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Analysis of Factors Contributing to Severity of Breast Cancer Related Lymphedema

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Abstract

Background—Upper extremity lymphedema is a well-described complication of breast cancer treatment. Risk factors for lymphedema development include axillary lymph node dissection (ALND), obesity, increasing age, radiation and postoperative complications. In this study, we seek to evaluate a cohort of patients who have either self-referred or been referred to the department of physical therapy for lymphedema treatment. Our goal is to evaluate specific risk factors associated with the severity of lymphedema in this patient population.

Methods—All patients who presented to the Wexner Medical Center at the Ohio State University between January 1, 2009 and December 31, 2010 with a chief complaint of upper extremity lymphedema following breast cancer treatment were reviewed retrospectively. Upper extremity lymphedema index (UELI) was used as a severity indicator and patient factors including demographics and breast cancer treatments were evaluated. Univariate and multivariate statistical analyses were performed.

Results—Fifty (4.5%) patients presented for upper extremity lymphedema treatment following breast cancer treatment (total of 1106 patients treated surgically for breast cancer). Greater UELI's were found in patients 50 years and older, those with ALND, radiation, chemotherapy, pathologic stage greater than 3, and an International Society of Lymphology (ISL) lymphedema stage 2 ($p<0.05$). The multivariate model showed age greater than 50 and pathologic stage greater than 3 were significant predictors of higher UELI ($p<0.05$).

Conclusion—In this study, we report that in patients who present for lymphedema treatment, increased UELI is significantly related to ALND, radiation therapy, chemotherapy, age and pathologic stage. An improved understanding of the patient population referred for lymphedema treatment, will allow for the identification of patients who may be candidates for therapeutic intervention.

Introduction

Breast cancer, either invasive or in situ, is newly diagnosed in greater than 275,000 women each year¹. These women subsequently undergo treatment that most often includes surgical intervention, with a combination of other treatments such as chemotherapy, radiation therapy, hormone therapy and/or targeted therapy¹. However, these potentially curative treatments are not without side effects.

One well described complication of axillary surgery and/or radiation is lymphedema of the upper extremity.¹ Agreement among studies on the true incidence of lymphedema is lacking, with reported incidence ranging from 2% to 56%.² Moreover, some authors have reported a decreased incidence of lymphedema in women undergoing sentinel lymph node biopsy (SLN), compared to women undergoing axillary lymph node dissection (ALND).^{2,3} Apart from ALND, potential risk factors for the development lymphedema described in the literature have included obesity, increasing age, postoperative complications and radiation therapy^{2,4,5}

In this study, we seek to evaluate patients who have undergone breast cancer treatment and have then presented to physical therapy for the treatment of lymphedema. A variety of modalities have been described to establish a diagnosis of lymphedema. These include water displacement techniques, lymphangiography, lymphoscintigraphy, and MR lymphography^{6,7}. Although these modalities have been employed with varying degrees of acceptance, there is no gold standard modality to establish a diagnosis of lymphedema. In clinical practice, these modalities remain infrequently utilized. Clinically, the diagnosis is established by patient symptomatology and documented most often by physical therapy utilizing circumferential arm measurements with comparison to the unaffected extremity. In this study, we have chosen to evaluate patients that have been referred to a physical therapy unit as our study cohort.

The most common treatment for lymphedema is currently complex decongestive therapy which includes skin care, compression garments, exercise therapy and manual lymph drainage^{4,8}. These interventions may provide improvement, but treatment may be lifelong. Therefore other treatments, such as surgical interventions, are currently under evaluation⁹⁻¹⁶. Indications for surgery are still under debate, and the current gold standard for long-term management remains with physical therapists specifically trained to treat lymphedema. An improved understanding of patients presenting to physical therapy for lymphedema treatment is necessary as these patients are likely to present for surgical intervention should medical management fail to manage symptoms¹⁷. Our goal is to evaluate whether the variables commonly associated with a diagnosis of lymphedema correlate with UELI in a patient population referred to physical therapy.

Methods

All patients who presented to the Wexner Medical Center at the Ohio State University between January 1, 2009 and December 31, 2010 for breast cancer treatment were reviewed retrospectively, following approval by the Institutional Review Board. Those presenting

with a chief complaint of upper extremity lymphedema became our study population. While some patients may not have had specific diagnostic tests to confirm the diagnosis of lymphedema, we felt that those presenting for medical attention are most important to evaluate. This time period was chosen for the ease of data collection, as an electronic medical record had been implemented.

Patient factors were collected from their medical record. These included age at diagnosis, smoking status, and medical comorbidities. Physical therapy records were examined for each patient, and the most severe upper extremity lymphedema index (UELI) was recorded. In this study we have utilized the UELI as a measure of the severity of lymphedema. Our UELI is a variation of the index previously described by Yamamoto et al¹⁸. The original description of UELI was the sum of the squares of arm circumference at the olecranon, 5cm above and below the olecranon, the wrist and the dorsum of the hand, divided by BMI. Our UELI is the sum of the squares of arm circumference at the mid-upper arm, elbow, mid-forearm, wrist, and palmar crease, divided by BMI. This measurement was chosen because these are the measurements taken by our physical therapists at every appointment to evaluate size and change in lymphedema. We also felt it was important to use a measurement that incorporated the entire arm and body habitus of the patients. The stage of lymphedema, using the International Society of Lymphology staging system¹⁹, at the time of most severe UELI was also recorded. The staging is as follows: stage 0, latent condition with no evident swelling but impaired lymph transport, stage 1, early accumulation of fluid that subsides with limb elevation, stage 2, limb elevation alone does not reduce swelling and pitting may or may not be present, and stage 3, lymphostatic elephantiasis. Inclusion of ISL data in this study was done to validate the UELI, as increasing ISL stage should correlate with increasing UELI.

Breast cancer treatments were noted for each patient. Factors examined included the following: axillary lymph node dissection (ALND), sentinel lymph node (SLN), immediate breast reconstruction, complications of surgery (seroma, hematoma, infection, fat necrosis), radiation therapy, chemotherapy, clinical stage and pathologic stage.

Univariate analyses included the comparison of UELI between categorical variables with two sample t-tests. Variables with significant univariate results ($p < 0.05$), with the exception of ISL stage, were included in a linear regression model and stepwise methods were used to develop the final multivariable model. All analyses were performed using either SAS version 9.2 (SAS Institute Inc., Cary, NC) or STATA version 10.0 (StataCorp LP, College Station, TX). We have no conflicts of interest to declare.

Results

Fifty consecutive patients presented during the study time period who presented for treatment for upper extremity lymphedema following breast cancer treatment out of a total of 1106 patients treated surgically for breast cancer (4.5%). Patient demographics are shown in Table 1. The mean age was 51.7, range from 28 to 78. The mean BMI was 32.92, range from 18 to 63. The mean UELI of all patients was 103.58, range from 73.38 to 143.27.

Univariate analyses of the potential predictors of increased lymphedema severity are shown in Table 2. Patients with a history of axillary lymph node dissection had a significantly higher mean UELI compared to those with a history of sentinel lymph node biopsy ($p=0.006$). Patients who had received radiation therapy also had a significantly higher mean UELI compared to patients who had not received radiation therapy ($p=0.045$). Chemotherapy was also found to result in higher UELI's ($p=0.023$). Other factors associated with a significantly higher UELI included age older than fifty years ($p=0.018$), pathologic stage greater than 3 ($p=0.005$) and ISL stage 2 (<0.001), which is expected due to the definition. No significant differences were found in regards to clinical stage, smoking (defined as ever smoked or never smoked), comorbidities, development of a surgical complication, and immediate breast reconstruction.

The multivariable model found age 50 and pathologic stage greater than 3 are associated with higher UELI (Table 3).

Discussion

Lymphedema is a well-recognized complication of breast cancer treatment¹.

Lymphedema symptoms include increased volume and weight of the limb that causes physical impairments, increased skin tension, pain, infection and can negatively affect emotional and mental status¹⁷. In our patient population, the prevalence of lymphedema is 4.5%, which is within the wide range of 2 and 56% reported in the literature².

Multiple authors have published on the risk factors for the development of lymphedema. In a study of 516 patients, Veronesi et al showed a decreased incidence of lymphedema in patients receiving sentinel lymph node (SLN) biopsy compared to those receiving an axillary lymph node dissection (ALND)³. Further, other authors have described significant risk factors for development of lymphedema include obesity, increasing age, postoperative complications and radiation therapy^{2,4,5}. In this study, we seek to evaluate a cohort of patients who have either self-referred or been referred to the department of physical therapy for lymphedema treatment. Our goal is to evaluate the factors associated with increasing lymphedema severity in this patient population.

The criterion used to establish a diagnosis of lymphedema are poorly defined and objective measurement techniques for lymphedema classification are well known to have a high degree of inaccuracy. Therefore, currently the diagnosis of lymphedema is largely based on patient symptomatology. Moreover, certain symptoms may be predictive of eventual lymphedema development. Amer et al utilized the Lymphedema and Breast Cancer Questionnaire and found that changes in sensations and range of motion may be early indicators of developing lymphedema²⁰. In terms of objective measurements, water displacement techniques have been considered in the literature for the diagnosis of lymphedema⁶. Although theoretically a useful measure for the diagnosis of lymphedema, this technique is seldom utilized in the clinical practice. Lymphoscintigraphy has been considered as an imaging modality to formulate the diagnosis of lymphedema⁷. While this technique does give insight into lymphatic vascular flow, the modality is limited in

rendering a diagnosis of lymphedema that can be serially measured and compared over time to evaluate clinical progression of the disease. The most commonly employed method not only for the diagnosis but also for serial evaluation of the patient is extremity circumferential measurement. However, these measurements can vary due to time of day, degree of decongestive therapy or operator error. For the purposes of this study, we have elected to examine patients who have reported signs and symptoms of lymphedema and have then been independently verified by a trained physical therapy expert using an UELI for evaluation of the severity of disease. Further, we believe UELI was a valid measure of lymphedema severity in this study since our results show patients with ISL stage greater than 2 also had greater UELI's.

In this study, we report that in patients who present for lymphedema treatment, a greater UELI is significantly related to ALND, radiation therapy, chemotherapy, age, and pathologic stage independently. ALND, when compared to SLN, usually involves a more extensive disruption of tissues and is therefore likely to cause more damage to local lymphatics. The impact of radiation treatment on lymphedema severity is likely due to progressive radiation fibrosis of the irradiated axillary region and the resulting impairment of drainage into the axillary lymph node basin. The mechanisms through which chemotherapy, advanced pathologic stage and advanced age may impair lymphatic drainage is less clear. Multiple authors have noted a correlation between these variables and the presence of lymphedema^{21,22}. One can hypothesize that advanced age, advanced pathologic stage and chemotherapy may affect the number of lymphovenous anastomoses that may open in response to increased extremity interstitial pressure². Therefore patients with advanced pathologic stage, advanced age, or chemotherapy may have a reduced ability to compensate for increased lymphatic pressure, thus leading to more severe lymphedema^{23,24}.

While conventional therapy has been used for years as treatment for lymphedema, newer surgical procedures such as lymphatic reconstruction and microvascular lymph node transfer are under investigation. An improved understanding of patients who have been referred for lymphedema treatment is important in helping the plastic surgery community develop surgical treatments. It is this patient population that will most commonly present for surgical evaluation should medical management fail to manage disease progression. Early-stage studies of surgical intervention show promising results. In a study of 20 patients by Chang, a reduction in lymphedema volume of 35% and a symptom improvement of 95% was found at 1 year following lymphaticovenular bypass¹⁰. Becker et al reported a decrease in lymphedema following inguinal lymph node transfer to the axilla in 22 patients¹³. Inguinal lymph node transfer to the distal extremity has also been shown to decrease lymphedema and cellulitis¹².

Future studies with larger sample sizes are needed to confirm our results. Although significance in univariate analyses were found with ALND, chemotherapy and radiation, these variables were not significant in the multivariable model. This may be due to the strong correlation between ALND and pathologic stage and our small sample size. Further, most patients (82%) with a pathologic stage greater than 3 also underwent radiation therapy. While this point needs to be further investigated in a future study, pathologic stage greater than 3 did remain significant in our multivariate analysis, when controlling for radiation.

Another limitation was that data regarding duration of lymphedema treatment was not available. This study is also limited in that patients may not have undergone testing to confirm lymphedema diagnosis. The diagnostic criterion used to establish a diagnosis of lymphedema remain poorly defined. Therefore, in this study we have chosen to study patients who have self-referred to physical therapy or have been referred to physical therapy for signs and symptoms of lymphedema.

Conclusion

In this study, we report that in patients who present for lymphedema treatment, an increased UELI is significantly related to ALND, chemotherapy, radiation therapy, age and pathologic stage. An improved understanding of variables in the development of lymphedema may allow for better identification of patients who are candidates for surgical intervention.

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Table 1

Patient demographics (n=50)

Demographic	n (range or %)
Mean Age at Diagnosis (years)	51.7 (28-78)
Mean BMI	32.9 (18-63)
Mean UELI	103.6 (73.4-143.3)
Lymphedema stage	
Stage 1 lymphedema	16 (32%)
Stage 2 lymphedema	34 (68%)
Axillary lymph node evaluation	
ALND	39 (78%)
Mean number of ALN	22 (10-49)
Median number of ALN	20
Mode number of ALN	13, 22
SNL biopsy	11 (22%)
Mean number of SLN	6 (0-17)
Median number of SLN	3
Mode number of SLN	2, 3, 13
Radiation	32 (64%)
Chemotherapy	40 (80%)
Adjuvant	24 (48%)
Neoadjuvant	16 (32%)
Immediate Reconstruction	3 (6%)
Complication	12 (24%)
Smoking	
Never Smoked	26 (52%)
Ever Smoked	24 (48%)
Comorbidities	
Hypertension	17 (34%)
Dyslipidemia	9 (18%)
Diabetes	4 (8%)

BMI indicated body mass index; UELI upper extremity lymphedema index; ALND axillary lymph node dissection; SNL sentinel lymph node

Table 2

Univariate analysis of the predictors of lymphedema severity

Factor	Mean UELI (SD)	p value
Axillary lymph node evaluation		
ALND	106.9 (16.6)	
SLN biopsy	91.8 (10.1)	0.006*
Radiation		
History of radiation	107.1 (16.2)	
No history of radiation	97.4 (15.8)	0.045*
Chemotherapy		
History of chemotherapy	105.2 (18.0)	
No history of chemotherapy	97.2 (5.8)	0.023*
Smoking		
Never smoked	104.1 (15.86)	
Ever smoked	103.0 (17.65)	0.807
Surgical Complication		
History of complication	106.5 (15.1)	
No complication	102.7 (17.1)	0.490
Reconstruction		
Immediate	99.6 (14.1)	
No reconstruction or delayed	103.8 (16.8)	0.673
ISL Stage		
Stage 1	90.5 (9.4)	
Stage 2	109.7 (15.7)	<0.001*
Age		
Less than 50 years	97.9 (13.1)	
Greater than 50 years	108.8 (17.9)	0.018*
Clinical stage		
Less than 3	103.9 (17.3)	
Greater than 3	107.0 (13.0)	0.654
Pathologic stage		
Less than 3	98.4 (14.7)	
Greater than 3	112.1 (15.3)	0.005*

UELI upper extremity lymphedema index; ALND axillary lymph node dissection; SNL sentinel lymph node; ISL international society of lymphology

Table 3

Multivariable linear regression analysis of the predictors of lymphedema severity

Factor	Coefficient	Std. Err.	95% Confidence Interval	p value
Age 50	9.65	4.28	1.01-18.29	0.045*
Pathologic Stage >3	12.88	4.41	3.98-21.77	0.011*
Intercept	93.56	3.44	86.61-100.51	