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Original Article

Clinicopathological characteristics of primary squamous cell carcinoma of breast

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Abstract: Primary squamous cell carcinoma of breast (PSCCB) is a rare type of breast malignancy that has low hormone receptor expression and poor outcomes. So far no validated prognostic markers for the tumor have been available yet. The purpose of this study is to evaluate its clinicopathologic characteristics, immunohistochemical profile, molecular subtypes, clinical managements and prognosis. Twenty-four cases of PSCCB were identified in the archive of our hospital between January 2003 and October 2014. The medical records and pathologic materials were retrieved and reviewed. The cases accounted for 0.097% of invasive breast carcinoma (total 24666 cases), including 17 cases of pure type and 7 cases of metaplastic type. All patients were female with a median age of 55 years (28 to 87 years). The average tumor size was 4.2 cm (1.2 to 10.0 cm), and axillary lymph node metastasis was identified in 6 out of 20 (30.0%) patients. The most common molecular subtype was basal-like (15 cases). The median OS and DFS were 54 months (6-105 months) and 37 months (5-105 months) respectively. During the follow up, one patient was lost and six patients developed tumor recurrence at chest wall and/or metastasis to bone or lung. On univariate analysis, tumor metastasis to axillary lymph nodes and advanced stage at diagnosis were associated significantly with reduced OS. Tumors with basal-HER2 phenotype seemly have particularly poor prognosis associated with frequent local recurrence and/or distant metastasis. Due to its rarity and lack of ER, PR and HER2 expression in majority of the tumors, treatment of PSCCB is often refractory and remains controversial, although tumors with ER and PR expression may response to hormonal therapy. New therapy regimens, like EGFR tyrosine kinase inhibitors, are currently under active exploration.

Keywords: Breast tumor, squamous cell carcinoma, molecular type, treatment, prognosis

Introduction

Primary squamous cell carcinoma of breast (PSCCB) was first reported by Troell in 1908 [1]. It is histologically characterized by presence of identifiable keratinization and intercellular bridges among tumor cells. The tumor origins in the mammary glands and must be independent from the adjacent skin and adnexa. It is classified as metaplastic breast carcinoma in the WHO Classification of Tumors of Breast [2], and predominantly occurs in older women with larger tumor size and rapid painful growth. PSCCB usually presents as a cystic mass and the cavity is lined by squamous cells with varying degree of nuclear atypia and pleomorphism. The neoplastic cells infiltrate the adjacent stroma in the form of sheets, cords and nests, which often elicit a conspicuous stromal reaction [2]. Due to its rarity, accounting for less 1% of all invasive mammary carcinomas, it is so far not well studied yet. We identified 24 cases of PSCCB diagnosed between January 2003 and October 2014 from the archive of our hospital. The study is undertaken to evaluate its clinicopathologic characteristics, and to analyze its molecular subtypes, clinical managements and prognosis.

Materials and methods

Case selection

Twenty-four cases of PSCCB were identified and retrieved from 24666 cases of invasive breast carcinoma diagnosed between January 2003

Table 1. Clinical characteristics of 24 cases of PSCCB

Characteristics		*Number*	*Percentage %*
Age at diagnosis	≤50	10	41.7
	>50	14	58.3
Recurrence/metastasis	Yes	6	25.0
	No	17	70.8
	Unknown	1	4.2
Ultrasonography	Malignant	18	94.7
	Benign	1	5.3
Mammography	Calcification	16	84.2
	No calcification	3	15.8
Fine-needle aspiration	Invasive carcinoma	6	54.5
	Primary squamous cell carcinoma	2	18.2
	Other results	3	27.3
Type of surgery	Modified/Radical mastectomy	20	83.3
	Other	4	16.7
Chemotherapy	Yes	18	75.0
	No	6	25.0
Radiotherapy	Yes	2	8.3
	No	22	91.7
Endocrine therapy	Yes	2	8.3
	No	22	91.7

and October 2014 from the Department of Breast Cancer Pathology and Research Laboratory, Tianjin Medical University Cancer Hospital, Tianjin, China. All patients were female, with a median age of 55.0 years (ranging from 28 to 87 years). The follow-up time was 6-105 months with a median follow-up of 54 months. Twenty (83.3%) patients received modified or radical mastectomy. The pathologic materials were reviewed and the diagnosis was verified independently in each case by 3 senior pathologists (X.G., L.F. and R.L.), using the criteria specified in the 2012 WHO Classification of Tumors of Breast [2], and the tumor was further divided into pure type and squamous metaplastic type, depend whether there was any associated adenocarcinoma identified in the cancer nest or not.

Immunohistochemistry

Immunohistochemistry (IHC) is performed using the avidin-biotin-immunoperoxidasetechnique for estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), Ki67, p53, cytokeratin 5/6 (CK5/6) and epidermal growth factor receptor (EGFR). All primary antibodies were purchased from Abcam (Cambridge, MA, USA). Formalin-fixed paraffin embedded tissue sections were employed using a standard protocol. Briefly, 4 um tissue sections on coated slides were heated for antigen retrieval, pretreated with a 3% solution of hydrogen peroxide for 5-10 minutes, and incubated with10%normalgoatserum as the blocking agent. The sections were then incubated sequentially with the primary antibodies followed by a biotinylated secondary antibody and avidin-peroxidase conjugate (obtained from Santa Cruz Biotechnology). All steps were preceded by rinsing of sections with PBS (pH 7.6). The chromogen was 3, 3'-diaminobenzidine (DAB). The sections were counterstained with hematoxylin, dehydrated and mounted. The immune-reaction was evaluated independently by the 3 pathologists.

For ER and PR, nuclear staining in ≥1% of the tumor cells was considered positive [3]. HER2 immunoreactivity was evaluated on a standardized scale from 0-3 based on the intensity of membranous staining and the proportion of invasive tumor cells stained, with strong complete membranous staining in >10% of tumor cells (3+) was considered positive [4]. Ki-67 and p53 immunoreaction presented with nuclear staining, and CK5/6 and EGFR with membranous/cytoplasmic stain. Ki-67 labelling index was calculated and high tumor proliferation was defined as a labelling index ≥14% [5]. Overexpression of p53 was defined as nuclear stain in ≥10% tumor cells [6], and a cut-off of staining in >10% tumor cells were adopted for CK5/6 positivity [7]. EGFR immunoreaction was evaluated based on the staining intensity, with 0 indicating absence of staining, and 1+, 2+, and 3+ representing respectively weak, moderate, and strong staining intensity. EGFR overexpression was defined as cases with 2+ or 3+ immunoreaction. Molecular classification of tumor was performed using the established criteria [8]. Tumors negative for ER, PR, and HER2

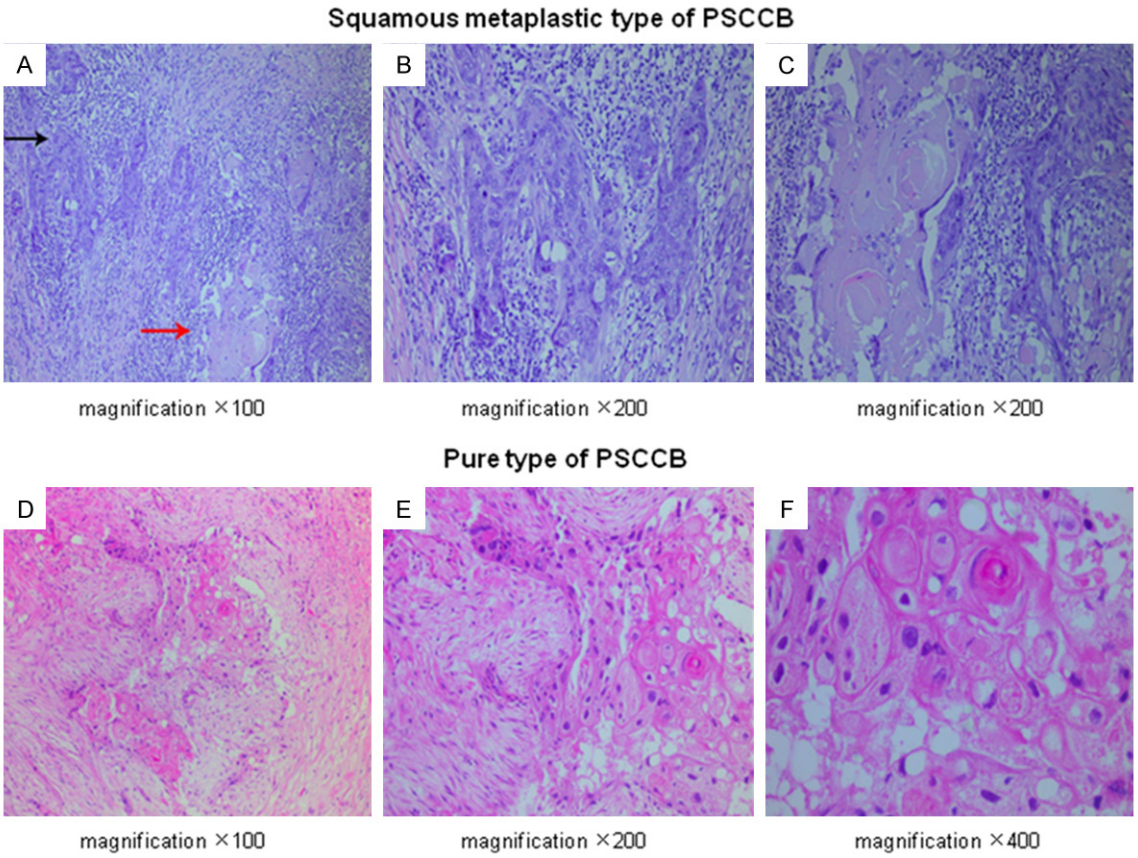

Figure 1. Histologic features of primary squamous cell carcinoma of the breast (PSCCB) (H&E staining). (A-C) showed squamous metaplastic type of PSCCB, and (D-F) showed pure type of PSCCB. Squamous metaplastic type of PSCCB (A) was coexisting invasive carcinoma (B) mixed with metaplastic squamous cell carcinoma (C). In (A), the red arrow and black arrow showed the component of metaplastic squamous cell carcinoma and coexisting invasive carcinoma, respectively. The pure type of PSCCB (D-F) showed squamous cells with varying degrees of nuclear atypia and pleomorphism (A and D. Original magnification ×100; B, C and E. Magnification ×200; F. Magnification ×400).

expressions, and positive for CK5/6 and/or EGFR immunoreactions were classified as basal-like carcinoma [9-11].

Fluorescent in situ hybridization

Fluorescent in situ hybridization (FISH) detection of HER2 gene amplification was performed in selected cases with equivocal IHC reaction for HER2 (2+) using FDA-approved PathVysion HER2 DNA Probe Kit (Abbott Laboratories). At least 20 invasive carcinoma cells in each case were evaluated to determine HER2 gene copies and the ratio of HER2 gene vs chromosome 17 centromere signals. HER2/CEP17 ratio >2.0 was considered HER2 gene amplification, per the 2013 ASCO/CAP recommendations [4].

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis until death or the date patients were last known to be alive. The disease-free survival (DFS) was calculated from the date of diagnosis until relapse or the date patients were last known to be alive. The correlation between DFS, OS and the clinicopathologic characteristics of PSCCB was analyzed using the Kaplan-Meier method and Log-rank test. The statistical analysis was performed with the use of software packages SPSS version 19.0. All statistical tests were two-sided, and a P value of <0.05 was considered significant.

Results

Clinical characteristics

Clinical information of the 24 patients was summarized in **Table 1**. All patients were female, with a median age of 55.0 years (ranging from 28 to 87 years). The PSCCB accounted for 0.097% of all invasive mammary carcinomas

Table 2. Pathological characteristics of 24 cases of PSCCB

Characteristics		*Number*	*Percentage %*
Tumour size	≤5 cm	18	75.0
	>5 cm	6	25.0
LN metastasis	Yes	6	30.0
	No	14	70.0
Stage	I	2	8.3
	II	18	75.0
	III	4	16.7
Histological features	Pure type	17	70.8
	Squamous metaplastic type	7	29.2
Molecular Classification	Luminal A	0	0
	Luminal B	4	16.7
	HER2-overexpression	4	16.7
	Triple-negativity	16	66.6
ER	Negative	21	87.5
	Positive	3	12.5
PR	Negative	22	91.7
	Positive	2	8.3
HER2	Negative	20	83.3
	Positive	4	16.7
Ki67	Negative	2	8.3
	Positive	22	91.7
p53	Negative	9	37.5
	Positive	15	62.5
CK5/6	Negative	2	8.3
	Positive	22	91.7
EGFR	Negative	5	20.8
	Positive	19	79.2

ER, estrogen receptors; PR, progesterone receptors; HER2, human epidermal growth factor receptor 2; CK5/6, cytokeratin 5/6; EGFR, epidermal growth factor receptor.

(total of 24666 cases) at the same period. Nineteen patients were evaluated preoperatively by ultrasonography, and all except one were diagnosed as "malignancy". Calcifications were found in 16 patients (16/19, 84.2%) in mammographic evaluation. Histological diagnosis of squamous cell carcinoma was only achieved in 2 of 11 patients who had preoperatively fine-needle aspiration.

Twenty of 24 patients received modified or radical mastectomy. Eighteen patients received adjuvant chemotherapy (predominantly paclitaxel+anthracycline), and one patient received neoadjuvant chemotherapy. Two patients had radiotherapy, and received modified mastectomy and breast-conserving surgery, respectively. Three patients received platinum-based chemotherapy showed no local recurrence and distant metastasis during follow-up. Two patients with ER and/or PR positive tumors accepted endocrine therapy, and no recurrence and/or metastasis during the follow-up time were identified.

Histopathological features

According to the criteria of 2012 WHO Classifications of Breast Cancer, the pure type and squamous metaplastic type were 17 cases and 7 cases, respectively (**Figure 1**). In gross examination, cut surface of the tumor demonstrated grey/grey red and hard texture with indistinct margins. Five cases showed cystic degeneration and 2 cases exhibited necrosis. The average tumor size was 4.2 cm (1.2 cm to 10.0 cm). Axillalry lymph node metastasis was identified in 6 of 20 cases (30.0%). Eighteen cases (75%) were staged as II at diagnosis, followed by stage III (4 cases, 16.7%) and stage I (2 cases, 8.3%) (**Table 2**).

Molecular classification

The immunohistochemical results were shown in **Table 2**. Positive immunoreactions of ER, PR, HER2, Ki67, p53, CK5/6 and EGFR were observed in 12.5%, 8.3%, 16.7%, 91.7%, 62.5%, 91.7% and 79.2% of the cases respectively. No luminal A type case was identified in this cohort; 4 cases were classified as luminal B type (16.7%), 4 cases were HER2-overexpression type (16.7%), and 16 cases were triple-negative type, including 15 cases being basal-like type (62.5%) of breast carcinomas.

EGFR expression

The EGFR high expression was identified in 19 of the 24 cases (79.2%). Twelve of 19 cases were pure type and the remaining 7 cases were squamous metaplastic type. One squamous

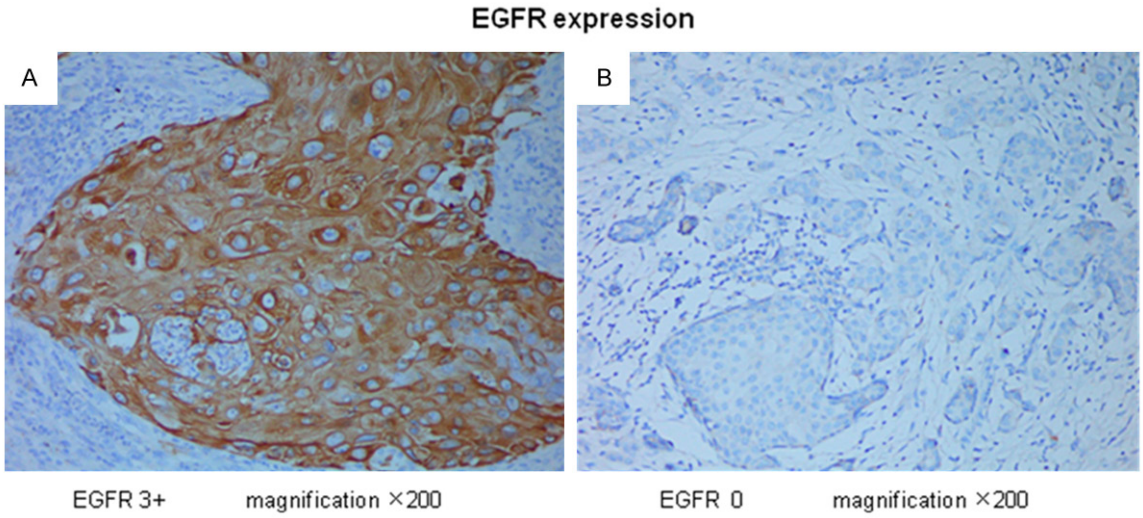

Figure 2. The immunohistochemical study revealing images of one case with squamous metaplastic type of PSCCB with different EGFR expression in different component. The EGFR expression was 3+ in the component of metaplastic squamous cell carcinoma (A), while there was no EGFR expression in the coexisting component of adenocarcinoma (B) (A and B. Original magnification ×200).

metaplastic carcinoma had varying EGFR expression in different tumor components, with diffuse overexpression (3+) in squamous cell carcinoma, while partial expression in adenocarcinoma (**Figure 2**).

Survival analysis

The postoperative follow-up time was 6-105 months with a median follow-up of 54 months, during which 1 patient was lost. An 88.8% of three-year OS and an 80.1% of three-year DFS were identified separately in this cohort of patients. Six patients had local tumor recurrence in chest wall and/or distant metastasis (bone or lung) in the follow-up period of 5-37 months, among which 4 cases were pure type and 2 cases were squamous metaplastic type. Four patients died in the follow-up period of 16-39 months. On univariate analysis (**Table 3**), lymph node metastasis (P=0.046), and advanced tumor stage at diagnosis (P=0.012) were significantly associated with reduced OS. In addition, 3 of 4 cases with HER2-overexpression manifested tumor overexpression of EGFR and CK5/6 (**Table 4**) and tumor recurrence and/or distant metastasis were identified in 2 of the 3 patients.

Discussion

PSCCB is a rare type of breast cancer, reported in 0.04%-0.075% of all invasive mammary carcinomas [12]. The tumor incidence in our study was on the upper edge of the range (0.097%). Most of patients present with lump in breast, and some may manifest with redness of the overlying skin. The tumor was clinically characterized by rapid progression and tendency to develop cyst [13]. In our study, there were 5 cases with cystic degeneration in gross examination. Compared with triple-negative invasive ductal breast carcinoma, PSCCB intends to occur in patients of older age at diagnosis, with less lymph node involvement, and frequent distant metastasis [14]. Aparicio et al [15] found the mean age of patients with pure PSCCB in Spain was 64 years. Other studies reported median ages of 52-55 years [13, 14, 16-18], similar to the findings in our cohort (median age 55). Lymph node with tumor metastasis was reported in 40.7% of patients in France [17], and 52% patients in USA [18], while a lower rate of 20% was found in Japanese patients [13] and 30% in our patients. Small case numbers in each study and geographic difference may contribute to the variation and more data accumulation is warranted.

Accurate diagnosis rate of PSCCB is less likely than that of no specific type (NST) of breast cancer by fine-needle aspiration (FNA) [19]. In our study, the diagnosis was made only in 18.2% (2/11) of the cases in preoperative FNA materials. Tumor heterogeneity is presumably the major contributing factor to the challenge.

Table 3. Univariate analysis of patient's survivals

Characteristics	*DFS*		*OS*	
	3-year DFS %	*p Value**	*3-year DFS %*	*p Value**
Age				
≤50	100		100	
>50	61.5	0.057	78.8	0.279
T stage				
≤5 cm	80.4		92.9	
>5 cm	80.0	0.405	80.0	0.648
N stage				
Negative	84.4		90.9	
Positive	80.0	0.263	100	0.046
Stage				
I	100		100	
II	81.4		92.9	
III	50.0	0.259	50.0	0.012
Histological features				
Pure type	86.2		85.1	
Squamous metaplastic type	64.3	0.416	100	0.995
ER				
Negative	83.5		93.8	
Positive	66.7	0.959	66.7	0.601
PR				
Negative	84.3		94.1	
Positive	50.0	0.563	50.0	0.273
HER2				
Negative	87.4		92.3	
Positive	50.0	0.254	75.0	0.815
Ki67				
<14%	100		100	
≥14%	79.0	0.523	88.1	0.603
P53				
<10%	100		100	
≥10%	71.1	0.065	83.9	0.160
CK5/6				
≤10%	100		100	
>10%	78.3	0.478	87.8	0.564
EGFR				
-/1+	100		100	
2+/3+	74.0	0.649	86.2	0.313
Chemotherapy				
Yes	73.2		84.4	
No	100	0.890	100	0.774
Endocrine				
Yes	100		100	
No	77.8	0.349	87.4	0.446
Operation				
Modified/Radical mastectomy	82.0		92.9	
Other	75.0	0.932	66.7	0.525

DFS, disease-free survival; OS, overall survival. *Log-rank test.

Xu et al [20] identified specific imaging features of PSCCB at preoperative Nuclear Magnetic Resonance Imaging (MRI) studies and suggested that a combination of MRI and ultrasonography evaluations, and core needle biopsies might improve the diagnostic accuracy, and might have vales in selection for surgical protocols and in choice of postoperative therapy.

Surgery is the current major step of PSCCB in patient managements that includes mastectomy (simple or modified radical), lumpectomy and breast conservation [21]. Due to the large mass of patients, modified or radical mastectomy was the primary surgical procedure in most series [14, 16], including that in our study (83.3%). Because of the low frequency of axillary lymph node metastasis, Menes et al [22] recommended sentinel node biopsy, instead of routine axillary dissection for PSCCB. Wang et al [14] found that tumor lymphatic metastasis was significantly associated with worsen 5-year OS (P=0.027) and 5-year DFS (P= 0.015). In our study, lymph node metastasis was identified in 30% of patients and its impact on the 3-year OS of patients was statistically significant.

Table 4. The clinicopathologic characteristics of 4 cases with HER2-overexpression type

Characteristics	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Age	35	64	41	56
Tumour size (cm)	7	4	4.7	6.5
LN metastasis	No	No	No	Yes
Recurrence/metastasis	No	Yes	No	Yes
Death or not	No	No	No	Yes
Stage	II	II	II	III
ER	-	-	-	-
PR	-	-	-	-
HER2	+	+	+	+
CK5/6	80%	30%	80%	90%
EGFR	-	+	+	+
Type of surgery	Modified mastectomy	Modified mastectomy	Modified mastectomy	Cytoreductivesurgery
Chemotherapy	Postoperative	Postoperative	Preoperative+Postoperative	Postoperative

ER, estrogen receptors; PR, progesterone receptors; HER2, human epidermal growth factor receptor 2; CK5/6, cytokeratin 5/6; EGFR, epidermal growth factor receptor.

Some investigators have reported that more than 80% of MBC patients received adjuvant chemotherapy [23, 24]. Wang et al [14] identified no difference in OS and DFS between platinum-based and anthracyclines-based chemotherapy in their recent study of 29 PSCCB patients. However, they did found that the platinum-based chemotherapy significantly improved OS of patients with tumor that overexpressed EGFR and CK5/6. Tsung et al [25] noted in their literature review the success of cisplatin-based regimens in managing pure PSCCB with locoregional and distant metastasis. Interestingly, 3 patients in our study who received platinum-based chemotherapy showed no local recurrence and distant metastasis during the follow-up. The average OS of these patients was 60 months, comparing with the OS of 40.9 months of patients who received other types of chemotherapy. The potential of cisplatin-base adjuvant chemotherapy deserves further studies. Furthermore, 2 patients with ER and/or PR positive tumors in our cohort accepted endocrine therapy, and no recurrence and/or metastasis at follow-up were identified. These indicate that PSCCB with special immunoprofiles may respond well to certain therapeutic protocols. Further exploration of these options is with obvious clinical significance.

The lack of efficient standard care has prompted to seek other therapeutic options, including those targeting EGFR. Bae et al [26] reported MBC had a higher frequency of EGFR overexpression in comparison to that of triple-negative infiltrating carcinoma. Others found variations in EGFR overexpression of PSCCB from 55.2% to 85% [14, 17]. In our study, its overexpression was identified in a large portion (79.2%) of tumors. Aberrant signaling through EGFR is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, and angiogenesis [27]. Patients harboring EGFR mutations showed increased sensitivity to gefitinib treatment [28]. The question is whether PSCCB patients with EGFR overexpression will benefit from EGFR tyrosine kinase inhibitor and/or EGFR monoclonal antibody (cetuximab). Further exploration of this therapeutic option is clinically meaningful.

Patients with PSCCB had higher recurrence rate, varying from 57.2% to 85.7% [13, 14], and lack of efficient treatments could be a contributing factor. In our study, the 3-year OS and DFS was 88.8% and 80.1%, respectively. Six of 24 patients developed recurrence or/and metastasis within 5-37 months of follow-up, and the most common metastatic site was bone and lung, a similar finding to another study [16].Some studies identified that the clinical tumor stage at diagnosis, lymph node metastasis and the co-expression of EGFR and CK5/6, were associated with decreased DFS and OS [14, 15]. Nayak et al [16] showed that presence of a spindle cell component comprising >10% of the tumor was statistically significant feature associated with locoregional recurrence-free survival. In our study, lymph node metastasis and high pathological stage were also identified significantly associated with worse OS of patients.

In molecular subtyping, most of the tumor in our study belonged to the basal-like group (62.5%), which is well known for decreased disease free survival, disease-specific survival, and OS of patients, in comparison to those of other intrinsic molecular subtypes of breast cancer [29]. In a recent study on a group of PSCCB cases that were negative for ER and PR expression, but with HER2 overexpression and/or HER2 gene amplification, and positive for at least two basal markers (basal-HER2 phenotype), a worse prognosis was noted in this group of patients comparing to those with typical basal-like PSCCB [30]. In our study, 3 of 4 cases with HER2-overexpression manifested tumor overexpression of EGFR and CK5/6 (**Table 4**) and tumor recurrence and/or distaht metastasis were identified in 2 of the 3 patients.

In summary, our study indicates that PSCCB is a rare group of breast cancer that presents with large tumor size, higher clinical stage and worse prognosis. Tumors with basal-HER2 phenotype seemly have particularly poor prognosis associated with frequent local recurrence and/or distant metastasis. Due to its lack of ER, PR and HER2 expression in majority of the tumors, the current treatment modalities are limited and inefficient. However, some tumor with specific profiles, such as tumors with ER and/or PR expression, may succumb to certain therapeutic regimes that are currently available. Further exploration of new therapeutic protocols, including EGFR tyrosine kinase inhibitor and/or EGFR monoclonal antibody (cetuximab), and cisplatin-based adjuvant chemotherapy, is urgently needed.

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Disclosure of conflict of interest

None.

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