

Gastric cancer with breast metastasis: Clinical features and prognostic factors

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Abstract. Metastatic spread of gastric carcinoma to the breast is rare. In previous decades, reports on this subject were minimal and primarily limited to case reports. At present, little is known on the clinicopathological features and prognosis of this condition, and breast metastasis remains a challenging clinical problem. A total of 54 cases of breast metastasis from gastric cancer were collected from databases between January 1960 and December 2016. The present study included 3 cases of gastric cancer with breast metastasis from Renji hospital and 51 additional cases from previous studies. The clinicopathological features of patients, including epidemiology, symptoms, macroscopic presentation, pathological diagnosis, imaging, treatment and overall survival time, were analyzed. The median survival time was 8.6 months. All but one of the patients were female, and the median age at diagnosis of breast metastasis was 43 years old (age range, 22-72 years). A majority of patients presented with Borrmann class III disease, signet ring cell carcinoma, T4 tumor types, lymph node involvement, initial stage IV gastric cancer, primary lesions in the gastric antrum, left breast metastasis and palpable breast nodules. The median interval between the primary gastric carcinoma diagnosis and presentation of breast metastasis was 1.25 months (range, 0-72 months). The expression of the estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2 and gross cystic

disease fluid protein-15 was negative in the patients with breast metastases. In univariate analysis, age, gastric tumor size, gastric lymph node involvement and breast metastasis histology were significantly associated with overall survival (OS) time ($P=0.001$, 0.039, 0.034 and <0.001 , respectively). Therapeutically, gastric surgery and chemotherapy were not associated with OS ($P=0.959$ and 0.290, respectively). In further multivariate analysis, the time between occurrence ($P=0.017$), age ($P=0.009$), histology ($P=0.045$) and breast metastasis localization ($P=0.043$) were independent indicators of OS time. Although breast metastasis from gastric cancer is rare, physicians should be vigilant when patients with a history of gastric cancer present with newly developed mammary symptoms and signs.

Introduction

Primary breast cancer is a common malignancy in females and remains the leading cause of cancer-associated mortalities among females globally despite advances in screening, diagnosis, and treatment (1); however, breast metastasis from an extramammary neoplasm is uncommon, constituting only 0.5-2.0% of all mammary malignancies (1,2). The most common origins of breast metastasis are malignant melanoma, lymphoma, lung cancer, ovarian carcinoma and soft tissue sarcoma, followed by gastrointestinal and genitourinary tumor types (3-6).

Gastric carcinoma is the third most common carcinoma in Korean females, followed by breast and thyroid carcinoma in the past decade (7). There were estimated to have been ~1,000,000 new cases of gastric cancer in 2012, making it the fifth most common malignancy and the third leading cause of cancer mortality for females and males globally (8). Common sites of distant metastasis of gastric cancer include the peritoneum, liver, lymph nodes, and lungs. The breast is a rare site of metastasis in gastric cancer (9). Metastatic tumors frequently contain similar immunohistochemical characteristics to the primary tumors, and it is important to determine whether the breast lesions are primary or metastatic from gastric cancer, in order to determine the surgical intervention required (10-17). Owing to the low frequency of the disease, only sporadic cases or a small series of cases of patients with breast metastases from gastric cancer have been published so far (18). The majority of

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the previous studies focused on clinical presentation and immunohistochemical characteristics rather than specific treatment and prognostic variables (2,19-22); therefore, little is known about the biological behavior, clinicopathological features, optimal treatment and prognosis of this condition. Thus, clinical researchers may face numerous challenges when conducting a prospective randomized case-control clinical study to compare the treatment programs and outcomes in this rare clinical entity. The previous study demonstrated that treatment strategies, including intensive multi-agent chemotherapy, surgery, radiation and targeted therapy, however, the treatment strategies to achieve complete remission or partial remission remain controversial (23). The present study included 3 cases of gastric cancer with breast metastasis from Renji Hospital (Shanghai, China) and 51 additional cases from previous studies (9,10,12,13,23-66). The primary origin, clinicopathological features, treatments and survival data were systematically collected and analyzed in order to evaluate whether these factors may serve potential roles as prognostic and predictive biomarkers of patients with gastric cancer and breast metastasis.

Materials and methods

Data collection. The inclusion criteria included: A pathological diagnosis of gastric cancer with breast metastasis; and willing to sign informed consent. The exclusion criteria included: No definite pathology; and unwilling to sign informed consent. To obtain data on studies detailing patients with gastric cancer with breast metastasis, studies in databases from between January 1960 and December 2016, including PubMed, MEDLINE, Embase, Google Scholar, Wanfang Database, China Science, Technology Periodical Database and China Journal Net, were assessed using the keywords 'gastric or stomach', 'tumor or cancer or carcinoma', 'breast or mammary' and 'metastasis'. All titles, abstracts and associated citations were scanned and reviewed. Relevant references from which these data were obtained have been included (9,10,12,13,23-66). A total of three patients diagnosed with gastric cancer and breast metastases in the Renji Hospital, from January 2003 to December 2017 were retrospectively reviewed. All patients were female with a median age of 49.00±1.73 years old (age range, 48-51 years). Of these patients, two of them were diagnosed with breast lesions 3 years following gastric cancer surgery, and one was concurrently diagnosed with gastric cancer and breast metastasis. All of the patients received chemotherapy, and one of them received surgery for breast lesions. Ethical approval was obtained from Human Clinical and Research Ethics Committees of Renji Hospital Affiliated to Shanghai Jiaotong University and written informed consent was obtained from the patients prior to the study. The following data were collected: Epidemiological, symptomatological, macroscopic presentation, pathological diagnosis, imaging performance, time between primary gastric cancer diagnosis and breast metastasis detection, treatment and prognosis.

Hematoxylin-eosin (H&E) and immunohistochemical staining. Tissue samples derived from resected and core needle biopsy specimens were fixed in 10% formalin at room temperature for 24 h, paraffin embedded and subjected to histological or immunohistochemical analysis. Sections (4 µm) were heated

at 58°C for 2 h and then deparaffinized in xylene and hydrated with a series of graded alcohols, including anhydrous ethanol for 5 min, 95% ethanol for 2 min, 90% ethanol for 2 min, 80% ethanol for 2 min and 70% ethanol for 2 min. H&E staining was used for histological analysis. Antigen recovery was performed by heating and immersing the slides in citrate buffer (0.01 M, pH 6.0; cat. no. P0020; Noble-Ryder Technology Co., Ltd., Beijing, China) in a microwave oven (121°C) for 10 min twice. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 30 min at 20°C, and the sections were incubated with anti-cytokeratin 7 (CK7; 1:50; cat. no. OV-TL12/30; Dako; Agilent Technologies, Inc., Santa Clara, CA, USA), CK20 (1:80; cat. no. M7019; Dako; Agilent Technologies, Inc.), mucin 1 (1:50; cat. no. MRQ-17; AmyJet Scientific, Inc., Wuhan, China), Ki-67 (1:100; cat. no. MIB-1; Dako; Agilent Technologies, Inc.), gross cystic disease fluid protein-15 (GCDFP-15; 1:50; cat. no. 23A3; Dako; Agilent Technologies, Inc.), mammaglobin (1:100; cat. no. TA327698, OriGene Technologies, Inc., Beijing, China), villin (1:100; cat. no. 1D2C3) and carcinoembryonic antigen (CEA; 1:100; cat. no. II-7; both Dako; Agilent Technologies, Inc.), respectively, at 4°C overnight. Subsequently, the sections were washed with PBS three times for 2 min and incubated with a biotinylated anti-mouse (cat. no. D0486) /anti-rabbit secondary antibody (cat. no. D0487; 1:500; Dako; Agilent Technologies, Inc.) at 37°C for 15 min. The signal was detected with a 3,3'-diaminobenzidine kit (Dako; Agilent Technologies, Inc.). Finally, the sections were counterstained with hematoxylin solution at room temperature for 5 min. The positive immunostaining cells were counted and imaged under a light microscope (Olympus BX43; Olympus Corporation, Tokyo, Japan) with a magnification of x100 and x400. The negative control was conducted by replacing the primary antibody with 0.1% bovine serum albumin (cat. no. BAH62-0100; AmyJet Scientific, Inc.)/PBS.

Statistical analysis. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA) and numeric parameters presented as the mean ± standard deviation. Survival data were defined as the time from breast metastasis until the date of mortality or last follow-up, and median overall survival (OS) time was estimated using the Kaplan-Meier method and the log-rank test was used for comparison of outcomes. Multivariate analysis was performed to confirm independent predictors by using a step-forward logistic regression approach for the Cox proportional hazards model, and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics of patients with primary gastric cancer. A total of 54 cases that were enrolled in the present study, 51 of which were from previous studies (9,10,12,13,23-66). The primary gastric cancer characteristics are summarized in Table I. All but one of the patients were female. A total of 30 cases were available with Borrmann classification (67) data, including Borrmann I in 3 cases (5.6%), II in 2 cases (3.7%), III in 17 cases (31.5%) and IV in 8 cases (14.8%). For the primary gastric carcinoma location, 33 cases were available for analysis. Of these cases, 9 cases (16.7%) had lesions in the gastric corpus, 19 (35.2%) in the gastric antrum,

Table I. Clinicopathological information of patients with primary gastric tumor types.

Variables	Patients, n	%	Log rank-value	Univariate P-value
Sex				
Female	53	98.1		
Male	1	1.9	2.203	0.138
Borrmann's classification				
I	3	5.6		
II	2	3.7		
III	17	31.5		
IV	8	14.8		
Unknown	24	44.4	3.067	0.381
Tumor position				
Gastric corpus	9	16.7		
Gastric antrum	19	35.2		
Gastric fundus	1	1.9		
Linitis plastica	4	7.4		
Unknown	21	38.9	7.746	0.052
Tumor size				
T1	3	5.6		
T2	3	5.6		
T3	4	7.4		
T4	14	25.9		
Unknown	30	55.6	8.342	0.039
Lymph node involvement				
Positive	19	35.2		
Negative	3	5.6		
Unknown	32	59.3	4.474	0.034
Coexisting metastasis in other organs				
Positive	24	44.4		
Negative	20	37.0		
Unknown	10	18.5	0.090	0.764
Initial stage				
I	2	3.7		
II	4	7.4		
III	6	11.1		
IV	24	44.4		
Unknown	18	33.3	4.231	0.238
Histology				
AC	1	1.9		
SIG	37	68.5		
PDA	12	22.2		
MAC	3	5.6		
Unknown	1	1.9	0.605	0.895

PDA, poorly differentiated adenocarcinoma; SIG, signet ring cell carcinoma; MAC, mucinous adenocarcinoma; AC, adenocarcinoma; T, tumor.

4 cases (7.4%) in the linitis plastica and 1 case (1.9%) in the gastric fundus (Table I).

Tumor-Node-Metastasis staging was performed according to the 2003 American Joint Committee on Cancer staging

system (68). Information on patient T staging were provided in the previous studies that were analyzed. Not all data provided was complete, hence not all patients had tumor staging data. Tumor size was available in only 24 cases; of these, 14 cases

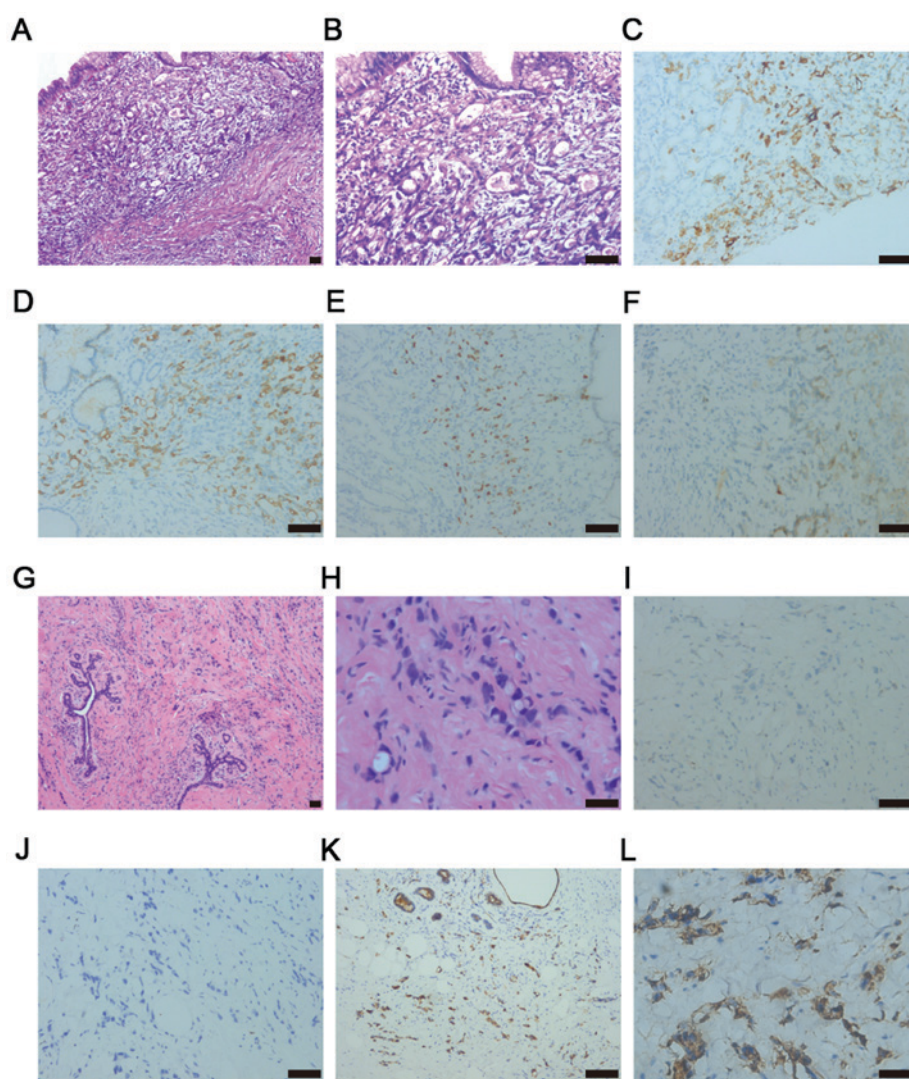


Figure 1. H&E staining and immunohistochemical analysis of one gastric cancer and breast metastasis case that was positive for CK7, CK20 and MUC-1 and 30% positive for Ki-67. Scale bar, 100 μ m. (A) H&E staining of a low-power field (x10) of gastric cancer tissue. (B) H&E staining of a high-power field of gastric cancer tissue. (C) Gastric cancer tissue positive for CK7. (D) Gastric cancer tissue positive for CK20. (E) Gastric cancer tissue that is positive for Ki-67. (F) Gastric cancer tissue positive for MUC-1. (G) H&E staining of a low-power field of metastatic breast cancer tissue. (H) H&E staining of a high-power field of metastatic breast cancer tissue. (I) Metastatic breast cancer tissue negative for gross cystic disease fluid protein-15. (J) Metastatic breast cancer tissue that is negative for mammaglobin. (K) Metastatic breast cancer tissue positive for villin. (L) Metastatic breast cancer tissue positive for carcinoembryonic antigen. H&E, hematoxylin and eosin; CK7, cytokeratin 7; CK20, cytokeratin 20; MUC-1, mucin 1, cell surface associated-1.

(25.9%) were T4 gastric cancer types, 4 cases (7.4%) were T3, 3 cases (5.6%) were T1 and 3 cases (5.6%) were T2. A statistically significant difference was identified between the different T groups ($P=0.039$). Of the 22 patients with lymph node involvement data, 19 patients presented with lymph node involvement, with a statistically significant difference between the lymph node involvement groups ($P=0.034$). In the 44 cases with data available on whether there were coexisting metastasis in other organs, 24 cases (44.4%) were positive. Of the 24 patients with coexisting metastasis in other organs, 4 had bone metastases and 14 had ovarian metastases. The remaining metastases were cutaneous (1 case), orbital metastases (1 case), liver (1 case) and other organs (3 cases) (data not shown). The most common additional metastases were ovarian (25.9%; data not shown). A total of 36 cases provided information on the initial TNM stage as follows: 2 cases (3.7%) of stage I disease; 4 cases (7.4%) of stage II; 6 cases (11.1%) of stage III and 24 cases (44.4%) of stage IV. Staging information

was unavailable for 18 patients owing to unknown tumor size, lymph node status or both (Table I).

For pathological diagnoses, 37 cases (68.5%) were identified with signet ring cell carcinoma (SIG), 12 cases (22.2%) with poorly differentiated adenocarcinoma (PDA), 3 cases (5.6%) with mucinous adenocarcinoma (MAC) and 1 case (1.9%) with adenocarcinoma (AC) (Table I). The immunohistochemistry images from one patient from Renji Hospital diagnosed with PDA and partial SIG are presented in Fig. 1A and B. This gastric cancer tumor tissue was positive for CK7, CK20 and mucin 1, cell surface associated-1 and was positive for Ki-67 (Fig. 1C-F).

Clinicopathological characteristics of breast metastasis. Clinicopathological characteristics of the breast metastases are presented in Table II. These were the same aforementioned patients with gastric cancer, but the clinical presentation data for breast lesions were available only in 52 cases (96.3%). The median age of the patients with breast metastasis diagnosis

Table II. Clinicopathological characteristics of patients with breast metastases.

Variables	Patients	%	Log rank-value	P-value
Sex				
Female	53	98.1		
Male	1	1.9	2.203	0.138
Age, years				
<45	29	53.7		
≥45	25	46.3	10.867	0.001
Median	43			
Clinical presentation				
Nodule	40	74.1		
Inflammatory	12	22.2		
Unknown	2	3.7	0.195	0.659
Localization				
Bilateral	13	24.1		
Left	26	48.1		
Right	15	27.8	4.367	0.113
Axillary lymph node involvement				
Positive	23	42.6		
Negative	21	38.9		
Unknown	10	18.5	0.626	0.429
Ultrasonography manifestation				
Nodules	19	35.2		
Skin thickening	4	7.4		
Negative	5	9.3		
Unknown	26	48.1	0.974	0.614
Time between occurrence of gastric cancer and breast metastasis				
Heterochronia	30	55.6		
Concomitant	24	44.4	0.235	0.628
Diagnostic method				
Needle biopsy of breast	32	59.3		
Surgery of breast	13	24.1		
Unknown	9	16.7	0.400	0.527
Histology				
AC	6	11.1		
SIG	42	77.8		
PDA	4	7.4		
MAC	1	1.9		
Unknown	1	1.9	58.014	<0.001
Gastric surgery				
Positive	26	48.1		
Negative	19	35.2		
Unknown	9	16.7	0.003	0.959
Chemotherapy				
Positive	32	59.3		
Negative	6	11.1		
Unknown	16	29.6	1.117	0.290

PDA, poorly differentiated adenocarcinoma; SIG, signet ring cell carcinoma; MAC, mucinous adenocarcinoma; AC, adenocarcinoma.

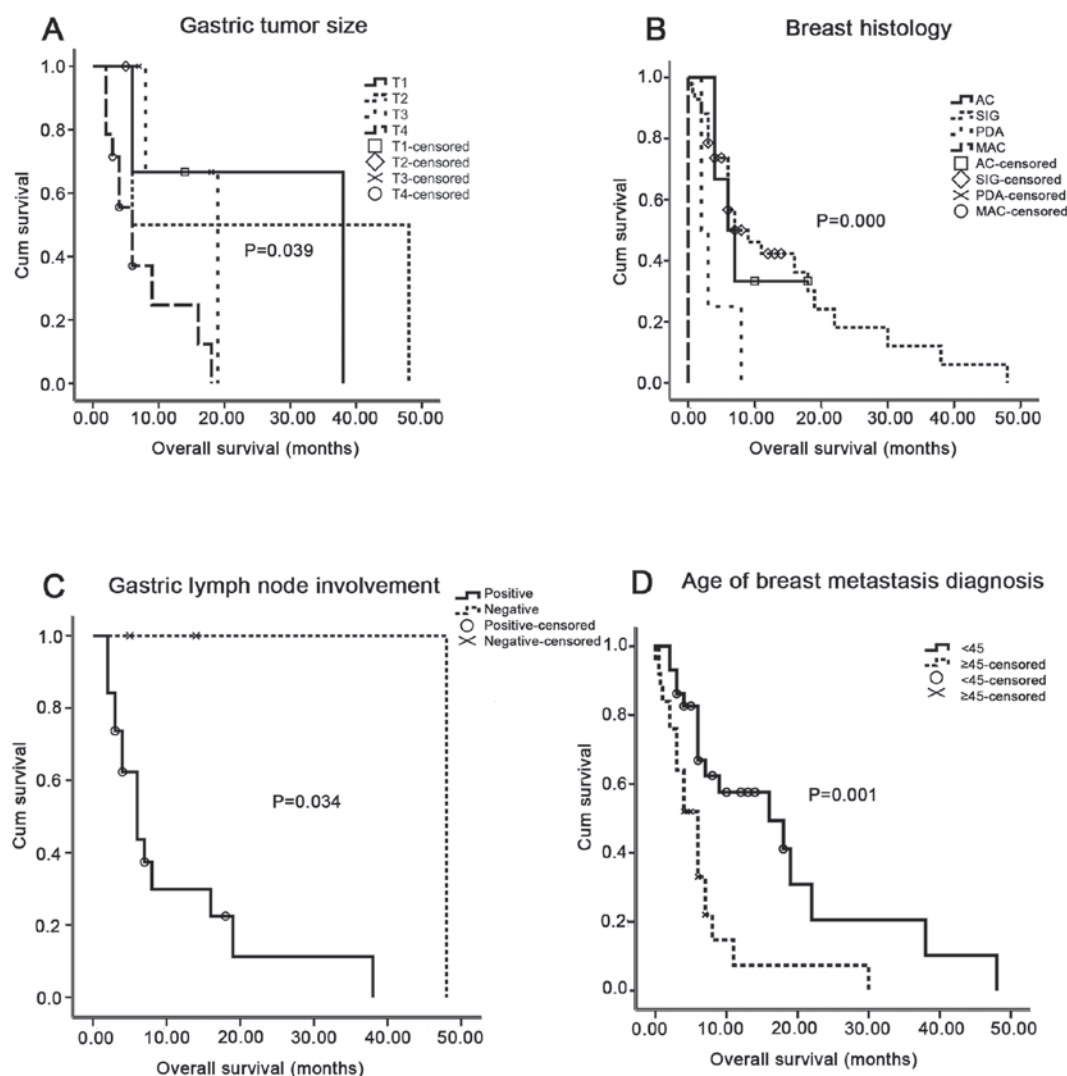


Figure 2. Association of OS time with clinic pathological factors, primary gastric tumor and breast metastasis characteristics. (A) Univariate analysis revealed that gastric tumor size was significantly associated with OS. Patients with a T4 stage tumor had the poorer survival time than those with T1-3 stage tumors. (B) Univariate analysis revealed that breast histology was significantly associated with OS. Patients with SIG had better survival time compared with patients with AC, PDA or MAC. (C) Univariate analysis revealed that gastric lymph node involvement was significantly associated with OS. Patients with gastric lymph node involvement had poorer survival time than those without involvement. (D) Univariate analysis revealed that the age at breast metastasis diagnosis was significantly associated with OS. Patients aged <45 years had better survival time than those aged ≥45 years. OS, overall survival; AC, adenocarcinoma; SIG, signet ring cell carcinoma; PDA, poorly differentiated adenocarcinoma; MAC, mucinous adenocarcinoma.

was 43 years (range, 22-72 years). A significant difference was identified between the <45 and the ≥45 year old age groups ($P=0.001$). Upon physical examination, palpable nodules and inflammatory changes in the breast were identified in 40 cases (74.1%) and 12 cases (22.2%), respectively. A total of 26 cases possessed lesions in the left breast (48.1%), 15 had lesions in the right breast (27.8%) and 13 were bilateral (24.1%). Axillary lymph node involvement data were available in 44 cases (81.5%), 23 of which were positive for nodal involvement (42.6%). Data from ultrasonic manifestation of breast metastasis were available for 28 cases (51.9%), with nodules (19 cases; 35.2%) being the most common manifestation (Table II). However, there was no significant difference identified for any of these factors.

The median interval between primary diagnosis and metastatic presentation was 1.25 months (range, 0-72 months). Breast metastasis and gastric cancer were diagnosed simultaneously in 24 cases (44.4%). Needle biopsy was performed for breast metastasis diagnosis in 32 cases (59.3%) and surgery

was performed in 13 cases (24.1%). For breast histological diagnosis, 42 cases (77.8%) were identified as SIG, 6 cases (11.1%) as AC, 4 cases (7.4%) as PDA and 1 case (1.9%) as MAC, with a significant difference identified between these groups ($P<0.001$). (Table II) Notably, 10 cases differed in their pathology between the primary gastric cancer and breast metastasis.

Estrogen receptor (ER) expression data were available in 28 cases, progesterone receptor (PR) in 25 cases, human epidermal growth factor receptor-2 (Her-2) in 15 cases and GCDPF15 in 11 cases; all cases presented negative results. The result of one patient is presented in Fig. 1G-H. Three years later, this patient with metastatic breast cancer was diagnosed with primary gastric cancer and was positive for CEA and villin, and negative for mamaglobin (Fig. 1I-L).

Information on surgical treatment was available for 45 cases, of which 26 (48.1%) received gastric surgery, whilst

Table III. Multivariate analysis of prognostic factors for overall survival time in patients with breast metastases.

Variables	P-value	HR	95% CI
Age at breast metastasis diagnosis	0.009	1.061	1.015-1.110
Gastric histology	0.351	1.561	0.613-3.978
Breast histology	0.045	3.662	1.029-13.036
Clinical presentation	0.819	1.129	0.398-3.208
Localization of breast metastasis	0.043	2.200	1.025-4.723
Axillary lymph node involvement	0.617	0.779	0.293-2.071
Time to occurrence of the breast metastasis	0.017	0.960	0.929-0.993
Gastric surgery	0.051	3.283	0.996-10.823

P-values from multivariate analysis were calculated using Cox proportional hazards regression analysis. HR, hazard ratios; CI, confidence interval.

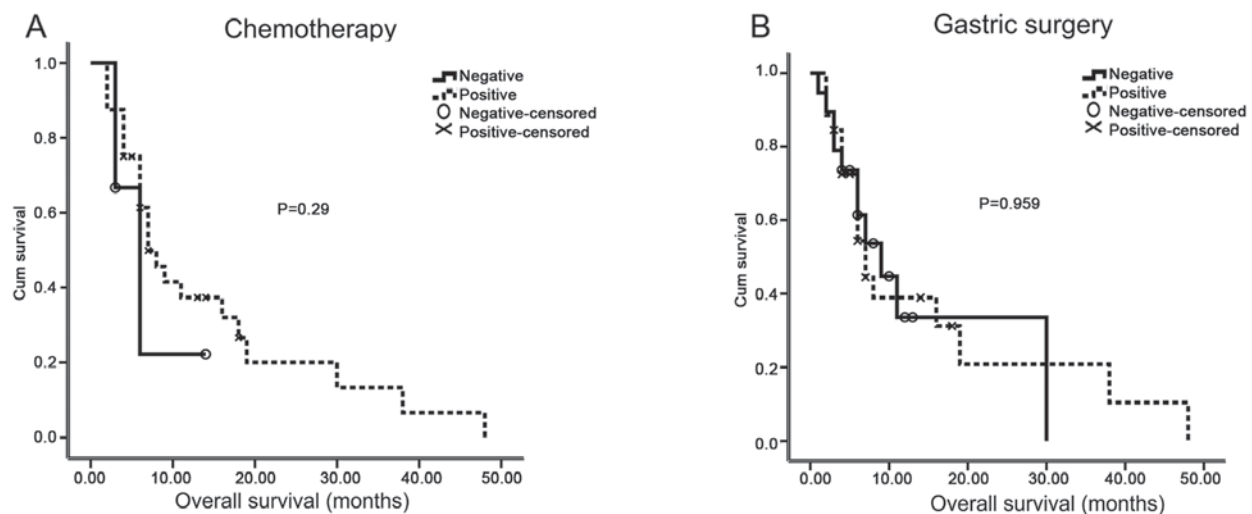


Figure 3. OS time in association with the type of therapy for patients with gastric cancer with breast metastasis. (A) Univariate analysis revealed that chemotherapy was unassociated with the OS of patients with breast metastasis. (B) Univariate analysis revealed that gastric surgery was unassociated with the OS of patients with breast metastasis. OS, overall survival.

the other 19 (35.2%) did not. A total of 32 cases received chemotherapy (59.3%), 6 cases did not, and 16 cases provided incomplete data (Table II).

Survival. Data were available for 54 patients. The median survival time was 8.6 months (range, 0-48 months). Univariate analysis of the association among OS time, clinicopathological factors, primary gastric tumor and breast metastasis characteristics was performed, and gastric tumor size, gastric lymph node involvement, age at breast metastasis diagnosis and breast histology were all significantly associated with OS time ($P=0.039$, 0.034 , 0.001 and <0.001 , respectively; Fig. 2). However, survival analysis revealed that sex, Borrmann's classification, co-existing metastases in other organs, initial stage, tumor position and primary gastric cancer histology were not associated with OS time ($P=0.138$, 0.381 , 0.764 , 0.238 , 0.052 and 0.895 , respectively; Table I). At first, the association between the number of breast metastases and the OS time was analyzed using univariate analysis, and a significant association was identified ($P<0.05$) (69). Clinical presentation, localization of the breast metastasis, axillary

lymph node involvement, ultrasonography performance, diagnostic method and time from occurrence of breast metastasis were also not associated with OS time ($P=0.659$, 0.113 , 0.429 , 0.614 , 0.527 and 0.628 , respectively; Table II). In addition, gastric surgery and chemotherapy were not associated with breast metastasis patient overall survival ($P=0.959$, 0.290 , respectively; Table II; Fig. 3). From further multivariate analysis, the time to occurrence ($P=0.017$), age ($P=0.009$), histology ($P=0.045$) and breast metastasis localization ($P=0.043$) were significant independent OS time indicators (Table III).

Discussion

The estimated rate of occurrence of non-primary breast malignancy reported in literature varies from 0.5-1.3% in clinical observation to 1.7-6.6% in autopsy series (70,71). In the present study, all but one of the patients were female, and their median age was 43 years. In previous reports, the median age at diagnosis of patients with gastric cancer with breast metastasis was 46 years (9), and for patients with primary breast cancer was

61 years in the USA and 56.99 years in Japan (72,73). Breast metastases originating from gastric carcinoma tend to occur at younger ages than primary breast carcinomas (9). In the present study, the age was defined as the age at the diagnosis of breast metastasis. In univariate and multivariate analyses, patients aged <45 years had longer survival times than those ≥ 45 years ($P=0.001$ and $P=0.009$, respectively). Thus, an age at diagnosis of breast metastasis of <45 years appears to be a positive prognostic factor. Breast metastasis from gastric cancer is rare, and the mechanism is not yet clear. The present study analyzed the results of current clinical observations. In one previous study, the majority of patients were at a higher stage (above AJCC stage III) and Borrmann IV type (4). In the present study, stage IV and Borrmann III types were the most common. In univariate analysis, patients with T4 or those with gastric lymph node involvement presented with the poorest cumulative survival rates of all patients ($P<0.05$), as these gastric cancer types are usually invasive. However, insufficient data were available for gastric tumor size and lymph node involvement; thus, these factors were not included in the multivariate analysis.

Breast metastasis symptoms are unspecific in terms of breast nodules, swelling, tenderness and pain compared with the symptoms of primary breast cancer (10). In the present study, nodules (74.1%) were a more common clinical symptom than inflammation (22.2%), and axillary lymph node involvement was also common. Ultrasound results including skin thickening and breast nodules, indistinguishable from those of primary breast cancer, were unassociated with OS time ($P>0.05$); thus, it suggests that it is difficult to diagnose metastatic breast cancer by clinical presentation or diagnostic imaging. Breast metastases were most common on the left side, consistent with the results of a previous study (13). This laterality may indicate the potential presence of another lymphatic pathway or preponderance to the breast from other organs including the left supraclavicular lymph node metastasis from gastric carcinoma. In multivariate analysis, breast metastasis localization was a significant prognostic factor of OS time ($P=0.043$).

Biopsy and surgery on the breast masses were generally performed for diagnosis. Needle biopsies of the breast, including core needle biopsy or fine needle aspiration, may differentiate between primary and metastatic breast tumor types (74,75). In the present study, a needle biopsy was used for 59.3% of the patients, providing a quick and accurate diagnosis, thus avoiding an unnecessary mastectomy. Immunohistochemistry was the primary method for identifying the tumor origin (32,34). Of all the patients in a previous study, ~77.8% presented with breast SIG, and 68.5% of patients presented with gastric SIG, which accounted for ~10% of the gastric cases (11). In previous studies, SIG of the stomach was often observed in younger women (aged <40 years), and SIG of the primary breast was rare (43,44,48,68). Differing histology of breast metastases was associated with OS time in univariate ($P<0.001$) and multivariate analyses ($P=0.045$) in the present study. In one reported case, immunohistochemical staining for breast metastasis from gastric cancer was negative for ER, PR, erb-B2 receptor tyrosine kinase 2 and GCDPF15 but positive for CEA, CK7 and CK20 (24). This phenomenon was also observed in the present study. It was identified that that breast tumors were metastatic from gastric carcinoma using immunohistochemistry. However, chemokines

or chemokine receptors associated with breast metastases in gastric carcinoma were not identified in the present study; this should be investigated further.

In the metastatic process, mammary involvement may either be the first step or there may be a polymetastatic context (63). In the present study, 44.4% of patients suffered from concurrent metastasis at the time of breast metastasis, and 44.4% of patients presented with gastric cancer and synchronous breast metastases. The median interval between diagnosis of the primary disease and identification of the metastatic lesion was only 1.25 months. This result indicated that gastric carcinoma with breast metastasis progresses rapidly and that the potential of metastasis from gastric carcinoma is high, even in patients with no history of gastric cancer. The time to occurrence of breast metastasis was a significant independent OS time indicator in the multivariate analysis ($P=0.017$). In the present study, the overall prognosis of patients with breast metastasis from gastric carcinoma was generally poor; the median survival time was only 8.6 months. For clinical treatment, careful attention is required, particularly when a breast lesion is the first manifestation of an unknown primary malignancy. Unexpectedly, surgical intervention and chemotherapy were not associated with the survival of patients with breast metastases in the present study. However, previous advances in the development of anticancer agents, including trastuzumab and apatinib, have improved the prognosis of patients with unresectable advanced or recurrent gastric cancer (1,24). Although there are no current clinical case reports to confirm this, to the best of our knowledge, these novel drugs may be effective in treating this rare disease.

A number of limitations should be noted regarding the retrospective design and long time span of the present study. Furthermore, with a few exceptions, certain information concerning the primary tumor and prognosis was unavailable, despite this being a large study concerning this disease. Nevertheless, the present study may shed light on the different factors that contribute to the improved survival rates of patients with this disease and provide impetus for future research on gastric cancer with breast metastasis.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

All authors read and approved the final manuscript. YX, YM and WL participated in selecting cases and the writing of the manuscript. HW designed and supervised the project. YX and JL collected the clinical details of the patients and carried out statistical analysis.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Renji Hospital Affiliated to Shanghai Jiaotong University and written informed consent was obtained from all patients.

Patient consent for publication

All patients signed written informed consent for the publication.

Competing interests

The authors declare that they have no competing interests.

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