Development and clinimetric properties of the Dutch Breast Edema Questionnaire (BrEQ-Dutch version) to diagnose the presence of breast edema in breast cancer patients

Introduction

Breast-conserving surgery (BCS) followed by radiation therapy is a safe and effective procedure to treat patients with early stage breast cancer [1]. For many women this type of treatment results in a good survival as well as a good cosmetic result [2]. Despite these advantages, some women however, develop breast edema on the operated and irradiated breast. In contrast to lymphedema of the upper limb as a morbidity of breast cancer treatment, breast edema is little described in the literature. In a systematic review of the literature done by our own research group, an incidence for breast edema between 0 and 90.4% was found in breast cancer patients following BCS and radiation therapy [3]. This broad range in incidence can be explained by the lack of a uniform definition and standardized assessment criteria concerning breast edema. Common criteria for breast edema, as found in scientific literature, are peau d'orange [4–9], redness of the skin [5–7], pain in the breast [4–7,9], a positive pitting sign [5], increased breast volume [5–11], skin thickening [5,11,12], heaviness of the breast [6,8,9] and hyperpigmented skin pores [7]. Up till now, both diagnosis and stage of breast edema are mainly made by physical examination, by observing and palpating the breast [2,13]. Breast ultrasound (US) is considered to be a more reliable and quantitative measure for breast edema [12,14]. By measuring the skin thickness, US can provide a measure of cutaneous edema on a continuous scale [12]. Other assessment tools found in literature were questionnaires like the LENT-SOMA, Common Toxicity Criteria and the EORTC-BR23 questionnaire [3]. However, these questionnaires are often not specific and inclusive enough. Despite the relative high incidence seen in literature, breast edema is largely underdiagnosed, hence untreated, in clinical practice. The development of a standardized assessment tool for the early detection of breast edema is warranted in order to provide an adequate treatment. For clinical practice, a valid and feasible questionnaire for the diagnosis of breast edema is a recommended addition to the current, expensive and time-consuming, investigations provided by US. Therefore, the aim of this study is to develop a patient-reported questionnaire to assess breast edema and to determine its clinimetric properties; being content validity, construct validity (convergent and known-groups validity), test-retest reliability, internal consistency and cut-off point.

Methods

Development of the breast edema questionnaire (BrEQ)

The development of the BrEQ consisted of 3 phases [15]. In the *first phase*, relevant information about breast edema was collected through (1) a systematic review of the literature [3], (2) information from experts in the field, being health care professionals involved in breast cancer treatment and lymphedema treatment, and (3) information from patients suffering from breast edema. The International Classification of Functioning, Disability and Health (ICF) model was used as a framework to describe the patient's health condition in a bio-psychosocial context (www.who.int/classifications/icf/en). Impairments in body functions and structures, activity limitations and participation restrictions were collected [16]. This information was used to make a pilot version of the BrEQ.

In the *second phase*, the pilot version of the BrEQ was tested and discussed by a response group. Patients (n=4) and health care professionals (breast surgeon (n=1), breast nurses (n=2), physiotherapists specialized in lymphedema treatment (n=6)) , gave feedback on the BrEQ concerning completeness of the questionnaire, relevance of the questions and scoring system. Based on this feedback, the BrEQ was adjusted; the item hardness was added as a complaint related to breast edema. This final questionnaire consists out of 2 parts. In the first part, symptoms of breast edema are scored on a scale from 0 to 10. Taking into account the ICF, besides the aforementioned breast edema symptoms, focusing on impairments of body structures and body functions, a number of activity limitations and participation restrictions are scored on a scale from 0 to 10 as well. This is part 2 of the questionnaire. For both parts, a higher score means more disabilities related to breast edema. The BrEQ (Dutch version) is provided in Appendix 1. An English translation of the BrEQ is provided in Appendix 2. Note that the English translation has not yet been validated.

Clinimetric properties of part 1 of the BrEQ

In the *third phase*, clinimetric properties of the BrEQ were tested in a group of patients. Content validity, construct validity, test-retest reliability, internal consistency and a cut-off point were examined for part 1, i.e. the patient-reported breast edema symptoms. It was not possible to examine criterion validity, because we were unaware of a gold standard for measuring breast edema. For now, only part 1 was examined for clinimetric properties, since both diagnosis and detection were our primary focus. Part 2 concentrates on the impact of breast edema on daily functioning. Clinimetrics were not determined for the second part of the BrEQ.

C*ontent validity* refers to the extent to which a measure represents all facets of a given construct. Content validity was measured by means of an attached questionnaire, consisting of 4 questions about the comprehensiveness of the BrEQ and its scoring system: (1) Was each question understandable? (2) Were all items relevant to your current

situation? (3) Do you think the questionnaire is complete? (4) Was the scoring system clear? An explanation was asked if the patient answered "no" on an item. The number of positive and negative answers was counted [17,18].

Construct validity is a process in which validity is evaluated in terms of the extent to which a measure correlates with variables in a manner consistent with theory [19]. The construct validity of the BrEQ was investigated in 2 ways. First, *convergent validity* refers to the degree in which 2 independent measures of the same construct are in fact related [20,21]. This was investigated by correlating skin thickness of the thickest quadrant of the operated breast, with all questions of part 1 of the questionnaire. Second, *known-groups validity* was investigated by comparing the BrEQ-scores between patients with and patients without breast edema in order to verify whether the BrEQ can differentiate between "breast edema" and "no breast edema".

To measure *test-retest reliability*, the patients were asked to fill out the BrEQ again, within 24 to 48 hours after the first consult, because problems with functioning related to lymphedema, can change from one day to another [22]. Scores obtained on these 2 different time points were compared to one another [23,24].

The *internal consistency* was investigated to determine whether the different questions measure the construct in the same consistent matter [24,25].

The receiving operating curve (ROC) was generated to determine a BrEQ-score *cut-off point* which can differentiate between patients with and patients without breast edema.[26].

Patient selection and recruitment

In this methodological study with descriptive design, patients were recruited from the multidisciplinary Breast Clinic of the University Hospital of Antwerp during their annual routine US appointment. The electronic agenda was screened from 23 November 2015 till 10 June 2018 for patients who had an appointment at the Radiology Department of the Antwerp University Hospital for an US and mammogram investigation. The electronic medical files of the patients were used to determine if patients met the inclusion criteria. Women older than 18 who underwent unilateral BCS followed by radiation therapy were enrolled. Exclusion criteria were (1) other disorders which can cause breast edema like angiosarcoma, conditions of the skin, heart diseases and lung diseases, (2) plastic surgery such as reconstructive surgery, (3) pregnancy and (4) not capable of understanding the Dutch questionnaire. In total, 57 patients were asked to participate; 55 agreed and were included in the study. Based on a Spearman correlation coefficient >0.50 with a significance of $p<0.05$ and a power of 0.80, sample size of 15

participants in each group was calculated. Taking into account a drop-out of 20%, a minimum of 18 participants in each group needed to be included. At the time of inclusion, patients and researchers were unaware whether patients had breast edema or not. All participants received an information brochure informing them about the study and requesting their voluntary participation. Patients received information about the nature and purpose of the research, the expected duration of their participation, a statement that participation is voluntary; risks and benefits, information about confidentiality, details of insurance coverage in case of injury; reference contacts for any further answers to pertinent questions about the research and the subject's rights, a statement offering the subject the opportunity to withdraw at any time from the research without consequences. All participants provided written informed consent. Information about participant characteristics is provided in Table 1.

Additionally, a sample of 10 breast cancer patients who underwent BCS and radiation therapy were included in order to assess the test-retest reliability for the item redness. They were asked to fill out the BrEQ twice, within 24 to 48 hours, in order to eliminate the interference of redness induced by the mammogram. None of them received a mammogram before filling out the BrEQ.

Data collection

At the time of their appointment at the Radiology Department (immediately after the US examination), the selected patients were asked to complete the BrEQ. The patients completed it at their own pace and completely independently. Subsequently, a second questionnaire regarding comprehensiveness of the BrEQ was given. Afterwards, participants received a pre-stamped envelope with a copy of the BrEQ and they were asked to fill it out and return it within 24-48 hours.

Ultrasound

In addition, all patients underwent an US of both breasts in order to measure skin thickness (i.e. epidermal and dermal thickness) of the 4 quadrants of each breast, to determine the degree of cutaneous breast edema. The US was performed by 2 experienced radiologists of the Antwerp University Hospital (M.V.G. and L.H.). Skin thickness was measured with a high frequency probe (13 MHz), using Logic E9, GE medical systems (Wauwatosa, WI, USA). The probe was placed perpendicular to the skin 4 cm remote from the nipple for all 4 quadrants. All patients were examined in supine position. Breast edema on US was considered as a deviation of more than 2

standard deviations (SD) from the average skin thickness. Cut-off values were determined by calculating the average thickness and SD's of the non-operated, non-irradiated breast of the entire sample. If the difference of more than 2 SD's was noticeable in at least one quadrant of the operated and irradiated breast, patients were allocated to the breast edema group.

Data analysis

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS, IBM, USA) version 24 was used. The socio-demographic data were descriptively analyzed and displayed as frequencies and rates. Frequencies were used to determine the content validity. The number of positive answers on each of the 4 questions concerning content validity was counted and percentages were calculated. Subsequently, convergent validity was tested by Spearman correlation coefficients, correlating skin thickness of the thickest quadrant of the operated and irradiated breast, with all items of part 1 of the BrEQ. Spearman correlation coefficients were chosen because data were not normally distributed. The known-groups validity was tested by means of a Mann-Whitney U-test in order to verify whether the different items of the BrEQ can significantly differentiate between patients with and without breast edema. Test-retest reliability was investigated by determining the reliability of the total sum of the breast symptoms (part 1) and of the individual items, between the first and second (24 to 48 hours later) measurement, using a two-way mixed intraclass correlation coefficients (ICC) with single measures. The internal consistency of part 1 of the questionnaire was determined by the Cronbach alpha coefficient. To assess whether a cut-off point is available for the BrEQ, a ROC-curve was generated, using the total symptom score of the second measurement as classifier and skin thickness as true status reference (>2 SD's in at least one quadrant of the operated and irradiated breast on US). The area under the curve (AUC) was calculated and the coordinate with the greatest sum of sensitivity and specificity was identified as the BrEQ-score cut-off point [26,27]. AUC is interpreted as follows: 90 -100 = excellent; 80 - 90 = good; 70 - 80 = fair; 60 - 70 = poor; 50 - 60 = fail [28].

Results

Phase 1: Development of the BrEQ

The BrEQ consists of 2 parts. In part 1, breast symptoms are assessed and part 2 concentrates on the impact on daily functioning. For part 1, the following 8 breast edema symptoms were selected based on information collected

through systematic literature search, health care professionals and breast edema patients: pain, heaviness, swelling, tensed skin, redness, pitting sign, enlarged skin pores and hardness of the operated and irradiated breast. Concerning part 2, the following 14 activity limitations and participation restrictions were found: sleeping, lying down, sitting, standing, vocational activities, household chores, driving a car, handicraft, walking, sports, getting (un)dressed, putting on a bra, wearing a bra, computer work.

The constructed BrEQ consisted of 8 questions related to breast edema symptoms (part 1) and 14 questions related to activity limitations and participation restrictions (part 2). Each item was scored on an 11-point Likert scale (0-10). The anchor points for part 1 were "not at all" and "very severe". For the total symptom score, the scores of the individual items of part 1 of the BrEQ were added up, resulting in a total symptom score ranging from 0 to 80. The anchor points for part 2 were "no complaints" and "unbearable complaints". Participants were asked to score their average breast edema symptoms and activity limitations and participations restrictions related to their breast complaints in the preceding week. The BrEQ takes about 5 minutes to complete.

Phase 2: Clinimetric properties of part 1 of the BrEQ

In phase 2, the clinimetric properties of part 1 of the BrEQ were determined. A total of 55 eligible patients participated in phase 2 of the study. Informed consent was obtained from all participants. Breast edema on US was considered as a deviation of more than 2 standard deviations (SD) from the average skin thickness. Following cut-off values were used to determine if the patient had breast edema: 2.192 mm for the superior internal quadrant (SIQ), 2.131 mm for the inferior internal quadrant (IIQ), 2.0518 mm for the inferior external quadrant (IEQ) and 1.774 mm for the superior external quadrant (SEQ). US showed that 35 patients had breast edema with a mean age of 58.20 (±11.48). Twenty participants without breast edema (mean age 63.05 ±10.10) were included. The characteristics of the participants are shown in Table 1.

The mean total skin thickness of the treated breast (sum of the 4 quadrants) was 7.42 mm (±2.11) versus 5.47 mm (±1.09) for the untreated breast. This difference was significant ($p<0.001$). Skin thickness of the operated and irradiated breasts is significantly higher for the breast edema group (8.45 mm ±1.84) compared to the non-breast edema group (5.61 mm ±1.08) ($p<0.001$). For the untreated side, there is no significant difference between both groups (5.61 mm ±1.17 and 5.22 mm±0.90 respectively).

The additional questionnaire concerning the comprehensiveness of the BrEQ was completed by all but one patient in order to determine the *content validity*. Of these patients, 53 (98.1%) understood all questions and 49 patients (90.7%) found the questions relevant to their current situation. The other 5 patients answered "no" because their surgery was performed a longer time ago. Forty-seven patients (87.0%) stated that the BrEQ was complete. The other patients felt that questions concerning arm edema and axillary web syndrome should also have been included. The last question about the scoring symptom was answered with "yes" by all participants (see Table 2).

Concerning the *convergent validity*, the thickness of the thickest quadrant of the operated and irradiated breast is correlated with part 1 of the BrEQ. The correlation coefficients and p-values are shown in Table 3. All separate breast edema symptoms correlate moderately with skin thickness. The total symptom score has a strong correlation with skin thickness. All items reach the level of significance.

Table 4 provides an overview of the *known-groups validity*. The questions of part 1 of the questionnaire were compared between the breast edema group and the non-breast edema group. Patients with breast edema have higher symptom scores. This difference is significant for the total symptom score ($p=0.03$) and for the items heaviness ($p=0.026$), swelling ($p=0.035$), redness ($p=0.009$) and pitting sign ($p=0.020$). For the other items (pain, tensed skin, enlarged skin pores and hardness) there is a trend towards significance.

Out of 55 patients, 45 patients filled out the BrEQ a second time after 24 to 48 hours (drop-out 18%). Table 5 gives an overview of the ICC's of the breast edema symptoms between first and second measurement. It is shown that the *test-retest reliability* of the total symptom score and the items pain and heaviness is strong. For the other symptoms, reliability is moderate. All items were significant (see Table 5). The item redness had the lowest ICC. For this item, the test-retest reliability was analyzed in an additional sample of 10 breast cancer patients. They filled out the BrEQ twice, with a time difference of 24 to 48 hours and without a prior mammogram. For these 10 extra patients, the test-reliability for the item redness was strong (ICC=0.773, $p=0.003$).

The *internal consistency* was good for all items of part 1 of the BrEQ and for the total symptom score. The Cronbach alpha coefficients were 0.830 for the total symptom score and 0.839 to 0.869 for scores on the separate items (see Table 5).

A ROC curve was created using the total symptom score 24 to 48 hours after the US as the classifier and skin thickness as true-status reference (>2 SD's in at least one quadrant of the operated and irradiated breast on US) (Fig. 1). The AUC was 0.815. Therefore the accuracy of the test can be considered good [28]. The coordinate with the greatest sum of sensitivity and specificity was 8.5, suggesting that this value can be used to discriminate

between individuals who have breast edema and those who have not. A cut-off value of ≥ 8.5 demonstrated a sensitivity of 75.0% and a specificity of 82.4%.

Discussion

The BrEQ (Dutch version) is the first self-reported questionnaire with evidence of validity and reliability for assessing breast edema in breast cancer patients who underwent BCS and radiation therapy.

Content validity was measured by means of an additional questionnaire and was found very good. Some patients felt that the BrEQ was not relevant for their current situation, because their breast cancer treatment was a longer time ago and they currently did not experience any breast complaints. While analyzing the demographic data, it is noticeable that many of the included patients underwent surgery quite a long time ago (range 8-183 months). Literature shows that the prevalence of breast edema diminishes over time. Although some patients still suffer from breast edema more than 5 years after breast surgery. Clarke et al. demonstrated that breast edema occurs in the first 2 months (early onset breast edema) or in about 20 months (late onset breast edema) after breast cancer treatment [8]. Wratten et al. described the time course of cutaneous breast edema based on the increase in skin thickness. In most cases skin thickness increases to a minor extent during radiation therapy, but more significantly in the post-treatment period. Skin thickness usually peaks at 4 to 6 months post-treatment and in most cases shows signs of returning to baseline levels at 12 months post-treatment [12]. Still, it was useful to include patients who had surgery a longer time ago. First, because more than 5 years after surgery, there is still a (smaller) risk of developing breast edema and secondly, to compose an extensive control group. Concerning the content validity, other patients would like to add questions about lymphedema of the arm, however this is not the objective of the BrEQ. Perhaps for those patients a specific questionnaire for lymphedema of the arm, like the Lymphedema Functioning, Disability and Health Questionnaire – Upper Limb (Lymph-ICF-UL), is more appropriate [22].

Construct validity was tested by examining convergent validity and known-groups validity. Concerning convergent validity, all breast symptoms have a moderate correlation with skin thickness of the treated breast. For the total symptom score of the BrEQ, correlation is strong. From these results, we conclude that the thicker the skin, the higher the total symptom score. Regarding the known-groups validity, it is seen that for the total symptom score of the BrEQ, patients with breast edema score significantly higher than patients without breast edema. It means that, with regards to the total score of part 1, the BrEQ can differentiate between breast edema and no breast edema.

The test-retest reliability was investigated by filling out the BrEQ a second time 24 to 48 hours later. The lowest ICC was found for the item redness. This can be explained by the fact that the first measurement was preceded by a mammogram of both breasts. It might be possible that patients score lower for this item 24 to 48 hours later. To clarify this, the BrEQ was used in an additional sample of 10 breast cancer patients. None of these patients received a mammogram before filling out the questionnaire, in order to eliminate the interference of the redness induced by the mammogram. These patients filled out the BrEQ for a second time, 24 to 48 hours later. These 10 additional patients were not recruited during their annual mammogram and US appointment, and therefore, could not be included for the entire study. Based on the results of these 10 additional patients, we can conclude that the test-retest reliability of the item redness is strong.

We found that the BrEQ has good strength (AUC 0.815) to discriminate between patients with and without breast edema. The value with the greatest sum of sensitivity and specificity was 8.5 (cut-off point), suggesting that patients with a total symptom score of 9 or more, have breast edema. A score of 8 or less indicates that the patient has no breast edema. This makes the BrEQ a useful instrument for the diagnosis of breast edema in clinical practice.

In total, 55 patients were included in this study, of which 35 patients had breast edema, based on US measurements of skin thickness. No significant differences in the patients' characteristics were found. In the existing literature, we found only 1 study that reported a cut-off value for the presence of breast edema on US [29]. Rönkä et al. considered breast edema on US as a skin thickening over 2 mm. They included additional US measurements as well to determine whether a patient has breast edema, namely increased echogenicity disturbance or poor visibility of the deeper echogenic line and interstitial fluid accumulation [29]. In our study, we only focused on skin thickening. However, we noticed a difference in the average skin thickness between the 4 quadrants. Therefore, we decided to determine our own cut-off values and considered breast edema as a deviation of more than 2 SD's from the average skin thickness of each quadrant of the non-operated breast. The motivation herein is that breast edema may occur in 1 quadrant only, without affecting the rest of the breast. With this method, we calculated cut-off values between 1.774 (SEQ) and 2.192 (SIQ), which is comparable with the 2 mm boundary [29]. We feel that this method is more accurate. A disadvantage however is that each quadrant is calculated with other complex cut-off values. Another limitation is the potential impact of the mammogram and US on the data gathered with the BrEQ, as mentioned above. Some patients experienced complaints like redness or pain caused by the mammogram. Test-retest reliability was run concurrently with validity of the BrEQ instead of separately from the main sample of the study. This is a limitation of the study. Furthermore, this study was conducted at a single hospital radiology department.

The BrEQ is developed with the intention to cover all domains of disability according to the ICF framework related to breast edema. This study wanted to focus more on the diagnosis of breast edema, than on the impact on daily functioning. Future research in order to validate part 2 of the questionnaire (activity limitations and participation restrictions) needs to be done. The present study did not investigate clinical responsiveness of the BrEQ or cross-cultural validity. Further investigation of those properties is needed. This Dutch questionnaire is the first to specifically assess breast edema. A translation and further investigation of the degree to which the items on a translated or culturally adapted BrEQ adequately reflect the items on the original Dutch version, is mandatory.

The BrEQ may be used in clinical practice to diagnose or assess breast edema in patients who underwent BCS and radiation therapy. It is known that the survival rate of breast cancer is fairly high, certainly compared to other cancers. Therefore, the quality of life (QOL) becomes more important. Since breast edema has a significant impact on body image, it can negatively influence the QOL [2,30]. With an early detection of breast edema in clinical practice, breast edema could be treated in an earlier stage, potentially leading to an improved outcome. Due to its ease of use, the BrEQ could be used by any health care professional involved in breast cancer treatment. In this way, breast edema could be detected more quickly, and the patient could be redirected to a specialist more rapidly to start the appropriate treatment. In addition, the BrEQ could be applied in clinical research.

Conclusion

In conclusion, the first part of the BrEQ is a reliable and valid Dutch questionnaire for assessing clinical indicators of breast edema after breast cancer treatment. We identified that a score cut-off point of 8.5 (AUC = 0.815) discriminates between patients who have breast edema and those who have not. Currently, part 1 of the questionnaire is a useful tool to asses and diagnose breast edema in clinical practice.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committee of the Antwerp University Hospital (registration: B300201317503).

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Appendices