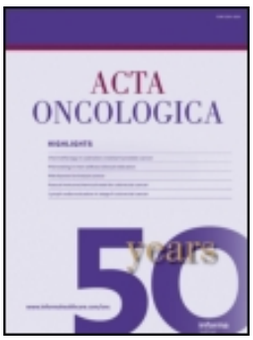

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ORIGINAL ARTICLE

Factors associated with increased breast cancer-related lymphedema volume

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Abstract

Background. Upper limb lymphedema occurs in approximately 15–20% of women after breast cancer treatment. We analysed the factors associated with lymphedema volume. *Method.* Cross-sectional study of 807 patients with secondary arm lymphedema was performed in a single lymphology unit. Data collected included patient characteristics, characteristics of breast cancer treatment, past history of cellulitis, Body Mass Index, delay from cancer to onset of lymphedema and duration of lymphedema. Lymphedema volume was calculated for each 5-cm segment by utilizing the formula for a truncated cone. Univariate and multivariate regression models were fitted to study the factors associated with increased lymphedema volume. *Results.* In univariate analysis, factors associated with lymphedema volume were duration of lymphedema, Body Mass Index, mastectomy, and past history of cellulitis. Treatment with anti-estrogen drugs was negatively associated with lymphedema volume ($p = 0.02$). In multivariate analysis, factors associated with lymphedema volume were duration of lymphedema ($p < 0.001$), Body Mass Index ($p < 0.001$), delay from cancer to onset of lymphedema ($p = 0.002$), mastectomy ($p = 0.02$) and past history of cellulitis ($p = 0.011$). *Conclusion.* Early diagnosis and management of lymphedema, weight control and advices to avoid cellulitis are the main controllable parameters in women to prevent severity of breast cancer-related lymphedema.

Lymphedema remains an important problem in women treated for breast cancer, occurring between 12 to 28% of the cases even with modern therapies [1–4]. Various risk factors of developing lymphedema after breast cancer treatment have been published including number of axillary lymph node excised, radiotherapy, obesity, weight gain after treatment and aircraft flights [5–8]. Factors associated with lymphedema severity, i.e. lymphedema volume, are incompletely known and very few studies are available about this topic. Ferrandez et al. have suggested that mastectomy was associated with lymphedema volume as compared to conservative therapy [9]. The Body Mass Index (BMI) was also considered as a factor associated with lymphedema volume. Severe lymphedema, defined by a perimetric difference (>3 cm), was more frequent in patients with higher BMI [5]. The aim of our study was to analyse the factors associated with the volume of upper limb lymphedema in women previously treated for breast cancer.

Methods

Patients

Eligible patients were women referred for treatment of an upper limb lymphedema after breast cancer treatment to one single center dedicated to lymphedema management. All patients without any previous reduction attempt were enrolled between January 2001 and June 2006.

Patients were referred by their oncologist, surgeon or general practitioner. Fifteen cancer centers were referring patients on a regular basis; in addition some patients were self-referred. Precise information on treatment modalities (especially for radiotherapy: fields, dose, fractions) was not available. All patients (but 13 with no surgery) underwent axillary lymph

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node dissection (standard Berg's level I and II axillary lymph node dissection) and none had sentinel lymph node biopsy.

Data collected

Data included patient characteristics, characteristics of breast cancer stage and treatment (age at cancer diagnosis, mastectomy/lumpectomy, radiotherapy, chemotherapy, anti-estrogen drugs, metastatic cancer), complications (cellulitis, radiation-induced brachial plexopathy), BMI (calculated as weight/height^2), date of onset lymphedema, delay from cancer to onset of lymphedema and lymphedema volume at inclusion. Lymphedema volume was calculated for each 5-cm segment by using the formula for a truncated cone: $H \times (C2 + Cc + c2)/12\pi$, H = height, C = circumference of the top of the cone, c = circumference of the base of the cone [10,11]. This method demonstrated excellent inter- and intra-observer reproducibility in comparison to water displacement which is considered the gold standard [12,13]. Lymphedema volume was defined as the difference between the lymphedematous limb (VL) and the healthy limb volume (VH).

Statistical analysis

Data are presented as counts and percent for categorical variables and median with range for continuous variables, unless otherwise stated. Volumes were compared across groups using t-tests and adjusted analyses were performed by fitting linear regression models. Significant variables in univariate analyses at a 0.20 threshold were selected for multivariate analysis. All tests were two-sided and p-values under 0.05 were considered as significant. Analyses were performed using SAS 8.2 (SAS Inc, Cary, North Carolina, USA).

Results

Descriptive characteristics

A total of 807 women were included in our study. Main clinical characteristics of patients, breast cancer treatment and upper limb lymphedema characteristics are presented in Table I.

Univariate analysis

In the univariate analysis, age at cancer diagnosis, cancer side, delay from cancer to onset of lymphedema, radiotherapy and chemotherapy were not associated with lymphedema volume. BMI, duration of lymphedema, past history of cellulitis, mastectomy and anti-estrogen drugs were significantly associated with lymphedema volume (Table II). Past history of cellulitis was associated with a mean increase of lymphedema volume of 187.3 ml in comparison with patients without past history of cellulitis. Lymphedema volume of patients with previous mastectomy was significantly higher (+141.4 ml) in comparison with patients previously treated with lumpectomy. Conversely, previous treatment with anti-estrogen drugs (mainly tamoxifen, 20 mg/day) for breast cancer was significantly negatively associated with lymphedema volume.

Table I. Patient characteristics.

	Patients n = 807
Age at time of study, median (range), years	62 (34–91)
Body Mass Index, median (range), kg/m^2	27.1 (15.4–64.1)
Breast cancer characteristics	
Age at breast cancer, median (range), years	53 (24–81)
Side (right side), n (%)	392 (49)
Type of surgery	
Mastectomy, n (%)	402 (50)
Lumpectomy	395 (50)
None	13 (2)
Radiotherapy, n (%)	781 (97)
Chemotherapy, n (%)	533 (66)
Anti-estrogen drugs, n (%)	427 (53)
Metastatic cancer at inclusion, n (%)	145 (18)
Radiation-induced brachial plexopathy, n (%)	51 (6)
Breast reconstruction, n (%)	94 (12)
Lymphedema	
Lymphedema onset delay, median (range), months	22 (6–60)
Duration of lymphedema, median (range), months	20 (1–656)
Past history of cellulitis, n (%)	263 (33)

Multivariate analysis

In multivariate analysis, BMI, duration of lymphedema, past history of cellulitis, delay from cancer to onset of lymphedema and mastectomy were associated with lymphedema volume (Table III). Past history of cellulitis was associated with a mean increase of lymphedema volume of 107.8 ml in comparison with patients without past history of cellulitis. Lymphedema volume of patients with previous mastectomy was significantly higher (+91.2 ml) in comparison with patients previously treated with lumpectomy. One point of BMI was associated with a mean increase of lymphedema volume of 40.5 ml. One additional year of duration of lymphedema and from cancer to onset of lymphedema was associated with a mean increase

Table II. Univariate analysis of factors associated with upper limb lymphedema volume.

	Estimate	Standard error	P-value
Age at cancer diagnosis	1.6	2	0.4189
Right side	16.1	42.2	0.7025
Body Mass Index	39.4	3.7	<.0001
Duration of lymphedema	18.6	3.1	<.0001
Delay from cancer to onset of lymphedema	5.1	3.5	0.1399
Metastatic cancer	16.4	55	0.77
Past history of cellulitis	187.3	44.5	<.0001
Mastectomy	141.4	42.0	0.0008
Radiotherapy	26.7	126.9	0.8336
Chemotherapy	−72.7	44.5	0.1026
Anti-estrogen drugs	−99.2	42.1	0.0187

of lymphedema volume of 19.2 ml and 10.3 ml, respectively. Radiotherapy, chemotherapy and anti-estrogen drugs were not associated with lymphedema volume.

Discussion

Our study analysed in a large series different factors associated with the severity of lymphedema. We found that BMI was associated with lymphedema volume and we confirmed the results of previous published studies [5,9]. So, the role of body weight, and therefore BMI has also been considered an influent factor in the development of lymphedema [5,14]. The weight gain after surgery may also be an independent risk factor for lymphedema [7]. Duration of lymphedema appears also an important parameter associated with lymphedema severity. Empirically, duration of lymphedema may induce a progressive increase of lymphedema volume if the patient does not receive specific treatment, called complete decongestive physiotherapy and including low stretch bandages, manual lymph drainage, exercises and skin care [15]. Tissue alterations progressively occur in lymphedema evolution. Chronic lymph stasis produces an accumulation of proteins and cellular metabolites in the extracellular space which raise the tissue colloid osmotic pressure, causing water accumulation and edema formation. The accumulation of proteins also attracts macrophages, stimulates collagen production by fibroblasts, and enhances the stimulation of fibroblasts, keratinocytes and adipocytes leading to fragmentation and degeneration of elastic fibers, skin thickening and subcutaneous fibrosis [16]. Delay from cancer to onset of lymphedema appeared as a risk factor of lymphedema severity. The main hypothesis to explain this relationship is the difficulty to diagnose lymphedema after breast cancer treatment. Arm volume is not systematically measured by the physicians during the follow-up and patients may underdiagnose moderate lymphedema until its volume becomes important or it involves the hand.

Past history of cellulitis (erysipelas) was shown to be associated with lymphedema volume. This association can be interpreted in two opposite ways as our study does not allow causal relationships to be analysed. Two hypotheses might account for this finding. Firstly, Dupuy et al. showed that lymphedema was the main risk factor for lower limb cellulitis [17]. Lymphatic impairment plays a major role in the pathophysiology of cellulitis of the leg and probably of the upper limb after breast cancer treatment. Indeed, lymphedema represents a localized immunodepression favoring infections. Accumulation of stagnant, protein-rich fluid into the interstitial matrix between cells reduces the delivery of oxygen and other molecules to cells and

Table III. Multivariate analysis of factors associated for upper limb lymphedema volume.

	Estimate*	Standard Error	P-value
Body Mass Index	40.5	3.6	<0.0001
Duration of lymphedema	19.2	3.4	<0.0001
Delay from cancer to onset of lymphedema	10.3	3.4	0.0024
Past history of cellulitis	107.8	42.2	0.0108
Mastectomy	91.2	39.2	0.0204
Radiotherapy	54.2	117.1	0.6435
Chemotherapy	−0.5	43.4	0.991
Anti-estrogen drugs	23.6	41.7	0.57

* Adjusted estimates on all the variables presented in the table.

attenuates immune response in tissues [18]. Secondly, cellulitis may alter lymphatic pathways previously damaged by node excision and external radiotherapy. De Godoy et al. have evaluated lymphoscintigraphy after cellulitis and found significant abnormalities in 77% of the tested patients [19]. It is difficult, however, to assess if lymphatic abnormalities are secondary to cellulitis or are revealed by cellulitis. Cellulitis may alter lymphatic system, lead to degradation of lymph transport and increase lymphedema volume. Mastectomy is considered as a risk factor to develop upper limb lymphedema [3,20] and is also a factor associated with lymphedema volume. This increased risk with mastectomy should also be kept in mind when making treatment decisions. Treatment-related factors can be seen as confounders for cancer characteristics. However, screening based on cancer characteristics or on treatment type should select the same patients.

The main strengths of our study were to be monocentric and to deal with an homogeneous group of patients with lymphedema after breast cancer. All patients were recruited in a single department of lymphology and lymphedema volume was measured by the same method before intensive decongestive physiotherapy. Our study has some limitations, however. We analysed only few clinical and treatment parameters which represent not probably all the factors implicated in lymphedema severity. Moreover, because it was a cross-sectional study, only associations can be evidenced without information on temporal sequence and no causal inference can be evidenced.

Although we cannot ascertain causal relationships, our results suggest that some advices could be of value after breast cancer treatment. Firstly, women overweight or obese should be encouraged to lose weight. After breast surgery, weight gain should be avoided to limit the risk of lymphedema and its severity [7]. Physicians should be aware of the poor influence of overweight or obesity after breast cancer treatment. Secondly, advices should be known to prevent cellulitis (erysipelas). Patients were instructed to avoid cutaneous effractions (e.g. cuts, burn, insect bites, cat scratch, cracks in dry skins) and to protect their skin during daily activities (e.g. using gloves for gardening, thimble when sewing). Skin dryness was systematically treated with moisturizer. Long-term antibioprophylaxis may be proposed for recurrent episodes [21]. More, a long-term effective reduction of lymphedema volume may reduce the incidence of recurrent infection and also promotes the maintenance of limb function [15].

We conclude that mastectomy, BMI, delay from cancer to onset of lymphedema, duration of lymphedema and past history of cellulitis are associated with increased lymphedema volume. These factors are important for physicians and women after breast cancer treatment to be aware of those potentially controllable. Low lymphedema volume may trend to an improvement of the quality of life in women after breast cancer treatment [22].

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