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Original Article

Clinicopathological Characteristics and Outcomes of Metaplastic Breast Cancer: Experience from a Tertiary Cancer Center in India

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Abstract

Introduction Metaplastic breast carcinoma (MBC) is a rare heterogeneous subtype of breast cancer, with limited data. Currently, it is treated according to the invasive breast cancer consensus guidelines, but it has a more distinct, aggressive biology and needs a more specific management.

Objectives Our study aimed to evaluate the clinicopathological features, treatment response, and survival outcomes of our MBC patients treated with standard treatment modalities.

Materials and Methods We retrospectively analyzed clinicopathological characteristics, treatment, and survival outcomes of 20 patients diagnosed with MBC between 2012 and 2025.

Results Twenty MBC patients were analyzed. The median age of presentation was 59.5 years. Fifty percent of patients had a clinical T3 tumor. Twenty percent had axillary lymph node involvement. Preoperative core biopsy was MBC in 40%. Most patients underwent mastectomy, and five patients underwent breast conservation surgery. Seventy-five percent had triple-negative receptor status. Of the 35% patients who received neoadjuvant chemotherapy (NACT), only one patient had a complete response. Adjuvant radiation was administered to 65%. Twenty percent received hormone therapy, and 5% received HER2-targeted therapy. At a median follow-up of 13.5 months (range: 3–72 months), 12 patients (60%) were alive with no evidence of disease, and eight patients (40%) died. Tumor recurrence was seen in five patients (25%). Overall survival (OS) at 1, 3, and 5 years was 84.4, 65.1, and 48.8%. Median OS was 55.2 ± 21.8 months. Recurrence-free survival was 64.7 ± 15.8 months. Statistically significant variable worsening the OS on univariate analysis was NACT (HR: 6.13, 95%

Keywords
- metaplastic breast cancer
- clinic-pathological
- outcomes
- lymph node
- mastectomy
- chemotherapy
- surgery

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CI: 1.09–34.46, $p = 0.040$). However, none of the variables were statistically significant by multivariate analysis.

Conclusion MBC is a rare and pathologically challenging diagnosis at core biopsy. Despite the large size at presentation, initial surgery should be preferred whenever feasible. Though lymph node metastasis is rare, when present, it has a worse prognosis.

Introduction

Metaplastic breast cancer (MBC) is a very rare (<5%) and aggressive subtype of breast cancer.[1] It was recognized as a distinct pathological entity in 2000. It is a heterogeneous group of neoplasms encompassing metaplastic transformation of glandular tissue to squamous epithelium and mesenchymal differentiation, like osteoid, chondroid, and spindle cell. They are treated like invasive breast cancer (IBC), but they differ in their response to treatment and prognosis, which is much worse. Robust guidelines on its management are lacking owing to its rarity. The study was done to analyze the clinicopathological characteristics, treatment response, and survival outcomes of MBC patients to the standard treatment modalities at a tertiary care cancer center in Southern India.

Materials and Methods

This is a descriptive and retrospective study of 21 consecutive patients diagnosed with MBC in the resected tumor in our institution during the 13 years from January 2012 to January 2025.

The patients were staged according to the American Joint Committee on Cancer guidelines for breast carcinoma (eighth edition) based on clinical and radiologic findings. Patient demographics (age, gender), clinicopathological features (tumor size, nuclear grade, lymph node status, stage of the disease), receptor status (semiquantitative estrogen receptor and progesterone receptor) positivity were defined as immunohistochemical staining with more than 1%. Positivity for HER2 receptor was defined as strong complete membrane staining in more than 10% of tumor cells or positive with fluorescent in situ hybridization technique FISH), treatment details (locoregional treatment—surgery, and or radiation, systemic therapy and hormonal treatment based on the molecular subtype) and outcomes (response to chemotherapy was evaluated using the "Response Evaluation Criteria for Solid Tumors," overall survival [OS, breast cancer specific survival, recurrence free survival) were analyzed. The patients received treatment as per the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for IBC. To follow up with patients, a telephonic interview and electronic medical records were used.

OS duration was defined as the time from diagnosis to death from any cause or last follow-up. Breast cancer-specific survival (BCSS) duration was defined as the time from diagnosis to death due to breast cancer or last follow-up. Recurrence-free survival (RFS) was defined as the time from diagnosis to the development of any recurrence (distant or locoregional) or last follow-up.

Statistical analysis was done using Jamovi software (2023) for Windows version 2.4 (open source statistical software), Sydney, Australia. Baseline patient characteristics were described using mean, median, and standard deviation for continuous variables, and frequency and percentages were used for categorical variables. Kaplan–Meier estimates were calculated for OS, RFS, and BCSS. Cox regression analysis was used to identify notable risk factors for survival outcomes. The variables with statistically significant associations on the univariate analysis were used in Cox proportional-hazards models for multivariate analysis. We reported hazard ratios (HRs) and 95% confidence intervals (CIs) with two-tailed *p*-values. *p*-Value < 0.05 was considered statistically significant.

Ethical Approval

An institutional review board approval was obtained to conduct this study (IEC no. 123/2024 dated May 4, 2024). All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A waiver of consent was granted by the institutional ethics committee because this work involves no more than minimal risk to the participants or their privacy.

Results

Twenty-one of the 1,050 breast carcinoma patients between 2012 and 2025 were metaplastic breast carcinoma (MBC) patients (2%). Of these, one patient had come for pathology review only and had not taken treatment at our hospital, and is excluded from the study. The clinicopathologic features of the patients have been described in ►**Table 1**.

The median age (Q1, Q3)of presentation was 59.5 (48.7, 67.0). All the study patients were female. The mean tumor size at presentation was 6.69 cm (range: 3–13 cm). At diagnosis, 50% of the patients had T3 disease. One patient presented with lung metastasis. None of the patients had T1 disease. Only 40% of patients were diagnosed to have MBC at core biopsy. Accompanying DCIS was seen in 20% patients. Three-fourths of the study population had a high-grade tumor with Ki67 of $\geq$ 50. The molecular profile of 75% ($n = 15$) of the patients was triple negative (TNBC) status.

Table 1 Patient and tumor characteristics

Sl. No.	Parameters	Number	Percentage
1	Age (y)		
	<60	10	50
	>60	10	50
2	Clinical T stage		
	T1	0	0
	T2	9	45
	T3	10	50
	T4	1	5
3	Clinical N stage		
	N0	13	65
	N+	7	35
4	Clinical M stage		
	M0	19	95
	M+	1	5
5	Diagnosis on core biopsy		
	Diagnosed as MBC	8	40
	Suspicious of MBC	1	5
	Invasive breast carcinoma	7	35
	Phyllodes	3	15
	Could not be categorized (poorly differentiated malignancy)	1	5
6	Histopathology—final		
	Spindle cell carcinoma	5	25
	MBC with squamous differentiation	4	20
	Squamous cell carcinoma	4	20
	Mixed metaplastic carcinoma	3	15
	MBC with heterologous mesenchymal differentiation	4	20
7	Lymph vascular invasion		
	Yes	4	20
	No	16	80
8	Ductal carcinoma in situ		
	Present	4	20
	Absent	16	80
9	Triple negative status		
	Yes	15	75
	No	5	25
10	Hormone receptor status		
	Positive	4	20
	Negative	16	80
11	HER2 neu status		
	Positive	1	5
	Negative	19	95
12	Type of surgery		
	Mastectomy	13	70
	Breast conservation surgery	5	25
	No surgery	1	5

(*Continued*)

Table 1 (*Continued*)

Sl. No.	Parameters	Number	Percentage
13	Pathological tumor stage		
	pT0	1	5
	pT1	0	
	pT2	11	55
	pT3	5	25
	pT4	2	10
	NA	1	5
14	Pathological nodal stage		
	pN0	16	80
	pN1	2	10
	pN2	2	10
15	Chemotherapy		
	NACT alone	4	20
	Adj Chemo alone	9	45
	NACT + Adj Chemo	3	15
	Palliative chemotherapy	1	5
	No Chemotherapy	3	15
16	Adjuvant radiotherapy		
	Yes	13	65
	No	7	35
17	Hormone therapy		
	Yes	4	20
	No	16	80
18	Clinical response to NACT		
	Complete response	1	16.7
	Stable disease	1	16.7
	Partial response	1	16.7
	Progressive disease	3	50
19	Recurrence		
	Yes	5	25
	No	15	75
20	Site of recurrence		
	Lung	3	60
	Brain	1	20
	Lung and liver	1	20
21	Patient status		
	No evidence of disease	12	60
	Died of disease	6	30
	Died of another cause	2	10
22	Survival outcomes		
	Median overall survival	55.2 ± 21.8 mo	
	Median breast cancer-specific survival	67.2 ± 25.1 mo	
	Recurrence-free survival	64.7 ± 15.8 mo	

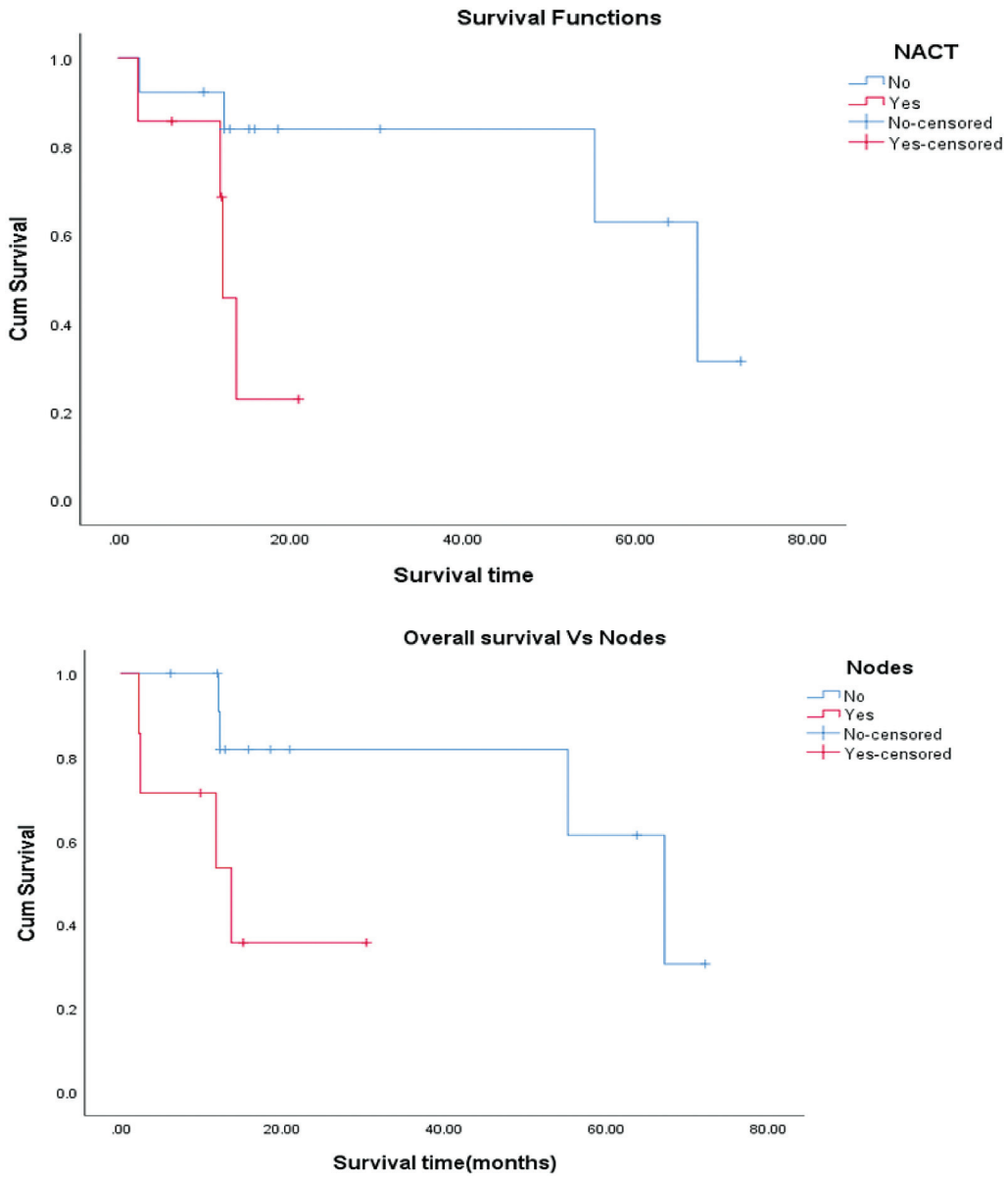

Fig. 2 Kaplan–Meier overall survival curves with nodal involvement and neoadjuvant chemotherapy (NACT).

HER2neu was positive in one patient. The hormone receptor was positive in four patients. The most common pathologic subtype was spindle cell carcinoma (25%). The other histologic subtypes were squamous cell differentiation (20%), squamous cell carcinoma (20%), heterologous mesenchymal differentiation (20%), and mixed metaplastic carcinoma (15%) as represented in ►**Fig. 1**.

Neoadjuvant chemotherapy (NACT) was administered to seven (35%) patients. Only one patient had a complete response. Notably, there was disease progression in three of them. One patient has stable disease. One patient had a partial response. One patient died suddenly 2 days after chemotherapy. Using Cox regression analysis, NACT alone (n4 [reference]) was compared with adjuvant chemotherapy alone (n9 HR: 0.13, 95% CI: 0.01–1.47, $p = 0.099$), both NACT and adjuvant (n3 HR: 0.00, 95% CI: 0.00–inf, $p = 0.999$), and no chemotherapy (n3 HR: 0.86, 95% CI: 0.12–6.24, $p = 0.880$). None of the above types of sequencing of chemotherapy had a significant p-value. The majority of the patients had a mastectomy, nine had upfront surgery, and five after NACT. Five patients underwent breast conservation surgery. The type of surgery did not have any statistically significant difference in OS ($p = 0.3$). Free margin was achieved in the entire study population. Close margin (<2 mm) was noted in 15.8% of the patients. Only one-fifth of patients had regional lymph node involvement. The majority (75%) of the axillary lymph node involvement was seen in the squamous cell variant, though the histological subtype was not statistically significant ($p = 0.8$). When there was lymph node involvement, the median survival was 13.7 months compared with 67.2 months when the lymph node was not involved (as depicted in ►**Fig. 2**). Adjuvant radiation was received by 13 patients (65%). Hormone therapy was taken by 20%. HER2 neu targeted therapy was taken by 5%.

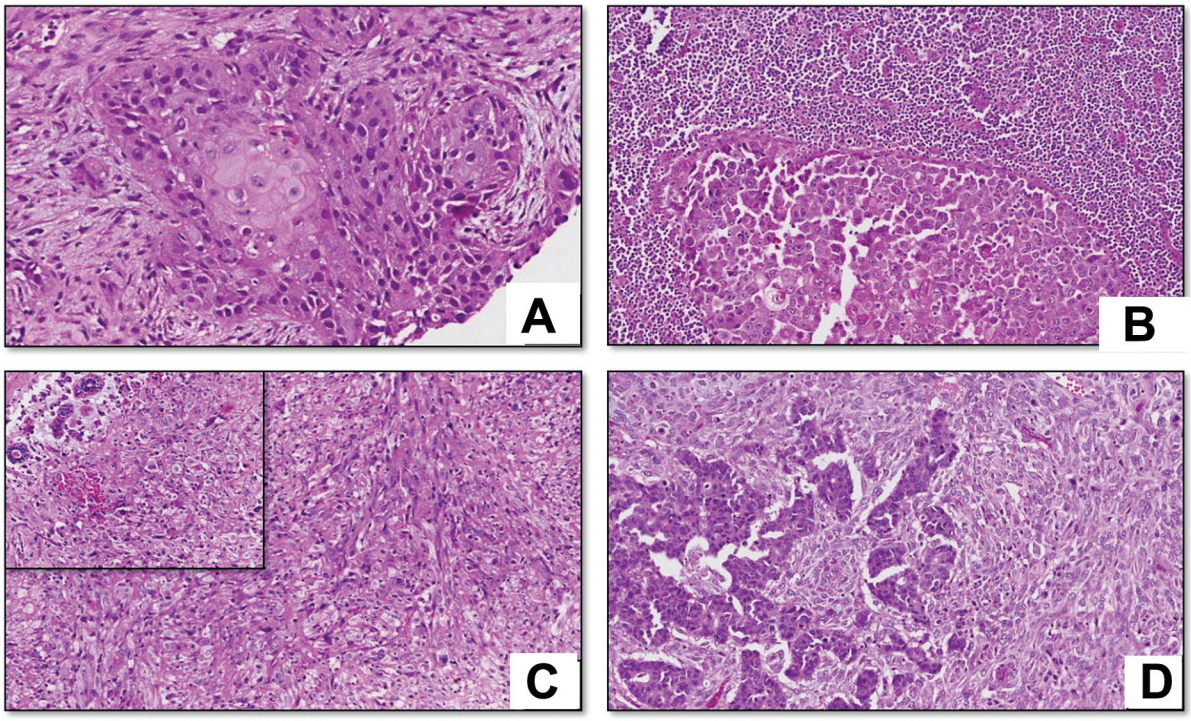

Fig. 1 Photomicrographs of the histopathology of MBC. (**A**) Squamous cell carcinoma, H&E, 10 ×. (**B**) Lymph node involved by metaplastic carcinoma with squamous differentiation, H&E, 10 ×. (**C**) Spindle cell carcinoma, H&E, 5 ×. Inset: spindle cell carcinoma, H&E 10 ×. (**D**) Metaplastic carcinoma with heterologous mesenchymal differentiation, H&E, 10 ×.

At a median follow-up of 13.5 months (range: 3–72 months), tumor recurrence was seen in five patients (25%; three in the lung, one in the brain, one in the lung, liver, and adrenal) and 12 patients (60%) are alive with no evidence of disease, eight patients (40%) died. Six patients died due to the disease, and two died due to other causes.

OS at 1, 3, and 5 years was 84.4, 65.1, and 48.8%. Median OS was 55.2 ± 21.8 months. Median breast cancer-specific survival was 67.2 ± 25.1 months (18.0–116.3). RFS was 64.7 ± 15.8 months.

Statistically significant factor affecting the OS on univariate Cox regression analysis was NACT (HR: 6.13, 95% CI: 1.09–34.46, $p = 0.040$). However, none of the variables were statistically significant by multivariate analysis. There was no OS difference concerning age, TNBC status, grade of the tumor, morphologic subtype, type of surgery, adjuvant radiation therapy, as shown in ►**Table 2**.

Discussion

MBC is a very rare and unique subtype of breast cancer. It is a heterogeneous entity with the inclusion of malignant epithelial (carcinoma) and stromal (sarcoma) elements. Twenty-one patients with MBC were identified from our database over the past 13 years. As was also noted in Damera et al[2] study, most of our patients (up to 80%) were diagnosed in the past 5 years. This could suggest that the unusually aggressive behavior of MBC has increased its awareness.

Due to the very rare occurrence of MBC, the sample size is small. This might limit the ability to extrapolate the findings of our study. Because it is a retrospective study, selection bias may exist. We need large multi-institutional prospective studies to definitively identify prognostic and predictive factors in MBC. However, it adds to the limited literature on MBC cases from Southeast Asia, and it is among the largest series of MBC patients with detailed clinicopathological data and survival outcomes.

The incidence of MBC in our sample was 2% which is consistent with 0.2 to 5% reported in the global literature.[1] In line with the literature, the mean age at diagnosis was 57.6 ± 12.8 years (range: 29–78).[2–4] All our MBC patients were female, as seen in the more common types of breast cancer, though male MBC has been reported.[5]

Clinical and radiological presentation is nonspecific to MBC; they are similar to other breast cancers.[6] All the study patients presented with a palpable mass on physical examination. The symptom onset in the majority of our patients (90%) was less than 6 months (range: 60–2,000 days). MBCs are known to grow rapidly and present with large tumor sizes. Because of the fast growth of these tumors, they could be missed in the annual screening mammogram and present as interval cancers. Mammography, ultrasonography, and MRI in MBC are identical to those in any other invasive breast carcinoma (IBC).[7]

Compared with invasive ductal carcinoma, MBC has a larger tumor size, a higher grade, higher Ki67, a higher stage, a lower likelihood of axillary lymph node involvement, and higher recurrence.[8] And rapid growth, as witnessed in our study, too. Unlike IBC, MBC has a preferential hematogenous dissemination.[9]

In our study, associated DCIS was lower, seen in 20% of our patients, whereas it was 39.5% in Erjan et al study,[10] and 42%

Table 2 Cox regression analysis for the association of patients' baseline characteristics with overall survival

Patient and tumor characteristics	Median survival (mo)	Univariate Cox regression		Multivariate Cox regression	
		Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age < 60 y	67.2	Ref	–	–	–
Age > 60 y	55.2	1.3 (0.29–5.81)	0.73	14.29 (0.28–723.17)	0.18
Pathological nodal involvement absent	67.2	Ref	–	–	–
Pathological nodal involvement is present	13.7	5.35 (0.97–29.52)	0.05	2.91 (0.12–68.85)	0.50
Grade 2	60.2	Ref	–	–	–
Grade 3	41.8	2.82 (0.34–23.65)	0.34	3.31 (0.07–160.32)	0.54
DCIS absent	46	Ref	–	–	–
DCIS present	52.2	0.86 (0.10–7.48)	0.89	0.29 (0.00–59.24)	0.64
TNBC absent	42.1	Ref	–	–	–
TNBC present	49.4	0.34 (0.06–2.09)	0.24	[a]	–
Hormone receptor > 1% absent	67.2	Ref	–	–	–
Hormone receptor > 1%	11.8	4.88 (0.78–30.5)	0.09	[a]	
NACT absent	67.2	ref	–	–	–
NACT present	12.1	6.13 (1.09–34.46)	0.04	4.84 (0.14–163.3)	0.38
Surgery—BCS	55.2	Ref	–	–	–
Mastectomy	67.2	2.09 (0.24–18.05)	0.5	7.75 (0.10–596.12)	0.35
Adjuvant RT not taken	43.7	Ref	–	–	–
Adjuvant RT taken	45.3	1.07 (0.25–4.53)	0.93	1.22 (0.06–24.86)	0.897

Abbreviations: BCS, breast conservative surgery; NACT, neoadjuvant chemotherapy; ref, reference; TNBC, triple negative breast cancer.
[a]Removed from the multivariate analysis after accounting for the multicollinearity.

in Rakha et al study.[11] DCIS is associated with 80% of IBC,[12] suggesting that the MBC biology is distinct from the IBC.

MBC poses a diagnostic challenge in the core biopsy. IHC is important for accurate diagnosis, with p63, cytokeratin five-sixth (CK5/6), and EGFR[12] being typically overexpressed. MBC diagnosis by core biopsy was made in only 40% of our patients, whereas it was seen in 17.9% in Damera et al study.[2] The other core biopsy diagnoses before treatment initiation were invasive breast carcinoma IBC (35%), phyllodes (15%), suspicious of MBC (5%), and poorly differentiated malignancy (5%). These have varied prognoses and varied treatment approaches.

MBCs are aggressive and have a higher incidence of TNBC. In the present study, most (75%) patients had TNBC status, 20% were hormone receptor positive, and the remaining 5% were HER2 neu positive. Hormone receptor, HER2neu, and TNBC status ($p = 0.2$) in MBC does not appear to be prognostic, unlike in invasive ductal carcinoma not otherwise specified, as also noted in Thomas et al study.[7] The retrospective analysis of the national oncology database reported that MBC patients had a worse OS, regardless of the receptor status (5-year OS for the TNBC subset was 71% for MBC and 78% for non-MBC).[9]

Due to its uncommon occurrence and lack of randomized data, the NCCN[13] clinical practice guidelines currently recommend MBC to be treated as IBC, not otherwise specified. Surgery is the principal treatment modality, and the choice of surgery depends on the location of the tumor and the clinical stage of the disease. The majority of our patients (70%) underwent mastectomy due to the larger tumor size at the clinical presentation, and also a poorer response to conventional chemotherapy. However, MBC is not a contraindication for breast preservation, and there was no survival difference between the two surgeries ($p = 0.3$).[3] Comparison of the present study variables with other studies is given in ►**Table 3**.

Axillary staging is similar to IBC, sentinel lymph node in the node-negative axilla, and axillary dissection in the node-positive axilla. Various studies[14,15] have reported axillary nodal spread of approximately 27 to 64%. In our study, the axilla was involved in only 20% patients, and the majority (75%) of the axilla involvement was seen in the squamous cell carcinoma variant. The axillary lymph node involvement varies in MBC, with the squamous cell variant having the highest rate of lymph node involvement, but there is no statistical significance among the histologic subtypes as observed by Murphy et al.[16] When the lymph node was involved, the median survival was 13.7 months compared with 67.2 months when the lymph node was not involved. Therefore, lymph node involvement suggests a worse prognosis.

In our series, in half of the patients receiving NACT, the disease had progressed. This finding is consistent with the literature.[2,14] Wong et al[17] and He et al[18] and many others[19,20] observed a poor response or even disease progression with

Table 3 Comparison with other studies

study	No. of cases	Median age (y)	Mean tumor size (cm)	cT3, T4%	cN%	TNBC%	BCS%	M%	NACT response%	RT%	Follow-up (mo)	Outcome
Esbah, 2012	14	45.5	5.7	NR	NR	NR	7.14	85.7	NR	92.8	52	NR
Lai, 2013	45	55.84	4.8	24.3	24	38.46	30.2	69.7	NR	40.4	NR	NR
Ghosh, 2017	9	50	5.5	NR	NR	NR	22.2	77.7	NR	55.5	12	DM3
Samoon, 2019	42	54	4.5	26.1	45.20	38.10	19	73.8	cr + pr 70. sd + pd 30	66.6	34	NR
Erjan, 2021	81	48	NR	NR	NR	67.80	NR	66.70	cr 3 pr 36.4 sd 18.2 pd 42.4	75.3	54	DM 28
Balasubramanian, 2022	40	47	6	50.4	31.40	45.70	NR	NR	cr 5.9 pr 23.5 sd 53 pd 17.6	68.6	NR	DM 7
Damera, 2022	28	47 y	NR	60.7	39.3	53.6	21.4	67.8	cr 0 pr 28.6 sd 35.7 pd35.7	57.1	13.2	DM 9
This study	20	59.5	6.69	55	35	75	25	70	cr 16.7 pr 16.7 sd 16.7 pd 50	65	13.5	DM 5

Abbreviations: BCS, breast conservation surgery; cN, clinical nodal involvement; cr, complete response; cT, clinical tumor size; DM, distant metastasis; M, mastectomy; NACT, neoadjuvant chemotherapy; pd, progressive disease; pr, partial response; sd, stable disease; TNBC, triple negative breast cancer.

NACT. In the present study, seven patients (35%) received NACT. Of them, one patient (14%) had a pathological complete response, in three patients (42%) there was disease progression, one patient (14%) had stable disease, one patient (14%) had a partial response, and one patient (14%) died 2 days after receiving the chemotherapy. Unlike TNBC, MBC response to NACT is dismal. And in our study, NACT was significantly associated with worse OS ($p = 0.04$). Therefore, our study recommends primary surgery as the best treatment approach for nonmetastatic MBC if operable, even in HER2neu positivity and TNBC status.

Adjuvant RT was received by 13 patients as part of breast conservation therapy or because of locally advanced presentation of the disease. It did not have any OS benefit in our study cohort. In some studies, RT showed a survival benefit in MBC, but the patient cohorts are small.[10,21]

Recurrence was seen in five patients (25%), with the most common site being the lung, in concordance with other studies.[10,15] Conversely, IBC typically metastasizes to bone.[15,22] Regardless of the lesser involvement of the regional lymph node, MBC has a high chance of distant metastasis through the hematogenous route. Song et al[15] (41.8%) reported a higher distant metastasis with MBC compared with IBC.

Song et al[15] compared the 5-year OS of MBC and IBC, and found it to be 54.5 and 85.1%, respectively. He et al[19] retrospectively studied MBC patients over three decades and found them to have decreased survival outcomes compared with IBC. Five-year OS in our study was 48.8%. One retrospective study[4] of 42 MBC patients from Pakistan, however, reported a higher OS of 76%. This could be because of their higher hormone receptor positivity (45.2%).

Due to the uncommon occurrence of the MBC and its histological heterogeneity, clinical trials are challenging. More aggressive and tumor-specific targeted therapies and immunotherapies may improve the prognosis of this disease.

Conclusion

To maintain a high level of suspicion for MBC, when breast cancer has grown rapidly:

- At the core biopsy, diagnosing MBC is a pathological challenge.
- Primary surgery is the best treatment approach, whenever operable, as the response to standard NACT is dismal.
- The type of breast surgery, whether breast conservation surgery versus mastectomy, has no bearing on OS.
- Lymph node metastasis was only 20% despite the large tumor size.
- Though axillary lymph node involvement is uncommon, it decreases the OS.
- Following the treatment, aggressive surveillance measures are required for early identification and management of recurrence, if it recurs.
- Large studies are needed for a better understanding of the MBC tumor biology and specific tailormade management of these cancers.

Authors' Contributions

V.L.V.V.: Conceptualization, methodology, data analysis, supervision, and writing—original draft and review, and editing.
D.C.P.T.: Data curation, formal analysis, methodology, and writing—original draft and review, and editing.
G.V.: Data interpretation and writing—original draft and review, and editing.
R.S.R.: Data interpretation and writing—review and editing.
N.S.: Data interpretation, formal analysis, validation, and writing—review and editing.
A.C.K.: Validation and writing—review and editing.

Patient's Consent

This is a retrospective study. Hence, waiver of consent was granted by the institutional ethics and review board.

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None.

Conflict of Interest

None declared.

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