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Original Research Article

Upper limb lymphedema related to breast cancer therapy: incidence, risk factors, diagnostic techniques, risk reduction and optimal management

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ABSTRACT

Background: Lymphedema remains to be a great source of morbidity for breast cancer survivors. The aim of this work is to study upper limb lymphedema following breast cancer therapy for breast cancer patients regarding its incidence, risk factors, diagnostic techniques, risk reduction and optimal management.
Methods: This prospective study was done on two hundred breast cancer patients who underwent breast cancer management. The study was done in the period between May 2016 and July 2018. Exclusion criteria were Male patients, Female patients with metastatic breast cancer and who already had upper limb lymphedema before breast cancer management. All patients underwent follow up for incidence, risk factors, diagnostic techniques and management of lymphedema. Statistical analysis used: The collected data were organized, tabulated and statistically analyzed using SPSS software
Results: The incidence of lymphedema was (18 %) distributed as follow: grade I = 55.6%, grade II = 33.3%, grade III = 11.1 % and grade IV = 0 %. The most relevant risk factors for development of lymphedema were: age between 41 and 50 years and diabetes mellitus. Higher incidence of pain (66.7%) and restricted motion (61.1%) were observed in lymphedema cases.
Conclusions: Old (41:50 years) and diabetic patients are at the highest risk for developing lymphedema. Breast cancer patients of stage IIIB who had undergone modified radical mastectomy or who developed postoperative seroma are at higher risk for developing lymphedema. Physical exercises and compression garment are important part of treatment plan.

Keywords: Breast Cancer, Compression garment, Lymphedema

INTRODUCTION

Breast cancer is the most common invasive cancer affecting women both in North America and in the world. It is the 2nd highest cause of cancer death in women after lung cancer. Improvements in methods of breast cancer detection have increased incidence, but mortality has steadily declined.[1] Breast cancer is estimated to be the most common female cancer in Egypt. Its incidence differs considerably among rural and urban populations, with the higher urban incidence being consistent across all women above the age of 45 years.[2]

Breast cancer treatment is a multimodal treatment and includes surgery, radiotherapy, chemotherapy and hormonal therapy. Axillary lymph-node dissection and/or external beam radiotherapy represent an important component in the treatment of the great majority of invasive breast cancer. The treatment of this condition depends on its staging, with surgical removal of the tumor constituting an important step in an attempt to cure the disease.[3]

Breast cancer-related lymphedema is a chronic swelling of the upper limb following surgery to the axillary lymph nodes, which was originally described by Handley.[4] Halsted coined the phrase 'elephantiasis chirurgica' to describe this condition.[5] Lymphedema is an accumulation of fluid in the interstitial tissues due to the inability of the lymphatic system to transport lymph fluid out of the affected area.

Women who have undergone surgical or radiation treatment for breast cancer are at a lifelong risk of developing lymphedema, which can cause swelling in the arm, hand, shoulder, breast, or chest wall.[6]

The condition may result in physical and psychological consequences, which can negatively impact a woman's quality of life and compromise her emotional wellbeing.[7] The upper arm lymphedema is reported as being the most frequent late reaction and complication that influences breast cancer patients' quality of life after lymph node dissection and radiotherapy.[3]

Lymphedema remains to be a great source of morbidity for breast cancer survivors with axillary lymph node dissection. The progressive nature and lack of effective therapies continue to challenge health care professionals. The incidence of Lymphedema ranges from 6 to 30% after breast cancer treatment whereas the incidence is reported in 33-47 % of BC patients with axillary lymph node dissection.[8]

Early detection and timely intervention have gained prominence because of no definitive treatment for Lymphedema. Early detection allows for reduced physical limitations, reduced joint pains, decreased medical costs, improved quality of life, and decreased complications such as cellulitis, lymphangitis, and compartment syndrome.[9] The aim of this work is to study upper limb lymphedema following breast cancer therapy for breast cancer patients regarding its incidence, risk factors, diagnostic techniques, risk reduction and optimal management.

METHODS

This prospective study was done on two hundred patients with breast cancer who underwent breast cancer management and satisfied the inclusion and exclusion criteria to be enrolled in the study during the period between May 2016 and July 2018.

Inclusion criteria

Female patients with Breast Cancer who had been managed by surgery, radiotherapy, chemotherapy and / or hormonal therapy.

Exclusion criteria

Male patients with breast cancer, female patients with metastatic breast cancer, female patients who already had upper limb lymphedema before breast cancer management or female patients with previous surgery in the ipsilateral upper limb.

All patients in the study were subjected preoperatively to: Personal history taking: name, age, residence and occupation.

Past history taking: diabetes mellitus, hypertension and obesity. Imaging (mammography with complementary ultrasonography). Fine needle aspiration cytology (FNAC). Metastatic work-up: abdominal ultrasound, chest X-ray and CT chest, CT abdomen and pelvis (if necessary).

Type of surgery was assessed, either conservative breast surgery or modified radical mastectomy. Postoperatively the patients were assessed for: Tumor size. T1 ≤ 2 cm, T2 > 2 ≥: 5 cm and T3 < 5 cm, number of excised lymph nodes, number of involved lymph nodes: N0=0. N1=1:3. N2=4:9. N3≥10, stage of disease: either stage I, IIa, IIb, IIIa or IIIb, post-operative seroma, radiotherapy technique, chemotherapy, hormonal receptors and therapy, morbidity: either Pain, Restricted motion and / or Paresthesia.

Arm circumferences were measured at 5 points in two arms. These points were: hand (at the first and fifth metacarpal), wrist (at the distal edge of the styloid process), 10 cm below elbow, and 5 and 15 cm above elbow. A circumference difference of 2 cm or higher at any point, was considered as a clue for diagnosis of lymphedema.

Lymphedema cases were assessed for: Incidence, side (dominant hand or not), grading: according to the Late Effects Normal Tissue Task Force (LENT) - Subjective, Objective, Management, Analytic (SOMA) scale: Grade 1:2-4 cm, grade 2:4-6 cm, grade 3:> 6 cm and grade 4: non-functional arm.

Lymphedema patients were divided into 2 groups. Each group consists of 18 patients. The selection was done alternately. The first group was treated only with exercise treatment.

The second group was treated with the compression garment and the exercise treatment program. The exercise program consisted of light resistive exercises, including cane stretches, praying child, wall walking, and pulleys.

Both groups were given the same exercise program. They were asked to carry out these exercises 3 times a day, with ten repetitions each time for the duration of 6 months. The patients in the second group were asked to wear the garments on at all times expect when they go to sleep.

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 19, SPSS Inc. Chicago, IL, USA).

RESULTS

The ages of the 200 patients ranged from 32 years and 69 years with a mean age of 48.65±8.17 years.

During the follow-up period, the overall cumulative incidence of lymphedema was (4%) after 3 months, (7%) after 6 months, (14.0%) after 1 year and (18.0%) after 2 years (Table 1).

Table 1: Incidence of lymphedema during follow up of the studied patients (n=200).

Incidence of lymphedema over 2 years of follow up	The studied patients (n=200)	
	Cumulative frequency N	%
After 3 months	8	4
After 6 months	8+6	7
After one year	14+14	14
After two years	28+8	18

The highest incidence of lymphedema (38.9%) was among patients with an age range from 41 years to 50 years while the lowest incidence (11.1%) was among patients with an age range from 32 years to 40 years.

According to grading, lymphedema cases (36) were found to be distributed as follows: grade I = 20 cases (55.6%), grade II = 12 cases (33.3%), grade III = 4 cases (11.1 %) and there was no any grade IV case (0 %) (Table 2).

Table 2: Grading of lymphedema among the studied patients with lymphedema (n=36).

Grading of lymphedema	The studied patients with lymphedema (n=36)	
	N	%
Grade I	20	55.6
Grade II	12	33.3
Grade III	4	11.1
Grade IV	0	0.0

A peak incidence in the age 51 to 60 for grade I (60.0%), 41 to 50 for grade II (83.3%) and equally at 41 to 50 and 61 to 69 for grade III (50.0%) (Table 3).

The percentage of diabetic patients among non-lymphedema cases was (7.3%) and that percentage raised up to (27.8%) in lymphedema cases. With a P value of (0.025) (Table 4). In 61.1% of patients with lymphedema, the dominant arm and affected one were the same.

The most common procedure done was modified radical mastectomy (MRM), performed on (79%) patients

Table 3: Relationship between grade of lymphedema and demographic data among lymphedema patients (n=36).

Demographic data	Grading of lymphedema among lymphedema patients (n=36)						χ2	P
	Grade I (n=20)		Grade II (n=12)		Grade III (n=4)			
	n	%	n	%	n	%		
Age (years)								
- 32-<40	4	20.0	0	0	0	0	13.257	0.039*
- 41-<50	2	10.0	10	83.3	2	50.0		
- 51-<60	12	60.0	0	0	0	0		
- 61-69	2	10.0	2	16.7	2	50.0		
Occupation								
- Employed	10	50.0	6	50.0	2	50.0	0.000	1.000
- Housewife	10	50.0	6	50.0	2	50.0		
Residence								
- Rural	10	50.0	12	100	2	50.0	4.500	0.105
- Urban	10	50.0	0	0	2	50.0		

*Significant (P<0.05)

We also analyzed the treatment plan regarding the type of surgery, radiotherapy, chemotherapy and hormonal therapy as risk factors for occurrence and development of arm lymphedema, but none of them were found to be risk

factors. Regarding TNM staging, the highest incidence of lymphedema is observed in T2=24 cases (66.7%) and N2=18 cases (50%), while patients with distant metastasis were excluded from present study. Regarding the stage of breast cancer, the highest incidence of lymphedema was at stage IIIB with a percentage of (44.4%). While the lowest incidence was equal at stage I and IIIA with a percentage of (5.6%). (Table 5). Among patient who developed postoperative seroma, we found that the incidence of lymphedema was 11.8% compared to (9.1%) in non-lymphedema cases.

Table 4: History of medical disease among the studied patients (with and without lymphedema) (n=200).

Variables	The studied patients (n=200)						χ2 or FE	P
	Without lymphedema (n=164)		With lymphedema(n=36)		Total (n=200)			
	n	%	n	%	n	%		
Diabetes mellitus								
- No	152	92.7	26	72.2	178	89.0		
- Yes	12	7.3	10	27.8	22	11.0	FE	0.025*
Hypertension								
- No	136	82.9	24	66.7	160	80.0		
- Yes	28	17.1	12	33.3	40	20.0	FE	0.189
Obesity								
- No	48	29.3	12	33.3	60	30.0	0.112	0.733
- Yes	116	70.7	24	66.7	140	70.0		

*Significant (P<0.05); FE: Fisher Exact test

Pain and restricted motion were predictors of value for development of lymphedema as 66.7% and 61.1% of lymphedema cases compared to 34.1% and 31.7% of non-lymphedema cases complained of pain and restricted motion respectively (Table 6).

Table 5: Management procedure among lymphedema patients (n=36).

Variables		Group 1 (n=18) mean±SD	Group 2 (n=18) mean±SD	P
Mean arm circumference difference improvement after 6 months at:	Hand	0.68±0.37	0.99±0.26	0.0572*
	Wrist	0.90±0.33	1.40±0.27	0.0045*
	10 cm below elbow	1.02±0.34	1.86±0.28	0.000035*
	5 cm above elbow	1.23±0.36	2.33±0.32	0.0000042*
	15 cm above elbow	1.64±0.51	3.01±0.40	0.000012*

Table 6: Morbidity occurrence among the studied patients (with and without lymphedema) (n=200).

Variables	The studied patients (n=200)						χ2	P
	Without lymphedema (n=164)		**With lymphedema (n=36)**		**Total (n=200)**			
	n	**%**	**n**	**%**	**n**	**%**		
Pain								
No	108	65.9	12	33.3	120	60.0	5.220	0.022*
Yes	56	34.1	24	66.7	80	40.0		
Restricted motion								
No	112	68.3	14	38.9	126	63.0	5.475	0.019*
Yes	52	31.7	22	61.1	74	37.0		
Paresthesia								
No	106	64.6	16	44.4	122	61.0	2.529	0.112
Yes	58	35.4	20	55.6	78	39.0		

Regarding management of lymphedema patients, we found that, mean arm circumference difference improvement of the 2 groups after 6 months at 5 points: (hand, wrist, 10 cm below elbow, and 5 and 15 cm above elbow) was (0.68, 0.99), (0.90, 1.40), (1.02, 1.86) (1.23, 2.33) and (1.64, 3.01) respectively.

There was statistical significance between the 2 groups.

DISCUSSION

Lymphedema is a common complication of cancer therapy. It can occur anywhere that lymph nodes have been surgically removed or disturbed.[10] Lymphedema, following breast cancer treatment, occurs due to lymphatic interruption following surgical trauma or radiotherapy induced fibrosis that leads to chronic inflammation and consequent fibrosis of the hypodermal and dermal connective tissue.[11]

In the present study, the overall cumulative incidence of lymphedema has increased from 4% at 3 months to 7% at 6 months to 14% at 12 months to 18% at 24 months postoperatively which is quite different to a study by Warren et al. 12 in which only 6.8% of patients developed lymphedema at 24 months and 13.7% at 60 months postoperatively.

Other studies by Rebegea et al and Shahpar et al showed that the overall incidence of lymphedema was 5.9 % and 30% respectively.[3,10]

The National Institute for Clinical Excellence in the United Kingdom has reported a lymphedema incidence of 25–28% and recommends lymphedema assessments 1 and 3 years after diagnosis.[13]

In study by Bani et al which included a large sample of 742 breast cancer survivors, 31.67% of the patients reported having lymphedema after a median follow up period of 4.3 years.[14] The mean age of the participants was 53.0±11.0 years while in present study the ages of participants patients ranged from 32 years and 69 years with a mean age of 48.65±8.17 years.

We found that, the most common procedure done was modified radical mastectomy (MRM), performed on (79%) of patients. While in another study by Pillai et al. 11 was performed on (87.9%) of patients.

In 61.1% of patients with lymphedema, the dominant arm and affected one were the same. This is opposite to a study by Shahpar et al where about 62% of patients whose dominant hand and involved limb were the same had no defined lymphedema.[10]

In present study, we also analyzed the treatment plan regarding the type of surgery, radiotherapy, chemotherapy and hormonal therapy as risk factors for occurrence and development of arm lymphedema, but none of them were found to be risk factors.

This is similar to a study by Bani et al. except for radiotherapy.[14] On the other hand a meta-analysis by Disipio et al supports the association of extensive surgery (chest wall and axilla) with increased risk of lymphedema and there is a moderate evidence that supports its association with adjuvant therapy (radiation and chemotherapy).[15]

Another study by Shahpar et al also showed that none of these treatment modalities have a significant relation with lymphedema.[10]

On the contrary a study by Rebegea et al showed that adjuvant radiotherapy including lymph node regions association after radical or conservatory surgery with lymph node dissection represents a statistically significant risk factor.

While like present study it showed that adjuvant chemotherapy, hormonal therapy did not influence lymphedema occurrence.[3]

Regarding concomitant diseases we found that, diabetes mellitus was a risk factor for development of arm lymphedema. This is opposite to the study by Rebegea et al which showed that diabetes mellitus did not influence lymphedema occurrence.[3]

In present study, obesity did not influence lymphedema occurrence. This similar to a study by Larson et al which did not find the BMI to be an important risk factor for lymphedema occurrence.[16]

On the other hand, a study by Ozaslan el al found that a BMI > 25 is an important risk factor with statistical significance for lymphedema occurrence.[17]

While Soran et al believe that it is not clear whether obesity is a direct risk factor for arm edema; it is certainly a risk factor for infection and poor wound healing.[8]

In present study, the number of excised lymph nodes was found to be an independent statistically significant risk factor for development and lymphedema occurrence.

This is supported by several studies by Authors like Larson et al and Kiel et al who found in their studies that the number of removed lymph nodes is an important risk factor with statistical significance for lymphedema occurrence.[18,16]

Other Studies like Ozaslan et al and Edwards et al do not report the number of removed lymph nodes as being a risk factor correlated with lymphedema occurrence.[17,19] In present study pain has been reported in 66.7% and 34.1% of patients with and without lymphedema respectively. While is a study by Clark et al the frequency of pain has been reported in 38% and 37.5% of patients with and without lymphedema respectively.[20]

Bani et al reported that, Pain in the breast/chest wall was 44.3% of patients with lymphedema, compared with 36.9% of patients without lymphedema. Pain in the axilla was 55.3% versus 31.8% and pain in the arm was 57.0% versus 28.6%.[14]

There is a great variation of reporting subjective pain in lymphedema patients. For example, in Paskett et al study,

72% of the lymphedema patients reported pain and 57% of them had intermittent pain and Moffatt et al showed that 50% of patients had experienced pain or discomfort from their edema.[21,22] The treatment that can be administrated in order to prevent the arm lymphedema development and occurrence consists of: physical exercises at a short time after surgery, self-massage, compressive contention, medication that facilitate the microcirculation, daily hygiene and diet.[3] Various strategies for management of LE are available. Conservative treatment of lymphedema includes various procedures such as elevation, exercise, massage, manual lymphatic drainage, compression garments and intermittent pneumatic compression pumps.[23]

According to present study, there was a great advantage of treatment of lymphedema patients by physical exercises with a compression garment over by physical exercises only.

This is supported by the study by Îrdesel et al which suggested that the combination of exercise therapy and compression garment is more effective than exercise alone program in the treatment of breast cancer related lymphedema.[24]

CONCLUSION

Old (41:50 years) and diabetic patients are at the highest risk for developing lymphedema. Breast cancer patients of stage IIIB who had undergone modified radical mastectomy or who developed postoperative seroma are at higher risk for developing lymphedema. Physical exercises and compression garment are important part of treatment plan.

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