

## Retrospective literature review of primary neuroendocrine neoplasms of the breast (BNEN) in 209 Chinese patients: Treatment and prognostic factor analysis



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### ABSTRACT

**Background:** The prognostic factors and optimal choice of treatment for primary neuroendocrine neoplasms of the breast (BNEN) remain to be defined.

**Methods:** Patients diagnosed with BNEN in China were retrospectively reviewed from the literature following the systematic search of China National Knowledge Infrastructure (CNKI), Chinese biomedical literature service system (sinomed), wanfang medical network, and Pubmed database. The clinical characteristics and different treatment modalities of patients with BNEN were evaluated.

**Results:** A total of 209 cases with BNEN were enrolled. There were 204 female and 5 male patients. The median age was 51 years old (range, 17–82). Out of 209 patients with BNEN, 208 (99.5%) patients were treated with surgery (SG), 44 patients (21.1%) had received radiotherapy (RT), 173 patients (82.8%) experienced chemotherapy (CT). A total of 158 patients with hormone receptor (HR) positive (87.8%, 158/180) were treated with endocrine treatment (ET). The median follow-up time was 52.4 months (range, 6–144). The 3-year overall survival (OS) rate and 3-year disease-free survival (DFS) rate for the whole group were 93.7% and 85.3%, respectively. In univariate analyses, Ki67 expression  $\geq 20\%$ , HR negative, neuroendocrine carcinomas (NECs) were associated with decreased OS and DFS ( $P < 0.05$ ). Patients treated with anthracycline/taxane-containing CT regimens, or taxane-containing CT regimens had superior OS and DFS than patients without those ( $P < 0.05$ ). Among 69 patients with stage I who received CT had no significant differences in OS or DFS compared to those without CT. Multivariate Cox regression analysis showed that gender, HR expression, pathologic subtype, and CT were independent prognostic factors for DFS but not OS ( $P > 0.05$ ).

**Conclusions:** The best selection of patients to get the most benefit from different treatment modalities warrant further exploration. The clinicopathological parameters including gender, HR expression, ki67 expression, pathologic type, stage, tumor size, and lymph node status may serve as both indicators of diagnosis and prognosis, and guide treatment decisions for BNEN.

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## 1. Introduction

Primary neuroendocrine neoplasms of the breast (BNEN) was a rare group of malignant neoplasms, accounting for less than 1% of neuroendocrine neoplasms (NENs) [1]. Then BNEN was classified as a unique type of breast carcinoma (BC) in the 2003 World Health Organization (WHO) classification with the definition of having >50% neoplastic cells expressing neuroendocrine (NE) markers [2]. BNEN was further divided into 3 categories by WHO in 2012: NE tumor, well-differentiated; NE carcinoma, poorly differentiated/small cell carcinoma; and invasive BC with NE differentiation [3]. It was reported that BNEN accounted for 2–5% of all invasive BC [4]. With the trending adoption of a unified terminology for all NE neoplasms in different organ systems, as well as the WHO tumor classification, these NE tumors were classified as NEN when most of the tumor cells (>90%) showed typical histomorphology and express NE markers by immunohistochemical (IHC) staining [5,6]. The 2019 WHO tumor classification of tumors subdivides BNENs into two distinct families: neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) [7]. NECs include small cell neuroendocrine carcinoma (SCNC) and large cell neuroendocrine carcinoma (LCNC). Regarding NENs grading, NETs should be graded (with variations in different anatomical sites) according to proliferation index, using a three-tiered score (G1, G2, and G3) based on mitotic count and/or Ki-67 labeling index, and/or the presence of necrosis, whereas NECs are high grade by definition, which reached a consensus in a conference held at the International Agency for Research on Cancer (IARC) in November 2017 [8]. Special histologic types (solid papillary carcinoma and hypercellular variant of mucinous carcinoma) were excluded from BNEN in 2019. Before the advent of the WHO 5th edition of BNEN, BNEN was referred to as neuroendocrine breast carcinoma (NEBC) in a general way. A Surveillance Epidemiology and End Results (SEER) database analysis of 142 patients with NEBC between 2003 and 2009 showed that the prevalence rate of NEBC was <0.1% [9]. Past studies have shown that BNEN predominantly occurred in women patients aged between 60 and 70 years. However, recent researches have revealed that younger females and males could also experience BNEN and the proportion of males seemed to be higher than other types of BC [1].

There is a lack of large-scale clinical studies to identify

clinicopathological features and prognostic factors of BNEN due to the low incidence and relatively few case reports of BNEN. With respect to the treatment, current treatment strategies for BNEN focus on surgery (SG), in combination with chemotherapy (CT), endocrine treatment (ET), and radiotherapy (RT). However, the optimal choice of treatment for BNEN remains to be defined. Therefore, we retrospectively analyzed the clinicopathological characteristics, treatment and prognostic factors of BNEN in the Chinese population reported in public databases, aiming to provide a theoretical basis for clinics to select appropriate prognostic factors and treatment modalities of BNEN.

## 2. Materials and methods

### 2.1. Literature search and selection

A retrospective literature search for case reports of BNEN in Chinese patients from 2000 to 2021 was conducted on the China National Knowledge Infrastructure (CNKI), Chinese biomedical literature service system (sinomed), wanfang medical network, and Pubmed database. Meanwhile, relevant references and guidelines were hand-searched, and tracked the references of the included studies to supplement data. When necessary, we contacted the authors of the included studies to inquire some missing information. The search strategy was conducted using the following keywords: “neuroendocrine breast carcinoma”, “neuroendocrine neoplasms of the breast”, “neuroendocrine”, “neuroendocrine tumors”, “neuroendocrine carcinomas”, “small cell neuroendocrine carcinoma”, “large cell neuroendocrine carcinoma”, “China”, and “Chinese patients”.

The inclusion criteria were as follows: 1) Chinese patients; 2) histopathologically diagnosed with BNEN according to corresponding WHO tumor classification of 2003, 2012, or 2019; 3) no prior treatment; 4) completed data of follow-up. Exclusion criteria were: 1) solid papillary carcinoma and hypercellular variant of mucinous carcinoma; 2) had two or more pathology types; 3) pregnancy and lactation; 4) patients who lost to follow-up; 5) repetitive published studies. This study was approved by local ethics committees.

## 2.2. Evaluation of clinical variables

The baseline clinical characteristics of patients with BNEN enrolled in this study including age at diagnosis, gender, initial symptom, primary site, pathologic subtype, estrogen receptor (ER) expression, progesterone receptor (PR) expression, Her-2 expression, Ki67, chromogranin A (CgA), synaptophysin (Syn), neuron-specific enolase (NSE), tumor size, lymph node status, stage, treatment modalities, CT regimens, surgical information, and RT data. The expression of ER, PR, Her-2, and proteins Ki67 in the BNEN tumor tissues was based on IHC staining. Immunohistochemical Syn, CgA and NSE scores at least 1+ were considered positive, while HER-2 scores 3+ were considered Her-2 positive. Patients without results of IHC Her-2 or patients with HER-2 scores 2+ without FISH identification were considered Her-2 unknown. ER and/or PR scores 1+ or >1% were defined as hormone-receptor (HR) positive. Disease recurrence was verified by clinical and imaging evaluations which included magnetic resonance imaging of breast and brain, and computed tomography scans of the chest, abdomen, and pelvis areas. The staging was determined according to the AJCC Clinical Staging System (version 8).

## 2.3. Statistical analysis

Disease-free survival (DFS) was defined as the time from SG to recurrences. Overall survival (OS) referred to the time from diagnosis until death from any cause or last follow-up. Categorical data were performed using the chi-square test. Univariate analyses and survival curves were conducted by the Kaplan-Meier curves with the log-rank test. Multivariate analyses were performed using Cox proportional hazards regression models. A *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software (SPSS Standard v 22.0, Chicago, United States).

## 3. Results

### 3.1. Patient characteristics

A total of 3520 articles were first identified for pre-selection. After screening the abstract of these articles according to the inclusion and exclusion criteria, 209 cases with BNEN from 37 studies were enrolled (Fig. 1). Five of 37 studies written in English were searched from Pubmed [10–14], the remaining 32 studies written in Chinese were from CNKI, sinomed and wanfang medical network databases. The characteristics of the included studies were shown in Table 1. The study population's characteristics at the baseline are listed in Table 2. There were 204 female and 5 male patients. The median age was 51 years old (range, 17–82). 24 (11.5%) patients were NETs, among whom 9 (4.3%) patients were G1, 11 (5.3%) patients were G2, and 4 (1.9%) patients were G3. 22 (10.6%) patients were NECs, among whom 20 (9.6%) patients were SCNC and 2 (1.0%) patients were LCNC. The pathologic subtypes of 163 (78.0%) patients were unclear based on the 2019 WHO tumor classification due to different WHO tumor classifications in different years. The most common symptom was an asymptomatic lump in the breast (206, 98.6%), followed by discharge from nipple (2, 1.0%), and enlargement of the left axillary lymph node (1, 0.5%). Unilateral symptoms were observed in 179 (85.6%) patients, bilateral symptoms in 22 (10.5%) patients, and 8 (3.8%) patients were unknown.

Sixty-nine patients (33.0%) was classified as stage I, 119 patients (56.9%) as stage II, 16 patients (7.6%) as stage III, one patient (0.5%) as stage IV and 4 patients (1.9%) were unavailable. The findings of the T stage were distributed as follows: 70 patients (33.5%) with size ≤2 cm, 90 patients (43.1%) with size larger than 2 cm and

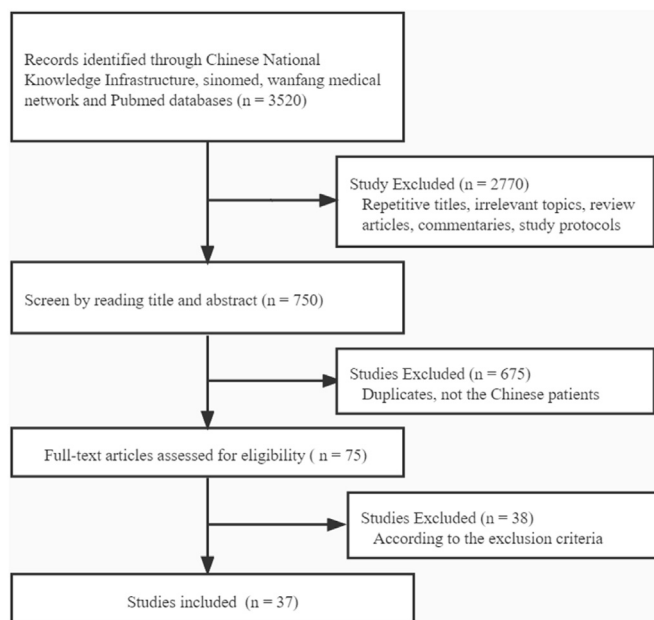


Fig. 1. Flow-chart of the literature search.

smaller than 5 cm, 14 patients (6.7%) with size > 5 cm and 2 patients (1.9%) with direct tumor invasion to chest. For N staging, there were 48 N0, 120 N1, and 7 N2 stage cases.

### 3.2. IHC findings

Of patients with IHC staining results, the NSE, CgA, Syn, HR and HER-2 positive rates were 91.1% (123/135), 81.6% (129/158), 86.5% (141/163), 87.8% (180/205) and 1.5% (2/135), respectively. The median Ki67-positivity was 26.8% (range, 1.0–90.0%) (56/209).

### 3.3. Treatment

Out of 209 patients with BNEN, 208 (99.5%) patients were treated with SG, including 188 patients who underwent a mastectomy and 20 patients who underwent breast-conserving SG. Forty-four patients (21.1%) had received RT. One hundred and seventy-three patients (82.8%) experienced CT, of which 9 patients were treated with neoadjuvant chemotherapy (NAC) and 170 patients were treated with adjuvant chemotherapy (ADC). Baseline characteristics of patients with BNEN treated with or without RT, and with or without adjuvant CT are listed in Supplemental Table 1 and Supplemental Table 2, respectively. BNEN patients with Her-2 positive ( $P = 0.001$ ), Ki67 ≥ 20% ( $P = 0.028$ ), G2 NETs ( $P = 0.011$ ), stage I ( $P < 0.001$ ), stage II ( $P = 0.011$ ), and after breast-sparing SG ( $P < 0.001$ ) were more inclined to choose RT. BNEN patients with stage I ( $P = 0.006$ ) and stage II ( $P = 0.027$ ) were more inclined to choose ADC. Baseline characteristics of 9 patients treated with NAC are listed in Supplemental Table 3. Three of 9 patients treated with NAC were stage II, 4 patients were stage III and one patient was stage IV. Except for 2 patients without clear information of T stage and N stage, 8 patients with size ≥2 cm and 7 patients with N1–N2 were treated with NAC.

Of the 129 patients who had clear CT regimens, 110 patients (85.3%) received anthracycline/taxane-containing CT regimens, 83 patients (64.3%) received taxane-containing CT regimens and 15 patients (11.6%) received platinum/etoposide combination CT. A total of 158 patients with HR positive (87.8%, 158/180) were treated with ET, including adjuvant ET ( $n = 156$ ), neoadjuvant ET ( $n = 1$ ), or

**Table 1**  
Summary of published articles about neuroendocrine neoplasms of the breast included in this study.

Year	Author	Number of cases	Publication information
2002	He et al.	3	Journal of the Third Military Medical University 2002, (07), 789
2005	Zhang et al.	5	Chinese journal of Clinical Oncology 2005, (13), 755-758
2008	Cui et al.	3	Zhong Guo Shi Yong Waikae Zazhi 2008, (07), 550-552
2008	Zheng et al.	1	Chinese Journal of General Surgery 2008, (01), 44
2008	Zhou et al.	7	Lingnan Modern Clinics in Surgery 2008, 8 (06), 420-423
2008	Zhong et al.	3	Modern Medicine Journal of China 2008, (07), 61-62
2009	Lv et al.	1	International Journal of Surgery 2009, (07), 498
2009	Pan et al.	13	Zhong Guo Shi Yong Waikae Zazhi 2009, 29 (03), 226-228
2009	Cui et al.	2	Chinese Journal of Clinical Rational Drug Use 2009, 2 (03), 33
2009	Ren et al.	1	China Oncology 2009, 19 (05), 399-400
2010	Wang et al.	1	Chinese Journal of Breast Disease (Electronic Edition) 2010, 4 (01), G106-108
2010	Geng et al.	3	Journal of Dalian Medical University 2010, 32 (04), 447-449
2010	Shi et al.	1	Chinese Manipulation & Rehabilitation Medicine 2010, 7, 128
2011	Zhang et al.	1	Surgical Today 2011, 41 (11), 1575-1578
2011	Qiu et al.	2	Journal of Yangtze University (Natural Science) 2011, 8 (10), 168-170
2011	He et al.	1	West China Medical Journal 2011, 26 (11), 1754-1755
2012	Li et al.	1	Oncology progress 2012, 10 (03), 313-317
2012	Zhang et al.	1	Drug Evaluation 2012, 9 (21), 47-48
2012	Li et al.	1	Chinese Journal of Cancer Prevention and Treatment 2012, 19 (23), 1827-1828
2013	Mao et al.	10	Tumor 2013, 33 (02), 171-176
2013	Zhu et al.	32	Guide of China Medicine 2013, 11 (32), 12-13
2014	Jiang et al.	1	OncoTargets and Therapy 2014, 7, 663-666
2014	Wu et al.	15	Journal of Logistics University of PAPF (Medical Sciences), 2014, 23 (11), 919-921
2014	Chi et al.	9	Zhong Guo Shi Yong Waikae Zazhi 2014, 34 (03), 268-269
2014	Feng et al.	6	Contemporary Medicine 2014, 20 (03), 105
2014	Zhu et al.	1	Jinagsu Medical Journal 2014, 40 (06), 737
2014	Zhong et al.	1	Chinese Journal of Gerontology 2014, 34 (16), 4679-4681
2014	Chen et al.	41	Chinese Journal of Clinical Oncology and Rehabilitation 2014, 21 (05), 602-603
2014	Ao et al.	1	Chinese Journal of Laboratory Diagnosis 2014, 18 (04), 680-681
2016	Wang et al.	10	Oncology progress 2016, 14 (10), 993-995
2017	Li et al.	6	Chinese Journal of Cancer 2017, 36 (1), 45
2017	Yang et al.	15	OncoTargets and Therapy 2017, 10, 397-407
2017	Wang et al.	3	Chinese Journal of General Surgery 2017, 26 (11), 1453-1459
2019	Zhang et al.	1	Chinese Journal of Endocrine Surgery 2019, (05), 387-388
2020	Zhang et al.	1	International Journal of Clinical and Experimental Pathology 2020, 13 (6), 1457-1462
2021	Bi et al.	3	China Medical Herald 2021, 18 (33), 181-183
2021	Ma et al.	2	Clinical Education of General Practice 2021, 19 (08), 755-757

ET alone ( $n = 1$ ). 15 of 20 patients with SCNC received ADC, including 8 patients received anthracycline/taxane-containing CT regimens, 2 patients received platinum/etoposide combination CT and 2 patients received CMF regimens (cyclophosphamide, methotrexate, fluorouracil).

Of 69 patients with stage I, all patients underwent SG, 4 patients (5.8%) received RT, 49 patients (71.0%) received ADC, 55 patients (79.7%) received adjuvant ET and 1 patient (1.4%) received neo-adjuvant ET. Of 119 patients with stage II, 118 patients (99.2%) were treated with SG, 31 patients (26.1%) were treated with RT, 3 patients (2.5%) were treated with NAC, 103 patients (86.6%) were treated with ADC, 93 patients (78.2%) were treated with adjuvant ET and 1 patient (0.8%) was treated with ET alone. Among the 16 patients with stage III, all patients underwent SG, 6 patients (37.5%) underwent RT, 4 patients (25.0%) underwent NAC, 14 patients (87.5%) underwent ADC, 8 patients (50.0%) underwent adjuvant ET. One patient with stage IV was treated with NAC + SG + ADC.

### 3.4. Survival

The median follow-up time was 52.4 months (range, 6–144) with a follow-up rate of 100%. During the follow-up, 18 (8.6%) of the patients were dead, including 15 patients who died due to disease progression and 3 patients who died because of other diseases. The 1-year, 2-year, 3-year, and 5-year OS rates for the whole group were 98.5%, 96.0%, 93.7%, and 91.2%, respectively. In terms of the DFS, the 1-year, 2-year, 3-year, and 5-year DFS rates were 95.1%, 90.3%, 85.3%, and 80.8%, respectively.

3-year OS and DFS rate was 96.8% and 92.5% in patients with

stage I, 93.5% and 89.5% in patients with stage II, 72.2% and 57.1% in patients with stage III. 3-year OS rate and 3-year DFS rate for patients with HR positive were 97.0% and 89.1% while 59.0% and 53.6% for those with HR negative ( $P < 0.001$ ).

### 3.5. Prognostic factors

In univariate analyses, gender, HR expression, ki67 expression, pathologic type, stage, tumor size, lymph node status, SG were associated with DFS while gender, HR expression, pathologic type, ki67 expression, tumor size and recurrences were associated with OS ( $P < 0.05$ ) (Table 2, Fig. 2, Fig. 3). Ki67 expression  $\geq 20\%$ , HR negative, NECs were associated with decreased OS and DFS ( $P < 0.05$ , Fig. 1b, c, Fig. 2b, c, 1d and 2d). Patients treated with anthracycline/taxane-containing CT regimens or taxane-containing CT regimens had superior OS and DFS than patients without those ( $P < 0.05$ , Fig. 1e, f, Fig. 2e, f). ET were not significantly associated with OS ( $P = 0.354$ ) and DFS ( $P = 0.149$ ) of patients with HR positive (Fig. 4c, Fig. 4d). Among 69 patients with stage I, patients who received CT had no significant differences in OS or DFS compared to patients without CT ( $P > 0.05$ ) (Fig. 4a and b). Multivariate Cox regression analysis showed that gender (hazard ratio (HR), 0.072, 95% confidence interval (CI): 0.015–0.340;  $P = 0.001$ ), HR expression (HR, 0.254, 95%CI: 0.103–0.627;  $P = 0.003$ ), pathologic subtype (HR, 3.645, 95%CI: 1.022–12.998;  $P = 0.046$ ) and CT (HR, 10.180, 95% CI: 2.002–51.756;  $P = 0.005$ ) were independent prognostic factors for DFS but not OS ( $P > 0.05$ ) (Table 3).

**Table 2**  
Baseline characteristics, OS and DFS of patients with BNEN.

Characteristics	Total (n = 209) (%)	3-year DFS rate (%)	P	3-year OS rate (%)	P
Median age (range)	51 (17–82)				
Sex			<0.001*		<0.001*
Male	5 (2.4)	26.7		50.0	
Female	204 (97.6)	89.1		94.1	
Symptom			0.240		0.096
Unilateral	179 (85.6)	89.4		93.3	
Bilateral	22 (10.5)	74.2		95.0	
Unknown	8 (3.8)	75.0		85.7	
ER ± PR			<0.001*		<0.001*
Positive	180 (86.1)	89.1		97.0	
Negative	25 (12.0)	53.6		59.0	
Unknown	4 (1.9)	100.0		100.0	
Her-2			0.343		0.325
Positive	2 (0.9)	100.0		91.7	
Negative	133 (63.6)	82.8		100.0	
Unknown	74 (35.4)	91.3		95.6	
Ki-67			0.004*		0.001*
≥20	23 (11.0)	67.1		75.5	
<20	33 (15.8)	90.2		100.0	
Unknown	153 (73.2)	86.4		93.8	
Pathologic subtype					
NETs			<0.001*		<0.001*
G1	9 (4.3)	100.0		100.0	
G2	11 (5.3)	75.0		100.0	
G3	4 (1.9)	33.3		100.0	
NECs					
SCNC	20 (9.6)	48.1		49.0	
LCNC	2 (1.0)	100.0		96.6	
Unknown	163 (78.0)	89.7			
Stage			<0.001*		0.159
I	69 (33.0)	92.5		96.8	
II	119 (56.9)	89.5		93.5	
III	16 (7.6)	57.1		72.2	
IV	1 (0.5)	100.0		100.0	
Unknown	4 (1.9)	100.0		100.0	
T			<0.001*		<0.001*
1	70 (33.5)	89.5		96.8	
2	90 (43.1)	85.5		93.8	
3	14 (6.7)	47.1		61.1	
4	2 (1.9)	50.0		50.0	
Unknown	33 (15.8)	97.0		100.0	
N			0.001*		0.101
0	48 (23.0)	89.0		95.3	
1	120 (57.4)	71.8		83.9	
2	7 (3.3)	62.8		83.3	
Unknown	34 (15.8)	97.1		100.0	
Surgery			0.008*		0.790
Yes	208 (99.5)	85.8		93.1	
No	1 (0.5)	0.0		100.0	
Radiotherapy			0.530		0.374
Yes	44 (21.1)	84.1		90.2	
No	165 (78.9)	85.7		94.0	
Chemotherapy			0.204		0.995
Yes	173 (82.8)	84.1		94.1	
No	36 (17.2)	90.6		93.0	
Recurrence			–		<0.001*
Yes	33 (15.8)	–		56.1	
No	176 (84.2)	–		99.4	

**Abbreviations:** OS: overall survival; DFS: disease-free survival; BNEN: neuroendocrine neoplasms of the breast; ER: estrogen receptor; PR: progesterone receptor; NETs: neuroendocrine tumors; NECs: neuroendocrine carcinomas; G: grade; SCNC: small cell neuroendocrine carcinoma; LCNC: large cell neuroendocrine carcinoma.

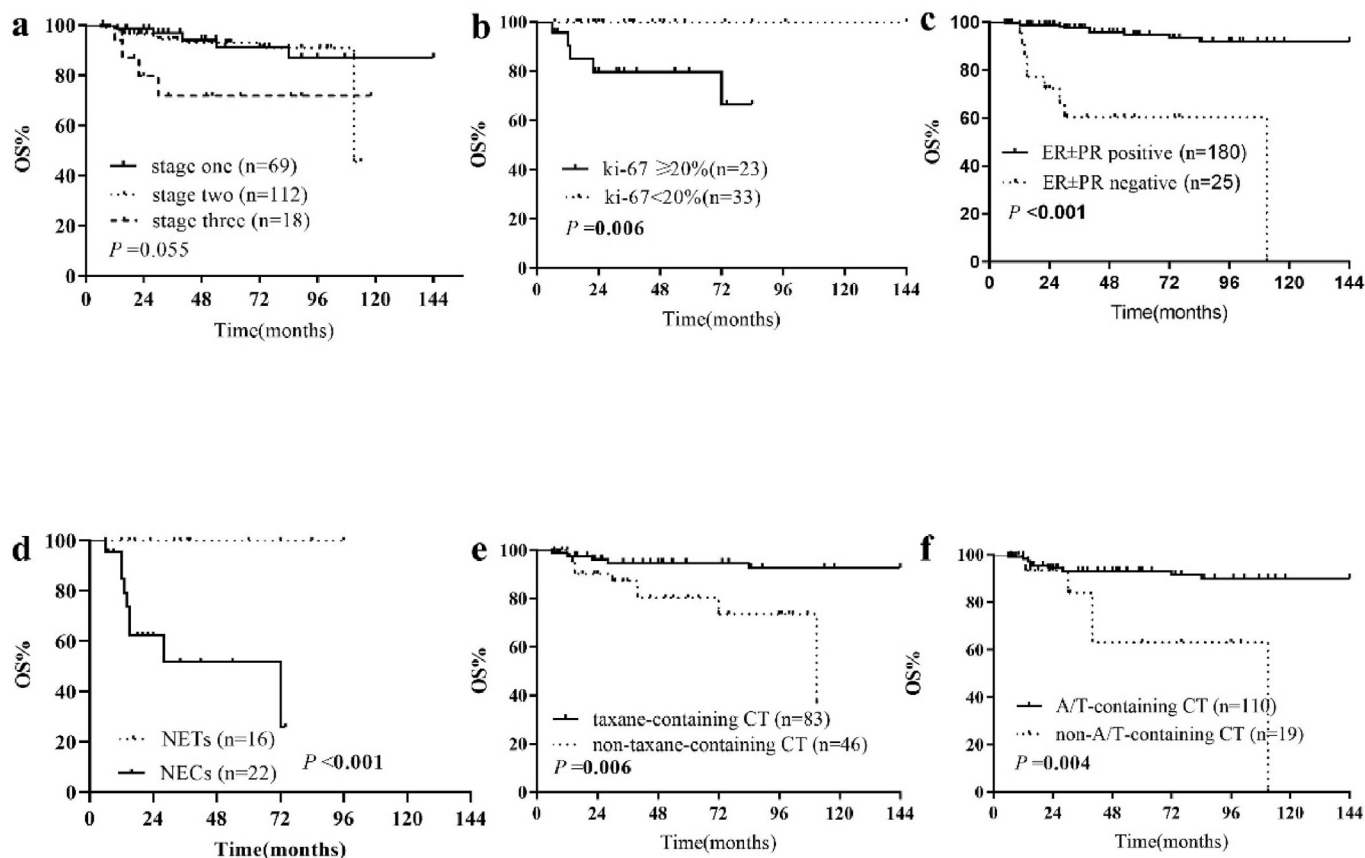
### 3.6. Failure patterns

The median time to recurrence was 20 (4–107) months. During the follow-up period, a total of 34 (16.3%) patients experienced postoperative recurrence, including 6 patients with metastases in lung, 6 patients with metastases in cervical and supraclavicular lymph nodes, 5 patients with metastases in bone, 1 patient with metastasis in liver, 2 patients with recurrences in chest wall and 14 patients were not available.

### 4. Discussion

NE neoplasms could be found in several organ systems, such as the respiratory system, digestive system, urinary system, and reproductive system, etc., and were rarely reported in BC. Due to the low incidence of BNEN, large-scale cohort investigation was difficult to be performed which limited our understanding of this disease. To date, this is one of the largest retrospective literature reviews aiming to evaluate the clinicopathological characteristics, prognostic factors, and survival outcomes of Chinese patients with BNEN.





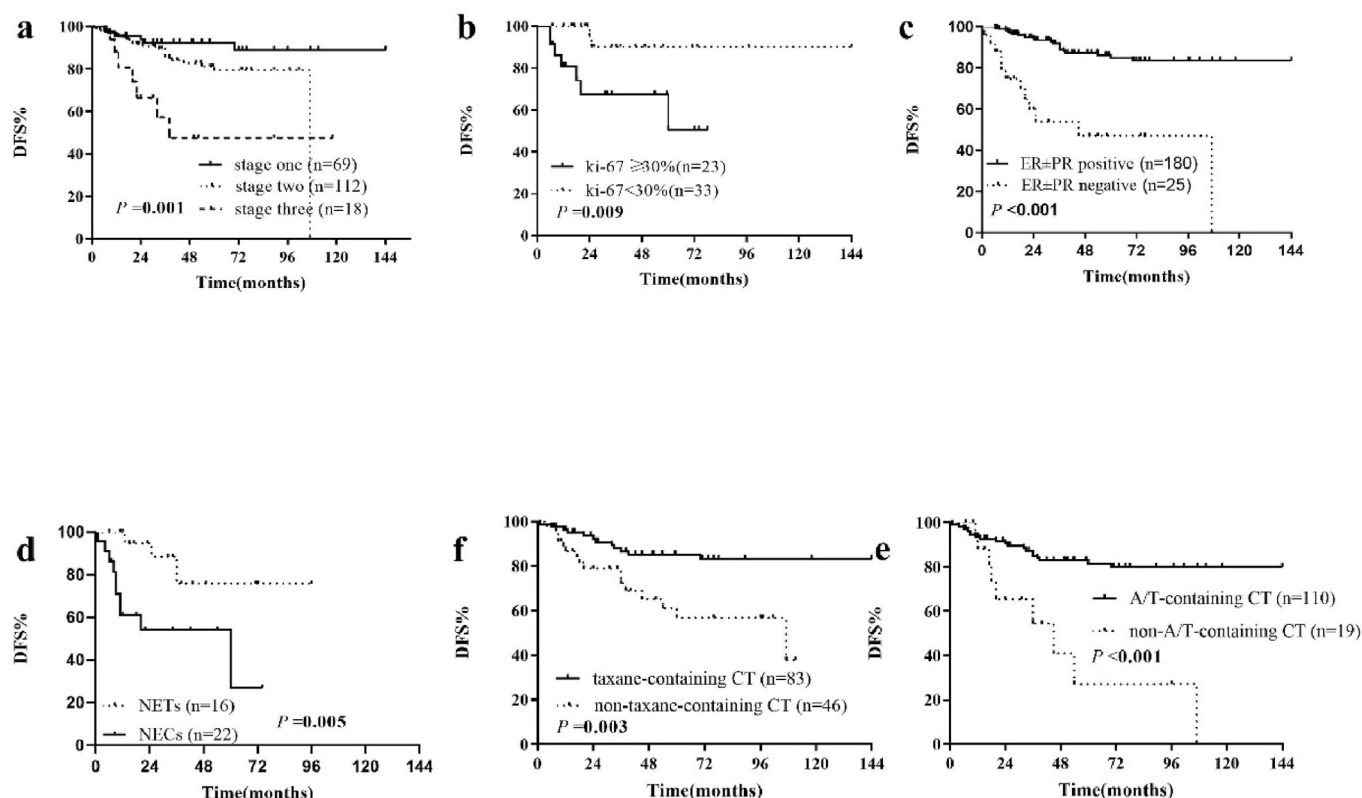
**Fig. 2.** Kaplan-Meier OS for patients with BNEN stratified by various clinicopathological factors: a. Survival curves for patients with different stages; b. for patients stratified by ki67; c. for patients with and without ER and/or PR expression; d. for patients with NETs and patients with NECs; e. for patients with or without taxane-containing CT; f. for patients with or without A/T-containing CT. **Abbreviations:** OS: overall survival; BNEN: neuroendocrine neoplasms of the breast; NETs: neuroendocrine tumors; NECs: neuroendocrine carcinomas; ER: estrogen receptor; PR: progesterone receptor; A/T: anthracycline/taxane; CT: chemotherapy.

According to the 2019 WHO tumor classification, Chinese patients with BNEN were classified into NETs (including G1, G2, and G3) and NECs (including SCNC and LCNC). Of 46 patients who had definitive pathological subtypes, SCNC (47.8%) were the most common subtypes, followed by G2 NETs (23.9%), G1 NETs (19.6%), G3 NETs (8.7%), and LCNC (4.3%). Etoposide-based regimens were the preferred regimens to treat patients with SCNC in most reported case reports that were reviewed by Mirza et al., in 2007 [15]. In 2020, a recent review by Trevisi et al. reported 99 references and also showed that poorly differentiated or SCNC have been mostly treated with platinum/etoposide-containing regimens, while anthracyclines and/or taxanes-based chemotherapy have been used for other types of BNEN [16]. In our study, 2 of 15 patients with SCNC who had clear data of CT regimens were treated with platinum/etoposide-containing regimens, 8 patients were treated with anthracycline/taxane-containing CT regimens, and 2 patients received CMF regimens. Our study demonstrated that CT regimens for Chinese SCNC were mostly based on primary BC or clinical experience of Chinese doctors. This might be one of the reasons for the poor prognosis of SCNC patients. NECs were associated with decreased OS ( $P < 0.001$ ) and DFS ( $P = 0.005$ ). The 3-year OS and 3-year DFS of patients with SCNC were both  $< 50\%$  (49.0% and 48.1%, respectively), which showed a relatively poor prognosis compared with those of patients with other pathological subtypes. The most suitable CT regimens for different pathological subtypes of patients with BNEN deserved further exploration.

It was reported that BNEN was usually found in elderly females with the onset age of 60–70 years [9]. In our study, there were 204

female and 5 male patients with the median age of 51 (range, 17–82) years old, which were slightly younger than those in the previous studies [9]. These results suggested that BNEN could occur primarily in young and middle-aged patients. Meanwhile, there were 5 male patients with BNEN which indicated that BNEN could also present in male patients with unclear mechanisms [17]. BNEN lacks specific features of clinical manifestations. Early-stage BNEN patients usually presented as painless breast lumps without typical dimple signs or orange peel-like skin changes [18]. Almost all patients (98.6%) enrolled in this study presented with an asymptomatic lump in the breast as the initial symptom. More than half of patients (85.6%) had unilateral symptoms. Therefore, early diagnosis is likely to be difficult and it is vitally important to explore the diagnostic markers of BNEN.

Currently, it is considered that Syn and CgA were the most sensitive NE markers and could be used as a reliable indicator for the diagnosis of BNEN. BC with IHC Syn and CgA scores 2+ or more was diagnosed as BNEN in the past [19–21]. NSE was believed to be a less sensitive and less specific marker for BNEN [22]. In our study, the positive rate of NSE, CgA, and Syn was 91.1%, 81.6%, and 86.5%, respectively. NSE also played an important role in the diagnosis of BNEN. In addition, BNEN was mostly hormone-dependent with high HR-positive expression and low Her-2 positive expression [15,16,23]. Similar results were obtained in our study with the HR-positive rate of 87.8% and the HER-2 positive rate of only 1.5%. The HR-positive rate was higher than that previously reported in the United States population (68%) [9]. Compared to other types of invasive BC, the HR-positive rate of patients enrolled in our study



**Fig. 3.** Kaplan-Meier DFS for patients with BNEN stratified by various clinicopathological factors: a. Survival curves for patients with different stages; b. for patients stratified by ki67; c. for patients with and without ER and/or PR expression; d. for patients with NETs and patients with NECs; e. for patients with or without taxane-containing CT; f. for patients with or without A/T-containing CT. **Abbreviations:** DFS: disease-free survival; BNEN: neuroendocrine neoplasms of the breast; NETs: neuroendocrine tumors; NECs: neuroendocrine carcinomas; ER: estrogen receptor; PR: progesterone receptor; A/T: anthracycline/taxane; CT: chemotherapy.

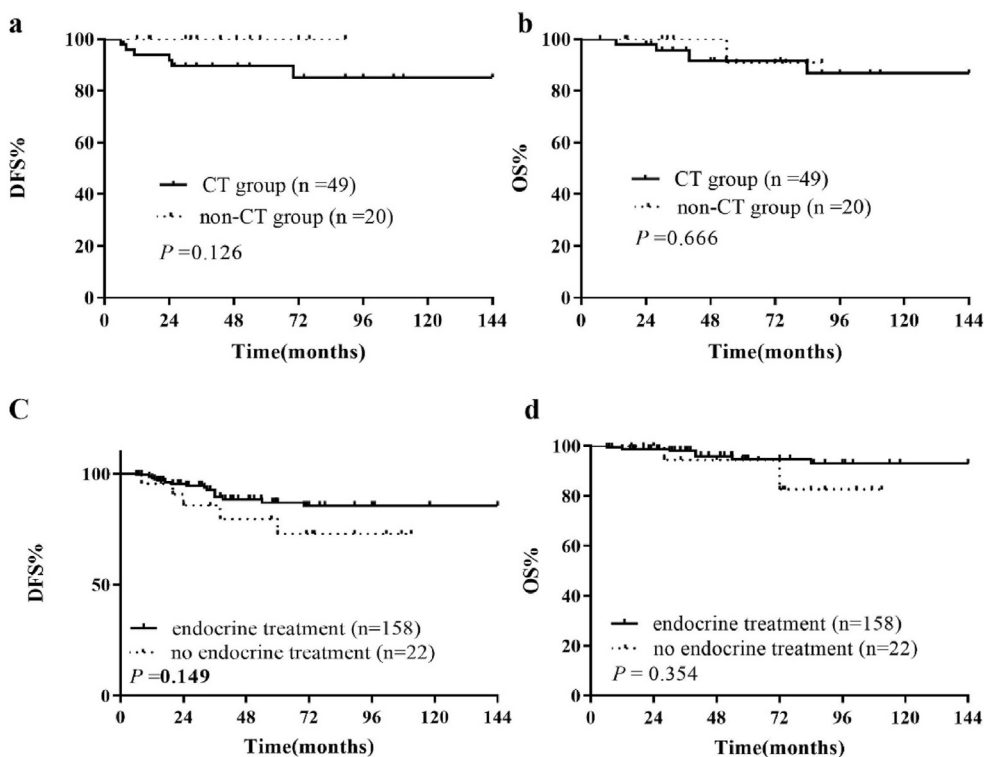
was also relatively higher [24,25].

BNEN was a rare type of BC. At present, since there has been no uniform criterion for the treatment of patients with BNEN at home and abroad, the indications for SG, RT, ET, NAC, and ADC, as well as the reason for different regimens used were in reference to those of invasive BC or according to clinical experience of doctors in China. The primary treatment of BNEN was a comprehensive treatment modality which was based on SG, combined with RT, CT, and ET. The SG procedure included breast reconstruction, breast-conserving SG, total mastectomy, radical mastectomy, and modified radical mastectomy. Almost all patients (99.5%) enrolled in our study were treated with SG, which sufficed to identify the irreplaceable status of SG in the treatment of BNEN. Forty-four patients (21.1%) in our study were treated with RT. However, RT did not significantly influence OS or DFS in our series ( $P > 0.05$ ) which distinct from other types of BC. Then we compared the baseline characteristics of patients with BNEN treated with RT versus without RT. The results showed that BNEN patients with Her-2 positive ( $P = 0.001$ ), Ki67  $\geq 20\%$  ( $P = 0.028$ ), G2 NETs ( $P = 0.011$ ), stage I ( $P < 0.001$ ), stage II ( $P = 0.011$ ), and after breast-sparing SG ( $P < 0.001$ ) were more inclined to choose RT, which was consistent with the indications of RT of primary BC [26]. Therefore, the application of RT in the treatment of BNEN needed to be further investigated.

CT comprises NAC and ADC in the treatment of BNEN. In our series, 173 patients (82.8%) experienced CT, of which 9 patients were treated with NAC and 170 patients were treated with ADC. In the univariate analysis, CT has not shown significant benefits in OS or DFS for the whole group ( $P > 0.05$ ). In addition, stage I BNEN patients did not benefit from CT by subgroup analysis ( $P > 0.05$ ). The optimal combination of CT agents for the treatment of BNEN

was further explored. Among 129 patients with recorded CT regimens, patients treated with anthracycline/taxane-containing CT regimens or taxane-containing CT regimens had superior OS and DFS than patients without those ( $P < 0.05$ ). These results illustrated that BNEN may not be sensitive to CT, similar to pulmonary and gastrointestinal NE tumors [27]. At present, regimens of ADC of patients with BNEN are mainly carried out according to those of patients with invasive BC, and similar therapeutic efficacies and prognoses have been obtained [28]. Additionally, CT may not be essential for stage I BNEN patients. Early-stage, small, node-negative, and low/intermediate grade BNEN patients were less aggressive tumors, which may be spared CT and managed with ET, as luminal-like BC. 90% of the patients enrolled in this study were in stage I or II, T stage 1 or 2, and mostly with 0 to max 3 positive lymph nodes. For these patients, the estimated need for ADC was  $<20\%$ , 21-gene recurrence score calculation may be suggested according to TailorX and RXpander trials [29,30]. The best selection of patients to get the most benefit from CT and the optimal CT regimens warrant further exploration.

Most patients in our study were hormone-dependent and required ET [31,32]. ET were divided into adjuvant ET ( $n = 156$ ), neoadjuvant ET ( $n = 1$ ), or ET alone ( $n = 1$ ). Although the univariate analysis revealed that ET was not significantly associated with OS ( $P = 0.354$ ) and DFS ( $P = 0.149$ ) of patients with HR-positive ( $P > 0.05$ ), the Kaplan–Meier curve of DFS showed a trend of separation after a 2-year follow-up time and OS showed a trend of separation after a 6-year follow-up time. This hinted that ET may have a long-term superior effect on patients with HR-positive. One patient received neoadjuvant ET without disease progression for 72 months at the last follow-up date. Only 2 patients were with known



**Fig. 4.** Kaplan-Meier survival for patients with BNEN. a. DFS for patients with stage I BNEN with or without chemotherapy; b. OS for patients with stage I BNEN with or without chemotherapy; c. DFS for patients with or without endocrine treatment; d. OS for patients with or without endocrine treatment. **Abbreviations:** OS: overall survival; DFS: disease-free survival; BNEN: neuroendocrine neoplasms of the breast; CT: chemotherapy.

**Table 3**  
Results of multivariate analyses of different factors on DFS and OS of BNEN.

Characteristics	DFS			OS		
	HR	95%CI	P value	HR	95%CI	P value
Gender (female/male)	0.072	0.015–0.340	0.001*	0.180	0.021–1.540	0.117
Primary symptom (Bilateral/unilateral)	1.675	0.295–9.519	0.561	1.730	0.229–13.067	0.595
ER ± PR (positive/negative)	0.254	0.103–0.627	0.003*	0.305	0.088–1.056	0.061
Ki-67 (≥20%/<20%)	1.538	0.260–9.084	0.635	24581.507	0.000–6.413*10 <sup>112</sup>	0.937
Pathologic subtype (NETs/NECs)	3.645	1.022–12.998	0.046*	<0.001	0.000–6.088*10 <sup>146</sup>	0.957
Chemotherapy (Yes/No)	10.180	2.002–51.756	0.005*	2.346	0.463–11.890	0.303

**Abbreviations:** OS: overall survival; DFS: disease-free survival; BNEN: neuroendocrine neoplasms of the breast; HR: hazard ratio; CI: confidence interval; ER: estrogen receptor; PR: progesterone receptor; NETs: neuroendocrine tumors; NECs: neuroendocrine carcinomas.

HER-2 positive. The entire group of patients did not receive Her-2-targeting therapies, which may be due to the lack of Her-2-targeting therapeutic drugs or reagents in the earlier years. In recent years, new drugs have developed continuously. In 2018, the combination of palbociclib and fulvestrant has accomplished promising results in the treatment of a patient with BNEN [33]. In addition, potential targets have been identified to explore potential novel therapeutic approaches for BNEN, such as PIK3CA, trophoblast cell surface antigen-2 (TROP-2), and programmed cell death ligand-1 (PD-L1) [23,34–36]. We look forward to the development of new drugs to bring a new dawn to the treatment of BNEN.

According to the previous studies, the prognosis of BNEN being better or worse compared with unselected BC was controversial [9,37,38]. Rovera et al. conducted a retrospective study in 2008 with 13 patients with BNEN and find no recurrent disease during the 60-month follow-up time, which seemed to show a less aggressiveness of BNEN [38]. In 2013, a retrospective study enrolled 96 patients with BNEN, and a 10-year OS rate of 87% was obtained, which seemed to have a better OS than other types of BC [39]. Another

retrospective study conducted by Zhang et al., in 2013 involving 107 patients showed that BNEN possessed a relatively higher local recurrence rate and lower OS rate [40]. In the current study, the median follow-up time was 52.4 months (range, 6–114), and the 5-year OS rate for the whole group was 91.2% which was superior to 53.6% of 142 patients from a SEER database [9].

Current small sample studies have pointed out that age, the field, the capacity of tumor secretion, grade, ER/PR expression, ki67 expression, tumor size, lymph node status, the existence or not of distant metastases were associated with survival [41,42]. In our series, gender, HR expression, ki67 expression, pathologic type, stage, tumor size, lymph node status were associated with DFS while gender, HR expression, pathologic type, ki67 expression, tumor size, and recurrences were associated with OS ( $P < 0.05$ ). Ki67 expression  $\geq 20\%$ , HR negative, pathologic type of NECs were associated with decreased OS and DFS. The stage was not observed to be associated with OS but with a significant trend of separation of the Kaplan–Meier curve of OS between stage I or stage II versus stage III. In addition, compared with DFS, OS was affected by many



factors (such as treatments after disease progression, economics, etc.), which may explain that stage was not significantly associated with OS in the univariate analysis. Multivariate Cox regression analysis showed that gender (HR, 0.072, 95% CI: 0.015–0.340;  $P = 0.001$ ), HR expression (HR, 0.254, 95%CI: 0.103–0.627;  $P = 0.003$ ), pathologic subtype (HR, 3.645, 95%CI: 1.022–12.998;  $P = 0.046$ ) and CT (HR, 10.180, 95%CI: 2.002–51.756;  $P = 0.005$ ) were independent prognostic factors for DFS but not OS ( $P > 0.05$ ). These clinicopathological parameters may serve as both indicators of diagnosis and prognosis, and guide treatment decisions for BNEN.

BNEN metastasized to multiple organs, such as liver, bone, lung, pancreas, soft tissues, and brain, even after several years of SG [43]. A large-scale retrospective study conducted by Maren et al., in 2018 showed that among 8062 BC patients, 4482 (56%) were luminal A and 2090 (26%) luminal B with recurrence rates of 14.9% and 29.5%, respectively. Distant metastases were experienced by 9.5% of patients with luminal A BC and 20.0% in luminal B BC [35,44]. Bone and Lung were the most common metastatic sites of luminal BC patients [45]. In our study, the median time to recurrence was 20 (4–107) months with a recurrence rate of 16.3%. The most common site was lung ( $n = 6$ ), followed by cervical and supraclavicular lymph node ( $n = 6$ ) and bone ( $n = 5$ ). The patterns of recurrences and sites of metastases of BNEN patients were consistent with previously reported in patients with invasive BC [45]. Long time follow-up even for 10 years or more may be recommended for patients with BNEN.

There were still some limitations of this type of analysis. First, all patients enrolled in this study lacked central revision of histology. Second, the data presented did not necessarily represent individual patients. Thirdly, this review analysis was based on the data published in the articles. In addition, this review analysis was limited to the Chinese population. A prospective study was warranted to be conducted to verify conclusions in this study.

## 5. Conclusions

SG is a cornerstone of BNEN. ET may have a long-term superior effect on patients with HR-positive. The best selection of patients to get the most benefit from CT and the optimal CT regimens warrant further exploration. The clinicopathological parameters including gender, HR expression, ki67 expression, pathologic type, stage, tumor size, and lymph node status may serve as both indicators of diagnosis and prognosis, and guide treatment decisions for BNEN.

## Statement of ethics

An ethics statement was not required for this study as all data were taken from the public domain.

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## Author contributions

Yue Chai, Qiao Li and Binghe Xu conceived the idea for this study. Yue Chai, Ming Liu, Zhijun Li, Yujie Chen, Fei Qi collected clinical data. Yue Chai and Qiao Li analyzed the data and wrote the manuscript. All of the authors commented on and edited the manuscript.

## Data availability statement

The datasets developed and analyzed during this study are available from the corresponding author on reasonable request.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.01.013>.

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