I, 59 (55.14%) were stage II, 6 (5.61%) were stage III, and 3 (2.80%) were stage IV. There were no significant differences in TNM stage between the NEC and IDC, NOS groups.

Mitotic figure. In the NEC cohort, 77 (71.96%) patients had less than 10 mitosis per high power field, while in the IDC, NOS group, the number was 290 (61.05%). There were statistical differences in mitotic figure between the two groups (P=0.036)

Receptor status. Most NECs of the breast were ER/PR positive and HER-2 negative. 101 (94.39%) patients were ER positive and 91 (85.05%) were PR positive. ER/PR expression was significantly higher in NEC patients than that in IDC, NOS patients (P<0.0001). In NEC patients, 97.20% were HER-2 negative, and only 2.80% were HER-2 positive. HER-2 expression was significantly lower in NEC patients than that in IDC, NOS patients (P<0.0001).

Clinical outcomes. The median follow-up for patients with NEC of the breast was 27 months (range, 3 to 134 months), and that with IDC, NOS was 100 months (range, 92 to 149 months). Clinical outcomes for NEC and IDC,NOS can be seen in *Fig 2.*

Overall survival. Overall survival rate was lower in NEC patients (85.1%) than in IDC, NOS patients (92.4%). Log-rank

Table 2. Demographic and Clinical Features of the NEC Cohort (n=107) Compared With the Invasive Mammary Carcinoma (n=475) Cohort at Clinical Presentation

Features	NEC cohort N=107		IDC,NOS cohort N=475		P
	No. of patients	%	No. of patients	%	
Age					<.0001
≦60	46	42.99	332	69.89	
>60	61	57.01	143	30.11	
Menopausal status					<.0001
Premenopausal	29	27.10	248	52.21	
Postmenopausal	78	72.90	227	47.79	
Tumor stage					.014
T1 (≦2cm)	48	44.86	281	59.16	
T2 (2-5cm)	54	50.47	169	35.58	
T3 (≧5cm)	5	4.67	22	4.63	
T4 (skin or chest wall involvement)	0	0.00	3	0.62	
Regional lymph node metastasis					.026
N0	81	75.70	305	64.21	
N1	18	16.82	102	21.47	
N2	2	1.87	37	7.79	
N3	6	5.61	31	6.53	
Distant metastasis					NS
Negative	103	96.26	431	90.74	
Positive	4	3.74	43	9.26	
AJCC TNM stage					NS
I	39	36.45	173	36.42	
II	59	55.14	226	47.58	
III	6	5.61	44	9.26	
IV	3	2.80	32	6.74	
Mitotic figure					.036
Negative(<10/HPF)	77	71.96	290	61.05	
Positive(>10/HPF)	30	28.04	185	38.95	
ER					<.0001
Negative	6	5.61	168	35.37	
Positive	101	94.39	307	64.63	
PR					<.0001
Negative	16	14.95	215	45.26	
Positive	91	85.05	260	54.74	
HER2					<.0001
Negative	104	97.20	340	71.58	
Positive	3	2.80	135	28.42	

NEC indicates neuroendocrine carcinoma; NS, not significant; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

test demonstrated statistical significance between these two groups (P=0.030).

Local recurrence. 4 of 107 NEC patients and 14 of 475 IDC, NOS patients had local recurrence. Log-rank test revealed a significantly higher rate of local recurrence in NEC(7.5%) than in IDC, NOS(2.8%) (P=0.043).

Distant recurrence. The rate of distant recurrence in NEC patients was 5%, while that in IDC, NOS was 8.3%. Nevertheless the difference between the two groups in our hospital did not reach statistical significance (P=0.061). Distant recurrence occurs most commonly in bone and liver, as well as other less common sites, such as the lungs, pleura, contralateral breast, ribs, maxilla and mandible [16].

Prognostic factors of NEC. Analyses of prognostic factors are summarized in *Table3*. Kaplan-Meier showed that larger tumor size and TNM stage are inversely associated with OS and DRFS (P=0.003, <0.0001, and <0.0001, <0.0001 respectively). Lymph node metastasis was no longer significant in predicting OS and DRFS.

Distant metastasis was significantly associated with poor OS and DRFS (P<0.0001, <0.0001, respectively). In the NEC cohort, survival rate of patients with distant recurrence was 25%, which was much lower than that of 95% in patients without distant recurrence. Further test of Cox regression revealed that it was a dependent prognostic factor for poor OS (P<0.0001).

Table3. OS and DRFS of Patients With NEC of the Breast

	OS		Median OS, mo	P	DRFS		Median DRFS, mo	P
	No. of Patients at Risk	Survival Rate, %			No. of Patients at Risk	Survival Rate, %		
Age, y				NS				NS
≤60	5	89	25		1	98	22.5	
> 60	3	95	35		2	97	21	
Menopausal status				NS				NS
Premenopausal	4	86	32		2	93	23	
Postmenopausal	4	95	24		1	99	21	
T classification				.003				<.0001
T1	2	96	32		0	100	29	
T2	4	93	21		1	98	18	
T3	2	60	14		2	60	11	
T4	--	--	--		--	--	--	
N classification				NS				NS
N0	6	93	24		2	98	21	
N1	0	100	21		0	100	18	
N2	0	100	40		0	100	37	
N3	2	67	32.5		1	83	30	
M classification				<.0001				<.0001
M0	5	95	24		0	100	21	
M1	3	25	33.5		3	25	25.5	
AJCC TNM stage				<.0001				<.0001
I	2	95	33		0	100	30	
II	2	97	21		0	100	18	
III	2	67	31.5		1	83	29	
IV	2	33	35		2	33	21	
Mitotic figure				NS				NS
0	4	95	25		1	99	23	
1	4	87	21		2	93	18	
ER				NS				NS
0	2	67	41.5		1	83	38.5	
1	6	94	24		2	98	21	
PR				.001				.004
0	4	75	17.50		2	88	16	
1	4	96	25		1	99	23	
HER-2				NS				NS
0	8	92	17.5		3	97	21	
1	0	100	25		0	100	42	
Sy				NS				NS
0	1	91	24		0	100	21	
1	7	93	45		3	97	21	
CgA				NS				NS
0	5	89	24		2	96	21	
1	3	95	24		1	98	21	
Ki67				.009				.019
0	2	97	23.5		0	100	22	
1	6	85	25		3	93	20.5	

OS indicates overall survival; DRFS, distant recurrence-free survival; NEC, neuroendocrine carcinoma; NS, not significant; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; Sy, synaptophysin; CgA, chromogranin A; Ki67, proliferation marker.

Kaplan-Meier test also showed that PR is a significant positive prognostic factor for OS, DRFS, and LRFS in NEC patients (P=0.001, 0.004, 0.009, respectively). Survival rate in patients with PR expression was 96%, whereas in PR-negative patients, the number was 75%. Moreover, Ki67 was inversely correlated with OS and DRFS in NEC patients (P=0.009, 0.019, respectively). The survival rate of Ki67-positive patients to Ki67-negative patients was 85% to 97%.

Discussion

Our study is the largest series of NEC of breast to date, and the only one conducted in Chinese patients to reveal the clinicopathological features and prognostic significance of NEC. Although NEC of the breast was first demonstrated by Feyrter and Hartmann in 1963 [1] and had been sporadically reported since then[17, 18, 3] , there was no consensus on the definition of NEC, including how many of the tumor cells need to show NE differentiation and whether NE differentiation should be based on morphology alone or in conjunction with immunohistochemical studies of NE markers until 2003 when WHO defined it as a distinct type of mammary carcinoma, with more than 50% of neoplastic cells expressing NE markers by immunohistochemistry [6].

In this study, we reveal that NEC of the breast is a distinct tumor that differs from IDC, NOS in various clinicalpathological features and outcomes. This result is consistent with the study conducted by Weigelt that neuroendocrine carcinomas of the breast are molecularly distinct from histological grade- and molecular subtype-matched invasive ductal carcinomas [19]. Hypothesis might be that NEC of the breast did not rise from preexisting endocrine cells, but rather expressed a potentially differentiated pathway within breast carcinomas [20, 21]. Our data also support the earlier studies that NEC of the breast tended to be ER/PR positive and HER-2 negative [20, 21 ,22, 24], and presented at an older age than IDC, NOS. Furthermore, our study indicates that NECs had less LN metastasis and mitotic figure. Unfortunately, up until now, there is no such study on the differences of LN metastasis and mitotic figure between NEC and IDC,NOS. Therefore, we assume that more studies may be needed to verify these results.

Our study also shows that NEC of the breast has a poorer overall survival (OS) and local recurrence-free survival (LRFS) rate. A recently conducted study revealed that apart from poorer OS and LRFS rate, NEC also had a higher rate of distant recurrence[22,23,24]. Three other studies on small number of NEC patients revealed it to have a better prognosis [25, 26]. However, Sapino [27] and Makretsov [28] revealed that there was no significant difference in prognosis between NEC and IDC, NOS. We believe that the larger number of patients in our series and our strict case controls account for these differences.

Our study shows that several factors contribute to prognosis of NEC of the breast. Higher T classification, M classification, TNM stage are inversely relevant to OS, LRFS, DRFS. Such conclusions are not yet been reported in other studies. We also demonstrate that PR is a predictor for better prognosis and Ki67 a predictor for worse prognosis. This also applies to IDC,NOS [29, 30, 31], which means that NEC of the breast have some similar biochemical characteristics with IDC,NOS. Although Sapino [7] suggested that ER was highly correlated with long overall survival, our data reveal no specific information on whether ER expression is correlated with prognosis of NEC. Yao [32] and Bofin [9] revealed neuroendorine differ-

entiation in breast carcinoma to be associated with a higher grade of differentiation and a lower malignancy grade, whereas some other studies [33, 8, 34] suggested that NE markers had no prognostic significance. In this paper, we demonstrate that NE differentiation is not statistically significant in predicting prognosis.

In summary, the results of this comparative study of 107 NEC of the breast and 475 IDC, NOS patients reveal that NEC is a rare mammary carcinoma with distinct clinicopathological features and outcomes. With an older age at presentation, NECs are more likely to be ER/PR positive and HER-2 negative, and have a higher propensity for local recurrence and poorer OS. We confirm the significant prognostic role of tumor size, distant metastasis, TNM stage, PR and Ki67 expression. Since most NECs of the breast at our hospital are treated with traditional therapies that we use on IDC, NOS patients, the findings of our study may suggest that endocrine therapy and individualized therapies can be a promising alternative for NEC patients. Further studies with larger case number and longer follow-up will be needed in future researches.

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