RISK FACTORS FOR DEVELOPMENT OF LYMPHEDEMA FOLLOWING BREAST CANCER TREATMENT: A RETROSPECTIVE STUDY

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ABSTRACT: OBJECTIVES: The aim and objective of this study is to identify the factors associated with secondary lymphedema after breast cancer treatment. **BACKGROUND:** Lymphedema of the arm is a complication of breast cancer treatment that affects 2-40% of breast cancer survivors. The pathophysiology of lymphedema following breast cancer treatment is poorly understood, probably suggesting a multifactor nature. As the breast cancer survival rate increases, lymphedema will potentially impact more women. **METHODS:** A retrospective study of 506 patients who underwent modified radical mastectomy for breast cancer in our institute between January 2009 to December 2013. Available follow up period varied from 8 months to 5 years. **RESULTS:** Out of 506 patients studied 70 patients developed lymphedema. Lymphedema was associated with younger age group at diagnosis, positive history of hypertension, obesity, Involvement of more than 4 lymph nodes, higher TNM stage, and axillary RT. **CONCLUSION:** Post treatment lymphedema continues to be a significant problem following breast cancer therapy. Combination of axillary dissection and axillary radiotherapy should be avoided whenever feasible to avoid lymphedema. Control of hypertension and weight reduction via dietary and exercise interventions may be most effective preventive and therapeutic measures.

KEYWORDS: Carcinoma breast, BMI, Axillary dissection, Axillary radiotherapy, LABC.

INTRODUCTION: Early detection and multimodality therapy has resulted in an overall improvement of survival among breast cancer patients.^[1] Post treatment lymphedema continues to be a significant problem following breast cancer therapy causing physical and psychological morbidity and measurable reduction in quality of life in respect to functional, emotional, physical and social well-being.^[2,3] The objective of this study is to identify the factors associated with secondary lymphedema after breast cancer treatment.

MATERIALS AND METHODS: A retrospective study of 506 patients who underwent modified radical mastectomy for breast cancer in the department of surgical oncology of our Institute between January 2006 to December 2009. Available follow up period varied from 8 months to 5 years.

Inclusion Criteria: Female breast cancer patients, early & locally advanced breast cancer patients who underwent surgery and patients undergoing modified radical mastectomy as the surgical treatment.

Exclusion Criteria: Male breast cancer patients, patients with distant metastases, patients with recurrent disease, patients undergoing breast conserving surgery, patients undergoing lumpectomy before presentation to our hospital.

ORIGINAL ARTICLE

OBSERVATIONS AND RESULTS: Out of 506 patients studied 405 were more than 40 years of age, 164 patients had increased BMI, 75 patients had hypertension, 308 patients had more than 10 lymph nodes removed, 194 patients had 4 or more lymph nodes involved, 243 patients had LABC (stage III), 361 patients received radiotherapy out of which 39 patients received axillary irradiation also, wound complications were seen in 85 patients.

In our series lymphedema was associated with younger age (< 40yrs) at diagnosis ($p=0.024$), increased BMI ($p<0.001$), hypertension ($p<0.001$), involvement of 4 or more lymph nodes ($p<0.001$), LABC ($p=0.001$), and axillary RT ($p<0.001$) [ref table].

Parameter		Lymphedema Group(70)	p-value	Odd's Ratio(OR)	95% CI of OR
Age	>40years	49/405(12.1%)	0.024	1.907	(1.08-3.36)
	<40years	21/101(20.8%)			
BMI	Abnormal	42/164(25.6%)	<0.001	3.861	(2.29-6.51)
	Normal	28/342(8.2%)			
Hypertension	Present	23/75(30.7%)	<0.001	3.614	(2.03-6.43)
	Absent	47/431(10.9%)			
No. of Nodes harvested	>10	46/308(14.9%)	0.371	1.273	(0.75-2.16)
	<10	24/198(12.1%)			
No. of Nodes involved	4 or more	54/194(27.8%)	<0.001	7.136	(3.94-12.91)
	3 or less	16/312(5.1%)			
RT	Yes	56/361(15.5%)	0.084	1.718	(0.92-3.195)
	No	14/145(9.7%)			
Axillary RT	Yes	39/134(29.1%)	<0.001	5.071	(2.73-9.42)
	No	17/227(7.5%)			
Stage of disease	Early breast ca	15/263(5.7%)	<0.001	4.837	(2.65-8.83)
	LABC	55/243(22.6%)			

Table 1

DISCUSSION: The prevalence of upper extremity lymphedema varies from 2% to 40% in women with breast cancer who have been treated with surgery, radiation or both.^[4,5] In the current study incidence of lymphedema was 13.8% (70 out of 506).

In our study it was found that arm lymphedema was associated with younger age group (<40yrs) at diagnosis [$P=0.024$; $OR=1.907$; 95% $CI= 1.08-3.36$] and positive history of hypertension [$P<0.001$; $OR= 3.614$; 95% $CI= 2.03-6.43$]. These results are similar to the work of Meeske K. A et al,^[6] whereas Hayes S.C et al^[7] reported threefold increased odds of developing lymphedema in patients aged more than 50 years. However majority of studies have found no statistical significant association between age and lymphedema incidence.^[8-12]

Overweight and obesity have been reported as an important factor that increases the risk of lymphedema development.^[13-18] Our study also demonstrates a definite correlation between increased BMI and risk of development of lymphedema [$P<0.001$; $OR=3.861$; 95% $CI= 2.24-6.51$]. A clinical trial conducted by Shaw et al^[19] has shown that weight loss can significantly decrease the breast cancer related lymphedema incidence.

ORIGINAL ARTICLE

Lymph node status is an important predictor for prognosis and treatment option in women with breast cancer.^[13] In the current series involvement of more than 4 lymph nodes carried a 7 fold increased odds of developing lymphedema [P=0.001; OR=7.136; 95% CI= 3.94-12.91], positive lymph nodes mean more aggressive treatment like chemotherapy, radiotherapy or combined therapy and may increase damage to lymphatic system and surrounding tissues. This may explain why lymph node positive patients are more prone to lymphedema.^[13] It is interesting to note that our study did not show any association between lymphedema and number of lymph nodes harvested [P=0.371] which is in contrast with the work of Yen et al^[20] who found that removal of > 5 lymph nodes is an independent predictor of lymphedema.

Our data demonstrates that higher TNM stage is an independent predictor of lymphedema [P=<0.001; OR=4.837; CI=2.65-8.83]. Again it may be due to more aggressive treatment causing increased damage to lymphatics.

Radiotherapy has been found to be a major and independent risk factor of lymphedema development in some studies,^[13,16,17,21] however the receipt of radiotherapy in the current study was not associated with development of lymphedema [P=0.084; OR=1.718; CI=0.92-3.195]. The lack of association between radiotherapy and lymphedema is consistent with more recent studies^[6,22-24] and is likely due to more modern radiation techniques that are confined to breast and chest wall.^[20]

Axillary irradiation has emerged as a significant risk factor for lymphedema in the current series [P=<0.001; OR=5.071; CI=2.73-9.42]. Based on the available literature and results of the current study a combination of surgery and axillary radiotherapy seems to be acting in synergistic fashion in the causation of lymphedema, resulting in 3 to 7 folds increase of lymphedema incidence.^[11,25]

In summary, the current study showed a correlation between increased lymphedema rates and younger age, hypertension, increased BMI, higher stage, lymph node status and axillary irradiation. BMI, lymph node status, higher stage and axillary radiotherapy were the independent predictors of upper extremity lymphedema.

CONCLUSION: Lymphedema is a distressing complication among breast cancer survivors. A combination of axillary dissection and axillary irradiation should be avoided whenever feasible to avoid lymphedema. Control of hypertension and weight reduction via dietary and exercise intervention may be the most effective preventive and therapeutic measures. Since there is no ideal treatment available for established lymphedema, future efforts should be focused on optimizing treatment combinations and educating the patients and their caretakers.

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ORIGINAL ARTICLE

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ORIGINAL ARTICLE

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