Original paper

Clinicopathologic characteristics of mixed epithelial/mesenchymal metaplastic breast carcinoma (carcinosarcoma): a meta-analysis of Chinese patients

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Breast carcinosarcoma is a rare and aggressive subtype of metaplastic breast cancer. Data focusing on breast carcinosarcoma is limited. The purposes of this study are to describe the clinicopathological features of breast carcinosarcoma and to evaluate post-surgical outcomes. Material and methods: All case reports about breast carcinosarcoma in China were collected from eligible papers published in Chinese core periodicals between 1990 and 2015 with key words of breast carcinosarcoma, breast cancer, carcinosarcoma, or metaplastic carcinoma. The survival rates, clinical behaviour, and pathological characteristics were analysed. Results: The mean age of the cohort of 215 patients was 53 years (range, 25-82 years). The tumour size ranged from 2.5 cm to 18 cm. The incidence of pathologically confirmed lymph node metastases was 30.81%. The epithelial component in a tumour may be composed of invasive ductal carcinoma (84.21%), squamous cell carcinoma (7.89%), lipid-rich carcinoma (6.58%), or adenocarcinoma (1.31%). Mesenchymal components may contain different elements ranging from fibrosarcoma (63.16%) to chondrosarcoma (19.73%), osteosarcoma (9.21%), liposarcoma (3.95%), or leiomyosarcoma (3.95%). The five-year survival of the breast carcinosarcoma in 149 patients is 62.6% (CI: 54.9%~0.703%). Conclusions: Breast carcinosarcoma is a rare subtype of metaplastic breast cancer. It is characterised by large tumour size, higher rates of axillary nodal involvement, higher rates of both local and distant recurrence, and is difficult to diagnose with preoperative core needle biopsies. Adjuvant treatment after surgical operation may improve the five-year OS of patients with breast carcinosarcoma.

Key words: breast carcinosarcoma, metaplastic breast carcinoma, breast cancer, clinicopathology, CBMDISK.

Introduction

Breast carcinosarcoma, also known as metaplastic carcinoma of the breast with mesenchymal differentiation (MCMD), is an uncommon mixed tumour composed of both malignant epithelial and mesenchymal cells, with an incidence of less than 0.2% [1]. Although the exact histogenesis has not been clearly defined, MCMD has been suggested to derive from malignant transformation of myoepithelial cells or myofibroblastic metaplasia of malignant epithelial cells. Recently, MCMD has been classified by the World Health Organisation (WHO) as a subtype of metaplastic breast carcinoma (MBC) [2, 3, 4, 5, 6]. To date, because of its rarity, only relatively small series have attempted to delineate several pathological and clinical aspects that make breast carcinosarcoma different from common malignant breast cancer. For the purposes of the cur-

rent study, we analysed 215 breast carcinosarcoma patients identified through Chinese databases to describe clinical and pathologic characteristics.

Material and methods

Patients' characteristics

Studies were identified from the following electronic databases: China Biology and Medicine data disc (CBMDISK), China National Knowledge Infrastructure (CNKI), MEDLINE, and Wanfang medicine database. We conducted a comprehensive review on reported cases of breast carcinosarcoma from January 1990 to March 2015 in China. The titles and abstracts of the search findings were screened for potentially eligible studies. In order to meet the analysis requirements and reduce deviation, included studies fulfilled the following criteria: I the study was based on population samples rather than volunteers; I case collection was based on a field survey; II there were accurate study dates and validated diagnostic criteria; and III if there were many articles based on the same sample, only the one that reported the most detailed data was included. The following combination of key words was used to search the databases: breast carcinosarcoma, breast cancer, carcinosarcoma, or metaplastic carcinoma. No attempt was made to retrieve unpublished studies. The search yielded 34 articles, including 215 cases. All patients in this study underwent surgical treatment with or without adjuvant oncologic treatment. The patients' medical records were retrospectively reviewed to obtain demographic, clinicopathologic, treatment, and prognostic information as well as the immunohistochemistry of biologic factors such as ER, PR, HER2, CK, EMA, S100, and vimentin.

Statistical analysis

Descriptive statistics were used to characterise the patient population. Variables were presented as absolute numbers and percentage or median values and range. The chi-square test was used to analyse the significance of difference in the proportion of variables, and Kaplan-Meier analysis was used to assess the five-year survival. Statistical analysis was performed by SPSS 19.0 software, and the meta-analysis was conducted using Stata 12.0 statistical software. Heterogeneity was assessed with I-squared statistics. An I-squared value of more than 50% was considered to indicate high statistical heterogeneity.

Results

Figure 1 summarises the process of identifying eligible breast carcinosarcoma studies. There were 34 studies left after the quality assessment (Table I). Table II shows the characteristics of the studies, which covered the location of lesions, tumour size, and axillary lymph node metastasis. The clinical and pathological features were calculated separately for studies, and the incidence can be found.

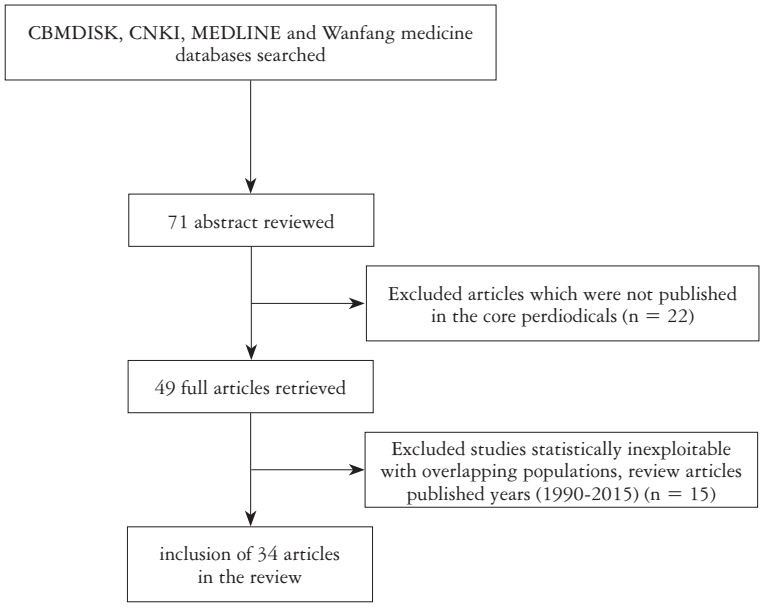

Figure 1. Flow of information through the different phases of a systematic review

Table I. The 34 breast carcinosarcoma studies included in the analysis

No.	First author	Published (Year)	Publications
1	Hongyuan Wang	2003	*China Journal of Cancer Prevention and Treatment*
2	Min Dai	2005	*Chinese Journal of Clinical and Experimental Pathology*
3	Qunli Shi	1994	*Chinese Journal of Oncology*
4	Jian Yao	1996	*Tianjin Medical Journal*
5	Yanfang Yang	2012	*Chinese Journal of Oncology*
6	Qingwen Cai	2003	*Hebei Medical Journal*
7	Shaoying Chen	2000	*Chinese Journal of Diagnostic Pathology*
8	Junming Dong	2011	*Chinese Journal of Diagnostic Pathology*
9	Qiang Feng	2003	*Chinese General Practice*
10	Binyan Fu	2000	*The Practical Journal of Cancer*
11	Mingjie Fu	2011	*Chinese Journal of Laboratory Diagnosis*
12	Zhaoyi Geng	1998	*Chinese Journal of Surgery*
13	Jianbing Hu	2006	*Chinese Journal of Diagnostic Pathology*
14	Jiangong Hu	1999	*Chinese Journal of Clinical Oncology*
15	Yufang Ji	1998	*Acta Academiae Medicinae Bengbu*
16	Qiumo Lei	2008	*Chinese Journal of Breast Disease*
17	Zhiliang Lu	2000	*China Journal of Modern Medicine*
18	Rihai Ma	2007	*The Journal of Practical Medicine*
19	Xiuyan Qi	2002	*Chinese Journal of Oncology*
20	Xia Ren	2002	*Chinese Journal of Bases and Clinics in General Surgery*
21	Xingxue Jia	2004	*Chinese Journal of Clinical Oncology*
22	Yingxu Yang	2013	*Tumor*
23	Xianghui Du	1995	*The Practical Journal of Cancer*
24	Fengping Sun	2000	*Chinese Journal of Diagnostic Pathology*
25	Hongwen Sun	2003	*Chinese Journal of Clinical Oncology*
26	Xiangde Wu	1990	*The Practical Journal of Cancer*
27	Dequan Xu	2013	*Chinese Journal of Practical Surgery*
28	Feng Xu	2004	*Chinese Journal of Radiology*
29	Xinzheng Yang	2003	*Journal of Third Military Medical University*
30	Lu Yin	2003	*Chinese Journal of Radiology*
31	Hongyan Zhang	2008	*Chinese Journal of Misdiagnostics*
32	Yi Zhang	2010	*Chinese Journal of Gerontology*
33	Yi Zhang	2009	*Chinese Journal of General Surgery*
34	Zailiang Zhang	2012	*Chinese Journal of Clinical Rational Drug Use*

Patient and tumour demographics for the cohort

The mean age of the cohort of 215 patients was 53 years (range: 25-82 years). Although male breast cancer was quite rare, three male breast carcinosarcoma cases were diagnosed in the current cohort. There were no significant differences in left or right breast or in the quadrant of the breast. The tumour size ranged from 2.5 cm to 18 cm. The incidence of pathologically confirmed lymph node metastases was 30.81% (Table II). Very few cases were at pT1 stage (15%); most of them were either pT2 or pT3.

Pathological elements of breast carcinosarcoma

Mixed epithelial/mesenchymal metaplastic carcinomas are often regarded as "matrix producing carcinomas" and show carcinoma mixed with heterologous mesenchymal elements ranging from areas

Table II. General information about breast carcinosarcoma

Clinical features	Case (n)*	% Total points
Sex, n	215	
Males	3	1.40
Females	212	98.60
Tumour size/(d/cm)	205	
≤ 5 (the smallest tumour diameter was 2.5 cm)	98	47.80
> 5 (the largest tumour diameter was 22 cm)	107	52.20
Location of lesions	121	
Bilateral	3	2.48
Unilateral (left)	63	52.07
Unilateral (right)	55	45.45
Lesions in the quadrant of the breast	100	
Lower outer quadrant	22	22.00
Upper outer quadrant	36	36.00
Lower inner quadrant	11	11.00
Upper inner quadrant	22	22.00
Quadrant uncertainty	20	20.00
Axillary lymph node metastasis	198	
No	137	69.19
Yes	61	30.81

** Statistical data accumulated from the identified articles. If the data were not included in the literature, the paper was excluded temporarily.*

Table III. The elements of the tumour in 76 patients with breast carcinosarcoma detected by pathology

Item	Case	%Total points
Carcinoma	76	
Invasive ductal carcinoma	64	84.21
Squamous cell carcinoma	6	7.89
Lipid-rich carcinoma	5	6.58
Adenocarcinoma	1	1.31
Sarcoma	76	
Fibrosarcoma	48	63.16
Chondrosarcoma of bone	15	19.73
Osteosarcoma	7	9.21
Liposarcoma	3	3.95
Leiomyosarcoma	3	3.95

of bland chondroid and osseous differentiation to frank sarcoma. When the mesenchymal component is malignant, the designation of carcinosarcoma is used. Among the 215 breast carcinosarcoma patients, 76 with available pathological and IHC data were included in our studies (Table III). The epithelial component in a tumour may be composed of invasive ductal carcinoma (84.21%), squamous cell carcinoma (7.89%), lipid-rich carcinoma (6.58%), or adenocarcinoma (1.31%). Mesenchymal components may contain different elements ranging from fibrosarcoma (63.16%) to chondrosarcoma (19.73%), osteosarcoma (9.21%), liposarcoma (3.95%), or leiomyosarcoma (3.95%).

Of these 76 patients, 11 (14.4%) were HER2+, and 28 (36.8%) were triple-negative breast cancer (TNBC) (ER– and PR– and HER2–). The result of immunohistochemistry showed that the positive rates of CK (cytokeratin), EMA (epithelial membrane antigen), ER, and PR in breast epithelial components were significantly higher than those in mesenchymal components, while the positive rates of vimentin and S100 in mesenchymal components were higher than those in epithelial components. Detailed immunohistochemistry characteristics of the studied cases are presented in Table IV.

Five-year survival of breast carcinosarcoma

Thirty-four articles were identified by the search terms, but data on five-year survival could be obtained only from two studies including 119 patients. For the rest, the following data were independently extracted from each identified study: first author,

Table IV. The positive-expression rates of EMA, CK, Vimentin,S100, ER, PR and HER-2 proteins in 76 patients with breast carcinosarcoma were detected by immunohistochemistry [N = 76, n (%)]

Item	EMA	CK	Vimentin	S100	OR	PR	HER-2
Carcinoma	66 (86.84)	69 (90.79)	17 (22.37)	19 (25.00)	18 (23.68)	19 (25.00)	11
Sarcoma	14 (18.42)	15 (19.74)	63 (82.89)	55 (72.37)	7 (9.20)	5 (6.58)	
χ^2 value	71.36	77.60	55.83	31.13	5.79	9.70	Not available
p-value	0.000**	0.000**	0.000**	0.000**	0.016**	0.002**	

EMA – epithelial membrane antigen; CK – cytokeratin; S100 – one of the calcium binding proteins; OR – oestrogen receptor; PR – progesterone receptor.

***p < 0.05, carcinoma tissue vs. sarcoma tissues.*

study period, sample size, pathology reports, and duration of follow-up. Overall, 30 patients with duration of follow-up were identified and assigned to group A. For those patients, survival curves were performed by Kaplan-Meier method. Survivals were expressed as median five-year percentages. Figure 2 shows the overall percentage survival in the 30 patients who belonged to group A. The overall five-year survival rate was 56.7% with a median survival time of 71 months.

Meta-analysis including three studies with comparative data revealed the five-year survival of the breast carcinosarcoma to be 62.6% (D + L pooled ES = 0.626; 95% CI: 0.549-0.703; p = 0.606; I^2=0.0%). Figure 3 shows meta-analysis forest plots of five-year survival of breast carcinosarcoma in 149 patients from three studies.

Owing to the lack of controlled, clinical trials, the present analysis exclusively included retrospective, uncontrolled studies. Some important details like immunohistochemistry and adjuvant treatment after surgical operation were not adequately found in the databases. Yang *et al*. reported on retrospectively collected patients with breast carcinosarcoma, who were resected from January 1995 to January 2012 [7]. Several key points were made by Yang *et al.* as follows (Table V): in univariate analysis tumour size, axillary lymph node metastasis, treatment, and clinical stage were significant factors for local relapse; the five-year OS (overall survival) rate of patients with breast carcinosarcoma, who received adjuvant treatment after surgical operation was higher than those who only received surgical operation.

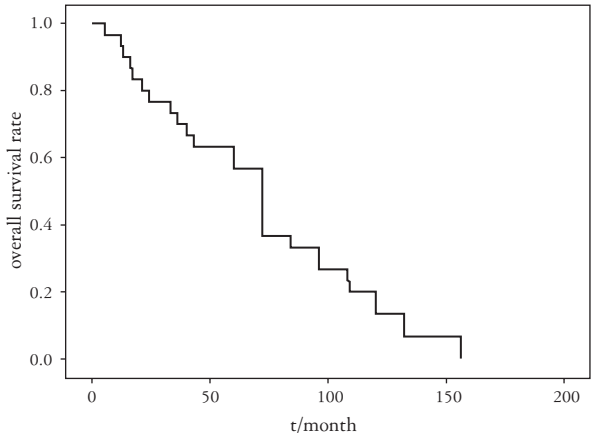

Figure 2. The overall percentage survival in the 30 patients who belonged to group A

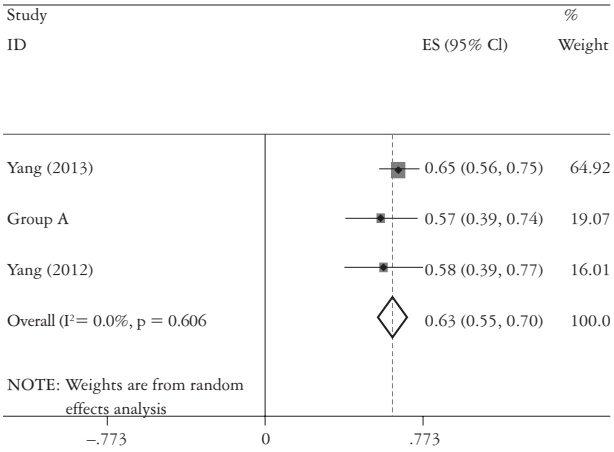

Figure 3. The forest plots of 5-year survival of the breast carcinosarcoma in 149 patients

Discussion

To our knowledge, this is to date one of the largest analyses systematically summarising the available evidence on the feature and survival of patients with breast carcinosarcoma. True carcinosarcoma of the breast is extremely rare. Since its first description by Pasternak and Wirth in 1936 as sarcomatous adenoacanthoma, these admixed breast tumours have been crowned with a plethora of names and have long been referred to as carcinosarcoma (CS) of the breast [8]. The strict definition of this tumour requires both a carcinomatous component and a malignant non-epithelial component of mesenchymal origin, without evidence of a transition zone between the two elements [9].

Classification of metaplastic carcinoma was proposed by the World Health Organisation in 2003

Table V. Univariate analysis of the prognosis in 94 patients with breast carcinosarcoma [6]

Clinicopathological parameter	case	Overall survival rate/%	p-value
		5-year	
Age/year			0.497
< 50	38	63.1	
≥ 50	56	67.0	
Tumour size/(d/cm)			0.001
≤ 5	39	97.2	
>5	55	73.6	
Axillary lymph node metastasis			0.000
No	66	78.9	
Yes	28	34.6	
Treatment			0.000
Operation	11	17.8	
Operation + radiotherapy	12	25.0	
Operation + chemotherapy	23	66.1	
Operation + radiotherapy + chemotherapy	29	85.8	
Operation + RCE	19	93.8	
Pathology			0.03
Carcinoma tissues in the majority	48	61.4	
Sarcoma tissues in the majority	46	80.7	
Clinical stage			0.000
I	15	100.0	
II	28	88.9	
III	33	61.1	
IV	18	11.1	

RCE – radiotherapy + chemotherapy + endocrine therapy. The bold values mean statistically significant p-values

as: 1) squamous cell carcinoma; 2) adenocarcinoma with spindle cell proliferation; 3) adenosquamous, including mucoepidermoid; and 4) mixed epithelial and mesenchymal. It should be noted that upon extensive sampling, a large proportion of metaplastic breast cancers display a mixture of different elements. The wide variety of mixed epithelial/mesenchymal metaplastic carcinomas, some of which are also regarded as "matrix producing carcinoma", show infiltrating carcinoma often mixed with heterologous mesenchymal elements ranging from areas of bland chondroid and osseous differentiation to frank sarcoma (chondrosarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma) [10, 11]. When the mesenchymal component is malignant, the designation of carcinosarcoma is used (Figure 4) [12]. Undifferentiated spindle cell elements may form part of the tumour. In our study, the epithelial component in a tumour may be composed of invasive ductal carcinoma (84.21%), squamous cell carcinoma (7.89%), lipid-rich carcinoma (6.58%), or adenocarcinoma (1.31%). Mesenchymal components may contain different elements ranging from fibrosarcoma (63.16%) to chondrosarcoma of bone (19.73%), osteosarcoma (9.21%), liposarcoma (3.95%), or leiomyosarcoma (3.95%).

Given the multiple histological appearances exhibited by metaplastic breast cancers, the fourth edition of the WHO Classification of Tumours of the Breast stated that a plethora of terms have been coined to refer to subgroups of metaplastic breast cancers, including carcinosarcoma, sarcomatoid carcinoma, carcinoma with pseudosarcomatous metaplasia, etc. [6]. However, the definitions of the different types of mixed metaplastic carcinomas are confusing in the fourth edition of the WHO Classification of Tumours of the Breast. It was stated that a large proportion of metaplastic breast cancers display a mixture of different elements. Different types of metaplastic carcinomas have been described arising in association with complex sclerosing lesions and papillomas [13]. Microarray-based gene-expression profiling has

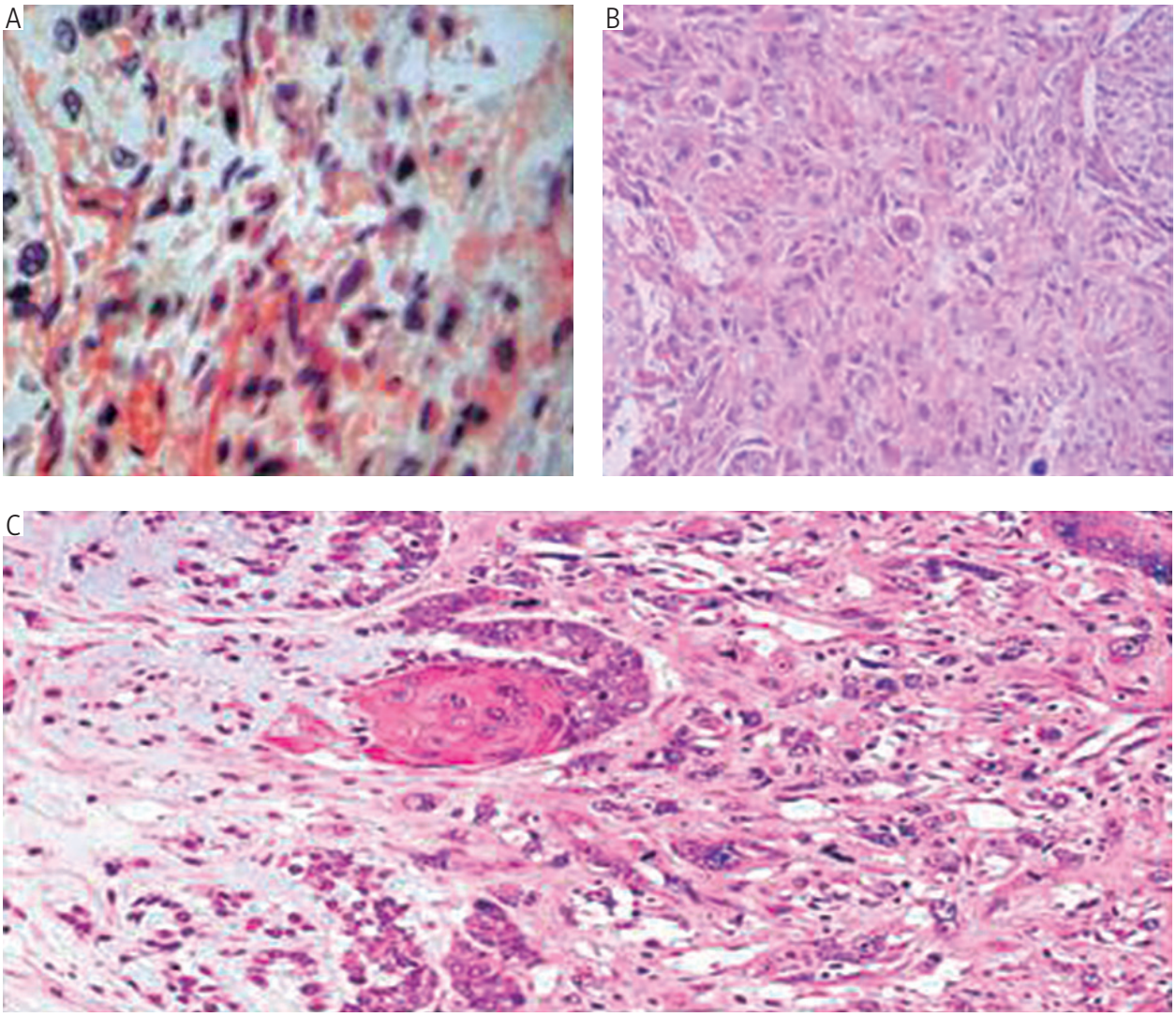

Figure 4. Mesenchymal components

demonstrated that metaplastic breast tumours are preferentially classified as of basal-like subtype [14]. However, specific genetic aberrations may be restricted to specific components within a cancer.

Mammography, sonography, and magnetic resonance mammography are frequently used breast imaging techniques in the diagnosis of breast neoplasms. However, all three techniques have unsatisfactory specificity in the diagnosis of breast carcinosarcoma [15]. Frozen section diagnosis of breast lumps is of high accuracy, with a sensitivity and specificity of more than 90 and 99%, respectively [16]. However, there may be some limitations to frozen section diagnosis because the small selected piece of tissue for frozen section diagnosis is unable to represent the overall profile of the tumour.

Lymph node invasion frequently occurs in breast carcinosarcoma. Tokudome *et al.* [17] reported a case of recurrence in a patient with breast carcinosarcoma. In their study, the recurrent tumour showed proliferation of carcinoma cell, resembling the epithelial component of the breast tumour without any sarcoma. Some studies concluded that the tissue types of recurrent breast carcinosarcoma might consist of carcinomatous or sarcomatous components or an admixture of both [18]. In our studies, the incidence of pathological confirmed lymph node metastases was 30.81%. However, the histological type of invaded lymph nodes is often complicated. It may consist of carcinomatous or sarcomatous components or an admixture of both.

The findings clearly show that five-year survival of breast carcinosarcoma is 62.6% (CI: 54.9%～0.703%). The mean age of the patients was 53 years (range, 25-82 years). Hennessy *et al.* [19] reported on 100 patients with biphasic metaplastic sarcomatoid carcinoma and 98 patients with carcinosarcoma identified through the SEER database.

The authors identified five-year overall survival at stage I, II, III, and IV as 0.73, 0.59, 0.44, and 0.00, respectively. However, data from our study showed five-year overall survival at stage I, II, III, and IV as 1.00, 0.889, 0.661, and 0.111, respectively. Adjuvant treatment after surgical operation may improve the five-year OS of patients with breast carcinosarcoma.

Expertise and evidence-based information on optimal treatment is very limited due to the low incidence and inconsistent classification. A multidisciplinary approach is required for treatment. Mastectomy was often performed with or without axillary dissection [20, 21]. Anthracycline/taxane-based chemotherapy is recommended for chemotherapy [22]. Wargotz *et al.* [8] reported that in breast carcinosarcomas, 55% of the sarcomatous component is immunoreactive for keratin and 98% for vimentin. The aggressiveness of this tumour is attributed to its high grade and negativity for oestrogen and progesterone receptors. These tumours also do not overexpress HER-2/neu oncogene, ER, and PR [23]. Jia *et al.* reported that most cases of metaplastic breast cancer did not express ER and PR (89.4%) and showed negative expression of HER-2 (78.9%) [24]. In our study, unlike others, positive-expression rates of cytokeratin and vimentin in sarcomatous tissue were 19.74% and 82.89%, respectively. Eleven patients (14.4%) were HER-2+, and 19 patients (25%) expressed ER and PR.

The prognosis of breast carcinosarcoma remains controversial. Some studies reported that, compared to patients with invasive ductal carcinoma (IDC), those with breast carcinosarcoma have a worse prognosis. Their overall survival and disease-free survival are both lower despite presenting more commonly as node-negative disease; however, almost all MCDC recurrences happened during the first five years, whereas recurrence curves for IDC continued to fall over time, suggesting the possibility that MCMD may show an earlier recurrence than IDC [25].

Because neoplastic cells often extend into the perivascular tissue and beyond the tumour capsule, local recurrence is common. Data from our study showed that the recurrence rate is around 50% (64/133) and tends to be locoregional in approximately 1/3 of the cases. Hematogenous spread is the common route of metastasis, and lung and pleura are the most common locations of distant metastasis. Accordingly, careful periodic follow-up after the initial treatment is strongly recommended to detect metastasis and recurrence early.

Despite the previous findings, this study has some limitations. The studies cannot capture every subtle factor, some of which may be critical for clinicians. In addition, other important details like immunohistochemistry and adjuvant treatment after surgical operation were not recorded enough in the databases. We did not perform a further analysis of factors that might affect survival, given that there are no demonstrated data. Moreover, out study cannot assess the gene modules associated with these basal like tumours. Owing to the lack of controlled, clinical trials, the present analysis exclusively included retrospective, uncontrolled studies with an inherent risk of bias.

Although the present study represents the most comprehensive analysis of the clinicopathological features and survival status of patients with breast carcinosarcoma, one should consider that the aggregate study population of patients was rather small and heterogenous with respect to the surgical procedures and adjuvant treatment after surgical operation. In conclusion, this is a very rare, malignant tumour, the diagnosis of which is made easier with detailed histological investigation to differentiate it from other, similar tumours. There are not enough data and standard guidelines for its optimal treatment, and information about management is based on small retrospective studies rather than randomised trials. Further research is required in order to fully evaluate the potential of such therapy in patients with carcinosarcoma of the breast.

The authors declare no conflict of interest.

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