Optimizing breast symmetry analysis using three-dimensional stereophotogrammetry images of Deep Inferior Epigastric Perforator flap reconstruction patients

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Master Thesis
Technical Medicine

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Abstract

Background: The Deep Inferior Epigastric Perforator (DIEP) flap reconstruction is the preferred autologous breast reconstruction in most hospitals. During this procedure, a tissue flap from the abdomen is shaped into a breast and transferred to the thorax. However, a secondary correction is often required to reshape one or both breasts to improve symmetry and patient satisfaction. A three-dimensional (3D) printed breast mold could improve breast symmetry during breast reconstruction, and therefore reduce the number of secondary corrections required. Level I evidence is required to prove the added value of the breast mold. This thesis contributes to the set-up of the efficiency study required to gather the level I evidence. This thesis focused on 1) the validation of the current breast mold design, focusing on the breast borders, 2) the development and validation of an objective algorithm that quantitatively scores breast symmetry, and 3) the exploration of the predictive value of patient satisfaction and multiple symmetry scores for the wish of a secondary correction.

Methods: For the breast mold validation study, breast molds were created for two participants with a recent unilateral DIEP flap reconstruction. The delineation of the breast mold was quantitively compared to the breast delineation of a plastic surgeon. Additionally, a questionnaire determined the plastic surgeon's satisfaction with the breast mold borders and volume. In the second study, curvature, face normal directions, and distance maps were explored to objectively quantify breast symmetry. Multiple linear regression was used to determine the optimal combination of breast shape analysis methods. The algorithm was developed using the symmetry scores from three plastic surgeons of fifty 3D photos of DIEP flap reconstruction patients from Radboudumc as gold standard. The algorithm was validated using the symmetry score of one plastic surgeon per 3D photo of DIEP flap reconstruction patients (n=29) from ZGT/MST. The third study was a multicenter (MST and ZGT) observational study with DIEP flap reconstruction patients (n=17) with a two- and twelve-week follow-up. Questionnaires and 3D photo analyses were used as study parameters. The Mann-Whitney U test and the Chi-square exact test were used to find differences between the participants with and without a secondary correction wish. The Spearman correlation coefficient was used to find the correlation between the different study parameters.

Results: The overall differences in delineated areas between the plastic surgeon and the breast mold was 23-30%. However, the breast molds were rated as an accurate representation of the breast border according to the plastic surgeon. The final algorithm uses curvature and the root mean square of the distances found between superimposed breasts to determine an overall breast score between 0 and 10. Based on a small number of observers for the gold standard during development (n=3) and validation (n=1), a high correlation was found between the gold standard and the algorithm (ρ = 0.849, p=0.000) during development. A substantial interclass correlation coefficient (ICC) was found between the algorithm and the gold standard during validation (ICC=0.66, p=0.000). Furthermore, the algorithm had a near-perfect reproducibility (ICC=0.95, p=0.000). Lastly, a difference (although not significant due to the small sample size) was found between the patient satisfaction of the group with (n=2) and without (n=6) a secondary correction wish after DIEP flap reconstruction. Based on preliminary data, no substantial correlations were found between the patient's satisfaction and the different symmetry scores during the two-week follow-up. A correlation of 0.64 was found between the patient's satisfaction and the algorithm's symmetry score during the twelfth-week follow-up.

Conclusion: Based on the small group sizes of these studies, the breast mold may be used in a clinical setting based on its current design. The objective breast symmetry algorithm is found promising to quantify the aesthetic result after a DIEP flap reconstruction. Although the study parameters of the observational study must be further explored with larger groups, preparations can be made to set up a randomized control trial to gather the required evidence of the effectiveness of the breast mold.

Table of contents

Chapter 1. Introduction 1

Outline of thesis 2

Chapter 2. A clinical evaluation of the determined breast borders used for the breast mold 3

Introduction 3

Method 4

Participants 4

Study design 5

Methods of measurements 5

Analysis 6

Results 6

Participants 6

Border delineation 6

Discussion 6

Interpretation of results 7

Comparison with previous literature 7

Limitations 8

Clinical relevance 8

Conclusion 8

Chapter 3. Developing an algorithm to objectively evaluate breast symmetry based on three-dimensional images 9

Introduction 9

Method 10

Data collection 11

Development of the algorithm 12

Validation of the algorithm 17

Results 17

Interobserver analysis development dataset 17

Assessment of method outputs 18

Development of the algorithm 19

Validation of the algorithm 20

Discussion 20

Interpretation of results 21

Comparison with previous literature 22

Limitations 22

Clinical relevance 23
Conclusion 24
Chapter 4. An evaluation of the usability of multiple breast symmetry scores to objectify patient satisfaction to quantify the DIEP flap reconstruction performance 25
Introduction 25
Method 26
Participants 26
Study design 26
Methods of measurements 28
Analysis 29
Results 30
Participants 30
Data characteristics 30
Primary outcomes 32
Secondary outcomes 33
Discussion 34
Interpretation of results 34
Comparison with previous literature 36
Limitations 36
Clinical relevance 37
Conclusion 37
Chapter 5. Future perspectives 38
Breast mold 38
Future perspective 38
Regulations 39
Algorithm 39
Current algorithm 39
Optimizing the algorithm 40
Randomized clinical trial 40
Study parameters 40
Study design 41
Chapter 6. Conclusion 42
Chapter 7. References 43
Chapter 8. Appendix .... **Error! Bookmark not defined.**

Chapter 1. Introduction

In the Netherlands, more than 17.000 women were diagnosed with breast cancer in 2019 [1,2]. One in three of these women must accept mastectomy as treatment [1,2]. A mastectomy has a high mental impact on women. Studies show that mastectomy patients have a lower quality of life than patients that had breast-conserving surgery or breast reconstruction [3,4]. The lowered quality of life is mostly related to a lower body image of which asymmetry is an important factor [5,6]. Therefore, well-executed breast reconstructions that restore symmetry are of high importance [7].

The Deep Inferior Epigastric Perforator (DIEP) flap reconstruction is the preferred autologous breast reconstruction in most hospitals [8]. A visualization of the DIEP flap reconstruction can be seen in Figure 1. During this reconstruction, a flap of subcutaneous fat and skin is removed from the lower abdomen, while vascularization by the deep inferior epigastric artery and vena remains intact. The flap is then transferred and reshaped to reconstruct the breast [9]. However, the transformation of a two-dimension flap into a three-dimensional (3D) breast is challenging. Hence, a secondary correction is often required to reshape one or both breasts to improve symmetry and patient satisfaction. This correction is a burden for the patient and a costly procedure [10]. Although costs can be reduced with quicker procedures, expenses can be cut down even further if the first reconstruction is successful [11,12]. Continuous developments are done to improve the reconstruction outcome and thus reduce the number of reconstructions required for a satisfactory aesthetic result. The creation of a patient-specific 3D-printed breast mold is one of these developments [10,13,14].

Multiple studies explored the use and further optimization of breast molds. The molds are created using data from a pre-operative 3D stereophotogrammetry, an imaging technique that creates a 3D surface model of the subject [14,15]. Tomita et al. and Hummelink et al. explored the added value of the mold during DIEP flap reconstruction. They found that the mold effectively guides the surgeon during flap shaping [13,14]. Additionally, Gelati et al. studied the effect of molds on reconstruction duration. They found a significant average time saving of 80 minutes or more, considering a minimal reconstruction duration of 500 minutes [16]. However, these studies stated that accurate breast segmentation remains challenging and that this technique is only sufficient for patients that are satisfied with their unaffected breast. Furthermore, a study focused on mold optimization showed that a stiff, sterile mold with holes to manipulate the tissue through is found to be the preferred design

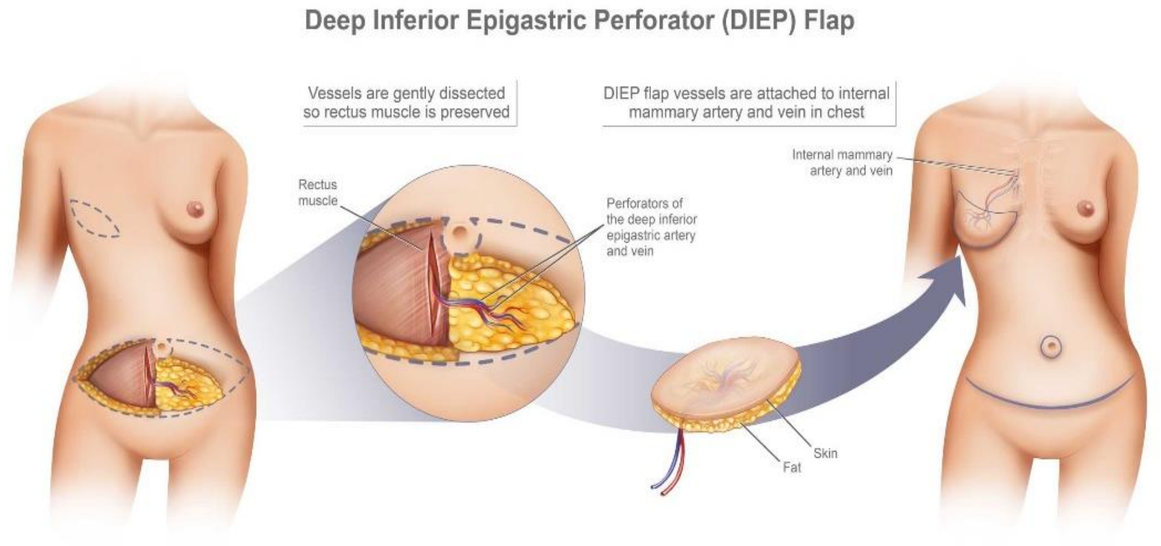

Figure 1. The Deep Inferior Epigastric Perforator (DIEP) flap reconstruction visualized. The flap is harvested from the abdomen with dissected vessels and preserved abdominal muscle. The flap is then reattached to the mammary artery at the chest to restore the blood supply of the flap

[17]. Different mold designs of the different studies are shown in Figure 2. Lastly, a study is done to explore the cost-effectiveness of the addition of a breast mold during the DIEP flap reconstruction [10]. This study found that the breast mold would reduce both operating time and the number of secondary corrections and thus seems cost-effective. Although all aforementioned studies have explored the usage of breast molds, level I evidence is still required to prove the added value of the mold during DIEP flap reconstruction.

Figure 2. Different molds created during different studies. Top left is Tomita et al. [13], top right is Hummelink et al. [14], bottom left is Gelati et al. [16], and bottom right is Troost et al. [17]

A randomized control trial (RCT) can provide the required evidence of the effectiveness of the breast mold. Within an RCT, a control group (initial treatment) is compared with an intervention group where a mold will be used during the reconstruction. However, quantifying this effectiveness remains challenging, since the subjective patient's satisfaction is decisive to initiate a secondary correction, i.e.: the patient's satisfaction determines the success of the breast reconstruction [18]. An objective outcome that can quantify the likelihood of a secondary correction, and therefore the success of the DIEP flap reconstruction, would enhance further breast reconstruction studies. In this thesis, the breast mold design was validated, and breast symmetry analysis was explored and optimized to find relevant study parameters for the upcoming breast mold effectiveness study.

Outline of thesis

In Chapter 2, a clinical evaluation of the breast mold was done. Based on findings of a previous study and literature, new landmarks were chosen to delineate the breast for the breast mold [17,19]. The objective of this clinical evaluation was to evaluate these new landmarks on accurate breast delineation. If the breast delineation was accurate, the breast mold can be used for the upcoming RCT.

In Chapter 3, an algorithm was developed to objectively evaluate breast symmetry based on 3D images. Multiple breast shape analysis methods were explored and combined to create the optimal breast symmetry analysis method. This algorithm could enhance future breast reconstruction studies by providing an easy and objective method to quantify breast symmetry.

In Chapter 4, the predictive value of patient satisfaction and multiple breast symmetry scores for the wish of a secondary correction after a DIEP flap reconstruction was explored. Breast symmetry scores were determined using 1. a questionnaire for both the patient and the plastic surgeon, 2. distances between landmarks, and 3. the algorithm developed in Chapter 3. This study evaluated the different symmetry scores and enables the possibility to choose the most relevant measurement parameters for the upcoming RCT.

In Chapter 5, the future perspectives of the breast mold and the algorithm are stated. Most importantly, the relevant study parameters for the RCT are discussed.

Chapter 2. A clinical evaluation of the determined breast borders used for the breast mold

Introduction

A breast mold must accurately indicate the required breast flap for the Deep Inferior Epigastric Perforator (DIEP) flap reconstruction. Thus, a correct delineation method of the breast must be used to determine the breast mold borders. This delineation method has two requirements. First, the delineation must be reproducible among researchers, to avoid variance between patients' breast molds. Secondly, the breast mold must not over- or underestimate the required breast volume. Therefore, a validated breast delineation method is required to produce breast molds.

During the previous breast mold study, landmarks were used to determine the borders of the breast mold [17,20]. The used landmarks were the upper breast point (UBP), the sternal point (SP), the axillar point (AP), and the lower breast point (LBP). These landmarks can be seen in Figure 3 [20,21]. The upper breast point was determined using the second rib. The axillar point was determined using the front armpit. During the usability study, the breast mold was found to be oversized on both the axillar and cranial sides [17]. Therefore, a new method had to be found to accurately delineate the breast for the breast mold.

Different breast delineation methods of different studies were explored. Wesselius et al. delineated the breast to determine breast volume [22]. They used the midaxillary line to find the axillar point of the breast. Although they found the midaxillary line to be an adequate landmark, the midaxillary line is more dorsal than the axillar point used in the previous breast mold study [17,20]. Therefore, the axillar point of Wesselius et al. would contribute to an oversized breast mold [22]. Both Losken et al. and Eder et al. validated the three-dimensional (3D) imaging of the breast using volume determination [15,23]. They used the lateral point of the inframammary fold (IMF) to delineate the lateral side of the breast. Eder et al. found that the used landmarks were reproducible. Losken et al. found that their breast landmarks contributed to an accurate breast volume determination [15,23]. Lee et al. used the front armpit point and the side waist point to determine the lateral side of the breasts [19]. However, these points are less reliable for participants of higher age. Additionally, they proposed the folding line method to find the upper and medial breast points. This method can be seen in Figure 4. By pressing the bulk of the breast hard in the medial-cranial direction, a folding line appears where the breast is

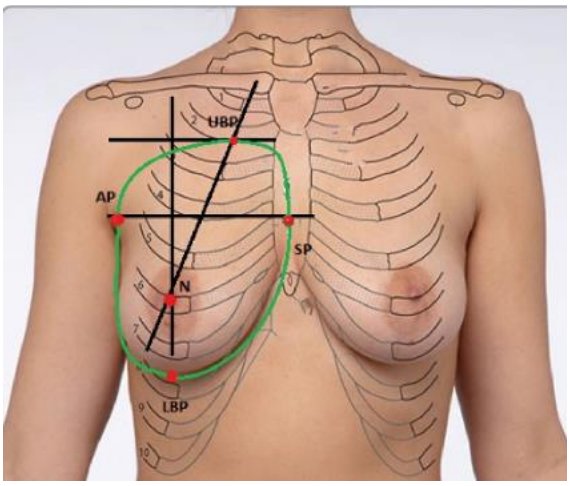

Figure 3. Landmarks used in previous studies to determine the borders of the breast mold. [19,20,21] UBP = Upper Breast Point; SP = Sternal Point; LBP = Lower Breast Point; AP = Axillar Point; N = Nipple.

Figure 4. The folding line method proposed by Lee et al. [19] Pressure is applied on the breast in the cranial direction to find the line where the breast is loosely connected to the epimysium of the pectoralis major muscle. In this figure, the folding line method is visualized using a breast phantom

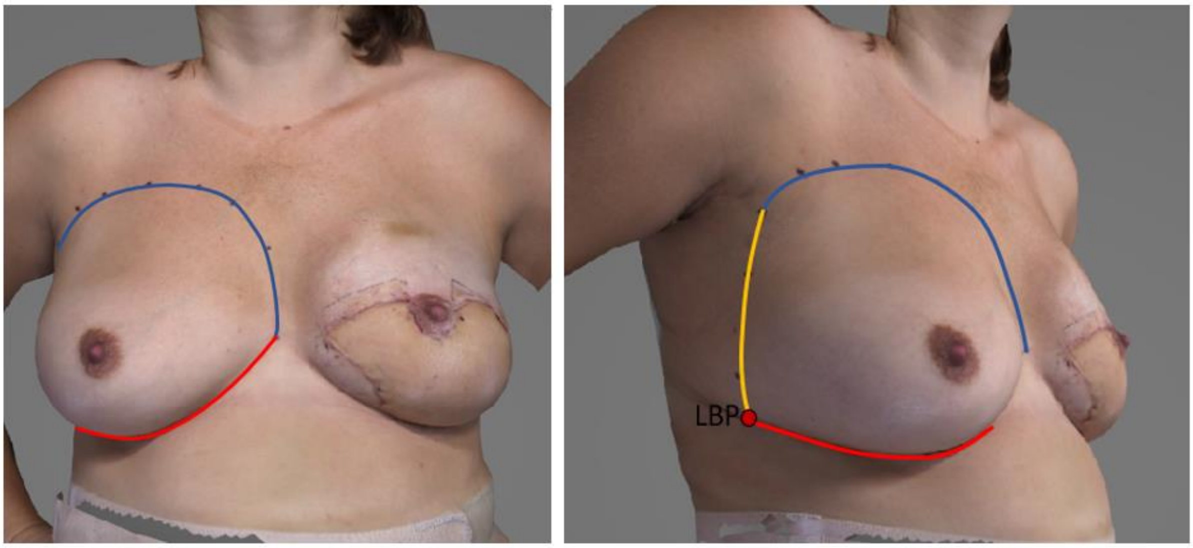

Figure 5. Breast delineation method proposed in this study. Red = Inframammary fold, Blue = breast border found using the folding line method, Yellow = lateral breast border that connects the lateral breast point (LBP) and the folding line method line

loosely connected to the epimysium of the pectoralis major muscle. They found this method to be reliable and reproducible to determine the breast border [19].

The proposed breast delineation is visualized in Figure 5. In summary, the lateral point of the IMF, used by Losken et al. and Eder et al., is chosen for the lateral border of the breast mold (yellow line in Figure 5) [15,23]. Additionally, the folding line method of Lee et al. will be used to find both the cranial and medial breast border (blue line in Figure 5) [19]. Lastly, the IMF is used for the caudal breast border (red line in Figure 5).

The goal of this study is to validate the borders of the breast mold, using these breast delineations (Figure 5). It is expected that the new-found landmarks accurately determine the borders of the breast and therefore accurately visualize the required flap volume and shape for the DIEP flap reconstruction. This study will evaluate the breast mold design, specific for the breast boundaries, using both the expert's opinion and quantified measurements.

Method

Participants

Patients with a planned or recent unilateral DIEP flap reconstruction without adjustment on the collateral breast or patients with a planned or recent unilateral DIEP flap reconstruction with a minor reconstruction on the collateral breast were asked to participate in this study. Minor reconstruction was described as breast reduction or breast lift. Other minor breast reconstructions were excluded from this study. The collaborating hospitals were Ziekenhuisgroep Twente (ZGT) Hengelo and Medisch Spectrum Twente (MST). The aimed number of participants was five. Informed consent was signed before the patient could participate in the study.

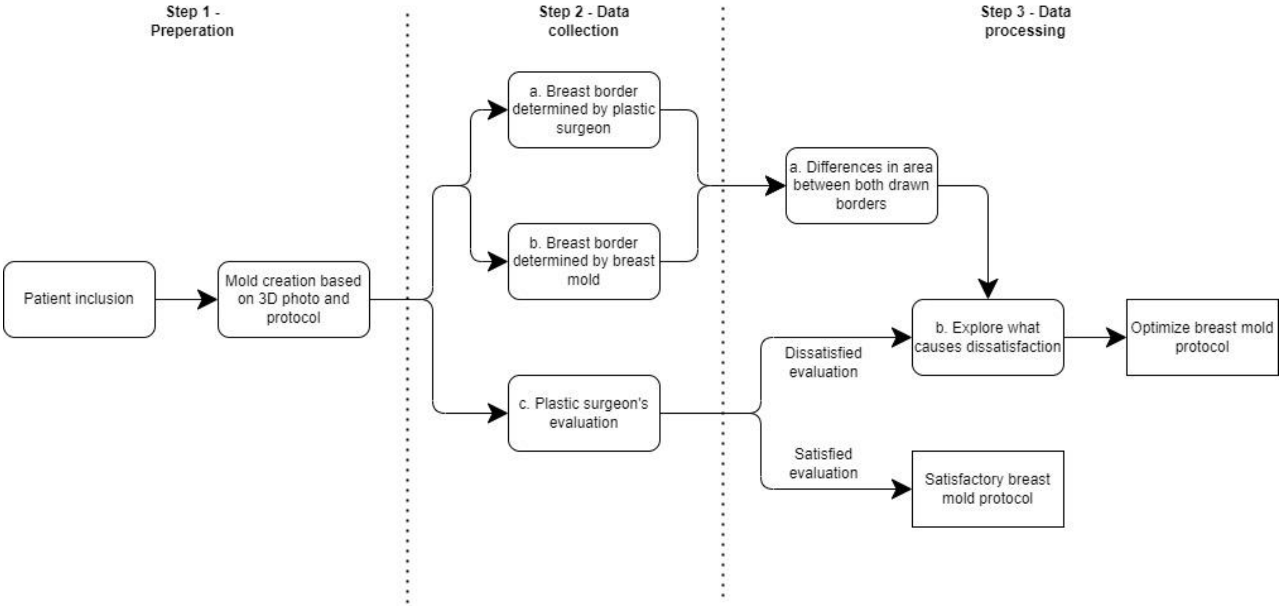

Figure 6. Workflow of the mold validation study, divided in three steps. Step 1 is the preparation of the study, including patient inclusion and creating the breast molds for the participants. Step 2 is the data collection, in which the participant's breast is delineated by a plastic surgeon (2a) and by using the breast mold (2b). Additionally, the plastic surgeon evaluates the breast mold using a questionnaire (2c). During step 3, the data processing, the differences between the two delineation methods is determined using a 3D photo (3a). The required optimization of the breast mold is then determined using the filled questionnaires and the differences found in delineated breast area (3b).

Study design

This study used a qualitative study approach to investigate the current mold design. Figure 6 gives an overview of the study design. The participants were seen two times. The first time, the breast contour of the contralateral breast was marked using the landmarks described in the Introduction. A 3D photo was then taken of the participant's chest using the Vectra XT (Canfield Sci, New Jersey, USA). A non-mirrored breast mold was then created according to the protocol found in **Error! Reference source not found.** (Figure 6, Step 1). The second time, the participant was seen by a plastic surgeon. The plastic surgeon was asked to delineate the participant's breast border that would be relevant for a DIEP flap reconstruction. (Figure 6, Step 2a) The breast mold was then taken and placed on the breast of the participant, using the landmarks on the breast mold for correct placement. The border of the mold was drawn on the patient using a dotted line (Figure 6, Step 2b). Additionally, the plastic surgeon was asked to fill in a questionnaire to evaluate the breast mold fit (Figure 6, Step 2c). The questionnaire can be seen in **Error! Reference source not found.**. A 3D image was taken of the double delineated breast. The differences between the two drawn borders were determined during the postprocessing of the 3D photo (Figure 6, Step 3a). If the plastic surgeon's breast mold evaluation is dissatisfied, the found differences will be used to further optimize the breast mold (Figure 6, Step 3b).

Methods of measurements

Border delineation

The 3D photo with the delineated borders was processed and analyzed using 3-Matic (Materialise, Leuven, Belgium). A curve was created on both drawn borders. The breast was separated from the rest of the body using the largest drawn border. The overall area of both breast delineations was determined using 3-Matic. The delineated breast was separated into four sections to determine which section, and therefore which landmark, had the highest difference in delineated area. Two parallel planes through the nipple were created in the yz-plane (frontal view). One plane was rotated +45 degrees around the z-axis, the second plane was rotated -45 degrees around the z-axis. The breast was

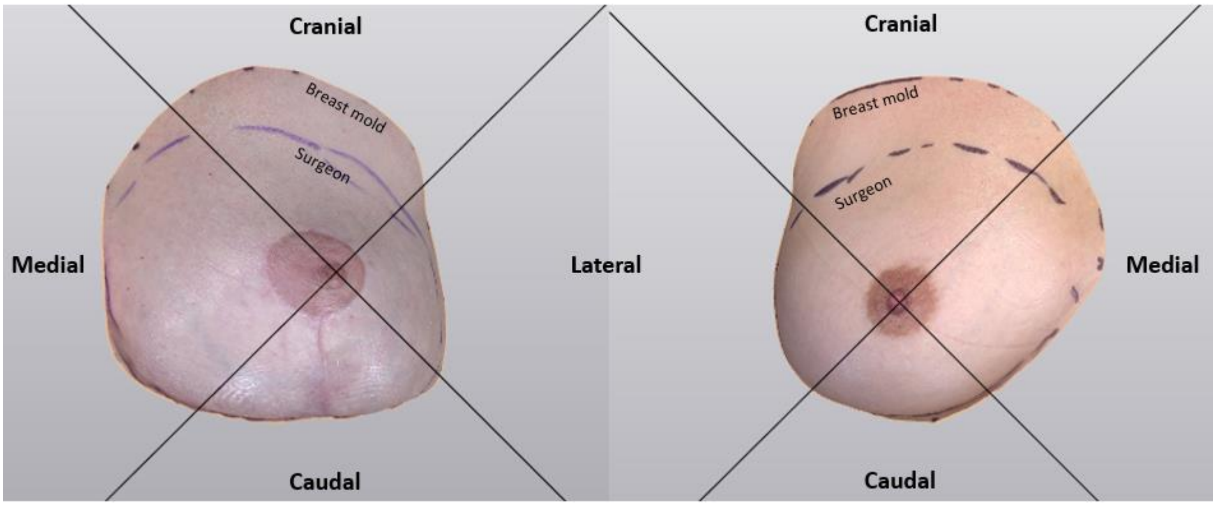

Figure 7. Delineated breasts used in the breast mold validation study. The planes that divide the breasts in a cranial, caudal, medial, and lateral section are shown. Left: Left breast of participant 1; Right. Right breast of participant 2

then cut using these planes, which resulted in a cranial, caudal, medial, and lateral section (Figure 7). For every section, the area was determined of both delineations.

Analysis
Both the filled questionnaires and the differences between the drawn borders were analyzed qualitatively.

Results
Participants
Two patients were included in this study. The first participant was from MST. She had a recent unilateral DIEP flap reconstruction with a breast lift at the collateral side at the moment of inclusion. Her cup size was C/D. The second participant was from ZGT. She had a recent unilateral DIEP flap reconstruction with no adjustments at the collateral side at the moment of inclusion. Her cup size was C.

Border delineation
The delineated breast of the plastic surgeon was for both participants smaller than the delineated breast of the breast mold. The differences in area between the plastic surgeon and the breast mold can be seen in Table 1. In both cases, the caudal side of the breast was most similar between the plastic surgeon and the breast mold. The cranial side had in both cases the largest difference.

The questionnaire was filled in by one plastic surgeon for both participants. In both cases, the plastic surgeon totally agreed with the borders of the breast mold. This can be seen in Table 2. According to the plastic surgeon, the mold estimated a correct volume for the breast flap and the positioning of the mold was clear in both cases. Lastly, the plastic surgeon noted that the breast mold estimated the breast border almost more accurately than the drawn border of the plastic surgeon himself.

Discussion
This study evaluated the mold design, focusing on breast delineation. Differences in breast delineation were found between the breast mold and the plastic surgeon. However, the plastic surgeon was satisfied with the breast mold size. Important to note is the small sample size (n=2), which impedes absolute conclusions.

Table 1. Differences in breast area found between the delineation of the breast mold and the plastic surgeon. The percentage indicates the percentage that the breast mold area is larger than the plastic surgeon's delineated breast area

	Overall area difference		Lateral area difference		Medial area difference		Caudal area difference		Cranial area difference	
	mm^2	%	mm^2	%	mm^2	%	mm^2	%	mm^2	%
Participant 1	6098	23,1	1459	31,5	739	7,5	149	2,0	3750	87,8
Participant 2	9496	30,1	387	4,3	2199	29,2	162	2,3	6747	85,0

Table 2. Results of the breast mold evaluation questionnaire filled by the plastic surgeon. ++ indicates a total agreement of the delineated border for the breast mold

Questionnaire					
	Estimation of the required flap volume	Lateral border fit	Medial border fit	Caudal border fit	Cranial border fit
Participant 1	Correct	++	++	++	++
Participant 2	Correct	++	++	++	++

Interpretation of results

Differences in area are found between the plastic surgeon's delineation and the delineation of the breast mold. These differences are mostly caused by the delineation on the cranial side of the breast, the upper breast point. In both cases, the difference in upper breast boundary causes more than 60% of the total area difference. Furthermore, the difference in medial surface area between both participants is notable. The difference in the medial area between the breast mold and the plastic surgeon is smaller for the first participant than for the second participant. The first participant had a larger IMF, that continued at the medial side of the breast. Both the surgeon and the breast mold followed the IMF. The second participant had a smaller IMF that did not continue at the medial side. Therefore, larger variances were found for the delineation at the medial side between the plastic surgeon and the breast mold for the second participant. On the other hand, the second participant had a smaller area difference at the lateral side between the plastic surgeon and the mold than the first participant. For both participants, the IMF continues dorsally on the lateral side of the breast. Since it was established that the mold must not continue too far dorsal, a point on the lateral side of the IMF had to be chosen for the lateral breast border. This lateral point differed between breast mold and plastic surgeon.

Important to mention is that the plastic surgeon did not have a specific method to delineate the breast. Additionally, this is the first time he had to delineate the breast for this reason. He delineated the area of the breast that he thought was relevant for a DIEP flap reconstruction, based on his experience. However, the questionnaires stated that the plastic surgeon totally agrees with the delineation of the breast mold. Additionally, the comment for the first participant was that the delineation of the breast mold was almost more accurate than the delineation of himself. Therefore, it is difficult to determine if the delineation of the breast mold is excessive, or if the plastic surgeon underestimated the delineation.

Comparison with previous literature

The breast mold delineations included in both cases more breast tissue than the delineations of the plastic surgeon. The largest area differences were found at the cranial side of the breast. Therefore, the used landmarks for delineation must be critically evaluated. Wesselius et al. uses the second rib as the upper breast point [22]. Alternatively, Kovacs et al. and Liu et al. use a point 1 cm caudal of the clavicula as cranial breast point [24,25]. Tepper et al. defines the upper breast point as the point at which the breast takes off from the chest wall [26]. However, this is difficult to determine since there are no objective landmarks that indicate this point. Furthermore, all these methods find an upper breast point superior to the landmark found with the folding line method used for the breast mold. No literature is found that uses a lower, reproducible landmark for the upper breast boundary.

Furthermore, the delineations of the breast mold would indicate a slightly larger volume than the delineations of the plastic surgeon. However, Tomita et al. state that the reconstructed breast reduces 5-10% in volume as swelling disappears [13]. The slightly larger breast volume of the breast mold could improve the postoperative results.

Limitations

Most importantly, a limitation of this study was the small number of participants. A larger number of participants would give a more trustworthy validation. Furthermore, there is no method to determine which delineation is more correct. The delineation of the breast is not a standard procedure for a plastic surgeon. Thus, the plastic surgeon's delineation cannot be seen as gold standard. If a similar study would be conducted in the future, it is advised to ask the plastic surgeon to delineate the breast area of a patient repeatedly over several days. Those results could give more insight into the consistency of the delineation method of the plastic surgeon. Additionally, only one plastic surgeon evaluated the breast mold delineation for both participants. It is a possibility that this plastic surgeon was more positive about the breast mold than the average plastic surgeon. Therefore, the findings of this study could be biased.

Although differences in area were found between the delineation of the plastic surgeon and the breast mold, it is unknown what difference it makes for the breast volume. Visually, it appears that the difference in the found upper breast point does not significantly change the total delineated breast volume. Ideally, a breast mold delineation validation would be done by comparing the delineated breast volume of both the breast mold and the plastic surgeon. However, breast volume determination is challenging and sensitive to errors and therefore not preferred.

Clinical relevance

This study found a mismatch in breast delineation between the breast mold and the plastic surgeon. However, the plastic surgeon was satisfied with the breast mold delineations. The best breast delineation is difficult to determine because of the unavailability of a gold standard. Based on the limited results found in this study, no alteration of the breast mold is suggested, since no additional landmarks were found to improve the delineation. Furthermore, the folding line method is easy to learn. Therefore, this method seems adequate to be used by plastic surgeons and other medical staff to delineate the breast in future breast mold studies. However, it is advised to continue this validation study and to include more plastic surgeons for a more thorough evaluation.

Conclusion

This study has shown that the breast molds of the two participants were rated as an accurate representation of the breast border according to the questionnaire filled in by the plastic surgeon. However, overall differences in delineated areas between the plastic surgeon and the breast mold were between 23-30%. Although there is still a discrepancy between the breast mold borders and the breast borders drawn by plastic surgeons, the overall score of the questionnaires was positive. Furthermore, no sufficient alternative landmarks were found to optimize the breast mold delineation. Therefore, the limited results of this study imply that the use of the current breast mold design is adequate for further breast mold studies.

Chapter 3. Developing an algorithm to objectively evaluate breast symmetry based on three-dimensional images

Introduction

Breast symmetry is a valued measurement to evaluate breast reconstruction results [27,28]. Satisfactory aesthetic outcomes after breast reconstruction have a positive effect on the psychological recovery of the patient [5,29,30]. For example, significant correlations were found between the patient's self-esteem and the aesthetic outcome after a Deep Inferior Epigastric Perforator (DIEP) flap reconstruction [30]. Additionally, the patient's symmetry satisfaction after a DIEP flap reconstruction is significantly related to overall patient satisfaction [31]. However, breast symmetry evaluations are often based on subjective measurements for both the patient and the plastic surgeon [29].

A subjective measurement for breast symmetry impedes breast reconstruction research, i.e. breast mold research. A standardized and objective measurement of aesthetic outcome would enable the comparison of breast reconstruction outcomes for clinical and research purposes [29]. Furthermore, a mismatch is seen between the subjective patient's and plastic surgeon's symmetry scoring. The plastic surgeon tends to score the aesthetic breast outcome after breast reconstruction higher than patients [30]. This mismatch may cause incomprehension between the patient and the attending physician. Over the last few years, multiple attempts were done to develop an objective measurement tool for aesthetic evaluation.

Examples of objective breast symmetry measurement tools are breast ptosis computation based on three-dimensional stereophotogrammetry images (from now on referred to as 3D images) and breast anthropometric measurements based on landmarks [15,21,32]. Li et al. examined breast curvature and face normal directions to categorize the breast ptosis level. They found a high correlation between the objective ptosis categorization and the surgeons' assessment [32]. Mikolajczyk et al. developed a reliable tool using digital landmarks to determine breast measurements with a near-perfect precision compared to direct measurements [21]. Eder et al. developed a tool to superimpose the mirrored left breast over the right breast and to objectively determine the mean 3D contour difference between the two breasts. Their method was found to be more precise than already excising symmetry evaluation tools [15,33]. However, these tools use the nipple as a necessary landmark. DIEP flap reconstruction patients, both pre- and postoperatively, often had their nipples removed during mastectomy. Therefore, a robust symmetry scoring method must be found that does not require the nipple for analysis.

There are already objective breast symmetry evaluation tools that do not use the nipple as landmark. They determine breast areas [34] and anatomic curves [35], or visualize curvatures [36] and a deviation map [37]. Fitzal et al. developed a tool that determines the size and circumference of both breasts in frontal and lateral view and subtracts these from each other [34]. This method could significantly differentiate between good and bad aesthetic outcomes. However, this tool is based on two-dimensional images, while shape analysis on 3D models is more reliable [38]. Bowman et al. use a combination of local curvature, smoothing splines, and principal component analysis to identify the boundary of the breast using 3D images. This method gives a quantified and fully automatic shape analysis of the breasts [35]. Catanuto et al. explored multiple objective outcome variables and found that curvature provides an easy-to-understand visualization of the breast shape [36]. Losken et al. superimposed the right breast onto the left breast and calculated the distances between the two surfaces. The degree of asymmetry was then quantified using the root mean square [37]. All studies named above perform a type of objective shape analysis of the breasts. A visual example of these four

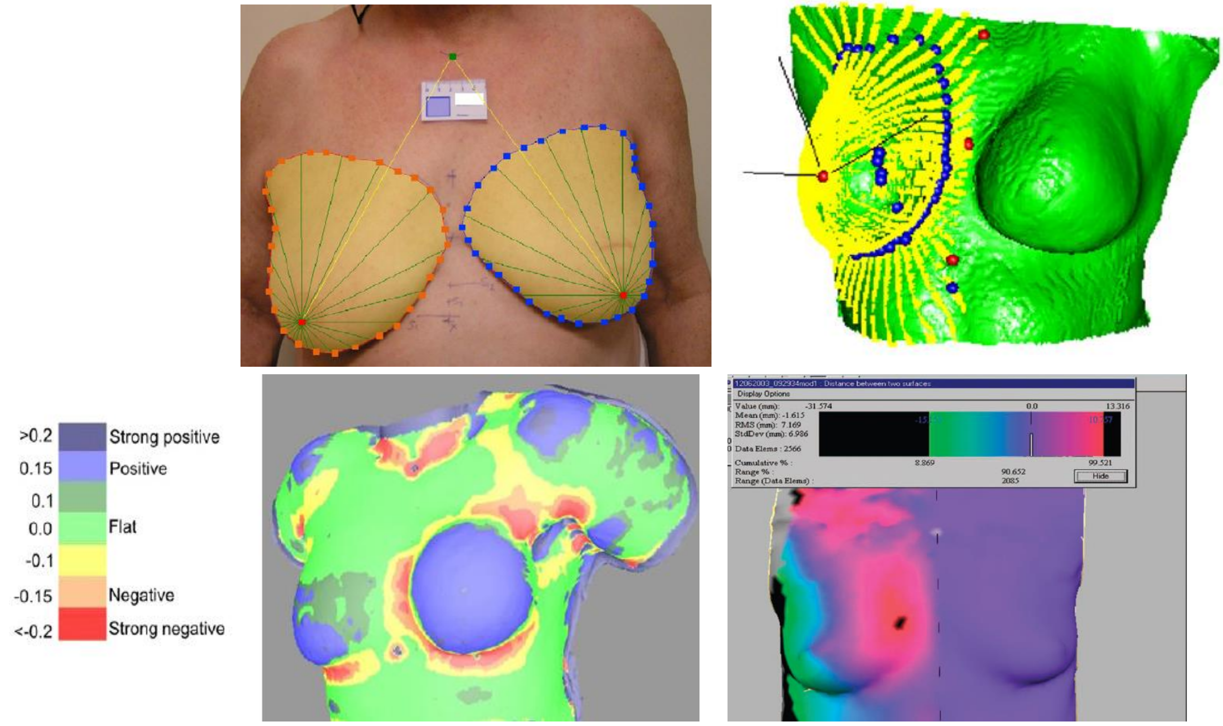

Figure 8. Overview of four different breast shape analysis methods. Top left shows the breast area determination by Fitzal et al. [34] Top right shows the use of breast curvature for breast segmentation by Bowman et al. [35]. Lower left shows the visualization of breast asymmetry using curvature by Catanuto et al. [36]. Lower right shows a deviation map to determine breast asymmetry by Losken et al. [37]

studies can be seen in Figure 8. However, all these methods did not convert their objective breast shape analysis to an easy-to-understand symmetry score.

In this study, a new modular algorithm will be developed that combines different breast shape analysis methods to improve the accuracy of the analysis. Additionally, the output of this algorithm will be a score between zero and ten, with zero being no symmetry and ten being perfect symmetry. Based on the previous studies, curvature calculations were done for the first method, since this is an often-used method to describe breast shape [32,36,39]. The second method used face normal directions combined with principal component analysis based on Li et al. and Catanuto et al [32,40]. These studies showed that the face normal directions can be used to distinguish different breast shapes [32,40]. Lastly, a third method was added that superimposed the breasts onto each other. The distances between the two breasts were determined and the root mean square was calculated [37].

The goal of this study was to create an algorithm that objectively and quantitively scores the overall breast symmetry score. The algorithm was developed and validated using 3D images. It is expected that a combination of the three different methods will objectively score breast symmetry with a high correlation to the surgeon’s symmetry score.

Method

An overview of the study design can be seen in Figure 9. The first step was to collect both the development dataset and the validation set (Figure 9, steps 1a and 1b). Additionally, both datasets had to be scored by plastic surgeons (Figure 9, steps 1c and 1d). The first step of the development was to develop the first module of the algorithm (Figure 9, step 2a). The symmetry score found with this module was then correlated to the symmetry score given by the plastic surgeon (Figure 9, step 2b). If

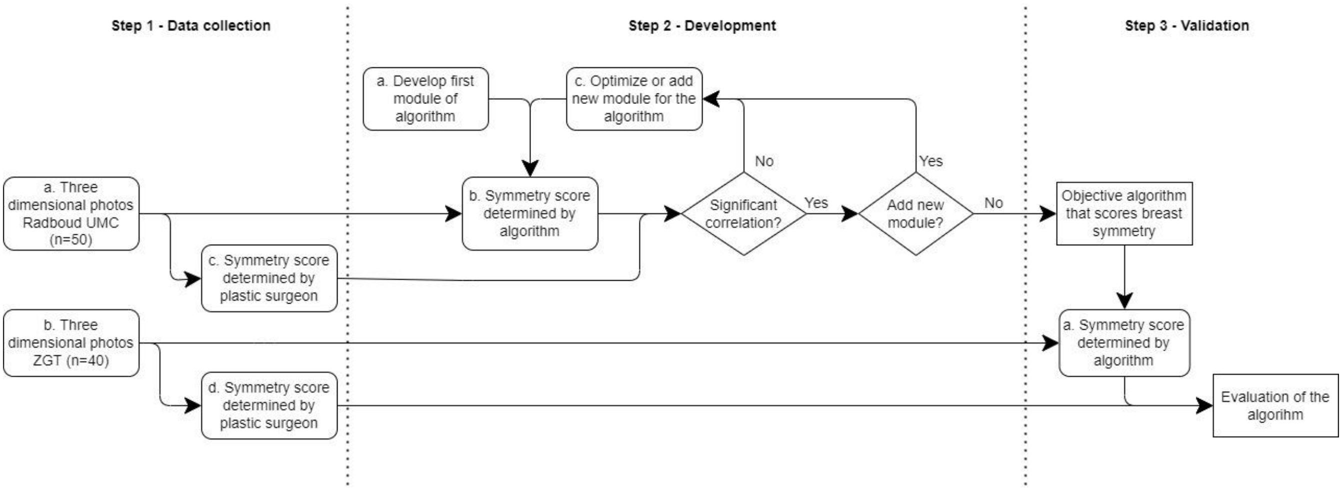

Figure 9. Overview of the algorithm development and validation steps of this study. During the first step, the development and validation databases were collected (step 1a and b). These databases where then scored by different plastic surgeons on breast symmetry (step 1 c and d). Step 2 was the development of the algorithm, in which the first module was build (step 2a), the symmetry score correlation between the plastic surgeon and the module was determined (step 2b), and the module was optimized, or a new module was created (step 2c). In step 3, the symmetry score correlation between the final algorithm and the symmetry scores of the validation database was determined.

the correlation was not significant, the module was optimized. (Figure 9, step 2c). Otherwise, it was determined if another module had to be added to the algorithm. When no other module was added, the final algorithm determined the symmetry scores of the validation dataset (Figure 9, step 3a). The algorithm was then evaluated by comparing the found symmetry scores with the symmetry scores of the plastic surgeon.

Data collection

This study used a total of two databases, the development, and the validation database. The development database was used during the development of the algorithm. Fifty 3D images of patients with a planned DIEP flap reconstruction or after the DIEP flap reconstruction were included from Radboud Universitair Medisch Centrum (Radboudumc). The validation database was used for the validation of

the algorithm. 36 3D images of seventeen patients with a planned or previous DIEP flap reconstruction were included from Ziekenhuisgroep Twente (ZGT) and Medisch Spectrum Twente (MST). The validation database consists out of pre-operatively 3D images and one to four months postoperatively 3D images. The exclusion criteria for both databases was the absence of one or two breasts at the moment the 3D photo was taken. Therefore, seven 3D images were excluded from the development database. Written informed consent was available from all participants. All 3D images were taken with a Canfield Vectra XT system (Canfield Sci, New Jersey, USA) with the patient's arms at a 45-degree angle from the body. A summary of the two databases can be seen in Table 3.

Gold standard

Three plastic surgeons from Radboudumc scored the 3D images of the development database on breast symmetry from one to ten. The visualization of the 3D images can be seen in **Error! Reference source not found.**. The mean symmetry score per 3D image was used as gold standard. Both the absolute and the consistency method of the two-way random interclass correlation coefficient (ICC) were determined to examine the interobserver variability between the three expert scores.

Table 3. Summary of the participants in both the development and validation dataset. The participants of the development dataset are from Radboud Universitair Medical Centrum. The participants of the validation dataset are from Ziekenhuisgroep Twente and Medisch Spectrum Twente

		Development data	Validation data
Number of participants		42	17
Number of 3D images		50	36
	Excluded	0	7
	Pre-operative	7	10
	Postoperative (< two months)	19	12
	Postoperative (> two month)	24	7
Number of breasts		100	65
	Natural breast	29	27
	Augmented breast	63	33
	Tissue expander	8	5

Development of the algorithm

A detailed overview of the final algorithm steps can be seen in **Error! Reference source not found.**. Three methods to quantify the breast symmetry were developed to be included in the algorithm using Matlab 2021a (The MathWorks, Inc., Natick, Massachusetts, USA). However, the 3D images had to be prepared for analysis first.

Preparation

Each 3D image is stored as a stereolithography-file (STL-file) consisting of a mesh with vertices and faces in the 3D space. The first step was to equally distribute the vertices for all meshes. This was done manually using the relative remesh function of Meshmixer (Autodesk Inc., San Rafael, USA). Further steps were done in Matlab. The STL-file in which the 3D image was stored was imported with the function 'stlread' [41]. The mesh was compressed, which means that every vertices with a second identical vertices was removed from the mesh. Additionally, the mean curvature (H) was determined to improve the upcoming manual landmark selection. An explanation for the chosen curvature can be found in **Error! Reference source not found.**. The mean curvature is the mean of the two principal curvatures (*k1* and *k2*), as can be seen in Equation 1. The principal curvatures are the maximum and minimum bending at a given point on a surface and are perpendicular to each other. They are calculated with the eigenvalues and the eigenvectors of the hessian matrix, as described by Soeud et al [39]. Furthermore, the function 'patchcurvature' by DJ Kroon was used for curvature calculations in Matlab [42].

$$H = \frac{k_1 + k_2}{2} \qquad Equation\ 1$$

The mesh of the 3D image with the corresponding mean curvature was then visualized in the xz-plane as can be seen in Figure 10. The user was asked to select the anterior point on each shoulder. The angle between these two points relative to the x-axis was determined and the mesh was rotated around the y-axis using the found angle. This corrects for any skewness of the patient around the y-axis.

The next step was to remove irrelevant mesh using manually selected landmarks. The original mesh and the mesh with curvature were shown for optimal visualization (see Figure 11). The manually selected landmarks are: right lower breast points (1); left lower breast point (2); right medial breast point (3); left medial breast point (4); right lateral breast point (5); left lateral breast point (6); jugular notch (7); right axillar point (8); left axillar point (9). Landmarks 8 and 9 are selected using a lateral view of the patient. The mesh is then cropped using these landmarks. The inferior border is determined using the lowest y-value of landmarks 1 and 2. All vertices with a lower y-value were removed from the mesh. The posterior border is determined using the lowest z-value of the axillary points. All vertices with a lower z-value were removed. The next step was to determine the midline between the breasts. This was done using stepwise decisions. First, the midpoint between the two x-values of the axillary points was determined. If this midpoint was between the x-values of the medial breast points, this x-value was chosen for the midline. If this was not the case, the x-value of the jugular notch landmark was evaluated. If this value was between the two medial breast points, this x-value was chosen for the midline. If this was not the case, the midline was determined using the midpoint between the two x-values of the medial breast points. The mesh was then separated into a left and right mesh using the midline. Next, a sloping line was drawn for each side between the axillary point and the jugular notch.

All vertices superior to these lines were removed. Lastly, all vertices lateral to the two lateral breast

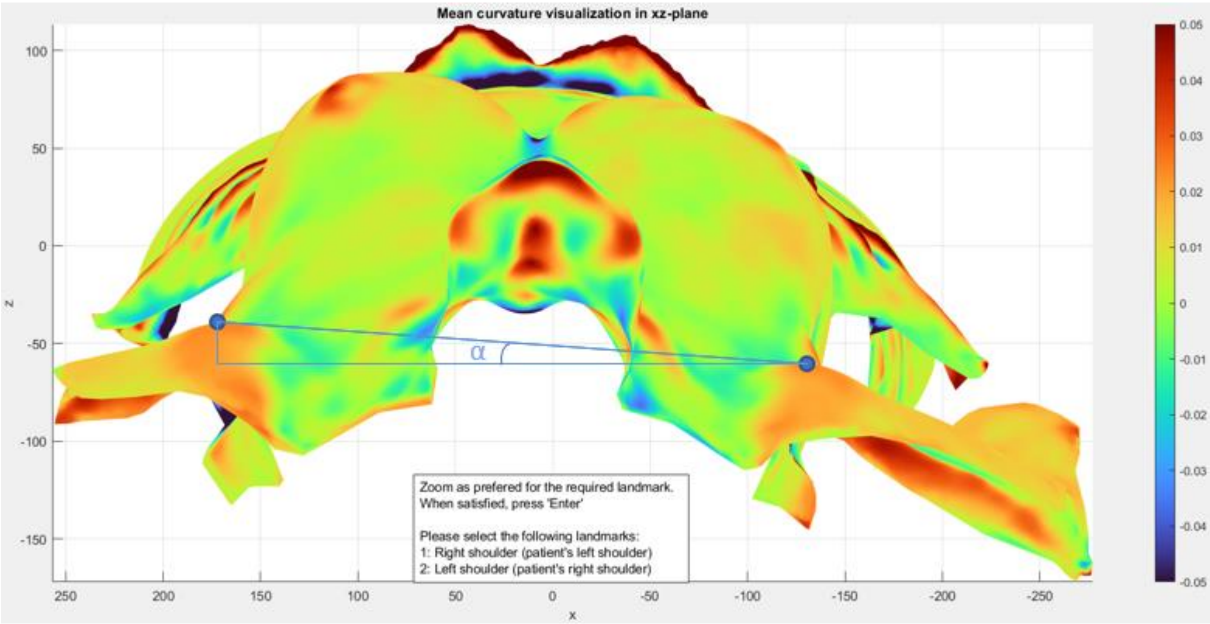

Figure 10. Visualization of the mean curvature on the patient's mesh in the xz-plane. Selected shoulder landmarks (blue dots) were used to determine the angle α of skewness of the patient around the y-axis. The color bar indicates the mean curvature

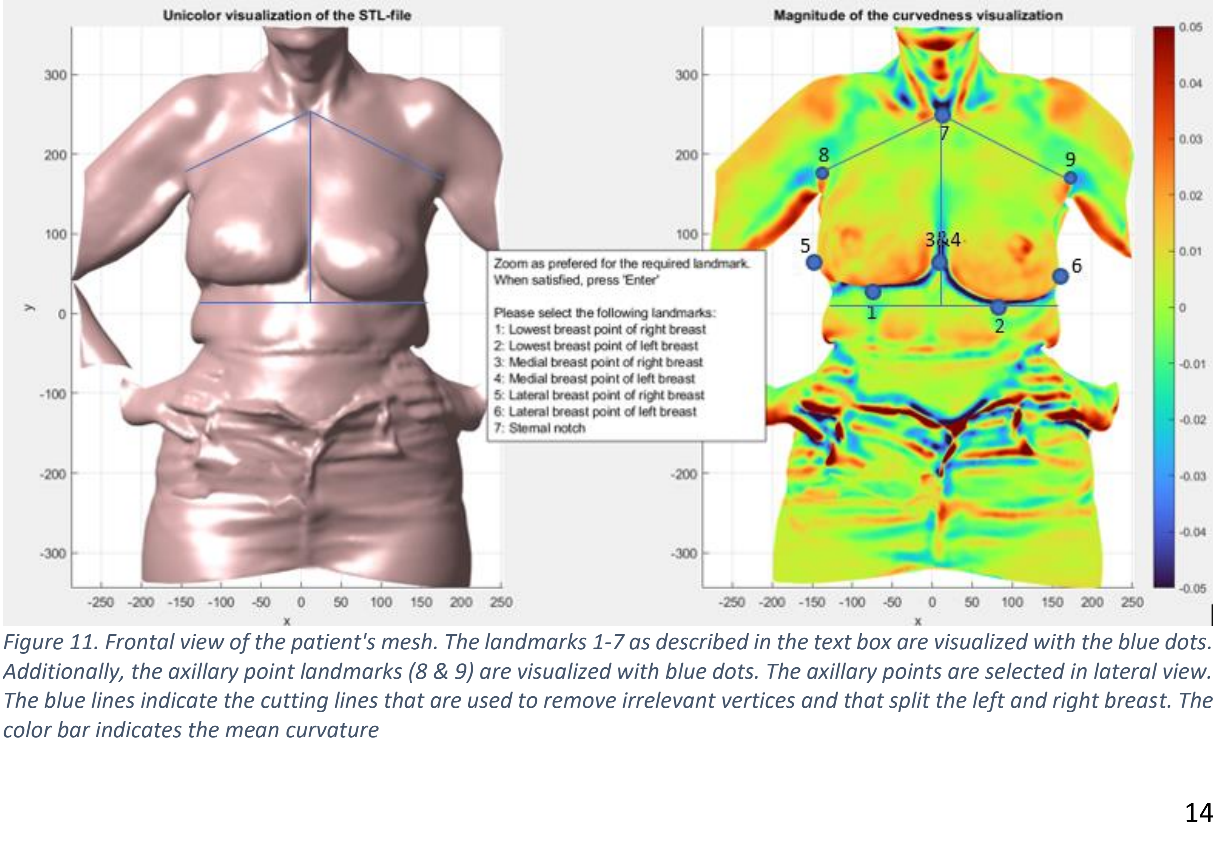

Figure 11. Frontal view of the patient's mesh. The landmarks 1-7 as described in the text box are visualized with the blue dots. Additionally, the axillary point landmarks (8 & 9) are visualized with blue dots. The axillary points are selected in lateral view. The blue lines indicate the cutting lines that are used to remove irrelevant vertices and that split the left and right breast. The color bar indicates the mean curvature

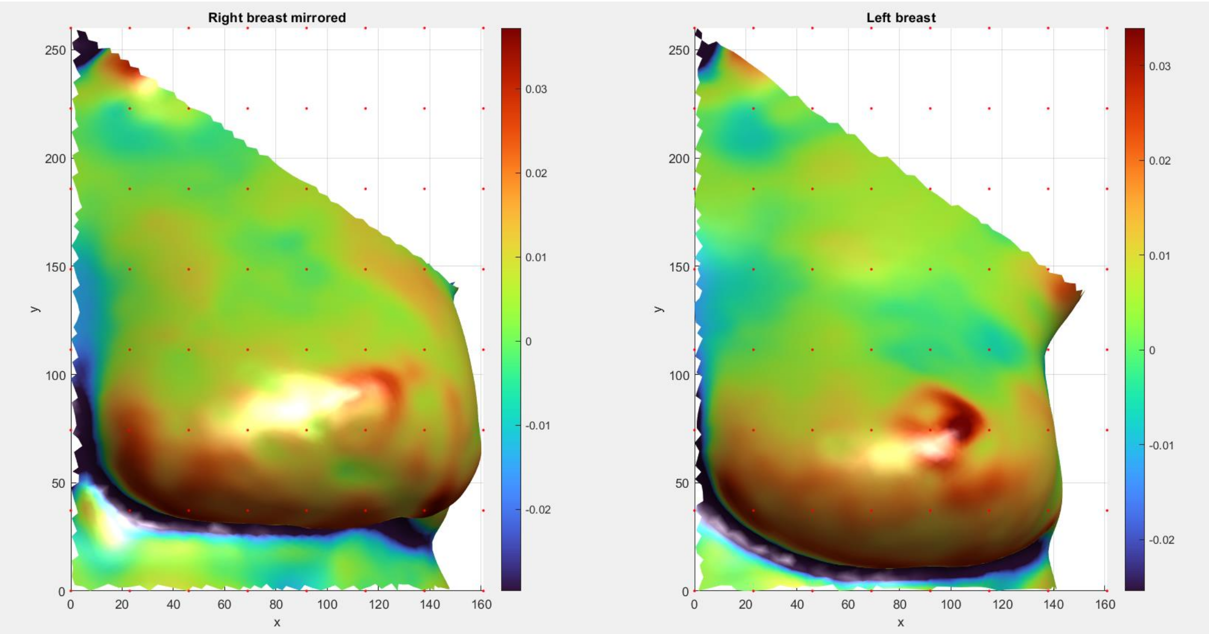

Figure 12. A visualization of both segmented breasts using the mean curvature. A 7x7 grid is shown

points were removed to remove remainders of the arms. This results in two cropped meshes of respectively the right and left breast. The delineated cropped meshes are visualized in Figure 11. The cropped meshes were shown and confirmation was requested from the user to confirm a correct segmentation of the breasts.

The last step in the preparation was the mirroring of the right breast around the y-axis and translation of both breasts to the origin. The translation was done based on the coordinates of the lower-left vertices of both meshes.

Method 1 – Curvature

The first shape analysis method uses the mean curvature (from here on referred to as 'curvature') to quantify the breast shape. The curvature was already determined using Equation 1 during preparation. The next step was to convert the curvature to a value that can be used for a quantified symmetry score. The mean of the curvature was determined for both breasts. A ratio between the left and right mean curvature was determined by dividing the smallest curvature by the largest curvature. However, the mean of the curvature of the total breast would be too general for breast analysis. Therefore, a grid was created to determine the ratio between smaller areas of the left and right breast. The corners of the grid were determined using the origin, the highest y-value of the cropped meshes, and the highest x-value of the cropped meshes. A visualization of this grid can be seen in Figure 12. However, it was unknown which grid size would be optimal to find a symmetry score. Therefore, the mean curvature ratios were determined for different grid sizes varying between 1x1 to 10x10. If a grid area had no curvature for one or both sides, that grid area was excluded.

Additionally, the cases in which the grid square of one side had a positive curvature and the other side had a negative curvature had to be processed. The ratio between such cases is negative, which would strongly affect the symmetry score. If the negative and positive curvature are both almost a flat surface due to small curvature values, the absolute ratio was used. This was only done if the difference between the two curvatures were smaller than a threshold. Based on visual inspection, a threshold of 0.0075 mm^{-1} was chosen (**Error! Reference source not found.**). Additionally, thresholds of 0.006, 0.009, and 0.01 mm^{-1} were also used to verify that a threshold of 0.0075 mm^{-1} was correct. If the difference between curvatures was greater than the threshold, the ratio would be set to 0 or would be excluded from the symmetry score determination.

Method 2 – Face orientation

The second method uses principal component analysis (PCA) with the orientation of every face normal. Therefore, the face normal direction must be determined. First, the orientation and position of every mesh had to be similar. Therefore, the centroid of both meshes was determined by finding the mean vertices coordinate. The meshes were then translated such that the centroid was positioned in the origin. Additionally, the normalized normal ($n_{normalized}$) of every face was determined using Equations 2 and 3, using the three vertices (v) of every face to determine the normal vector (n).

$$n = (v_0 - v_1) \times (v_0 - v_2) \qquad Equation\ 2$$

$$n_{normalized} = \frac{n}{|n|} \qquad Equation\ 3$$

The mean of all face normals was taken to find the normal of the centroid. The angle between the mean face normal and the x-axis ϕ and the angle between the mean face normal and the z-axis θ were determined using Equations 4 and 5. X-, y-, and $z_{normalized}$ are the x-, y-, and z-coordinates of the mean face normal.

$$\phi = arctan\left(\frac{y_{normalized}}{x_{normalized}}\right) if\ y > 0$$

$$\phi = arctan\left(\frac{y_{normalized}}{x_{normalized}}\right) + \pi\ if\ y < 0 \qquad Equation\ 4$$

$$\phi = \frac{1}{2}\pi\ if\ y = 0$$

$$\theta = arccos(z_{normalized}) \qquad Equation\ 5$$

The rotation matrixes around the z- and y-axis (R_z and R_y) were determined and applied to both the vertices and the found face normal.

$$R_z = \begin{bmatrix} cos\theta & -sin\theta & 0 \\ sin\theta & cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

$$R_y = \begin{bmatrix} cos\theta & 0 & sin\theta \\ 0 & 1 & 0 \\ -sin\theta & 0 & cos\theta \end{bmatrix}$$

After all meshes were correctly transformed, the orientation of the face normals was clustered in 64 groups. These groups were based on four orientation ranges (-1:-0.5, -0.5:0, 0:0.5, 0.5:1) along the x-, y-, and z-axis. This led to 64 values per mesh to describe the breast orientation. PCA was performed to reduce this 64-dimensional data to two-dimensional (2D) data [43]. PCA computes a 64x64 correlation matrix with their corresponding eigenvalues and eigenvectors. The largest eigenvalues indicate the principal components. The correlation matrixes of the first two principal components were used to transform the 64-dimensional datapoints to 2D coordinates. This was done for every individual breast in the development database, which gave one hundred 2D data points. The distance between the coordinates of the two breasts of one patient in the PCA-plot were determined to find a correlation with the gold standard. Additionally, the position of the two breasts coordinates in the PCA-plot was evaluated.

Method 3 – Point distance

For the third method, the distances between the coordinates of the left and right breasts are examined. First, the mirrored right breasts had to be translated such that both meshes have the optimal overlay. Since it was unknown what the optimal method was for the translation, three methods were performed parallel. The outcomes of the three methods were evaluated and the method with the highest correlation to the gold standard was chosen. The three methods were:

1. No translation, since the left lower corner of both meshes are already translated to the origin (ICP_0)
2. Iterative Closest Point algorithm based on the cropped mesh of both breasts for optimal overlay (ICP_with_breasts)
3. Iterative Closest Point algorithm for which the breasts are not taken into account during the determination of the transformation matrix (ICP_without_breasts)

The iterative Closest Point (ICP) algorithm was used for the second and third method [44]. The ICP algorithm translates and rotates the vertices of a mesh over the fixed mesh to find the best fitting overlay. When this best-fitting overlay is found, a transformation matrix is returned. For method 2, the transformation matrix is determined based on the cropped mesh as can be seen in Figure 12. However, the mesh could be transformed to a non-anatomically correct position, especially for patients with high breast asymmetry. Method 3 compensates for this by removing the breasts before the transformation matrix is determined. This method was preferred since it was expected that this would contribute to a more robust algorithm. The removal of the breasts is done by manual selection of 1&2) the upper breast point for both breasts, 3) the most superior point on the mesh just below the chin, and 4) the most inferior point on the mesh just above the bellybutton or the clothes. Together with the selected landmarks of the preparation, the original mesh is cropped using the most inferior point for the inferior border, the most superior point for the superior border, the lateral breast points for the lateral borders, and the found midline to separate the two breasts. The mesh of the right breast was then mirrored around the y-axis. Additionally, the mesh between the lowest breast points and the

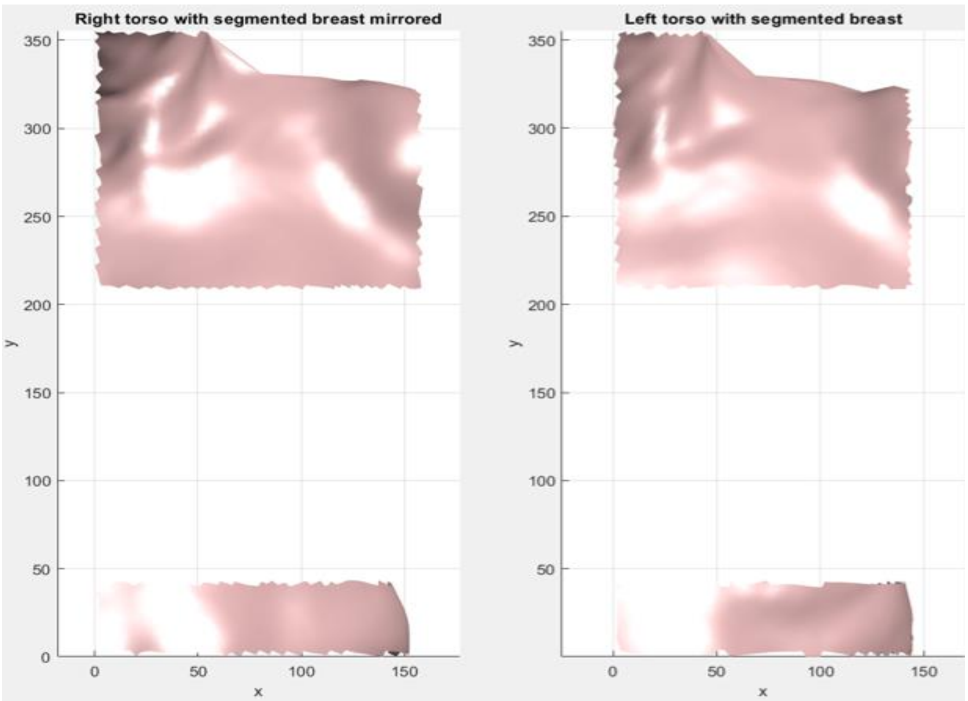

Figure 13. Left and right (mirrored) torso of the patient with segmented breasts used to find the transformation matrix with the Iterative Closest Point algorithm

upper breast points was removed. This resulted in a mesh as can be seen in Figure 13. The optimal transformation matrix was then found for these meshes and applied to the original cropped meshes as can be seen in Figure 12. All transformation matrixes were used to rigidly transform the mirrored right breast.

Both the Hausdorff Distance (HD) and the Root Mean Square (RMS) of all distances between the points of the two meshes were determined. The smallest distance between every vertices of both breasts was determined and stored. The Hausdorff Distance is the maximal value of all these found distances. For the RMS, all found distances were squared and the square root of the mean value was determined. A deviation map based on the found smallest distances was created for visualization.

The final algorithm

An overview of the final algorithm with the preparation and the three described methods can be found in **Error! Reference source not found.**. The output of the methods described above was examined for normal distribution. If necessary, the data was transformed for normal distribution. The correlation coefficient between the different outputs and the gold standard was found using Pearson's rho or Spearman's rho. The best methods were chosen based on their correlation coefficients. Multiple linear regression was then used to combine the different methods to predict the symmetry score. The forward building method was executed to improve the linear regression model stepwise. When the final algorithm was made, the total duration of the algorithm, from loading one 3D image to computing the symmetry score, and the duration of the individual modules were measured.

Validation of the algorithm

The 3D images of the validation database were scored with a score from one to ten by an independent plastic surgeon from MST/ZGT. The visualization of these 3D images was similar to the development database and can be seen in **Error! Reference source not found.**. The 3D images of the validation database were given to the final algorithm. The algorithm determined the symmetry score for every 3D image. The correlation between the plastic surgeon's symmetry score and the algorithm symmetry score was evaluated using the two-way mixed ICC. Additionally, the development database was given to the algorithm three times to determine the reproducibility of the algorithm. The absolute and consistency random model ICC was determined.

Results

Interobserver analysis development dataset

The mean given score per plastic surgeon was respectively 8.1, 5.2, and 5.9. The maximal difference in symmetry score between two observers for individual cases is 5. Observer 1 scored the 3D images in the range of 5 to 10, while observer 2 and observer 3 scored the 3D images in the range of respectively

Table 4. An overview of the relevant Pearson's correlation coefficients between the different modules (curvature, face orientation, and point distance) of the algorithm and the gold standard (breast symmetry scores of the development database from plastic surgeons). The different subsections are mentioned in the abbreviations.

		M1 - Curvature	M2 – Face orientation	M3 – Point distance					
		1	1	1	2	3	4	5	6
Gold standard	Pearson Correlation ρ	0.781	-0.693	-0.663	-0.636	-0.696	-0.641	-0.824	-0.805
	Sig.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Abbreviations: M1.1 = Grid_7_threshold_0.0075; M2.1 = LN(PCA_distance); M3.1 = HD_ICP_0; M3.2 = HD_ICP_with_breasts; M3.3 = HD_ICP_without_breasts; M3.4 = LN(RMS_ICP_0); M3.5 = RMS_ICP_with_breasts; M3.6 = RMS_ICP_without_breasts

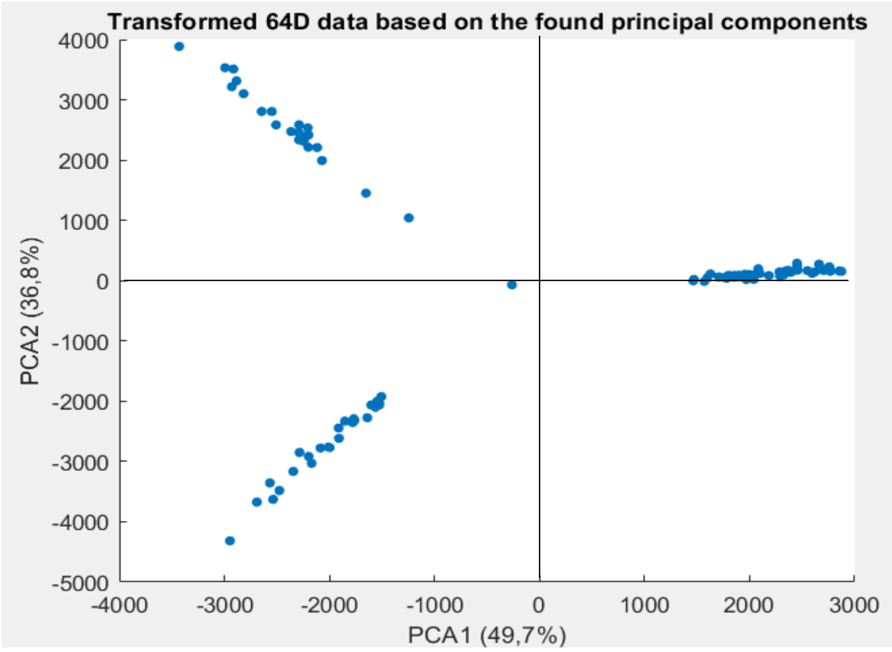

Figure 14. 64D coordinates transformed to 2D coordinates of all breasts in the development dataset using the found principal components of the face normal directions in module 2.

1 to 9 and 1 to 10. The absolute ICC is 0.49 (95% CI: 0.07-0.744, p=0.000). The consistency ICC is 0.75 (95% IC: 0.64-0.84, p=0.000).

Assessment of method outputs

An overview of the relevant Pearson's correlation coefficients for every method can be found in Table 4.

Method 1 – Curvature

The correlation coefficients between the gold standard and the different grid size curvature ratios can be found in **Error! Reference source not found.**. A grid size of 7x7 gave the best correlation coefficient for all methods and thresholds. The highest correlation coefficient (ρ=0.781, p=0.000) was found for the thresholds 0.0075 mm^{-1} and 0.009 mm^{-1}. In both cases, the highest correlation coefficient was found with the method that excluded the grid square from further analysis if the difference between the curvatures of that grid square was larger than the threshold. Upon closer inspection, the found mean ratio was identical for the 0.0075 mm^{-1} and 0.009 mm^{-1} thresholds for all cases of the development dataset. Therefore, only the mean ratio found with a threshold of 0.0075 mm^{-1} was included for further analysis.

Method 2 – Face orientation

Principal component analysis was performed for the face orientations. Two principal components were identified, respectively principal component 1 (PC1) and principal component 2 (PC2). These two principal components had an explained variance of 50% + 37% = 87%. The two principal components were utilized to transform the original 64-dimensional data of a breast into a 2D Cartesian coordinate. These coordinates can be found in Figure 14.

Distances between the coordinates of the two breasts of the same patient were determined. A normal distribution is found after a natural logarithm transformation. A Pearson's correlation coefficient ρ of -0.693 (p=0.000) was found between these transformed distances and the gold standard. No relation was found between principal component values and breast type or breast shape.

Method 3 – Point distance

The root mean square and the Hausdorff distance were determined for every patient for the original cropped meshes and the two types of rigidly transformed meshes. The distribution of the data was examined. The root mean square data for the original cropped mesh was the only non-normal distributed dataset. A normal distribution is found after a natural logarithm transformation. The highest Pearson's correlation coefficient (ρ=-0.824, p=0.000) was found for the root mean square after transforming the right breast mesh with a transformation matrix found with the iterative closest point algorithm applied on the meshes with breasts. The correlation coefficient for the RMS after transforming the right breast mesh with a transformation matrix found with the ICP algorithm applied on the meshes without breasts is second-best (ρ=-0.805, p=0.000).

Development of the algorithm

A multiple linear regression model was built based on the found correlation coefficients seen in Table 4. The steps of the forward building method can be seen in Table 5. The first variable added was from the point distance method. The highest correlation coefficient was found for the method with the ICP algorithm based on the mesh with breasts. However, the ICP algorithm based on the mesh without breasts is preferred. Therefore, the second-best independent variable of the third module is added to the linear model first. The second variable that was added to the model is the curvature ratio of the first method. Lastly, the natural logarithmic variable of the face orientation output was added. It can be seen in Table 5 that the addition of the face orientation output does not further optimize the model. For comparison, the RMS method with ICP algorithm with breasts replaced the RMS method without breasts of step 2. This can be seen in the last row of Table 5. This increased the adjusted R^2 slightly. However, the preferred linear regression model is found with the second step. The final model approximates the gold standard with the model:

$$Symmetry\_Score \;= 2.047 - 0.26 * \mathrm{M1}_{\mathrm{RMS\ ICP\ without\ breasts}} + 11.356 * \mathrm{M2}_{Grid\ 7, threshold\ 0.0075}$$

This model has a high correlation to the gold standard (ρ = 0.849) and an adjusted explained variance of 71%. This can be seen in Figure 15. The algorithm was updated in Matlab according to the found model. Pseudocode can be found in **Error! Reference source not found.**. The mean duration from loading one 3D image to computing the symmetry score is 106 seconds. The mean duration for the preparation and the individual modules is respectively 76, 0.04, and 30 seconds.

Table 5. The different steps of building a multiple linear regression model that approximates the gold standard. The forward building method was used. During every step, a new module was added to the model to determine of the adjusted explained variance (Adjusted R^2) improved. The independent variables are the modules noted in the abbreviations. Coeff B is the coefficient that must be used in the final regression model

	R	R^2	Adjusted R^2	Independent variables	Coeff. B	Sig.	95% Confidence Interval for B	
							Lower bound	Upper bound
Step 1	0.805	0.648	0.640	M3.6	-0.418	0.000	-0.508	-0.329
Step 2	0.849	0.721	0.709	M3.6	-0.260	0.000	-0.381	-0.139
				M1.1	11.356	0.001	4.856	17.856
Step 3	0.849	0.721	0.703	M3.6	-0.256	0.002	-0.411	0.102
				M1.1	11.291	0.002	4.532	18.051
				M2.1	-0.048	0.934	-1.219	1.123
Alternative	0.856	0.732	0.721	M3.5	-0.486	0.000	-0.696	-0.275
				M1.1	10.086	0.004	3.477	16.695
Abbreviations: M1.1 = Grid_7_threshold_0.0075; M2.1 = LN(PCA_distance); M3.5 = RMS_ICP_with_breasts; M3.6 = RMS_ICP_without_breasts								

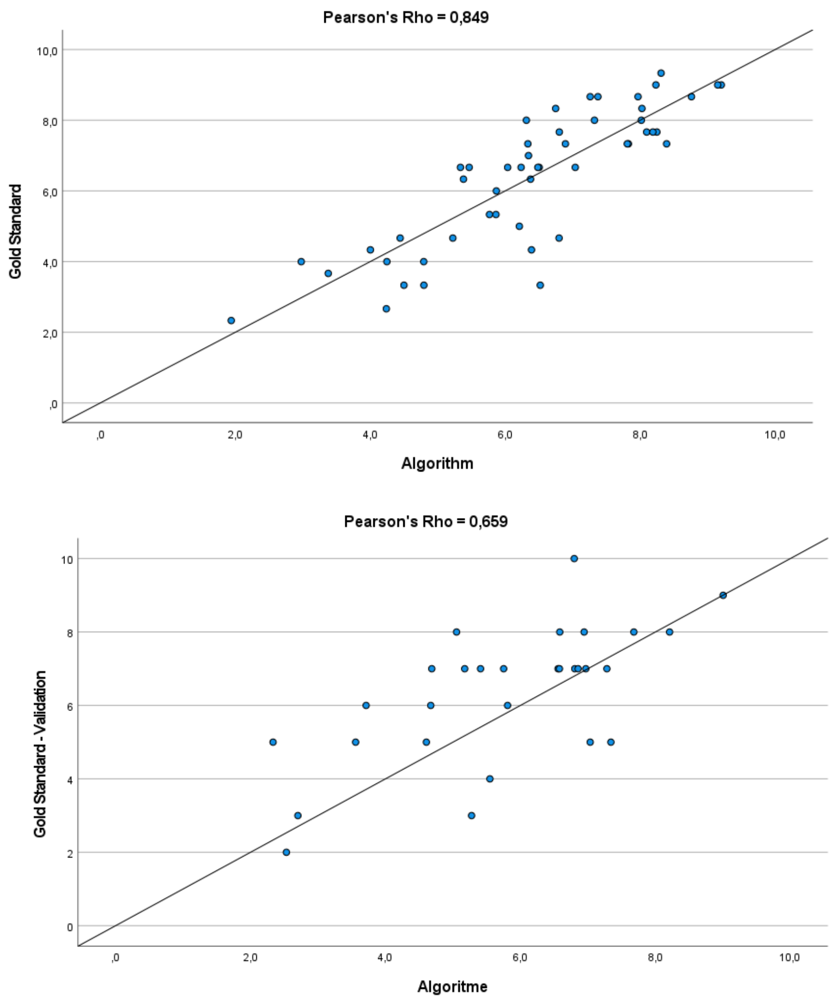

Figure 15. Scatterplot of the gold standard (plastic surgeons breast symmetry score) and the algorithm symmetry score for both development dataset (upper) and validation dataset (lower)

Validation of the algorithm

The 3D images of the validation dataset were scored for breast symmetry by non-attending plastic surgeons. Additionally, the breast symmetry of the same 3D images was scored using the algorithm. The mean given score of the plastic surgeon was 6.34 with a range between 2 and 10. The mean algorithm symmetry score was 5.78 with a range between 2.33 and 9.00. The found absolute mixed model ICC between these two symmetry scores is 0.632 (p=0.000). The consistency ICC is 0.657 (p=0.000). A scatterplot with both symmetry scores can be seen in Figure 15.

Reproducibility

The algorithm scored the validation dataset three times. The three mean symmetry scores were respectively 5.9, 5.8, and 6.0, with a range of 2.33-9.00, 2.40-8.59, and 2.30-9.12. The absolute mixed model interclass correlation coefficient is 0.955 (95% CI: 0.919-0.977, p=0.000). The consistency interclass correlation coefficient is 0.958 (95% CI: 0.923 – 0.978, p=0.000).

Discussion

In this chapter, an algorithm to objectively score breast symmetry based on 3D images was developed. The final algorithm uses curvature and the root mean square of the minimal distances between the left and right breast after superimposing. A decent consistency interobserver correlation coefficient is found during validation. It should be noted that the gold standard is based on only three observers. The upcoming interpretations and conclusions are based on the assumption that these three observers were representative for the national gold standard. However, the findings of this study are tentative, until this study is confirmed with a larger number of observers.

Interpretation of results

The interobserver analysis of the three plastic surgeons that scored the breast symmetry score of the development data showed a mediocre absolute interobserver correlation. However, the consistency correlation is of higher importance. A high consistency ICC means that the observers agree on a difference between high symmetry breasts and low symmetry breasts. Therefore, the used gold standard seems decent to use as the base for the algorithm. The maximal difference in symmetry score between two observers for individual patients is five. This is a large difference in a scale from 1 to 10. This difference can be explained when the differences in used range per observer (5-10 and 1-10) is taken into consideration. Ideally, the gold standard would be the mean symmetry score of tens of plastic surgeons with different amounts of experience, and from both peripheral and academic hospitals.

The first method that was added to the algorithm was the mean ratio found with the curvature. The curvature method focused on the difference in curvedness between the left and right breast. The chosen grid size of 7x7 gives a more detailed indication of these differences for multiple areas of the breast. For example, asymmetrical breasts often have a different location of the inframammary fold (IMF). For the grid squares where one side has a high curvature because of the curvedness of the IMF and the other side has no curvedness because the IMF lays more superior, the found curvature ratio will be very low. These differences would be less notable if the grid areas were bigger. Furthermore, curvature analysis does not account for shape measurement differences. For example, the right columns of both breasts in Figure 12 show different breast shapes. However, the curvature ignores these differences because one of the two breasts has an empty grid. In summary, the curvature method gives a lot of breast shape information. However, the addition of another method is required for a more robust system.

The second method was not added to the final algorithm, although a decent correlation coefficient was found. However, it did not give additional shape information that was not already found with the curvature and point distance method. It was expected that this method would give shape information about the ptosis grade. It could be argued that the level of ptosis is also quantified with the found curvature since high ptosis grade breasts often have high curvedness. Notable is the three group formations that can be seen in the PCA plot (Figure 14). An attempt is done to categorize these groups based on breast shape. Ptosis level, cup size, and tissue expanders are explored. Every category is scattered over the three groups, without a found correlation. This does not correlate with the findings of Li et al. and Catanuto et al. They found that the face orientation analysis using PCA provides a method to categorize breasts on ptosis level [32,40]. More extensive research should be done to explore the cause of these groups.

The third method was the found point distances between the two superimposed meshes. This method gave the highest correlations to the gold standard. This can be explained by the versatility of this method. The point distances give a higher RMS if one side is a breast with high volume and one side is a low volume breast. Additionally, the RMS will give a higher value if one side has smaller measurements than the other side. As mentioned before, the curvature method is not affected by differences in breast measurements such as the differences seen in the right columns in Figure 12. However, the found point distances will be larger for these differences and therefore the RMS will become larger. Therefore, this method can give a good overall quantified shape analysis.

The final algorithm consists of two modules. The first module uses the RMS of the point distances after superimposing the left and right breast. This method gives an overall quantified shape analysis. The second module focuses on the found mean curvature. This module adds by giving a more detailed quantified shape analysis. Together they have a high correlation with the gold standard of this study. It can be argued that the correlation could be even higher if the point distance method was chosen where the breasts were not removed to find the optimal transformation matrix. However, it is believed that the method with removed breasts will compensate for additional patient skewness around different axis. This will make the algorithm more robust. Additionally, the method that uses the breasts to find the optimal transformation matrix will most likely try to compensate for breast asymmetry. Although this seems not to be an issue during this study, it is expected that this will affect the symmetry score during larger studies. Therefore, the ICPA method without breasts is chosen for the algorithm.

The performance of the final algorithm seems decent. The correlation with the validation dataset has room for improvement. However, this dataset was small, and every 3D image was scored by only one expert. Additionally, the development data was scored by plastic surgeons from an academic hospital, while the validation data was scored by plastic surgeons from a peripheral hospital. It is therefore difficult to prove if the lower correlation is caused by an inadequate algorithm or if the subjective scoring of the experts varied significantly between observers. However, the final algorithm seems like an adequate start for further development. Additionally, the performance of the algorithm is adequate with an acceptable process duration and high reproducibility.

Comparison with previous literature

The algorithm developed in this study found a moderate to high correlation coefficient between the three breast shape analysis methods and the plastic surgeon's symmetry score. Previous studies examined the use of these methods for breast shape analysis. Catanuto et al. used curvature for visualization [36]. Seoud et al. used curvature shape analysis to segment the breast and determine breast volume [39]. Li et al. and Catanuto et al. used both the curvature analysis and the face orientation analysis for ptosis estimation [32,40]. This study is the first to correlate both the curvature shape analysis and the face orientation analysis to a symmetry score.

Losken et al. used the RMS found with the point distances between the two superimposed breasts to determine breast symmetry [37]. However, they only used healthy participants without previous breast augmentation. Additionally, they correlated the RMS to a subjective symmetry score of <1 (no asymmetry) 1-2 (mild-moderate symmetry), and >2 (marked asymmetry). This is a limited scale in which the mean RMS only increased severely for the marked asymmetry. This study uses a larger scale of symmetry scores which enables a more profound usage of the RMS.

Limitations

The gold standard used for the development of the algorithm is the symmetry score, determined by only three plastic surgeons. Furthermore, their score remains an opinion and is therefore subjective. Some plastic surgeons expressed their difficulties scoring the breast symmetry without being distracted from the patient-specific details. For example, in some cases, the presence of scar tissue from previous radiotherapy could be seen. Previous radiotherapy often affects the aesthetic outcome of breast reconstruction. Therefore, some plastic surgeons tend to give these patients a higher symmetry score when the breast symmetry is decent. Another example is the presence of active scaring or necrotic skin. Although the symmetry seems to be close to perfect, some plastic surgeons tend to give these patients a lower symmetry score. These interobserver differences in symmetry scoring are also shown with the mediocre absolute ICC. It can be argued that the algorithm is not objective when the gold standard is not. However, it highlights the need for an objective breast symmetry scoring system. A more visual scoring method for the plastic surgeon is advised for future studies, where an example image is given for a symmetry score of 1 and for a symmetry score of 10. This could help in normalizing the scoring range of the observers.

The future goal for the algorithm is to be fully automated. However, the current algorithm requires two manual actions before a symmetry score can be found. First, the original 3D image must be manually remeshed in Meshmixer before it can be given to the algorithm. Although the manual labor is low, this step makes the algorithm less user-friendly. Future development of the algorithm should focus on including the remesh step into the algorithm itself.

Secondly, the landmarks must be manually selected. Manual landmark selection can be slow, is user-dependent, and may result in faulty breast segmentation. To overcome this, the algorithm requested confirmation of accurate breast segmentation for every 3D image. Additionally, the mean curvature was visualized during landmark selection for simplified landmark recognition. This resulted in a reproducibility of the algorithm of 0.96. However, automated landmark selection will simplify the usage of the algorithm and possibly shorten the duration time. Additionally, the assistance of clinical experts would be no longer required to use the algorithm. Unfortunately, automatic landmark selection or breast segmentation remains challenging because of the soft tissue and lack of bone structure.

Another limitation of this study is the small database used for both the development and validation of the algorithm. Furthermore, the separation of the development from academic hospital data and the validation from peripheral hospital data is not ideal. Preferably, both databases would be bigger by using data from a large number of plastic surgeons with different amounts of experience and from different hospitals for a more robust algorithm. However, attention is given to the variation of breasts that was added to the validation data. Variations like different cup sizes, maximal and minimal symmetry, tissue expanders, active scars, and different timestamps before and after breast reconstruction were taken into account to create a robust algorithm. Further development of the algorithm using a larger database would enable the addition of machine learning. Furthermore, the development of a machine learning algorithm would enable the automatic registration of landmarks. This would reduce the manual labor required to train and validate the algorithm.

Clinical relevance

After further development, the algorithm may have a high impact on both clinical studies and communication between plastic surgeons and patients. The variation in plastic surgeons' symmetry scores emphasizes the lack of objective scoring methods. Studies executed by different hospitals cannot be compared due to their differences in gold standard. This impedes small groups to execute relevant studies about optimizing breast reconstructions or to execute studies about evaluating current breast reconstruction methods. An algorithm will enable the possibility to execute small studies in different hospitals and combine or compare the results.

Additionally, an algorithm could aid in disagreements between the plastic surgeon and the patient. In most cases, the patient decides if she is pleased with the aesthetic results of the breast reconstruction. If she is not satisfied, a secondary correction will be performed. However, there are cases in which the plastic surgeon will disagree with the patient. In those cases, a secondary correction will most likely have a minimal positive effect on the aesthetic outcome. The challenge is to harmonize the two opinions that do not agree. In most cases, the expertise of the plastic surgeon will make the difference. However, an objective breast symmetry score could aid in this conversation. A database with different patients and their objective symmetry scores could help visualize the current situation of the patient and what effect a secondary correction will most likely have. This would aid the plastic surgeons in their communication and improve the patients' understanding for optimal decision making.

Conclusion

This study is the first to develop an algorithm that objectively scores breast symmetry between one and ten based on 3D images using multiple shape analysis methods. This algorithm uses the mean curvature and the point distances between the superimposed left and right breast for breast shape analysis. Based on the limited finding of this study, a moderate to high correlation was found between the algorithm symmetry score and the plastic surgeon's symmetry score. Furthermore, the algorithm has a high reproducibility despite manual landmark selection. The high correlation hints at the usability of the algorithm in future clinical studies. However, further development is required using larger databases and a higher number of observers to create a robust and full-automatic objective scoring algorithm.

Chapter 4. An evaluation of the usability of multiple breast symmetry scores to objectify patient satisfaction to quantify the DIEP flap reconstruction performance

Introduction

The success of a Deep Inferior Epigastric Perforator (DIEP) flap reconstruction performance is mainly based on the patient's satisfaction with the results since there is no physical benefit to the procedure [45,46]. It is known that the patient's self-esteem does increase with an improved aesthetic outcome [30,47,48]. Additionally, the patient's satisfaction is decisive to initiate a secondary correction [18].

The BREAST-Q questionnaire is an often-used tool to quantify the patient's satisfaction. This questionnaire focuses on different aspects, such as aesthetic satisfaction, psychosocial well-being, sexual well-being, and physical well-being [49,50]. Although all these aspects are important, the subjective experience of the patient influences the outcome [51]. This is accepted in clinical practice. However, objective outcomes would improve breast reconstruction performance evaluations and may predict if secondary corrections are necessary.

Multiple studies were done to explore objective measurement methods to quantify the DIEP flap reconstruction's success. Maass et al. did a systematic review on questionnaires that evaluated aesthetic reconstruction outcomes, such as multiple point scales [30,52], Harris [19], Baker [53], and Cohen [54]. They concluded that a professional aesthetic scale that could be used as gold standard was not yet available and had to be developed [29]. However, these scales remain patient-reported, or subjective observer ratings [55]. Leser et al. found that the subjective patient satisfaction cannot be determined by the aesthetic satisfaction of the surgeon or an objective symmetry measurement tool [56]. Yip et al. confirmed this by comparing the BREAST-Q outcome with an objective breast symmetry measurement tool using three-dimensional (3D) laser scans. They found no correlation between the patient's satisfaction and the objective symmetry measurements [48]. Furthermore, no studies have been found to predict the chance of secondary corrections after DIEP flap reconstruction.

An objective outcome that quantifies the likelihood of a secondary correction, and therefore the success of the DIEP flap reconstruction, would enhance further breast reconstruction studies, such as the breast mold study. The algorithm created in the previous study (Chapter 3) could be this objective outcome. Therefore, this study explores the correlations between patient satisfaction and different symmetry measurements before and after DIEP flap reconstruction. Multiple studies have shown that the BREAST-Q questionnaire is a sufficient indicator of patients' breast satisfaction, both pre- and postoperative [49,57,58]. This study focused on the BREAST-Q module 'Satisfaction of the breasts'. Modules such as 'Psychological well-being' and 'Satisfaction with information' will be excluded to minimalize non-relevant factors. Both the patient and the plastic surgeon will use the Harris score to score the breast symmetry. This score is used in multiple breast symmetry studies and is found as a simple and well-established scale with proven utility [21,22,59]. Furthermore, the algorithm and landmark measurements are used for objective symmetry measurements. Additionally, the patient is asked postoperatively if she considers secondary corrections. The found correlations will give new insights into breast reconstruction outcomes and could optimize further breast reconstruction studies.

The first primary outcome of this study is the difference in both patients' satisfaction and symmetry scores for the patients that do consider secondary corrections and the patients that don't consider secondary corrections. Secondly, the correlation between patient satisfaction and breast symmetry determined with the symmetry scoring methods is a primary outcome. It is expected that the patient's satisfaction and symmetry scores are lower for the patients that consider secondary correction.

Additionally, the highest correlation with the patient's satisfaction is expectedly found with the algorithm or landmark symmetry score since these symmetry scores are the most objective. Secondary outcomes are; 1) The relation between patient satisfaction and the number of complications; 2) The relation between the different symmetry scores; 3) The change in patient satisfaction and symmetry score over time (pre- and post-operatively).

Method

In April 2021, an observational study was approved by the Medical Research Ethics Committees United (MEC-U). While this study is still going, this chapter will use the preliminary data of this study for analysis.

Participants

The research population consists of women with a planned DIEP flap reconstruction or planned secondary correction with previous DIEP flap reconstruction at Medisch Spectrum Twente (MST) or Ziekenhuisgroep Twente (ZGT) Hengelo. The goal was to include 40 patients. Participants were included in the order they enter the regular clinical workflow until February 2022. Women with a planned DIEP flap reconstruction were asked to participate in the study. The physician or investigator gave adequate verbal and written information to the patient. Informed consent was signed if the patient agrees to participate.

To be eligible to participate in this study, a subject had to meet all the following criteria:

- A planned DIEP flap reconstruction
- Age > 18
- A signed informed consent

Additionally, an available database was used to find the correlation between horizontal, vertical, and projection symmetry and the overall breast symmetry score. This database was not used for other analyses in this study. Fifty 3D photos of patients with a planned DIEP flap reconstruction or after the DIEP flap reconstruction were included from Radboud Universitair Medisch Centrum (Radboudumc). All 3D photos were taken with a Canfield Vectra XT system (Canfield Sci, New Jersey, USA) with the patient's arms at a 45-degree angle from the body.

Study design

The study was an observational, uncontrolled, and open multicenter study. The participants were treated according to the current DIEP flap procedure. Subjects had 3D stereophotogrammetry photos taken (one without landmarks, one with landmarks) pre-operatively, and two and twelve weeks postoperatively. Additionally, participants filled out a BREAST-Q questionnaire and a symmetry scoring form (overall, vertical, horizontal, and projection symmetry) on the same days. The post-operative participants were asked if they considered a secondary correction with the current state of their breasts. An independent surgeon used the same symmetry scoring form to evaluate the patient's

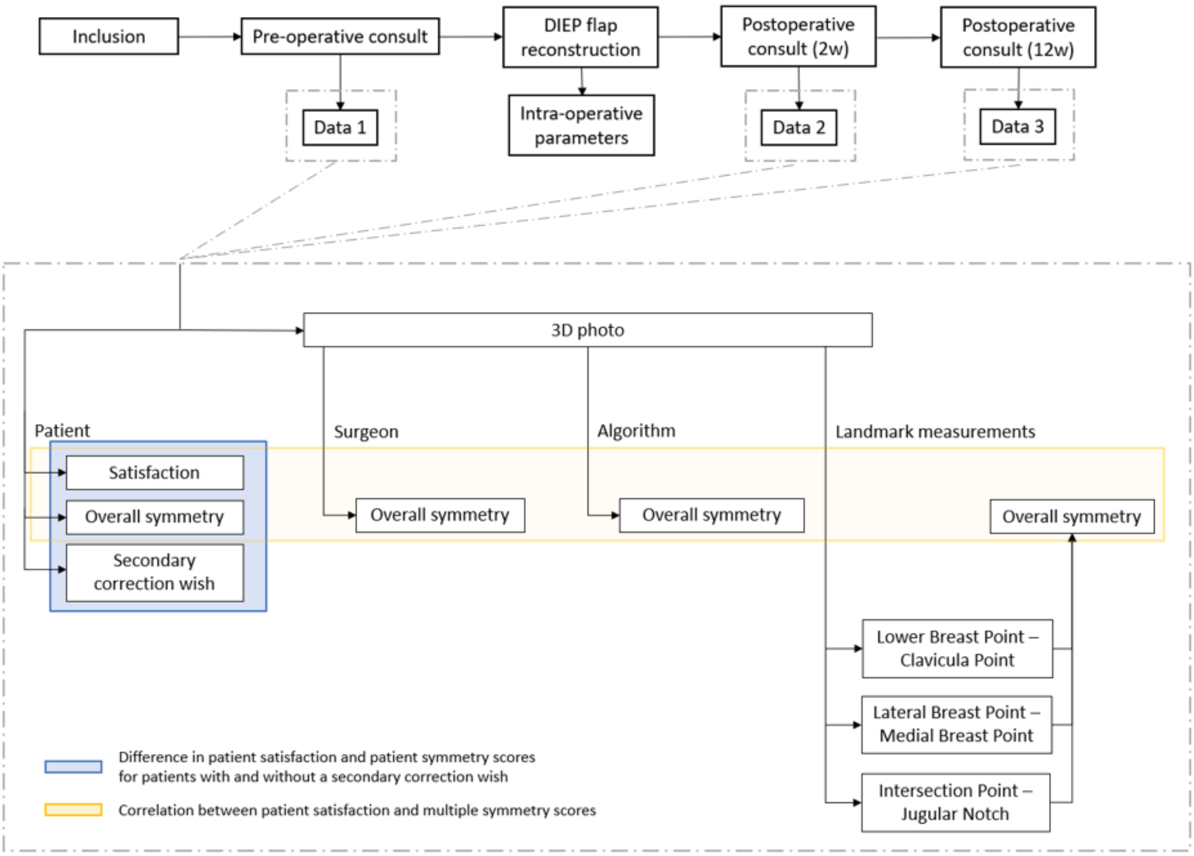

Figure 16. Overview of the study design with the found parameters and the primary outcomes. After inclusion, the participant is seen three times (one time pre-operative and two times post-operative). During every consult, the study parameters as can be seen in the figure were collected. In blue, the study parameters of the first primary outcome are shown. In yellow, the study parameters that were compared to each other for the second primary outcome are shown.

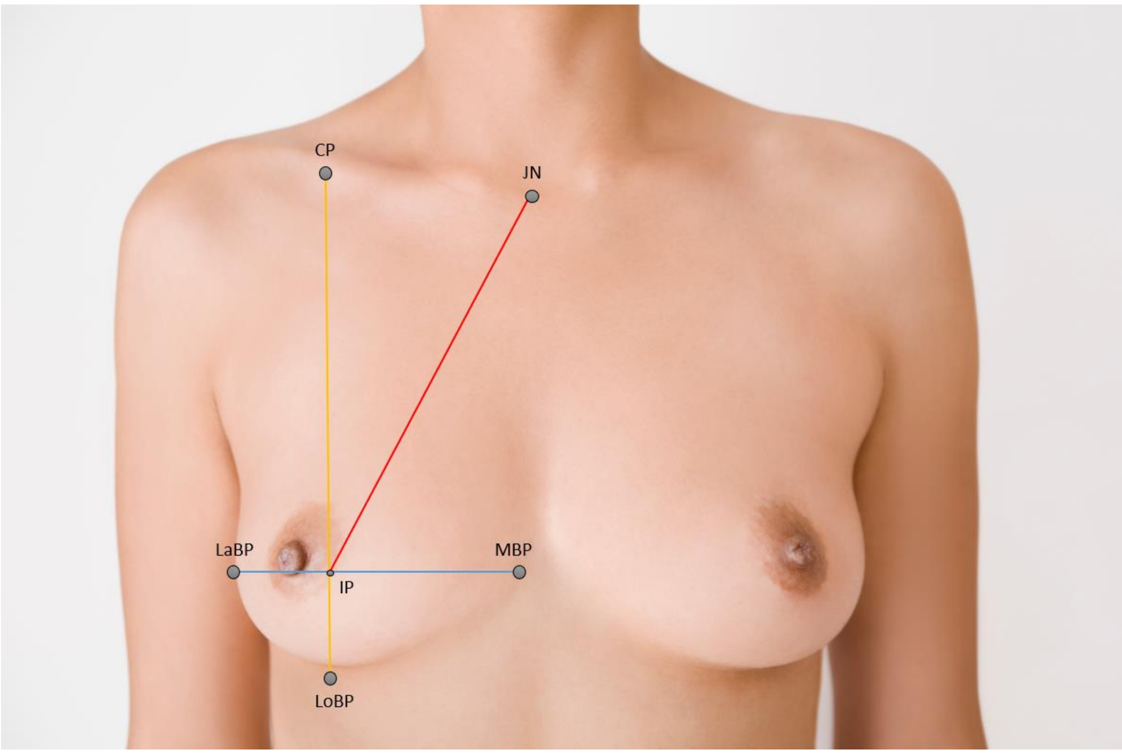

Figure 17. The landmarks used for the landmark measurements symmetry score. Blue: Lateral Breast Point (LaBP) - Medial Breast Points (MBP). Yellow: Clavicula Point (CP) – Lowest Breast Point (LoBP). Red: Jugular Notch (JN)– Intersection Point (IP). Blue: Lowest Bresat Point (LoBP) – Jugular Notch Line (JNL)

breasts symmetry based on the 3D photo. The 3D photo was then used to find a breast symmetry score using the algorithm described in Chapter 3. Additionally, distances between landmarks were found on the 3D photo and converted to a symmetry score. The duration of the study was one year. The study design and the corresponding outcome parameters can be seen in Figure 16.

3D photos

A total of two 3D photos were taken per consult. The 3D photos were taken following protocol with a Canfield Vectra XT system at ZGT Hengelo [60]. The participant had to put her hands on her waist and breath through her stomach. The first photo was taken without markings. The second photo was taken with marked anatomical landmarks. The landmarks are shown in Figure 17 and were marked with a marker on both breasts. The used landmarks were the jugular notch (JN), the lowest breast point (LoBP), the medial breast point (MBP), the lateral breast point (LaBP), and the clavicula point (CP). The nipple was not used as a landmark because the nipple is removed for most mastectomy patients. The lowest breast point was found using the lowest point of the inframammary fold (IMF). The medial breast point was found using the natural skin fold on the medial side of the IMF [22]. If the natural skin fold was not clearly visible, pressure on the breast was applied to find the natural border of the breast. This method is used in different studies and is proven effective [19,21]. The lowest, most medial point was chosen as MBP. An imaginary horizontal line was drawn from the MBP to determine the LaBP. The LaBP will be directly above or on the lateral side of the IMF. Lastly, an imaginary vertical line was drawn from the LoBP to find the clavicula point.

Methods of measurements

The methods of measurements are described based on the visualization of the measured parameters in Figure 16.

Patient's score

The participant had to fill in a BREAST-Q questionnaire on the same days the 3D photos were taken. The pre- and postoperative version of the module 'Satisfaction with the breasts' was used. The questionnaire scored the patient's satisfaction in the range of 0 to 100.

Additionally, the participant scored her breast symmetry. Symmetry scores were given for overall, horizontal, vertical, and projection breast symmetry between one (poor symmetry) and four (excellent symmetry). The scoring method was based on the Harris scoring. The scoring form can be found in **Error! Reference source not found.**. The horizontal symmetry was based on the width of both breasts. The vertical symmetry was based on the position of the IMF, the lowest point of the breast, and the superior breast boundary. The projection symmetry was based on the volume distribution and shape of the breasts. The participant scored her breast symmetry based on the recently made 3D photo.

Surgeon's score

The surgeon's symmetry score was based on the 3D photo without landmarks. The scoring method was the same as the symmetry scoring method the participant used (**Error! Reference source not found.**). An independent surgeon scored the participant's breast symmetry since it was found that the involved surgeon will score the symmetry higher [56]. This scoring system gave four individual scores in the range of 1 to 4.

Algorithm score

Additionally, the 3D photo without landmarks was given to the algorithm as described in Chapter 3. An independent symmetry score was found for every image.

Landmark measurement score

Lastly, the distances between the landmarks were determined. The distances were found using validated Vectra CT and Sculptor software (Canfield Sci, New Jersey, USA) to avoid the inaccuracy of measurements done with measuring tape. The direct distances between the medial and lateral breast point, and the lowest breast point and the clavicula point were determined. The intersection point (IP) between these two lines was marked digitally. The surface distance was then determined between the JN and the IP. The measurements of both breasts were compared. The ratio between both breast measurements was determined which gave three symmetry scores (horizontal, vertical, and projection) in the range of 0 to 100. However, weight factors (WF) had to be found to combine the three symmetry scores into one overall symmetry score, using Equation 1. Therefore, the database of Radboudumc was used. Three plastic surgeons scored the images in this database with a score between 1 and 10 for overall, horizontal, vertical, and projection symmetry. The effect of the different types of symmetry scores on the overall symmetry score was then found using multiple linear regression. The overall symmetry score was then determined using Equation 6.

$$\begin{aligned} Overall\ Symmetry = {} & Horizontal\ Symmetry * WF_{horizontal} + \\ & Vertical\ Symmetry * WF_{vertical} + \\ & Projection\ Symmetry * WF_{projection} \end{aligned} \qquad Equation\ 6$$

Inter-operative parameters

Surgical times were noted. These are the dissection time of the abdominal flap, breast shaping time, ischemia time, and dissection time of the internal mammary artery (IMA). Additionally, the weight of the final flap and the weight of spilled tissue were noted.

Lastly, any complications were noted. The complications were found by asking the participant during follow-up and by accessing the electronic health report. In case of a complication, the relation with the DIEP flap reconstruction was explored, and the effects on the participant and the study were noted.

Analysis

All data was stored in Castor EDC. Statistical analysis was performed using IBM SPSS Statistics Version 27 (IBM Corp., Armonk, New York, USA). The results of the BREAST-Q questionnaire, the algorithm symmetry scores, and the landmark measurements symmetry scores were continuous. The patient's and surgeon's symmetry scores were ordinal. The number of complications was presented as nominal data. If data was missing from a specific time point, that subject was excluded for analysis for that and further time points.

Primary outcomes

For the first primary analysis, participants that considered a secondary correction because of asymmetry were compared to participants that do not consider a secondary correction. A Mann-Whitney U test was done to find the difference in satisfaction between the secondary correction groups. Additionally, Fischer's exact test was done to find the difference in symmetry score between the two groups. Both analyses were done individually for the two- and twelve-week follow-up.

For the second primary analysis, the relation between the patient's satisfaction and different symmetry scores was found. The Spearman correlation was found between the patient's satisfaction score and both the patient's and surgeon's symmetry score. Additionally, a Kruskal-Wallis exact test was done to find the differences in patient satisfaction within the different symmetry scores. The Pearson's correlation was found, if normally distributed, between the patient's satisfaction and both the algorithm and landmark measurements symmetry scores. If not normally distributed, Spearman's correlation was found. Since the data of the different follow-up moments was paired, analysis was done for the three follow-up moments individually. However, this study focused on the relation between the patient's satisfaction and the different symmetry scores. Therefore, another analysis was done in which all data was used as if it was unpaired. This could give more insight into the mutual relation between the parameters since the analysis was done with more data. However, no well-founded conclusions could be drawn from this analysis.

Secondary outcomes

In addition to the primary outcome, three secondary outcome measurements were done. First, the relation between the patient's satisfaction and complications was explored using descriptive statistics. Secondly, the relations between the different symmetry scores were examined. The relation between the surgeon's symmetry scores and the patient's symmetry scores was analyzed using kappa. Furthermore, the Spearman correlation was used between the patient's and surgeon's symmetry score and both the algorithm and landmark measurements symmetry score. Additionally, the Kruskal-Wallis exact test was used to find differences within the ordinal symmetry scores. Like the first secondary outcome, the follow-up moments were both individually and combined analyzed for the third secondary outcome. Lastly, the patient's satisfaction and symmetry scores over time were explored. For the satisfaction over time, the mixed-model repeated measures test was used. The Friedman test using the Holm–Bonferroni correction method was used to find the differences in the patient's symmetry score over time.

Power analysis

The expected number of patients that would be able to join this study in one year was at least forty. The software G*Power was used to compute the required effect size with a given power, p-value, and sample size [59]. A p-value of 5% and a power of 80% was chosen. Additionally, an effect size of 0 was chosen as H0. This gave a correlation effect size of 0.41. The effect size criteria identified by Cohen state that an effect size of 0.41 must be chosen if a moderate to large effect will be found [61]. However, more subjects are required to find a significant correlation if the effect size is smaller.

Results

Participants

A total of 17 participants were included in the study. Eight of these seventeen participants were present during all follow-up moments. Five participants were not seen after the DIEP flap reconstruction. Three participants were excluded due to flap loss and termination of the DIEP flap reconstruction. Two participants terminated their participation due to postoperative complications. Four participants did not have their twelve weeks follow-up. One participant terminated her participation due to complications requiring surgery. Two participants were lost to follow up. One participant had the last follow-up appointment planned after data analysis. During the two-week follow-up, two participants noted that they considered a secondary correction. One of them wanted a scar correction, the second participant noticed an asymmetry. During the twelve-week follow-up, four participants considered a secondary correction. Two of them wanted an aesthetic correction such as the removal of bumps. The other two wanted asymmetry correction. Additional participant characteristics can be found in Table 6.

Data characteristics

An overview of the mean found values of the patient's satisfaction (normal distribution) and the median of the algorithm's and landmark measurements symmetry scores (non-normal distribution) can be found in Table 7. Furthermore, this table shows the patient's and surgeon's overall symmetry scores. The horizontal, vertical, and projection symmetry scores can be found in **Error! Reference source not found.**.

Table 6. Characteristics of the included participants in this symmetry study

Participants included	17
Follow-up moments	
1	5 (29%)
2	4 (24%)
3	8 (47%)
Age	56 (45-75)
BMI	25,0 (19,9-29,1)
Smoking	
Yes	1 (6%)
Former	1 (6%)
No	15 (88%)
Cup size	
AB	3 (18%)
CD	13 (76%)
E+	1 (6%)
Breast History	
Tissue expander	5 (29%)
Flat	7 (41%)
Other	4 (24%)
No history	1 (6%)
Reconstruction	
Direct	3 (18%)
Delayed	12 (70%)
Both	2 (12%)
Side	
Unilateral	8 (47%)
Bilateral	5 (29%)
Unilateral with augmentation contralateral	4 (24%)

Table 7. Overview of the mean study parameters found in this study. The BREAST-Q is the score for patient satisfaction (1-100). The algorithm and landmark symmetry scores give a continuous score between 1 and 100. The patient and surgeon's symmetry score is ordinal and is scored between 1 (poor symmetry) and 4 (excellent symmetry).

				Symmetry score									
			Mean	**Median**	**Median**	**Patient**				**Surgeon**			
		n	**BREAST-Q**	**Algorithm**	**Landmarks**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Follow up	Pre-op	17	42	3.6	84.2	12	1	2	1	10	1	4	2
	2w	12	65	5.8	95.5	0	5	5	1	1	5	4	2
	12w	8	67	6.9	95.4	0	3	4	1	0	3	4	1

Table 8. Overview of the mean patient satisfaction (BREAST-Q, score between 1-100) and the patient's symmetry score (ordinal, score between 1 (poor symmetry) and 4 (excellent symmetry)) for the patients that do and do not consider a secondary correction at both follow-up moments

Secondary correction wish

		Yes						No					
			Mean	Symmetry Patient					Mean	Symmetry Patient			
		n	BREAST-Q	1	2	3	4	n	BREAST-Q	1	2	3	4
Follow up	2w	1	50	0	1	0	0	10	66.7	0	4	5	1
	12w	2	55	0	2	0	0	6	70.1	0	1	4	1

Weight factors landmark measurement symmetry score

The symmetry scores of the three plastic surgeons for the Radboudumc database were fairly consistent (consistency interclass correlation coefficient (ICC) = 0.628 and higher). The consistency and absolute ICCs of the overall, horizontal, vertical, and projection symmetry scores can be found in **Error! Reference source not found.**. The mean of the overall, horizontal, vertical, and projection symmetry was taken per 3D image. Multiple linear regression was performed to find the weight factors of the horizontal, vertical, and projection symmetry for the overall symmetry score of the landmark measurements. The weight factors can be found in **Error! Reference source not found.**. These weight factors are combined to determine the overall symmetry score, as can be seen in Equation 7. This equation explains 97% of the data (adjusted R^2 = 0.971).

$$\begin{aligned} &Overall\ Symmetry \\ &\quad = -0.053 + Horizontal\ Symmetry * 0.454 + Vertical\ Symmetry * 0.367 \\ &\quad + Projection\ Symmetry * 0.194 \qquad Equation\ 7 \end{aligned}$$

Primary outcomes

Secondary correction wish

As can be seen in Table 7, for both follow-up moments, the mean patient satisfaction is lower for the participants that considered a secondary correction. Using the Mann-Whitney U test, no significant difference in satisfaction was found between the groups that do and do not consider a secondary correction for both the two (p=0.583) and twelve-week follow-up (p=0.107). Additionally, the participants that considered secondary correction scored their symmetry with a 2. The participants without a secondary correction wish scored their symmetry between 2 and 4. No significant difference was found for the given symmetry score between the two groups for both follow-up moments (respectively p=1,000 and p=0.214).

Correlation between patient satisfaction and symmetry scores

The Spearman's correlation coefficients between the patient's satisfaction score and the patient's and surgeon's symmetry score can be found in Figure 18 and **Error! Reference source not found.**. A significant correlation is found between the patient's satisfaction and the patient's symmetry score if all data is analyzed together (ρ=0.758, p=0.000). However, only the pre-operative data shows a decent and significant correlation when looking at the follow-up moments individually. A Spearman's correlation of 0.365 (p=0.026) is found between the patient's satisfaction and the plastic surgeon's symmetry score. No significant correlation is found for the individual post-operative follow-up moments.

The found Spearman's correlation coefficient between the patient's satisfaction and the landmark measurements symmetry score is 0.503 (p=0.000) for all data together. For the individual follow-up moments, no significant correlation was found. A significant Pearson's correlation coefficient was found between the patient's satisfaction and the algorithm's symmetry score (ρ=0.489, p=0.000) for all data together. The highest individual correlation coefficient was found for the twelve-week follow-up (ρ=0.639, p=0.088).

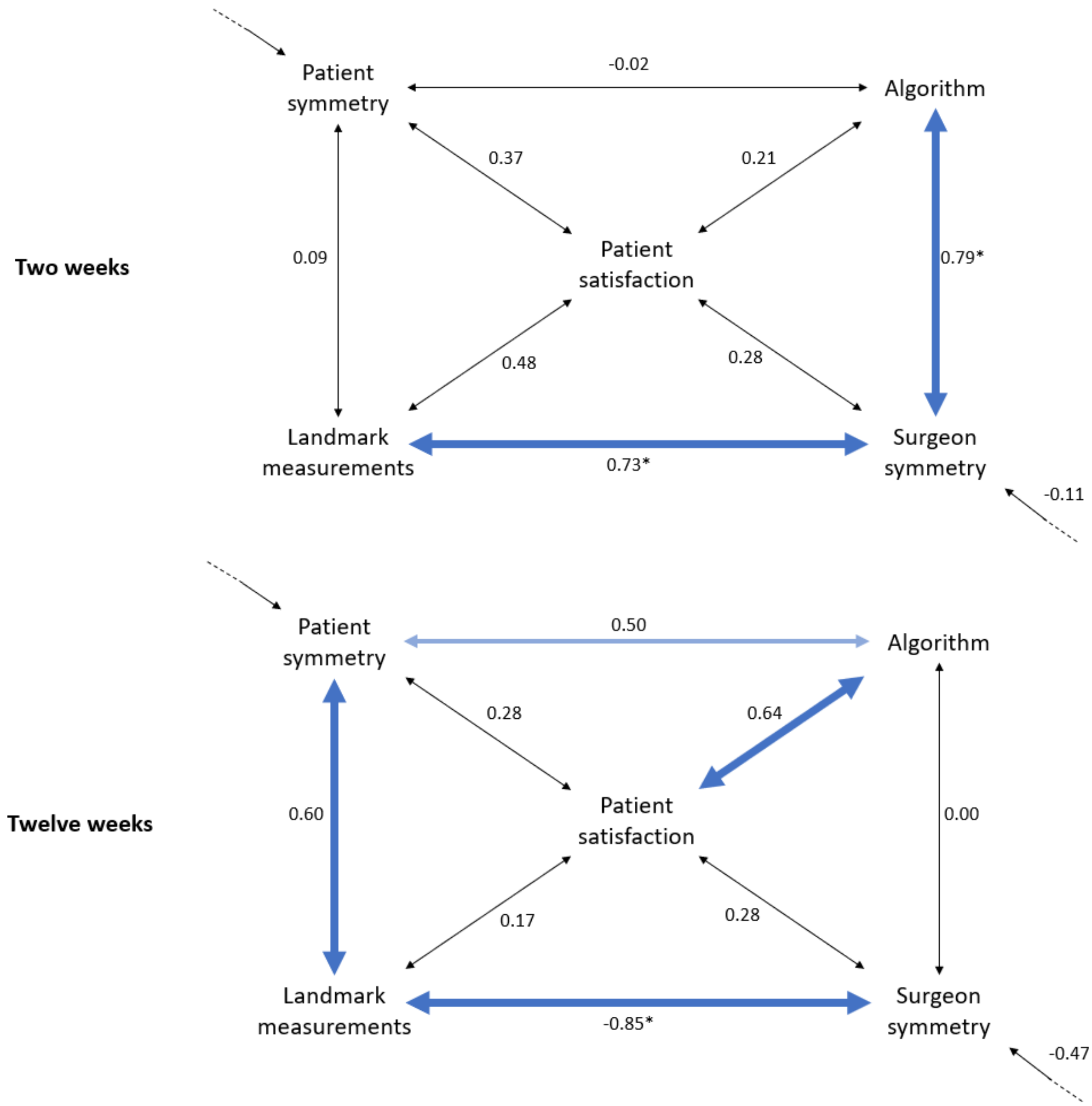

*Figure 18. Spearman's and Kruskal Wallis correlation coefficients between multiple study parameters of the two- and twelve-week follow-up. The Kruskal Wallis test is only used between the surgeon and patient symmetry score. All other correlations were found using the Spearman's rank correlation test. The boldest and dark-blue arrows indicate a correlation of 0.60 or higher. The semi-bold and light-blue arrow indicates a correlation between 0.50 and 0.60. * means a significant correlation*

Secondary outcomes

Correlation patient satisfaction and complications

Nine of the seventeen participants experienced complications after the DIEP flap reconstruction. Three participants suffered (partial) flap loss and were excluded from the study. One participant got venous thrombosis postoperative, which required secondary surgery. This participant withdrew her participation from the study. Three participants with complications continued their participation in the study. Complications varied from a hematoma, wound infection, and an allergic reaction to the prescribed corset. Two participants were lost to follow-up after the two-week postoperative follow-up. These participants suffered from nipple loss and a hematoma.

The participants with complications had a postoperative mean satisfaction of 64.3. The overall postoperative mean satisfaction was 66.0. No significant difference was found between the satisfaction of participants with or without complications.

Correlation multiple symmetry scores

An overview of all found correlations can be found in Figure 18 and **Error! Reference source not found.**. A non-significant, poor agreement was found between the patient's and surgeon's symmetry score (kappa=0.131, p=0.198).

A substantial correlation was found between the algorithm and both the patient and surgeon's symmetry score pre-operatively (respectively ρ=0.673, p=0.000; ρ=0.688, p=0.000). Additionally, a significant correlation was found between the algorithm and the surgeon's symmetry score for the two-week follow-up (ρ=0.789, p=0.000). Furthermore, a poor correlation was found between the algorithm and the two-week follow-up of the patient's symmetry score and the twelve-week follow-up of the surgeon's symmetry score.

A significant correlation was found between the landmark symmetry score and the patient's symmetry score for all data together (ρ=0.636, p=0.000). Exclusively significant correlations were found between the landmark symmetry score and the surgeon's symmetry score. Noteworthy is the negative correlation found for the twelve-week follow-up (ρ=-0.848, p=0.000).

Patient's satisfaction and symmetry score over time

The mean pre-operative patient's satisfaction was 41.8, and the two- and twelve-week postoperative patient's satisfaction was respectively 65.3 and 66.9. Only the data between pre-operative measurement and the twelve-week follow-up was significantly different. For the patient's symmetry score, a significant difference was found between the different follow-up measurements (p=0.042). However, the statistical power was not strong enough to determine the groups which have a significant difference.

Discussion

The relation between patients' breast satisfaction and multiple breast symmetry scoring methods, with a focus on the postoperative wish for secondary corrections, was explored in this study. Based on the small group sizes of this study, no significant decrease in both satisfaction and symmetry scores was found for the patients that considered secondary corrections. This emphasizes the challenge in quantifying the success of the DIEP flap reconstruction and in predicting the desire for secondary corrections. The following interpretation of the results is based on the small sample sizes of this study. Therefore, these interpretations are not conclusive. Similar analysis with larger sample sizes must be done to confirm these interpretations.

Interpretation of results

Secondary correction wish

This study found no significant differences in both patient satisfaction and patient symmetry score between the participants that did and did not consider a secondary correction during both follow-up moments. The hypothesis was that patients that were less satisfied with the outcome of the breasts, would also give themselves a lower symmetry score, and will therefore be more likely to request a secondary correction. However, the patient's satisfaction has a higher significance than the patient's symmetry score during the twelve-week follow-up. This could emphasize that the way the patient feels about her breasts after reconstruction is more important than what she objectively sees.

Correlation between patient satisfaction and symmetry scores

The patient's symmetry score has the highest overall correlation with the patient's satisfaction. However, this high correlation only agrees with the pre-operative data. The post-operative analysis has found a fair correlation. The high pre-operative correlation could be explained by the high number of participants that had a flat breast or tissue expander at the moment of pre-operative data collection. Most of these participants are not satisfied and give themselves the lowest symmetry score. Additionally, a few participants still had their natural breasts and were, therefore, more likely to be satisfied, thus giving themselves a high symmetry score. Because of the high variety, a high correlation is more easily found. The post-operative measurements are more similar to each other. It is therefore more challenging to correlate with the patient satisfaction postoperatively.

The correlation between the patient's satisfaction and the surgeon's symmetry score is low and non-significant for all follow-up moments. Besides the low number of participants, it is unknown what caused this low correlation. Both the landmark measurements and the algorithm symmetry score have a similar correlation with the patient's satisfaction when all data is combined. However, the algorithm is the only symmetry score that has a substantial correlation with the patient's satisfaction post-operatively, specifically during the twelve-week follow-up. This is not unexpected, since the algorithm is developed using fifty post-operative and pre-operative 3D photos. 3D photos with a removed breast were not used for the development of the algorithm. The algorithm is thus developed to differentiate small differences in breast symmetry. Based on these findings, the post-operative symmetry differences found using the algorithm correlate with the differences in patient satisfaction among the participants.

Correlation patient satisfaction and complications

No significant difference was found between the patient satisfaction of participants who experiences complications and participants that did not experience complications. However, the patients with more significant complications were excluded or terminated their participation. It is expected that these patients were less satisfied. Therefore, the group of participants with complications used for this analysis is not representative of all patients that experience complications after DIEP flap reconstruction.

Correlation multiple symmetry scores

Unexpectedly, no correlation is found between the patient's and surgeon's symmetry score, both overall and for the individual follow-up analysis. The low pre-operative correlation can be explained by the pre-operative state of mind. For example, a patient with tissue expanders could give her symmetry a 1, since the tissue expanders are not the breasts she wants. However, the plastic surgeon looks more objectively and sees two symmetrical breast shapes. This was reversed post-operatively. Participants scored their own symmetry higher than the plastic surgeons. It seems that the participants looked less critical at symmetry after the reconstruction. The plastic surgeons could have less difficulty to objectively score the post-operative symmetry, without considering the pre-operative state of the breasts.

Both the landmark measurement and the algorithm symmetry score have an overall substantial correlation with the surgeon's symmetry score. The algorithm had a slightly better correlation overall and two-week post-operative. However, no correlation was found for the twelve-week follow-up. Additionally, a negative correlation was found for the landmark measurements symmetry score for the twelve-week postoperative analysis. A larger study sample is required to confirm this unexplained negative correlation.

Patient's satisfaction and symmetry score over time

For both the patient's satisfaction and the patient's symmetry score, a significant difference is found between the groups over time. For the patient's satisfaction, this difference is specifically found between the pre-operative and 12-week postoperative measurements. For the patient's symmetry, the specific groups could not be determined due to the low power. However, it is expected that a difference will be found between the pre-operative and 12-week postoperative measurements. This indicates that there is a significant improvement in both patient satisfaction and symmetry score after reconstruction.

Comparison with previous literature

The mean twelve-week post-operative patient satisfaction was 67. Kouwenberg et al. found a mean satisfaction with the breasts six months after reconstruction, using the BREAST-Q questionnaire, of 71 (95% CI: 68.66–73.92) for mastectomy patients with autologous breast reconstruction (n=330) [47]. Therefore, the participants of this study scored slightly lower on satisfaction. However, the difference could be explained by the difference in follow-up moment, since the participants of Kouwenberg et al. had more recovery time. The small difference in satisfaction does implicate that the participants of this study are quite similar to the overall breast reconstruction population.

Both Yip et al. and Lesser et al. determined that no relation could be found between objective symmetry measurements and patient satisfaction [48,56]. However, this study showed that almost a significant correlation is found between the patient's satisfaction and the objective algorithm symmetry score during the twelve-week follow-up (p=0.088). The difference between these studies is that this study only used the breast satisfaction module of the BREAST-Q, instead of all modules of the questionnaire. Because this study focused on breast satisfaction, a correlation with an objective breast symmetry score could be more easily found.

A poor correlation was found between the patient's and surgeon's 12-week post-operative symmetry score. Haekens et al. found that surgeons rate breasts aesthetics higher after reconstruction than the patients [30]. Their results show a mean patient symmetry score of 5.8 for breast symmetry. The mean plastic surgeon's symmetry score is 7.3. Based on the poor correlation found in our study, no consistent difference was found between the patient's and the surgeon's symmetry scores. In our study, participants had to score their symmetry, while a 3D image of their breasts was shown. It is expected that the image helped the participants to look at their breasts more objectively. Additionally, the different breast symmetry questionnaires used in these studies could explain the difference.

Limitations

This study is the first to explore predictive outcomes for secondary corrections after a DIEP flap reconstruction. However, both time and number of participants were limited in this study. The number of participants required found with the power analysis was not met. However, the analysis of this study is done with preliminary data. It is expected that this study will continue, and more data will be collected. When the required participants found with the power analysis are met, a more conclusive analysis can be done.

Because of the small population, the correlations found in this study are speculations. For example, no correlation was found between the algorithm and the surgeon's symmetry score during the twelve-week analysis. This is unexpected since the algorithm was developed using surgeon's symmetry scores. During the algorithm validation of Chapter 3, a correlation of 0.66 was found between the surgeon's and the algorithm symmetry score. The surgeons of the validation were the same during this study. The only difference between the two scoring moments was the questionnaire. In Chapter 3, a score was given between 1-10, while a score between 1-4 was given in this symmetry study. It is expected that the limited scoring questionnaire of this study caused the correlation of 0. A larger number of participants and different questionnaires are required to determine if the findings of this study are valid.

Additionally, the follow-up period was short. The follow-up period of twelve weeks was not enough to determine the number of secondary corrections. A follow-up period of a year would give more knowledge about the number of secondary corrections and the satisfaction and symmetry scores of these participants.

Clinical relevance

Currently, the patient's aesthetic satisfaction after breast reconstruction determines if a secondary correction is required and determines therefore the success of the breast reconstruction. This study found no significant difference between the satisfaction of patients with and without a secondary correction wish. However, the number of participants in both groups was low and a p-value of 0.107 was found. It is expected that a significant difference in the patient's satisfaction will be found if a larger number of participants are included. This would mean that the patient's satisfaction would accurately predict the wish for secondary correction after breast reconstruction. The BREAST-Q questionnaire could then be used in studies such as the breast mold study, to quantify the success of the method used for the DIEP flap reconstruction.

However, the patient's satisfaction is not an objective measurement. This study found that the algorithm's symmetry score has the highest correlation with the patient's satisfaction twelve weeks post-operatively. This indicates that the algorithm could be the objective alternative to predict the wish for secondary correction and therefore the success of the breast reconstruction. The semi-automatic algorithm could improve clinical efficiency since no time is lost to questionnaires. Additionally, the algorithm eliminates differences between hospitals, which provides the possibility to directly compare studies from multiple hospitals.

For now, the study must continue to confirm the tentative conclusions drawn from the preliminary data. However, adjustments could be made to optimize the study. First, the second-week post-operative follow-up does not give consistent data among the participants. An explanation could be that two weeks after the reconstruction, the participants are more focused on recovery than the aesthetic outcome. Therefore, removing the two-week follow-up will facilitate both the participants and the researchers. Additionally, it would decrease the participants lost to follow up because of complications since they have more time to recover. Moreover, a six-month follow-up will provide data such as the execution of secondary corrections and final patient satisfaction. This would help to solidify the findings of this study.

Conclusion

This study explored the predictive value of patient satisfaction and patient symmetry scores after a DIEP flap reconstruction for the wish for a secondary correction. Furthermore, the correlations between patient satisfaction and multiple symmetry scores were explored. Based on preliminary data of this study, patient satisfaction after breast reconstruction has the highest potential to predict the patient's wish for secondary correction. Additionally, the algorithm symmetry score had the highest correlation with patient satisfaction after breast reconstruction (ρ=0.64, p=0.088). This could imply that the algorithm symmetry score can predict the wish for a secondary correction. Therefore, this study should be continued to enlarge the number of participants and therefore affirm the preliminary found conclusions.

Chapter 5. Future perspectives

A 3D printed breast mold is expected to lower the number of secondary corrections after a DIEP flap reconstruction. Level I evidence is required to prove the added value of the breast mold as compared to the current procedure. In this thesis, preparations were done for a future randomized control trial to gather the required evidence. First, the validation of the breast mold delineation protocol was performed. Second, an algorithm for objective symmetry scoring was developed. Finally, the predictive value of patient satisfaction and multiple symmetry scores for secondary corrections after a DIEP flap reconstruction was explored. Based on small sample sizes, the breast mold delineation method seems adequate to be used in future studies. Furthermore, an algorithm is developed using the mean curvature and the point distances between the superimposed left and right breast for breast shape analysis. The found symmetry scores of the algorithm had a high correlation with the used gold standard (n=3). Lastly, the potential predictive value of the patients' satisfaction was found for the wish for a secondary correction after DIEP flap reconstruction. Additionally, promising correlations were found between the patient's satisfaction and the algorithm symmetry score and the surgeon's symmetry score and the algorithm symmetry score respectively two and twelve weeks after the DIEP flap reconstruction. It should be noted that the findings of these studies are based on small sample sizes and therefore not conclusive. However, the outcomes of this thesis contribute to an efficiency study, using a randomized clinical trial that is needed to provide the level I evidence.

Breast mold

Future perspective

Differences were found in the delineated breast area between the plastic surgeon and the breast mold. However, the questionnaire filled in by the plastic surgeon showed that the delineation for the breast mold is correct. The usage of alternative landmarks to reduce the area delineated for the breast mold was explored. However, no landmarks that would make the delineated breast area smaller were found. Therefore, this study advised to accept the current breast mold design and to use this breast mold in future studies.

Currently, the Canfield Vectra XT system (Canfield Sci, New Jersey, USA) is used as imaging technique for the breast mold. The Vectra is only available in both Radboudumc and ZGT Hengelo, resulting in a large travel distance for patients from MST and ZGT Almelo. In the last few months, studies evaluated the use of different handheld 3D scanners to create a 3D model of the patient's chest [62,63]. Advantages of a handheld 3D scanner are the mobility of the scanner and the lower costs than the Vectra. It was found that both the Structure Sensor Pro (Occipital, Inc, Boulder, CO, USA) and Revopoint Pop had higher accuracy compared to the Vectra when scanning the breasts. The Structure Sensor is slightly more preferred, because of the user-friendliness and low costs [63]. However, a sufficient and secure method to export the data must be found before this handheld scanner could be used in the clinic.

The breast mold is only useable for patients with a planned unilateral DIEP flap reconstruction while being satisfied with their contralateral breast. Based on the experience of plastic surgeons, the number of unilateral DIEP flap reconstructions without a direct lift or reduction on the contralateral side is reduced over the last years. Therefore, the breast mold can only be used on an unknown percentage of the total DIEP flap reconstruction patients. However, the breast mold could also be used for patients that require a secondary correction after DIEP flap reconstruction. The breast mold could increase the success rate of these corrections. A clinical trial is required to establish the added value of the breast mold for both the unilateral DIEP flap reconstruction patients and the secondary correction patients.

Regulations

A standardized workflow is required for the correct implementation of the breast mold. The first workflow was developed specifically for Radboudumc and was adjusted for MST and ZGT procedures [64]. This workflow consists of the following steps: informed consent of the patient is obtained; a 3D photo of the patient is taken; the breast mold is designed by 3D lab MST based on the 3D photo; the breast mold is printed at Oceanz in Polyamide 12 (PA12); the breast mold is sent to the hospital's Centrale Sterilisatie Afdeling (CSA) by Oceanz; the breast mold is sterilized by CSA; the sterilized breast mold is sent to the operation complex by the CSA.

The breast mold is classified as 'class Is' according to the Medical Device Regulation (MDR). At the moment, 3D Medical Models is responsible for the fabrication of the breast mold. 3D lab MST delivers the breast mold designs according to pre-arranged agreements. Oceanz 3D prints the breast molds by order of 3D Medical Models. Oceanz possesses the required ISO certification (ISO 13485) and complies with the MDR. Therefore, the breast mold complies with all requirements for medical devices. However, 3D lab MST aims to print the breast mold themselves with Surgical Guide Resin using the Form 3 3D printer (Formlabs Inc., Somerville, USA) in the future. This aim will make 3D lab MST the responsible fabricator. At the moment, 3D lab MST is working on the procedure to meet all requirements of the MDR.

Algorithm

Current algorithm

An algorithm was developed to objectively quantify breast symmetry based on 3D photos. This algorithm uses the mean curvature and the point distances between the superimposed left and right breast for breast shape analysis. The algorithm explained 70.3% of the dataset used during development (adjusted R^2). The found consistency interclass correlation coefficient during validation was substantial (0.657). Additionally, the reproducibility of the algorithm was high, with an absolute interclass correlation coefficient of 0.962. The substantial ICC between surgeon and algorithm found during validation was also found in the two weeks follow-up of the symmetry study described in Chapter 4 (see Figure 19). However, no correlation was found between the surgeon and the algorithm during the twelve-week follow-up. Using visual inspection per patient, the algorithm seemed to give a higher symmetry score if the breast symmetry improved between the two- and twelve-week follow-up. The surgeon's symmetry score does not seem to behave aberrantly. However, in some cases, the algorithm symmetry score improved for a patient while the surgeon's symmetry score remained the same. Additionally, the surgeon's symmetry score increased for some participants, while the algorithm symmetry score did not change. This behavior, in combination with the low number of participants in the twelfth week and the limited surgeon's scoring method (score of 1-4), could explain the found correlation coefficient of 0.00.

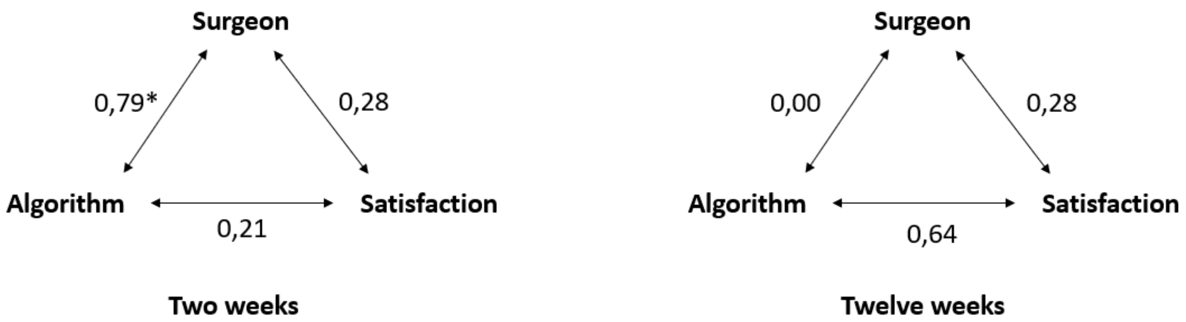

*Figure 19. Spearman's correlation coefficients found between the surgeon's symmetry score, the algorithm's symmetry score, and the patient satisfaction at two and twelve week follow up. The star * indicates a significant correlation*

Optimizing the algorithm

Based on the studies described in this thesis, the algorithm delivers promising results. However, a critical note remains that the algorithm is developed using the surgeon's opinion as the gold standard. This means that the objective algorithm is based on a subjective gold standard. The surgeon's symmetry score was chosen because of the lack of alternative, validated, and objective symmetry scores. Only three plastic surgeons from the same hospital were used to determine the gold standard. The gold standard would be more objective if the symmetry scores were determined using a larger number of plastic surgeons, who differ in experience and are working in different hospitals throughout The Netherlands. Additionally, the more 3D photos are added to the database, the better the algorithm will become.

Randomized clinical trial

Study parameters

During the symmetry study described in Chapter 4, the added value of various study parameters was explored for the upcoming RCT. The first study parameter was the patient's satisfaction. This parameter is the gold standard for secondary corrections and therefore recommended to be used in the RCT. A second reason to use the patient's satisfaction is the potential difference between patients with and without a secondary correction wish.

Secondly, the surgeon's symmetry score was explored. Although no correlation between the surgeon's symmetry score and the patient's satisfaction was found in this study, it is advised to keep this parameter in upcoming studies, since this symmetry score is the gold standard of the semi-objective symmetry scores. However, an alternative symmetry questionnaire is suggested. The alternative questionnaire should have a wider range such that the output becomes continuous instead of ordinal, preferably between 0 and 10. This will enable a more accurate statistical analysis. Furthermore, this score could be directly used for the development database during the further development of the algorithm.

The third study parameter was the patient's symmetry score. This score does not correlate with the surgeon's symmetry score, and only a substantial correlation was found with the patient's satisfaction pre-operatively. It is expected that the physiological aspect significantly affects the objectiveness of this symmetry score. Therefore, it is advised to remove this parameter from future studies. Alternatively, an alternative scoring method should be chosen if the patient's symmetry score will be used in future studies.

The fourth parameter was the landmark symmetry score. This study found no correlation between the landmark symmetry score and the patient's satisfaction. However, high correlations were found between this symmetry score and the surgeon's symmetry score. Notable is the negative correlation found between this symmetry score and the plastic surgeon's symmetry score. No explanation has been found for this occurrence, other than unreliable outcomes due to the small sample size. It must be considered if the landmark measurement score will have added value for future studies. Viewing from one side, this method is the first to quantitively score symmetry based on landmarks, without including the nipple and therefore inclusive for all DIEP flap reconstruction patients. This could therefore fill a gap in current DIEP flap reconstruction studies. On the other hand, this method is not validated. If this parameter would be added to the RCT, this will only be done to validate this landmark measurement method using the surgeon's symmetry score. Furthermore, interobserver variations are often found during landmarks selection [65]. Lastly, a secondary 3D photo with landmarks must be taken for this measurement. This more than doubles the time required to collect the 3D photos. Therefore, it is suggested to not use the landmark symmetry score during the upcoming RCT.

The fifth and last study parameter was the algorithm’s symmetry score. Of all postoperative measurements, the algorithm’s symmetry score has the highest correlation with the patient’s satisfaction during the twelfth week. Additionally, a high correlation between the algorithm and the surgeon’s symmetry score was found both pre-operatively and two weeks postoperatively. Although the algorithm is not yet validated and must be further developed, the results of the symmetry study are promising. Additionally, the algorithm requires no time or burden from the physician or patient. Therefore, it is suggested to add the algorithm during the RCT.

In conclusion: it is advised to use the patient’s satisfaction score using the BREAST-Q questionnaire, the surgeon’s symmetry score using an alternative questionnaire, and the algorithm’s symmetry score for upcoming studies. However, it should be noted that these conclusions are based on preliminary data.

Study design

The proposed study design for a future RCT is a national multicenter double-blinded randomized control study. MST, ZGT, and Radboudumc will be participating centers. The number of required participants should be estimated using a power analysis. The intervention and control groups will have an equal number of participants. The breast mold will be used during the DIEP flap reconstruction for the intervention group. Both the participant and the non-attending plastic surgeon will not know if a mold is used for the participant when scoring the breast symmetry. A follow-up period of 52 weeks is advised to confirm any secondary corrections. The duration of the study will be based on the required number of participants.

Chapter 6. Conclusion

Level I evidence is required to prove the added value of the 3D-printed breast mold during the DIEP flap reconstruction. This study 1) found that the landmarks used for breast delineation for the breast mold seem adequate for future studies, 2) developed an objective algorithm that quantitatively scores breast symmetry using curvature and the root mean square of the distances found between superimposed breasts, and 3) found the potential predictive value of patient's satisfaction for the wish of a secondary correction after breast reconstruction. Furthermore, promising correlations were found between the patient's satisfaction and the algorithm symmetry score and the surgeon's symmetry score and the algorithm symmetry score respectively two and twelve weeks after the DIEP flap reconstruction, based on preliminary data. In conclusion, the breast mold may be used in a clinical setting based on its current design, although continued validation with a larger sample size is advised. Furthermore, promising study parameters were found to quantify the success of a DIEP flap reconstruction. Although these study parameters must be further explored, preparations can be made to set up a randomized control trial to gather the required evidence of the effectiveness of the breast mold.

Chapter 7. References

1. NKR Cijfers. Accessed March 31, 2022. https://iknl.nl/nkr-cijfers

2. Borstkanker. Accessed March 31, 2022. https://www.nabon.nl/download/folder-borstkankercijfers-1989-2019

3. Kouwenberg CAE, De Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg*. Published online 2020:1-13. doi:10.1097/PRS.0000000000006887

4. Howes BHL, Watson DI, Xu C, et al. Quality of life following total mastectomy with and without reconstruction versus breast-conserving surgery for breast cancer: A case-controlled cohort study. *J Plast Reconstr Aesthetic Surg*. 2016;69(9):1184-1191. doi:10.1016/j.bjps.2016.06.004

5. Engel J, Kerr J, Schlesinger-Raab et al. *Quality of Life Following Breast-Conserving Therapy or Mastectomy: Results of a 5-Year Prospective Study*. Vol 10.; 2004.

6. Guyomard V, Leinster S, Wilkinson M. Systematic review of studies of patients' satisfaction with breast reconstruction after mastectomy. *Breast*. 2007;16(6):547-567. doi:10.1016/j.breast.2007.04.004

7. Sarwer DB, Infield AL. Body Image and Other Psychological Issues in Breast Augmentation. *Breast Augment Princ Pract*. Published online 2009:117-125. doi:10.1007/978-3-540-78948-2_14

8. Farhangkhoee H, Matros E, Disa J. Trends and concepts in post-mastectomy breast reconstruction. *J Surg Oncol*. 2016;113(8):891-894. doi:10.1002/JSO.24201

9. Allen R, Treece P. Deep inferior epigastric perforator flap for breast reconstruction. *Ann Plast Surg*. 1994;32:32–38. doi:10.1097/00000637-199401000-00007

10. Jonker J. *A Cost-Effectiveness Analysis of a Breast Reconstruction Method Combined with a 3D Printed Mold Compared to a Conventional Breast Reconstruction without a 3D Printed Mold for Unilateral Reconstruction [Unpublished Work]s*.; 2021.

11. Ries E. *The Lean Startup: How Today's Entrepreneurs Use Continuous Innovation to Create Radically Successful Businesses*. Crown Business; 2011.

12. Liker J. *The Toyota Way: 14 Management Principles from the World's Greatest Manufacturer*. McGraw-Hill; 2004.

13. Tomita K, Yano K, Hata Y,et al. DIEP Flap Breast Reconstruction Using 3-dimensional Surface Imaging and a Printed Mold. *Plast Reconstr Surg - Glob Open*. 2015;3(3):e316. doi:10.1097/GOX.0000000000000288

14. Hummelink S, Verhulst AC, Maal TJJ, et al. Applications and limitations of using patient-specific 3D printed molds in autologous breast reconstruction. *Eur J Plast Surg*. 2018;41(5):571-576. doi:10.1007/s00238-018-1430-3

15. Eder M, Waldenfels F v., Swobodnik A, et al. Objective breast symmetry evaluation using 3-D surface imaging. *Breast*. 2012;21(2):152-158. doi:10.1016/j.breast.2011.07.016

16. Gelati C, Lozano Miralles ME, Morselli PG, et al. Deep Inferior Epigastric Perforator Breast Reconstruction With Computer-Aided Design/Computer-Aided Manufacturing Sizers. *Ann Plast Surg*. 2020;84(1):24-29. doi:10.1097/SAP.0000000000002020

17. Troost J. *Usability Study to Obtain Design and Manufacturing Recommendations for the Optimal*

3D Printed Mold for Autologous Breast Reconstruction. *[Unpublished Work]*; 2020.

18. Enajat M, Smit JM, Rozen WM, et al. Aesthetic refinements and reoperative procedures following 370 consecutive DIEP and SIEA flap breast reconstructions: Important considerations for patient consent. *Aesthetic Plast Surg*. 2010;34(3):306-312. doi:10.1007/s00266-009-9424-y

19. Lee HY, Hong K, Kim EA. Measurement protocol of women's nude breasts using a 3D scanning technique. *Appl Ergon*. 2004;35(4):353-359. doi:10.1016/j.apergo.2004.03.004

20. Van Kuipers T. *Improvement of Autologous Breast Reconstruction Using 3D Techniques [Unpublished Work]*.; 2020.

21. Mikołajczyk M, Kasielska-Trojan A, Antoszewski B. A New Tool for Breast Anthropometric Measurements: Presentation and Validation for Women and Men. *Aesthetic Plast Surg*. 2019;43(5):1160-1170. doi:10.1007/s00266-019-01467-6

22. Wesselius TS, Vreeken RD, Verhulst AC, et al. New software and breast boundary landmarks to calculate breast volumes from 3D surface images. *Eur J Plast Surg*. 2018;41(6):663-670. doi:10.1007/s00238-018-1431-2

23. Losken A, Seify H, Denson DD, et al. Validating three-dimensional imaging of the breast. *Ann Plast Surg*. 2005;54(5):471-476. doi:10.1097/01.sap.0000155278.87790.a1

24. Kovacs L, Eder M, Hollweck R, et al. New aspects of breast volume measurement using 3-dimensional surface imaging. *Ann Plast Surg*. 2006;57(6):602-610. doi:10.1097/01.SAP.0000235455.21775.6A

25. Liu C, Luan J, Ji K, et al. Measuring volumetric change after augmentation mammaplasty using a three-dimensional scanning technique: An innovative method. *Aesthetic Plast Surg*. 2012;36(5):1134-1139. doi:10.1007/S00266-012-9944-8/FIGURES/7

26. Tepper OM, Unger JG, Small KH, et al. Mammometrics: The standardization of aesthetic and reconstructive breast surgery. *Plast Reconstr Surg*. 2010;125(1):393-400. doi:10.1097/PRS.0b013e3181c4966e

27. Filiberti AI, Rimoldi A, Tamburini M, et al. *Breast Reconstruction: A Psychological Survey*. Vol 12.; 1989.

28. Eltahir Y, Werners LLCH, Dreise MM, et al. Quality-of-life outcomes between mastectomy alone and breast reconstruction: comparison of patient-reported BREAST-Q and other health-related quality-of-life measures. *Plast Reconstr Surg*. 2013;132(2). doi:10.1097/PRS.0B013E31829586A7

29. Maass SWMC, Bagher S, Hofer SOP, et al. Systematic Review: Aesthetic Assessment of Breast Reconstruction Outcomes by Healthcare Professionals. *Ann Surg Oncol*. 2015;22(13):4305-4316. doi:10.1245/s10434-015-4434-2

30. Haekens CM, Enajat M, Keymeulen K, et al. Self-esteem and patients' satisfaction after deep inferior epigastric perforator flap breast reconstruction. *Plast Surg Nurs*. 2011;31(4):160-166. doi:10.1097/PSN.0B013E318231AD8A

31. Damen THC; Mureau MAM; Timman R; et al. The pleasing end result after DIEP flap breast reconstruction: a review of additional operations | Elsevier Enhanced Reader. Journal of Plastic, Reconstructive & Aesthetic Surgery. doi:10.1016/j.bjps.2007.09.045

32. Li D, Cheong A, Reece GP, et al. Computation of breast ptosis from 3D surface scans of the female torso. *Comput Biol Med*. 2016;78:18-28. doi:10.1016/J.COMPBIOMED.2016.09.002

33. Cardoso MJ, Cardoso J, Amaral N, et al. Turning subjective into objective: The BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. *The Breast*. 2007;16(5):456-461. doi:10.1016/J.BREAST.2007.05.002

34. Fitzal F, Krois W, Trischler H, et al. The use of a breast symmetry index for objective evaluation of breast cosmesis. *Breast*. 2007;16(4):429-435. doi:10.1016/j.breast.2007.01.013

35. Bowman AW, Katina S, Smith J, et al. Anatomical curve identification. *Comput Stat Data Anal*. 2015;86:52-64. doi:10.1016/j.csda.2014.12.007

36. Catanuto G, Spano A, Pennati A, et al. Experimental methodology for digital breast shape analysis and objective surgical outcome evaluation. *J Plast Reconstr Aesthetic Surg*. 2008;61(3):314-318. doi:10.1016/j.bjps.2006.11.016

37. Losken A, Fishman I, Denson DD, et al. An objective evaluation of breast symmetry and shape differences using 3-dimensional images. *Ann Plast Surg*. 2005;55(6):571-575. doi:10.1097/01.sap.0000185459.49434.5f

38. Xi W, Perdanasari AT, Ong Y, et al. Objective Breast Volume, Shape and Surface Area Assessment: A Systematic Review of Breast Measurement Methods. *Aesthetic Plast Surg*. 2014;38(6):1116-1130. doi:10.1007/s00266-014-0412-5

39. Seoud L, Ramsay J, Parent S, et al. A novel fully automatic measurement of apparent breast volume from trunk surface mesh. *Med Eng Phys*. 2017;41:46-54. doi:10.1016/j.medengphy.2017.01.004

40. Catanuto G, Taher W, Rocco N, et al. Breast Shape Analysis with Curvature Estimates and Principal Component Analysis for Cosmetic and Reconstructive Breast Surgery. *Aesthetic Surg J*. 2019;39(2):164-173. doi:10.1093/asj/sjy070

41. stlread - File Exchange - MATLAB Central. Accessed March 31, 2022. https://nl.mathworks.com/matlabcentral/fileexchange/6678-stlread

42. Patch Curvature - File Exchange - MATLAB Central. Accessed March 31, 2022. https://nl.mathworks.com/matlabcentral/fileexchange/32573-patch-curvature?s_tid=srchtitle

43. Smith LI. A tutorial on Principal Components Analysis Chapter 1. Published online 2002.

44. Besl PJ, McKay ND. A Method for Registration of 3-D Shapes. *IEEE Trans Pattern Anal Mach Intell*. 1992;14(2):239-256. doi:10.1109/34.121791

45. Ochoa O, Garza R, Pisano S, et al. Prospective Longitudinal Patient-Reported Satisfaction and Health-Related Quality of Life following DIEP Flap Breast Reconstruction: Relationship with Body Mass Index. *Plast Reconstr Surg*. 2019;143(6):1589-1600. doi:10.1097/PRS.0000000000005616

46. Tallroth L, Velander P, Klasson S. A short-term comparison of expander prosthesis and DIEP flap in breast reconstructions: A prospective randomized study. *J Plast Reconstr Aesthetic Surg*. 2021;74(6):1193-1202. doi:10.1016/j.bjps.2020.10.104

47. Kouwenberg CAE, De Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg*. 2020;146(1). doi:10.1097/PRS.0000000000006887

48. Yip JM, Watson DI, Tiggemann M, et al. Determinants of breast reconstruction outcome: How important is volume symmetry? *J Plast Reconstr Aesthetic Surg*. 2015;68(5):679-685. doi:10.1016/j.bjps.2014.12.038

49. Sugrue R, MacGregor G, Sugrue M, et al. An evaluation of patient reported outcomes following breast reconstruction utilizing Breast Q. *Breast*. 2013;22(2):158-161. doi:10.1016/j.breast.2012.12.001

50. Cano SJ, Klassen AF, Scott AM, et al. A Closer Look at the BREAST-Q©. *Clin Plast Surg*. 2013;40(2):287-296. doi:10.1016/J.CPS.2012.12.002

51. Chen CM, Cano SJ, Klassen AF, et al. Measuring Quality of Life in Oncologic Breast Surgery: A Systematic Review of Patient-Reported Outcome Measures. *Breast J*. 2010;16(6):587-597. doi:10.1111/j.1524-4741.2010.00983.x

52. Thomson HJ, Potter S, Greenwood RJ, et al. A prospective longitudinal study of cosmetic outcome in immediate latissimus dorsi breast reconstruction and the influence of radiotherapy. *Ann Surg Oncol*. 2008;15(4):1081-1091. doi:10.1245/S10434-007-9772-2/TABLES/3

53. Spear SL, Baker JL. Classification of capsular contracture after prosthetic breast reconstruction. *Plast Reconstr Surg*. 1995;96(5):1119-1123. doi:10.1097/00006534-199510000-00018

54. Cohen M, Evanoff B, George LT, et al. A subjective rating scale for evaluating the appearance outcome of autologous breast reconstruction. *Plast Reconstr Surg*. 2005;116(2):440-449. doi:10.1097/01.PRS.0000173214.05854.E4

55. Teo I, Reece GP, Huang SC, et al. Body image dissatisfaction in patients undergoing breast reconstruction: Examining the roles of breast symmetry and appearance investment. *Psychooncology*. 2018;27(3):857-863. doi:10.1002/pon.4586

56. Leser C, Tan YY, Singer C, et al. Patient satisfaction after breast cancer surgery: A prospective clinical trial. *Wien Klin Wochenschr*. 2021;133(1-2):6-13. doi:10.1007/s00508-020-01730-w

57. Cohen WA, Mundy LR, Ballard TNS, et al. The BREAST-Q in surgical research: A review of the literature 2009-2015. *J Plast Reconstr Aesthetic Surg*. 2016;69(2):149-162. doi:10.1016/j.bjps.2015.11.013

58. Dean NR, Crittenden T. A five year experience of measuring clinical effectiveness in a breast reconstruction service using the BREAST-Q patient reported outcomes measure: A cohort study. *J Plast Reconstr Aesthetic Surg*. 2016;69(11):1469-1477. doi:10.1016/j.bjps.2016.08.015

59. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods 2007 392*. 2007;39(2):175-191. doi:10.3758/BF03193146

60. Van Kuipers T. *Werkprotocol Fotografie (3)*.; 2020.

61. Cohen J. Statistical Power Analysis for the Behavioral Sciences Second Edition.

62. Linden S. *Comparing IPhoneX, Revopoint Pop and Vectra XT 3D Scanners for Patient-Specific Molds Used for Autologous Breast Reconstruction. Master 2 Technical Medicine Internship Report [Unpublished Work]*.; 2021.

63. Everink S. *A Handheld 3d Scanner as Alternative for the Vectra Xt for the Creation of 3D Breast Models. Master 2 Technical Medicine Internship Report [Unpublished Work]*.; 2022.

64. Ooms A. *Implementation of Sterilized 3d-Printed Breast Molds for Autologous Breast Reconstructions. Master 2 Technical Medicine Internship Report [Unpublished Work]*; 2021.

65. Henseler H, Smith J, Bowman A, et al. Objective evaluation of the latissimus dorsi flap for breast reconstruction using three-dimensional imaging. *J Plast Reconstr Aesthetic Surg*. 2012;65(9):1209-1215. doi:10.1016/j.bjps.2012.03.043