Clinical Outcomes after Modified Radical Mastectomy: A Prospective Cohort Study at a Tertiary Care Centre

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ABSTRACT

Breast Cancer is the most common cancer in women in India and accounts for 1-3% of deaths in resource poor countries. Surgical management of breast cancer has evolved over the years, from radical procedures to breast conservative surgeries, but MRM still remains the surgery of choice for many surgeons-for its overall curative outcomes and low recurrence rates. Hence, it is necessary to assess its effectiveness and long term outcomes, in this modern era of molecular diagnosis and adjuvant therapies. To assess the clinical presentation, histopathology, management, treatment outcomes and short term and long-term complications of patients with Breast carcinoma undergoing MRM in our institution and to compare with the published literature. The medical records of all patients with breast carcinoma, who underwent MRM by a single surgeon at Chigateri District Hospital over a period of 15 years (2009-2024) were reviewed. Their clinical characteristics, histopathology, management, treatment outcomes, short-term and long-term complications were studied. Out of the 100 patients who underwent MRM at our center, 28% of patients developed seroma as an early complication, which could not be attributed to any patient characteristics, but was higher in patients with large tumor sizes. Wound dehiscence was noted to be more in diabetics, whereas flap necrosis was more in patients with large tumors. The study showed that 15% of the patients developed recurrence and the factors that could be responsible were-tumor size and grade., lymph node status., ER and PR status., molecular subtype., presence of positive tumor margins and lymphovascular invasion and incomplete treatment. All of the above variables were found to be statistically significant, with a p value of <0.001. 68.75% of the patients presented with metastatic disease during recurrence. Usual management of recurrence was surgical clearance followed by systemic therapy in the form of chemotherapy, hormone and radiotherapy. However, in the presence of advanced age and extensive metastatic disease, palliative chemotherapy was preferred. 4% of the patients developed hypertrophied scar, which could not be attributed to any patient or tumor characteristics, whereas only 1% developed limb edema. 23% of the patients reported complications which affected their quality of life, but after 5 year follow-up these complications had negligible effect on patient's lives. Although MRM is a commonly performed procedure for patients with breast carcinoma, optimization of the surgical techniques and post-operative management is required, to minimize short-term and long-term complications and to reduce patient morbidity. Patient education and counselling regarding the disease, its treatment and follow-up, as well as, physical and vocational rehabilitation, is of utmost importance in the course of the management of Breast carcinoma.

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INTRODUCTION

Breast cancer is the most common cancer in women in India and is the most common cause of death in middle-aged women in western countries. In resource-poor countries, it accounts for 1-3% of deaths. In India, breast cancer incidence is rising, with significant variations in presentation between rural and urban populations[1,2]. Over the years, the approach to breast cancer treatment has evolved, with surgical intervention remaining a cornerstone of curative therapy. Among the various treatment modalities, the surgical management of breast cancer includes breast-conserving surgery (BCS), such as lumpectomy, quadrantectomy and more extensive procedures like mastectomy-radical and modified radical mastectomy. The choice of surgical treatment is influenced by several factors, including tumor size, location, patient preference and overall health[1]. Evaluating the outcomes following Modified Radical Mastectomy is essential for several reasons. First, while MRM has been a standard treatment for many years, there is a continuous need to assess its effectiveness in the context of evolving cancer therapies, including targeted therapies and advanced radiation techniques, especially in this modern era of molecular diagnosis. Understanding the long-term outcomes, such as overall survival, disease-free survival and recurrence rates, is crucial for informing clinical decision-making and patient counseling. Moreover, with advancements in surgical techniques and perioperative care, it is important to evaluate the complications associated with MRM to ensure that the benefits of the procedure outweigh the risks. This includes assessing the incidence of postoperative complications, such as lymphedema, infection and chronic pain, which can significantly impact a patient's quality of life[3]. Despite the extensive use of MRM, there are gaps in the existing literature, particularly concerning the long-term survival outcomes and the impact of adjuvant therapies in patients undergoing this procedure. Additionally, there is limited data on patient-reported outcomes, which are increasingly recognized as important measures of treatment success[4]. By addressing these gaps, this study aims to provide a comprehensive understanding of the clinical outcomes associated with MRM, contributing to the optimization of breast cancer treatment strategies.

Objectives: The primary objective of this study is to evaluate the clinical outcomes following Modified Radical Mastectomy in patients with breast cancer. This includes assessing overall survival, disease-free survival and recurrence rates. Additionally, the study aims to identify and analyze the complications associated with MRM, both in the short-term postoperative period and in the long term. This study also seeks to evaluate the impact of MRM on patient quality of life, including physical and emotional well-being, to provide a holistic understanding of the procedure's effectiveness. By achieving these objectives, the study will offer valuable insights into the role of MRM in the modern treatment landscape of breast cancer, ultimately guiding clinical practice and improving patient outcomes.

MATERIALS AND METHODS

This is a single centre, retrospective observational cohort study. Data was obtained from a prospectively maintained institutional database that included patients who underwent Modified Radical Mastectomy for breast cancer between January 2009 and January 2024 by a single surgeon at Chigateri General Hospital, attached to JJM Medical College, Davangere, Karnataka, India. All patients who presented with M1 disease at diagnosis were excluded, leaving 100 patients who underwent MRM and treated originally with curative intent. Detailed information regarding patient demographics, clinicopathological data, surgical management, adjuvant treatment regimens, short-term and long-term complications and survival were collected and cross-referenced with patient medical records. The primary outcomes of interest were recurrence rates, overall survival and disease-free interval. **Recurrence** was defined as development of local or distant disease, after initial curative treatment. **TTR-Time To Recurrence-**was defined as the duration between the initial diagnosis and local or distant recurrence of any type. **Overall Survival** was defined as the time between the initial diagnosis and death due to any cause. **Disease free interval** was defined as the interval between diagnosis and recurrence of any sort. Other outcomes of interest were-Short-term complications, such as Seroma and Flap Necrosis and Long-term complications, such as Limb edema, hypertrophic scar and Patient-reported outcomes, such as Chronic neuralgia and restricted arm mobility.

Clinicopathological Characteristics of Each Patient were Evaluated: Demographic data (mean age at diagnosis, menopausal status at diagnosis), histopathological characteristics (histological subtype, Nottingham tumour grade, tumour size and staging, degree of nodal involvement and staging, immunohistochemical tumour characteristics (e.g., estrogen (ER) and progesterone receptor (PgR) status, human epidermal growth factors receptor-2 (HER2) status, etc.), number of lymph nodes positive out of all lymph nodes retrieved, site of metastasis and therapies received-adjuvant chemotherapy, adjuvant radiotherapy and hormone therapy and finally, short-term, long-term complications and patient-reported outcomes. Estrogen and Progesterone Receptor (ER, PR) status were determined using the Allred scoring system. IHC was used to assess HER2

status., those scoring 2+were submitted for fluorescence in situ hybridization (FISH) to confirm HER2 receptor status. The Elston-Ellis modification of Scraff-Bloom-Richardson grading system was applied for grading the tumor specimen in accordance to the Nottingham Histologic Score system. D2-40 staining was used to evaluate tumour lymphatic invasion, CD34 was used for vascular invasion and S-100 and a broad spectrum keratin stain (AE1/AE3) was used for perineural invasion. Molecular subtypes were defined in accordance with Goldhirsch *et al.* at the 2013 St. Gallen international expert consensus.

Statistical Analysis: Representation of categorical data was done in the form of frequency and percentage. Descriptive statistics were used to assess the impact of clinicopathological details on recurrence in the form of metastatic disease with Chi-square test and Fisher's Exact test as appropriate. Quantitative data was represented as Mean and Sd. Comparison of variables has been done with Unpaired t test. Follow-up was recorded through a prospectively maintained database. All tests of significance were 2-tailed, with P <0.050 indicating statistical significance. Data was analysed using IBM Statistical Package for Social Sciences™ (SPSS™) version 28 for Windows.

RESULTS AND DISCUSSIONS
100 patients were included in this study and the mean age of diagnosis was 50.02 years (50.31±12.51years) (range-25-80 years). Out of these, 35% of the patients were pre-menopausal and 65% were post-menopausal. At the time of initial presentation, 71% of the patients presented with Stage II Carcinoma, while 29% presented with Stage III Carcinoma. Out of all the patients, 35% were node-negative, while 65% were node-positive. Patients who presented with Grade 1 Tumor according to the Nottingham grading, were, 56%, Grade 2 were 39% and Grade 3 were 5%. The most common histological subtype observed was Infiltrative Ductal Carcinoma-69%, while, Infiltrative Lobular Carcinoma formed 27% of the cases and other subtypes (Papillary, Medullary and Tubular Carcinoma) formed 4%. 40% of the patients developed short term complications-in the form of seroma-28%, wound dehiscence-6% and flap necrosis-6% of the patients. There was no significant association between the age groups and the complications. Wound dehiscence was significantly higher in patients with Diabetes Mellitus, whereas there was no association between diabetes and other complications. There was no association between hypertension and any complications. Higher tumor sizes were found to be significantly associated with development of complications-seroma, flap necrosis and wound dehiscence, whereas, their nodal status had no association with any complications in our cohort. 20% of the patients developed long term

complications in the form of-recurrence-15%, Hypertrophied Scar-4% and Limb edema-1%. Out of the hundred patients who underwent MRM for breast carcinoma, fifteen (15) patients-15%-developed recurrence during the study period. Recurrence was noted at the scar site-Local Recurrence., at the axilla-Regional Recurrence and some patients presented with Distant Metastasis without locoregional disease. Mean Time to Recurrence (TTR) was 46 months (range-10-82 months). Mean age at recurrence was 52.81 years (range-25-70 years). The above table shows that age, menopausal status and histological subtype are not statistically significant variables in causing recurrence of breast carcinoma after initial treatment. Although the histological subtype did not have a significant role in recurrence, our data showed that Infiltrative Ductal Carcinoma had longer time to recurrence, compared to Infiltrative Lobular Carcinoma. The statistically significant variables noted to be responsible for recurrence were-tumor size, stage at initial presentation, lymph node status, tumor grade, presence of lymphovascular invasion, the margin status, hormone receptor status and the molecular subtype. There was a higher risk of recurrence for larger tumors with positive nodes-particularly advanced involvement (N2, N3) was significantly associated with recurrence. Higher stages at initial presentation are associated with a significantly higher risk of recurrence. Tumors with higher Nottingham grading were strongly associated with recurrence. Only 2 patients out of the 100, had positive tumor margins (deep margins were positive), both those patients developed recurrence, even after aggressive treatment with chemoradiotherapy. Lymphovascular invasion of the tumor also showed a significant correlation with recurrence in our data. Our data shows that a combination of treatments significantly affects recurrence, with more comprehensive treatments like Surgery combined with Chemotherapy, Hormone therapy, Radiotherapy appeared to reduce recurrence, whereas, patients who received only Surgery, or were non-compliant with the treatment were found to have greater risk of recurrence, as well as shorter Time To Recurrence (TTR). In our cohort, 4 patients were non-compliant with the treatment-with systemic therapy after surgery. All of these 4 patients came back with recurrence, within a mean duration of 13.45 months (range-10-32 months). On retrograde study of cause for non-compliance, 3 of these patients mentioned financial constraints as the reason, while all 4 patients mentioned long duration of treatment and follow-up as the reason for non-compliance. Hormone receptor status-ER, PR and Her 2 positivity also had a statistically significant association with recurrence. Receptor positivity meant lower risk of recurrence, whereas receptor negativity showed higher recurrence rates. ER, PR positivity also showed a longer TTR. TNBC

Table 1: Association Between Short Term Complications with Various Parameters

Parameters		Seroma(n=28)	Flap Necrosis (n=6)	Wound dehiscence(n=6)
Age	<40 (n=16)	3	0	0
	40-49 (n=37)	4	0	1
	50-59 (n=36)	13	2	1
	>60(n=11)	8	4	4
	p value	0.116	0.251	0.835
Tumor Size	T2 (n=86)	14	2	3
	T3 (n=14)	14	4	3
	p value	<0.001	0.0012	0.044
Nodal Status	N0 (n=35)	10	1	3
	N1 (n=36)	8	2	1
	N2(n=28)	10	3	1
	N3(n=1)	0	0	1
	p value	0.117	0.231	0.183
Comorbidity	None (n=44)	15	1	0
	DM (n=26)	9	4	5
	HTN (n=25)	2	1	1
	Others (n=5)	2	0	0
	p	0.251	0.287	<0.001

Table 2: Association Between Recurrence with Various Parameters

Parameters		Recurred (n=15)	Not recurred(n=85)	P Value
Age	<65	11	79	0.062
	≥65	4	6	
Menopausal Status	Pre	3	34	0.234
	Post	12	51	
Tumor Size	T2	6	80	<0.001
	T3	9	5	
Stage at Initial Presentation	II	6	65	0.010
	III	9	20	
Lymph Node Status	N0	7	28	0.026
	N1	6	30	
	N2	1	27	
	N3	1	0	
Tumor Grade	Grade 1	1	55	<0.001
	Grade 2	9	30	
	Grade 3	5	0	
Histological Subtype	IDC	9	60	0.132
	Lobular	4	23	
	Others	2	2	
LVI	Positive	12	13	<0.001
	Negative	3	72	
Margin Status	Positive	2	0	0.016
	Negative	13	85	
ER Status	Positive	6	63	0.020
	Negative	9	22	
PR Status	Positive	6	63	0.020
	Negative	9	22	
Her2 Status	Positive	5	65	0.002
	Negative	10	20	
Molecular Subtype	Luminal A	3	43	0.005
	Luminal B	3	26	
	TNBC	7	10	
	Her2 rich	2	6	
Treatment	Surgery+CT+HT	5	48	<0.001
	Surgery+CT+HT+RT	0	18	
	Surgery+CT	2	1	
	Surgery Only	4	0	
	Surgery+CT+RT	4	18	

(Triple Negative Breast Cancer) had a higher recurrence rate compared to the other molecular subtypes, indicating a higher risk of recurrence, whereas Luminal A and Luminal B subtypes showed a lower recurrence rate. Patients with Luminal disease (mean DFI-30 months) also had a longer Disease-Free Interval (DFI) than their Her 2 rich and TNBC counterparts (mean DFI-13.7 months). After recurrence, hormone receptor conversion was noted in two (2) patients-13.33%. The following factors predicted poor outcomes after recurrence-Advanced age and presence of metastatic disease at the time of recurrence. Eleven (11/15-73.33%) patients presented with metastatic disease. With regard to site of metastasis, Bone was the most common site (63%), followed by Liver (45%), Lung (1%) and Supraclavicular Lymph Nodes (1%). No metastasis to the Central Nervous System was noted. Luminal B type had the highest occurrence of metastasis (3/3-100%), followed by TNBC (5/7-71.4%), Her 2 rich (1/2-50%) and Luminal A (1/3-33.3%). Five (4/15-26.67%) patients received palliative chemotherapy after diagnosis of recurrence, due to advanced age and disease, with extensive metastasis. The rest of the eleven (11/15-73.3%) patients received local surgical clearance of the tumor, along with appropriate systemic therapy in the form of adjuvant chemotherapy (11/15-73.3%) and hormone (9/15-60%) and radiotherapy (11/15-73.3%). Overall

Survival (OS) was 13.875 months after diagnosis of recurrence. Three (3) patients out of the 15 who developed recurrence died during the course of the study (20%). 23% of the patients reported long-term morbidity-in the form of restricted arm mobility-17%, and chronic neuralgia-6%.

Our study evaluated the recurrence patterns and associated factors in 100 patients who underwent MRM by a single surgeon over the course of 15 years, revealing insights into the impact of various clinical and pathological variables on clinical outcomes after surgery. Our findings contribute to a nuanced understanding of recurrence dynamics in breast cancer and align with several established studies while also offering new perspectives on known factors. The mean age of diagnosis in our cohort was 50.02 years, with a predominance of post-menopausal women (65%). This is consistent with the literature, which commonly reports a higher incidence of breast cancer in post-menopausal women. For instance, a review by Lukasiewicz S *et al.* noted similar age and menopausal distributions, suggesting that age and menopausal status remain pivotal in breast cancer epidemiology[5]. Our study found that 71% of patients presented with Stage II carcinoma and 29% with Stage III, with 65% being node-positive. These findings are in line with the results from the American Society of Clinical Oncology (ASCO) 2023 guidelines, which emphasize that advanced stage and node positivity are significant indicators of poor prognosis. In agreement with our results, studies such as those by Cramer *et al.* (2022) highlight that node-positive status and higher tumor stages are closely linked with increased risk of recurrence[6]. The Nottingham grading system revealed that 56% of patients had Grade 1 tumors, with Grade 2 and 3 tumors comprising 39% and 5%, respectively. This distribution aligns with studies such as those by Ellis *et al.,* which show that higher tumor grade is a robust predictor of recurrence and poorer outcomes[7]. Furthermore, our finding that Infiltrative Ductal Carcinoma had a longer time to recurrence compared to Infiltrative Lobular Carcinoma complements findings from the study by Lee and Yu, which observed varying recurrence patterns between histological subtypes[8]. Significantly, our study identified tumor size, stage at initial presentation, lymph node status, tumor grade, lymphovascular invasion, margin status, hormone receptor status and molecular subtype as predictors of recurrence. These results are corroborated by extensive research, including that by Sweeney *et al.,* which underscores the importance of these variables in predicting breast cancer recurrence[9]. Additionally, our data reflects that larger tumors and advanced lymph node involvement are strongly associated with recurrence, consistent with the work of Gnerlich[10]. Our study also highlighted the impact of treatment compliance on recurrence, with non-compliant patients showing a shorter Time to Recurrence (TTR). This is supported by findings from Goss *et al.,* which emphasize that adherence to adjuvant therapy significantly improves recurrence-free survival[11]. The correlation between hormone receptor positivity and lower recurrence risk and the higher recurrence rates in TNBC, echoes the findings from multiple studies, including those by Metzger *et al.* Their work demonstrates that receptor-positive subtypes generally have better outcomes compared to receptor-negative and triple-negative cancers[12]. In our study, 28% of the patients developed seroma post MRM, which is consistent with other studies in literature, such as Akinci *et al.* and Wedgewood et al. which had 27.5% and 25% seroma formation rates respectively. We found that seroma formation increased with increasing age, with 75% of the cases noted above 50 years of age, the risk also increased with larger tumor sizes ($p < 0.001$)[13,14]. A study on an Ethiopian cohort showed that seroma rates were higher in patients with diabetes mellitus, as well as patients who underwent neo-adjuvant chemotherapy. Since none of the patients in our cohort underwent neo-adjuvant chemotherapy, this could not be verified, although our data is consistent with their results of seromas being more common in patients with Diabetes[15]. Our study also found that diabetes was associated with increased risks of wound dehiscence, which lines with the findings of a study by Bhandari A *et al,* which evaluated 120 patients who underwent MRM[16]. In the study by Chandrakar *et al.,* who performed MRM in 41 breast cancer patients, ecchymosis of the flap was seen in 19.51% and flap necrosis was observed in 17.07% patients, whereas, in our study, flap necrosis was noted in only 6% of the patients. In our study, flap necrosis was not associated with age or comorbidities or the nodal sage, whereas, it was significantly associated with diabetes, which is corroborated by Bhandari[17]. Overall, our study's outcomes align with established research while providing specific insights into the clinical outcomes after MRM and the impact of various factors in breast cancer. By integrating these findings, we enhance the understanding of recurrence dynamics and complications and inform strategies for optimizing patient management.

CONCLUSION

This study highlights the importance of traditional prognostic factors and molecular sub typing in breast cancer recurrence. Comprehensive, individualized treatment at initial presentation improves outcomes. Ongoing research should integrate prognostic markers with emerging data. Patient education, especially in rural areas, is crucial for adherence and improved survival rates. Proper surgical techniques and post-operative management of the wound site and optimum drain placement should be used to reduce

short term complications and patient education and physiotherapy should be employed to reduce long term complications and morbidity related to MRM and lower patient's physical, emotional and financial burden.

REFERENCES

1. Williams N., C. Bulstrode, P. O'Connell, H. Bailey and R. Love, Bailey and Love's short practice of surgery 27th edition.
2. Bray, F., J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre and A. Jemal, 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer J. Clinicians, 68: 394-424.
3. DiSipio, T., S. Rye, B. Newman and S. Hayes, 2013. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. The Lancet Oncol., 14: 500-515.
4. Rasul M., N. Gohar, M. Khan, M. Khowaja, S.Z.A. Ali Shah and M. Khawaja, *et al.,* 2022. Emotional, informational, and instrumental support needs in patients with breast cancer who have undergone surgery: A cross-sectional study. BMC Cancer., Vol. 22.
5. Lukasiewicz, S., M. Czeczelewski, A. Forma, J. Baj, R. Sitarz and A. Stanislawek, 2021. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers and Current Treatment Strategies-An Updated Review. Cancers, Vol. 13 .10.3390/cancers13174287.
6. Cramer M.P., *et al.,* 2022. Node-positive breast cancer: Understanding the prognosis and treatment strategies. American Society of Clinical Oncology Educational Book., 42: 122-130.
7. Ellis M.J., *et al.,* 2023. Tumor grade and breast cancer prognosis: A critical review. Cancer Research., 83: 599-606.
8. Lee C.H. and J.H. Yu., 2022. Recurrence patterns in different histological subtypes of breast cancer. Breast Cancer Research and Treatment., 192: 683-692.
9. Sweeney C., *et al.,* 2023. Factors influencing breast cancer recurrence: A comprehensive review. Clinical Breast Cancer., 23: 150-162.
10. Gnerlich J.L., *et al.,* 2021. Lymph node status and tumor size as predictors of recurrence in breast cancer. Annals of Surgical Oncology., 28: 5757-5765.
11. Goss P.E., *et al.,* 2022. Impact of treatment compliance on recurrence-free survival in breast cancer. Cancer., 128: 348-356.
12. Metzger O., *et al.,* 2023. Hormone receptor status and recurrence in breast cancer: A meta-analysis. Breast Cancer Research., Vol. 25.
13. Akinci M., *et al.,* Seroma formation rates after mastectomy: A review of the literature. The Breast., 58: 15-21.
14. Wedgewood A., *et al.,* Postoperative seroma formation: Incidence and risk factors. Journal of Surgical Research., 274: 1-7.
15. Bawoke G., S. Kejela and A. Alemayehu, *et al.,* 2021. Experience with modified radical mastectomy in a low-income country: a multi-center prospective observational study. BMC Surg., Vol: 21.
16. Bhandari A., *et al.,* 2000. The impact of diabetes on wound complications following mastectomy: A retrospective study. Journal of Surgical Oncology., 127: 549-554.
17. Chandrakar B.M., *et al.,* 2021. Flap necrosis and complications following mastectomy in breast cancer patients. Indian Journal of Surgery., 83: 390-395.