Original Article

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Predictors of Unilateral Arm Lymphedema in Non-obese Locoregionally Advanced Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy, Modified Radical Mastectomy, and Postoperative Irradiation

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ABSTRACT

Objective: The most dreaded long-term complication of axillary lymph node dissection remains upper arm lymphedema. Our study has strategized the three most common identified causes of post treatment arm lymphedema, i.e., obesity, radiation, and neoadjuvant chemotherapy and tried to identify the histopathological and clinical or surgical factors which can predict arm lymphedema.

Materials and Methods: This is a prospective observational study was conducted at a tertiary care referral centre in India, with strict inclusion criteria of BMI <30 kg/m^2, age <75 years, presence of metastatic axillary node proven by FNAC, received anthracycline based neoadjuvant chemotherapy and postoperative nodal irradiation, and completed 24 months of regular follow-up.

Results: Total of 70 patients were included in the study. The mean age of the patients was 50.3 years (±12.9). lymphovascular invasion, total number of lymph nodes removed from level III, total number of days drain was left in situ and maximum drain output were found to be significantly ($p<0.05$) associated with arm lymphedema.

Conclusion: In patients undergoing modified radical mastectomy with level III dissection, and postoperative irradiation, the incidence of unilateral arm lymphedema is significantly influenced by several clinicopathological factors like the total number of lymph nodes removed in level III, higher maximal drain output, prolonged duration of drain placement and the presence of lymphovascular invasion.

Keywords: Axillary lymph node dissection; upper arm lymphedema; neoadjuvant chemotherapy; modified radical mastectomy; breast cancer; locoregional therapy

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Key Points

- Upper arm lymphedema is a serious long-term complication of axillary lymph node dissection.
- The study aimed to identify predictive factors for arm lymphedema in non-obese, locoregionally advanced breast cancer patients who underwent standard neoadjuvant chemotherapy and post-operative irradiation.
- Factors associated significantly with arm lymphedema are lymphovascular invasion, Total number of lymph nodes removed from level III, total number of days drain left *in situ* and maximum drain output.

Introduction

Breast cancer is the commonest cancer worldwide in women with incidence varying widely across countries and regions. It impacts over 2.1 million women each year, accounting for 25% of cancers and 15% of cancer deaths in women (1).

An age-adjusted rate as high as 25.8 and mortality up to 12.7 has been estimated per 100,000 Indian women. Besides this, young age has been identified as a major risk factor for breast cancer in the Indian subset (2). Age-standardized incidence rate is now annually increasing by 29 per cent in the world. This secular trend has been attributed to

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the changes in the population age structure (16 per cent), population growth (12 per cent), and the etiologic causes of the cancer (3).

Chemotherapy and surgery form the mainstay of treatment in early and locally advanced breast cancer. Axillary nodes are the primary draining area, hence management of the axilla is an important component of the treatment of invasive breast cancer.

Kiricuta and Tausch (4) in their seminal work and mathematical model in 1992 established that at least 10 nodes need to be dissected for proper staging. Over time, the management of the grossly uninvolved axilla has changed from complete (level I-III) lymph nodal dissection to sentinel lymph node biopsy. Even when the axilla is grossly involved, many surgeons avoid dissecting level III nodes. This change in practice was based on data that showed that level III dissection is associated with longer surgical time and morbidities without an associated improvement in overall survival (5). There is no consensus among surgeons as to what level of axillary nodes should be dissected for loco-regionally advanced breast cancer with axillary node positivity.

The National Institutes of Health consensus conference recommended level-I or level-II dissection as standard surgery and level-III dissection for patients with obviously involved level III nodes. NCCN clinical practice guidelines® recommends level III dissection when gross disease in levels I & II and/or level III is present (6, 7).

Arm lymphedema remains a dreaded long-term complication of axillary dissection affecting quality of life. The edema promotes recurrent soft tissue infections requiring intravenous antibiotics with other drastic financial and professional implications (8). Most studies, including the landmark study of Armer et al. (9) in 2019, have observed heterogeneity in the treatment of axilla, which makes it difficult to establish the factors affecting the development of lymphedema. Obesity [body mass index (BMI) >30 kg/m^2] and radiotherapy have been described as major risk factors for unilateral arm lymphedema (10).

Our study is an attempt to identify the clinicopathological factors associated with arm lymphedema in patients undergoing level III axillary lymph node dissection, over a two-year follow-up after controlling for contributing factors.

Materials and Methods

This prospective observational study was conducted at a tertiary care referral centre of the armed forces of India, where all modalities of treatment for breast carcinoma were available. Institutional Ethical Committee clearance was taken from the institutional board. Informed consent regarding the study was taken from each individual. Patients were accrued from 2018 to 2021 with the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Age between 18 and 75 yrs.

2. BMI <30 kg/m^2

3. Presented with metastatic axillary node proven by following neoadjuvant chemotherapy.

4. Received anthracycline and cyclophospamide based neoadjuvant chemotherapy and taxane based adjuvant chemotherapy.

5. Received postoperative chemotherapy and regional nodal irradiation.

Exclusion Criteria:

1. Age <18 yrs or >75 yrs

2. BMI ≥30 kg/m^2

3. Clinically N0 node status

4. Did not receive chemotherapy or regional nodal irradiation as per protocol above.

5. Did not complete the mandatory follow-up of 24 months.

6. Did not consent to the study

The selected patients underwent Modified Radical Mastectomy with level I-III axillary nodal dissection. These patients were followed up at 01, 03, 06, 09, 12, 18 and 24 months after completion of nodal irradiation. The last patient completed the 2-year follow-up in June 2022.

Technique of Level III Lymph Node Dissection

The axilla was dissected from the axillary vein superiorly to the angular vein inferiorly (11). The triangular space (bound by axillary vein superiorly, thoracodorsal pedicle and tendon of latissimus dorsi laterally, Halstead ligament medially and angular vein inferiorly) was cleared of all the fibrofatty tissue. For the dissection of level III nodes, the pectoralis minor was retracted and all the fibrofatty tissue medial to its tendon was removed (12). Nerve to serratus anterior, latissimus dorsi pedicle, medial and lateral pectoral nerves were meticulously preserved. This is the standard template of dissection which in experienced hands, adds little to the morbidity (13, 14). Fat pad over the axillary vein was not removed as it leads to increased incidence of upper limb lymphedema (15).

Assessment of Lymphedema

Lymphedema was defined as a difference of more than 2 cm in the upper arm circumference between the arm ipsilateral to the axillary dissection and the contralateral arm. The upper arm circumference (in cm) at 15 cm proximal to the lateral epicondyle ipsilateral to the axilla surgery site was compared with the contralateral upper arm circumference, just as described by Veronesi et al. (16). Measurements were carried out at each follow-up visit.

Drain output was measured each morning at 0800 hours. The drain was removed once the output reached fell below 15 mL. Maximum drain output in any 24 h period and the total days that the drain was *in situ*, were recorded for each patient.

Statistical Analysis

The cumulative incidence was generated with Kaplan-Meier estimators. The incidence of lymphedema was compared across patient groups using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to evaluate the association between baseline patient and disease characteristics and time to lymphedema. Point estimates [eg, number (percentage) of patients, hazard ratios (HRs)] and corresponding 95% confidence intervals (CIs) were used to summarize variables and associations. Statistical analysis was performed using Jamovi Software (Version 2.3.21). A *p*-value of 0.05 was considered significant.

Results

A total of 112 patients with locally advanced breast carcinoma were included in the study. However, 22 had a BMI of more than 30 kg/m^2, ten patients could not complete 24 months of follow up and ten patients did not complete the nodal irradiation protocol due to severe adverse effects. Hence, 70 patients were included in the final analysis, as depicted in Figure 1.

The mean age of the patients was 50.3 years (±12.9). The mean size of the tumour was 3.0 cm (±0.8). The cumulative incidence of arm lymphedema was 25.7% (18 out of 70). The average difference in mid-arm circumference in group A patients (patients with a midarm circumference difference of >2 cm) was 2.84 cm (95% CI; 2.51–3.17), whereas in the patients of group B (patients with a midarm circumference difference of <2 cm), it was 1.4 cm (95% CI; 1.42–1.56) (Figure 2).

On univariable analysis (Table 1), factors associated with reduced incidence of lymphedema were - hormone receptor-positive, presence of lymphovascular invasion, absence of perineural invasion or extracapsular extension, post-NACT tumour size, metastatic node to total lymph node removed ratio in level I, II and level III and total number of days the drain remained *in situ*. Factors associated with increase in lymphedema on univariate analysis were incomplete pathological response and total number of lymph nodes removed from level 3. Total number of lymph node retrieved from level I/II, age and drain output were not found to affect the lymphedema events on univariate analysis. The highest hazard rate for experiencing a lymphedema event was in patients without pathological complete response (HR: 1.86, CI: 0.54–6.42, p = 0.328) followed by patients with hormone receptors/HER2 Neu positivity (HR: 1.40, CI: 0.46–4.26, p = 0.552) and total number of lymph node nodes removed in level III (HR: 1.29, CI: 1.07–1.55, p = 0.007). In terms of protection from lymphedema events, the absence of lymphovascular invasion (HR: 0.23, CI: 0.09–0.62, p = 0.004) and low metastatic to total lymph node ratio in level III (HR: 0.25, CI: 0.04–1.44, p = 0.122) had the lowest hazard rates.

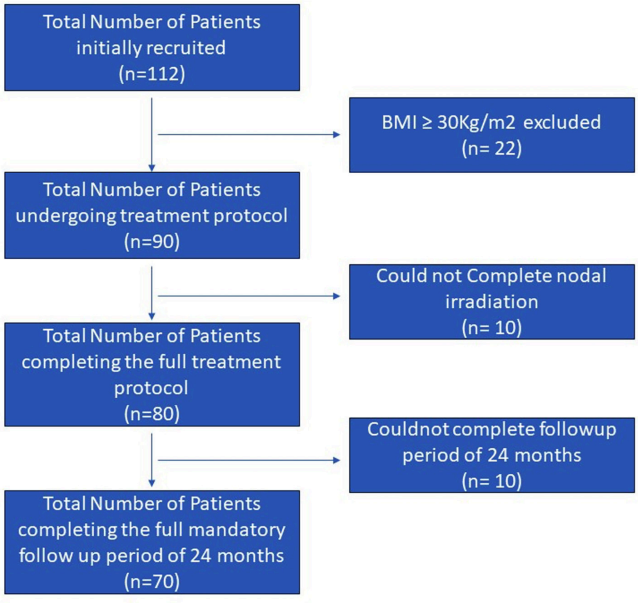

Figure 1. Patient flow chart

BMI: Body mass index

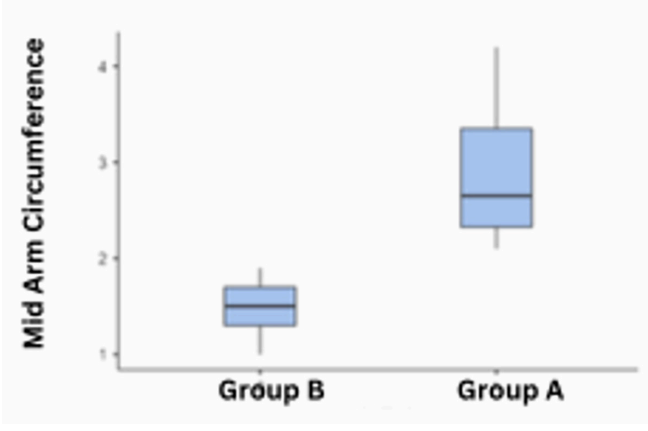

Figure 2. Box plot for arm circumference.

However, on multivariate analysis (Table 1), the effect of these factors was greatly modified. The absence of lymphovascular invasion, perineural invasion and the number of days the drain remained *in situ* retained their protective effect on lymphedema events. But, extracapsular extension, tumour size and the metastatic to total number of lymph nodes removed in level I and II ratio, lost their protective effect as its HR increased from 0.68 (CI: 0.24–1.90, p = 0.458) to 1.28 (CI: 0.18–9.85, p = 0.804), 0.66 (CI: 0.35–1.24, p = 0.192) to 1.39 (CI: 0.62–3.16, p = 0.425) and 0.71 (CI: 0.12–4.29, p = 0.711) to 1.77 (CI: 0.10–29.87, p = 0.693) respectively. The total number of lymph nodes removed in level III and the presence of hormone receptor/HER2 Neu receptor retained their effect to increase the number of lymphedema events even after multivariable analysis and in fact, the effect increased after multivariable analysis from 1.29 (CI: 1.07–1.55, p = 0.007) to 1.59 (CI: 1.23–2.06, p<0.001) and 1.40 (CI: 0.46–4.26, p = 0.552) to 3.22 (CI: 0.64–16.14, p = 0.156) respectively.

Figure 3 depicts the forest plot for the confidence intervals of the risk factors assessesed in this study. Only lymphovascular invasion, total number of lymph nodes removed from level III, total number of days drain was left *in situ* and maximum drain output were found to be significantly (p<0.05) associated with arm lymphedema.

Discussion and Conclusion

Breast cancer is ranked the number one cancer among Indian women with age adjusted rate as high as 25.8 per 100,000 women and a mortality of 12.7 per 100,000 women (3). A recent study of more than 500 patients of breast cancer at a tertiary care centre in north India concluded that the majority of the patients have advanced disease on presentation (17). Late diagnosis and advanced stage have been identified as major determinants of increased mortality. Reasons include lack of access to medical facilities, costs, poor screening programs, lack of awareness and social-cultural attitudes (2). Warmuth et al. (18) evaluated 432 patients who were free of recurrence after surgery and reported that numbness was the most frequent complication (35%), followed by pain (30%), arm swelling (15%), and limitation of arm movement (8%).

The most dreaded long-term complication of axillary lymph node dissection remains upper arm lymphedema. Our study has strategized the three most common identified causes of post treatment arm lymphedema, i.e., obesity, radiation, and neoadjuvant chemotherapy

and tried to identify the histopathological and clinical or surgical factors which can predict arm lymphedema.

To summarize, presence of hormone receptors, absence of complete response, presence of extracapsular extension, metastatic to total lymph node ratio in level I, II or III, total number of lymph node extracted in level III, and drain output were all associated with a higher risk of lymphedema events. Increasing the number of days the drain is left *in situ*, absence of LVI or PNI are associated with decreased number of lymphedema events. Age and total number of lymph nodes removed in level I/II may not have an association with lymphedema if level III node dissection is also done. However, it's important to note that only the absence of LVI, total number of lymph nodes removed in level III, the number of days the drain is left *in situ* and the maximum drain output were significantly associated with breast cancer lymphedema.

The most accurate technique of assessing lymphedema is volumetry. This is accurate but complex and hence not very practical (19). Ozcinar et al. (20) used a perimetric difference greater than 2 cm between the pre- and post-operative measures to diagnose lymphedema and this has been generally been used in routine clinical assessment. The lymphedema incidence and prevalence described in the literature vary widely, possibly due to different measurement methods and intervals between ALND and lymphedema measurement.

In a recently published meta-analysis of more than 84 studies the authors concluded that arm oedema post axillary node dissection is seen up to 30% of cases. Ethnicity (black *vs.* white), higher body mass index, increasing body weight , hypertension, higher cancer stage (III *vs.* I–II), larger tumor size, mastectomy (*vs.* breast conservation surgery), axillary lymph nodes dissection, more lymph nodes dissected, higher level of lymph nodes dissection, chemotherapy, radiotherapy, surgery complications, and higher increase in post operative volume of the limb are all positively correlated with lymphedema. Additionally, breast reconstruction surgery, and adequate finance were found to play a protective role. However, other variables such as age, number

Table 1. Univariate and multivariate analysis of various factors

Factors	Parameter considered	Number (percentage)	Hazard rate (univariable)	Hazard rate (multivariable)
Triple negative breast cancer	Yes	19 (27.1)	1.40 (0.46–4.26, $p = 0.552$)	3.22 (0.64–16.14, $p = 0.156$)
	No	51 (72.9)		
LVI[1]	Yes	25 (35.7)	0.23 (0.09–0.62, $p = 0.004$)	0.18 (0.04–0.87, $p = 0.033$)
	No	45 (64.3)		
PNI[2]	No	45 (64.3)	0.32 (0.09–1.11, $p = 0.072$)	0.67 (0.08–5.78, $p = 0.712$)
	Yes	25 (35.7)		
ECE[3]	Yes	46 (65.7)	0.68 (0.24–1.90, $p = 0.458$)	1.28 (0.18–9.85, $p = 0.804$)
	No	24 (34.3)		
Pathological complete response	No	63 (90.0)	1.86 (0.54–6.42, $p = 0.328$)	0.84 (0.08–8.91, $p = 0.886$)
	Yes	7 (10.0)		
Age	Mean (SD)	50.3 (12.9)	1.02 (0.98–1.06, $p = 0.292$)	0.98 (0.93–1.03, $p = 0.378$)
TLN2[4]	Mean (SD)	17.9 (6.2)	0.98 (0.91–1.06, $p = 0.678$)	0.94 (0.86–1.03, $p = 0.205$)
LNR[5]	Mean (SD)	0.4 (0.3)	0.71 (0.12–4.29, $p = 0.711$)	1.77 (0.10–29.87, $p = 0.693$)
Tumor size	Mean (SD)	3.0 (0.8)	0.66 (0.35–1.24, $p = 0.192$)	1.39 (0.62–3.16, $p = 0.425$)
TLN3[6]	Mean (SD)	4.9 (2.7)	1.29 (1.07–1.55, $p = 0.007$)	1.61 (1.24–2.09, $p<0.001$)
LNR3[7]	Mean (SD)	0.3 (0.3)	0.25 (0.04–1.44, $p = 0.122$)	1.11 (0.06–19.95, $p = 0.942$)
Indwell[8]	Mean (SD)	12.0 (2.0)	0.70 (0.56–0.88, $p = 0.002$)	0.46 (0.28–0.76, $p = 0.002$)
Maximum drain output	Mean (SD)	112.1 (14.0)	1.00 (0.97–1.04, $p = 0.775$)	1.12 (1.04–1.21, $p = 0.004$)

[1]Lymphovascular invasion
[2]Perineural invasion
[3]Extracapsular extension
[4]Total lymph node extracted in level I,II
[5]Positive to negative lymph node ratio in level I,II
[6]Total lymph node extracted in level III
[7]Positive to negative lymph node ratio in level III
[8]Total number of days drain was *in situ*
SD: Standard deviation; LVI: Lymphovascular invasion; PNI: Perineural invasion; ECE: Extracapsular extension; TLN2: Total lymph node extracted in level I,II; LNR2: Positive to negative lymph node ratio in level I,II; TLN3: Total lymph node extracted in level III; LNR3: Positive to negative lymph node ratio in level III; Indwell: Total number of days drain was *in situ*

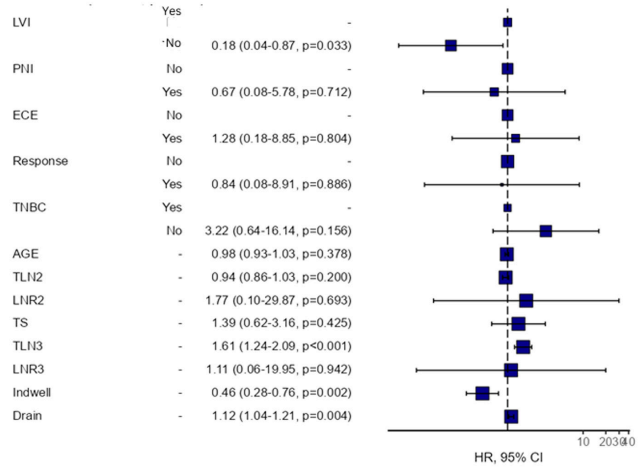

Figure 3. Forest plot depicting Hazard ratio for various factors

LVI: Lymphovascular invasion; PNI: Perineural invasion; ECE: Extracapsular extension; TLN2: Total lymph node extracted in level I,II; LNR2: Positive to negative lymph node ratio in level I,II; TLN3: Total lymph node extracted in level III; LNR3: Positive to negative lymph node ratio in level III; Indwell: Total number of days drain was *in situ*

of positive lymph nodes, and exercise were not correlated with risk of lymphedema (10).

In our study, presence of hormone receptor or Her-2/Neu was associated with increased incidence of arm lymphedema with a HR of 3.22 (0.64–16.14, p = 0.156). Morfoisse et al. (21) in their study of 2018 suggested the protective role of 17β estradiol and VEGF in breast cancer lymphangiogenesis and modulation of the fluid in the soft tissues of the arm. Since patients with hormone receptor positivity undergo anti estrogen therapy, the protective effect of these hormones is lost, resulting in increased incidence of lymphedema.

In our study, the absence of lymphovascular invasion, extracapsular extension and perineural invasion all were associated with a decreased risk of lymphedema events. This correlates well with the retrospective analysis by Invernizzi et al. (22) wherein among the patients who developed arm lymphedema, 46.8% had LVI (as compared to 29.6% in those who did not) and 74.2% had ENE as compared to 61%. Incomplete response to chemotherapy was associated with greater lymphedema events as compared to those having complete response with a HR: 1.86 (0.54–6.42, p = 0.328). This finding could be confounded by a more conservative lymph node dissection in the absence of gross lymphadenopathy (23). Guliyeva et al. (24) in their metanalysis in 2021, found that 13 studies did not find any association of age and breast cancer related lymphedema. Our study has also not demonstrated an increase or decrease in the arm lymphedema events with age [HR: 1.02 (0.98–1.06, p=0.292].

Multiple studies have found that the total number of lymph nodes removed is a significant risk factor for development of arm lymphedema (9, 10, 25). In contrast, our study did not show an increase in lymphedema events as the number of lymph nodes removed increased in level I/II. This is possibly because a significant increase in lymphedema events was observed, both on univariable and multivariable lymph nodes, as the total number of lymph nodes removed in level III increased HR: 1.61 (1.24–2.09, p<0.001).

In our study, we identified that as the metastatic to total lymph node ratio, both in level I/II & III increased, the chances of encountering a lymphedema event increased in multivariable analysis [HR: 1.77 (0.10-29.87, p = 0.693) & 1.11 (0.06–19.95, p = 0.942)]. Various studies have associated number of pathological nodes with increased risk of unilateral lymphedema. Kwan et al. (26) attempted to develop a risk model for breast cancer related lymphedema in which they included 3 patient factors (age, BMI and mammographic breast density), 1 cancer factor (number of pathological lymph nodes), and 1 treatment factor (axillary lymph node dissection) as independent prognostic variables. Zou et al. (27) in their prospective study of 387 women, found that number of positive lymph nodes (HR: 1.1, 95% CI 1.0–1.2) is an independent risk factor for development of lymphedema.

On multivariable analysis, as the post chemotherapy residual tumour size increased, the risk of having a lymphedema event also increased [HR: 1.39 (0.62–3.16, p = 0.425)]. Similar findings can be observed in the studies by Abouelazayem et al. (28), Ren et al. (29) and Aoishi et al. (30).

Suction drains are an important component of the surgical procedure of modified radical mastectomy/axillary node dissection. Drain output along with the number of days that drain remains *in situ* may be an important predictor of development of arm lymphedema (31). Ackroyd and Reed (31) in their study did not find any difference in seroma formation, lymphedema, infection rate between individuals in which drain was removed on 5th postoperative day vis-à-vis when drain output was <30 mL. We however noted a significant increase in lymphedema events as the maximum drain output increased and a decrease in risk of lymphedema events as the number of days the drain remain *in situ* is increased. This is a novel finding of our study and must be explored in further studies.

Our study was prospective with stringent follow up criteria. Strength of our study includes the fact that classical high-risk features like obesity, differences in surgery and irradiation were controlled for. Therefore, we can be confident about the association of the measured factors with the incidence of arm lymphedema.

Study Limitations

The study has many limitations some of which include the fact that it's a single institution study, surgical techniques may vary between surgeons, the use of circumferential measurement of arm as a marker of lymphedema may be less accurate, small sample size and 2 years' follow-up may be insufficient in some cases for development of lymphedema.

Future areas of research may use this study to develop nomograms or algorithms to calculate the risk of lymphedema and include novel factors like maximum drain output and total duration of days the drain remains *in situ* as important associations with breast lymphedema.

In non-obese, locoregionally advanced breast cancer patients undergoing neoadjuvant chemotherapy, modified radical mastectomy with level III dissection, and postoperative irradiation, the incidence of unilateral arm lymphedema is significantly influenced by several factors. Specifically, an increase in the total number of lymph nodes removed in level III and higher maximal drain output are associated with a higher likelihood of lymphedema events. Conversely, prolonging the duration of drain placement and the absence of lymphovascular invasion are correlated with a significant decrease in the occurrence of

lymphedema events. Further multicentric and high powered studies may be done regarding the contribution of hormone receptor positivity, lymph node ratio, and response to neoadjuvant chemotherapy towards lymphedema development.

Ethics Committee Approval: Institutional Ethical Committee clearance was taken from the institutional board (Army Hospital Ethics Committee - IEC no: 46/2018; dated: 06.08.2018).

Informed Consent: Informed consent regarding the study was taken from each individual.

Authorship Contributions

Surgical and Medical Practices: S.D., A.A., V.K.A., S.K.D., R.S., N.S.; Concept: S.D., A.A., R.S.; Design: S.D., V.K.A., N.S.; Data Collection or Processing: S.D., A.A., V.K.A., S.K.D., R.S., N.S.; Analysis or Interpretation: A.A., V.K.A., R.S., N.S.; Literature Search: A.A., V.K.A., N.S.; Writing: S.D., A.A., S.K.D., R.S.

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