

# Prevalence of Lymphedema and Associated Risk Factors Following Multimodal Breast Cancer Treatment

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## ABSTRACT

**Background:** Breast cancer related Lymphedema (BCRL) in the respective arm is a common but serious negative sequel of breast cancer management. Risk factors include dissection of Axillary lymph nodes and irradiation of Regional lymph nodes. Nearly 20% of patients receiving treatment of breast cancer develop this complication and it has a negative impact on quality of life of the patient. **Objective:** Current study aims to equip the medical professionals with all the details needed for prevention, early detection, intervention and management of this hazardous late treatment related complication. **Material and Methods:** Total 350 breast cancer patients (with their consent) treated at Government Cancer Hospital, Indore in the Radiotherapy and Oncology Department, in period from January 2019 till December 2021, with chest wall radiotherapy following subsequent hormonal therapy, as needed. Patients then analysed for occurrence of lymphedema. Subsequently, efforts were given for finding out the correlation between lymphedema and related treatment modality like adjuvant radiotherapy following definitive surgery with number of excised lymph nodes and number of involved lymph nodes, chemotherapy, hormonal therapy, subjective co-morbid condition (obesity, diabetes mellitus and high blood pressure). **Results:** Current study demonstrate a significant correlation of adjuvant radiotherapy, including progressive involvement of the lymph node stations, with radical or conservative breast surgery with lymph node dissection represents a statistically significant risk factor, with relative risk,  $RR=1.49$  (95%  $CI=0.72-3.05$ ),  $p<0.001$ . Subsequent increase in number of dissected lymph nodes shown a risk factor with statistical significance as relative risk for more than 25 removed lymph nodes, demonstrated significant risk of lymphedema than for 16-25 removed lymph nodes. Other analysed risk factors, which did not influence lymphedema development like, associated chemotherapy, hormonal therapy or presence of co-morbid illnesses. **Conclusions:** Arm lymphedema is a late sequel associated with carcinoma breast treatment using radiation or surgery, and quite capricious occurrence that can happen years after axillary clearance surgery. With the use of sentinel node sampling, could reduce the need of frank axillary clearance by showing either involvement of lymph node in axilla, so as to manage only by radiotherapy. That significantly reduces the risk of lymphedema from 16% with axillary clearance to 5% without dissection.

**KEY WORDS:** Lymphedema, Breast cancer, Risk factors, Axillary lymph node.

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## Introduction

With the advancement in breast cancer treatment protocols, medical professionals and cancer patients are positively focused on post-treatment Quality of Life of patients. Hence, detailed understanding of breast cancer-related lymphedema (BCRL) and its treatment is fundamental for all health care providers.<sup>[1]</sup> Etiopathogenesis of BCRL is due to interruption of lymphatic drainage which results in

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accumulation of protein rich lymph in the interstitial spaces.<sup>[2,3]</sup> This accumulation of fluid can result in unusual swelling in the breast, trunk or upper extremity (Unilateral or Bilateral) depending on the side of treatment. Patient may present with varied symptoms depending on extent of lymph accumulation such as, swelling, tightness, pain over swelling, tingling/numbness or abnormal limb function.<sup>[3-5]</sup> At later stages this lymph accumulation undergoes fatty deposition and therefore fibrosis starts developing.<sup>[6]</sup> This negative sequela hampers the patient's quality of life resulting in anxiety and depression among these cancer survivors in addition to physical deformity and impairment.<sup>[7-10]</sup>

Hence, it is the need of the time to understand the risk factors affecting BCRL as well as to apply this knowledge so as to follow adequate preventative measures and diagnostic approaches. The thought behind this review is to enlist evidence-based risk factors, preventative measures, and treatment guidelines to establish a comprehensive data from which health care providers and researchers can gain insight and improve quality of life of these cancer survivors.

## Materials & Methods

We studied 350 breast cancer patients (with their consent) who had taken treatment at the Government Cancer Hospital of a tertiary care centre in the Radiotherapy and Oncology Department, from January 2019 till December 2021. The median age of the patients was 57 years (range 30-78 years), with a majority of urban cases (67.14%). 40.58% of patients presented with loco-regional advanced disease, being in IIIB stage, and 38.57% of cases were in IIB stage of disease. The demographics and clinical characteristics are shown in Table 1 of all 350 breast cancer patients, 22 (6.28%) developed arm lymphedema, with majority cases involving the left arm (72.73%). Adjuvant Radiotherapy was advocated in patients with multiple (more than 4) metastatic lymph nodes or cases with extra-capsular extension of the involved nodes. In different combinations of chest wall and axillary lymph nodes along with supraclavicular regions, internal mammary lymph nodes were included in the radiotherapy field. Radiotherapy in conventional fractionation schedule with 50 Gray (Gy) in 25 fractions (#) with 2Gy/# in oblique and direct fields was performed after the patients signed the informed consent in accordance to the Hospital protocol. Toxicities were managed conservatively. Following the completion of treat-

ment with adjuvant radiotherapy with or without chemotherapy, hormonal therapy with selective estrogen receptor modulators (SERM) or aromatase inhibitor (AI) has been given on daily basis schedule in hormonal receptor positive patients.

## Statistical Analysis

Data analysis was done using Chi square test. Multivariate logistic regression model was applied for multivariate analysis. 95% confidence interval was used to report Relative risks and Odds ratio. P-values <0.005 was reported significant.

## Results

During the follow-up period, 22 patients (6.28%) developed arm lymphedema. The mean age of the patients in the lymphedema group at the time of surgery was 57 years. Our study concludes that patients who received adjuvant radiotherapy involving lymph node areas, especially after radical or conservative surgery with lymph node dissection as primary treatment represents a statistically significant risk factor ( $p < 0.005$ ). On the contrary, the radiotherapy technique which spares the axillary regions did not represent a risk factor for arm lymphedema.

Another statistically significant risk factor found was the number of lymph nodes excised. For more than 25 removed lymph nodes, the relative risk for lymphedema development was  $RR = 1.01$  ( $CI = 0.57-1.78$ ) and for 16-25 removed lymph nodes the relative risk,  $RR = 2.55$  ( $CI = 1.46-4.46$ ) indicate aggressive axillary clearance associate with augment probability of lymphedema (Table 2). In context with adjuvant radiotherapy, with subsequent radiation dose to more of lymph nodal regions, significant augmentation in the chances of lymphedema,  $RR = 1.49$  ( $CI = 0.72-3.05$ ). Another analysed risk factor was application of hormonal therapy and chemotherapy, but they failed to be statistically significant,  $RR = 0.6$  ( $CI = 0.31-1.35$ ) and  $0.34$  ( $CI = 0.16-1.03$ ) respectively. Hence, chemotherapy and hormonal therapy are not associated with development of lymphedema. Presence of co-morbidities as risk factors for occurrence and development of arm lymphedema such as obesity, diabetes mellitus and high blood pressure. But none of these diseases were found to be the statistically significant risk factors:  $RR = 0.9$  ( $CI = 0.41-1.85$ ) for obesity,  $RR = 0.3$  ( $CI = 0.1-0.9$ ) for diabetes mellitus and  $RR = 0.45$  ( $CI = 0.22-1.06$ ) for high blood pressure.

**Table 1: Demographics and Clinical details**

Parameters	No. of patients (%) N=350	Patients with Lymphedema N=22
<b>Median Age at surgery (in years)</b>	57 (30-78)	54 (38-75)
<b>Sex</b>		
Male	4 (1.14)	0
Female	346 (98.86)	22 (100)
<b>Locality</b>		
Urban	235 (67.14)	14 (63.63)
Rural	115 (32.86)	8 (36.37)
<b>Stage of disease</b>		
I	18 (5.14)	1 (4.55)
IIA	27 (7.72)	4 (18.18)
IIB	135 (38.57)	6 (27.27)
IIIA	24 (6.85)	2 (9.09)
IIIB	142 (40.58)	7 (31.82)
IV	4 (1.14)	2 (9.09)
<b>Site of lymphedema</b>		
Right arm		6 (27.27)
Left arm		16 (72.73)
<b>Number of Lymph nodes removed</b>		
<15	168 (48)	5 (22.72)
16-25	126 (36)	8 (36.37)
>25	56 (16)	9 (40.91)
<b>Metastatic Lymph nodes</b>		
Yes	256 (73.14)	16 (72.73)
No	94 (26.86)	6 (27.27)
<b>Surgery done</b>		
Mastectomy + LN dissection	286 (81.71)	16 (72.73)
Conservative surgery + LN dissection	64 (18.29)	6 (27.27)
<b>Chemotherapy given</b>		
Yes	270 (77.14)	18 (81.82)
No	80 (22.86)	4 (18.18)
<b>Radiotherapy</b>		
Chest wall/ mammary glands	86 (24.57)	5 (22.73)
Chest wall/ mammary glands + LN area	264 (75.43)	17 (77.27)
<b>Hormonal therapy</b>		
Yes	274 (78.29)	14 (63.64)
No	76 (21.71)	8 (36.36)
<b>Obesity</b>		
Yes	102 (29.14)	15 (68.18)
No	248 (70.86)	7 (31.82)
<b>Hypertension</b>		
Yes	78 (22.29)	6 (27.27)
No	272 (77.71)	16 (72.73)
<b>Diabetes</b>		
Yes	45 (12.86)	6 (27.27)
No	305 (87.14)	16 (72.73)

**Table 2: Relative Risk of lymphedema for different risk factors**

Risk factors	RR (95%CI)
<b>Number of removed lymph nodes</b>	
<15	1*
16-25	1.01(0.57-1.78)
>25	2.55 (1.46-4.46)
<b>Radiotherapy technique</b>	
thoracic wall/mammary gland	1*
thoracic wall/mammary gland + lymph regions	1.49 (0.72–3.05)
<b>Chemotherapy (CMT)</b>	
Yes	0.34 (0.16–1.03)
No	1*
<b>Hormonal therapy (HT)</b>	
Yes	0.6 (0.31–1.35)
No	1*
<b>Obesity</b>	
Yes	0.9 (0.41–1.85)
No	1*
<b>High blood pressure</b>	
Yes	0.45 (0.22–1.06)
No	1*
<b>Diabetes Mellitus</b>	
Yes	0.3 (0.1–0.9)
No	1*

1\*: standered reference

In the multivariate analysis variables included were number of lymph nodes removed, adjuvant radiotherapy, chemotherapy, hormonal therapy association and obesity. Logistic regression evidenced that only the number of excised lymph nodes and patients who received adjuvant radiotherapy involving lymph node areas, especially after radical or conservative surgery with lymph node dissection as primary treatment represents a statistically significant risk factor for developing arm Lymphedema.

## Discussions

The risk of developing arm lymphedema is associated with axillary lymph node dissection, external beam radiotherapy (EBRT) and with the combination of the both of them individually. Incidence varies between 10-37%, demonstrate significant correlation with the progressive number of lymph nodes resected and intensified axillary clearance. Current study established that adjuvant chemotherapy, hormonal therapy, high blood pressure and diabetes mellitus

were not found to be associated significantly with risk of lymphedema.

Etiology of arm lymphedema is proposed to be development of fibrosis after radiation, which causes constriction of lymphatic vessels, leading to improper drainage of lymphatics and thus altering the immune response.<sup>[9,11]</sup> Resultant stagnation of lymphatic causes lymphedema.<sup>[12,13]</sup> Another important risk factor for lymphedema is Body mass index (BMI). In the study by Ozaslan et al.,<sup>[14]</sup> it was noted that a BMI > 25 is statistically significant for lymphedema development. On the contrary, Larson et al.<sup>[9]</sup> did not corroborate with this finding. Present study proved that the number of lymphnodes removed is statistically significant for lymphedema development just like the authors Larson et al.<sup>[9]</sup> Kiel et al.<sup>[15]</sup> and Senofsky et al.<sup>[16]</sup>. While studies like Ozaslan et al.<sup>[14]</sup>, Eduard et al.<sup>[17]</sup>, Roses et al.<sup>[18]</sup>, failed to prove so. Our study also shows that the application of adjuvant EBRT after radical or conservative surgery with lymph node dissection poses a significant risk factor for lymphedema development as done by many literature studies like Ozaslan et al.<sup>[14]</sup>, Kiel et al.<sup>[15]</sup>, Senofsky et al.<sup>[16]</sup>, Mortimer et al.<sup>[19]</sup>, Brismar et al.<sup>[20]</sup>

Arm lymphedema occurs late after axillary EBRT in patients without axillary lymph node dissection comparative with lymphedema that occurs after combined treatment – axillary lymph node dissection and EBRT. Another point not be overlooked is the breast lymphedema developing after EBRT, in cases managed conservatively which can result in physical and psychological distress, pain, repeated episodes of cellulitis and poor cosmetic result of the affected breast.

Prevention of arm lymphedema development can be done by starting physical exercises shortly after surgery, teaching self-massage, compressive contention to prevent volume build up in limbs, medications like flavonoids etc, which improve the microcirculation and facilitate lymphatic drainage, hygiene and healthy diet. Wherever possible, post-treatment biopsy, which increases the risk of cellulitis and breast edema, can be avoided. The total dose administered must be restricted to 45-50Gy in conventional fractionation and the administration of EBRT must be restricted in elderly patients more than 55 years old, especially overweight patients. Health education of patients regarding skin care, avoiding breast infections, obesity, ipsilateral arm

and chest wall trauma plays a critical role in lymphedema prevention. Also, educating the patients about early diagnosis, presuming that early stage disease treatment will have diminished chances of developing lymphedema and performing cutting edge high technology EBRT, which affirms increased dose homogeneity within the treatment field, are also important.

## Conclusion

BCRL remains a potentially life-altering sequel of breast cancer treatment that affects approximately one in five patients. Well-established risk factors include ALND, RLNR, high BMI at time of diagnosis and cellulitis infections. Nevertheless, research has precipitated significant progress in BCRL screening and treatment. Specifically, knowledge of risk factors, following precautionary guidelines, and using surgical treatments that reduce lymphatic disruption are possible areas of evolving BCRL research and care. A multidisciplinary team-based approach to understanding, screening for, preventing, diagnosing, and treating BCRL is unequivocally suggested to provide best care for patients who have received treatment for breast cancer and who are at risk of BCRL.

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