INCIDENCE AND RISK FACTORS OF LYMPHEDEMA AFTER REGIONAL TREATMENT OF BREAST CANCER

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ABSTRACT

Background

Lymphedema is a limb swelling caused by the accumulation of protein- rich fluid in the body tissues secondary to the disturbance of lymphatic drainage. Moreover, the most common risk factor is the regional treatments for breast cancer.

Objectives

To find out the incidence of lymphedema and the risk factors for development of lymphedema after wide local excision, modified radical mastectomy, axillary lymph node dissection and radiotherapy in patients with breast cancer.

Patients and Methods

This retrospective study of 288 patients with breast cancer collected from Hiwa Oncology Hospital, Zhianawa Cancer Centre and Breast Diseases Center in Sulaimani Governorate who underwent surgery, chemotherapy and/or radiotherapy during 1st January 2016 to 31st December 2017. All patients had been followed up for duration of (6 - 36) months. Data were collected from each patient. Breast ultrasonography, mammography, fine needle aspiration cytology, and tru-cut biopsy were collected. The arm circumference of the affected-side was measured ten centimeters above and below supracondylar region and the diagnosis of lymphedema was considered if the arm circumference differences were two centimeters or higher.

Results

The mean ± standard deviation of age (year) was 48.6 ± 10.8 (ranged from 23 to 84) and the majority of the participants were females, with a male to female ratio of (0.03). 74 (25.7%) of the patients were developed lymphedema, 17% of them had lymphedema after surgery, 6.9% of them had lymphedema after radiotherapy and 1.7% of them had lymphedema after both surgery and radiotherapy.

Conclusions

The types of treatment for breast cancer will affect the occurrence of lymphedema especially if the treatment involves the disturbance of lymphatic drainages and there was a statistically significant association with the lymphedema.

Keywords: *Axillary lymph node dissection, Breast cancer, Lymphedema, Modified radical mastectomy, Wide local excision.*

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INTRODUCTION

Lymphedema is an abnormal limb swelling caused by the accumulation of high protein content interstitial fluid in the body tissues secondary to defective lymphatic drainage, e.g. due to breast cancer, in the presence of near normal net capillary filtration [1-3]. Subsequently, it is followed by inflammation, adipose tissue hypertrophy and fibrosis, which can lead to disfigurement of the involved region [3]. The appearance of a swollen and sometimes disfigured limb provides an ever-present reminder of breast cancer, which can lead to anxiety, depression, and emotional distress in the affected women [2].

Lymphedema is classified into two main types [1]:

1. Primary lymphedema: the cause is unknown or at least uncertain and unproven; it is thought to be caused by "congenital lymphatic dysplasia".

2. Secondary or acquired lymphedema: there is a clear underlying cause.

Breast cancer is the most common cancer diagnosed in women worldwide, and new advanced therapies continue to positively affect survivorship; an increasing number of women will be at risk for developing secondary lymphedema [4]. Approximately 12% of women (approximately 1:8) will develop breast cancer in their lifetime [4].

The secondary or acquired lymphedema is common in the western countries' women with breast cancer, particularly following cancer treatment [5]. The increased risk for this type of lymphedema is thought to be attributed to many factors such as disease burden, surgery, radiation, infection or trauma [5]. Moreover, the treatments of breast cancer are recognized as the most common cause of lymphedema [5].

In reviewing- literature, the incidence of the breast cancer-related lymphedema was 6-85% [5-6]. This variation in reported incidence can probably be explained by the differences in the length of follow up between studies, the varying methods for diagnosis, variable surgical/radiation treatments received by the affected women and an inconsistency in the measurement systems employed [7].

The incidence is increased up to two years after the diagnosis or surgery of breast cancer, is highest when assessed by more than one diagnostic method, and is four times higher in women who had an axillary lymph node dissection than in women whom who had sentinel lymph node biopsy [2].

The causes of lymphedema are multifactorial and not well understood [6]. Several factors had been identified as potential risk factors for development of breast cancer related lymphedema. Studies showed that radiotherapy, the number of lymph nodes excised , mastectomy, the size of the tumor, being overweight or obese were identified as significant prognostic factors that increase the risk of lymphedema in patients who undergo dissection of the axillary lymph nodes[2, 8]. In addition, as life expectancy improves for women with breast cancer, more women will be living with possible side effects of the treatment [9].

Upper extremity Lymphedema is one of the most common complications after breast cancer surgery [10]. Although lymphedema is not clearly defined within the medical community, there are several diagnostic tools available to the clinician, of which, the most widely accepted in the clinical setting are the arm circumference measurements and it is often under-recognized and mistreated [5].

Although three quarters of patients have symptoms within one year of surgery, the onset can be insidious and patients remain at risk for the rest of their lives [7, 11]. It is important to distinguish that breast cancer-related lymphedema can involve the upper extremities as well as the entire truncal region, including the breast, chest wall and supraclavicular area [12]. Lymphedema of the upper extremities can involve the entire extremity or be limited to specific regions of the extremity, such as the posterior elbow or hand [12].

Patients may initially report vague symptoms such as fatigue or aching within the arm or breast area, or sensations of heaviness or swelling [5]. These can often be mistaken or dismissed in the early postoperative period or falsely interpreted as due to multimodality treatment [5]. However, it is important to rule out other causes for these symptoms, such as cancer recurrence, infection or deep vein thrombosis [1].

A circumferential limb measurement is the most widely implemented method for assessing limb changes in clinical practice, although it has significant limitations due to the lack of baseline measurements from which to accurately record the changes, the anatomic location of the measurement is frequently variable and it is operator dependent, and the degree of change that represents lymphedema is not accurately defined [1, 13].

The perometry has been demonstrated to be reliable and efficient in the clinical setting; however, the perometer device is a costly unit [14]. Bioelectrical impedance spectroscopy measures the tissue opposition i.e. impedance of body tissues with a low, alternating electric current over a range of frequencies to determine extracellular fluid volume [14].

The magnitude of the impedance is used to determine the extracellular fluid volume and is expressed as an impedance ratio [13]. Alternatively, tissue tonometry is another method that measures the resistance of tissues to compression and quantifies tissue compliance. The degree of compressibility can then be correlated with limb swelling [13].

Imaging techniques are not usually used to diagnose lymphedema [15]. Until now, no clinically available macroscopic imaging method has sufficient temporal or spatial resolution to show tumor induced changes to the lymphatics in vivo, nor do they have the resolution to show the lymphatic changes associated with the causes of lymphedema or its response to therapy [15]. However, if imaging is required, lymphoscintigraphy is better than direct contrast lymphography as the imaging modality of choice for the evaluation of patients with suspected lymphedema [15]. The technique uses a radiotracer e.g. technetium TC 99m-filtered sulfur colloid, which is injected into the dermis of the affected limb [15]. Moreover, magnetic resonance imaging (MRI) and computed tomography (CT) imaging can be used as adjuncts to rule out primary or recurrent tumors [15].

The introduction of sentinel lymph node biopsy (SLNB) in the surgical treatment of breast cancer has significantly reduced the incidence of lymphedema with incidence of 1-17% in those receiving SLNB only, without complete axillary node dissection [16]. Moreover, SLNB is now the standard of care in early stage of breast cancer in developed countries, and it allows the removal of substantially fewer lymph nodes compared to axillary lymph node dissection in which, traditionally, all of the lymphatic contents within the level I and level II axillary nodal basin are excised [17]. However, although SLNB reduces the incidence of lymphedema, the risk is still remaining [17]. Furthermore, a new technique is emerging in the literature, axillary reverse mapping (ARM), in which it attempts to identify and protect the lymphatics draining the arm during axillary surgery for breast cancer [17].

PATIENTS AND METHODS

In this retrospective study Two hundred eighty eight (288) patients were enrolled from 1st January 2016 to 31st December 2017, all were diagnosed with breast cancer and underwent surgery, chemotherapy and or / radiotherapy. The patients were collected from Hiwa Oncology Hospital, Zhianawa cancer center and Breast Diseases Centers in Sulaymania Governorate. All patients gave their written informed consent.

Ethical approval was obtained from the ethical committee of the College of Medicine University of Sulaimani.

Demographic and medical data including: age, gender, occupation, level of education, marital status, residency, and body mass index (BMI), past medical histories of diabetes, hypertension, organ failure, hypothyroidism, and history of infection or surgery or trauma in affected limb, were obtained from medical record.

The investigations that had been performed were breast ultrasonography, mammography, fine needle aspiration cytology (FNAC), and trucut biopsy.

The treatment regimens were included: type of surgery for the breast (wide local excision and modified radical mastectomy) and axillary operation (sentinel lymph node biopsy, axillary sampling, and axillary lymph node dissection). The information about chemotherapy and radiotherapy were obtained from patients' files and physicians' notes. Additionally, the data pertained to the tumor stages were identified from the histopathological report. Furthermore, the onset of swelling and its duration were recorded from the time of either operation or radiotherapy regimen.

The measurements of affected-side arm circumference were performed ten centimeters above and below supracondylar region. The diagnosis of lymphedema was considered if the arm circumference differences were two centimeter or higher. Exclusion criteria were patients with stage IV breast cancer from this study.

Data analysis done using "IBM SPSS Statistics version 25", a P-value of ($\leq$0.05) was considered as statistically significant, and a P-value of ($<$0.001) as statistically very highly significant. In addition, Pearson Chi-Square test was used to find out the significance of the associations between independent and dependent variable pairs, and Pearson R Correlation was used to calculate the direction of the association between the two variables.

RESULTS

The mean ± SD (Standard deviation) of the age (year) of the patients was 48.6 ± 10.8 (ranged from 23 to 84) and the mean ± SD age (year) of the patients at diagnosis was 46.94 ± 10.9 (ranged from 21 to 83). The majority of the participant were female 280 (97.2%) and 8 (2.8%) were male with a male to female ratio of (0.03).

This-study showed a statistically insignificant association between occupations of patients and lymphedema and most of the participants were housewives (Table 1).

The majority of the patients underwent wide local excision (WLE) surgery but for the other patients, a modified radical mastectomy (MRM) has been performed (Table 2).

Seventy- four patients (25.7%) have lymphedema, and most of the patients developed lymphedema after surgery (Table 3).

Two hundred seventy- eight (96.5%) patients had axillary surgery and the highest frequency of axillary surgery was axillary lymph node dissection (ALND) (Table 4). There was a statistically highly significant association between the type of axillary surgery and lymphedema and the direction of the association was positive; ALND surgery had more association with lymphedema (Table 4).

The most frequent level of the ALND surgery was level II (Table 5).

The results of this study showed statistically non-significant association between the axillary surgeries and lymphedema although the direction of the association was positive (Table 6).

There is a statistically positive significant association between the numbers of lymph nodes removed and lymphedema (Table 7).

The mean ± SD of BMI (Kg/M^2) for all the patients were 29.6 ± 4.9 (ranged from 18.5 to 45.3) but it was 30 ± 5.2 (ranged from 20.6 to 42.7) for patients with lymphedema. Furthermore, 183 (63.5%) patients were overweight to morbidly obese (Table 8). Despite that, there was a statistically insignificant association between the BMI and lymphedema and the direction of the association between the two was positive i.e. obesity increased the frequency of lymphedema (Table 8).

There was no statistically significant association between radiotherapy and lymphedema but the direction of its association was positive (Table 9).

The association of chemotherapy was statistically insignificant with lymphedema and its direction was negative i.e. administration of chemotherapy decreased the occurrence of lymphedema (Table 10).

The stage of the breast cancer was not statistically significantly associated with lymphedema although its direction was positive, but there was a higher frequency of lymphedema when the stages become higher (Table 11).

Table 1. Insignificant association between occupations of patients and lymphedema.

Occupation	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Housewife	98 (34)	29 (10.1)	127 (44.1)	0.87 (-0.013)
Employee	12 (4.2)	6 (2.1)	18 (6.3)	
Teacher	11 (3.8)	3 (1)	14 (4.9)	
Nurse	2 (0.7)	1 (0.3)	3 (1)	
Engineer	1 (0.3)	1 (0.3)	2 (0.7)	
Officer	1 (0.3)	0 (0)	1 (0.3)	
Not known	89 (30.9)	34 (11.8)	123 (42.7)	
Total	214 (74.3)	74 (25.7)	288 (100)	

Table 2. Significant association between types of breast surgeries and lymphedema.

Type of breast surgery	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
WLE	121 (42)	29 (10.1)	150 (52.1)	
MRM	93 (32.3)	45 (15.6)	138 (47.9)	0.007 (0.152)
Total	214 (74.3)	74 (25.7)	288 (100)	

WLE = wide local excision; MRM = modified radical mastectomy

Table 3. Onset of lymphedema after the interventions performed for patients

Onset of swelling	Frequency	Percent
From surgery	49	17
From radiotherapy	20	6.9
From surgery and radiotherapy	5	1.7
No lymphedema	214	74.3
Total	288	100

Table 4. Significant association between types of axillary surgeries and lymphedema.

Type of Axillary surgery	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Sentinel LN Biopsy	16 (5.6)	0 (0)	16 (5.6)	
Axillary sampling	23 (8)	1 (0.3)	24 (8.3)	
ALND	165 (56.3)	73 (25.4)	238 (82.6)	0.001 (0.211)
No axillary surgery	5 (1.7)	0 (0)	5 (1.7)	
Not known	5 (1.7)	0 (0)	5 (1.7)	
Total	214 (74.3)	74 (25.7)	288 (100)	

ALND = axillary lymph node dissection; LN = lymph node

Table 5. Non-significant association between level of ALND surgery and lymphedema.

Level of ALND	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Level I	11 (3.8)	0 (0)	11 (3.8)	
Level II	52 (18.1)	23 (8)	75 (26)	
Level III	39 (13.5)	17 (5.9)	56 (19.4)	
Unknown level	63 (21.9)	33 (11.5)	96 (33.3)	0.1 (0.111)
Other types of surgeries	39 (13.5)	1 (0.3)	40 (13.9)	
No axillary surgery	5 (1.7)	0 (0)	5 (1.7)	
Not known	5 (1.7)	0 (0)	5 (1.7)	
Total	214 (74.3)	74 (25.7)	288 (100)	

ALND = axillary lymph node dissection

Table 6. Insignificant association between axillary surgery and lymphedema.

Axillary surgery	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Yes	206 (71.5)	72 (25)	278 (96.5)	0.48 (0.026)
No	3 (1)	2 (0.7)	5 (1.7)	
Not known	5 (1.7)	0 (0)	5 (1.7)	
Total	214 (74.3)	74 (25.7)	288 (100)	

Table 7. Association of numbers of lymph nodes removed and lymphedema.

Number of lymph nodes removed		Lymphedema		Total (%)	P-value (Pearson R correlation)
		No swelling (%)	Swelling (%)		
All lymph nodes	1-10	68 (23.6)	10 (3.5)	78 (27.1)	0.002 (0.136)
	11-20	93 (32..3)	29 (10.1)	122 (42.4)	
	21-30	35 (12.2)	23 (8)	58 (20.1)	
	>30	11 (3.8)	6 (2.1)	17 (5.9)	
	Not known	7 (2.4)	6 (2.1)	13 (4.5)	
Positive lymph nodes	1-10	112 (38.9)	40 (13.9)	152 (52.8)	0.02 (0.188)
	11-20	12 (4.2)	11 (3.8)	23 (8)	
	21-30	6 (2.1)	4 (1.4)	10 (3.5)	
	>30	2 (0.7)	2 (0.7)	4 (1.4)	
	Negative	76 (26.4)	9 (3.1)	85 (29.5)	
	Not known	6 (2.1)	8 (2.8)	14 (4.9)	
Negative lymph nodes	1-10	110 (38.2)	28 (9.7)	138 (47.9)	0.05 (0.069)
	11-20	69 (24)	22 (7.6)	91 (31.6)	
	21-30	17 (5.9)	13 (4.5)	30 (10.4)	
	>30	4 (1.4)	2 (0.7)	6 (2.1)	
	Not known	14 (4.9)	9 (3.1)	23 (8)	
Total		214 (74.3)	74 (25.7)	288 (100)	

Table 8. Statistically positive insignificant association between BMI and lymphedema

BMI Groups	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Normal BMI (18.5 - 24.99)	86 (29.9)	19 (6.6)	105 (36.4)	0.065 (0.143)
Over weight (25 - 29.99)	46 (16)	18 (6.3)	64 (22.2)	
Obese (30 - 40)	77 (26.7)	32 (11.1)	109 (37.8)	
Morbid obesity (> 40)	5 (1.7)	5 (1.7)	10 (3.5)	
Total	214 (74.3)	74 (25.7)	288 (100)	

BMI = body mass index

Table 9. Insignificant association between radiotherapy and lymphedema

Radiotherapy	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Yes	201 (69.8)	69 (24)	270 (93.8)	
No	13 (4.5)	5 (1.7)	18 (6.3)	0.97 (0.014)
Total	214 (74.3)	74 (25.7)	288 (100)	

Table 10. Insignificant association between chemotherapy and lymphedema.

Chemotherapy	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Yes	198 (68.8)	72 (25)	270 (93.8)	
No	16 (5.6)	2 (0.7)	18 (6.3)	0.33 (-0.033)
Total	214 (74.3)	74 (25.7)	288 (100)	

Table 11. Insignificant association between stages of tumor and lymphedema.

Stage of tumor	Lymphedema		Total (%)	P-value (Pearson R correlation)
	No swelling (%)	Swelling (%)		
Stage 0	5 (1.7)	1 (0.4)	6 (2.1)	
Stage 1	23 (8)	7 (2.4)	30 (10.4)	
Stage 2	99 (34.4)	32 (11.1)	131 (45.5)	
Stage 3	73 (25.3)	27 (9.4)	100 (34.7)	
Right 2A and Left 1	1 (0.4)	0 (0)	1 (0.4)	
Right 2B and Left 1	0 (0)	1 (0.4)	1 (0.4)	0.27 (0.044)
Right 3C and Left 1	0 (0)	1 (0.4)	1 (0.4)	
Right 2B and Left 3A	0 (0)	1 (0.4)	1 (0.4)	
Right 3A and Left 2A	1 (0.4)	0 (0)	1 (0.4)	
Not known	12 (4.2)	4 (1.4)	16 (5.6)	
Total	214 (74.3)	74 (25.7)	288 (100)	

DISCUSSION

Lymphedema is debilitating and disabling sequelae of regional treatment of breast cancer which interfere with the quality of life [18-19] and its incidence was variable (6-85%) in the reviewing literature [5-6, 18]. The occurrence of lymphedema in this study was 25.7%.

In the current study the mean ± SD of the patients' age (year) was 48.6 ± 10.8 and their age (year) at diagnosis was 46.94 ± 10.9 which is consistent with study that was done in Thailand by Kotepui et al. [20]. In the current research we could not find a significant association of patients' occupation with lymphedema (Table 1), in contrast to Canadian case-control study by Brophy JT [21] that showed association between the occupations of the patients with breast cancer

This study showed a statistically positive significant association between the types of the breast surgeries and lymphedema, this significant association may be due to the disturbance of the lymphatic drainages, In contrast to the study that was done by Clark et al. [10] in which they found that WLE as greater risk factor for lymphedema.

Lymphedema due to sentinel lymph node biopsy (SLNB) was 5% and it was 16% after ALND in the study that was done by McLaughlin et al. [22], in contrast to our study showed 0% lymphedema after SLNB, 0.3% lymphedema after axillary sampling and most of the lymphedema (25.4%) occurred after ALND surgery (Table 4); especially level II (Table 5). This finding can be compared to the study performed in Baghdad by Saood et al. [23] which showed a lower rate of lymphedema after axillary sampling as compared to the ALND.

Although the axillary surgery was not significantly associated with lymphedema (Table 6), but the types of axillary surgeries were statistically significantly associated with the lymphedema (Table 4). This may be due to the number of lymph nodes removed in each type of axillary surgeries because it was statistically significantly associated with lymphedema in this study (Table 7). In contrast to the study that was done by Clark et al. [10] showed no statistically significant association between the number of axillary lymph node removal and lymphedema.

Other risk factors that had been linked with lymphedema in patients with breast cancer such as obesity, infection, and injuries [10, 22]. We measured the BMI of the patients but it had a statistically insignificantly association with the lymphedema (Table 8). Furthermore, we also tried to find out if the radiotherapy or chemotherapy is a risk factor for lymphedema in patients with breast cancer, but results showed statistically insignificant association (Table 9 and 10). In addition, the stages of the tumor also had no statistically significant association with the lymphedema (Table 11). This may be explained by that the stages of the tumor do not disturb the lymphatic drainages directly.

In conclusions, the types of breast and axillary surgeries for the treatment of breast cancer were significantly associated with the occurrence of lymphedema because of their influence on disturbing the lymphatic drainage, but chemotherapy and radiotherapy had insignificant association with lymphedema.

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