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RESEARCH ARTICLE

# Risk Factors for Locoregional Recurrence and Distant Metastasis Following Modified Radical Mastectomy for Localized Breast Cancer in a Nigerian Teaching Hospital

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## Abstract

**Background:** Mastectomy plays a crucial role in the management of breast cancer, particularly in resource-limited healthcare settings. This retrospective study aimed to evaluate the incidence of locoregional recurrence (LRR) and distant metastasis (DM) after modified radical mastectomy (MRM) for breast cancer, as well as identify associated risk factors. **Methods:** The study included patients who underwent mastectomy between October 2012 and September 2017. Data analysis was performed using SPSS version 23.0, and the results were presented using descriptive statistics. Inferential statistics were conducted using the chi-square test, with statistical significance set at $p < 0.05$. **Results:** Out of 71 patients who underwent MRM during the study period, 63 (88.7%) were eligible for analysis. The age range of the eligible patients was 24-80 years, with a median age of 49 years (IQR, 43-59 years). The size of the breast lump ranged from 2-18 cm (mean, 7.8 ± 3.5 cm), and the duration of the lump varied from 1-48 months (median 6.0, IQR, 4.0-10.0 months). Sixteen (25.4%) patients developed LRR, with a median interval of 9 months (IQR, 6.0-20.0) after mastectomy. Eighteen (28.6%) patients experienced distant metastasis, occurring 9-60 months after surgery (median 19, IQR 12.0-37.0). Fifty percent of patients with LRR also developed metastasis, predominantly affecting the lungs and pleura (55.6%). Risk factors significantly associated with LRR included mean tumor size ≥10cm ($p < 0.000$), mean lump duration >11 months, advanced disease stage T3/4 ($p=0.01$), and a higher number of positive lymph nodes ($p=0.011$). Tumor size ($p=0.01$) and positive lymph nodes ($p=0.015$) were identified as predictors of LRR. **Conclusion:** LRR and distant metastasis are common occurrences following mastectomy. Early presentation of breast cancer and the availability of adequate adjuvant therapies can help reduce the incidence of these complications.

**Keywords:** Breast cancer- mastectomy- recurrence- metastasis- survival

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## Introduction

Breast cancer is the most common malignancy in Nigerian women [1] and a large number of patients usually present with a huge tumour requiring mastectomy as an integral component of standard multimodal treatments. Mastectomy is aimed at the locoregional control and alleviates the physical burden of the disease. In the developed countries where there are robust screening programs, the majority of the breast cancer patients are diagnosed early and breast conserving surgery is often feasible. Most breast cancer patients in Nigeria and Africa often require more radical treatments with a combination of neoadjuvant chemotherapy, mastectomy and radiotherapy for locoregional control because of late presentation with more advanced local and regional disease. Nigeria breast cancer patients present with one of the highest incidences of large locoregional tumour burden globally with potential for early and high incidence of treatment failure [2-5].

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Two very disturbing outcomes of treatment failure are locoregional recurrence (LRR) and metastatic progression (MP). Women who have completed initial treatments for breast cancer are not spared of local recurrence and/or metastasis [6]. Cheng et al. [7] in their study reported that the 4-year LRR rate was 16.1% after modified radical mastectomy. Some contributing factors to the increased risk of LRR include young age at diagnosis, huge tumour size, positive lymph node status, high tumour grade, triple negative or human epidermal growth factor receptor 2 (HER2/neu)-positive subtype, lack of endocrine therapy, omitting indicated adjuvant radiotherapy and treatment strategies [8-10]. Studies have shown that LRR correlates with increased risk of poor survival outcomes [7, 11].

Understanding the pattern of LRR and metastatic recurrence will help in identifying future interventions to improve the quality and effectiveness of palliative care for Nigerian and other African countries. Thus, the objective of this study was to describe the outcomes in terms of locoregional recurrence and metastasis after modified radical mastectomy for breast cancer in a teaching hospital in Ekiti, Nigeria.

## Materials and Methods

*Design, Setting and Participants*

This was a descriptive retrospective study of patients with histologically confirmed breast cancer who underwent mastectomy at Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti over a five-year period between October 2012 and September 2017. The study was approved by the Ethics and Research Committee of EKSUTH (EKSUTH/A67/2018/07/008).

The medical records of patients listed for mastectomy treatment of locoregional disease, corresponding to stage 0-3 disease, in the operating theatre register were obtained by the surgery residents. Patients diagnosed with metastatic disease before mastectomy and those with tumour-positive resection margin were excluded.

Data on patient demographics, time to presentation, clinicopathologic tumour findings including size, nodal status, stage and Scarff–Bloom–Richardson (SBR) grade, treatment received and follow up were collected with the aid of a well-designed proforma. Event of Locoregional recurrence and metastatic progression were primary outcomes. LRR was defined as the appearance of tumour in the chest wall, skin, or regional lymph nodes (ipsilateral axillary, supraclavicular, infraclavicular or internal mammary lymph nodes) at least six weeks after mastectomy while metastasis is the appearance of tumour in other organs/structures. Patients with concurrent LRR and distant metastasis were categorized as distant metastasis as first recurrence event.

During the period under review, provisional diagnosis of primary tumour was by clinicoradiologic review with pathologic confirmation by fine needle aspiration or histology. Staging and scouting for metastasis was limited to breast, axillary and supraclavicular ultrasound scanning, chest Xray, and abdominal ultrasound scanning, adopting the AJCC version 7,2010. Computerized tomography (CT), magnetic resonance imaging (MRI) and bone scan were not routine.

Locoregional recurrence was confirmed by repeat biopsy. Our protocol for salvage treatment for LRR comprises of local therapy, in form of wide local excision and axillary node dissection, and systemic treatment using chemotherapy and hormonal agents. Post excision radiotherapy was routinely recommended. Patients were followed up at the surgical outpatient clinic.

*Statistical analysis*

The data generated were analysed for frequencies and simple percentages using SPSS version 23 (SPSS Inc., Chicago, IL, USA). The results were presented using descriptive statistics: mean±SD, median and IQR. Associations between clinicopathological parameters and recurrence were assessed using the Chi-square and logistic regression analysis done to determine the predictor of locoregional recurrence. Life-table type analysis was used to describe the distribution of yearly event in the first 3 years. Statistical significance was set at $p < 0.05$.

## Results

Seventy-one patients had mastectomy over the study period, 63 (88.7%) with detailed information were eligible. Their ages ranged from 24 to 80 years with a mean age of 51.9±12.7 years. The patients' sociodemographic variables are shown in Table 1.

The lump size ranged from 2-18 cm (mean, 7.8±3.5 cm, median 7.0, IQR 6-10 cm) and the lump duration was 1-48 months (median 6.0 months, IQR 4-10). Other tumour characteristics are shown in Table 2.

All the patients had modified radical mastectomy. Sixteen (25.4%) patients developed recurrence. Median time to first recurrence was 9 months (range: 4–36 months). Chest wall was the most common site of LRR in 9 (56.3%) of the patients while 5 (31.3%) and 2 (12.5%) developed LRR on the skin and axillary lymph nodes respectively. The yearly risk of LRR in the first 3 years was 29% during the first year and 4% each in the second and third years

Eighteen (28.6%) patients developed distant metastasis. The median time to metastasis after surgery was 19 months (range: 9–60 months). The sites of metastasis were: lungs 6 (33.3%), pleural 4 (22.2%), bone 3 (16.7%), liver 2 (11.1%), brain 2 (11.1%) and one patient (5.6%) had multiple metastases. Among the patients with metastasis, only 8 (44.4%) had LRR. The time to LRR and distant metastasis after surgery are shown in Table 3. Risk of appearance of metastasis was 8.5% during the first-year post mastectomy, 10% during the second year and 3.5% during the third year.

The factors associated with locoregional recurrence are shown in Table 4. Advanced stage (p=0.01) and number of positive lymph nodes (p=0.011) in the resected specimen were significantly associated with cancer recurrence and these two factors also predicted the development of LRR (Table 5).

Although half of the patients with LRR developed

Table 1. Socio-demographic Characteristics of the Patients (N=63)

| Socio-demographic | Frequency | Percentage (%) |
|---|---|---|
| Age group (year) | | |
| 21-30 | 2 | 3.2 |
| 31-40 | 9 | 14.3 |
| 41-50 | 22 | 34.9 |
| 51-60 | 15 | 23.8 |
| 61-70 | 9 | 14.3 |
| >70 | 6 | 9.5 |
| Gender | | |
| Female | 61 | 96.2 |
| Male | 2 | 3.8 |
| Education | | |
| Low | 13 | 20.6 |
| High | 50 | 79.4 |
| Marital status | | |
| Single | 2 | 3.2 |
| Married | 52 | 82.5 |
| Divorced/separated | 1 | 1.6 |
| Widow (er) | 8 | 12.7 |
| Menopausal status | | |
| Premenopausal | 32 | 50.8 |
| Postmenopausal | 29 | 46 |
| Not applicable | 2 | 3.2 |
| Occupation | | |
| Employed | 47 | 74.6 |
| Unemployed | 16 | 25.4 |

metastasis, the T stage, SBR grade and lymph nodes involvement were not significantly associated with metastasis (P=0.852, 0.085 and 0.425 respectively).

Twelve (75%, n=16) of the patients with LRR had wide local excision while four (25%) were unresectable. Four (25%) had radiotherapy to the chest wall after excision and there was no further recurrence. All patients who developed metastasis commenced chemotherapy using Cyclophosphamide, Adriamycin/Epirubicin and 5-Fluorouracil (CAF/CEF) or Paclitaxel in combination with other agents.

At five years, 37 (58.7%) of the patients who had mastectomy were alive. Eighteen (28.6%) patients with metastasis died: 4 (22.2%) in the first year, 12 (66.7%) second year and 2 (11.1%) third year. Eight (12.7%) patients were lost to follow up. Survival after development of metastasis ranged from 6 to 30 months (median 16.5 months, IQR 12.75-20.0) . Periodic mortality was 18% during the first year, 86% during the second year and 100% during the third year.

The overall incidence of an event within 5 years, either LRR or metastasis, was 26 (41.3%) and 88.5% of events occurred within the first 24 months, with about 52% in between 6 and 12 months.

## Discussion

The most feasible option of treatment for resectable breast cancer in Africa and most parts of the world is modified radical mastectomy [12]. However, LRR and distant metastasis are common treatment failures attending mastectomy and this could be so devastating to the patients and distressing to the surgeon [13].

The LRR rate was 25% at a median follow-up period of 5 years in this study. Other authors from another center, also in Southwest Nigeria, reported a lower rate of 16% over 5 years [2]. The difference in this rate could be due to the availability of more adjuvant treatments (radiotherapy and immunotherapy) in the latter. Considering the advanced stage at which most of our patients presented, radiotherapy would have been a necessary adjuvant therapy to drive low the recurrence rate. Some studies have also reported LRR rate as high as 30% [7,14]. In early breast cancer (Stage T1 or T2) reported by Garg et al. [15], the 5-year risk for LRR was 5% and the routine inclusion of postmastectomy radiotherapy was adjudged unwarranted.

Advanced clinical stage (T3 & 4) and higher positive lymph nodes were associated with recurrence in our study and this was in consonance with other previous studies [2,10,16]. High tumour grade is a risk factor for recurrence. Despite the fact that only one patient out of 12 with well differentiated tumour developed LRR while a larger number of patients with moderate- and poorly differentiated tumour developed LRR, this was not statistically significant. The result is not unexpected as the small number of patients could have underpowered our analysis in this study.

All the locoregional recurrences occurred within three years with about two-thirds occurring within a year. This is most likely due to large tumour bulk at presentation making surgery to be more challenging. This finding was similar to those of Wangchinda and Ithimakin [17] in which larger and node-positive tumours were associated with greater chances of early recurrence. Our study also showed that more positive lymph nodes and large tumour size were predictors of recurrence. In the study by Mansell et al. [18], large tumour size, high grade tumour, more than 3 positive axillary nodes in addition to the presence of lymphovascular invasion were significant independent predictors of recurrence within 2.5 years. Other factors implicated in the early breast cancer recurrence include younger age of patients, positive resection margin, lack of postoperative irradiation, low estrogen receptor (ER) positivity and overexpression of human epidermal growth factor receptor 2 (HER2 Neu) and triple negative biologic status [17,19,20]. Vascular endothelial growth factor (VEGF) expression has been found to be correlated with tumour grade, tumour size and biological aggressiveness of the tumour which could affect recurrence and tumour metastasis.

The majority (87.5%) of our patients developed a local recurrence mainly involving the skin and the chest wall. With about three-quarters (76.2%) of patients presenting in stages T3 and T4 making adequate local

Table 2. Clinico-pathology Characteristics of the Sixty-three Postmastectomy Patients at Ekiti State University Teaching Hospital

| Tumour characteristics | Frequency | Percentage (%) |
|---|---|---|
| Laterality | | |
| Right | 27 | 42.9 |
| Left | 31 | 49.2 |
| Bilateral | 5 | 7.9 |
| Tumour stage | | |
| 1 | 1 | 1.6 |
| 2 | 14 | 22.2 |
| 3 | 36 | 57.1 |
| 4 | 12 | 19.1 |
| Clinical stage | | |
| I | 1 | 1.6 |
| II | 9 | 14.3 |
| III | 53 | 84.1 |
| Positive lymph nodes | | |
| <5 lymph nodes | 33 | 52.4 |
| ≥5 lymph nodes | 30 | 47.6 |
| Histology | | |
| Invasive ductal carcinoma | 61 | 98.4 |
| Others (tubular, papillary) | 2 | 1.6 |
| Scarff–Bloom–Richardson grade | | |
| Well differentiated | 12 | 19.1 |
| Moderately differentiated | 28 | 44.4 |
| Poorly differentiated | 23 | 36.5 |

control more challenging, it is thus not surprising to have a local recurrence in these "high risk" patients [21]. Adjuvant radiotherapy was indicated in most patients but for unavailability, high cost and difficulty in accessing at other distant centers. The lower axillary lymph nodes recurrence might be due to the adequacy of the axillary dissection and adjuvant chemotherapy.

Half of the patients with LRR developed distant metastasis and two-thirds (66.6%) of the distant metastases also occurred within two years. The median time to first recurrence was 9 months and this was similar to 8.0 months reported by Ali-Gombe et al. [22] in a center where majority received radiotherapy. Locoregional recurrences are typically associated with an increased risk of concurrent or subsequent distant metastatic disease [23-25]. Ordinarily, it would be expected that the clinical T stage and positive lymph nodes associated with LRR in this study would also affect metastasis. This was not established in our study as the factors were not statistically significant. The fact that the remaining patients with distant metastasis did not have prior LRR explains why different factors might be responsible for these two outcomes. This is buttressed by the theory that breast cancer might actually be a systemic disease from the outset [26]. More than half (55.5%) of our patients had lungs/pleural metastasis. Other sites of metastasis include bone, liver and brain. This is consistent with other studies from different centers [27-29]. However, the frequency and distribution of visceral and bone metastases also vary in these centers.

The overall frequency of post mastectomy events in this study was high, and particularly disturbing was finding more than half occurring within the first year. This might have implications for post mastectomy surveillance. Although there are no universal protocols for post mastectomy surveillance, with majority of events occurring from 6 months to 24 months we might suggest closer monitoring in the period from 6-24 months, starting slightly earlier than the 12 -24 months suggested for the COVID-19 era in the study by Agodirin and colleagues [30].

The management of LRR of breast cancer remains a challenge, and as such multidisciplinary care are usually required from different experts including surgeons,

Table 3. Durations of Development of Locoregional Recurrence (n=16) and Metastasis (n=18) after Mastectomy

| Duration (year) | Locoregional recurrence (N/%) | Distant metastasis (N/%) |
|---|---|---|
| 1 | 11 (68.8) | 6 (33.3) |
| 2 | 3 (18.8) | 6 (33.3) |
| 3 | 2 (12.5) | 2 (11.1) |
| 4 | 0 (0.0) | 2 (11.1) |
| 5 | 0 (0.0) | 2 (11.1) |

Table 4. Factors Associated with Tumour Recurrence

| Variables | No recurrence | Recurrence | p-value |
|---|---|---|---|
| Tumour stage | | | |
| Early (T1, 2) | 15 | 0 | |
| Advanced (T3, 4) | 32 | 16 | 0.01 |
| Scarff–Bloom–Richardson grade | | | |
| Well differentiated | 11 | 1 | |
| Moderately/poorly differentiated | 36 | 15 | 0.131 |
| Positive lymph nodes | | | |
| <5 | 29 | 4 | |
| ≥5 | 18 | 12 | 0.011 |

T1: ≤2cm, T2: 2.1-5cm, T3: >5cm, T4: Any size with direct extension to chest wall/skin

Table 5. Logistic Regression Showing the Predictor of Locoregional Recurrence of Tumour

| Variables | | B | P value | Odd Ratio | 95% C.I. | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| | Tumour size | -0.362 | .010* | 0.696 | 0.529 | 0.917 |
| | Duration of lump | -0.037 | 0.579 | 0.963 | 0.845 | 1.099 |
| | Number of Lymph Node (> 5 lymph nodes) | -2.097 | .015* | 0.123 | 0.023 | 0.661 |
| | Gender (female) | 2.488 | 0.174 | 12.035 | 0.333 | 435.606 |
| | Scarff-Bloom-Richardson (well differentiated) | 1.525 | 0.241 | 4.596 | 0.358 | 58.935 |
| | Stage of Tumor (early stage) | -0.607 | 0.647 | 0.545 | 0.041 | 7.333 |

B- Beta value, P- p-value, reference group in parenthesis. CI: confidence interval; *- statistically significant (P<0.05).

radiation oncologist, and medical oncologist. Surgery still plays a major role in achieving a good local control in resectable LRRs. A large portion (75%) of our patients had wide local excision followed by systemic chemotherapy. Although the effectiveness of additional systemic therapy for patients with LRR remains controversial, it would be worthwhile where other treatment options are not consistent as a result of limited facilities. Additional therapies such as radiotherapy, endocrine therapy, molecular target therapies or a combination of these can improve the treatment outcome of patients with locoregional recurrence.

The five-year survival rate of postmastectomy patients in our center was 58.7%. This rate is slightly lower than 65.3% reported by Ayandipo et al. [2, 31]. The observed difference could have been due to the availability of more adjuvant treatments in the latter study. In contrast, high-income countries still have higher rates of survival compared with low-and middle-income countries [32]. Advanced stage at presentation, unfavorable tumour grade, financial constraints with treatment inconsistencies and limited infrastructures account for the disparities [12, 13, 31, 33].

This study is limited by its retrospective nature which has the demerit of poor record keeping. We also did not have facilities for IHC and radiation therapy. These two would have impacted the quality of care, drive low the occurrence of LRR and metastatic disease, and make our study more robust. Furthermore, healthcare financing is by way of fees for service and out-of-pocket expenditures. This makes the cost of care out of reach, and the use of targeted/biologic therapy not feasible.

In conclusion, LRR and metastasis frequently occur following mastectomy and post-mastectomy patients may still remain at risk despite undergoing chemotherapy. Advanced tumour stage and lymph nodes positivity are risk factors identified for LRR Early presentation, availability of diagnostic and treatment facilities with more robust adjuvant therapies can reduce the rates.

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*Conflict of interest*

The authors declare no conflict of interest.

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