

## Breast cancer related lymphoedema (BCRL): Prevalence and evaluation of risk factors

Rohit Srivastava<sup>1</sup>, Sunil Kumar singh<sup>\*2</sup>, Amarjot Singh<sup>3</sup>, Priyanka Rai<sup>4</sup>, Mushtaq Ali<sup>5</sup>

<sup>1</sup>Deptt of General surgery, Dr RMLIMS Lucknow, UP

<sup>2</sup>Deptt of General surgery, Dr RMLIMS Lucknow, UP.

<sup>3</sup>Deptt of General surgery, Dr RMLIMS Lucknow, UP

<sup>4</sup>Deptt of General surgery, Dr RMLIMS Lucknow, UP

<sup>5</sup>Deptt Of General Surgery, Era's Lucknow medical college

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Daniel V.  
Department: Medical

### ABSTRACT

Among cancer related mortality and morbidity, the Breast cancer is commonest cause in women worldwide . Despite of improved treatment technique of the breast cancer, the incidence some refractory complications like breast cancer related lymphoedema (BCRL) of corresponding arm has increased ,which is related to treatment modalities like axillary staging, axillary irradiation or both . BCRL is an agonizing complication which limits day to day activity of the patient and becomes more relevant as the survival after diagnosis of breast cancer increases. Due to lack of standard definition and standardized criteria for evaluation, the incidence varies. This Cohort study with historical cohort and prospective follow-up for 1 year aimed to determine the prevalence , risk factors, influence of axillary staging and locoregional radiotherapy in the development of BCRL .

**Methods:** From May 2017 to March 2019 , clinical records of 180 Breast cancer patients were reviewed from 3 different institutes with Stage I to stage III breast cancer treated with BCT(breast conservation surgery ) , MRM (Modified Radical Mastectomy ) and RT( Radiotherapy) in addition to systemic chemotherapy and the patients were followed up till 1 year. Data were recorded in terms of age, menopausal status, body mass index (BMI) and presence of co-morbid conditions. Difference between both upper limb circumferences at any level of more than 2 cm was considered as significant lymphoedema. With the help of SPSS software, all the statistical calculation was done. **Results:** The prevalence of clinically significant lymphedema was 32.7%. The prevalence of lymphedema was 34% % in patients treated with MRM where as it was 20% in patients treated with Breast conservative surgery. Among sub group of MRM in which more than 4 LN came to be positive were having significant lymphedema(42%) as compared to less than 4 LN positive patients(21%). It was observed that BMI(Body mass index), presence of co-morbid conditions and chemotherapy were not significantly associated with BCRL. Post-operative radiotherapy (axillary irradiation) appears to be an independent risk factor for development of BCRL in multivariate analysis (P < 0.001) **Conclusion:** In our cohort of breast cancer patients, the prevalence of lymphedema was higher in BMI >25kg/m<sup>2</sup> patients . Women who underwent MRM with more than 4 positive lymph nodes had significantly more number lymphedema patients . Radiotherapy was found to be independent risk factor for the development lymphedema, suggesting that the combination of axillary staging and radiation therapy puts patient at much higher risk of lymphedema development.

**Key words:** Breast cancer–lymphoedema

## 1 INTRODUCTION

Breast cancer has been amongst one of the most common causes of cancer related mortality and morbidity among women worldwide. In India, though the incidence of breast cancer is lower (25.8 per 100000) than UK (95 per 100000), yet mortality is higher (17.1vs 12.7) per 100,000 [1] .

There has been a significant increase in the incidence of cancer associated morbidity and mortality in Indian sub-continent as described in global and Indian studies [2,3,5].

Modern era has seen improvements & advancements in the treatment of breast cancer but there has been significant rise in the incidence of breast cancer related lymphoedema (BCRL) of arm simultaneously, which is a difficult to treat complication of surgery or radiation [2,3,4]. Patients with BCRL can have axillary pain[4], shoulder stiffness, unsightly appearance, paraesthesia, functionally impaired limb and proneness for infection. There is increased risk of secondary malignancy like lymphangiosarcoma as well.

Lymphoedema is a chronic, progressive pathologic state characterised by chronic inflammatory fibrosis and hypertrophy of the hypodermal and dermal connective tissues due to lymphatic blockage following either surgical trauma or radiotherapy induced fibrosis . It is characterized by a difference in the circumference of arms ( $\geq 2$  cm) or difference in volume of the limb of  $\geq 200$  ml [6,7,8]. The pathophysiology of lymphoedema of arm is poorly understood. The etiology of lymphoedema can be attributed to lymphatic obstruction/ fibrosis. Factors related to treatment like number of lymph nodes removed via axillary lymph node dissection, adjuvant radiation therapy, late infections and factors related to patients like greater body mass index BMI[6]. Old age and low physical activity may play an important role in the etiology of lymphoedema.

During era of radical mastectomy, reported incidences of lymphedema varied from 49% to 63%[9,10]. Whereas in last 2 decades, the cumulative incidence of lymphoedema has been reported to be 13.5% to 41 % in various studies[11]. The wide range of reported incidence rates are due to lack of standard diagnostic means, universal assessment criteria, insidious nature of onset and prolonged clinical course.

Furthermore, patients with lymphedema have significantly more medical costs than those who do not have this condition. All health care providers involved in the care of breast cancer patients need to be aware of the risk of lymphedema and its impact on patients' quality of life. The treatment designs for breast cancers have changed in last 20 years and there is a trend towards less radical surgical procedures. In patients with early breast cancers with clinically negative axilla, sentinel lymph node biopsy has shown a significant decrease in lymphoedema as compared to axillary node dissection.

## 2 AIMS AND OBJECTIVES

1- To estimate the prevalence of BCRL in patients treated for carcinoma breast by axillary node dissection and/or radiation

2-To study the risk factors responsible for development of BCRL in patients treated for carcinoma breast.

## 3 MATERIAL AND METHODS

Study universe: Patients treated for stage I, stage II & stage III carcinoma breast by breast conservation surgery (lumpectomy) or modified radical mastectomy, with/without radiotherapy and with /without systemic chemo therapy axillary.

Study setting: Patients were recruited from 3 different tertiary care teaching and training institutes in India.

Period of study: May 2017 to March 2019.

Sample size: 180 Female patients.

Inclusion criteria:

CA Breast patients previously treated by breast conservation surgery (lumpectomy) or modified radical mastectomy, with or without radiation and with or without systemic chemo/hormonal therapy.

Exclusion criteria:

1. Patients with history of previous major surgery of the corresponding upper limb.
2. Patients who had history of prolonged intra venous cannulation for chemotherapy (of the same side as disease).
3. Patients who don't have completed treatment
4. Cases of bilateral breast cancer

Type of study: Cohort study with historical cohort and prospective follow-up for 1 year.

## 4 METHODOLOGY

Patient's demographic profile was recorded in terms of age, menopausal status, body mass index (BMI) and presence of co-morbid conditions. The details of disease and treatment including type of surgery, radiation therapy and systemic therapy (chemotherapy therapy) were also documented. The details of radiotherapy, extent of irradiation of chest wall and/or axilla (with or without supraclavicular irradiation) were noted.

Circumference of the affected upper limb was compared with that of the opposite limb and difference at any level of  $\geq 2$  cm was taken as clinically significant lymphoedema.

## 5 RESULTS

**The mean age of study participants was 45.9 years with range from 32-72 years.**

Table 1: Demographic profile and analysis of risk factors for Lymphedema-

Lymphedema subsequent to breast cancer treatment(BCRL) was identified in 59 (32.7%) of the patients. Mean age of presentation was 45.9 (32-72) years, 33.8% of patients had co-morbid Conditions and 33.3% of patients had body mass index of more than 25kg/m<sup>2</sup>.

120 patients were of BMI < 25 kg/m<sup>2</sup>, out of which 35 patients (29%) developed lymphoedema. Whereas 60 patients were of BMI > 25 kg/m<sup>2</sup>, out of which 24 (40%) developed lymphoedema. The difference was not statistically significant.

70 patients were pre-menopausal, out of which 14 (20%) developed lymphoedema. Whereas 45 (40%) of the post-menopausal group developed lymphoedema. The difference was found to be statistically significant. (p value = 0.004)

61 patients were having co morbid conditions, out of which 21 (34%) developed lymphoedema. Whereas 38 (32%) of those not having any co morbidity developed lymphoedema. The difference was not found to be statistically significant.

Table- 2 : Treatment given

It was seen that in 65 patients who underwent MRM, there were 4 nodes involved and out of these 16 (24%) developed lymphoedema. Whereas in 87 patients, there were > 4 nodes involved and out of these, 37 (42%) developed lymphoedema. 28 patients underwent breast conservation therapy and 6 (21%) out of them developed lymphoedema. The incidence of lymphoedema was highest in patients undergoing MRM with > 4 nodes involved followed by patients undergoing MRM with 4 nodes involved followed by patients undergoing breast conservation therapy. The difference was found to be significantly significant (p value = 0.03).

140 patients were subjected to loco regional (chest wall and axilla) radiation, out of which 53 (38%) developed lymphoedema. 18 patients were given radiation to chest wall only, out of which 4 (22%) developed lymphoedema. But the difference was not found to be statistically significant (p value = 0.19).

Overall, 158 patients were given radiation (either loco regional or to the chest wall), out of which 57 (36%) developed lymphoedema compared to 2 patients (9%) who developed lymphoedema amongst those who didn't receive any form of radiation.

156 patients were given chemotherapy, out of which 51 (33%) developed lymphoedema. 8 (33%) of 24 patients who didn't receive any form of chemotherapy developed lymphoedema. The difference was not found to be statistically significant.

28 patients belonged to stage I, out of which 6 (21%) developed lymphoedema, 65 patients were of stage II, out of which 16 (24%) developed lymphoedema. whereas 87 patients belonged to stage III, out of which 37 (42%) developed lymphoedema. It shows that lymphoedema was more likely to develop in higher stages (p value = 0.025)

## 6 DISCUSSION

Among all the complications of treatment of breast cancer, lymphoedema of the upper limb i.e. breast cancer related lymphedema (BCRL) is one of the most distressing and unpleasant complication, particularly frustrating for the surgeon as it is difficult to manage.

Although, in the last 6 decades, breast cancer related lymphedema has been discussed in literature extensively but not much emphasis has been given to its etiology and it continues to be a significant long-term morbidity in the current era[7,11].

There are various methods to assess lymphoedema like water displacement, bioimpedance spectroscopy and arm circumference in centimetres [9]. We used difference in limb circumference to diagnose clinically significant lymphoedema in our study.

The etiological factors of breast cancer related lymphedema can be classified into patient related like high BMI [6,19] and treatment related (lymphatic obstruction caused by surgical interruption or fibrosis).

Geller et, al observed that patient related factors like BMI [18] was associated with the development of lymphedema among obese patients and speculated that larger tissue volume and higher fat content may have contributed to development of lymphedema. Moreover, the increased amount of adipose tissue may act as a reservoir for lymphatic fluids [20]. Contrary to that, we didn't find any significant association of BMI with BCRL.

It was speculated by Paulus et al that conditions such as high blood pressure and diabetes may exacerbate a damaged lymphatic system due to increased hydrostatic pressure [21]. We did not find such an association in our study. Kidney failure may be associated with fluid retention that may cause oedema, thus further complicating an already delicate lymphatic system. In our study chronic kidney disease was found to present in only 4 patients out of which one developed lymphoedema and the association was not statistically significant.

Overall, published reports have both supported [23,24 ] and refuted [25,26 ] that increasing number of nodes excised is linked to the risk of BCRL. Axillary dissection is generally indicated in presence of positive nodes and leads to an increased number of nodes excised. In our study, we found that amongst those patients who were treated by axillary dissection (as part of MRM), the incidence of BCRL was higher in those with > 4 positive nodes as compared to those having ≤ 4 positive nodes and the difference was statistically significant.

In literature, the main treatment-related risk factors for development of BCRL include axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR). There are strong evidences that both ALND and RLNR are independent risk factors for BCRL [12,13]. Type of axillary surgery largely determines an individual's risk for developing lymphedema. Both ALND and the less invasive sentinel lymph node biopsy (SLNB) put patients at life-long risk for developing lymphedema [14]. In our study, incidence of

**Table 1. Demographic Profile**

	Lymphedema present	Lymphedema absent	
BMI <25 kg/m2 (n=120)	35 (29%)	85 (71%)	P=0.144
BMI ≥25 kg/m2 (n=60)	24 (40%)	36 (60%)	
Menopausal status			P=0.004
Pre-menopausal N=70	14 (20%)	56 (80%)	
Post-menopausal N=110	45 (40%)	65 (60%)	
Co-morbidities			P=0.736
DM/HT/CKD/CHF present n=61	21 (34%)	40 (66%)	
DM/HT/CKD/CHF absent n=119	38 (32%)	81 (68%)	

**Table 2. Treatment given**

	Lymphedema present	Lymphedema absent	
Type of MRM			P=0.03
MRM with ≤4 LN positive (n=65)	16 (24%)	49 (76%)	
MRM with >4 LN positive (n=87)	37 (42%)	50 (58%)	
Surgery			P=0.012
Breast conservative surgery (without ALND)(n=28)	6 (21%)	22 (79%)	
Radiation			P=0.19
Given (n=158)	57 (36%)	101 (64%)	
Not given (n=22)	2 (9%)	20 (91%)	
Type of Radiotherapy			P=0.581
Loco regional Radiotherapy (with RLNR) (n=140)	53 (38%)	87 (62%)	
Radiation to chest wall (without RLNR) (n=18)	4 (22%)	14 (78%)	
Chemotherapy			P=0.025
CA (n=56)	51 (33%)	105 (67%)	
CMF (n=24)	8 (33%)	16 (67%)	
Stage			
Stage 1 (n=28)	6 (21%)	22 (79%)	
Stage 2 (n=65)	16 (24%)	49 (76%)	
CA Stage 3 (n=87)	37 (42%)	50 (58%)	

BCRL was found to be more in the patients who received radiation as compared to those who didn't.

However, a recent meta-analysis of BCRL incidence in patients with unilateral breast cancer estimated that patients who receive ALND have a lymphedema incidence four times higher than those who receive SLNB (19.9% and 5.6% respectively) [15]. Thus, SLNB is an effective option for staging the axilla while minimizing the risk of lymphedema in patients with clinically node negative breast cancer [22].

Warren and colleagues demonstrated that RLNR, either supraclavicular with or without posterior axillary boost, significantly increased lymphoedema risk compared to breast/chest wall radiation alone [16].

In our study, the incidence of BCRL was found to be significantly higher in higher stages of the disease. This could be attributed to the fact that higher stages of the disease are more likely to receive radiation and also in these subsets of patients, the probability of higher number of nodes coming out positive (in axillary dissection) is higher.

The limitation of our study was shorter follow up as it has been observed that BCRL can develop even after a period of more than 1 year.

**7 CONCLUSION**

In our cohort of breast cancer patients, we found lymphedema to have a prevalence of 33 %. In particular, post-menopausal women were found to be at significantly more

risk for developing lymphoedema. The number of positive nodes excised was also significantly associated with increased risk of BCRL with more risk in patients in whom > 4 nodes were positive. Patients who receive radiation are more likely to develop lymphoedema as compared to those who don't. Lymphoedema was found to be more prevalent in higher stages of the disease. Though there was no statistically significant association found between factors like BMI, co morbidities, chemotherapy, type of radiation (to chest wall and axilla versus to chest wall only) and incidence of BCRL, further studies with larger sample size are required to evaluate the impact of these factors.

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**AUTHOR BIOGRAPHY**

**Rohit Srivastava** Deptt of General surgery, Dr RMLIMS Lucknow, UP

**Sunil Kumar singh** Deptt of General surgery, Dr RMLIMS Lucknow, UP.

**Amarjot Singh** Deptt of General surgery, Dr RMLIMS Lucknow, UP

**Priyanka Rai** Deptt of General surgery, Dr RMLIMS Lucknow, UP

**Mushtaq Ali** Deptt Of General Surgery, Era's Lucknow  
medical college