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Original Article

Survival and treatment outcomes of metaplastic breast carcinoma: Single tertiary care center experience in Pakistan

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Abstract

BACKGROUND: Metaplastic breast carcinoma (MBC) is a rare disease with incidence of less than 1%. MBC present with a larger tumor size, less number of nodes involved, mostly undifferentiated triple negative tumors. We aimed to determine progression-free and overall survival and reported hospital-based incidence of MBC.

MATERIAL AND METHODS: A retrospective closed Cohort study elicited data of 42 patients with MBC from January 2008 to December 2013; followed till August 2016. Kaplan-Meier method was applied to compute overall and progression-free survival analysis. Cox Proportional hazard ratios were computed to assess associations between survival and independent variables.

RESULTS: Hospital-based incidence of MBC was 1.92% (42/2187), 95% CI [1.41-2.56]. The median age at tumor diagnosis was 54 years (range, 25–81 years). Thirty-nine (92.9%) patients had Grade III tumor. The most common histopathology was squamous (69%). The median tumor size was 4.5 cm (range, 0.8–17 cm). Nineteen (45.2%) patients had nodal involvement at diagnosis. Four patients (9.5%) had metastatic disease at presentation. Hormone receptors were positive in 19 (45.2%) patients. Her-2 neu receptor was positive in 9 (19%) patients. Sixteen (38.1%) patients had triple negative disease. Neoadjuvant and adjuvant chemotherapy was received by 10 (31.25%) and 19 (45.2%) patients respectively. Both median progression-free and overall survival was 38 months.

CONCLUSION: Five-year progression-free and overall survival was 79.5% and 76.3%, respectively. We report better survival outcomes when compared to series described earlier despite our patient population presenting mostly with high grade, large tumors, and half of them exhibiting nodal and hormonal involvement.

Key Words: Breast, Kaplan- Meier analysis, metaplasia, neoadjuvant treatments, survival analysis

Introduction

Metaplastic breast carcinoma (MBC) is a rare disease. Its incidence is said to be less than 1% amongst all breast cancer sub-types.[1] In a study from India, its incidence was reported as 0.9%.[2] They are a heterogeneous group of diseases having epithelial and mesenchymal components. Two to three different components may occur within the tumor at the same time.[3-9] According to Wargotz *et al.* there are five variants of MBC which include matrix producing carcinomas, squamous cell carcinoma, spindle cell carcinoma, carcinosarcoma, and metaplastic carcinoma with osteoclastic giant cells.[3-8] Cumulative five-year survival rates of various subtypes ranges from 49% to 68%.[3-7] In comparison to invasive ductal carcinomas (IDC), MBC present with a larger tumor size, less number of nodes involved, mostly undifferentiated tumors, which are usually triple negative.[1,10,11] When compared with IDC, patients with MBC have a shorter overall survival.[12,13] In a study by Nelson *et al.* five-year disease specific survival was 78% in MBC as compared to 93% in those with IDC ($p < 0.0001$).[14] There is no optimum treatment approach for management of MBC. Its management has been essentially similar to that of IDC.[15]

In this study, we reviewed a single center attempt to report outcome in terms of overall and progression-free survival of MBC patients. We analyzed several parameters such as menopausal status, tumor grade, stage, hormonal receptor, and Her 2 Neu status. This study reports the hospital-based incidence rate/proportion of MBC among all breast cancer subtypes. There was a lack of scientific literature from the developing countries regarding treatment options of MBC. Therefore, the study results may help in meeting the void.

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Material and Methods

Overview of study

A retrospective close cohort study was designed to collect data. Data in this study were mainly collected from the Aga Khan University Hospital cancer registry and Health Information and Management System (HIMS) from January 2008 till December 2013. This system established in 2009, is managed by the HIMS to identify all new cases. According to the Cancer Registry Regulations, this system identifies cancer in patients who report to our hospital for medical advice from all over Pakistan. The Aga Khan University Hospital (AKUH) is one of the main private cancer hospitals in the region. The follow up of patients with MBC was prospectively done until August 2016 regarding disease progression and survival.

Study population

All cases in the AKUH cancer registry and management system were identified by the coding system of the International Classification of Diseases for Oncology, 3rd Revision (ICD-03), from the World Health Organization.[16] In order to confirm the diagnosis of MBC and examine the changes on coding, we retrospectively collected and checked records of diagnosis and pathological reports of these cases. A review of the biopsy specimen was done by an experienced pathologist in order to confirm

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the diagnosis of MBC. A total of 42 patients who were diagnosed from August 2008 to December 2013 were recruited to calculate the progression-free survival and overall survival in this study. Non-probability purposive sampling methodology was employed to enroll patients for the study from the Health Information and Management System (HIMS). Patients aged 16 and above diagnosed with MBC and treated at the hospital were recruited. Patients were excluded if they were treated at another center, did not have a histologically confirmed diagnosis or sufficient staging information. Patients with bilateral disease were also excluded.

Exposure variables under study

The following variables were recorded at baseline for each patient including age, menopausal status, tumor grade, histological subtype, tumor size, nodal status, and metastatic involvement at presentation. Hormone receptor status including estrogen receptor (ER), progesterone receptor (PR) and Her-2 positivity were also documented. Type of surgery, chemotherapy received, be it neo-adjuvant, adjuvant or palliative, types of radiation received were also recorded. Development of locally recurrent disease and sites of distant metastasis were documented.

Estrogen receptor (ER), and progesterone receptor (PR) was defined according to Allred scoring as positive when the sum of proportion and intensity was two and above.[17] Her-2 positivity was defined as more than 10% strong complete membrane staining or positive with fluorescent *in situ* hybridization technique (FISH).[18]

Outcome

We examined two outcomes in terms of progression-free survival and overall survival. Progression-free survival (PFS) was calculated from the date of diagnosis until disease progression, death for any reason or the date of last contact. Overall survival (OS) was calculated from the date of diagnosis until death for any reason or the date of last contact. The follow up was prospectively done; PFS and OS were recorded by reviewing the charts and documenting last clinic visit. Hospital-based incidence rate/proportion of MBC was also computed. This was calculated by taking into account the number of newly diagnosed MBC patients and dividing them with all breast cancer subtypes that reported to the hospital from 2008 till 2013.

Ethics approval

The study protocol was initially accepted from the Ethical Review Committee of Aga Khan University Hospital, Karachi, Pakistan, with ERC #3026-Med-ERC-14.

Statistical analysis

Data were entered into IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. software and were transported and analyzed on STATA. Hospital-based incidence rate/proportion of MBC was computed. Mean and standard deviation was computed for continuous variables and proportions were reported for categorical variables. The purpose of the analysis was to report progression-free survival and overall survival. Survival analysis was applied in order to determine progression-free survival rate and overall survival rate of patients with MBC. A *P* value of less than 0.05 was considered as statistically significant. Log rank test and Breslow test were assessed to check Proportional Hazard assumptions, *P* value 0.049 and 0.061, respectively. Therefore, the assumptions of survival analysis were met. Cox Proportional hazard ratios were computed to assess associations between survival and independent variables. The independent variables were menopausal status, tumor size, tumor grade, ER, PR, and Her 2 neu status, nodal involvement and disease stage. By applying non-parametric Kaplan-Meier survival curve technique, we estimated the PFS and OS rate.

Results

A total of 42 women were included from January 2008 until December 2013 in the study. They were followed up till August 2016. Their mean ± SD age at diagnosis was 55.52 ± 12.473 years. The median age at tumor diagnosis was 54 years (range, 25–81 years). The mean ± SD follow up period was 39.77 ± 24.19 months. Their median follow-up period was 34 months (range, 0–94 months). There were 3 censored cases and 9 deaths. The data were censored under circumstances of being diagnosed at AKUH, but not seeking treatment from our center. One patient died because of myocardial infarction while on surveillance; seven died due to disease progression and one due to unknown cause. At data cut off, thirty patients were alive, three with disease and twenty-seven without disease.

Hospital-based incidence rate of MBC was 1.92% (42/2187), 95% CI [1.41-2.56].

Patient characteristics

Thirteen patients (31%) were premenopausal, the remaining postmenopausal. Nineteen patients (45.2%) were reported as hormone receptor positive and nine patients (19%) as Her 2-neu positive disease. Sixteen (38.1%) patients presented with triple negative disease. Squamous cell was the most common histology found in twenty-nine patients (69%). The mean tumor size was 4.7 cm ± 3.210 SD, (range, 0.8–17 cm); 90% of patients presented with tumor size > 2 cm. In this study, 19 (45.2%) patients presented with nodal involvement at diagnosis. Even though majority (57.1%) of the patients were diagnosed with stage two diseases, most (92.9%) of them existed as Grade III tumor patients. Four patients (9.5%) presented with metastatic disease at presentation, lung being the most common site involved, followed by bone and liver. All four of them had squamous histology. The baseline characteristics are given in Table 1.

Curative treatment

Neoadjuvant chemotherapy was received by 10 patients (31.25%). Among these 8 (80%) were of squamous histology. Anthracycline- and taxane-based chemotherapy was the most common (70%) regimen used in this setting. Among these five (50%) had a complete response.

Twenty-seven (64.3%) patients underwent modified radical mastectomy, which was the most common surgery. Four (9.5%) patients underwent simple mastectomy and sentinel lymph node biopsy (+/- axillary lymph node dissection) and

Table 1: Baseline characteristics of patients with Metaplastic breast cancer patients

Variable	Number of patients	Percentage
Histological subtype	42	
Squamous	29	69
Spindle	4	9.5
Carcinosarcoma	3	7.1
Spindle cell and squamous	2	4.8
Spindle cell and chondroid	1	2.4
Squamous and chondromyxoid	1	2.4
Subtype not specified	2	4.8
Tumor size		
T1	3	7.1
T2	28	66.7
T3	8	19
T4	3	7.1
Nodal status		
N0	23	54.8
N1	12	28.6
N2	6	14.3
N3	1	2.4
Stage		
Stage I	3	7.1
Stage II	24	57.1
Stage III	10	23.8
Stage IV	5	11.9
ER receptor*		
Positive	18	42.9
Negative	23	54.8
Unknown	1	2.4
PR receptor ~		
Positive	14	33.3
Negative	27	64.3
Unknown	1	2.4
Her-2 neu receptor		
Positive	9	19
Negative	31	73.8
Unknown	3	7.2
Tumor grade		
Grade I	0	0
Grade II	2	4.8
Grade III	39	92.9
Unknown	1	2.4

*ER=Estrogen Receptor, ~PR=Progesterone Receptor

8 (19%) underwent lumpectomy and sentinel lymph node biopsy (+/- axillary lymph node dissection).

Nineteen patients (45.2%) received adjuvant chemotherapy among which 16 (84.2%) were of squamous histology. Anthracycline- and taxane-based chemotherapy was again the most common (57.9%) regimen used.

Twenty-eight (66.6%) patients received adjuvant radiation out of which 16 (38.1%) received radiation to the chest wall and axilla.

Fourteen (33.33%) patients received adjuvant hormonal therapy among whom 9 (64.29%) received anastrozole and 5 (35.71%) received tamoxifen.

Table 2: Details of treatment in the curative setting

Variable	Number of patients (%)
Neoadjuvant chemotherapy (NACT)	
Received	10 (23.8)
Not received	32 (76.2)
Chemotherapy regimen	
Anthracycline based	2 (20)
Taxane based	1 (10)
Anthracycline and taxane based	7 (70)
Response to NACT	
Complete response (CR)	5 (50)
Partial response (PR)	2 (20)
Stable disease (SD)	2 (20)
Progressive disease (PD)	1 (10)
NACT response	
Responsive (CR + PR)	7 (70)
Unresponsive (SD + PD)	3 (30)
Type of surgery	
MRM*	27 (64.3)
SM+SLNB/ALND§	4 (9.5)
BCS+SLNB/ALND ~	8 (19.0)
Adjuvant Chemotherapy	
Received	19 (45.2)
Not received	23 (54.8)
Chemotherapy regimen	
Anthracycline based	4 (21.0)
Taxane based	1 (5.3)
Anthracycline and taxane based	11 (57.9)
TC¤	3 (15.8)
Radiation	
Received	28 (66.6)
Not received	14 (33.3)
Hormone treatment	
Received	17 (40.5)
Not received	25 (59.5)

*MRM=Modified Radical Mastectomy, § SM+SLNB/ALND=Simple Mastectomy and Sentinal Lymph Node Biopsy/Axillary Lymph Node Dissection, ~BCS + SLNB/ALND=Breast Conservation Surgery and Sentinal Lymph Node Biopsy/ Axillary Lymph Node Dissection, ¤TC=Taxotere and Cyclophosphamide

The details of treatment in the curative setting are given in Table 2.

Palliative treatment

At a median follow-up of 34 months (range, 0–94 months), metastatic disease was seen in 4 (9.52%) [4/42] patients with lung being the most common site followed by bone and liver. Out of them, 1 died due to disease and 3 were lost to follow up. Progressive disease was observed in 9 (24.32%) [9/37] patients. Out of them, 6 died due to disease, 2 were lost to follow up, and 1 was alive at data cutoff. Among the patients with progressive disease, lung was the most common site followed by bone. Palliative treatment modalities and survival outcomes are given in Table 3.

Most of the patients with progressive disease had hormone receptor negative disease (77.7%). Three patients received hormonal treatment in the palliative setting.

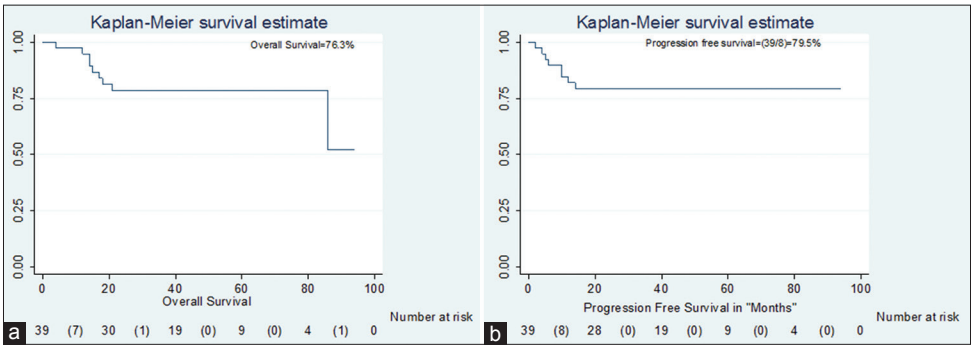

Figure 1: (a) Overall survival of Metaplastic breast cancer patients. (b) Progression-Free Survival of Metaplastic breast cancer patients

Table 3: Palliative treatment modalities and survival outcomes

Tumor histology	Palliative treatment	Overall survival (months)
Squamous	Cisplatin and Gemcitabine	22
Squamous	Temozolomide	15
Squamous	Anthracycline and cyclophosphamide–> Paclitaxel and transtuzumab –> Vinorelbine and transtuzumab –> Vinorelbine and lapatinib –> Lapatinib and Capecitabine –>Everolimus and Exemestane	22
Spindle cell	Docetaxel and Cyclophosphamide	14
Spindle cell	Paclitaxel –> Capecitabine	21
Spindle cell	Exemestane	18
Carcinosarcoma	Docetaxel	30

Table 4: Overall survival according to independent variables

	Number at risk	Overall Survival (%)
Age		
<50	9	88.9
>50	30	76.7
Her 2		
Positive	7	78.1
Negative	32	78.1
Stage		
Stage I	3	66.7
Stage II	23	87
Stage III	10	70
Stage IV	3	66.7
Tumor size		
T1 (<2 cm)	3	66.7
T2 (>2-5)	27	88.9
T3 (>5)	7	42.9
T4	2	100
ER*		
Positive	18	83.3
Negative	20	75
PR~		
Positive	14	92.2
Negative	24	70.8

*ER=Estrogen Receptor, ~PR=Progesterone Receptor

Survival analysis

By applying non-parametric Kaplan-Meier survival curve technique, we estimated the five-year PFS rate as 79.5% and five year OS rate as 76.3% [Figure 1a and b]. The median progression-free survival (PFS) and overall survival (OS) was 38 months (range, 2–94 months) and 38 months (range, 4–94 months), respectively. The censored patients were excluded from the survival analysis. The overall survival based on independent variables is given in Table 4.

The two primary endpoints were PFS and OS among patients diagnosed as MBC. Factors associated with better progression-free and overall survival were tumor grade and menopausal status. When stratified based on Her-2 neu status, tumor size, nodal size, tumor stage, or progesterone receptor status, neither of these factors were associated with any improvement in progression-free or overall survival. Adjusted analysis of MBC patient's survival is given in Table 5.

Discussion

MBC is a rare and heterogeneous group of diseases.[1,12,19] In our study it accounted for 1.92% (42/2187) of all invasive breast cancers. The median age at presentation varies between 45 to 61 years.[1,12,13,19,20] Our study reports a median age of 55.5 years, which is in concordance with published literature. There is a variability among the median tumor size ranging from 3.4-5.7 cm.[12,19,21] The median tumor size in our study was 4.5 cm supporting international data of these tumors presenting with a large tumor size. It is usually associated with negative nodal involvement with studies reporting between 4.4 to 35% lymph node metastasis.[12,22,23] This is in contrast to our series in which 53.1% patients had lymph nodes involved. However, in a similar Turkish study, 63.4% patients had axillary lymph nodes involved[19] suggesting that the Asian population had a propensity to involvement of lymph nodes. Leyrer *et al.* reported 35% rate of distant metastasis;[20] our study reported 24.32%.

The surgical approach has been comparative to patients with IDC, with breast conserving therapy showing similar overall survival to mastectomy in the appropriate patients.[24]

About 64.3% of our patients underwent modified radical mastectomy bearing in mind that 90% patients had a tumor size of more than 2 cm.

Standard chemotherapy regimens used for patients with IDC have little effect in women with MBC.[25] In a study by Rayson *et al*. 9 patients received adjuvant chemotherapy, among which 7 developed disease recurrence (77.7%).[12] In our series 19 patients received adjuvant chemotherapy and one developed disease recurrence (5.2%). We report 70% (50% PCR, 20% PR) response to neoadjuvant chemotherapy which is way higher than data reported in the past. In a study from Cleveland, 39% patients had a pCR.[20] In a Turkish study, none of the patients had a pCR, and 6.2% partial response.[26] Outcomes are better in patients who achieve pCR. In our study none of the patients with pCR developed metastatic disease versus 60% (3/5) in those without pCR. The percentage of metastatic disease was 11% vs. 50% in those with and without pCR in a similar study.[20]

Historically majority (71%) of MBC cases are triple negative.[11,22] Hence, hormonal therapy largely has no role in these patients.[10] In our series a total of 38.1% patients were found to have triple negative disease. In a study by Gultekin *et al.*[22] none of the patients were her 2-neu receptor positive; however, 9.4% of our patients were Her-2 neu receptor positive. Estrogen and progesterone receptor positivity has been reported up to11.3% and 10.4% respectively by Pezzi *et al.*[1] In our patients 45.2% were ER and PR receptor positive. Bae *et al*. report giving hormonal treatment to three patients, with no recurrence in the follow up period.[10] Rayson *et al.* gave palliative tamoxifen to 4 patients, but none of them reported any response.[12] Thirteen patients received adjuvant hormonal treatment among which one patient developed progressive disease. Only one patient in this study received palliative hormonal treatment and did not have progression till 18 months of follow up. She however was lost to follow up later.

Table 5: Adjusted analysis of Metaplastic breast cancer patient's survival

Characteristics	Overall Survival Analysis			Progression-Free Survival Analysis		
	HR*	95% CI¤	*P*	HR*	95% CI¤	*P*
Her2 Neu	1.8	0.22-15.14	0.6	1.6	0.197-13.04	0.7
Tumor size	1.5	0.54-39.14	0.5	1.9	0.57-6.5	0.3
Stage	1.46	0.62-3.49	0.4	1.4	0.548-3.46	0.5
Nodal Stage	1.54	0.83-2.89	0.2	1.3	0.64-2.78	0.4
Grade	0.3025	0.06-1.61	0.2	0.4	0.044-2.95	0.3
Menupause	0.8175	0.17-3.94	0.8	1.0	0.199-4.91	1.0
Progesterone receptor	4.68	0.58-38.18	0.1	4.6	0.56-37.21	0.2

*HR=Hazard Ratio, ¤CI=Confidence Interval

The five-year PFS from International data is reported between 30% and 69%.[23,27,28] We report a five-year PFS of 79.5%. Similarly, various studies report five-year OS between 65% and 69%.[20,23,27,28] In our study the five-year OS was 76.3%. Both the PFS and OS of our patient population are higher than survivals reported from the West. However, the higher survival is similar to that reported from three Asian countries, namely of patients reported from Turkey by Gultekin *et al.* (76% and 80% five-year PFS and OS, respectively), from China by Zhang *et al.* (67.9% and 78.7% five-year PFS and OS, respectively) and from Korea by Bae *et al.* (78.1% three-year PFS).[10,11,22] Comparison of previous literature in terms of PFS and OS of MBC patients with our study is given in Table 6.

MBC is associated with high potential of metastatic disease with lungs being the most common site involved.[12,19] In our study nine (9/42; 21.42%) patients developed metastatic disease, out of which six had lung involved. The median overall survival after disease progression was 21 months which is higher in comparison to previous study.[12]

In a study by Rayson *et al*. women younger than 60 years and with prior history of estrogen use were associated with decreased disease-free survival.[12] In contrast, women younger than 50 had better survival in our series. Negative nodal involvement was associated with better outcomes in a study reported by Dave *et al.*[24]. No such association was found in our study. In a study by Leyrer *et al.*, there was no difference in outcomes based on histologic subtype.[20] Squamous cell histology was the most common subtype in our series. However, outcome analysis could not be performed comparing various subtypes as the proportion of these was very small.

Unanswered questions and future directions for research

Multiple studies prove that MBC is said to have the worst prognosis among all cancer subtypes. There have been case reports of use of doxorubicin, ifosfamide, and etoposide in sarcomatoid and carcinosarcoma variant of MBC.[29,30] However, clinical trials are required to explore these potential new therapies.

Strengths of study

To the best of our knowledge, this is the first single center study reported at a tertiary care hospital from our

Table 6: Comparison of previous literature in terms of five-year progression-free and overall survival of MBC patients

Author	Country	Year of publication	Number of cases	Progression-Free Survival	Overall Survival
Fayaz D *et al.*	Kuwait	2017	31	50%¤	69%
Zein E *et al.*	USA	2017	46	30%¤	65.30%
Leyrer B *et al.*	USA	2017	113	*	69%
Esbah *et al.*	Turkey	2012	14	33%§	56%§
Cimino-Mathews *et al.*	USA	2016	45	64%	69%
Samoon *et al.*	Pakistan	2018	42	79.50%	76.30%

*Progression-Free Survival unreported by Authors. ¤Five-year Disease-Free Survival. §Three-year Survival

region. We report 70% (50% PCR, 20% PR) response to neoadjuvant chemotherapy, which is way higher than the data reported in the past.

Limitations of study

There were several limitations of the study. This was a retrospective study with a small sample. Some patients were lost to follow up and data regarding their treatment was not available.

Conclusion

In conclusion, MBC is a rare and aggressive variant of breast cancer. Five-year progression-free and overall survival was 79.5% and 76.3%, respectively. We report better survival outcomes when compared to series described earlier despite our patient population presenting mostly with high grade, large tumors, and half of them exhibiting nodal and hormonal involvement. Literature exploring molecular targets and clinical trial exploring tumor-specific therapies is required to improve disease prognosis.

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Conflicts of interest

There are no conflicts of interest.

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