



## Breast Carcinosarcomas

Savaş Yakan<sup>1</sup>, Erdem Sarı<sup>1</sup>, Nazif Erkan<sup>1</sup>, Mehmet Yıldırım<sup>1</sup>, Enver Vardar<sup>2</sup>, Ali Coşkun<sup>1</sup>, Durmuş Ali Çetin<sup>1</sup>, Nükhet Eliyatkin<sup>2</sup>

<sup>1</sup>Department of General Surgery, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

<sup>2</sup>Department of Pathology, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

### ABSTRACT

**Objective:** Carcinosarcomas of the breast are rare and aggressive breast tumors. The optimal treatment strategies and the classification of these difficult to diagnose tumors are not clear in the literature due to their very low incidence. In this study, we aimed to evaluate patients who were operated on for breast carcinosarcoma and discuss the current literature.

**Materials and Methods:** Ten patients who were treated with a diagnosis of breast carcinosarcoma between January 2000 - March 2013 at the İzmir Bozyaka Teaching and Training Hospital General Surgery Clinics were retrospectively analyzed.

**Results:** The mean age of the patients was 59.7 ( $\pm 13.4$ ) years. Eight patients underwent modified radical mastectomy, one patient lumpectomy and one patient breast conserving surgery + sentinel lymph node biopsy procedures. The TNM stage of patients were identified as stage 1 in 2 patients, stage 2 in 6 patients, and stage 3 in 2 patients. 60-month disease-free survival rate was 52.5% ( $\pm 18.6$ ). The overall survival rate was 53.3% ( $\pm 20.5$ ). Four patients died during follow-up.

**Conclusion:** It is reported that the prognosis of carcinosarcomas are as poor as triple negative epithelial tumors. In contrast to the literature, in our study the disease-free and overall survival rates according to stage were not different from epithelial tumors. In this regard, prospective studies including more patients are required.

**Key words:** Breast, carcinosarcoma, metaplasia

### Introduction

Metaplastic carcinomas of the breast are heterogeneous neoplasms that contain both malignant epithelial and mesenchymal components. Wargotz et al. divided metaplastic carcinomas into 5 groups (carcinosarcoma, matrix-producing carcinoma, spindle-cell carcinoma, squamous cell carcinoma and osteoclastic giant cell carcinoma) (1). If the mesenchymal component accompanying the tumor is malignant, it is defined as carcinosarcoma. The incidence of carcinosarcoma constitutes 0.2% of all breast cancers (2). The age of diagnosis ranges from 32 to 77 years in the literature (3, 4). These tumors are thought to originate from malignant myofibroblasts or metaplastic differentiation of malignant epithelial cells within myofibroblasts (5). It has been reported that breast carcinosarcomas have a poor prognosis and a high risk of local-regional recurrence (6). These tumors usually do not express estrogen or progesterone receptors and HER-2/neu oncogene. This triple-negative phenotype is stated to cause them to behave more aggressively (7).

The rarity of these tumors, the non-specific symptoms, the pathologic and morphologic variability, and controversial oncologic treatment protocols cause the surgeons, radiologists, and pathologists to experience more difficulties in the diagnosis, classification, and treatment strategies.

In this study, our aim was to evaluate patients who were treated for breast carcinosarcoma and discuss the current literature.

### Materials and Methods

Ten patients who were treated with a diagnosis of breast carcinosarcoma between January 2000 - March 2013 at the İzmir Bozyaka Teaching and Training Hospital General Surgery Clinics were retrospectively analyzed. Information regarding demographic characteristics of the patient, type of surgery, tumor size, axillary involvement, tumor stage and adjuvant therapy were obtained using the hospital database. Disease-free survival and overall survival data were obtained both from the database and from contact with the patients or their relatives through their registered phone number. Kaplan-Meier test was used for survival analysis. 36-month and 60-month disease-free survival and overall survival rates were calculated.

#### Address for Correspondence:

Erdem Sarı, Department of General Surgery, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey  
Phone: +90 506 882 13 14 e-mail: doktorerdemsari@gmail.com

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All patients received a breast ultrasonography (USG) and mammography (MMG). Magnetic resonance imaging (MRI) was not used as part of preoperative evaluation. All patients were informed on fine-needle aspiration biopsy (FNA) and core biopsy options to provide pathological diagnosis prior to surgery. However, none of our patients accepted a biopsy. Therefore, frozen section examination of the tissues during surgery was planned. Surgical treatment options were explained to the patients. Informed consent was obtained from all patients before the operation. Frozen section examination revealed malignancy in all patients, however the definitive histopathological diagnosis could only be established after paraffin evaluation. In patients who underwent modified radical mastectomy (MRM), tumor size, breast-tumor size ratio and patient preferences were taken into consideration. One patient with a tumor size below 5 cm only consented to lumpectomy and did not accept axillary dissection despite the described risks.

**Statistical Analysis**

Statistical Analysis was done using SPSS 15,0 for Windows statistical package program. Overall survival rate and disease-free survival rates are analysed by using Kaplan-Meier method.

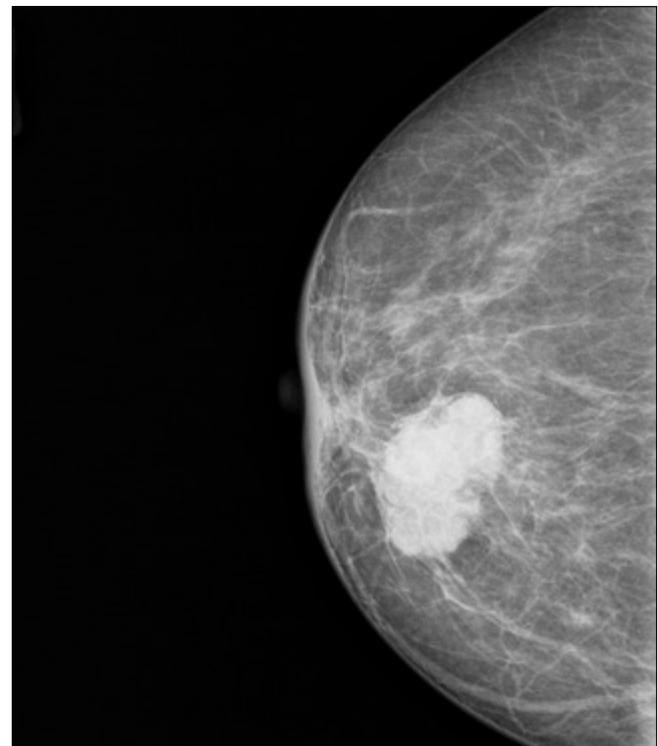
**Results**

2100 patients were diagnosed with breast cancer between January 2000 - March 2013 at the Izmir Bozyaka Training and Research Hospital General Surgery Clinics. Ten (0.47%) of were diagnosed histopathologically as carcinosarcoma and all were female. Mean age was 59.7 ( $\pm 13.4$ ) years, 2 patients were premenopausal and 8 were postmenopausal. The preoperative breast imaging revealed BIRADS 4 lesions in 6, and BIRADS 3 lesions in 4 patients (Figure 1). The mean tumor size was 4.8 cm (2.1- 7.2) according to USG and MMG. The tumor size was greater than 5 cm in 6 patients, and these patients underwent MRM. Although the tumor size below 5 cm (4.2 cm and 4.3 cm) in 2 patients, they received MRM due to the small breast volume, presence of palpable axillary lymph nodes, and patient preference. However, in these patients, axillary nodal metastasis was not detected in histopathological examination. From the patients with a tumor size of less than 5 cm, 1 patient had lumpectomy and 1 patient underwent breast conserving surgery (BCS) + sentinel lymph node biopsy (SLNB) procedures. In the patients with SLNB, sentinel lymph node metastasis was not detected therefore an axillary lymph node dissection was not performed. The pathological stages were identified as T1 in 2 patients, T2 in 2 patients and T3 in 6 patients (carcinosarcoma) (Figure 2).

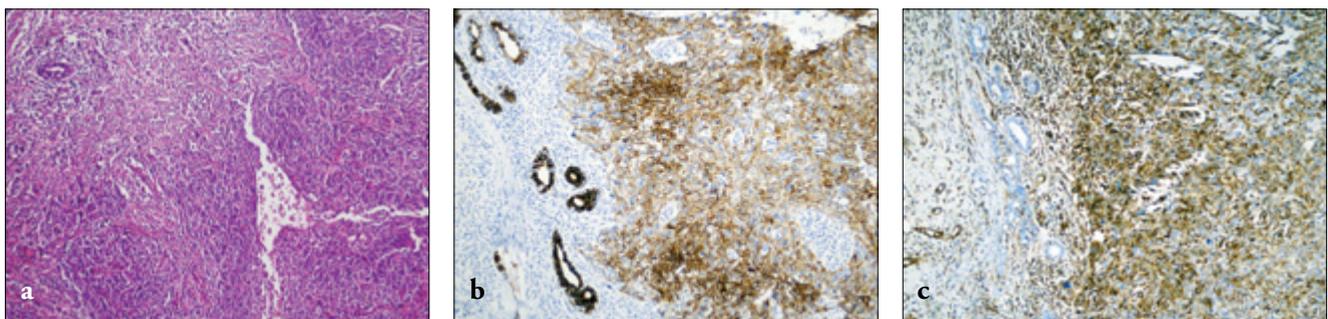
Axillary lymph node involvement was detected in 2 patients (20%) showed (1 patient:N1, 1 patient:N2). In eight patients, the axilla were negative. The TNM stage of patients were identified as stage 1 in 2 pa-

tients, stage 2 in 6 patients, and stage 3 in 2 patients. Considering receptor status: 3 patients were ER (+) (30%), and 7 were ER (-), and 1 patient was PR (+) (10%), and 9 patients were PR (-). C-erb2 was positive in 2 patients (20%). Triple-negative phenotype was detected in 5 patients (50%). 8 patients received adjuvant treatment. 8 patients had chemotherapy, 1 had radiotherapy, and 3 received hormonal therapy. FAC (5-fluorouracil, adriamycin, cyclophosphamide), and FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimens were used in chemotherapy patients. A synthetic anti-estrogen drug, tamoxifen was used in hormonal therapy. Herceptin (trastuzumab) was added to treatment in a patient with C-erb2 positivity. One patient who had a T1 tumor was recommended follow-up. The other patient who received lumpectomy with a T1 tumor, denied any surgical or adjuvant treatments directed to axillary involvement, and was followed-up (Table 1).

One patient who had completed her adjuvant chemotherapy in our hospital was lost to follow-up after 12 months (Table 1). The 36-month disease-free survival rate and the overall survival rate was determined as 52.5% ( $\pm 18.6$ ) and 71.1% ( $\pm 18$ ), respectively. 60-month disease-free



**Figure 1.** Mammographic view of the patient with pathologic T3 tumor (carcinosarcoma)



**Figure 2. a-c.** Small ducts and prominent lymphocyte in its periphery at the left upper field and tumor cells showing nodular pattern and layering containing lymphocytes at the other fields. (HE-x100) (a). On the left normal small ducts and adjacent cytokeratin positive tumor cells. (Pancytokeratin-x100) (b). Diffuse vimentin positivity in tumor cells within the fields with pancyctokreatin positivity (Vimentin-x100) (c)

Table 1. Demographic, surgical, pathologic properties of the patients and follow-up

	Age	Operation	T	N	Stage	ER (+/-)	PR (+/-)	Cerb2 (+/-)	Adj CT	Adj RT	Adj HT	Disease free survival (months)	Overall survival (months)
1	64	MRM	T1	N0	1	+	+	-	-	-	-	156	168
2	46	MRM	T3	N1	3	+	-	-	+	-	+	12	36 Exitus
3	54	MRM	T3	N0	2	+	-	-	+	-	+	24	48 Exitus
4*	83	Lumpectomy	T1	-	1	-	-	+	-	-	-	19	19
5	75	MRM	T3	N2	3	-	-	-	+	-	-	16	16
6	67	BCS+ SLNB	T2	N0	2	-	-	-	+	+	-	16	16
7	53	MRM	T3	N0	2	-	-	-	+	-	-	7	10 Exitus
8	46	MRM	T2	N0	2	-	-	+	+	-	+	96	108
9	66	MRM	T3	N0	2	-	-	-	+	-	-	12	Lost to follow-up
10	43	MRM	T3	N0	2	-	-	-	+	-	-	72	84 Exitus

MRM: Modified radical mastectomy; BCS: Breast conserving surgery; SLNB: Sentinel lymph node biopsy; ER: Estrogen receptor; PR: Progesterone receptor; Adj. CT: Adjuvant Chemotherapy; Adj. RT: Adjuvant Radiotherapy; Adj. HT: Adjuvant Hormonotherapy

\*The patient who refused axillary surgery and adjuvant treatment

survival rate was calculated as 52.5% ( $\pm 18.6$ ) and the overall survival rate in our study group was 53.3% ( $\pm 20.5$ ) (Table 2).

There was no local recurrence during follow-up in our study. 2 patients died with brain metastases, and two due to complications related to lung metastasis.

## Discussion and Conclusion

Carcinosarcomas can be detected in many different organs in the body including the breast, thyroid, lung, colon, esophagus, pancreas, prostate, ovary and uterus (8,9). These tumors are accepted as a variant of metaplastic carcinoma that arises from myo-epithelial cells (5). However, there are case reports on breast carcinosarcomas arising from fibroadenomas and phyllodes tumors in the literature (10). Primary sarcomas of the breast are rare and constitute 0.6-1.2 % of all breast carcinomas (11).

Clinically, carcinosarcoma of the breast is an aggressive type of breast cancer. The clinical diagnosis of these tumors is challenging. They usually present with a large, painful mass in the breast (12). Rarely, nipple discharge, nipple retraction and skin ulcerations may be observed (13). Depending on the lymphatic involvement of the disease, axillary lymphadenopathy may accompany. Breast imaging techniques (USG, MMG, MRI) are insufficient for a definitive diagnosis in these patients (14). These tumors are detected in the form of a heterogeneous mass containing cystic components on USG (15). They usually appear as well-defined, lobulated contoured and high-density masses on MMG, however they might also be seen in the form of spicules (15). They usually appear iso-hypointense on T1 MRI, due to glandular tissue. On T2-weighted images, they often reveal a hyperintense lesion, depending on the mucoid content and necrotic components of these tumors (16). USG and MMG were used as preoperative imaging methods in our series. BIRADS 4 lesions were detected in 6, and BIRADS 3 lesions in 4 patients. The mean tumor size was 4.8 cm (2.1- 7.2).

Table 2. Disease free and overall survival rates

	36 months (%)	60 months (%)
DFS	52.5 $\pm$ 18.6	52.5 $\pm$ 18.6
OS	71.1 $\pm$ 18	53.3 $\pm$ 20.5

DFS: Disease free survival; OS: Overall survival

Fine-needle aspiration biopsy does not provide an accurate diagnosis in these patients. Frozen section examination has high sensitivity (90%) and specificity (99%) rates in breast masses (17, 18). However, in some cases with breast carcinosarcoma, a small piece of the tumor sent for frozen section examination may not be sufficient to reveal the overall profile of the tumor (19). The correct diagnosis of metaplastic carcinoma of the breast can only be achieved by a diligent histological evaluation of the core biopsy or mastectomy specimens. Differential diagnosis includes spindle cell carcinoma, malignant phyllodes tumor and stromal sarcoma. Detection of epithelial and stromal component antigens such as epithelial membrane antigen (EMA), actin, keratin, vimentin, etc. by immunohistochemistry helps in the diagnosis (20). Carcinosarcomas are characterized as aggressive tumors, due to their estrogen and progesterone receptor negativity. They also do not express HER-2/neu (21). None of the patients in this series received fine-needle aspiration biopsy (FNA) or core biopsy. The reason for not performing a biopsy was either refusal of treatment or high level of clinical suspicion. 30% of our patients were ER (+), and 10% were PR (+). Cerb2 positivity was detected in 20%.

Breast carcinosarcomas are aggressive and treatment resistant tumors, similar to poorly differentiated and receptor-negative breast tumors (22).

They metastasize through both the bloodstream and lymphatics. The incidence of lymphatic metastases, in accordance with the sarcomatous phenotype, is lower than infiltrating ductal carcinoma (23). Two of our patients developed brain metastases, and 2 developed multiple lung metastases during follow-up. These patients died due to complications related to metastasis. The rate of axillary lymph node metastases in our study was determined as 20%, similar to the literature.

Due to the very low incidence of these tumors, the literature data is not sufficient regarding its classification and optimal treatment strategies. The treatment is usually based on the NCCN guidelines that are used for patients with invasive breast cancer. Treatment protocols in the literature are combinations of mastectomy with or without axillary dissection and various postoperative chemo-radiotherapy. Due to the large tumor size at diagnosis, breast-conserving surgery is usually not preferred (24-26). We performed MRM in 80% of the patients in our series.

It is reported that despite the low rate of axillary lymph node involvement, distant metastasis are more frequent in metaplastic carcinomas (27-29). Wargotz and Norris have reported lymph node involvement as 26% (30). On the other hand, Oberman (31) stated that prognosis of metaplastic carcinomas was not associated with axillary lymph node metastases. 80% of our patients underwent axillary dissection and axillary lymph node involvement was detected in 20%.

There is insufficient data regarding the use of neoadjuvant chemotherapy in metaplastic carcinomas in the literature (26). Hennessy et al (22) reported that patients with breast carcinosarcoma do not benefit enough from ordinary breast cancer chemotherapy.

Bae et al. have reported that chemotherapy had no survival benefit in 42 of 47 patients with metaplastic carcinoma (32). However, Gutman et al (2) determined a positive impact of adjuvant chemotherapy in patients with stage-1 and stage-2 on survival. 80% of the patients in our study received adjuvant chemotherapy.

Post-mastectomy radiotherapy is recommended for patients with four or more axillary lymph node metastases, with a tumor size of 5 cm or more, and in the presence of chest wall invasion (33-35). It has been reported that patients who underwent mastectomy, with a tumor size of less than 5cm and axillary lymph node involvement of fewer than four nodes, do not benefit from radiotherapy (20). None of the patients in our study had chest wall invasion. Only one of the patients (treated by BCS) underwent radiotherapy.

In parallel to the aggressiveness of carcinosarcomas, recurrence of the primary tumor can develop rapidly. Therefore, close follow-up is required after resection. Patients should be considered for routine screening in terms of metastases. Lung metastases, brain, bone and liver metastases are more frequent and the prognosis of these patients is worse (6). Tumor size, high nuclear grade, triple negative disease, lymphovascular invasion and distant metastasis are poor prognostic factors (20, 21, 24). The 5-year survival rate for metaplastic carcinomas is about 65% (36).

Beatty et al (13) have determined the 5-year survival rate for breast carcinosarcoma as 49-68%. In another study, the 5-year survival rates for stage 1, 2, 3 and 4 were reported as 73%, 59%, 44% and 0%, respectively (37). In our series, the 36-month disease-free survival rate was 52.5% ( $\pm 18.6$ ), and the overall survival rate was 71.1% ( $\pm 18$ ). The 60-month disease-free survival rate of our patients was determined as 52.5% ( $\pm 18.6$ ), and the overall survival rate as 53.3% ( $\pm 20.5$ ) (Table 2).

Four patients died during follow-up. These results are consistent with the literature.

With the advances in molecular biology, targeted drugs are being introduced to clinical practice. The detection of EGFR (epidermal growth factor receptor) positivity in 14 of 20 patients with metaplastic carcinoma revealed the importance of developing strategies targeting these receptors (38). With the development of drugs such as gefitinib and cetuximab that target EGFR receptors, new treatment options will be available.

Carcinosarcomas are being treated in a similar manner to epithelial tumors, despite belonging to a different pathologic group. Although the prognosis of carcinosarcomas are reported to be as poor as triple negative breast cancers, in contrast to previous reports the disease free and overall survival rates in our study were similar to those of epithelial tumors. Prospective studies including more patients are required.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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