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Relation between early disturbance visualized with lymphofluoroscopy and other clinical assessment methods in patients with breast cancer.

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Abstract

Introduction

Lymphedema of the upper extremity is one of the most feared complications following breast cancer treatment. Lymphofluoroscopy is a sensitive instrument for detection of lymphedema and visualization of superficial lymphatic transport, thus suitable for early detection. Early detection of lymphedema is important as it can prevent lymphedema to progress into more severe stages and minimalize impact on quality of life and medical costs.

Objective

To determine agreement between the presence of early disturbance of the lymphatic transport and outcome of clinical measurement tools evaluating the development of lymphedema.

Methods

A prospective study was conducted in 128 breast cancer patients scheduled for breast cancer surgery. Patients were evaluated before surgery and 1, 3, 6, 9 and 12 months post-surgery. Cohen's Kappa was used to determine agreement between presence of early disturbance in lymphatic transport and presence of pitting/increased skinfold thickness/increased Percentage Water Content ratio (PWC)/increased arm-hand volume (circumference measures and water displacement).

Results

For pitting status (Kappa 0.23), for skinfold thickness (Kappa 0.29) and the PWC ratio (Kappa 0.21) a minimal agreement was found. The circumference measurement had a minimal agreement for 5% volume difference (Kappa 0.22) and no agreement for 3% volume difference (Kappa 0.19). Sensitivity was weak for all clinical assessments. The specificity was excellent for pitting status, skinfold thickness, PWC ratio and for 5% volume difference. For 3% a high specificity was found.

Conclusion

The clinical tools assessed in this study were not able to predict an early disturbance of the lymphatic transport seen on lymphofluoroscopy.

Keywords: Breast Neoplasms, Diagnosing, Near-infrared fluorescence imaging, Lymphofluoroscopy, Lymphedema.

Introduction

Lymphedema of the upper extremity is a side-effect commonly seen following treatment for breast cancer. Although incidence rates vary among studies, likely due to different criteria and assessment of breast cancer-related lymphedema (BCRL), an overall incidence rate of 16.6% can be observed (1).

BCRL has a profound impact on quality of life (2-4). Since survival of breast cancer is currently increasing, so is the need for improving quality of life of these survivors (5, 6). Diagnosing a person with BCRL means the prospect of life-long treatment in order to control the condition, and prevent the lymphedema developing into more severe stages. It would be desirable to detect the lymphedema as early as possible so treatment can start early. In addition, treatment and medical costs would be less extensive and make the necessity of early detection even more important (7-9).

There are many different methods to detect BCRL. Unfortunately there is no consensus about the best method (10). Most measurement methods assess the water content, thickness of the skin (Stemmer sign test), amount of extracellular fluid (pitting test, tissue dielectric constant and bioelectrical impedance spectroscopy) or limb volume (circumference measurement, perometer and water displacement method) (11). The most commonly used imaging method to visualize the lymphatic system is lymphoscintigraphy (12-14). After a radioactive tracer is injected into the tissue, the uptake and transport in the lymphatic system is visualized using a scintillation camera that provides an image of the superficial and deep lymphatic system. By repeated imaging over time, the intensity of the radiant tracer is measured to assess the lymphatic transport (15). Another method to visualize the superficial lymphatic transport system of the upper limb is near-infrared fluorescence imaging (e.g. lymphofluoroscopy). In this method, indocyanine green (ICG) is injected intradermally into the hand. The fluorescence of the ICG can be obtained by an infrared camera. The images are then classified into either a normal linear pattern or three dysfunctional backflow patterns progressing from splash, stardust to diffuse (16). A dysfunctional backflow pattern may occur before the lymphedema becomes clinically detectable. This makes it possible to detect early abnormalities in lymphatic transport, enabling early intervention and prevent lymphedema progressing in more severe stages (10, 17, 18). In contrast to the lymphoscintigraphy, lymphofluoroscopy is capable of giving a detailed mapping of the superficial lymphatic architecture. According to the study of Mihara et al lymphofluoroscopy is more sensitive than lymphoscintigraphy for the diagnosis of lymphedema as lymphofluoroscopy scored excellent on sensitivity, as lymphoscintigraphy scored moderate. Both assessment methods scored 1.0 on specificity of detection of lymphedema of the upper limbs (17).

A major concern is that currently, the equipment to evaluate lymphatic transport by injection of ICG is not often available in clinical practice and that the procedure is time-consuming. Therefore, it is interesting to know whether there is an agreement between the presence of early disturbance visualized by lymphofluoroscopy and clinical assessment tools. In addition, the second aim was to investigate the sensitivity and specificity of the clinical assessment tools compared to early disturbance of the lymphatic transport seen on lymphofluoroscopy.

Material and methods

Study design and setting

A prospective cohort study part of the ongoing Dearly trial (Determining the role of pre-existing factors, early diagnostic options and early treatment in the development of BCRL) was performed (19). Breast cancer patients who were scheduled for surgery were assessed. These patients underwent an axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) for the treatment of breast cancer at the Multidisciplinary Breast Center of the University Hospitals Leuven, Belgium. The study was approved by the Ethical Committee of the University Hospitals Leuven (S-number 60382).

Patients

Recruitment started in November 2017 and ended in April 2019. Inclusion criteria were 1) Age ≥18y, 2) women/men with breast cancer and scheduled for unilateral ALND or SNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) age <18y, 2) edema of the upper limb from other causes, 3) cannot participate during the entire study period, 4) mentally or physically unable to participate in the study, 5) contra-indication for the use of ICG: allergy to ICG, iodine, hyperthyroidism, 6) metastatic disease.

All patients received written as well as oral information. All included patients signed an informed consent document prior to the start of the study

Assessment

All assessments were performed according to a standardized protocol by two assessors (ST and ND/NVL) at baseline and after 1, 3, 6, 9 and 12 months. Visits for the study were incorporated into the existing oncologic follow-up schedule. All patients were investigated with lymphofluoroscopy and clinical measurements at the different time points.

Lymphofluoroscopy

During lymphofluoroscopy, ICG was injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captured the fluorescence. The procedure consisted of three consecutive phases (Table 1): an early phase, a break and a late phase. All information about the lymphatic transport was documented in a standard evaluation document and in case of disturbance, this information was drawn on a body diagram according to the legend (Figure 1).

Clinical assessments

The water content of the skin was evaluated by the pitting test and tissue dielectric constant. The thickness of the skin was evaluated by the Stemmer sign. The change of volume in the arm was evaluated by the circumference measurement (after which the volume was calculated using a truncated cone formula) and the volume of the hand by the water displacement method. A 3% and 5 % relative volume difference increase compared to preoperative measurement was used. A ≥ 3% relative volume difference increase is described in literature as a risk for development of lymphedema and a ≥ 5% difference increase is considered clinical lymphedema (20). Table 2 discusses the procedure (i.e. position of the participant, the material, reference points used, cut-off values and the execution), the outcome and processing of the different clinical measurements: pitting status, skinfold thickness, Percentage Water Content (PWC), arm (including hand) volume.

Data processing

To be able to compare the outcomes the arm was divided in ten different zones (Figure 2). Interpretation of the lymphofluoroscopy and the clinical assessments were gathered for each patient at five different time points (1, 3, 6, 9 and 12 months).

Lymphofluoroscopy

The presence of dermal backflow at the ten zones was scored 0 if a normal, linear pattern was seen; 1 if a splash pattern was seen; 2 if a stardust pattern was seen, 3 if a diffuse pattern and 4 if no transport was seen.

Clinical assessment

Pitting status, skinfold thickness and PWC were evaluated at seven reference points (Figure 3). These seven reference points were matched with the ten zones of the lymphofluoroscopy: reference point 1 was matched to zone B, reference point 2 and 3 to zone D, reference point 4 to zone E, reference point 5 to zone F, reference point 6 to zone H and reference point 7 to zone I.

To determine the agreement between the arm (including hand) volume measured by circumference measurement and the lymphofluoroscopy, the outcome of the circumference measurements was clustered into four segments to match with the different zones of the lymphofluoroscopy (Table 3). For each segment the volume was calculated using the formula of the truncated cone ($V=4(C^2+Cc+c^2)/12\pi$; V: volume, C/c: circumference at each end of the segment) (21). If there was a difference in volume of ≥ 3% or ≥ 5% the outcome on the circumference measurement was scored positive for that particular clustered section. For the segment of the hand, the water displacement technique was used.

Statistical method

For each time point and each zone the presence of disturbance of the lymphatic transport and the presence of the clinical outcome measure was assessed.

When at a certain time point (1, 3, 6, 9 and 12M post-surgery) a disturbance of the lymphatic transport was seen, the clinical assessment at that time and in that zone was compared. In the statistical analysis, the data of the positive lymphofluoroscopy was compared to the outcome of the other clinical assessment methods at that same moment and same zone. For example, if a participant showed disturbance in lymphatic transport at 3 months post-surgery in zone D, the outcome of the other clinical measurement methods at 3 months post-surgery for zone D were evaluated to determine the agreement. Given the interest in early detection of lymphofluoroscopy, all data of a patient at a specific zone are discarded after the first positive lymphofluoroscopy (either splash, stardust or diffuse).

When no disturbance was seen at a certain time point/zone, the clinical assessment at that same time and in that same zone was assessed.

The data of the zones where early disturbance was seen the most, were also assessed separately.

The Cohen's Kappa was used to determine the agreement between the presence of early disturbance on lymphofluoroscopy and the other clinical assessment methods (presence of pitting/ increased skinfold thickness/ increased PWC ratio/ increased arm-hand volume). A Cohen's Kappa coefficient of <0.20 was interpreted as no agreement, 0.21-0.39 as a minimal agreement, 0.40-0.59 as a weak agreement, 0.60-0.79 as a moderate agreement, 0.80-0.90 as a strong agreement and >0.90 as an almost perfect agreement.

Diagnostic accuracy is quantified by sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy, estimated as proportions with 95% confidence intervals.

Sensitivity is the proportion correctly identified positive fluoroscopy results, specificity is the proportion correctly identified negative fluoroscopy results, positive predictive value is the proportion of patients with positive screening (clinical assessment) that has a positive fluoroscopy, negative predictive value is the proportion of patients with negative screening (clinical assessment) that has a negative fluoroscopy, and total accuracy is the proportion of all cases where clinical assessment and fluoroscopy result coincide. The sensitivity and specificity were calculated for the lymphofluoroscopy compared to the other clinical measurement methods. The sensitivity and specificity of < 60% was interpreted as weak, between 60% and 74% as moderate, between 75% and 90% as high and >90% as an excellent sensitivity or specificity.

Analyzes have been performed by the Leuven Biostatistics and Statistical Bioinformatics Centre, using SAS software (version 9.4 of the SAS System for Windows).

Results

Descriptive data

Hundred twenty-eight patients were enrolled for this trial. Patients' ages ranged from 29 to 82 years (mean 56.7 SD 12.25). The body mass index had a median of 24.8 (IQR 22.3-29.1). Hundred twenty-seven patients were female, and one patient was male. For detailed information about the patient characteristics, see table 4.

Before surgery, none of the patients had a disturbance of the lymphatic transport (i.e. dermal backflow). Table 5 shows the characteristics of the lymphatic transport after breast-cancer treatment. In total, 66 out of 115 patients (57.4%) showed early disturbance of the lymphatic transport on the lymphofluoroscopy during the 1-year follow-up. In thirteen patients (10.2%) no data was available as they discontinued participation in this study. In sixty-one patients a splash pattern was seen, in 4 patients a stardust pattern and in 1 patient no transport out of the injection sites was noticed. Fifteen patients showed disturbance of lymphatic transport at 1 month post-surgery, 17 at 3 months post-surgery, 13 at 6 months post-surgery, 12 at 9 months and 4 at 12 months. A dermal backflow pattern was seen in 104 different zones. The frequency of disturbance was the highest in the ventral site of the upper arm distal (zone D) and proximal part (zone E). No patients showed disturbance at the ventral side of the hand (zone A).

In 38 out of the 128 patients (29.6%) there was a ≥ 5% relative volume difference increase and in 32 patients (25%) we found a positive pitting test at any time point up to 12 months.

Outcome data

Results were presented over all locations and different time points (table 6).

For the pitting test a Kappa of 0.23 was found. Twenty-seven positive pitting tests were found out of the 140 positive lymphofluoroscopies leading to a sensitivity of 19.29%. The specificity was 98.27% as there were 2560 negative pitting tests out of the 2605 negative lymphofluoroscopies.

For the Stemmer sign test (Kappa 0.29) and for the tissue dielectric constant (Kappa 0.21) minimal agreement was found. The circumference measurement had a minimal agreement for the 5 % volume difference (Kappa 0.22) and no agreement for the 3% volume difference (Kappa 0.19).

Sensitivity was weak for the pitting test, for the Stemmer sign test and for the tissue dielectric constant. For the circumference measurement sensitivity was higher, but still weak. The specificity was excellent for the pitting test, Stemmer sign test, tissue dielectric constant and the 5% volume measurement. For the 3% volume measurement a high specificity was found.

Early disturbance of the lymphatic transport was seen mostly at Zone D and E. The findings of Table 7 are similar to the findings of Table 6.

Discussion

To our knowledge this is the first prospective study investigating the agreement between early disturbance of the lymphatic transport seen on lymphofluoroscopy and commonly used clinical assessment tools for early signs of lymphedema in patients receiving treatment for breast cancer.

This study showed low rates of agreement and sensitivity for all the clinical assessments used. The pitting test, Stemmer sign test and tissue dielectric constant are weak predictors for early disturbance of the lymphatic transport since the sensitivity was lower than 40%. Specificity for these clinical assessments were high to excellent, meaning that there is a high chance that a negative clinical test also means that there is a negative lymphofluoroscopy. Several studies have assessed the correlation between lymphofluoroscopy and some clinical measurements. However, these studies were not performed with a preventive purpose (i.e. to detect the development of lymphedema). In these studies, the correlation between disturbance of lymphatic transport (i.e. dermal backflow) and clinical outcomes was investigated in patients with clinical BCRL (22, 23). In one of our previous studies, a moderate to strong agreement was found for the clinical assessment pitting status, skinfold thickness and water content. Overall specificity was high for pitting status (83.4%) and moderate for skinfold thickness (61.6%) and water content (74.8%). So in patients with BCRL, in which the lymphatic disturbance is more pronounced, most of the common clinical assessments showed a good agreement with the presence of lymphatic disturbance (22). Another study of Medina-Rodriguez et al (23) showed a correlation between the increase of arm circumference and the lymphatic disturbance in patients with BCRL. This was the case at 4 specific anatomical zones: the wrist, elbow, anterior and posterior upper arm.

Since the aim was to detect early disturbance of lymphatic transport the cut-off of ≥3% and ≥5% relative volume increase were used in this study. The latter corresponds to the volume difference recommended for the diagnosis of lymphedema (20, 24). Specht et al found an increase of arm volume of ≥3% to be one of the risk factors for the development of lymphedema (25). Hence, the cut-off for the definition of subclinical lymphedema or early disturbance in lymphatic transport is still unclear. In our study lower cut-off values may have resulted in an increase in false positive outcomes (lower specificity) and less agreement with the early detection on lymphofluoroscopy. Perhaps some of these changes in arm volume could be explained by the presence of transient edema, which can be present in a portion of the patients. According to a study by Hayes (26), 58% had transitory lymphedema and 23% in another study (27) .

It could be possible that some of the patients developed a dermal collateral flow pathway which will protect them from developing clinical lymphedema. Suami identified four different pathways of lymphatic drainage in BCRL and suggested that an alternative detour to the deep lymphatics may be created (28). Perhaps these pathways can be sufficient to maintain the lymphatic drainage of the limb. According to Akita et al some of these early detected dermal backflow patterns can return to normal over time (18). Further research is needed to investigate if this early disturbance is indeed a risk factor for the development of BCRL.

Regarding the tissue dielectric constant several studies indicated that a threshold of 1.2 may not be applicable on all locations measured, as the forearm ratios in these studies ranged between 1.26 (29, 30) and 1.29 (31). Mayrovitz et al 2009 suggested that a threshold of 1.26 for the detection of early lymphedema should be used (29). This may implicate that a threshold of 1.2 may lead to false positives.

Strengths

The study has several strengths.

A first strength is the number of analyzes. The extensive analyses of commonly used assessment methods with the use of many reference points (pitting test, Stemmer sign test, tissue dielectric constant) and segments (circumference measurement) is a strength. A total of 6400 analyzes were done.

A second strength is the use of segments to analyze the clinical outcomes. Local changes in the arm were assessed since several studies indicated that segmental variations in lymphatic transport is seen and segmental volume may change before apparent changes in total limb volume occur (32, 33).

A third strength is that in the zones of the ventral upper arm (zone D and E) the most disturbance was seen, corresponding to other studies where the elbow regions and proximal parts of the arm are first described to have a disturbance in dermal backflow (16, 23, 34). In our study, splash pattern was seen in 53% of the patients this is also described in other studies as the splash pattern is considered to represent less severe dysfunction of the lymphatic transport and will appear first in most cases (16, 23, 34).

A fourth strength is the timing of the postoperative changes in lymphatic transport. BCRL is a chronic disease developing after breast cancer treatment but in 75% of the patients BCRL will develop in the first year after breast cancer treatment (35). In the study of Akita et al lymphatic disorder onset 5.2 (±3.0) months after surgery was seen (18). This is comparable to the study by Stout where the average time to onset of BCRL was 6.9 months (32). McDuff et al found a peak in lymphedema onset between 6-12 months in patients with ALND and without regional lymph node radiation and even a peak between 18-24 months in patients with ALND and regional lymph node radiation (36). Our findings showed that the time point of seeing disturbance for the first time, ranged from one month to nine months. Only 5 (4%) patients had the first visualization of disturbance at 12 months.

Limitations

A first limitation is that our sample is not completely representative for all breast cancer patients. With the mean age of 56.68 years the population studied is younger than the average breast cancer population according to the Belgian Cancer Registry, which is 63 years of age (37). As younger breast cancer patients (<40 years or premenopausal) seem to develop more aggressive cancer tumor subtypes, often more drastic treatments such as mastectomy, ALND or regional lymph node radiation are required (38, 39). This may explain why a higher percentage of participants (57%) had to undergo an ALND. More extensive surgery, higher number of lymph nodes removed, high body mass index, regional lymph node radiation and chemotherapy are known risk factors for the development of BCRL (1) and this may be the reason why in this population 32% of the patients developed disturbance in lymphatic transport. Furthermore, because people are more aware of the risk factors of BCRL, patients scheduled for ALND were probably more willing to participate in the study (selection bias).

A second limitation is that we matched the zones of the lymphofluoroscopy with the seven reference points. Another method could be to perform the clinical assessment at the exact same location of the disturbance of the lymphatic transport seen on lymphofluoroscopy. Possibly this would increase the agreement. However, in this way it was not possible to blind the assessor of the clinical measurements for the result of the lymphofluoroscopy.

A last limitation is that we did not analyze the results of the bioelectrical impedance spectroscopy in this study. This technique can assess extracellular fluid in the whole arm, but not in specific segments, therefore we decided not to incorporate this data. A study by Bundred et al (40) confirmed this underdiagnosis of segments of lymphedema such as hand or elbow by bioelectrical impedance spectroscopy.

Clinical implications

Early disturbance visualized by lymphofluoroscopy can't be predicted by the clinical assessment tools used in this study. If we want to detect early disturbance we will need to do a lymphofluoroscopy. Performing a lymphofluoroscopy as a screening tool in every patient after breast cancer treatment will not be feasible (high cost, time-consuming,…), but in high risk patients, such as more advanced cancer (positive lymph nodes), after radiotherapy of the axilla, after therapy with taxanes, screening with lymphofluoroscopy could be useful and cost-effective. Screening for lymphedema in these high risk patients in the first postoperative year and especially the first six months are recommended as 74% of the early disturbance is seen the first six months. This study also indicates that special attention should be taken in the assessment of the pericubital region and ventral upper arm as most of the disturbance appears in these zones.

Conclusion

The study results showed that there is no agreement between the pitting test, Stemmer sign test, tissue dielectric constant and water volume assessments (circumference measurement and water displacement method) and early disturbances in lymphatic transport as visualized by the lymphofluoroscopy. If we want to detect early disturbance we will need to do a lymphofluoroscopy. Therefore this lymphofluoroscopy can be used as a screening tool for early detection of abnormalities of the lymphatic transport, especially useful in high risk patients.

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Authorship confirmation statement

All authors critically revised the article for important intellectual content and approved the final article.

Author disclosure statement

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