Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Clinicopathological Features and Survival Outcomes of Metaplastic Breast Carcinoma – An Observational Multi-Centric Study

Maryam Sherwani[1,*], Lubna Vohra[1,*], Danish Ali[1,*], Rufina Soomro[2], Syed Adnan[1], Romana Idrees[3]

[1]Department of Surgery, Aga Khan University, Karachi, Pakistan; [2]Department of Surgery, Liaquat National Hospital, Karachi, Pakistan; [3]Department of Pathology, Aga Khan University, Karachi, Pakistan

*These authors contributed equally to this work

Correspondence: Lubna Vohra, Aga Khan University Hospital, Karachi Stadium Road, P.O. Box 3500, Karachi, 74800, Pakistan, Tel +92 21 34930051, Fax +92 21 3493 4294, Email lubna.vohra@aku.edu

Purpose: To describe the clinicopathological features, and subtypes of metaplastic breast cancer (MpBC) in Pakistan and further to understand its response to treatment, including region-specific survival outcomes.

Patients and Methods: This retrospective cohort study was conducted at two private tertiary care hospitals in Karachi, Pakistan. Our selection criteria included a total of 215 patients who were diagnosed with MpBC at an age older than 18 years from 1994 to 2021. Data regarding clinicopathological features, staging, receptor status, treatment modalities, recurrence, and survival was obtained. Death was scored as an event, and patients who were alive were censored at the time of the last follow-up.

Results: The incidence of MpBC at our study centers is 3.21%. The median age of diagnosis was 50 years (range 22 to 80 years) and most patients presented at Stages II (45.1%) and III (44.2%). Among patients who received neoadjuvant chemotherapy, 31.7% achieved complete pathological response. The 3-year survival of those who received neoadjuvant chemotherapy was 96%. During our study, 19.1% of patients died and the median survival duration was 9 years 7 months 9 days. Survival of patients was significantly lower in patients who had metastasis (p-value = 0.042) and those who had tumor recurrence (p-value = 0.001).

Conclusion: Metaplastic breast cancer is an extremely rare variant of breast cancer with features that exist as a spectrum. Our study demonstrated considerable success with the use of neoadjuvant chemotherapy. The pathological complete response achieved in our study is one of the highest ever reported. Our success, though limited, warrants further research in the use of neoadjuvant chemotherapy in MpBC.

Keywords: neoadjuvant therapy, triple negative, squamoid, overall survival

Introduction

Breast cancer has become ubiquitous, surpassing lung cancer as the most widely diagnosed cancer, and yet remains a unique challenge to clinicians and researchers. It is now the leading cause of cancer-related mortality in women, despite revolutionary developments in its understanding and treatment over the last few decades.[1] Up until the start of this millennium, there was a lack of clarity regarding the classification of invasive breast tumors which simulated a range of appearances from squamous cell carcinoma at one end to sarcomas at the other.[2] In the year 2000, the World Health Organization (WHO) recognized metaplastic breast cancer as a unique pathological entity that features both, epithelial and mesenchymal components. WHO further classified this heterogeneous neoplasm into seven histological subtypes. These include low-grade and high- grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, spindle cell carcinoma, squamous cell carcinoma, metaplastic carcinoma with heterologous mesenchymal (eg chondroid, osseous and rhabdomyoid) differentiation and mixed metaplastic carcinomas.[3] Now that there is sufficient understanding to

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classify breast cancer by histological, molecular, and genetic factors, efforts are being made to tailor treatments according to each subtype, with the goal of better prognoses.

Metaplastic breast cancer is a form of breast cancer that harbors amazing diversity in its presentation, histological findings, and therapeutic response.[4] With a worldwide incidence of 0.25%-2%, MpBC is a rare disease as defined by the Rare Diseases Act of 2002.[2,5] It is a unique neoplasm that comprises both, epithelial and mesenchymal components and has various histological subtypes. MpBC commonly occurs as triple-negative breast cancer (TNBC)[6] and the prevalence of metaplastic subtype among all triple-negative breast cancers is 2.7–5.9%.[7–11]

This distinct tumor has generated interest particularly since it is now found that this variant of breast cancer holds the worst prognosis among all breast cancer types.[12] Recent studies have shown a reduced 5-year overall survival of 53.7–71% versus 81.2–88% in non-MpBC TNBC along with a significant reduction in breast cancer-specific survival. Out of its various subtypes, the mixed metaplastic subtype was implicated in having the worst prognosis.[7,12,13] The overall prognostic markers associated with decreased survival include lymph node metastasis, lymphovascular invasion, large tumor size (greater than 5cm), personal history of breast cancer, and positive surgical margins.[13–15] Generally, MpBC is associated with larger tumors and less frequent nodal involvement; however, studies from Asia have reported higher rates of lymph node involvement among the Asian population.[16]

MpBC is a challenging tumor to treat as it is usually considered chemorefractory.[17] A questionably aggressive surgical approach has been adopted due to a lack of alternative therapeutic options. Fortunately, recent Western studies have shown some success in improving survival with radiotherapy in MpBC.[7,14] It has been demonstrated that radiotherapy post-lumpectomy and mastectomy can improve overall survival but does not contribute to disease-specific survival in MpBC.[18] The future of MpBC treatment relies on a global analysis of its molecular targets and radiotherapy regimens.

The stark geographic variations in pathological behavior and treatment response warrant further molecular and genetic research. It has been almost two decades ago since the identification of MpBC yet there is insufficient information about MpBC's pathogenesis, optimal treatment options, and clinical or surgical outcomes. The extremely low incidence rate of MpBC perpetuates the difficulty in studying this tumor effectively.[7] Due to the rarity of this disease and scarce epidemiological evidence, there is a lack of specific guidelines or management protocols defining the role of surgical resection, chemotherapy, and radiotherapy in MpBC.[7] Recent studies from Asia that describe the clinicopathological features of MpBC according to its histological subtypes along with the respective survival outcomes are mostly single-center studies and are usually limited by smaller sample sizes.[16] Hence, we conducted a multicentric study in Pakistan to describe the clinicopathological features, and subtypes of MpBC, and further to understand its response to treatment, including region-specific survival outcomes.

Materials and Methods

Participants

This retrospective cohort study was conducted at two private tertiary care hospitals in Karachi, Pakistan. These hospitals cater to a large population and has highly trained breast surgical oncologists. After obtaining approval from the Ethical Review Boards (ERC) of either hospital (Aga Khan University ERC# 2019-1910-5189) a written and informed consent was obtained from all the patients who fulfilled the eligibility criteria; the data was then collected via file review. The consenting individuals were assured that their data will follow the institutional data retention policy; it will only be accessible by the research team and will only be used for the purpose of research and advancement of knowledge. The retrospective chart review was in accordance with the institutional research policies and the Declaration of Helsinki. Initially, we sought all patients who were diagnosed with any kind of breast cancer between 1994 to 2021, which came to a total of 6764 patients. One patient was excluded as she was <18 years old. The selection criteria were then applied which included all patients who were diagnosed with MpBC at an age older than 18 years. A total of 215 patients fulfilled the criteria and were included in this study. Data regarding clinicopathological features, staging, receptor status, treatment modalities, recurrence, and survival were obtained.

Pathological Analysis

Histological grade was determined using the Modified Richardson-Bloom grading system and histological subtypes of metaplastic breast carcinoma were classified according to WHO classification.[3] Loco-regional recurrence was defined as tumor recurrence at the breast, ipsilateral axilla, thoracic wall, supraclavicular fossa, or parasternal region while distant recurrence was defined as recurrence at any other site.

Statistical Analysis

Outcome or survival was assessed in as overall survival (OS). OS is defined as survival from the date of diagnosis until death for any reason or the date of the last contact. Death was scored as an event, and patients who were alive were censored at the time of the last follow-up. The data was analyzed on Statistical Package for Social Sciences (SPSS) version 25.0. All qualitative variables have been presented as frequency and percentages and all quantitative variables are presented as mean and range. Logistic regression was used to find an association between tumor characteristics and tumor recurrence. Variables with a p-value ≤ 0.25 at univariate analysis were selected for multiple logistic regression analysis.[19] Unadjusted and adjusted beta coefficients with their 95% confidence intervals (CIs) were reported and a p-value < 0.05 at multivariable analysis was considered significant. For survival analysis, the Kaplan-Meier method was used and comparisons were made using the cox proportional hazards regression. For variables with a p-value ≤ 0.25 in the univariate analysis, the cox multivariable analysis was performed to determine factors associated with OS. Using the cox multivariable analysis adjusted hazard ratios (HRs) and their 95% Confidence Intervals (CIs) were reported; a p-value < 0.05 was considered significant.

Results

Clinicopathological Features

The incidence of MpBC at our study centers is 3.19%. Table 1 shows the demographic and clinicopathological features of the patients included in the study. The median age of diagnosis was 50 years (range 22 to 80 years).

Most patients presented at Stages II (45.1%) and III (44.2%). The majority of patients (88.4%) had a maximum of 3 nodal groups involved (N_0 and N_1) and a majority of patients (73.8%) had a histologic grade III tumor. The most

Table 1 Demographics and Clinicopathologic Features

N = 215	**n**	**%**
Characteristic		
Age at diagnosis, n = 215		
≤40	44	20.5
41–59	121	56.3
>60	50	23.3
Median – 50 years		
Range – 22 to 80 years		
T stage (pre-treatment), n = 215		
T_1	15	7.0
T_2	90	41.9
T_3	50	23.3
T_4	60	27.9
N stage (pre-treatment), n = 215		
N_0	94	43.7
N_1	96	44.7
N_2	23	10.7
N_3	2	0.9

(*Continued*)

Table 1 (Continued).

N = 215	n	%
Characteristic		
M stage (final), n = 215		
M_0	198	92.1
M_1	17	7.9
Sites of metastasis, n = 17		
Visceral (liver)	3	17.7
Bone	4	23.5
Lung	1	5.9
Multiple	9	52.9
TNM Staging (pre-treatment), n = 215		
Stage I	6	2.8
Stage II	97	45.1
Stage III	95	44.2
Stage IV	17	7.9
Type of metaplastic carcinoma, n = 215		
Chondroid	2	0.9
Choriocarcinomatous	1	0.5
Osteoid	6	2.8
Sarcomatoid	18	8.3
Squamoid	188	87.6
Receptor status, n = 171		
Luminal type	57	33.1
Her2 enriched	27	15.7
Triple negative	87	51.2
Histologic grading of tumor, n = 160		
Grade I	0	0
Grade II	42	26.3
Grade III	118	73.8

predominant subtype of MpBC was squamoid (87.6%) (Figure 1). Almost half (51.2%) of the tumors were triple-negative and 15.7% were Her2/neu enriched (Table 1). Most patients (77.4%) underwent mastectomy as the initial procedure (Table 2).

Neoadjuvant Chemotherapy and Disease Response

The most common neoadjuvant chemotherapy (NAC) agent used (76.7%) was a combination of doxorubicin hydrochloride and cyclophosphamide with a taxane (also known as Adriamycin cyclophosphamide + Taxol or AC + Taxol) and which produced a 3-year survival of 96%. Only patients with stage 2 and stage 3 disease received NAC (Table 3). Half the patients who received NAC had TNBC (Table 3). NAC administration led to a pathological complete response in 31.7% of patients while a partial response in 36.7% of patients (Table 4).

Survival Analyses

During our study, 19.1% of patients died and the median survival duration was 9 years 7 months 9 days (range 0.02 to 13.7 years) (Table 5). Figure 2 shows that the OS 2 years after diagnosis was 83% which declined to 65% by year 5 and 49% by the tenth year. Recurrence occurred in 12.1% of cases (Table 5). After 1.35 years (1 year 4 months 6 days) there was a significant difference in survival among patients who had recurrence versus patients who did not have a recurrence (p-value < 0.05)

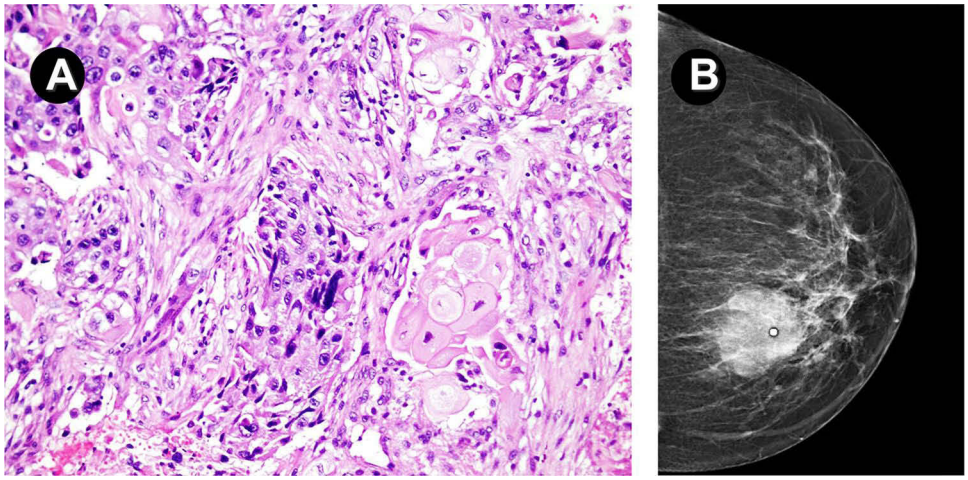


Figure 1 (**A**) is a histological slide prepared using H&E staining shows the squamous subtype at 200x. (**B**) is the mammogram of the same patient showing a large soft tissue density in the retroareolar area (47x42mm) of the left breast which shows spiculated margins.

(Figure 3). Only 7.9% of patients developed metastasis during their follow-up period of which bones were most commonly involved (23.5%). Survival of patients was significantly lower in patients who had metastasis (p-value = 0.042) and those who had tumor recurrence (p-value = 0.001) while TNM staging, type of surgical procedure undertaken, and deliverance of adjuvant

Table 2 Treatment Administered and Its Response

N = 215	**n**	**%**
Characteristic		
Type of procedure, n = 168		
Mastectomy	130	77.4
Breast conservation	38	22.6
Axillary lymph nodal positivity, n = 168		
None	113	67.3
1–5	39	23.2
>5	16	9.5
Neoadjuvant chemotherapy administered, n = 111		
No	70	63.1
Yes	41	36.9
Neoadjuvant chemotherapy regimen, n = 30		
FAC	1	3.3
TC	4	13.3
AC + Taxol	23	76.7
AC + Taxotere	1	3.3
Taxol	1	3.3
Adjuvant chemotherapy administered, n = 83		
No	45	54.2
Yes	38	45.8
Breast radiation, n = 176		
No	80	45.5
Yes	96	54.5

Table 3 Patient Stage and Tumor Receptors with Neoadjuvant Status

N = 41	n	%
Characteristic		
Stage (pre-treatment), n =41		
Stage 1	0	0
Stage 2	9	22
Stage 3	32	78
Stage 4	0	0
Receptor status, n = 36		
Luminal	12	33.3
Her-2 enriched	6	16.7
Triple negative	18	50

Table 4 Overall Response to Neoadjuvant Therapy

N = 41	Stage (Pre-Neoadjuvant)		Total	
	Stage 2	Stage 3	n	%
Stage (post-neoadjuvant)				
Stage 0	4	9	13	31.7
Stage 1	3	3	6	14.6
Stage 2	2	9	11	26.8
Stage 3	0	11	11	26.8
Total	9	32	41	
Response to neoadjuvant				
Pathological complete response	4	9	13	31.7
Pathological partial response	3	12	15	36.7
Pathological no response	2	11	13	31.7
Any response to chemotherapy?				
Yes	7	21	28	68.3
No	2	11	13	31.1

chemotherapy was also significant in univariate analysis (p-value < 0.25) (Table 6). Amongst patients who developed recurrence neither radiotherapy (p-value = 0.887) nor adjuvant chemotherapy (p-value = 0.566) was beneficial for survival (Table 7). None of the factors we studied were associated with the development of recurrence amongst patients in multivariable analysis (Table 8).

Table 5 Recurrence and Survival

N = 215	n	%
Characteristic		
Recurrent disease, n = 215		
No	171	79.5
Yes	26	12.1
Loss to follow-up	18	8.4

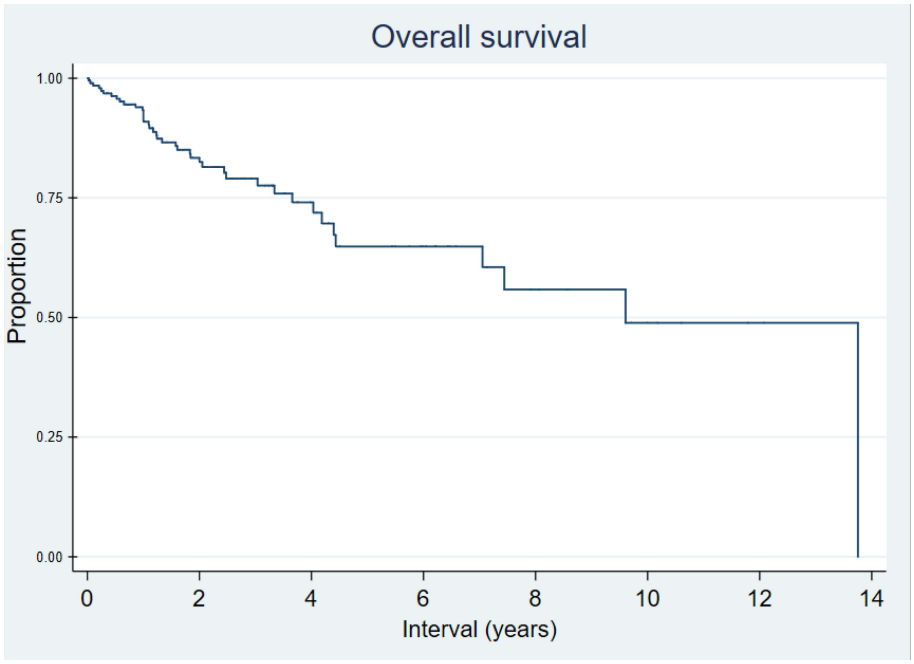
(*Continued*)

Table 5 (Continued).

N = 215	n	%
Characteristic		
Type of recurrence, n = 26		
Locoregional	11	42.3
Distant	15	57.7
Overall survival, n = 215		
Alive	158	73.5
Expired	41	19.1
Loss to follow-up	16	7.4
Median = 9.6 years (9 years 7 months 9 days)		
Range = 0.02 to 13.7 years		

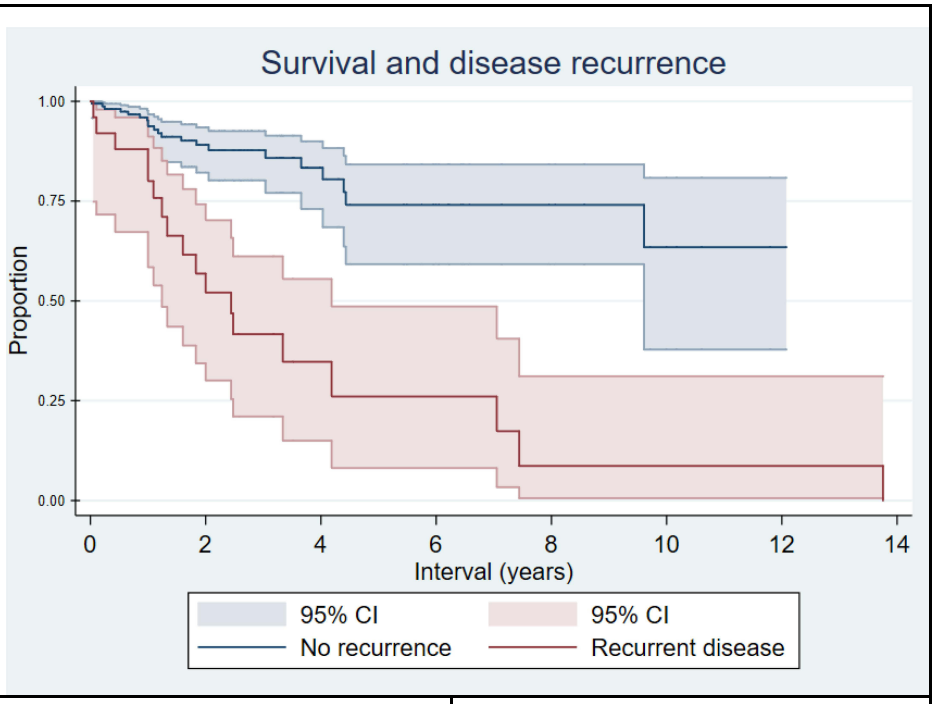
Discussion

Metaplastic breast cancer is an intriguing subset of breast cancer with a wide array of clinicopathological features but its rarity hampers exploration of its diversity. In this paper, we present a dual-centre cohort of patients who were diagnosed with metaplastic breast cancer. The MpBC features in this population are suggestive of a higher responsivity to chemotherapy than previously reported.



2 years – 83%
5 years – 65%
10 years – 49%

Figure 2 Kaplan–Meier curve for overall survival.



Patients with recurrence	Patients without recurrence
2 years – 52%	2 years – 90%
5 years – 26%	5 years – 74%
10 years – 9%	10 years – 64%

Figure 3 Kaplan–Meier curve for overall survival probability amongst patients with and without recurrence.
Abbreviation: CI, confidence interval.

In our study, the incidence of metaplastic breast cancers among all types of breast cancers was 3.21%. This is a marked increase from the reported worldwide MpBC incidence of <1%.[2] The incidence of MpBC in other Asian centers is similar (0.9–1.9%) to the data gathered from around the world.[16,20] A harbinger for this study, a previous report from our center demonstrated that MpBC comprises 10.7% of the total TNBCs, which is a 5-fold increase from other Asian countries.[21] In addition to our reports, nationwide studies need to be conducted to delineate the higher incidence in the region and thus form the basis of further investigation.

Table 6 Univariate and Multivariate Analysis with Survival

Characteristic	Univariate Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age (years)	0.998	0.975–1.020	0.846	NS		
T stage (pre-treatment)						
T_1	1 (reference)			1 (reference)		
T_2	2.759	0.361–21.085	0.328	0.949	0.059–15.252	0.970
T_3	2.967	0.362–24.307	0.311	0.121	0.003–5.374	0.276
T_4	7.539	1.000–56.822	0.050	0.199	0.003–13.250	0.451

(*Continued*)

Table 6 (Continued).

Characteristic	Univariate Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
N stage (pre-treatment)						
N_0	1 (reference)					
N_1	1.324	0.657–2.666	0.433			
N_2	2.028	0.767–5.365	0.154			
N_3	1.482	0.188–11.663	0.709			
M stage (final)						
M_0	1 (reference)			1 (reference)		
M_1	2.488	0.869–7.123	0.089	20.495	1.119–375.465	0.042
Surgical procedure undertaken						
Mastectomy	1 (reference)	0.018–0.953		1 (reference)		
BCS	0.129		0.045	0.448	0.042–4.775	0.506
Margin Involvement						
No	1 (reference)					
Yes	0.813	0.095–6.970	0.850	NS		
Histologic grade						
Grade II	1 (reference)					
Grade III	0.847	0.347–2.064	0.715	NS		
Receptor status						
Luminal type	1 (reference)					
HER2 enriched	1.125	0.412–3.075	0.818	NS		
Triple negative	0.710	0.310–1.629	0.419			
Neoadjuvant status						
No	1 (reference)					
Yes	1.260	0.352–4.507	0.722	NS		
Breast radiation						
No	1 (reference)					
Yes	0 0.692	0.327–1.466	0.337	NS		
Adjuvant chemotherapy						
No	1 (reference)			1 (reference)		
Yes	0.256	0.054–1.208	0.085	0.437	0.040–4.729	0.496
Recurrence						
No	1 (reference)			1 (reference)		
Yes	5.162	2.720–9.780	0.000	24.076	3.582–161.815	0.001

Note: Variables having a p-value >0.25 in univariate analysis are considered not significant (NS) in multivariate analysis.
Abbreviation: BCS, Breast Conservation Surgery.

The median age of diagnosis in the study population was 50 years, which matches the median age of diagnosis of breast cancer, in general, in Pakistan.[22] Metaplastic breast cancers are generally understood to be larger tumors with less nodal involvement, which is consistent with the findings of this study. The frequency of patients, however, who presented with tumors larger than 5 cm is considerably higher in our study population. An extensive study conducted by Duke University revealed that 17.8% of MpBC patients present with tumors staged T_4 or higher[23] whereas in our setting more than half (51.2%) of our patients presented with T_3 and T_4 tumors. This disparity may be explained by limited patient health awareness coupled with a lack of screening programs in Pakistan, both of which ultimately results from our country's longstanding catastrophic fiscal affairs.[24] However, the contribution of genetics to this variation cannot be

Table 7 Univariate Analysis of Radiation and Chemotherapy Given After Recurrence with Survival

Characteristic	Odds Ratio	95% CI	P value
Radiotherapy			
No	1 (reference)		
Yes	0.816	0.050–13.241	0.887
Adjuvant chemotherapy			
No	1 (reference)		
Yes	0.436	0.026–7.427	0.566

Abbreviation: CI, confidence interval.

Table 8 Characteristics Showing Association with Recurrence

Characteristic	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age (grouped)						
<39 years	1 (reference)			1 (reference)		
40–60 years	0.596	0.199–0.919	0.289	0.499	0.110–2.268	0.368
>60 years	0.356	0.377–1.824	0.114	0.365	0.058–2.275	0.280
T stage (pre-treatment)						
T_1	1 (reference)					
T_2	0.900	0.100–8.141	0.925	NS		
T_3	2.400	0.272–21.160	0.431			
T_4	3.385	0.395–28.367	0.266			
N stage (pre-treatment)						
N_0	1 (reference)					
N_1	1.425	0.575–3.533	0.444	NS		
N_2	1.852	0.512–6.670	0.347			
N_3	-	-	-			
M stage (final)						
M_0	1 (reference)					
M_1	0.644	0.079–5.250	0.681	NS		
Surgical procedure undertaken						
Mastectomy	1 (reference)			1 (reference)		
BCS	0.280	0.063–1.255	0.096	0.454	0.082–2.506	0.365
Margin Involvement						
No	1 (reference)					
Yes	0.286	0.033–2.438	0.252	NS		
Histologic grade						
Grade II	1 (reference)					
Grade III	1.652	0.518–5.265	0.396	NS		
Receptor status						
Luminal type	1 (reference)					
HER2 enriched	0.850	0.236–3.062	0.804	NS		
Triple negative	0.559	0.201–1.556	0.265			

(*Continued*)

Table 8 (Continued).

Characteristic	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Neoadjuvant status						
No	1 (reference)			1 (reference)		
Yes	2.564	0.804–8.177	0.112	1.014	0.217–4.734	0.986
Breast radiation						
No	1 (reference)					
Yes	1.707	0.653–4.467	0.276	NS		
Adjuvant chemotherapy						
No	1 (reference)			1 (reference)		
Yes	0.172	0.035–0.832	0.029	0.177	0.027–1.156	0.071

Notes: Variables having a p-value >0.25 in univariate analysis are considered not significant (NS) in multivariate analysis. [1]Due to a smaller sample in N_3 disease the univariate analysis could not be carried out for this value.
Abbreviations: BCS, Breast conserving surgery; CI, confidence interval.

excluded. A study based in India had a similar proportion of patients (57.5%) presenting with MpBC tumors > 5 cm.[25] As both Pakistan and India share a common origin, it raises concern that genetics may play a role in the aggressive nature of these tumors.

Metaplastic breast cancer can be categorised into triple negative, HER2- positive, and luminal subtypes. Metaplastic breast cancer is commonly triple negative, that is it lacks the estrogen, progesterone, and HER2 receptors. The proportion of TNBC tumors among MpBC in Europe and the US is 89%, and 69% respectively.[7,26] We have observed, that even though triple-negative cancers were the most common subtype of MpBC, making up 51.2% of the cohort, a fair share of tumors were receptor positive. Nearly one-third of the tumors were of the luminal subtype while HER2+ enriched tumors constituted 15.7% of the tumors in our study population. In comparison, a large Surveillance Epidemiology and End Results (SEER) based study from the United States (US) demonstrated a similar frequency of the luminal subtype while that of HER2+ enriched tumors was merely 3.7%.[7] The incidence of the Her2+ enriched subtype in our study is more than four times that of the US which begs further exploration. Overall, the proportion of breast cancer in Pakistan that is Her2+ enriched mirrors that of the US so it is interesting that in the metaplastic subtype of breast cancers a wide disparity exists in the frequency of Her2+ enrichment.[22,27] Triple-negative cancers are considered to have the worst prognosis among all breast cancer subtypes.[28] As with any other variant of breast cancer, the mainstay of non-metastatic metaplastic breast cancer treatment is surgery. There are no specific guidelines that are tailored to the metaplastic subtype of breast cancer; thus, treatment is largely trialed based on the tumor stage and characteristics. Radiation and chemotherapy (adjuvant and neoadjuvant) along with surgery have been conventionally used in the treatment of MpBc with varying amounts of success.[15]

The aforementioned SEER-based study concluded that MpBC is highly treatment resistive even though its results showed improved OS with radiotherapy ($p<0.001$) and chemotherapy ($p=0.025$). In the study, although chemotherapy was collectively associated with improved OS, further analyses revealed that chemotherapy did not improve survival in the triple-negative MpBC subset.[7] In our study, we did not find an association between radiation ($p=0.337$) or adjuvant chemotherapy ($p=0.085$) with overall survival. However, we had appreciable success in treatment with neoadjuvant chemotherapy (NAC). One hundred and eleven of our patients underwent neoadjuvant chemotherapy, out of whom 30 were assessed for pathological response. Our results show that 31.7% of patients achieved complete pathological response while 36.7% responded partially to chemotherapy. The majority of our patients received the AC-T regimen of anthracycline and cyclophosphamide followed by a taxane. Our institution has previously reported the highest rate (50%) of complete pathological response after NAC amongst MpBC.[16] Our study fortifies the former with a good response even when trialed in a larger population. The complete pathological response achieved in this study is among the highest reported. The results of other studies have been quite dismal. In a study done at Mayo Clinic, patients with

MpBC received a variety of NAC regimens out of which 11% achieved complete pathological response.[29] In another study based at the Memorial Sloan Kettering Cancer Centre (MSKCC), only one out of forty-four patients achieved a complete pathological response with AC-T-based NAC.[30] The 3-year overall survival of patients in the MSKCC study was 65%, while the 3-year survival in our study was significantly better at 96%. Despite the good response to neoadjuvant chemotherapy, our results show that there was no association between deliverance of neoadjuvant therapy and overall survival in patients ($p = 0.722$).

The mismatch of curative surgery and good response to neoadjuvant chemotherapy but poor overall survival in our cohort may be explained by general inaccessibility to healthcare in the region. Multivariate analyses of our results show that recurrence and metastasis were associated with poor survival. Both these factors are likely to be related to poor follow up after initial treatment. The predominant mode of healthcare payments in Pakistan is self-pay, and only a small proportion of the population is covered by health insurance or government funds, thus healthcare is inaccessible for many. Many of our patients come from far-flung areas of the country and with additional costs involving radiotherapy and surveillance, our concern is they may not receive adequate care after surgery which could potentially lead to recurrence, metastasis, and hence worse survival outcomes.

With the advent of chemotherapy and radiotherapy, there has been a paradigm shift in the treatment of breast cancer with the adoption of a "less is more" approach toward surgery. However, worldwide, there is a tendency to lean towards more aggressive surgical treatment for metaplastic breast cancer.[31,32] This is likely owing to the relatively large size of MpBCs at the time of presentation. In the US this shift translates to nearly equal rates of mastectomies and breast conservation therapies for MpBC.[23,26] However, in our population, an overwhelming number of women (77.4%) with MpBC were treated with mastectomies. This deviation is not surprising considering that there is a higher rate of mastectomies (62–85%) for all types of breast cancers among Pakistani women.[22,33,34] It is plausible that cultural fears of radiation therapy and fear of recurrence may propel women to undergo mastectomies in our setting, despite similar rates of recurrence with both surgical options. As discussed, a lack of access to resources for radiation and surveillance is also a major contributing factor to this decision. Thus, we believe the prognosis of metaplastic breast cancer is guided by a combination of biological and cultural factors in our region.

Our study contributes to the extremely limited pool of data on metaplastic breast cancer. It is a comprehensive review of clinicopathological features, treatment, and survival of study patients from a low-middle income country with a scarcity of data. There is missing data in our study which could potentially reduce the consistency of our findings. Owing to its rarity, with the limited data we are unable to make recommendations based on our study findings.

Conclusion

Metaplastic breast cancer is an extremely rare variant of breast cancer with features that exist as a spectrum. This makes it difficult to predict tumor behavior and responsiveness to various treatments. Our study has shown promising results with the use of neoadjuvant chemotherapy, achieving a complete pathological response in 31.7% of patients, which is amongst the highest to be reported. It is probable that the reason we achieved a good response to neoadjuvant chemotherapy is that triple negative metaplastic breast cancer was the most common variant in our patient cohort, since such tumors conventionally respond comparatively better to NAC. However, we would need a bigger sample of patients who underwent neoadjuvant chemotherapy to conclude so. Our success, though limited, warrants further research in the use of neoadjuvant chemotherapy in MpBC. Considering it has the worst outcomes amongst triple-negative breast cancers and that it has geographic variations in its incidence and tumor characteristics, we identify a need for studies to be conducted at the molecular level that will aid in tailoring treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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