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Metaplastic Breast Carcinoma Versus Triple-Negative Breast Cancer

Survival and Response to Treatment

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Abstract: Metaplastic breast carcinoma (MBC) differs from classic invasive ductal carcinomas regarding incidence, pathogenesis, and prognosis. The purpose of this study was to compare patients with MBC with clinicopathologic and treatment-matched patients with triple-negative breast carcinoma (TNBC) in terms of response to treatment, progression, and survival.

Fifty-four patients with MBC and 51 with TNBC, who were treated at Istanbul University, Institute of Oncology, between 1993 and 2014, were included in the study. After correctly matching the patients with 1 of the 2 groups, they were compared to determine differences in response to treatment, disease progression, clinical course, and survival.

At a median follow-up of 28 months, 18 patients (17.1%) died and 27 (25.5%) had disease progression. Metaplastic histology was significantly correlated with worse 3-year progression-free survival (PFS) ($51 \pm 9\%$ vs. $82 \pm 6\%$, $P = 0.013$) and overall survival (OS) ($68 \pm 8\%$ vs. $94 \pm 4\%$, $P = 0.009$) compared with TNBC histology. Patients who received taxane-based chemotherapy (CT) regimens or adjuvant radiotherapy had significantly better PFS ($P = 0.002$ and $P < 0.001$) and OS ($P < 0.001$ and $P < 0.001$) compared with others. In the multivariate analysis, MBC (hazard ratio [HR]: 0.09, $P < 0.001$), presence of neoadjuvant chemotherapy (NACT) (HR: 12.8, $P = 0.05$), and metastasis development at any time during the clinical course (HR: 38.7, $P < 0.001$) were significant factors that decreased PFS, whereas metastasis development was the only independent prognostic factor of OS (HR: 23.8, $P = 0.009$).

MBC is significantly correlated with worse PFS and OS compared with TNBC. Patients with MBC are resistant to conventional CT agents, and more efficient treatment regimens are required.

(*Medicine* 94(52):e2341)

Abbreviations: ALN = axillary lymph node, ANC = areola-nipple complex, BC = breast carcinoma, CSC = cancer stem cell, CT = chemotherapy, EMT = epithelial-to-mesenchymal transition, HRT = hormone replacement therapy, IDC = invasive ductal carcinoma, MBC = metaplastic breast carcinoma, NACT = neoadjuvant chemotherapy, NAT = neoadjuvant treatment, NCCN = National Comprehensive Cancer Network, OS = overall survival, PFS = progression-free survival, RT = radiotherapy, SEER = Surveillance Epidemiology and End Results, TNBC = triple-negative breast cancer.

INTRODUCTION

The incidence of the metaplastic breast carcinoma (MBC) subtype accounts for between 0.02% and 5% of breast carcinoma (BC), which is the most common cancer type in women.[1,2] MBC was first described as a mammary carcinoma with mixed epithelial and sarcomatoid components by Huvos et al[3] in 1973. MBCs are categorized by the presence of histologically different types of glandular and nonglandular subunits that are unique to this type of breast cancer.[4] The term metaplasia defines the nonglandular change of cancer cells through reprogramming of pluripotent stem cells.[5] This metaplasia may be epithelial, mesenchymal, or both. MBC may contain both epithelial and mesenchymal subunits and 3 different components may be observed within the same tumor at the same time. The mesenchymal differentiation occurs more frequently in the nonglandular component, which leads to cells with spindle, osseous, or cartilaginous characteristics.[1] The morphologic types of tumor cells determine the histologic classification of MBC as follows: purely epithelial (squamous, adenosquamous, and spindle cell carcinomas) or mixed epithelial and mesenchymal (carcinoma with chondroid/osseous metaplasia and carcinosarcoma).[6]

Unlike other types of BC, axillary lymph node (ALN) metastasis was reported to be quite rare and was found in about 20% of patients with MBC.[1] In contrast, it tends to spread thorough hematologic routes and has a high rate of systemic metastasis.[4] Understanding the pathobiology is critical to determining unusual clinical

Editor: László Boros.
Received: July 1, 2015; revised: November 23, 2015; accepted: November 30, 2015.
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AA, MM, and AI contributed to conception and design. FS participated in design, coordination, and revision. MT was involved in drafting the manuscript and revising it critically for important intellectual content. RS performed the statistical analysis. HK, YE, PS, MF, and SK made substantial contributions to interpretation of data. SO and EY carried out the histopathologic diagnosis and pathological details of metaplastic carcinoma and triple-negative breast cancer patients and provided the total numbers of all breast cancer patients, metaplastic carcinoma patients, and triple-negative breast cancer patients. AA, FS, MT, RS, YE, PS, HK, MF, SK, MM, and AI made substantial contributions to acquisition of data. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002341

outcomes and developing new and effective treatments.[5] The epithelial-to-mesenchymal transition (EMT) and cancer stem cell (CSC) characteristics of MBC cells seem to be the reason why they are resistant to therapy and have a tendency to metastasize.[7] The nonglandular component of MBC may vary from clinically insignificant, focal, squamous differentiated cells to diffuse mesenchymal differentiation that may result in very aggressive clinical behaviors.[8,9] EMT activators and CSS present especially in the nonglandular components of metaplastic carcinomas.[10] Therapies that target EMT and CSS may lead to better outcomes for patients with MBC.

MBC differs from classic invasive ductal or lobular carcinoma of the breast in terms of incidence and pathogenesis, but also clinical presentation, prognosis, and hormone receptor status. MBC cases are typically negative for hormone receptors and do not exhibit HER-2/neu overexpression.[2,5] Similarly, triple-negative breast cancer (TNBC) is ER-, PgR-, and HER-2-negative, and constitutes about 15% of BC.[11] TNBC develops at earlier ages more frequently, has higher relapse rates, and shorter survival time because of higher aggressiveness compared with other BC subtypes.[12] Even though MBC is similar to TNBC from a receptor status point of view, MBC is molecularly different and the clinical outcomes are even worse than for TNBC.[7,13] The National Comprehensive Cancer Network (NCCN) recommends that MBC should be treated like other breast cancer subtypes because it is thought to have the same prognosis; however, there have been several reports that suggest it has more aggressive clinical presentations and poorer prognosis, even compared with TNBC.[13,14]

The purpose of this study was to highlight the fact that patients with MBC had worse response to treatment, progression, clinical course, and survival than patients with TNBC who had similar detailed pathologic features, other than histology, and had received the same guideline-based treatment, as well as to discuss how MBC could be managed more effectively.

METHODS

A total of 106 women who were histopathologically diagnosed as having TNBC or MBC were evaluated retrospectively. The study was performed in accordance with the Declaration of Helsinki (5th revision, October 2000) of the World Medical Association and approved by the National Medical Ethics Committee of the Republic of Turkey. Institutional review board approval was provided before we started the study. Written consent from patients was not obtained since the study was designed retrospectively and needed no consent.

MBC Patients

We reviewed the surgical pathology files of 12,444 patients with breast cancer who underwent treatment at Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Breast Cancer Unit, between 1993 and 2014. A total of 108 patients had been diagnosed as having MBC. Among these, 55 whose detailed medical records were available were selected for the study. The medical files of these patients were evaluated retrospectively and their pathology reports were thoroughly analyzed. The clinicopathologic and demographic features of the patients were evaluated in detail.

The pathologic diagnoses of MBC were made by pathologists who specialized in breast cancer. The definitive diagnosis of MBC was made through detailed examination of histology sections of excised tumors. Metaplastic carcinoma was always considered when tumors showed varying proportions of epithelial and mesenchymal components. Mesenchymal components were known as squamous metaplasia and pseudosarcomatous metaplasia, which resemble malignant fibrous histiocytome, chondrosarcoma, osteosarcoma, rhabdomyosarcoma, or a combination of these. If there was a suspicion of MBC, extensive sampling was performed to define the epithelial and mesenchymal components or special matrix.

TNBC Patients

Our review of 12,444 patients with breast cancer also identified 1866 patients who had been diagnosed as having TNBC. Among these, 51 had detailed medical records available and were selected for the study. While selecting patients, attention was paid to matching them with the MBC group in terms of clinicopathologic and demographic features and treatment, which included surgery, chemotherapy (CT), and radiotherapy (RT). In order to prevent biased results, 2 patients who had metastatic disease at presentation were intentionally selected for the TNBC group because data concerning the stage of 4 patients in the MBC group were not clear.

Statistical Analysis

Distributions of numerical variables were assessed by the Kolmogorov–Smirnov test. Normally distributed numerical variables between the different groups were compared using Student *t* test, while variables with nonnormal distribution were compared using the Mann–Whitney *U* test. Categorical variables were compared by using χ^2, Fisher exact, or Kruskal–Wallis tests where appropriate.

We calculated progression-free survival (PFS) by subtracting the date of histopathological diagnosis from the date of first clinical progression or exitus. Overall survival (OS) was calculated by subtracting the date of histopathological diagnosis from the date of exitus resulting from any reason. For the estimation of PFS and OS rates, the Kaplan–Meier method was used and 3-year PFS and OS rates of different subgroups were compared by using the log-rank test. Parameters significant for OS and PFS in univariate analysis were also analyzed in multivariate Cox regression analysis to understand whether they had independent significant effect on survival. A P value less than 0.05 was considered to be statistically significant. SPSS version 16.0 was used for statistical analysis.

RESULTS

Patient Characteristics and Matched Group Comparisons

A total of 105 women (n = 54 with MBC; n = 51 with TNBC) were included in the study. The median follow-up period was 28 months (range 0–168 months) for the entire group. The median follow-up period was significantly shorter in the MBC group than in the TNBC group (17 months, range: 0–168 months, vs. 31 months, range: 13–129 months; $P = 0.001$, Mann–Whitney *U* test). Patients were compared according to their clinicopathologic characteristics and treatment; no statistically significant difference was found except for hormonal receptor status, which proved correct matching of the 2 groups. The median ages of the groups were 46 years and 49 years for MBC and TNBC groups, respectively ($P = 0.98$). Even though a majority of the patients had stage I–II disease (>70%), most of the tumors showed advanced pathologic features, such as high Ki-67 (median: 65%–70%) and grade

(grade 3: 76.5%–89%). The distribution of the histologic subtypes in the MBC group was as follows: 34.54% (n = 18) pure sarcomatoid, 21.81% (n = 12) pure epithelial, 21.81% (n = 12) epithelial + sarcomatoid, 10.9% (n = 6) invasive ductal carcinoma (IDC) + epithelial, 5.45% (n = 3) IDC + epithelial + sarcomatoid, 3.63% (n = 2) IDC + sarcomatoid. The demographic- and clinicopathologic features and detailed pathologic variables are summarized in Table 1.

Treatment and Response to Treatment

One hundred patients received CT (2: primary, 16: neoadjuvant, and 84: adjuvant). Seventy percent of patients who received CT were administered 6 cycles in which anthracycline- and taxane-containing combinations were the most common CT regimens. Sixteen patients who received neoadjuvant CT (NACT) were administered 6 to 8 cycles of CT regimens, which included anthracyclines and taxanes. The response to NACT was less in the MBC group compared with the TNBC group (MBC vs. TNBC, 12.5% vs. 75%).

In addition to CT, more than 70% of the patients in each group received adjuvant RT. In the MBC group, 6 (5.7%), 7 (6.8%), and 2 (2%) patients had estrogen, progesterone, and cerb-B2 positive tumors, respectively; and 9 (16.6%) patients received hormonal therapy. The treatment details and comparisons of both groups are shown in Table 2.

Survival Analysis

The median follow-up period was 28 months (± 34) (range 1–168 months). Among 27 (25.5%) patients who had progression during follow-up, brain, liver, locoregional, and lung sites were involved in recurrence in 2, 6, 10, and 9 patients at the first progression, respectively. When the 2 groups were compared according to first metastatic sites, nodal metastasis was significantly more common in the MBC group than in the TNBC group (MBC vs. TNBC, 14.2% vs. 4.7%, $P = 0.02$) (Table 3). No difference was determined between the 2 groups regarding the frequency of progression, local or axillary recurrence, metastasis, and other first metastatic sites. The progression, recurrence, metastatic sites, last status of patients during follow-up, and comparison of the 2 groups are shown in Table 3.

Univariate Analysis

At the time of analysis, 18 patients (17.1%) had died. Among the variables evaluated for 3-year PFS, skin (40 ± 15% vs. 77 ± 6%, $P < 0.001$) and involvement of the areola-nipple complex (ANC) (45 ± 13% vs.76 ± 6%, $P = 0.05$) by the tumor, tumor size ≥4 cm (53 ± 11% vs. 78 ± 6%, $P = 0.029$), ALN positivity at diagnosis (66 ± 8% vs. 76 ± 8%, $P = 0.05$), stage (IIA vs. IIIC, 86 ± 8% vs. 63 ± 17%, $P = 0.002$), and multifocality of the tumor (57 ± 14% vs. 74 ± 6%, $P = 0.015$) were significantly associated with poorer PFS. In the univariate analysis, tumor size ≥4 cm (63 ± 10% vs. 92 ± 4%, $P = 0.014$), T classification (T1+2 vs. T3+4, 90 ± 4% vs. 63 ± 11%, $P = 0.042$), stage (IIA vs. IIIC, 96 ± 4% vs. 63 ± 17%, $P = 0.008$), stage classification (I+II vs. III+IV, 90 ± 4% vs. 65 ± 11%, $P = 0.045$), involvement of ALN capsule (71 ± 9% vs. 92 ± 4%, $P = 0.026$) and extracapsular extension (62 ± 11% vs. 93 ± 3%, $P = 0.002$), and ANC involvement (58 ± 15% vs. 88 ± 4%, $P = 0.022$) were determined to be correlated with poorer 3-year OS rates.

When PFS and OS rates of the patient subgroups were analyzed according to histologic types, metaplastic histology was significantly correlated with worse 3-year PFS (MBC vs. TNBC, 51 ± 9% vs. 82 ± 6%, $P = 0.013$) (Figure 1) and OS (MBC vs. TNBC, 68 ± 8% vs. 94 ± 4%, $P = 0.009$) compared with TNBC histology (Figure 2).

Furthermore, patients who received only taxane-based CT regimens had significantly better OS compared with those who had anthracycline-based regimens (100 ± 0% vs. 86 ± 7%, $P < 0.001$). Adjuvant RT is another factor that improved both 3-year PFS (73+6% vs. 46+13%, $P < 0.001$) and OS (88 ± 4% vs. 53 ± 13%, $P < 0.001$) rates. Interestingly, hormone replacement therapy (HRT) did not provide better outcomes in MBC patients who had hormone-receptor positive tumors (HRT+ vs. HRT-, for PFS, 70 ± 6% vs. 66 ± 16%, $P = 0.34$, and for OS, 83 ± 4% vs. 77 ± 14%, $P = 0.42$).

Poorer OS regarding the effect of relapse and metastatic sites was associated with axillary relapse (50 ± 20% vs. 88 ± 4%, $P = 0.002$); development of metastasis at any time during follow-up (44 ± 11% vs. 97 ± 2%, $P < 0.001$); and lung (43 ± 17% vs. 88 ± 4%, $P < 0.001$), liver (33 ± 19% vs. 87 ± 4%, $P < 0.001$), and bone metastasis (43 ± 17% vs. 88 ± 4%, $P < 0.001$). Local relapse (86 ± 4% vs. 74 ± 16%, $P = 0.23$) and nodal metastasis (74 ± 11% vs. 85 ± 4%, $P = 0.08$) had no negative impact on OS.

Multivariate Analysis

In the multivariate analysis, MBC (hazard ratio [HR]: 0.09; 95% confidence interval [CI]: 0.02–0.33, $P < 0.001$), presence of neoadjuvant treatment (NAT) (HR: 12.8; 95% CI: 0.97–169.6, $P = 0.05$), and metastasis development at any time during the clinical course (HR: 38.7; 95% CI: 7.99–187.3, $P < 0.001$) were significant factors that decreased PFS. Patients who received NAT had more advanced disease compared with others, which may explain why the presence of NAT factored in the decrease of PFS.

Among the different clinicopathologic parameters, metastasis development was the only independent prognostic factor for OS in the multivariate analysis (HR: 23.8; 95% CI: 2.24–245.1, $P = 0.009$). Interestingly, in contrast to PFS, metaplastic cancer did not have an independent effect on OS in our Cox regression model (HR: 0.35; 95% CI: 0.07 to 1.69, $P = 0.19$). This result may be partially explained by the fact that the follow-up period of the metaplastic cancer group was significantly shorter than that of the TNBC group.

DISCUSSION

MBC is a rare subtype of breast cancer that comprises different histologic components, of both epithelial and mesenchymal origins. The term MBC itself comprises a broad spectrum of tumors, ranging from sarcomatoid carcinoma to carcinoma with squamous differentiation, depending on the histologic types and amount of different subunits.[15] Genomic profiling demonstrated MBC to be similar to basal-like carcinoma and consisted of breast cancer stem cells.[16,17] More data on the biologic characteristics of MBC may allow us to understand the reason why it behaves differently from IDC in terms of clinicopathology and survival.

In the present study, we aimed to determine the points at which MBC differentiates itself from TNBC, which is known to have poor survival among breast cancer subtypes. Thus, we selected 51 patients with TNBC who had similar clinicopathologic features to 54 patients with MBC and compared them statistically to ensure the correct matching. Our findings showed that even if both groups received similar current guideline-

TABLE 1. Comparison of Demographic and Clinicopathological Features of Patients in Metaplastic Carcinoma and Triple-Negative Cancer Groups

Variables	Metaplastic N of Patients (%)	Triple-Negative N of Patients (%)	P^*
Demographic and clinicopathological features			
Age (median ± SD), yr	46 ± 1.3	49 ± 1.1	0.98
Age			0.97
<50/≥50 yr	33 (31.4)/21 (20)	31 (29.5)/20 (19)	
Menopausal status			0.38
Pre/post	30 (28.6)/24 (22.9)	24 (22.9)/27 (25.7)	
Multifocality			0.89
(+)/(−)	8 (7.8)/45 (43.7)	8 (7.8)/42 (40.8)	
T status			0.68
T1/T2/T3/T4/unknown	13 (23.6)/24 (43.6) /8 (14.5)/6 (10.9)/4 (7.3)	16 (31.4)/22 (43.1)/5 (9.8)/8 (15.7)/0 (0)	
N status			0.69
N0/N1/N2/N3/unknown	23 (41.8)/17 (30.9)/6 (10.9)/4 (7.3)/5 (4.7)	28 (54.9)/10 (19.6)/8 (15.7)/5 (9.8)/0 (0)	
N status (at diagnosis)			0.37
(+)/(−)	27 (26.7)/23 (22.8)	23 (22.8)/28 (27.7)	
Stage			0.3
IA/IIA/IIB /IIIA /IIIB/IIIC/X	9 (16.4)/14 (25.5)/15 (27.3)/4 (7.3)/5 (9.1)/4 (7.3)/4 (7.3)	11 (21.6)/18 (35.3)/7 (13.7)/3 (5.9)/8 (15.6)/4 (7.8)/0 (0)	
Stage			0.65
I+II/III	38 (37.3)/13 (12.7)	36 (35.3)/15 (14.7)	
Detailed pathological features			
Tumor size <4/≥ 4 cm	33 (32.4)/18 (17.6)	35 (34.3)/16 (15.7)	0.67
Median TLN (±SD)‡	11 (7.4)	11.5 (1)	0.57
Median Inv LN (±SD)†	1 (4)	0 (6.3)	0.48
Positive/total LN rate			0.97
<0.5/≥0.5	43 (44.3)/5 (5.2)	44 (45.4)/5 (5.2)	
LN capsule invasion			0.24
Absent/present	29 (30.5)/18 (18.9)	35 (36.8)/13 (13.7)	
Extracapsular extension			0.14
Absent/present	32 (33.7)/15 (15.8)	39 (41.1)/0 (9.5)	
MBR grade			0.23
0/2/3/unknown	0 (0)/5 (9.1)/49 (89.1)/1 (1.8)	1 (2)/7 (13.7)/39 (76.5)/4 (8)	
In situ component			0.91
Absent/ present/unknown	21 (38.2)/27 (49.1)/7 (12.7)	22 (43.1)/24 (48.1)/5 (9.8)	
Lymphovascular invasion			0.4
Absent/present	26 (27.7)/21 (22.3)	30 (31.9)/17 (18.1)	
Necrosis			0.16
Absent/present	14 (15.2)/34 (37)	19 (20.7)/25 (27.2)	
Skin invasion			0.78
Absent/present	45 (43.7)/7 (6.8)	43 (41.7)/8 (7.8)	
ANC invasion			0.53
Absent/present	46 (44.2)/7 (6.7)	42 (40.4)/9 (8.7)	
Perineural invasion			0.1
Absent/present	5 (21.7)/3 (13)	14 (60.9)/1 (4.3)	
Estrogen receptor			0.02
Negative/positive	49 (46.2)/6 (5.7)	51 (48.1)/0 (0)	
Progesterone receptor			0.01
Negative/positive	45 (43.7)/7 (6.8)	51 (49.5)/0 (0)	
CERB B2			
Negative/positive	45 (45.9)/2 (2)	51 (52)/0 (0)	0.22
Median Ki67%(±SD)†	70 (2)	65 (2.6)	0.18

ANC = areola-nipple complex, Inv LN = involved lymph node, MBR = modified Bloom Richardson, N of patients = number(s) of patients, TLN = total dissected lymph node.

* χ^2, Fisher exact or Kruskal–Wallis tests.

† *T* test.

‡ Mann–Whitney *U* test.

TABLE 2. Comparison of Treatment Modalities Received, Responses to Treatment in Metaplastic Carcinoma and Triple-Negative Cancer Groups

Variables	Metaplastic N of Patients (%)	Triple-Negative N of Patients (%)	*P*
NACT			0.93
Not received/received	46 (43.8)/8 (7.7)	43 (41.3)/8 (7.7)	
Response to NACT*			N/A
CR/PR/SD/PD	0 (0)/1 (6.2)/2 (12.5)/5 (31.2)	5 (31.2)/1 (6.2)/2 (12.5)/0 (0)	
NACT response			N/A
Responsive (CR+PR)	1 (6.2)	6 (37.5)	
Unresponsive(SD+PD)	7 (43.8)	2 (12.5)	
Surgery type			0.62
MRM (+)/(−)	26 (24.8)/28 (26.6)	26 (24.8)/25 (23.8)	
Surgery type			0.79
BCS (+)/(−)	25 (23.8)/29 (27.6)	24 (22.9)/27 (25.7)	
Chemotherapy			0.24
Not received/received	4 (3.8)/50 (47.7)	1 (0.9)/50 (47.7)	
Chemotherapy regimen			0.67
Anthracycline based	18 (36)	14 (28)	
Taxane based	1 (2)	4 (8)	
Anthracycline +Taxane	24 (48)	32 (64)	
Other regimens	7 (14)	0 (0)	
Platinum			0.67
Received/not received	2 (1.9)/53 (50)	3 (2.8)/48 (45.3)	
Taxane			0.06
Received/not received	25 (25.8)/21 (21.6)	37 (38.1)/14 (14.4)	
Anthracycline			0.58
Received/not received	42 (43.3)/4 (4.1)	47 (48.5)/4 (4.1)	
Radiotherapy			0.61
(−)/(+)	9 (16.6)/41 (76)	7 (13.7)/42 (82.3)	
Hormonotherapy			0.007
Not received/received	40 (74)/9 (16.6)	50 (98)/1 (2)	

BCS = breast conserving surgery, CR = complete response, MRM = modified radical mastectomy, N/A = not applicable, N = number, NACT = neoadjuvant chemotherapy, PD = progressive disease, PR = partial response, SD = stable disease.
* In 16 patients receiving neoadjuvant CT.

based treatment, patients with MBC had significantly poorer PFS compared with those with TNBC. Several studies in the literature have demonstrated the poorer outcomes of patients with MBC, although there are others with conflicting results.[18]

We are also aware of a potential limitation of our study as the cohort size is limited regarding patients with stage IV disease. We considered excluding these patients from the study because only 4 patients had MBC with clinically suspicious stage IV disease, whereby metastases could not be proven with biopsies due to small metastatic lesions. In all scenarios of standard cohort diagnostics, MBC was associated with shorter survival time. We also point out that cohort size is limited in all MBC reports, as its histology is rare; MCB represents only 0.25% to 1% of all breast cancers.[19,20]

With regard to the entire group, the finding that capsular and extracapsular involvement of ALN was associated with poorer OS but not PFS is intriguing. A remarkable result of our study was the significantly increased nodal metastases in the MBC group as the first metastatic sites compared with the TNBC group. Even though MBC is generally reported to be an aggressive tumor with fewer or no nodal metastases,[1,21–24] there are some studies that demonstrated a frequency of nodal metastases of up to 21% to 64% in patients with MBC.[18,25]

The results for our entire study group revealed that adjuvant RT improved both PFS and OS outcomes. This is consistent with the literature because RT provided both OS and disease-specific survival benefits in patients with MBC in a Surveillance, Epidemiology, and End Results (SEER) database study.[26] On the other hand, although there was no difference in terms of progression, both PFS and OS were poorer in patients with MBC when relapse and development of metastasis were compared between the MBC and TNBC groups. The lack of effective CT regimens for MBC may have led to this striking result.

The response to conventional CT regimens in patients with MBC is significantly poorer compared with those with TNBC. In a study by Chen et al, the partial response rates to NACT and first-line CT in the metastatic setting in patients with MBC were only 18% and 8%, respectively, whereas no response was achieved with anthracycline-, vinorelbine-, or cyclophosphamide-based regimens.[24,27] These results suggest that the inefficiency of the current systemic therapeutics may result in worse survival rates in MBC patients. In our study, 62.5% of the MBC patients who received NACT had progressive disease despite CT, whereas 62.5% of the TNBC patients who received NACT achieved complete response with the same CT regimen. In addition, there was no complete response, but only partial

TABLE 3. Clinical Course Comparison of Metaplastic Carcinoma and Triple-Negative Cancer Groups During Follow-Up

Variables	Metaplastic N of Patients (%)	Triple-Negative N of Patients (%)	*P*
Progression			0.17
(−)/(+)	34 (63)/ 20 (37)	39 (76.5)/12 (23.5)	
Local recurrence			0.47
(−)/(+)	49 (80.7)/5 (9.3)	47 (92.2)/4 (7.8)	
Axillary recurrence			0.63
(−)/(+)	51 (94.5)/3 (5.5)	48 (94)/3 (6)	
Metastasis during follow-up			0.48
(−)/(+)	43 (80)/11 (20)	42 (82.4)/9 (17.6)	
Site of first metastasis			
Brain (+)/(−)	1 (0.9)/54 (50.9)	1 (0.9)/50 (47.2)	0.73
Lung (+)/(−)	4 (3.8)/51 (48.1)	5 (4.7)/46 (43.4)	0.73
Liver (+)/(−)	3 (2.8)/52 (49.1)	3 (2.8)/48 (45.3)	0.62
LN (+)/(−)	15 (14.2)/40 (37.7)	5 (4.7)/46 (43.4)	0.02
Bone (+)/(−)	3 (2.8)/52 (49.1)	6 (5.7)/45 (42.5)	0.3
Last status			0.83
NED/AWD/Exitus	40 (74)/1 (1.8)/13 (24)	40 (78.4)/6 (11.8)/5 (9.8)	

AWD = alive with disease, LN = lymph node, NED = no evidence of disease.

response was achieved in 12.5% of the patients in the MBC group. Due to the limited number of patients in our study, comparison of the response to NACT between the 2 types of cancer could not be performed.

CT regimens that are based on the histologic components of MBC might be more efficient. The clinical course of MBC differentiates from sarcoma to squamous cell carcinoma according to the subunits it contains. Some cases reported good responses to ifosfamide- and anthracycline-based CT for sarcomatoid types and to platinum-based CT for epidermoid MBC.[28,29] Furthermore, PI3K inhibitors may be beneficial because MBC contains cells with stem-like selectivity. Moreover, it was shown that MBC cells were epidermal growth factor receptor-positive,[21] and agents that target this receptor could be used for squamous cell MBC.[30]

The present study shows that MBC has significantly worse survival and behaves more aggressively compared with TNBC, and that there is need for an aggressive treatment approach. Consequently, further studies are required that focus on the molecular and pathologic characteristics of MBC to identify potential targets, which may lead to the development of more effective agents.

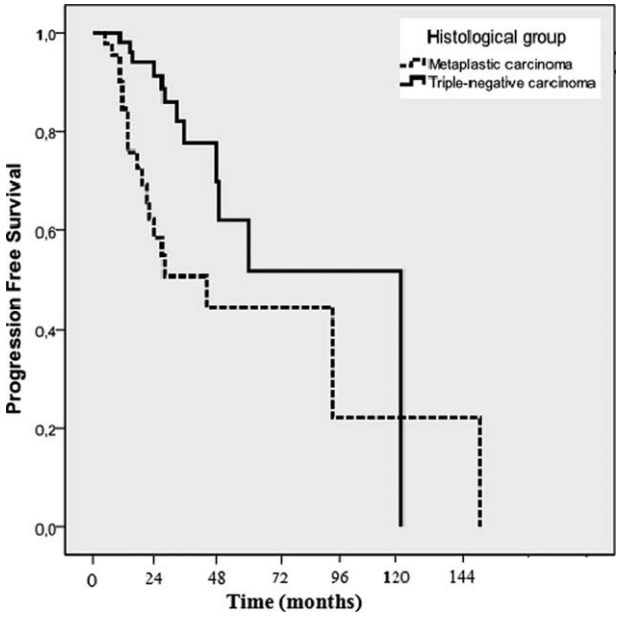

FIGURE 1. Progression-free survival curves of metaplastic and triple-negative breast cancer patients.

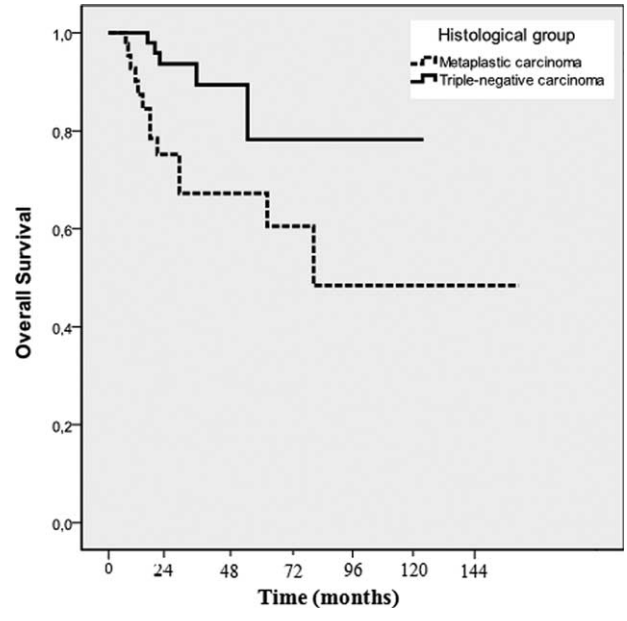

FIGURE 2. Overall survival curves of metaplastic and triple-negative breast cancer patients.

ACKNOWLEDGMENTS

We would like to thank Mr David Chapman, who is a native-English speaker with scientific expertise, for editing the language of the manuscript.

REFERENCES

1. Pezzi CM, Patel-Parekh L, Cole K, et al. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. *Ann Surg Oncol.* 2007;14:166–173.
2. Al Sayed AD, El Weshi AN, Tulbah AM, et al. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. *Acta Oncol.* 2006;45:188–195.
3. Huvos AG, Lucas JC Jr, Foote FW Jr. Metaplastic breast carcinoma. Rare form of mammary cancer. *N Y State J Med.* 1973; 73:1078–1082.
4. Tavassoli FDP. Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon, France: IARC Press; 2003.
5. Kumar V, Abbas AK, Aster JC, et al. Robbins and Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, PA; USA: Elsevier; 2010.
6. Reis-Filho JSLS, Gobbi H, Sneige N. Metaplastic carcinomas. In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, eds. *WHO Classification of Tumours of the Breast.* Lyon, France: IARC Press; 2012:48–52.
7. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. *Cancer Res.* 2009;69:4116–4124.
8. Gutmann JL. Biologic perspectives to support clinical choices in root canal treatment. *Aust Endod J.* 2005;31:9–13.
9. Davis WG, Hennessy B, Babiera G, et al. Metaplastic sarcomatoid carcinoma of the breast with absent or minimal overt invasive carcinomatous component: a misnomer. *Am J Surg Pathol.* 2005;29:1456–1463.
10. Zhang Y, Toy KA, Kleer CG. Metaplastic breast carcinomas are enriched in markers of tumor-initiating cells and epithelial to mesenchymal transition. *Mod Pathol.* 2012;25:178–184.
11. Chacon RD, Costanzo MV. Triple-negative breast cancer. *Breast Cancer Res.* 2010;12(Suppl 2):S3.
12. de Ruijter TC, Veeck J, de Hoon JP, et al. Characteristics of triple-negative breast cancer. *J Cancer Res Clin Oncol.* 2011;137:183–192.
13. Jung SY, Kim HY, Nam BH, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. *Breast Cancer Res Treat.* 2010;120:627–637.
14. Anderson BO, Blair SL, Burstein HJ, et al. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Cancer Netw.* 2016;1:16–20.
15. Wargotz ES, Norris HJ. Metaplastic carcinomas and sarcomas of the breast. *Am J Clin Pathol.* 1991;96:781.
16. Weigelt B, Kreike B, Reis-Filho JS. Metaplastic breast carcinomas are basal-like breast cancers: a genomic profiling analysis. *Breast Cancer Res Treat.* 2009;117:273–280.
17. Korsching E, Jeffrey SS, Meinerz W, et al. Basal carcinoma of the breast revisited: an old entity with new interpretations. *J Clin Pathol.* 2008;61:553–560.
18. Rakha EA, Tan PH, Shaaban A, et al. Do primary mammary osteosarcoma and chondrosarcoma exist? A review of a large multi-institutional series of malignant matrix-producing breast tumours. *Breast.* 2013;22:13–18.
19. Leddy R, Irshad A, Rumboldt T, et al. Review of metaplastic carcinoma of the breast: imaging findings and pathologic features. *J Clin Imaging Sci.* 2012;2:21.
20. Oberman HA. Metaplastic carcinoma of the breast. A clinicopathologic study of 29 patients. *Am J Surg Pathol.* 1987;11:918–929.
21. Bae SY, Lee SK, Koo MY, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. *Breast Cancer Res Treat.* 2011;126:471–478.
22. Song Y, Liu X, Zhang G, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. *World J Surg Oncol.* 2013;11:129.
23. Lai HW, Tseng LM, Chang TW, et al. The prognostic significance of metaplastic carcinoma of the breast (MCB): a case controlled comparison study with infiltrating ductal carcinoma. *Breast.* 2013;22:968–973.
24. Nelson RA, Guye ML, Luu T, et al. Survival outcomes of metaplastic breast cancer patients: results from a US population-based analysis. *Ann Surg Oncol.* 2015;22:24–31.
25. Esbah O, Turkoz FP, Turker I, et al. Metaplastic breast carcinoma: case series and review of the literature. *Asian Pac J Cancer Prev.* 2012;13:4645–4649.
26. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? *Ann Surg Oncol.* 2011;18:94–103.
27. Chen IC, Lin CH, Huang CS, et al. Lack of efficacy to systemic chemotherapy for treatment of metaplastic carcinoma of the breast in the modern era. *Breast Cancer Res Treat.* 2011;130:345–351.
28. Hennessy BT, Krishnamurthy S, Giordano S, et al. Squamous cell carcinoma of the breast. *J Clin Oncol.* 2005;23:7827–7835.
29. Brown-Glaberman U, Graham A, Stopeck A. A case of metaplastic carcinoma of the breast responsive to chemotherapy with Ifosfamide and Etoposide: improved antitumor response by targeting sarcomatous features. *Breast J.* 2010;16:663–665.
30. Kimura F, Iwaya K, Kawaguchi T, et al. Epidermal growth factor-dependent enhancement of invasiveness of squamous cell carcinoma of the breast. *Cancer Sci.* 2010;101:1133–1140.