RESEARCH ARTICLE

Metaplastic Breast Carcinoma: a Heterogeneous Disease

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Abstract

The aim of this study is to evaluate clinicopathologic characteristics and the multi-disciplinary treatment results of metaplastic breast cancer (MBC) patients treated in a single institute. Seventeen female patients with MBC treated in our department between June 2000 and January 2012 were identified and retrospectively evaluated. The median age at diagnosis was 46 years (range, 26-66 years). The median tumor size at diagnosis was 3.5 cm (range 1.5-12 cm). Six (35%) patients underwent breast conservation surgery and 11 (65%) mastectomy. Axillary lymph node metastasis was found in 6 (35%) patients. Twelve (71%) had triple negative tumors. Postoperative RT and systemic adjuvant treatment was given to all patients accordingly to stage and biological characteristics. Median follow-up time was 27 months (range, 12-151 months). At the time of this analysis, 14 (82%) patients were alive with no evidence of disease, and 1 (6%) was alive with disease. The 3-year OS was 91% and 5-year 80%, and DFS rates were 76% and 76%, respectively. Despite the young age of our patients with mostly high grade tumors, larger tumor size and higher rates of lymph node metastasis, the survival outcomes in our study are favorable in comparison with previously reported series.

Keywords: Adjuvant radiotherapy - metaplastic breast cancer - postoperative radiotherapy - prognosis

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Introduction

Metaplastic breast cancer (MBC) is an uncommon breast tumor and accounts for <1% of all breast malignancies (Tavassoli, 1992). The prognosis of these tumors is controversial but usually has been believed to have an aggressive clinical behavior with high local and distant metastases rates. The 5-year overall survival of MBC has been reported to be 49-68% (Rayson et al., 1999; Luini et al., 2007).

MBC is a heterogeneous group of malignancies and composed of epithelial and mesenchymal components (Wargotz et al., 1989a; 1989b; 1990a; 1990b). It is divided into purely epithelial or mixed epithelial and mesenchymal types according to the World Health Organization (WHO) Classification (Tavassoli et al., 2003). Although there is no standard classification scheme for MBC, they are categorized mainly into five subtypes including squamous cell carcinoma of ductal origin, spindle cell carcinoma, matrix-producing carcinoma, carcinosarcoma and metaplastic carcinoma with osteoclastic giant cells (Wargotz et al., 1989a; 1989b; 1990a; 1990b). In the updates of the WHO Classification of breast tumors, malignant myoepithelioma incorporated into MBC (Tan et al., 2013). Transformation of one type of metaplastic carcinoma to another can also be observed (Chuthapisith et al., 2013).

The clinical behavior of MBC is similar to basal-like tumors. Patients with MBC usually present with larger, higher grade, higher stage and more hormone receptor-negative tumors with less involvement of regional lymph nodes comparing patients with invasive ductal carcinomas (Pezzi et al., 2007; Lai et al., 2013; Song et al., 2013). The optimal treatment for MBC remains controversial. It is generally suggested that these tumors should be treated like other invasive breast carcinomas (Carlson et al., 2009). Historically, the role of radiation therapy (RT) has been controversial. However the current data showed that overall survival was significantly improved in patients receiving postoperative adjuvant radiotherapy (Tseng and Martinez, 2011). The aim of the current study is to evaluate clinicopathologic characteristics and the multi-disciplinary treatment evaluation of MBC patients treated in a single institute and to review the literature.

Materials and Methods

Seventeen female patients with MBC treated in our department between June 2000 and January 2012 were identified and retrospectively reviewed. Patient, tumor and treatment characteristics were recorded. All patients had histopathological diagnosis with MBC categorizing into purely epithelial or mixed epithelial and mesenchymal according to the WHO Classification (Ellis et al., 2003).

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The surgical procedure was either as breast conservative surgery (BCS) or mastectomy±axillary lymph node dissection or sentinel lymph node biopsy. Postoperative RT and systemic adjuvant treatment was given to all patients accordingly to stage and biological characteristics. RT was applied with tangential fields and additional supraclaviculary±internal mammary fields were added when regional lymph nodes were intended to treat. The median dose to chest wall or whole breast was 50 Gy. In case of BCS, a tumor bed boost dose of 10 Gy was applied. Again a total dose of 50 Gy was applied to regional lymphatics when indicated. The chemotherapy regimen was mainly composed of adriamycin and taxane-based regimens. Hormonal therapy was delivered when pathology specimen revealed hormone receptor positivity. In case of HER2 positivity, adjuvant Trastuzumab treatment was given similarly to other patients with different breast carcinoma histology.

Patients were followed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. All patients underwent a thorough physical examination in every follow-up visit. Annual mammography, chest x-ray and abdominopelvic ultrasonography in every 6 months of time were the other screening tools during follow-up. Symptomatic patients underwent computed tomography and bone scans as deemed necessary. Local or metastatic disease was defined by radiographically or histopathologically.

Overall survival (OS) was calculated from the date of diagnosis to the date of death or last control. Disease-free survival (DFS) was calculated from end of the radiotherapy to the date of relapse, death or last control. All statistical analysis was conducted using SPSS version 13.0 (SPSS Inc., Chicago, IL). Survival analysis was performed using the Kaplan-Meier method.

Results

Median follow-up time of 17 patients with MBC was 27 months (range, 12-151 months). The median age at diagnosis was 46 years (range, 26-66 years). Eleven patients (65%) were in premenopausal and 6 (35%) were in postmenopausal status (Table 1). All patients except one presented with a symptom of breast mass. The particular patient without symptom was diagnosed during screening mammography. In 9 (53%) patients tumors were localized in the left breast and 8 (47%) patients were with tumors in the right breast. Positive family history was found in 3 (18%) patients.

The median tumor size at diagnosis was 3.5 cm (range, 1.5-12 cm) and 76% of patients had tumors greater than 2 cm in diameter. None of the patients had distant metastasis. Six (35%) patients were treated with BCS and 11 (65%) patients with mastectomy. All patients except one had grade 3 tumors. Three patients (18%) had American Joint Committee on Cancer (AJCC) stage I disease, 8 (47%) stage II, and 6 (35%) stage III disease. The median number of axillary lymph nodes dissected was 18 (range, 1-33). Axillary lymph node metastases were found in 35% of the patients. The median number of positive nodes was 5 (range, 1-24). Nine (53%) patients were classified as purely epithelial; 4 (24%) adenosquamous, 2 (12%) squamous, 3 (17%) adenocarcinoma with spindle cell differentiation and 8 (47%) patients were classified as mixed epithelial and mesenchymal; 5 (29%) carcinosarcoma, 2 (12%) carcinoma with condroid metaplasia and 1 (6%) metaplastic carcinoma not otherwise specified (NOS). The histological subtype of the primary tumor in node positive patients was purely epithelial in 4 patients (3 adenosquamous, 1 squamous) and mixed epithelial and mesenchymal in 2 patients (1 carcinosarcoma, 1 metaplastic carcinoma NOS).

Estrogen receptor (ER) was positive in 3 (18%) patients, progesterone receptor (PR) was positive in 4 (24%) patients and human epidermal growth factor receptor 2 (HER2) was positive in 2 (12%) patients. Twelve (71%) patients had triple negative tumors. None

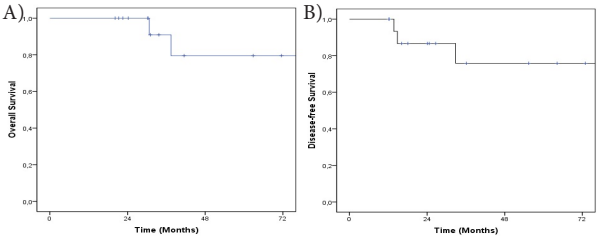

Figure 1. Kaplan Meier Curves of A) Overall Survival and B) Disease-free Survival

Table 1. Patients' Clinical and Tumor Characteristics, and Treatment Details

Characteristic		No.	%
Age at diagnosis	≤50 years	12	71
	>50 years	5	29
Menopausal status	Premenopausal	11	65
	Postmenopausal	6	35
T stage	T1	4	24
	T2	8	47
	T3	4	24
	T4	1	5
N stage	N0	11	65
	N1	1	6
	N2	3	18
	N3	2	11
TNM stage	I	3	18
	II	8	47
	III	6	35
Histologic subtype			
Purely epithelial		9	53
Adenosquamous		4	24
Squamous		2	12
Adenocarcinoma with spindle cell differentiation		3	17
Mixed epithelial and mesenchymal		8	47
Carcinosarcoma		5	29
Carcinoma with condroid metaplasia		2	12
NOS		1	6
Type of surgery	BCS	6	35
	Mastectomy	11	65
ER status	Positive	3	18
	Negative	14	82
PR status	Positive	4	24
	Negative	13	76
HER2 status	Positive	2	12
	Negative	14	82
	Unknown	1	6

*Abbreviation: BCS=Breast conservative surgery, NOS=Not otherwise specified, ER=Estrogen receptor, PR=Progesterone receptor, HER2=Human epidermal growth factor receptor 2

Table 2. Demographic Data of 17 Patients

No	Age	Menopausal Status	Tm size (cm)	TNM Stage	Pathology	Grade	ER	PR	HER2	Surgery	A-CT	Recurrence	Final status	Follow-up (Months)
1	46	Pre	3	IIIA	AS	3	Negative	Positive	Negative	MRM+ALND	AC (4)+P (4)	LR+DM	AWD	25
2	65	Post	3.5	IIIA	CS	2	Negative	Positive	Negative	MRM+ALND	FEC (3)+D (3)	No	ANED	24
3	35	Pre	7	IIB	C-CM	3	Positive	Positive	Positive	MRM+ALND	AC(4)+D (4)+H	No	ANED	73
4	49	Post	2	IIB	AS	3	Positive	Negative	Positive	MRM+ALND	DC (4)+ H	No	ANED	36
5	30	Pre	10	IIB	AC-SCD	3	Negative	Negative	Negative	MRM+ALND	AC (4)	DM	Exitus	26
6	36	Pre	7	IIB	CS	3	Negative	Negative	Negative	MRM+ALND	AC (4)	No	ANED	64
7	66	Post	5	IIB	CS	3	Negative	Negative	Negative	MRM+ALND	AC (4)	No	ANED	86
8	40	Pre	12	IIIB	AC-SCD	3	Negative	Negative	Negative	SM+ALND	MEtCispl (6)	No	ANED	151
9	38	Pre	3.5	IIIA	S	3	Negative	Negative	Negative	BCS+ALND	DAC (6)	No	ANED	12
10	66	Post	1.8	IIIC	AS	3	Negative	Negative	Negative	MRM+ALND	AC (4)+P (12)	No	ANED	12
11	26	Pre	4	IIA	CS	3	Negative	Negative	Negative	MRM+ALND	CAF (6)	No	ANED	91
12	55	Post	4.5	IIA	S	3	Negative	Negative	Negative	SM+SLNB	CAF (6)	No	ANED	55
13	46	Pre	2	IA	AC-SCD	3	Negative	Negative	Negative	BCS+ALND	AC (4)	No	ANED	16
14	62	Post	1.5	IA	AS	3	Negative	Negative	Negative	BCS+ALND	AC (4)+H	No	ANED	18
15	43	Pre	2.3	IIA	C-CM	3	Negative	Negative	Negative	BCS+SLNB	AC (4)	No	ANED	27
16	32	Pre	2	IA	CS	3	Negative	Negative	Negative	BCS+SLNB	AC (4)	No	ANED	25
17	48	Pre	3.5	IIIC	MC-NOS	3	Positive	Positive	NA	BCS +ALND	AC (4)	NA	Exitus	33

*Abbreviation: Tm=Tumor, AS=Adenosquamous, CS=Carcinosarcoma, C-CM= Carcinoma with condroid metaplasia, AC-SCD= Adenocarcinoma with spindle cell differentiation, S=Squamous, MC-NOS= Metaplastic carcinoma not otherwise specified, ER=Estrogen receptor, PR=Progesterone receptor, HER2=Human epidermal growth factor receptor 2, MRM=Modified radical mastectomy, ALND=Axillary lymph node dissection, SM=Simple mastectomy, BCS=Breast conservative surgery, SLNB=Sentinel lymph node biopsy, A=Doxorubicin, C=Cyclophosphamide, P=Paclitaxel, F=5-Fluorouracil, E=Epirubicine, D=Docetaxel, H=Herceptin, M=Methotrexate, Et=Etoposide, Cispl=Cisplatin, LR=Local recurrence, DM=Distant metastasis, AWD=Alive with disease, ANED=Alive with no evidence of disease

of the patients received neoadjuvant chemotherapy. Adjuvant chemotherapy was applied to all patients as 59% anthracycline-based regimens, 35% taxane-based regimens, and 6% cisplatin-etoposide-methotrexate. Adjuvant trastuzumab was administered to 2 patients with HER2 positive disease. Four patients with hormone receptor positivity received either aromatase inhibitor or tamoxifen depending on their menopausal status. Patient demographic data are summarized in Table 2.

At the time of this analysis, 14 (82%) patients were alive with no evidence of disease, and 1 (6%) was alive with disease. One patient died with disease. The cause of death in the other patient was unknown. Since she was lost to follow-up and the information of the death could be obtained from general directorate of population and citizenship affairs. Recurrences were observed in 2 patients during follow-up. The particular patient with death of disease developed brain, lung and bone metastases 14 months after the treatment and palliated with radiotherapy and chemotherapy (taxotere+capecitabine). She died with disease at the 26th months of follow-up. This patient had an adenocarcinoma with spindle cell differentiation. Other patient developed local recurrence at the 15th months and distant metastases at the 19th months of follow-up. She underwent surgery and reirradiation to the chest wall and received chemotherapy (cisplatin+gemcitabine). She was alive with disease at the last control (25th months). This patient had an adenosquamous component. On the whole cohort of patients, the 3-year OS was 91% and 5-year 80%, and DFS rates were 76% and 76%, respectively (Figure 1 and 2).

Discussion

MBC represents a heterogeneous group of tumors with different clinical features, behavior and response to treatments. The prognostic factors defined in the literature are age at diagnosis, tumor size, histopathologic subtype, tumor grade, TNM stage, axillary nodal status, hormone receptor status, type of primary surgery, and use of RT (Chao et al., 1999; Rayson et al., 1999). MBC is more commonly seen in postmenopausal women and the mean age at diagnosis is reported to be around 58.5 years (Pitts et al., 1991; Rayson et al., 1999; Toumi et al., 2011). However some studies reported a much younger age presentation similar to ours in which the median age at diagnosis was 46 years (Al Sayed et al., 2006; Esbah et al., 2012).

The significance of tumor size is controversial in MBC (Wargotz et al., 1989b; Chao et al., 1999; Rayson et al., 1999). Patients usually present with large tumors (≥5 cm) which is generally accepted as relative contraindication for BCS (Pogsi et al., 2003; Song et al., 2013). Therefore, the preferred surgical approach is often mastectomy (Pezzi et al., 2007; Tseng and Martinez, 2011; Hu et al., 2013). However, several studies have demonstrated there

is no difference in OS or DFS between mastectomy and BCS in these particular patients (Dave et al., 2006; Tseng and Martinez, 2011). Therefore, BCS, lumpectomy, local excision with cancer-free margins (≥3 cm) can be used in some appropriate patients (Hu et al., 2013). In our study, the most common presenting symptom was a palpable mass and the median tumor size at diagnosis was 3.5 cm (range, 1.5-12 cm). The majority of our patients (76%) were with tumors greater than 2 cm similar to Tseng and Martinez who reported 69% of patients with tumors larger than 2 cm in diameter (Tseng and Martinez, 2011). Due to the larger tumor size, the majority of our patients (65%) were treated with mastectomy.

Lymphatic spread of MBC is uncommon (Pezzi et al., 2007; Tseng and Martinez, 2011). The incidence of nodal spread has been reported to be between 0% and 63% (Pitts et al., 1991; Al Sayed et al., 2006; Pezzi et al., 2007; Toumi et al., 2011; Esbah et al., 2012). Tseng and Martinez analyzed Surveillance, Epidemiology, and End Results (SEER) database and they reported the frequency of axillary lymph node metastasis was 22% among 1501 MBC patients (Tseng and Martinez, 2011). In our study, 35% of our patients were with axillary lymph node metastasis. Al Sayed et al. and others reported that lymph node metastases only occurred in pure epithelial MBCs (Kurian et al., 2002; Al Sayed et al, 2006). It is recommended that axillary lymph node dissection is not required in spindle cell carcinoma or carcinosarcoma due to no risk of axillary lymph node involvement (Hu et al., 2013). However, only 4 out of 6 patients with lymph node metastasis had pure epithelial MBCs in our study. The other 2 patients with lymph node metastasis had carcinosarcoma and metaplastic carcinoma not otherwise specified subtype. In general, it has been believed that lymph node metastasis is not a prognostic factor for survival. However, Chao et al. (1999) showed that axillary lymph node metastasis was associated with worse survival (Chao et al., 1999). Since only one patient developed disease recurrence in our series and the low number of patients, we cannot make a comment on the possible effect of lymph node metastasis on survival.

Generally, MBC is considered to be associated with poor prognosis compared with invasive ductal or lobular carcinoma (Wargotz et al., 1989a; Rayson et al., 1999; Luini et al., 2007; Lai et al., 2013; Song et al., 2013). In contrary to some authors who reported higher survival rates for MBC patients (Chao et al., 1999). Fulford et al. hypothesized that MBC can be divided into two types: one represents an early relapse and an aggressive clinical behavior and the other types that do not relapse despite the poor prognostic factors (Fulford et al., 2007). The 5-year DFS and OS rates reported in the systematic review of the literature ranges from 42% to 84% and 64% to 83%, respectively (Toumi et al., 2011). Although larger tumor size and higher rates of lymph node metastases, the survival outcomes in our study are comparably favorable with previously reported series; with 5-year OS and DFS rates of 80% and 76%, respectively. The vast majority of our patients presented with early stage disease (65% ≤stage II) and this could be the reason of higher survival rates.

The most common route of disease recurrence in MBC is hematogenous (lung and bone) metastasis (Wargotz et al., 1989a; 1989b; Esbah et al., 2012). Local and/or distant metastases are observed in more than 50% of patients within 5 years which indicates poor prognosis and approximately half of patients developed distant metastases as a sole relapse pattern without local or regional recurrence (Brenner et al., 1998). Only 2 patients (12%) developed recurrence in our series, 1 with only distant and the other with both local and systemic metastasis. These patients had a purely epithelial subtype; 1 patient with an adenocarcinoma with spindle cell differentiation and the other patient with an adenosquamous component. There is no clear correlation between pathological subtype and prognosis in patients with MBC (Tavassoli et al., 2003). However, Tseng and Martinez demonstrated decreased OS (HR 1.52, CI 1.13-2.04, p=0.005) and DFS (HR 1.63, CI 1.16-2.31, p=0.005) in patients with carcinosarcoma subtype (Tseng and Martinez, 2011). Again the low number of patients and the low recurrence rates in our series preclude us to make a comment on the influence of tumor type on the oncological outcome.

The role of adjuvant RT in MBC is not clear (Gutman et al., 1995; Dave et al., 2006). Rosen and Ernsberger recommended the routine use of adjuvant RT in MBC patients (Rosen et al., 1987). In a study by Dave et al. (2006) 43 patients with MBC were treated with lumpectomy and adjuvant RT with 10.5% local recurrence rates, in mean 44.2 months of follow-up (Dave et al., 2006). Adjuvant RT on the other hand significantly affected both OS (HR 0.64; 95%CI, 0.51-0.82; p<0.001) and disease-specific survival (HR 0.74; 95%CI, 0.56-0.96; p<0.03), regardless of the type of surgery in patients treated between 1988 and 2006 in the SEER database (Rayson et al., 1999). Significant survival advantage was observed in high risk patients who were treated with mastectomy and adjuvant RT when they had tumors ≥5cm and/or ≥4 metastatic axillary lymph nodes. It was suggested that RT should be included in the multimodality treatment for MBC patients treated with BCS and patients with high risk features undergoing mastectomy (Tseng and Martinez, 2011). In our study, only 2 recurrences, 1 distant metastasis and 1 distant metastasis and local recurrence, recurrences were observed in patients with high risk factors defined by Tseng and Martinez and there was no local recurrence in 6 patients treated with lumpectomy and postoperative RT (Tseng and Martinez, 2011).

MBCs have usually low levels of ER, PR and HER2 receptor expression and no significant response is observed with adjuvant hormonal therapy (Pitts et al., 1991; Gutman et al., 1995; Chao et al., 1999; Rayson et al., 1999). They are frequently classified as basal-like breast cancers and approximately 75-85% are triple negative (Sørlie, 2004; Carey et al., 2007). Tseng and Martinez reported 70% of tumors were ER or PR negative (Tseng and Martinez, 2011). In a parallel study by Pezzi et al. (2007) 89-90% of patients had negative hormone receptor status (Pezzi et al., 2007). Toumi et al. (2011) on the other hand reported that ER positivity was only found in 12%, PR positivity in 10% and HER2 positivity in 6% of the patients (Toumi et al., 2011). ER, PR and HER2 receptor

expression were found to be positive in 18%, 24% and 12% of our patients, respectively. Generally, there is no role of adjuvant hormonal therapy in the treatment of MBC patients. Rayson et al. reported on 4 MBC patients with positive hormone receptor status treated with tamoxifen at the time recurrence but none of them responded to treatment (Rayson et al., 1999). However, Bae et al. treated 3 patients with hormonal therapy and they showed no recurrence during follow-up period (Bae et al., 2011). In our study, 4 patients were treated with additional hormonal therapy and only 1 patient developed local recurrence and distant metastases. Other 3 patients were alive with none evidence of disease at the last control.

The effectiveness of standard chemotherapy regimens used in invasive ductal carcinoma is controversial and MBCs are thought to be chemoresistant (Hennessy et al., 2006). However, patients with MBC received chemotherapy more often than invasive ductal carcinoma due to their hormone negative-receptor status and larger tumor size (Lai et al., 2013). It is generally believed that more aggressive treatment is required (Pezzi et al., 2007). New molecular cancer therapeutics including protein kinase inhibitors (gefitinib), angiogenesis inhibitors (bevacizumab), and mTOR inhibitors are an extremely active area of research. In a study by Bae et al. adjuvant chemotherapy was applied to 42 out of 47 patients without any survival advantage with chemotherapy (Bae et al., 2011). Similarly Rayson et al. (1999) and Chao et al. (1999) showed no significant survival advantage with systemic chemotherapy (Chao et al., 1999; Rayson et al., 1999). In contrast, Gutman et al. found both DFS and OS benefit with adjuvant chemotherapy in stage I-II MBC patients (Gutman et al., 1995). All patients in our study received adjuvant chemotherapy and the 5-year DFS and OS rates were 76% and 80%, respectively. The routine chemotherapy application rates in the literature are reported to be in the range of 33-86%. The good survival rates and the good prognosis in our patients led us to think about that these good survival figures can be due to routine adjuvant chemotherapy in contrary to the literature.

Despite the young age of our patients with mostly high grade tumors and high rate of lymph node metastasis, our data supports that a group of MBC patients may have a good survival. The low incidence of local failure and distant metastases in our study may be attributed to multidisciplinary approach including surgery, chemotherapy and radiotherapy to all patients. There is no standard treatment for MBC due to rarity and heterogeneity of these tumors. Prospective, multicentric and multi-institutional studies are necessary to find out the optimal treatment strategy in these patients.

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