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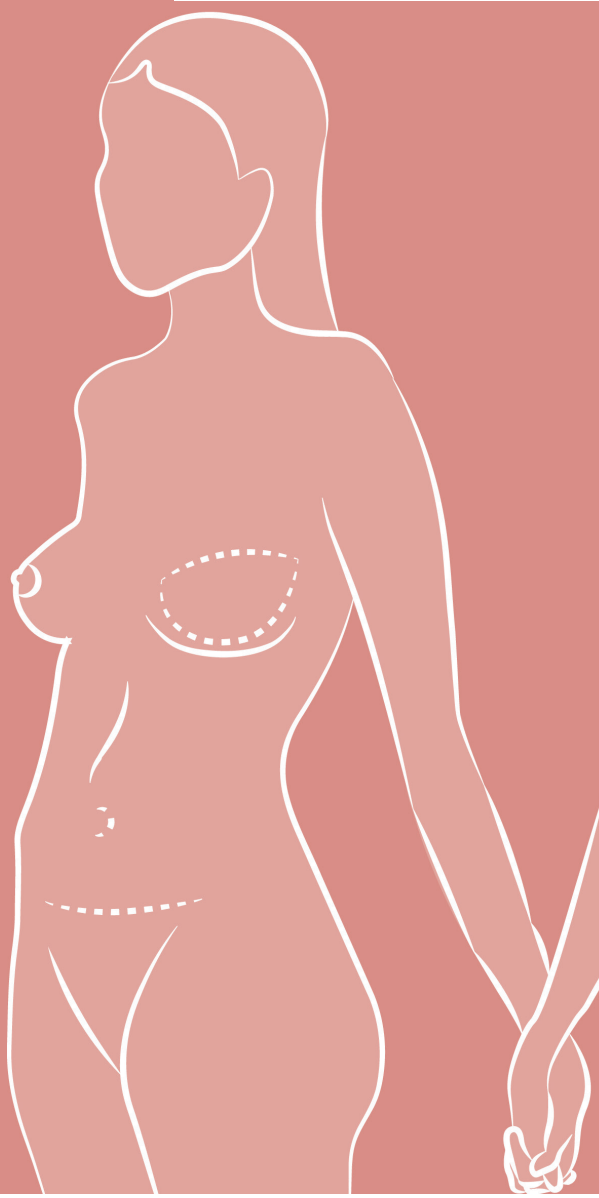
LINDA TALLROTH
DEPT OF CLINICAL SCIENCES MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY



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Linda Tallroth

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine, Lund University, to be publicly defended at 09.00 on May 12, 2023, in the Department of Otorhinolaryngology's lecture hall, Jan Waldenströms Gata 18, 1st floor, Skåne University Hospital, Malmö

Faculty opponent
Associate Professor Maria Mani, M.D., Ph.D.

Uppsala University Hospital, Sweden

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Abstract

A breast reconstruction is an integrated part of the breast cancer journey with the primary aim of improving quality of life (QoL). The overall aim of this thesis is to compare outcomes following use of two common breast reconstruction methods, the expander prosthesis (EP) and the deep inferior epigastric perforator (DIEP) flap.

In **Paper I**, 73 patients were randomised to breast reconstruction with an EP or with a DIEP flap. Complications and costs were recorded for the first 30 postoperative days. The patient-reported outcome (PRO) was measured with the BREAST-Q questionnaire preoperatively and two years postoperatively. The EP group had significantly fewer complications and costs, but the DIEP flap group had higher satisfaction with their breasts.

Paper II examined breast softness with applanation tonometry and with a BREAST-Q question. The DIEP flap group demonstrated softer breasts and reported a higher subjective satisfaction rate regarding the softness of their reconstructed breasts.

Paper III evaluated local oedema of the breasts and patient-reported symptoms related to breast oedema. No difference in measured local tissue water (LTW) was found between the EP and the DIEP flap reconstructions and no breast oedema-related symptoms were detected.

In **Paper IV**, the reliability of an aesthetic outcome assessment scale was evaluated. Overall, the intra-rater and inter-rater agreements were moderate to substantial. There was a tendency towards better aesthetic outcomes following breast reconstruction with the DIEP flap.

Paper V compared the PRO, breast sensibility and complications taking a five-year perspective. Satisfaction with breast was higher in the DIEP flap group. In contrast, sensibility was better in the EP reconstructions. The number of overall complications was comparable between the two breast reconstruction groups.

To conclude this thesis, a successful choice of breast reconstruction method begins with a well-informed patient, and professional guidance with respect to individual preferences and characteristics. A DIEP flap breast reconstruction may be preferred over an EP when considering many important aspects; however, it is not a suitable method for all patients.

Key words: Breast reconstruction, Deep inferior epigastric perforator flap, Expander prosthesis, Patient-reported outcome, Clinical outcomes

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DIEP flap and expander prosthesis in breast reconstruction

Linda Tallroth

LUND
UNIVERSITY

Main supervisor

Associate Professor Magnus Becker, M.D.,Ph.D.

Co-supervisors

Stina Klasson, M.D., Ph.D.

Patrik Velander, M.D.,Ph.D.

Nathalie Mobargha, M.D.,Ph.D.

Lund University, Faculty of Medicine

Department of Clinical Sciences Malmö

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To my family

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Original papers

Paper I

Tallroth L, Velander P, Klasson S. A short-term comparison of expander prosthesis and DIEP flap in breast reconstructions: A prospective randomized study. Journal of plastic, reconstructive & aesthetic surgery: JPRAS. 2021;74(6):1193-202.

Paper II

Tallroth L, Brorson H, Mobargha N, Velander P, Klasson S, Becker M. Breast softness in patients randomised to postmastectomy breast reconstruction with an expander prosthesis or DIEP flap. European Journal of Plastic Surgery. 2021.

Paper III

Tallroth L, Brorson H, Mobargha N, Velander P, Klasson S, Becker M. Assessment of local tissue water in breasts following breast reconstruction with an expander prosthesis or DIEP flap. Journal of plastic surgery and hand surgery. 2021:1-7.

Paper IV

Tallroth L, Mobargha N, Velander P, Klasson S, Becker M. Evaluation of an assessment scale for aesthetic outcome in breast reconstructions based on digital photos in both 2D and 3D format. Journal of plastic surgery and hand surgery. 2022:1-7.

Paper V

Tallroth L, Mobargha N, Velander P, Becker M, Klasson S. Expander prosthesis and DIEP flap breast reconstruction: A five-year follow-up study. In manuscript

Abstract

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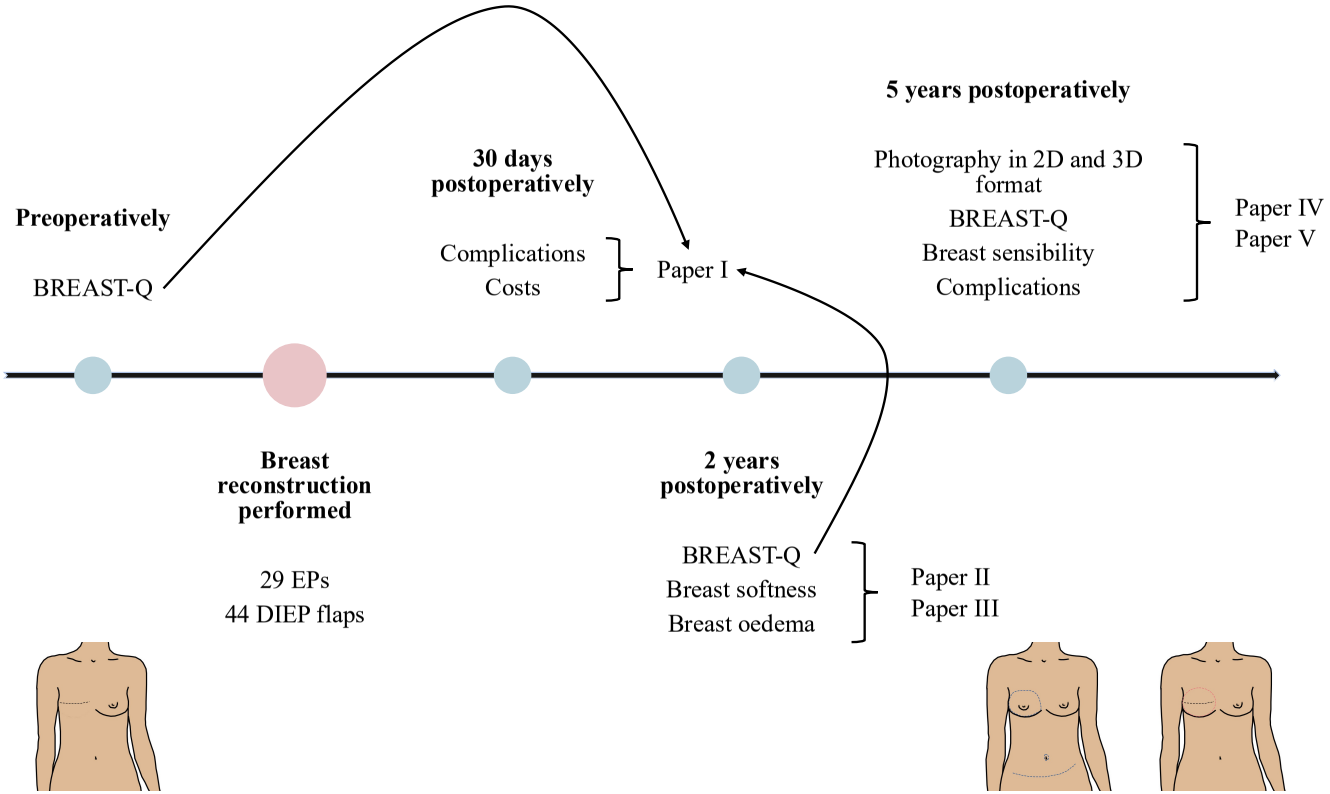
Thesis at a glance



Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ABR	Autologous breast reconstruction
BCCT.core	Breast cancer conservative treatment cosmetic results
BCS	Breast-conservation surgery
BIA-ALCL	Breast implant-associated anaplastic large cell lymphoma
BII	Breast implant illness
BMI	Body mass index
CDC	Clavien-Dindo Classification
DIEP	Deep inferior epigastric perforator
EP	Expander prosthesis
IBBR	Implant-based breast reconstruction
ICG	Indocyanine green
LTW	Local tissue water
MID	Minimal important difference
MRI	Magnetic resonance imaging
NAC	Nipple-areolar complex
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
RT	Radiation therapy
SIEA	Superficial inferior epigastric artery
TDC	Tissue dialectic constant
TRAM	Transverse rectus abdominis myocutaneous
QoL	Quality of life

Introduction

The breast

Development of the female breast starts at the fifth to seventh gestational week and its maturation process proceeds during thelarche (1). The breast consists of adipose, glandular, and ductal tissues and is located between the second and the sixth rib. There is little inherent structural support to the breast tissue, which becomes evident in women with large breast volumes. Through gravitational forces, the breast will adopt a natural ptotic shape with a lower fullness. However, some support and shape are provided by fibrous structures called Cooper's ligaments. With age, the breast undergoes several changes as the Cooper's ligaments relax, and the skin loses its elasticity. Decreasing oestrogen levels result in a reduction of glandular and ductal tissues, making the breast softer and more ptotic (2).

Arteries and veins circulating the breast follow different pathways. The breast receives its arterial supply from perforators of the internal mammary artery arising medially from intercostal spaces, from the lateral thoracic artery and, from anterior and lateral intercostal arteries. The venous drainage is divided into a superficial and a deep system with its main drainage into the internal mammary vein. Lymphatic vessels in the breast follow similar pathways as the venous system. In contrast, the lymphatic vascular system drains mainly into the ipsilateral axillary lymph nodes (75%), and a smaller part into other nodes as with the internal mammary lymph nodes (3).

The breast is well innervated by sensory nerve branches. Deep and superficial branches derived from the second to sixth anterior and lateral cutaneous intercostal nerves, and the supraclavicular nerve supply the breast (**Figure 1**). The nipple-areolar complex (NAC) receives its innervation primarily from the fourth lateral intercostal nerve and partially, with individual variations, from the second to sixth intercostal nerves (3, 4).

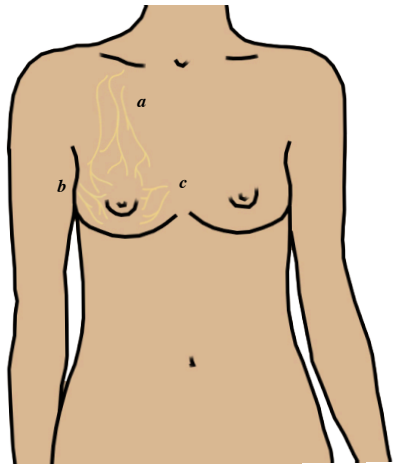


Figure 1. An illustration of the nerve supply to the breast.
The breast is innervated by branches from the supraclavicular nerve (a), the lateral cutaneous intercostal nerves (b) and the anterior cutaneous intercostal nerves (c).

Breast cancer

In Sweden in 2021, 8619 women were diagnosed with breast cancer, thus making it the most common type of cancer in women (5). During the same year, the highest incidence occurred between the ages of 70 and 74. As a result of advancements in breast cancer treatments in the last few decades, the ten-year relative survival rate in Sweden 2020 was 86.2% (6).

Most breast cancers are sporadic. Risk factors include postmenopausal obesity, early menarche, older age at first pregnancy, and exposure to oestrogen (7-10). Breast cancers can also be inherited. The two most common gene mutations are the BRCA1 and the BRCA2 genes. Today, women carrying these high-risk genes are offered genetic counselling and risk-reducing surgeries.

Lymphoma of the breast is currently an issue of high interest with its reported association to breast implants (11). The breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) differs from breast cancer regarding histopathology and treatment. The primary treatment for BIA-ALCL is capsulectomy with removal of the implant (12). Although an association with macro-textured implants has been found, the absolute risk of BIA-ALCL is very small. A cumulative risk of 82 per million at age 70 was reported in a Dutch population (11). In Sweden in 2020, a total of eight cases was confirmed (13).

Breast cancer treatment includes surgery, radiation therapy (RT), chemotherapy, endocrine therapy, and immune therapy. Surgery is the most common treatment, and the options are complete surgical removal of the breast tissue, mastectomy, and breast-conserving surgery (BCS). The choice of surgical technique is guided by tumour-specific factors, the size of the breast and the patient's own preference. In a review of breast cancer patients in Sweden between the years 2017 and 2020, mastectomy was performed in 26% and BCS in 73% of case (14). Patients who undergo a mastectomy are offered breast reconstruction, aiming to increase or preserve quality of life (QoL). In a recently performed national survey-based study, the breast reconstruction rate following a mastectomy was estimated to be 31% in Swedish women (15).

Breast reconstruction

Compared to healthy women, patients undergoing mastectomy have been associated with higher levels of depression and lower QoL (16, 17). Mastectomy followed by breast reconstruction minimises these adverse outcomes (18-21). A breast reconstruction can be performed either immediately, concurrently to the mastectomy, or in a delayed setting.

The history of breast reconstruction

The first documented successful attempt at a breast reconstruction was performed by the German surgeon Vincenz Czerny in 1895. In his published work, he transferred a lumbar lipoma to a mastectomy site (22). At the beginning of the 1900s, the Italian surgeon Iginio Tansini was the first to describe the latissimus dorsi (LD) myocutaneous flap in postmastectomy breast reconstruction (23, 24).

The use of implants for breast reconstruction dates back to the 1960s when the silicone breast implant was introduced and later refined (25). Although developed for augmentation purposes, implants were soon also used for breast reconstruction. An increased use of breast implants was followed by concerns regarding their longevity (24). The alternative to implant-based breast reconstruction (IBBR) was use of autologous methods. Use of the abdomen as a donor site gained popularity with the introduction of the free and pedicled transverse rectus abdominis myocutaneous (TRAM) flap in the 1970s and 1980s (26-28). Refinements of microsurgical techniques have further guided the evolvement of free perforator flaps, of which the DIEP flap has become the method of choice (29, 30).

Implant-based breast reconstruction

Implant-based breast reconstruction (IBBR) is considered as a safe option for patients with comorbidities. An IBBR can be performed either as a one-stage or a two-stage procedure. In immediate IBBR, a permanent silicone implant can be used in patients with smaller breasts allowing a one-stage procedure. A mesh may be placed in the inferior pole of the breast if coverage from the major pectoral and serratus anterior muscles is insufficient. At our clinic, we use the long-term absorbable TIGR® Matrix Surgical Mesh (Novus Scientific, Uppsala, Sweden). To create a larger breast, the first step is to expand the mastectomy skin flaps by placement of an EP. Subsequently, using a two-stage approach, the EP is replaced by a silicone implant following the expansion process (31). In delayed postmastectomy breast reconstructions, tissue expansion is required to establish a breast mound and is accomplished by either a permanent or a temporary EP (32). The two-stage approach is similar in immediate and delayed IBBR. Comparisons of one- and two-staged IBBR have demonstrated various results and most studies focus on immediate breast reconstructions. The two-stage approach has been associated with better cosmetic outcomes and fewer reoperations compared to the one-stage approach (31, 32). In contrast, two larger studies found comparable complication rates between the two approaches (33, 34).

Moreover, implant placement is a debatable topic. Subpectoral placement has been preferred during the past few decades but recently, prepectoral implants have regained popularity. A systematic review concluded that patients with prepectoral implants have higher satisfaction outcomes and have less postoperative pain than patients with subpectoral implants (35). In addition, fewer unintended reoperations, reconstruction failures and animation deformities have been demonstrated in prepectoral implants, but, at the expense of implant rippling (36).

Expander prosthesis

In 1984, Becker introduced a permanent inflatable EP for single-stage breast reconstruction (37). The Becker EP has one outer silicone lumen and one fillable lumen. A filling tube is connected to the prosthesis and is accessed through an injection dome placed in a subcutaneous pocket. At our clinic, the EP is placed in the subpectoral position (**Figure 2**). The port is positioned lateral to the breast in the mid-axillary line. Following the reconstruction surgery, the EP is inflated repeatedly with saline over a period of months until the desired size is reached (38). By choosing a permanent EP, only one operation is needed to complete the breast reconstruction. The filling tube can be removed in local anaesthesia when expansion of the breast mound is completed. The permanent EP used in this thesis was the Mentor® Contour Profile Becker -35 Cohesive I (**Figure 3**) (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08,933, USA).

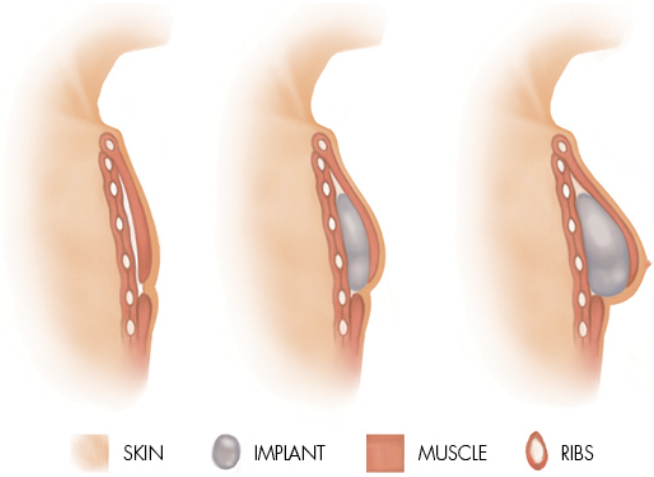


Figure 2. Subpectoral placement of an expander prosthesis (EP) undergoing expansion.
The left image illustrates the chest wall following a mastectomy. In the middle image, an EP has been implanted beneath the major pectoral muscle and, in the right image, the EP has been expanded. Permission to reprint by the Breast Cancer Foundation New Zealand (39).

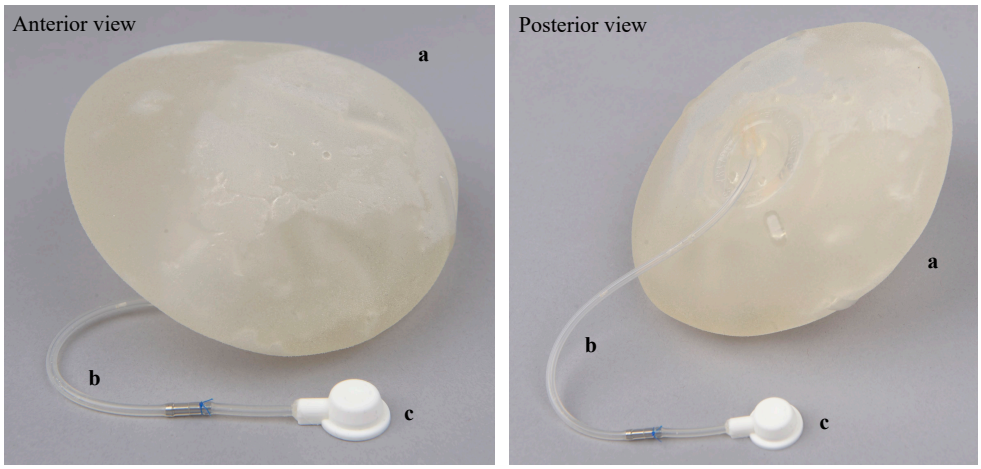


Figure 3. Photographs of a Mentor® Contour Profile Becker -35 Expander Implant.
An anterior and posterior view of the expander prosthesis (a) used in this thesis. The implant is connected to a detachable filling tube (b) with an injection dome (c).

Autologous breast reconstruction

Autologous breast reconstruction (ABR) comprises different types of flaps from various parts of the body. The flap of choice is dependent on advantages and disadvantages of the donor site, the patient's characteristics and on the patient's preferences. Experience in microsurgery is another important factor. From the abdomen, the pedicled and free TRAM flaps, the DIEP flap, and the superficial inferior epigastric artery (SIEA) flap are harvested. Harvesting of TRAM flaps includes a part of the rectus abdominis muscle. The muscle harvest increases the safety of the flap at the expense of donor site morbidity. Abdominal weakness and bulge are associated with TRAM flap harvest (40). The DIEP and SIEA flaps are based on different perforators but share the other donor site features. Both methods are muscle-sparing, in contrast to the TRAM flaps. The absence of perforators or inadequate perforator size are reasons why a DIEP flap is often chosen over a SIEA flap (41). The pedicled LD flap is a good option for patients with insufficient abdominal tissue. It provides an adequate skin and muscle coverage to the mastectomy site with the drawback of impaired shoulder function (42). To achieve projection, an LD breast reconstruction may be augmented with an implant in a second surgery. Furthermore, the gluteal and thigh regions are other possible donor sites for perforator flaps used in breast reconstruction. These flaps comprise the superficial gluteal artery perforator flap, the inferior gluteal artery perforator flap, the profunda artery perforator flap and, the transverse upper gracilis flap.

DIEP flap

The DIEP flap is the gold standard ABR method today and can be used for both immediate and delayed breast reconstructions (**Figure 4**). The flap in based on perforators from the deep inferior epigastric artery and vein, branching from the external iliac artery superior to the inguinal ligament. To guide surgeons during harvesting, the DIEP flap has been divided into different zones of perfusion. The highest perfusion has been found medial to the umbilicus, ipsilateral to the perforator. However, regarding the other zones, findings from perfusion analyses suggest a high individual variability (27, 43).

The DIEP flap surgery

Before surgery, perforators supplying the flap are identified and marked using a hand-held Doppler. In short, the flap is harvested in a similar fashion as in an abdominoplasty, with care taken to preserve the perforators. The perforators are dissected through the rectus abdominis muscle until they unite with the external iliac vessels. At the same time as the flap harvest, the internal mammary artery and vein are prepared as recipient vessels. Traditionally, a portion of the third costal cartilage was removed to achieve sufficient access to the internal mammary vessels (44). Since 2019, our institution has adopted a rib-sparing technique in which the vessels

are accessed via the second intercostal space without concurrent cartilage sacrifice. This technique has been demonstrated as safe and is accompanied by less early postoperative pain and no parasternal depression (45-47). Following vessel preparation, the flap perforators are anastomosed with the recipient vessels in a microscope, the veins with a venous coupler and the arteries with non-absorbable 9-0 sutures. The flap is sculptured into a new breast, the umbilicus is repositioned, and the donor site is repaired and closed. If the flap displays any signs of venous stasis, a second venous anastomosis may be required, and most commonly, the cephalic vein is used.

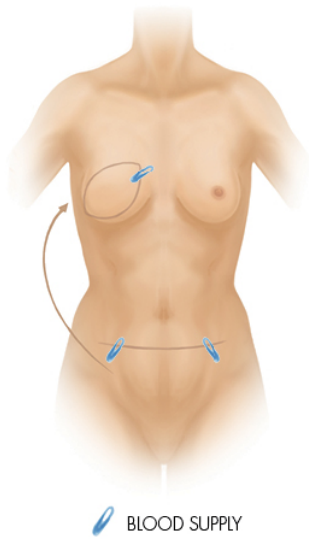


Figure 4. A unilateral deep inferior epigastric perforator (DIEP) flap breast reconstruction. An illustration of a patient following a unilateral DIEP flap breast reconstruction. The image illustrates the final scars at the abdomen (donor site) and at the right breast (recipient site). The localisation of the donor vessels and the anastomosis site are marked at the abdomen and at the breast respectively. Permission to reprint by the Breast Cancer Foundation New Zealand (39).

Complications in breast reconstruction

Implant-based breast reconstruction

There is a spectrum of complications associated with IBBR. In the early postoperative period, IBBR is more susceptible to mastectomy skin flap necrosis, hematoma, and wound infection (48, 49). Other types of problems can develop with

time, for example, implant rotation, rupture, and dislocation (36, 50). Perhaps the most well-known complication following a breast implantation is the development of capsular contracture. Capsular contracture is a thickening of the fibrotic capsule surrounding the implant, and manifests as a hard, aesthetically deformed, and sometimes painful breast. One important risk factor is postmastectomy RT (51-53).

Diagnosis of capsular contracture

The severity of capsular contracture can be assessed clinically with the Baker classification (54). The four-graded classification scale is well-established and used frequently in breast implantation research (52, 55-58). However, the scale relies on physical evaluation of appearance and palpation of the breast and thus, the reliability of the method is highly dependent on the investigator experience. Poor inter-rater reliability of this method has previously been described (59).

Applanation tonometry measures breast softness and is an alternative method to estimate capsular contracture (60-63). An applanation tonometer is a plexiglass disc, engraved with a circular scale ranging from 0 to 100 millimetres (**Figure 5**). By placing the plexiglass disc on the breast, an imprint appears, and the area of that imprint is calculated (64, 65). The objective method is suggested to give more consistent results than the Baker classification. A potential drawback is that, as the applanation tonometer measures the breast's imprint area, the results may not be comparable in patients with different types of implants (66).

Recommended imaging methods to assess capsular contracture are ultrasound, mammography, and magnetic resonance imaging (MRI) (67, 68). Signs of capsular contracture are thickening of the capsule, contour abnormalities and an increased anteroposterior diameter. Both ultrasound and MRI allow for measurement of these parameters. High correlations have been reported between capsule thickness on ultrasound, MRI, and the Baker classification (67).

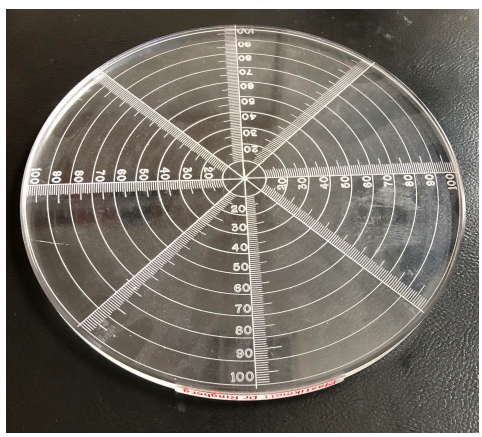


Figure 5. An applanation tonometer.

Breast implant illness

A different category of complications concerns extra-mammary symptoms reported by patients with breast implants. Breast implant illness (BII) entails a broad range of systematic symptoms such as brain fog, headache, muscle pain, and heart palpitations (69). BII has gained increasing attention recently and there are ongoing studies in this field. An association with autoimmune diseases has been reported, an interesting finding to be confirmed in future studies (70). The current knowledge concerning BII is, however, scarce (69).

DIEP flap breast reconstruction

Highly experienced surgeons and use of microsurgical techniques are essential for a free flap reconstruction. The complexity of a free flap surgery is reflected by a high risk of complications, which also includes the more routinely performed procedures such as the DIEP flap breast reconstructions (71, 72). Adverse events that may follow a DIEP flap surgery are bleeding, seroma, and wound infection, at both the donor and the recipient sites. Fat necrosis is another complication that may require revisional surgery in the postoperative period (40). Moreover, a free flap reconstruction is predisposed to vascular complications. These include venous stasis, arterial thrombosis, or a combination of the two (73). Vascular complications often occur within the first 48 hours following surgery and an immediate salvage procedure is in such circumstances performed to save the flap (74, 75). Over time, a DIEP flap reconstructed breast is generally considered stable. However, there are reports suggesting that additional surgeries are performed many years after the initial breast reconstruction surgery (76, 77).

Clavien-Dindo Classification

The Clavien-Dindo Classification (CDC) is a grading system for surgical complications (**Table 1**) (78). It is a modified version of a classification system which was originally developed for cholecystectomy surgery (79). The possible advantage of grading according to the CDC is to mitigate the problems arising when comparing reports with different complication definitions. Its use in breast reconstruction research has increased in recent years, providing a better foundation for comparisons between studies (80-83).

Table 1. Definitions of the Clavien-Dindo Classification grades (78).

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs or as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic, or radiological intervention.
A	Intervention not under general anaesthesia.
B	Intervention under general anaesthesia.
IV	Life-threatening complication (including central nervous system complications) requiring intermediate care or intensive care unit management.
A	Single organ dysfunction (including dialysis).
B	Multi-organ dysfunction.
V	Death of a patient.

Healthcare costs

Costs related to different breast reconstruction procedures are important knowledge for decision-makers in public healthcare systems when considering the allocation of resources. Healthcare costs related to specific patients and procedures can be estimated through rates from public hospitals' financial departments. In terms of healthcare costs, there is a distinction between intramural and extramural costs. Intramural costs are those directly related to the hospital care and are available from the financial department, for example the rate per hospital day. Absence due to sick leave is an example of an extramural cost.

The short-term economic burden of a DIEP flap breast reconstruction is expected to be high. There are often two experienced surgeons performing the operation together and the patient requires hospital care postoperatively. In contrast, an EP reconstruction is a shorter operation, occupying one surgeon, and can be performed in an outpatient setting. These are all factors that contribute to higher costs for DIEP flap reconstructions in the initial postoperative period (84). In contrast, there are reports indicating a tendency towards higher costs for IBBR in longer follow-ups (76, 85, 86). Thus, statistically significant differences in costs between the two reconstruction methods have not yet been demonstrated (76, 86).

Patient-reported outcome and the BREAST-Q

Patient-reported outcome (PRO) is central in healthcare. Patient-reported outcome measures (PROM) are developed to scientifically capture the perception of the patients. The Q-Portfolio team, comprising researchers from all around the world, has created PROMs used in different areas of healthcare. One of these is the BREAST-Q, a PROM including modules specific to cosmetic and reconstructive breast surgery. The BREAST-Q Reconstruction Module was developed through systematic reviews, and qualitative methods and is validated and internationally well-recognised (87-90). In addition, the BREAST-Q was constructed using Rasch Measurement Theory. In a Rasch model, a patient's response to a specific item is compared with the predicted response from a mathematical model to assess the fit of the item to the scale's construct. Furthermore, use of the Rasch model enables conversion of collected ordinal data to interval scale data (89, 91).

Minimal important difference

Repeated measurements with the BREAST-Q may detect important changes in breast surgery patients over time. To determine whether a change is clinically significant or not, a minimal important difference (MID) is warranted. Voineskos et al. recommended a MID score of three or four points, depending on the subscale, for the BREAST-Q postoperative Reconstructive Module (92).

Oedema

In normal microcirculation, there is an ongoing exchange of fluids between the intracapillary space and the interstitium. The principle of fluid exchange is described by Starling's equation (93). In tissues with a net pressure gradient directed out from the capillary walls, fluids and plasma proteins are transported to the interstitium. To preserve the normal fluid balance in the body, lymphatic vessels drain tissues of the excess fluids and plasma proteins. The excess fluid, also called the lymph, is transported via regional lymph nodes and collection ducts. Subsequently, most is drained into the thoracic duct that in turn drains into the subclavian vein. The lymphatic system also constitutes an important part of the immune system. It is responsible for maturation of lymphocytes and transportation of antigens to lymph nodes, hence, assisting in activation of the immune system (93).

Oedema is the pathological condition where excess fluid has accumulated in the interstitium. This is due to an imbalance between capillary filtration and lymphatic drainage. A common cause of subcutaneous lymphoedema is damage to the lymphatic vascular system during a surgical intervention (93). Surgically inflicted lymphoedema is further defined as secondary lymphoedema, different to congenital

lymphoedema which is classified as primary. In most patients, lymphoedema develops within the first three years of surgery (94).

Breast cancer surgery may result in breast cancer-related arm lymphoedema, often a consequence of axillary lymph node dissection (95). Studies have found that lymphoedema-affected arms have a decreased lymphatic flow compared with unaffected arms (96). In PROMs, patients with arm lymphoedema reported a negative effect on their QoL (97). Similarly, the less known condition of breast oedema has also been associated with lower QoL. Breast oedema has been observed in breasts following BCS and RT and causes symptoms such as heaviness and pain (98-101). The presence and clinical importance of breast oedema following breast reconstruction has been sparsely studied.

Diagnosis of subcutaneous oedema

The pitting test is a popular and easy method to assess subcutaneous oedema. The test is conducted by pressing a finger onto the affected limb for 5-10 seconds. If an indentation of the tissue sustains after removal of the finger, oedema is present (102). However, the method is hampered by its inability to assess later stages of lymphoedema, referred to as non-pitting oedema. Another physical measurement method is water displacement. The limbs are placed in a barrel with water, one at a time, and the displaced water is weighed. The difference between the affected and the unaffected limb is calculated (103). Lymphoedema is also frequently assessed with circumferential measurements using a tape measure (94, 97, 104).

Imaging methods used are lymphoscintigraphy, MRI, indocyanine green (ICG) lymphography, bioelectrical impedance analysis, and measurement of the tissue dialectic constant (TDC) (96, 104-109). Of these, lymphoscintigraphy is considered the gold standard method for diagnosis of lymphatic dysfunction (110). A radioactive tracer, technetium-99m, is injected in the distal part of the affected limb. The radiotracer is absorbed by the lymph vessels and transported to the lymph nodes; a process visualised by a gamma camera. A decreased radioactive clearance rate and abnormal dermal backflow are lymphoscintigraphical findings present in lymphoedema-affected limbs (96, 104). Similarly, on ICG lymphography, abnormal dermal backflow patterns indicate malfunction of the lymphatic system (111). Compared to lymphoscintigraphy, ICG lymphography, or near infrared fluorescent imaging, provides real-time observations with finer visualisation, and no radioactive exposure (110-112).

Less invasive TDC measurements can be performed with the MoistureMeterD® instrument. This is an accessible method for diagnosis and potentially early detection of oedema in a clinical setting (108). The instrument probe transmits an ultra-high-frequency electromagnetic wave at 300 MHz from the skin into the subcutaneous tissue. The data reflected to the probe generates the TDC. The TDC value is directly proportional to the tissue water content, further referred to as local

tissue water (LTW) (113). The method has shown high intra- and inter-rater reliabilities (114).

Aesthetic outcome and assessment

The perception of aesthetics is subjective. This is why aesthetic outcome assessments may differ and are challenging to draw conclusions from. Nonetheless, the aesthetic result is an important outcome in breast reconstruction surgery. Aesthetic assessments of breast reconstructions have been performed previously with different scales, and different panel compositions have been reported (115-118). Agreements between the assessments vary and yet there is no consensus on which scale to choose (117, 119, 120). In an overview of the published literature, results from aesthetic outcome assessments with panels have been in favour of ABR when compared with IBBR (51, 121, 122).

Objective assessment

Methods have been developed to perform more standardised aesthetic outcome assessments following breast surgery (123, 124). One of these is the use of breast cancer conservative treatment cosmetic results (BCCT.core), which is a software that evaluates parameters of two-dimensional (2D) photographs. The software calculates the symmetry of the breasts based on measures of predetermined reference points. In addition to symmetry, the BCCT.core analyses scar appearance and skin colour (123). Previous reports have found high inter-rater reliability using the software but low agreements with the PRO (125, 126). Moreover, objective evaluation with three-dimensional (3D) imaging has been reported (127, 128). In a study by Godden et al., the authors presented a 3D surface-imaging evaluation model for symmetry assessment following BCS. The consistency between panel assessments was moderate to high and thus, the authors proposed replacement of the traditional panel assessments for aesthetic evaluations (128).

Aims of the thesis

The main purpose of this thesis is to compare the two breast reconstruction methods, the EP and the DIEP flap. The idea behind the thesis came from the Swedish national guidelines for breast reconstruction with autologous tissue, published in 2011. The guidelines recommend the EP as the standard method of breast reconstruction and the DIEP flap to be pertained to previously irradiated patients (129). In the absence of previous randomised studies, this thesis intends to contribute to the current state of knowledge and thus aid patients and surgeons in the decision-making process concerning their breast reconstruction method.

The specific aims:

Paper I: To investigate short-term differences regarding complications, healthcare costs, and QoL after breast reconstruction with the EP and the DIEP flap.

Paper II: To evaluate softness between EP and DIEP flap breast reconstructions.

Paper III: To assess the role of local breast oedema in EP and DIEP flap breast reconstructions.

Paper IV: To evaluate the reproducibility of aesthetic outcome assessments of breast reconstructions with photographs in 2D and 3D format.

Paper V: To investigate five-year outcomes following breast reconstruction with the EP and the DIEP flap. A secondary aim was to compare PRO between patients randomised to an EP reconstruction and patients who chose an EP reconstruction.

Methods

Patients

The Swedish national guidelines for breast reconstruction with autologous tissue published in 2011, recommended DIEP flap reconstructions only to previously irradiated patients or to patients who were predicted to have unsatisfactory results with IBBR (129). In 2018, the guidelines changed and today, patients may choose their breast reconstruction method. Between 2012 and 2018, women who had undergone unilateral mastectomy but no RT, were asked to participate in a randomised study at the Department of Plastic and Reconstructive Surgery in Malmö. The participants were randomised to either the standard method at that time, an EP, or to the alternative method, a DIEP flap. One-hundred and thirty-five eligible patients were referred to the department. The final number of patients who underwent breast reconstruction was 73, of which 29 patients underwent reconstruction with an EP, and 44 with a DIEP flap. **Figure 6** presents a flowchart with the inclusion and exclusion of patients to the study.

The randomised cohort is studied in the papers included in this thesis. In Papers I, II, III and V, all 73 patients were invited to participate. Photographs of the first 34 consecutive patients who completed the five-year follow-up were studied in Paper IV. Additionally, in Paper V, PRO was evaluated in patients who were eligible to participate in the randomised study but declined in favour of an EP breast reconstruction.

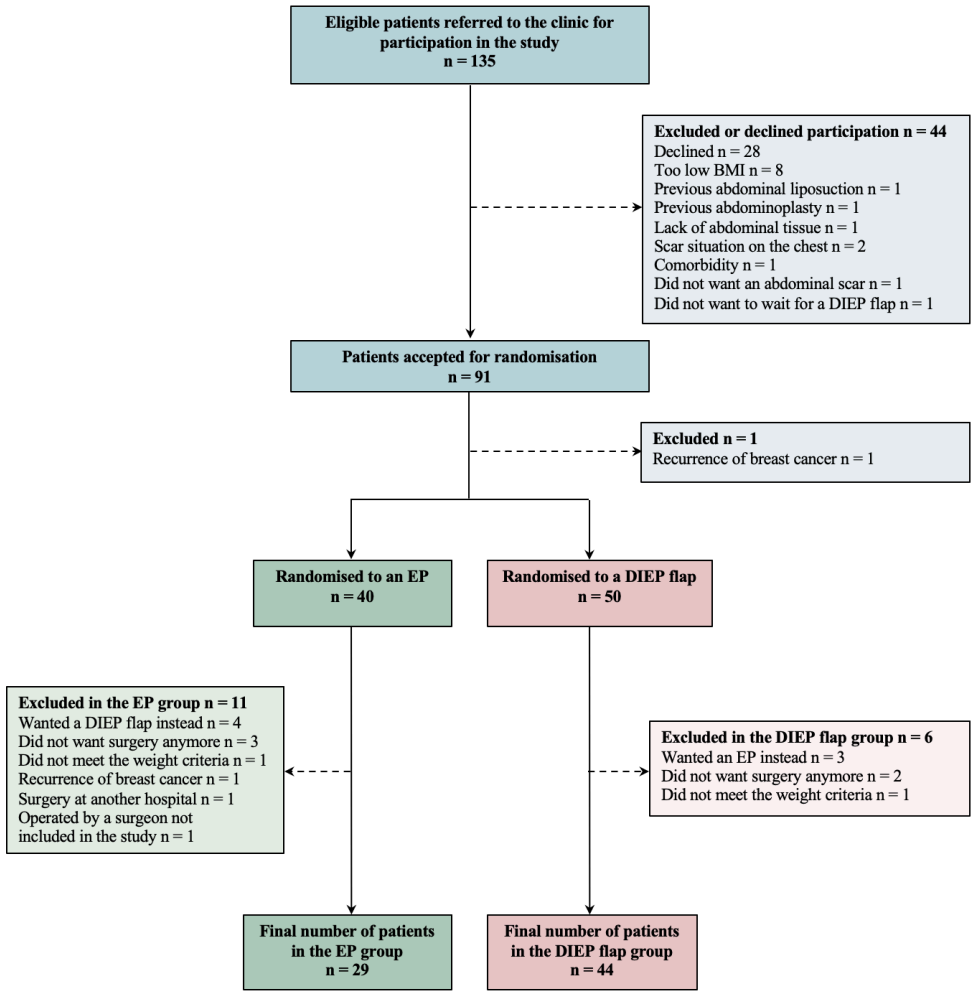


Figure 6. A flowchart of the study.

Paper I

Complications were retrieved and classified from a medical chart review in the Melior (Siemens Health Care, Upplands Väsby, Sweden) journal system. From the chart review, the length of hospital stay, the number of outpatient clinic visits, and the type of implant were recorded. Surgery-specific details were collected from the Orbit (SYSteam Health&Care, Huskvarna, Sweden) surgery planning system.

Intramural costs were calculated with rates from the Southern Health Care Region for Plastic and Reconstructive Surgery according to the 2018 calendar year (130).

PRO was measured with the BREAST-Q preoperative and postoperative Reconstruction Module Version 1.0. The preoperative Reconstruction Module Version 1.0 includes one satisfaction subscale; *Satisfaction with breasts*, and four QoL subscales; *Physical well-being of chest, Physical well-being of abdomen*, *Psychosocial well-being*, and *Sexual well-being*. In the postoperative module, subscales on *Satisfaction with outcome*, *Satisfaction with nipples*, *Satisfaction with implants*, *Satisfaction with care*, *Satisfaction with information*, *Satisfaction with surgeon*, *Satisfaction with medical team*, and *Satisfaction with office staff* are added. The collected BREAST-Q scores are transformed by the Q-score software to results on a linear interval scale between 0 and 100 for each subscale. There is no overall BREAST-Q score (89, 90).

Papers II and III

A total of 69 patients completed the two-year follow-up. All measurements were performed by two registered nurses experienced in breast reconstruction care.

Breast volume was recorded with plastic breast cups (Emballageform AB, Limhamn, Sweden) and jugulum-nipple distance, clavicular-submammary fold distance, and ptosis with a tape measure (131). Fractional ratios, the value of the reconstructed breast divided by the sum of the reconstructed and the contralateral breasts' values, were calculated to assess symmetry. A value of 0.5 corresponded to perfect symmetry between the breasts (60). Grading according to the Baker classification was performed. The Baker classification scale ranges from I to IV, where grades III and IV indicate more severe capsular contracture (54).

The BREAST-Q preoperative and postoperative questionnaires were used to assess patients' satisfaction with breast softness and breast oedema-related symptoms. In Paper II, the selected question was "How satisfied or dissatisfied have you been with the softness of your reconstructed breast?"

Applanation tonometry

At the two-year follow-up, breast softness was evaluated with applanation tonometry. The patient was placed in a supine position, slightly tilted. By placing the tonometer horizontally on the breast, an imprint with the form of an ellipse appeared. Subsequently, the area of the imprint was calculated with the formula of an ellipse Area = πAB/4. The area estimates the intramammary pressure through the formula Pressure = Force × Area. With a set tonometer weight, the force from

the tonometer is constant. Hence, the relationship between the imprint area, or the tonometric area, and the intramammary pressure is proportional (64, 65).

The MoistureMeterD® instrument

Assessment of local oedema of the breasts was conducted with the multiprobe MoistureMeterD® instrument (Delfin Technologies Ltd, Finland) (**Figure 7**). The breast was divided into four quadrants. Each quadrant was measured three times and a mean TDC value was calculated (132, 133). At the two-year follow-up, the M25 probe was used measuring to a depth of five millimetres from the skin surface.

Figure 7. The MoistureMeterD® instrument.
A picture of the MoistureMeterD® instrument connected to the M25 probe.

Paper IV

Photography

At the follow-up, five years after breast reconstruction, the patients were photographed with a digital 2D camera (Nikon Corporation, Tokyo, Japan) and a

3D camera. The 3D camera system 3dMD trio system (3dMD LLC, Atlanta, GA) was used for 3D photography. **Figures 8a** and **8b** show examples of a patient reconstructed with a DIEP flap in 2D format (a) and in 3D format (b).

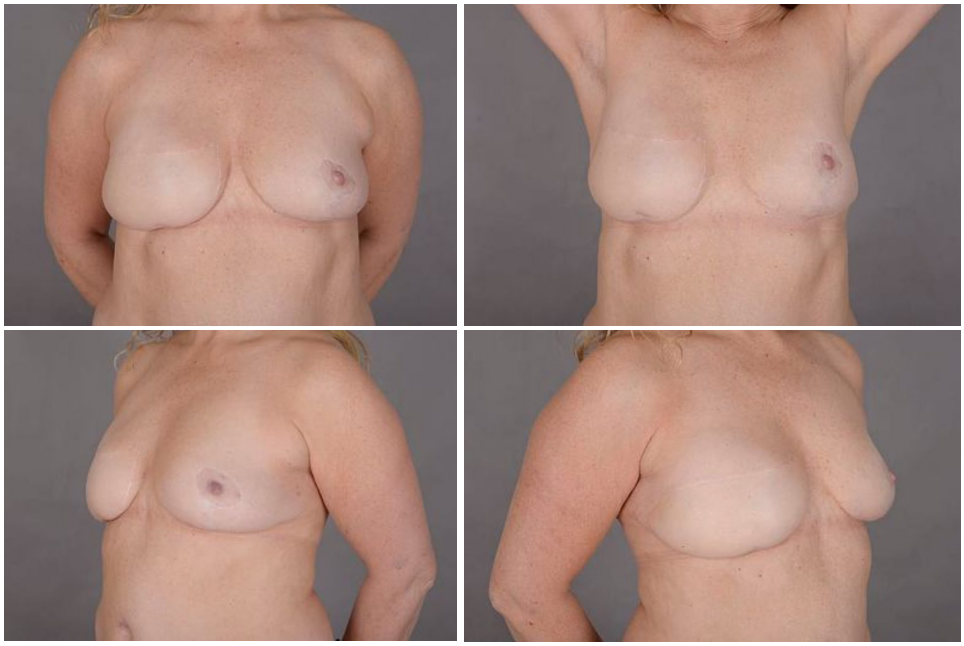


Figure 8a. A photograph of a DIEP flap breast reconstruction in 2D format.

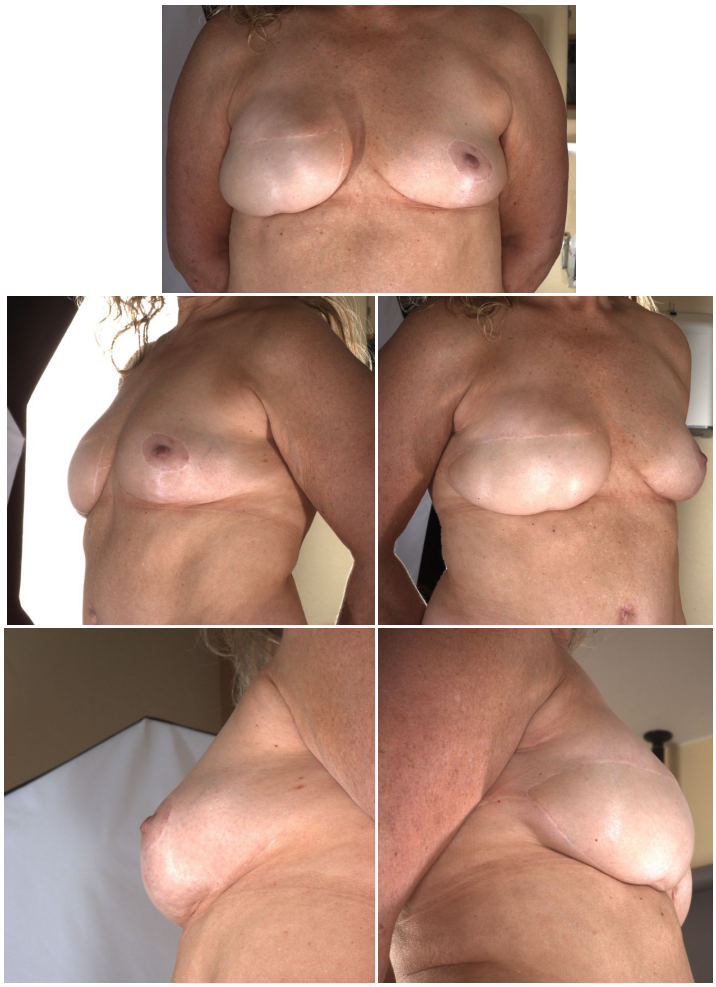


Figure 8b. A photograph of a DIEP flap breast reconstruction in 3D format.

The aesthetic outcome assessment scale

The scale by Visser et al. was chosen for the aesthetic outcome assessments (134). The scale has previously been recommended in a review article (135). The items assessed were breast size, shape, symmetry, scar appearance, NAC, and the overall aesthetic outcome. All items were graded on a five-point Likert scale except for the overall aesthetic outcome, which was graded on a ten-point Likert scale.

Panel evaluation

Research Electronic Data Capture was used for data collection and for the creation of questionnaires to evaluate the photographs (136, 137). The questionnaires were sent twice to expert panels, layman panels, and a patient panel. The expert panels comprised consultant physicians in plastic surgery and breast surgery. Intra-rater agreements concerning the aesthetic outcome were calculated for the repeated assessments of each panellist. Agreements concerning the aesthetic outcome assessments between members of the same panel, i.e. inter-rater agreements, were also calculated. In addition, analysis of agreements between assessments of matched photographs in 2D and 3D format was conducted.

Paper V

In total, 65 patients completed the five-year follow-up. **Figure 9** presents a flow chart of the inclusion process in Paper V. All measurements were performed by the author (LT).

PRO was measured with the BREAST-Q postoperative Reconstruction Module Version 1.0. In addition, BREAST-Q questionnaires were collected from patients who had undergone an EP breast reconstruction without randomisation. Of these patients, 15 returned completed questionnaires.

Complications were retrieved from the individual medical charts. Grading of complications was done according to the CDC. Additional corrections were defined as a minor revision including scar revision, excision of a dog ear, and liposuction for symmetry, and were not regarded as complications.

Symmetry was assessed by measurement of breast volume, jugulum-nipple distance, ptosis, and breast softness. The methods used were the same as in Paper II.

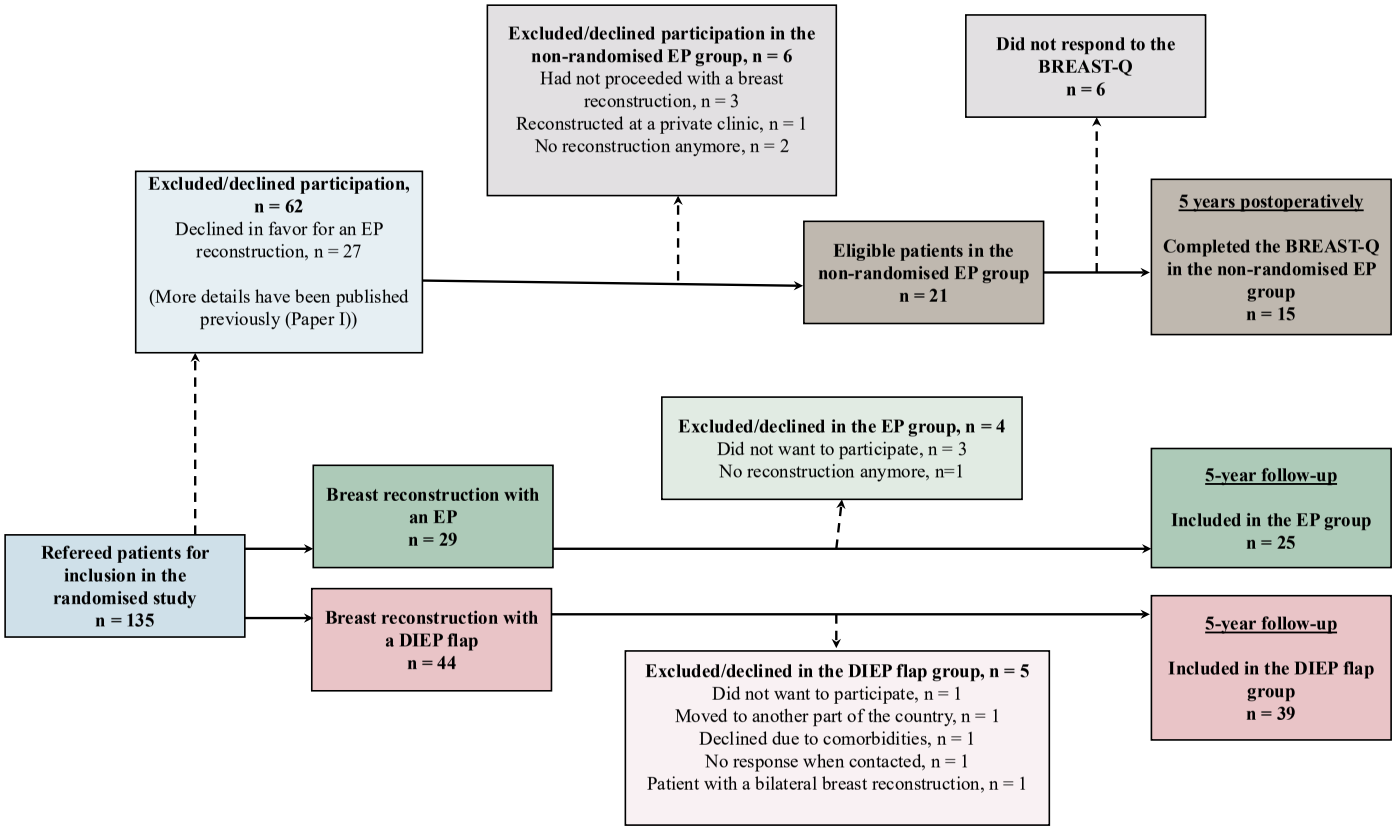


Figure 9. A flow chart of the inclusion process in Paper V.

Semmes-Weinstein monofilaments

Breast sensibility was evaluated with the Semmes-Weinstein monofilament five-piece hand-kit (Aesthesio®, DanMic Global LLC, USA). The five-piece kit comprises monofilaments with index values ranging from 2.83 to 6.65. Each monofilament is attached at 90 degrees to the handle and bends when a certain target force is applied. The index values correspond to the logarithm of the force in millimetres needed to bend the monofilaments and represent specific sensibility thresholds. Hence, index values below 4.31 indicate protective sensation and monofilaments above 4.56 indicate loss of protective sensation (138-140). Nine areas of the breasts were assessed with the patient in the supine position (**Figure 10**). Each area was measured three times per monofilament.

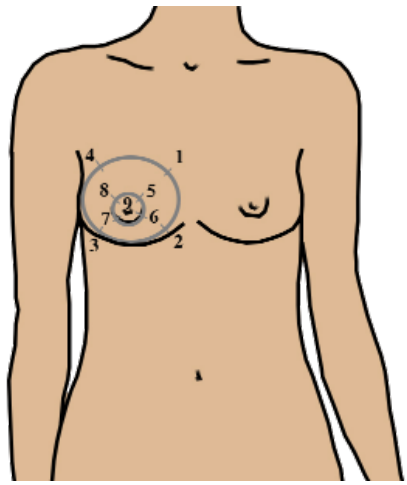


Figure 10. Anatomical landmarks for the nine assessment areas for breast sensibility.
Illustration of the nine areas measured with Semmes-Weinstein monofilaments. Areas 1 to 4 include the outer quadrants, 5 to 8 the border of the areola and 9 the nipple.

Statistical methodologies

The Statistical Package for the Social Sciences (IBM Corp. Armonk, NY) was used for statistical analysis. A p-value below 0.05 was set to indicate statistical significance. All papers involved consultations with statisticians affiliated to Lund University or to Clinical Studies Sweden.

Paper I

In the planning phase of the randomised study, the number of included patients had to be determined. A powered study is acquired by having a large sample size, hence increasing the possibility to detect a difference between two groups. However, recruitment of patients can be difficult and time-consuming. Recruitment is further hampered by narrow inclusion criteria to randomised studies and by low patient volumes in single centres. Thus, the sample size was considered from a clinical perspective, accounting for the number of patients who underwent breast reconstruction per year at that time and using a reasonable inclusion period. During a four-year inclusion period, 80 patients were anticipated to be included and randomised to one of the two reconstruction methods. Hence, the aim was to assign 40 patients to each group.

Comparison of the groups was carried out with parametric methods according to the central limit theorem. The central limit theorem is the assumption that the sample's mean will approximate the mean of the normal distribution in large samples (141). A minimum sample size of 30 in each group is commonly recognised to fulfil this assumption.

The Student's t-test and the Paired t-test were used for group comparisons of parametric data. The Mann-Whitney U test was used when the data was nonparametric. Categorical data was compared with the Chi^2-test or the Fisher's exact test in small samples.

The Student's t-test with bootstrapping was used to compare costs between the groups. Bootstrapping is a statistical procedure used to assess the robustness of a test. In bootstrapping, random resampling is carried out based on the collected data sample and a multitude of new resampled data sets are created. The resampled data is presented as a 95% confidence interval. The bootstrapping confidence intervals can be compared with the confidence intervals from the collected sample to assess its accuracy.

Papers II and III

Independent groups were compared with the Student's t-test and the Mann-Whitney U test for parametric and nonparametric data respectively. Paired data was compared with the Paired t-test or the Wilcoxon signed-rank test. Categorical data was compared with the Chi^2-test or Fisher's exact test. For the correlation analysis, the Spearman's rank correlation was used.

Paper IV

The aesthetic outcome assessment scale in Paper IV was rated on an ordinal Likert scale, hence, intra-rater and inter-rater reliabilities were assessed statistically with the weighted kappa. Calculations were made with the weighted kappa for all

pairwise combinations of panel members within each panel to assess inter-rater reliability. Subsequently, the inter-rater reliability was set as the median value.

Paper V

In this paper, normality was checked with the Shapiro-Wilk test, skewness, and visually with histograms. Groups were compared with the parametric and nonparametric statistical tests described in Papers I to III.

Analysis of predictors for continuous independent variables was made with univariate and with multivariate linear regression. Logistic regression was used for categorical independent variables and results were presented as odds ratios with 95% confidence intervals. The low sample size prevented further analysis with adjusted regression models for complications. To perform adjusted regression analysis, there is a need for at least 10 events per variable.

Ethical considerations

The papers of this thesis are based on patient participation and the collection of sensitive data. Participation in the randomised study was voluntary. All patients signed a written informed consent before inclusion and received information on the possibility to drop out during the study's follow-up period.

Data collection was performed through measurement of the breasts, photography and through the PROM BREAST-Q. Each of these parts had the potential to inflict a feeling of discomfort or to revive memories from the participant's breast cancer journey. On the other hand, all participating patients were offered a consultation with a senior consultant physician in plastic surgery in connection to the follow-ups. Performing clinical studies would not have been possible without voluntary patients. Accordingly, we have a responsibility to use the results in a way that will benefit patients in the future and that will impact clinical care and routines when necessary.

The studies were approved by the Regional Ethical Review Board in Lund (ref. no. 2012/187) and the Swedish Ethical Review Authority (ref. no. 2021-00555 and ref. no. 2020-00809).

Results and discussion

Since 2012, when the data collection for this thesis began, breast reconstruction care has evolved. Revised national guidelines for breast reconstruction in 2018 facilitated greater patient influence in the decision-making process. An increased use of BREAST-Q in breast reconstruction research has enabled comparison of PRO data from clinical centres throughout the world. Furthermore, the Q-Portfolio team has refined their questionnaires and is currently developing a module for BII, a condition requiring further research (142).

The results from the thesis are presented and discussed in the following section based on each studied outcome. In **Table 2**, the patients' baseline characteristics are displayed.

Table 2. Patients' baseline characteristics.

	All (n=73)	EP (n=29)	DIEP flap (n=44)	p-value
Age, in years	53.7 ± 9.4 (34-70)	55.8 ± 8.9 (36-70)	52.3 ± 10 (34-70)	0.13[a]
BMI, in kg/m^2	25.7 ± 2.9 (19.0-33.0)	25.1 ± 3.1 (19.0-30.8)	26.1 ± 2.7 (20.5-33.0)	0.15[a]
Smoking status, n (%)				
Never smoker	45 (62)	16 (55)	29 (66)	0.36[b]
Former smoker	22 (30)	11 (38)	11 (25)	0.24[b]
Stopped before surgery	6 (8)	2 (7)	4 (9)	0.74[b]
Abdominal scars, n (%)	31 (42)	13 (45)	18 (41)	0.74[b]
Open surgery	22 (30)	9 (31)	13 (30)	0.89[b]
Laparoscopic surgery	5 (7)	2 (7)	3 (7)	1[c]
Open and laparoscopic surgery	4 (5)	2 (7)	2 (4)	1[c]
Parity, n (%)				
Nulliparity	8 (11)	6 (21)	2 (4)	**0.05**[c]
Parity	65 (89)	23 (79)	42 (95)	**0.05**[c]
Chemotherapy, n (%)	38 (52)	13 (45)	25 (57)	0.32[b]
Concurrent diseases, n (%)				
Hypertension	16 (22)	7 (24)	9 (20)	0.71[b]

Type I diabetes	1 (1)	1 (3)	0	0.4[c]

P-values from the Student's t-test[a], the Chi^2-test[b], and Fisher's exact test[c]. Age and BMI are presented with mean ± standard deviation and minimum and maximum values in parentheses. Numbers are presented with percentages in parentheses.

Complications

In the thesis, complications were analysed at 30 days (Paper I) and five years (Paper V) following breast reconstruction. During the first 30 days, two patients (7%) in the EP group and 16 (36%) patients in the DIEP flap group presented with complications ($p < 0.01$). Of the 16 patients in the DIEP flap group with complications, seven had a vascular compromise.

In the five-year follow-up, there was no significant difference in overall complications between the two groups ($p = 0.27$). Seventeen (58.6%) patients in the EP group and 20 (45.5%) patients in the DIEP flap group had a complication. The corresponding numbers for late complications were 16 (55.2%) patients and nine (20.5%) patients in the two respective groups. Of the patients recorded with a complication in the EP group, nine were related to the filling system, of which four underwent repositioning of the injection dome. Eleven (38%) of the original EPs were exchanged or removed during the follow-up period. Additional corrections in the five-year perspective were more frequent in the DIEP flap group (EP n=2, DIEP flap n=16). **Table 3** shows the complications within the first 30 days in the DIEP flap group and **Tables 4a** and **4b** show the late complications, beyond the first 30 days, in the EP and the DIEP flap groups. Comparison of the groups according to the CDC showed no significant difference ($p = 0.19$, **Table 5**). Results from the regression analysis with the two groups combined found age to be a risk factor for an overall complication. Moreover, an increase in BMI was a predictor for reoperation in general anaesthesia and for developing a superficial wound infection.

The short-term results are in line with previous reports comparing IBBR and DIEP flap breast reconstructions (71, 72). In relation to other reports, our DIEP flap group demonstrated a somewhat high complication rate (71, 143). One possible explanation could be the high number of cases of venous stasis in patients in Paper I (**Table 3**). However, we propose that venous stasis would be less frequent today, as the threshold of conducting an additional venous anastomosis perioperatively is generally lower.

In contrast to the 30-day outcome, the number of complications had shifted in favour of the DIEP flap breast reconstructions in the five-year follow-up. The longevity of implants is known to diminish with time, and an increase of complications is therefore expected (144, 145). A common complication following

implant reconstruction is capsular contracture, which has been reported to range from 9% to 50% of cases in long-term follow-ups (52, 72, 76, 77, 144, 145). This can be further illustrated by a high number of reconstructive failures reported up to two years postoperatively following IBBR (146, 147). Although previously varying findings, the explantation rate in Paper V is similar to previously reported explantation rates of 26% and 34% for permanent EPs (50, 144). Another reflection from the five-year outcome in the EP group was the high number of corrections associated with the EP's filling system (**Table 4a**). The issue of injection dome rotation has been observed in other studies, with our rate corresponding to the higher one (50, 144). Furthermore, it could be debated whether filling tube removal should be considered a complication. According to the Mentor® Memorygel® Siltex™ Becker Expander/Breast Implants Product Insert Data Sheet, removal of the filling tube is recommended for all patients after the expansion process is completed (148). In comparison to studies reporting delayed two-staged IBBR, the EP used is temporary and is always exchanged, and thus, future filling tube problems are eliminated. The absence of complications associated with the permanent EPs' filling systems could be attributed to the somewhat lower complication rates reported in long-term follow-ups in these studies (72, 76). Subsequently, rotation of the injection dome is a potential area of improvement and warrants further investigation. Explanations of injection dome rotations could be a manufactural problem, technical aspects of injection dome placement, and potentially, excessive movement of the patient postoperatively. Possibly, to the detriment of injection dome rotations, a deeper subcutaneous position may decrease the postoperative filling tube discomfort.

The results obtained from this thesis demonstrate five-year complications to be similar between the two methods. Our results are comparable to the findings by Naoum et al. and Hangge et al. (34, 149). Given that IBBR tends to deteriorate with time and ABR demands further corrective surgeries, longer follow-ups are warranted to capture the reconstructions' complete lifespans.

There are several risk factors associated with complications following breast reconstruction. Compared with non-irradiated breasts, IBBR in the setting of RT has been associated with significantly higher reconstructive failures (52, 150). RT was thus an exclusion criterion for this randomised study. Increased BMI and age were risk factors for complications in Paper V, results that confirm findings from previous reports (81, 147, 151-153). The advocated BMI limit for a breast reconstruction in Sweden is a BMI below 30. All but five patients in the randomised cohort fulfilled this requirement before undergoing the surgery. Nevertheless, BMI was a significant predictor for both a reoperation in general anaesthesia and a superficial wound infection. A higher rate of postoperative complications was found following DIEP flap breast reconstruction in an overweight group (BMI 25 to 29.9 kg/m^2) compared with a normal weight group (BMI 18.5 to 24.9 kg/m^2), in a previous study,

confirming our results (152). The findings emphasise the need for honest and objective preoperative discussions with high BMI patients, explaining the possible benefits of undergoing surgery with a normal BMI. Advantages could be fewer reoperations, fewer prescriptions of antibiotics, and thus an overall reduced healthcare burden. Guiding and motivating patients to achieve a healthy, stable body weight benefits both patients and healthcare givers.

Table 3. Complications within the first 30 days following breast reconstruction with a DIEP flap.

Patients	Arterial stop	Venous stasis	Hematoma flap	Necrosis flap <2 cm	Hematoma donor site	Infection donor site	Seroma donor site	Necrosis donor site
1	x	x	x					
2			x				x	
3		x						
4						x		
5			x					
6		x			x			
7		x						
8					x			
9	x							
10		x						
11						x		
12				x				
13						x		
14		x	x					
15						x		x
16						x		x

Table 4a. Late complications and additional surgical corrections, following the first 30 days of breast reconstruction, in the EP group.

Patients	Rotation of injection dome in LA	Removal of filling tube in LA	Prosthesis exchange	Prosthesis repositioning	Prosthesis extrusion	Superficial wound infection	Additional corrections in LA
1				1			
2	1		1				
3			1				
4			1				1
5							1
6	1	1					
7			1				
8			1				
9		1	3				
10		1	1				
11		1	1				
12			1				
13	1						
14		1					
15		1				1	
16					1		
17	1						

Abbreviations: LA = Local anaesthesia.

Table 4b. Late complications and additional surgical corrections, following the first 30 days of breast reconstruction, in the DIEP flap group.

Patients	Small necrosis donor site	Revision of flap fat necrosis in GA	Revision of flap fat necrosis in LA	Revision of donor site seroma in GA	Additional flap corrections in LA	Additional corrections in GA	Additional donor site corrections in LA
1					1		
2	1				1		
3		1					
4				1			
5		1					
6			1				
7							1
8				1			
9							1
10			1		1		
11							2
12						1	
13		1					
14					1		
15					2		1
16					1		
17						1	
18							1
19			1		1		1

Abbreviations: LA = Local anaesthesia, GA = General anaesthesia.

Table 5. Five-year complications according to the Clavien-Dindo Classification.

	EP n=29 n (%)	DIEP flap n=44 n (%)	p-value
Clavien-Dindo Classification			0.19
0	10 (34.5)	18 (40.9)	
I	2 (6.9)	6 (13.6)	
II	2 (6.9)	5 (11.4)	
IIIA	5 (17.2)	1 (2.3)	
IIIB	10 (34.5)	14 (31.8)	

P-value from the Chi^2-test.

Healthcare costs

Intramural mean costs ± standard deviation within the first 30 days from surgery was estimated to be 3839 ± 1327 euros in the EP group and 9187 ± 2465 euros in the DIEP flap group. A DIEP flap breast reconstruction was significantly more expensive in the short-term perspective ($p < 0.01$). This was a result of longer hospital stays, longer operations, and more reoperations in the DIEP flap group. In fact, we believe that the actual difference in cost between the groups is larger than reported in Paper I, mainly due to factors that were not adjusted for. One example is that the predetermined rate for surgery time per minute is based on only one surgeon. Consequently, the cost of having an additional experienced surgeon at a DIEP flap breast reconstruction was not accounted for. Another distinguishable factor in the care of the two patient groups is the high level of monitoring that follows a DIEP flap breast reconstruction. During the first 24 hours, the flap is assessed clinically and with a Doppler every hour. The difference in cost between the methods has been confirmed in a previous study (84).

A cost analysis comparing IBBR and DIEP flap breast reconstructions was conducted by Lagares-Borrego et al. in a public healthcare system (76). The authors found higher total costs, but not significantly higher, in the EP group compared with the DIEP flap group. Thus, the follow-up time in the EP group was longer (76). These results are congruent with another report presenting comparable costs between ABR and IBBR reconstructions in a two-year perspective (146). In contrast, significantly higher costs following EP breast reconstruction were reported in a Swiss study with a two-and-a-half-year follow-up. However, in their study, the EP group consisted of only 12 patients (85).

Instead of comparing incremental costs, cost-effectiveness can be estimated with the BREAST-Q as breast health-related quality-adjusted life-years. In one report conducting a cost-effectiveness analysis, breast reconstruction with DIEP flaps was found to be favourable (154).

Patient-reported outcome

PRO was evaluated with BREAST-Q at three different timepoints. Analysis of the scores showed that a breast reconstruction increased satisfaction and QoL in both groups (**Table 6**). Between the two-year and the five-year follow-ups, satisfaction rates decreased by three points and by two points in the EP and the DIEP flap group respectively (**Figure 11**). However, the changes were less than four points and therefore did not indicate clinically significant differences for the patients (92). The BREAST-Q scores were similar in the two-year and the five-year follow-ups in the two groups. All subscales received higher scores in the DIEP flap group; however, the difference was only significant for *Satisfaction with breast* and *Physical well-being of chest* in the five-year comparison.

Table 6. Comparison of preoperative and two-year postoperative BREAST-Q results.

BREAST-Q subscale	Pre-op	Post-op	p-value
Satisfaction with breasts			
EP	42.7 ± 14.2	63.4 ± 11.8	**<0.01**
DIEP flap	39.9 ± 18.3	72.1 ± 17.7	**<0.01**
Psychosocial well-being			
EP	48.8 ± 16.0	78.8 ± 20.1	**<0.01**
DIEP flap	53.8 ± 19.2	79.1 ± 21.5	**<0.01**
Physical well-being of chest			
EP	73.8 ± 13.2	72.0 ± 21.5	0.74
DIEP flap	81.3 ± 15.3	79.6 ± 21.1	0.66
Physical well-being of abdomen			
EP	83.6 ± 14.1	n/a	
DIEP flap	89.6 ± 10.6	81.0 ± 15.3	**0.02**
Sexual well-being			
EP	39.0 ± 14.1	58.4 ± 23.1	**<0.01**
DIEP flap	41.8 ± 18.6	67.1 ± 28.1	**<0.01**

Scores from 0-100. Values are presented in mean ± standard deviation. Abbreviations: DIEP = Deep inferior epigastric perforator; n/a = Not applicable.

P-values from the Paired t-test.

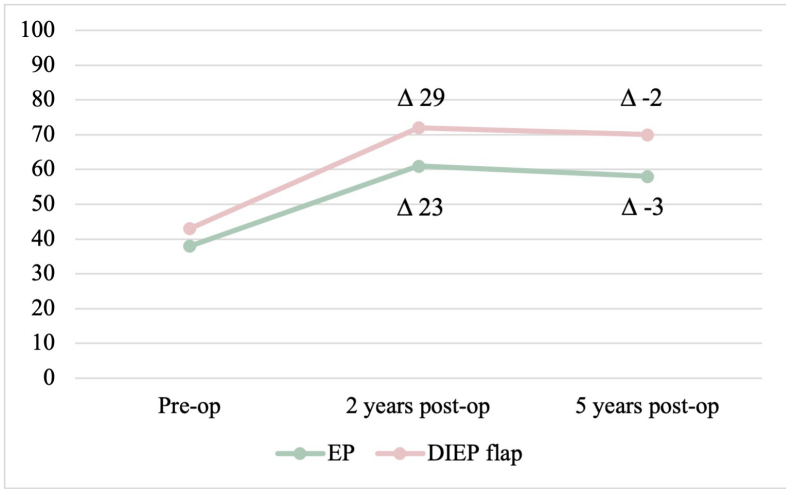


Figure 11. Changes in Satisfaction with breast between the assessment timepoints.
Graphic illustration of the changes in the BREAST-Q subscale Satisfaction with breast in the EP group (green) and in the DIEP flap group (pink).

There is agreement with earlier studies regarding the superiority of ABR in PRO. In an eight-year follow-up study by Nelson et al., higher *Satisfaction with breast* was reported following ABR compared with IBBR at all individual follow-ups (155).

Our results corroborate the findings of a previous report, in which a steady state for satisfaction was observed for both breast reconstruction methods (155). In addition to higher *Satisfaction with breast*, an increase in QoL has also been observed following ABR in previous studies (156-158).

An interesting finding was the significant decrease in *Physical well-being of abdomen* in the two-year follow-up, which, from the perspective of MID, was restored at the five-year evaluation. Hypothetically, the patients' expectations regarding the abdomen did not respond to reality. Due to similarities between a DIEP flap harvest and an abdominoplasty, patients may expect a flat, sculptured abdomen postoperatively as advertised by aesthetical plastic surgery clinics. These expectations may not be addressed in preoperative counselling as the primary focus is on the breast. Consequently, irregular abdominal scars, wound healing problems and discomfort may present as unexpected outcomes.

Comparison of BREAST-Q scores between the patients randomised to an EP with those who chose an EP and did not participate in the randomised study, showed no significant differences in any subscale. This result was unexpected. Previous reports have found that patients who are involved in the decision-making process are more satisfied postoperatively (159-161). Possible explanations for why our results differ

may be that there were discrepancies in patients' characteristics between the EP groups, or that those who answered the questionnaires were less satisfied than those who did not answer. The response rate in this group was 71% (15 patients of 21 eligible). Furthermore, participation in the randomised study facilitated contact with a surgeon during a longer follow-up time. Subsequently, any concern during the postoperative process could be handled during these visits. **Figure 12** shows the BREAST-Q results from the five-year follow-up for all groups.

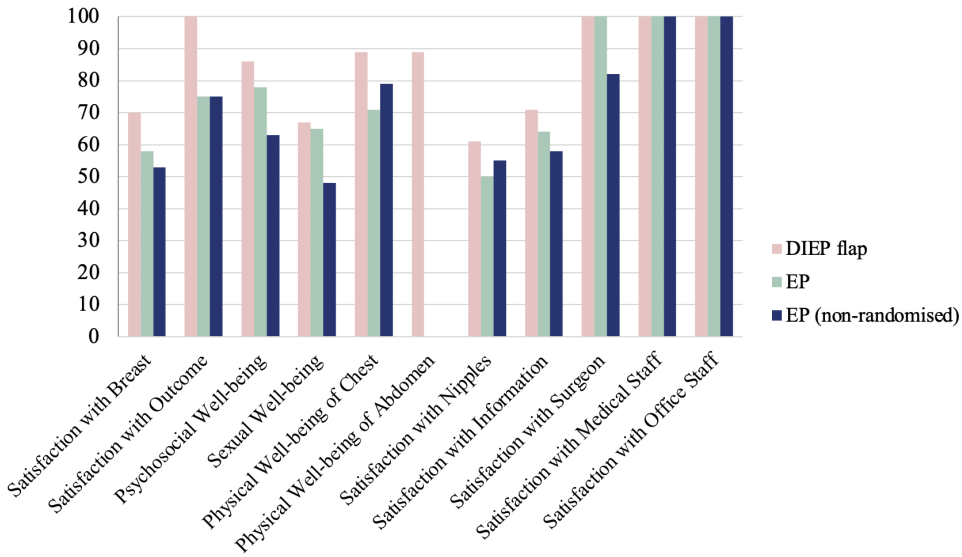


Figure 12. BREAST-Q five-year results.
A bar chart illustrating the median BREAST-Q scores per subscale for the EP (green), the DIEP flap (pink) and the non-randomised EP groups (blue).

Breast softness

The tonometric areas and the fractional tonometric areas, as indications of softness, were significantly larger in the DIEP flap compared with the EP breast reconstructions. In both the EP and the DIEP flap groups, contralateral breasts were softer than the reconstructed breasts (**Table 7**). Symmetry with the matched contralateral breast was higher in the DIEP flap group for jugulum-nipple distance, ptosis, and softness. In the EP group at the two-year follow-up, none of the breasts were graded as Baker III or IV. The median response to the BREAST-Q question was 3, corresponding to *somewhat satisfied*, in the EP group and 4 in the DIEP flap

group, corresponding to *very satisfied*, and the difference was significant ($p < 0.01$). The Spearman's rank correlation between the tonometric areas and the BREAST-Q question was 0.37 ($p < 0.01$), indicating a fair positive correlation (162).

Table 7. Breast softness comparison between the EP and the DIEP flap breast reconstructions.

	EP n=28		p-value	DIEP flap n=41		p-value
	RB	CB		RB	CB	
Tonometric areas (cm^2)	32.5 ± 11.4	59.6 ± 24.3	**<0.01**	61.6 ± 16.0	67.8 ± 14.8	**<0.01**
Fractional areas	0.36 ± 0.12	0.64 ± 0.12	**<0.01**	0.47 ± 0.06	0.53 ± 0.06	**<0.01**

Values are presented in mean ± standard deviation. Abbreviations: RB = Reconstructed breast, CB = Contralateral breast.

P-values from the Paired t-test.

Applanation tonometry has previously been used to identify capsular contracture following breast reconstruction (52, 63). In one study, capsular contracture was investigated with both the Baker classification and with applanation tonometry. The authors reported a good correlation between the two methods (52). However, investigating capsular contracture was not the aim of Paper II. Thus, applanation tonometry has also been used to assess breast symmetry. Edsander-Nord et al. reported that breast reconstruction with free TRAM flaps provided better symmetry with breast softness than with pedicled TRAM flaps (65). A free TRAM flap and a DIEP flap are two very similar breast reconstruction methods. In contrast to a pedicled TRAM flap, and even more so to an implant, a free flap can more easily be adjusted to match the contralateral breast.

A weak correlation between an objective method and the patient-reported satisfaction has similarly been reported in a previous study assessing breast reconstructions (163). This is most likely explained by the vast array of additional factors that could influence patient satisfaction. For example, the BREAST-Q subscales are constructed with questions that relate to each other (92). Therefore, qualities of the breast such as "how naturally the breast hangs", may influence the response to the breast softness question. Additionally, personality traits represent an external factor which has been found to impact the PRO (164).

Breast oedema

In the reconstructed breasts, the median absolute TDC values were 29.3 in the DIEP flap group and 28.6 in the EP group. The highest TDC ratio was found in patients reconstructed with an EP who had a non-operated contralateral breast (ratio = 1.16). No significant difference was found between absolute TDC values or ratios between the EP and the DIEP flap reconstructed breasts. Division into subgroups by axillary surgery or the presence of arm lymphoedema did not alter these results. However, the non-operated, contralateral breasts demonstrated lower TDC values than the matched reconstructed breasts (**Table 8**). The preoperative and postoperative median scores from the subscale *Physical well-being of chest* ranged between 1 and 2 in both reconstruction groups, indicating a low burden of breast oedema-related symptoms.

Table 8. Tissue dialectic constant values of the reconstructed breasts and the matched non-operated contralateral breasts.

	Tissue dialectic constant		
	RB	Non-operated CB	p-value
EP, n=12	29.5 (27.4, 32.9)	26.4 (25.1, 28.9)	**<0.01**
DIEP flap, n=25	28.7 (27.4, 30.7)	26.5 (25.1, 28.2)	**<0.01**

Values are presented in median and interquartile range in parentheses. Abbreviations: RB = Reconstructed breast, CB = Contralateral breast.

P-values from the Wilcoxon signed-rank test.

Lymphoedema is associated with an increased risk of infection and lower QoL (97, 165). Therefore, early detection and treatment with compression garments is a priority. Breast oedema has primarily been detected in patients following BCS and axillary surgery (98-100). Comparison of oedema-affected breasts with healthy breasts has found alterations in lymphatic drainage pathways and in addition, increased dermal backflow (106). Alteration of lymphatic drainage and differences in measured tissue water have also been demonstrated in breasts following other types of breast surgeries (109, 166, 167). In previous reports using the MoistureMeterD® instrument, absolute TDC values in healthy breasts have been suggested to be 29.5 ± 4.5 (133, 168). Thus, there is no consensus on a TDC threshold for breast oedema diagnosis. In a recent report, Mayrovitz et al. investigated non-oedematous breasts and proposed an absolute TDC value of 41, or an interbreast TDC ratio of 1.28, to indicate breast oedema (133). This proposition challenges a TDC ratio of 1.4 which was previously reported (168). The true ratio is probably somewhere in between, a suggestion supported by the finding that only half of the clinically diagnosed breasts with breast oedema had a TDC ratio above 1.4 in a third study (106). Notably, the absolute TDC values and the ratios measured

in Paper III should not be considered as breast oedema. The objective results were also confirmed by the low scores from the BREAST-Q questions. Although there ought to be damage to the lymph vessels following a mastectomy and a breast reconstruction, the results from Paper III illustrated a residual lymphatic capacity.

Reliability of the assessment scale

Photographs of 33 breast reconstructions, 14 EP and 19 DIEP flaps, were assessed in 2D and 3D format. The overall intra-rater agreements were moderate to substantial (**Table 9**). The inter-rater agreements, presented in **Table 10** separated by the panels, were moderate overall. Analysis of the matched photographs in 2D and 3D format demonstrated moderate to substantial agreements in all panels. In the patient panel, scar appearance was rated differently in 2D and in 3D format. The most frequent grade in 2D format for scar appearance was grade 5, *very good*, and in 3D format grade 2, *somewhat bad*. There was a tendency towards higher aesthetic outcome scores in the DIEP flap group compared with the EP group for all panels.

Table 9. Intra-rater agreements.

	Expert Panel n=11	Layman Panel n=7	Patient Panel n=12
2D format	0.70 (0.62 - 0.75)	0.70 (0.58 - 0.74)	0.73 (0.50 - 0.89)
3D format	0.67 (0.54 - 0.80)	0.66 (0.60 - 0.69)	0.72 (0.29 - 0.83)

Values are presented in median weighted kappa values with minimum and maximum values in parentheses.

Table 10. Inter-rater agreements.

	Expert Panel n=13	Layman Panel n=9	Patient Panel n=12
2D format	0.60 (0.36 - 0.74)	0.62 (0.44 - 0.73)	0.46 (0.19 - 0.73)
3D format	0.55 (0.35 - 0.77)	0.57 (0.38 - 0.67)	0.48 (0.04 - 0.73)

Values are presented in median weighted kappa values with minimum and maximum values in parentheses.

Ideally, assessment scales developed for clinical use should have agreements between 0.8 and 1.0. The agreements obtained in this paper did not meet those requirements. However, subjectivity is inherent in the concept of aesthetics and subsequently, high agreements are almost impossible to reach. Both agreements, choice of statistical analysis method and scales have varied in previous studies (116-119, 169). Thus, in reports that have used the same statistical method as we did, the

weighted kappa, the results were consistent with our findings (117, 169, 170). Therefore, we believe that our results were acceptable. In the context of scale variety, consensus on which scale to use is warranted within the research community. In the report by Godden et al., a Delphi consensus process agreed on a five-point scale to be preferred for evaluation of breast reconstruction aesthetics (169). To the detriment of moderate agreements, a consensus on a single scale would improve aesthetic comparisons in published literature.

A lower grade for the item scar appearance in 3D format in the patient panel could have several explanations. 3D format enhances details as with scars, creating a more realistic photo. In addition, patients may have a strong focus on the scar's appearance. This reasoning could be supported by a report demonstrating less satisfaction with the abdominal scars following DIEP flap breast reconstructions in patients compared with experts (117). Additions to the clinical care may prepare patients better for the postoperative outcome and provide more realistic expectations. Information sheets with details on possible outcomes of surgery, concerning both donor and recipient sites, could be sent to patients before the consultation. At the time of consultation, all patients should be presented with photographs of a good, an acceptable, and a bad outcome.

Breast sensibility

The EP reconstructed breasts were significantly more sensate compared to the DIEP flap reconstructed breasts five years following breast reconstruction. In the medial outer quadrants and the lower lateral outer quadrant, the EP group had protective sensibility. In contrast, none of the measured areas in the DIEP flap group had protective sensibility. Area nine, corresponding to the NAC or the proposed position of the NAC, had only deep pressure sensation in both groups.

A Dutch research group has performed a number of studies on breast sensibility following breast reconstruction (138, 140, 171). One of these studies demonstrated results in accordance with ours for IBBR, with protective sensibility in the outer quadrants of the breasts (140). Furthermore, sensibility assessments of DIEP flap breast reconstructions have been performed. The result obtained from Paper V, that there was only deep pressure sensation in the DIEP flap reconstruction, confirms previous reports of non-innervated DIEP flaps (138, 172). However, in DIEP flaps with a nerve coaptation, a significant improvement of sensibility was found compared with non-innervated flaps at a one-year follow-up. Subsequently, DIEP flap patients with a nerve coaptation reported higher QoL (171, 173). Breast sensitivity from the patient's perspective may be further investigated through the recently developed BREAST-Q Sensation Module (174, 175). Lastly, sensibility

may be better preserved following skin-sparing mastectomy compared with conventional mastectomy (173).

Conclusions and future perspectives

The conclusions are provided in the same order as in the results and discussion section. I believe that the findings from the thesis have increased our knowledge about breast reconstruction with the EP and the DIEP flap during the first five postoperative years. I hope that the results will have a clinical impact and that they may inspire further research.

Complications and costs

In the short-term perspective, EP breast reconstructions had fewer complications compared with DIEP flap breast reconstructions. The five-year analysis found an inverse relationship. The short-term healthcare burden in the DIEP flap group was supported by a high number of complications and by initial high, and probably also underestimated, healthcare costs. Compared with previously published reports, this thesis presented a relatively high number of vascular complications and injection dome-associated problems. Additionally, the increased risk of complications with a higher BMI warrants attention in preoperative patient counselling. In terms of breast reconstruction surgery, it is crucial to have knowledge of the early postoperative time and of the coming years. Not even a five-year follow-up is sufficient to cover all events associated with the reconstructions. Probably, additional corrections will be performed in the DIEP flaps group and more implants will be exchanged as a result of capsular contracture or implant dislocation. Longer follow-ups are warranted to detect BIA-ALCL as it develops at a median of 11 years following breast implantation (12). BII is an additional area of high interest, and results from ongoing studies are anticipated. In summary, there is a demand for multicentred, long-term follow-up studies with the aim of assessing complications in a standardised way.

Patient-reported outcome

PRO indicated a general increase in satisfaction and QoL from mastectomy to a completed breast reconstruction. The increase was thus higher for *Satisfaction with breast* following a DIEP flap breast reconstruction, both in the two-year and the five-year evaluation. Patients who had undergone EP breast reconstruction as their

method of choice did not have higher satisfaction and QoL compared with patients randomised to an EP breast reconstruction.

The effect of an additional surgical correction can be further evaluated, especially due to the high rate of additional corrections in the DIEP flap group (Paper V). By comparing BREAST-Q results pre- and postoperatively, the MID could be used to evaluate the impact of the additional surgery.

Breast softness

With an objective measurement method, breasts reconstructed with DIEP flaps were confirmed to be softer than breasts reconstructed with the EP. Satisfaction with the softness of the reconstructed breast was also higher in the DIEP flap group. The fair correlation between the methods could be due to the multifactorial influence on patients' responses to PRO questions.

Breast oedema

The results obtained from the LTW assessments found reconstructed breasts to have a higher amount of LTW, presented as higher TDC values, compared with non-operated contralateral breasts. The TDC values and the results from questions assessing breast oedema-related symptoms suggested that breast oedema was not present in the patient cohort. In a future investigation, it would be of interest to perform TDC measurements over time, starting with measurements before mastectomy, and then repeatedly following the reconstruction process. Further research is needed to determine whether breast reconstruction after RT is associated with breast oedema.

Reliability of the assessment scale

The intra-rater and inter-rater agreements of the aesthetic outcome assessment scale ranged from moderate to substantial and were deemed to be acceptable. The patient panel rated scar appearance differently in 2D and 3D format. This was interpreted to be caused by more realistic appearances of breast reconstructions in the 3D format. By presenting patients with photographs of a good, a bad and an average outcome in 3D format at preoperative consultations, more realistic patient expectations may be achieved.

Breast sensibility

Five years postoperatively, EP breast reconstructions had better sensibility compared with DIEP flap breast reconstructions. Protective sensibility was found in

peripheral parts of the EP reconstructed breasts. Only deep pressure sensation was recorded in the DIEP flap breasts. Notwithstanding the impact on QoL, it is not clear if the absence of protective sensibility has any consequences for the DIEP flap, for example in respect to a wound infection. However, the possible advantage of an innervated DIEP flap breast reconstruction was beyond the scope of this thesis. It would be of interest to compare sensibility in DIEP flaps following skin-sparing mastectomy with DIEP flaps following conventional mastectomy, and to include a subjective evaluation with the recently developed BREAST-Q Sensation Module (174, 175).

Strengths and limitations

One of the main strengths of this thesis is the randomised design in which patients were randomly allocated to a breast reconstruction method. Overall, randomised studies are rare in breast reconstruction research. To justify a similar study today would not be possible, primarily as a result of the changed national guidelines, but also due to reports emphasising the importance of high patient involvement in the decision-making process (159-161). The use of the validated BREAST-Q is also considered a strength in the included papers. The response rates were high and with measurements at several timepoints, changes over time could be detected. However, a high response rate was not achieved in the non-randomised EP group, a limitation that may have altered the results. Only three experienced microsurgeons conducted the breast reconstructions included in the thesis. Furthermore, the data collection was performed by a limited number of investigators. In Papers II and III, two registered nurses collected the data and in Paper V, the author (LT) performed the data collection.

There were also limitations to the papers of this thesis. A higher number of included patients would have provided more robust results and a possibility to perform subgroup analyses. For example, in Paper IV, a statistical analysis of the aesthetic outcome between the EP and DIEP flap reconstructions was not performed due to the low number of patients. However, the inclusion of patients was a time-consuming process. Unequal group sizes were a consequence of a larger drop-out in the EP group. A reconstruction with a DIEP flap was the main incentive to participate in the randomised study. Other limitations concern the lack of an inter-rater reliability analysis for applanation tonometry and that reliability analyses in Paper IV were performed on different sets of photographs for the patient panel.

Populärvetenskaplig sammanfattning

Under år 2021 erhöll 8619 kvinnor i Sverige en bröstcancerdiagnos. Bröstcancer är den vanligaste cancerformen hos kvinnor och antalet drabbade per år fortsätter att öka. Komplett borttagande av bröstvävnad, så kallad mastektomi, är för många kvinnor den rekommenderade kirurgiska behandlingen. De som genomgår en mastektomi erbjuds en rekonstruktion av bröstet. Uppskattningsvis väljer en tredjedel av de drabbade kvinnorna att genomgå en bröstrekonstruktion efter mastektomi. En bröstrekonstruktion har som syfte att öka kvinnornas livskvalitet. Ett bröst kan rekonstrueras med implantat, med kroppsegen vävnad eller med en kombination av båda teknikerna. Vid en sen bröstrekonstruktion med implantat, när mastektomi och rekonstruktion sker vid olika tillfällen, används en expanderprotes (EP). En EP består delvis av silikon och delvis av ett hålrum som efter operationen kan fyllas på via en ventil. Den vanligaste kroppsegna bröstrekonstruktionsmetoden är rekonstruktion med patientens egen vävnad från buken, så kallad deep inferior epigastric perforator (DIEP)-lambå. Denna operation innebär att hud, fett och kärl från buken flyttas till bröstet där vävnaden får blodförsörjning genom nya kärlkoppningar. Vävnaden från buken formas sedan till ett nytt bröst.

En bröstrekonstruktion är en självklar del i behandlingen för bröstcancerdrabbade kvinnor. Kunskap om hur de tillgängliga bröstrekonstruktionsmetoderna skiljer sig åt är viktigt för att patienterna ska kunna göra ett informerat val om metod. Det övergripande syftet med denna avhandling var att jämföra de två bröstrekonstruktionsmetoderna EP och DIEP-lambå i ett kort och långt perspektiv i en randomiserad patientgrupp. De patienter som studerats i avhandlingen genomgick ensidig bröstrekonstruktion och hade inte fått strålning mot bröstet. Samtliga studier omfattar 73 patienter som randomiserats till bröstrekonstruktion med EP eller med DIEP-lambå.

I studie I utvärderades komplikationer och sjukvårdskostnader de första 30 dagarna efter bröstrekonstruktion med EP och med DIEP-lambå. I studien användes det patientrapporterat utfallsmåttet BREAST-Q för att undersöka nöjdhet och livskvalitet före operation samt två år efter operation. De patienter som rekonstruerades med en EP hade färre komplikationer och lägre kostnader de första 30 dagarna. DIEP-lambågruppen hade å andra sidan högre nöjdhet med sitt rekonstruerade bröst. Båda grupperna uppvisade en ökad nöjdhet och livskvalitet efter att ha genomgått en bröstrekonstruktion.

Studie II jämförde mjukhet hos bröst rekonstruerade med en EP och med en DIEP-lambå två år efter bröstrekonstruktion. En objektiv metod som kallas applanationstonometri användes för att mäta bröstens mjukhet. Patienternas subjektiva nöjdhet med bröstens mjukhet mättes med en specifik fråga från BREAST-Q-enkäten. Resultaten visade att DIEP-lambårekonstruktionerna var objektivt mjukare och att dessa patienter var nöjdare med mjukheten hos sitt rekonstruerade bröst. Dessutom var mjukheten mer lik det kontralaterala bröstet i DIEP-lambågruppen. Korrelationen mellan applanationstonometri-resultaten och BREAST-Q frågan var svag. En förklaring till detta är att patientens upplevelse om sin bröstrekonstruktion är multifaktoriell och inte kan återspeglas med en enskild objektiv mätmetod.

Lokal vätskeansamling i vävnad, även kallat ödem, förekommer i bröst efter bröstkirurgi. Ödem kan uppstå som ett resultat av skada på lymfkärl och av borttagande av lymfkörtlar i armhålan, och ger upphov till bland annat tyngdhetskänsla och smärta. I studie III undersöktes lokalt ödem i brösten med instrumentet MoistureMeterD® två år efter bröstrekonstruktion. Frågor som motsvarar de symtom som förekommer vid bröstödem valdes ut från de pre- och postoperativa BREAST-Q enkäterna. Resultaten från denna studie visade att bröstrekonstruktionerna innehöll en större mängd vätska lokalt jämfört med de kontralaterala icke-opererade brösten. De mätvärden som uppmättes i studien överskred ej de i litteraturen föreslagna gränsvärdena för bröstödem. Det framkom dessutom inga bröstödem-relaterade symtom vilket ytterligare bekräftade frånvaron av bröstödem vid mätningarna.

I studie IV undersöktes överensstämmelsen mellan bedömningar av foton på bröstrekonstruktioner i 2D och 3D format avseende estetik. Expertpaneler, lekmannapaneler och en patientpanel bedömde fotografier med hjälp av en bedömningsmall med sex frågor. Överensstämmelsen mellan en och samma bedömare vid två olika tillfällen var måttlig till bra. Inom panelerna var överenstämmelsen måttlig. Även överensstämmelsen mellan bedömningar av samma bröstrekonstruktion i 2D och i 3D format var måttlig till bra. Motsvarande resultat har visats i tidigare studier vilket tyder på att det är svårt att uppnå perfekt överensstämmelse vid subjektiva bedömningar avseende estetik. Vidare gav patientpanelen sämre omdömen om ärrens utseende vid bedömning av bilderna i 3D format jämfört med i 2D format. Det kan förklaras med att 3D formatet ger mer realistiska bilder där ärren framhävs mer. Slutligen visade studien en tendens till att DIEP-lambårekonstruktionerna hade bättre estetiska resultat jämfört med EP-rekonstruktionerna. Dock var antalet patienter för få för att kunna dra några statistiska slutsatser.

I studie V utvärderades bröstrekonstruktionernas känsel, patientrapporterat utfall och komplikationer fem år efter bröstrekonstruktion med EP och med DIEP-lambå. Känsel mättes med Semmes-Weinstein monofilament i fem olika storlekar och

patientrapporterat utfall mättes med BREAST-Q. De EP-rekonstruerade brösten hade bättre känsel jämfört med de bröst som rekonstruerats med en DIEP-lambå. I tre av fyra av de yttre bröstkvadranterna på de EP-rekonstruerade brösten uppmättes skyddskänsel. Resultaten avseende patientnöjdhet och komplikationer var till fördel för DIEP-lambågruppen. I jämförelse med studie I drabbades EP-rekonstruktionerna av fler komplikationer under den totala uppföljningsperioden jämfört med DIEP-lambårekonstruktionerna, dock var skillnaden mellan det totala antalet komplikationer inte signifikant. Resultaten visade även att ett stigande BMI ökade risken för komplikationer som behövde åtgärdas i sövt tillstånd samt ökade risken för ytliga sårinfektioner. Under femårsperioden behövde en betydande andel av patienterna i EP-gruppen en kirurgisk åtgärd för att korrigera läget på påfyllnadsventilen eller för ta bort påfyllnadsslangen. Dessutom genomgick en tredjedel av patienterna i DIEP-lambågruppen en korrigerande kirurgi.

Sammanfattningsvis illustrerar resultaten från denna avhandling en bild av hur de två bröstrekonstruktionsmetoderna EP och DIEP-lambå förändras över tid samt fördelar och nackdelar mellan de två metoderna. Vad gäller resultatens påverkan på den kliniska vården har studie V belyst områden som behöver undersökas vidare – positionering av påfyllnadsventilen vid EP-rekonstruktion samt rådgivning till patienter med ett högt BMI. Det har även framkommit ett möjligt behov av att informera och att med bilder illustrera hur ärren kan se ut postoperativt. Detta som i ett led att skapa rimliga förväntningar inför en bröstrekonstruktion. Det vore av intresse att framöver studera bröstödem i samband med en bröstrekonstruktionsprocess samt att använda BREAST-Q enkäten för att utvärdera effekt av korrigerande ingrepp i det efterföljande förloppet.

Oavsett vad kliniska mätningar och journalgranskningar visar är nöjdhet och livskvalitet det centrala vid utvärdering av bröstrekonstruerade patienter. Hur den individuella patienten uppnår en god livskvalitet beror på många olika faktorer och vår uppgift är att skapa så goda förutsättningar som möjligt. Resultaten från denna avhandling kan användas som stöd vid guidning av patienter som står inför att välja bröstrekonstruktionsmetod.

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Paper I

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A short-term comparison of expander prosthesis and DIEP flap in breast reconstructions: A prospective randomized study

Linda Tallroth, Patrik Velander, Stina Klasson*

Skåne University Hospital, Department of Plastic and Reconstructive Surgery, Jan Waldenströms gata 18, 20501 Malmö, Sweden

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Summary *Background:* There is yet no clear consensus on which method is preferable in secondary breast reconstructions, prosthesis, or autologous tissue.
Methods: In this first prospective randomized study, 29 women underwent reconstruction with expander prosthesis (EP) and 44 with deep inferior epigastric perforator (DIEP) flap. Inclusion started in 2012 and ended in 2018. Demographic data, complications, surgery time, hospital days, and consulting visits were recorded. Patient satisfaction was evaluated pre- and postoperatively using the BREAST-Q questionnaire. Health care costs were calculated based on rates from the financial year 2018. Here, we report the results related to the surgery and the first 30 postoperative days.
Results: The two groups were comparable regarding demographics and clinical characteristics. Satisfaction with breasts, measured with BREAST-Q, was significantly higher in patients who had undergone reconstruction with DIEP flap compared with EP. Within 30 days after breast reconstruction, significantly fewer women ($n = 2$) in the EP group suffered complications compared to the DIEP flap group ($n = 16$; $p < 0.01$). The health care cost was also significantly higher in the DIEP flap group relative to the EP group ($p < 0.01$).
Discussion: This patient cohort will be studied systematically over time, and results concerning the need for complementary surgery, costs, esthetics, and the patient-reported outcome (PRO) will be reported in future work. In this short-term report, EP seems to be preferable in regard to cost and complications, and DIEP flap is to choose from the patient's perspective.

* Corresponding author.
E-mail address: stina.klasson@med.lu.se (S. Klasson).

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Introduction

Breast cancer is the most common type of cancer in women. Although new surgical techniques have been developed, mastectomy is still recommended in many cases. It has been known for a long time that mastectomy has a major impact on patients' self-image. Reconstruction of the breast results in a better psychosocial state and, subsequently, higher quality of life and is an established part of modern breast cancer treatment.[1-3]

The most used methods for breast reconstruction are implant-based reconstruction and reconstruction with autologous tissue. At our clinic, one-stage implant reconstruction with expander prosthesis (EP) is the standard procedure in delayed reconstructions. However, EP is contradicted in cases of prior radiation therapy (RT) to the breast.[4-6] Since 1998, autologous reconstruction with deep inferior epigastric perforator (DIEP) flap has, therefore, been our first choice for breast reconstruction in patients treated with radiation therapy.

Selecting the most appropriate method for breast reconstruction is a complex process. Choices are narrowed by consideration of patient characteristics, patient satisfaction, potential complications, and costs. Body mass index (BMI), active smoking, and the amount of donor tissue are patient-related characteristics influencing the likelihood of surgical complications and morbidity.[6-12] In our present prospective randomized study, BMI above 33 and current smoking were exclusion criteria. Furthermore, patients with insufficient donor site tissue of the abdomen to create a new breast were excluded from participation.

National guidelines strongly influence decisions about the choice of reconstructive method. According to the guidelines presented by The National Board of Health and Welfare in Sweden 2011, autologous reconstruction should be offered to women having RT or predictions of, for other reasons, a poor cosmetic outcome from implant reconstruction.[13] From an international perspective, this might be perceived as a limitation, but at the same time, it makes prospective randomized studies possible regarding women who have not undergone RT.

The indication for breast reconstruction is the woman's own desire for a new breast. As a result, patient satisfaction is a high-importance criterion when choosing the method of breast reconstruction. Patient-reported outcome (PRO) has been measured in several previous studies using a self-reported instrument, such as BREAST-Q.[1,3,14-17] BREAST-Q is an instrument developed in agreement with the relevant international criteria and designed to evaluate patient perception. There are pre- and postoperative modules concerning three breast cancer surgery procedures with individual items, one of them being reconstruction. The PRO instrument is built on six domains, including psychosocial well-being, physical well-being, sexual well-being, satisfaction with breast, overall outcome, and care.[18]

A comparison of complications is one way of evaluating different breast reconstruction options. There have been multiple published studies comparing implants and autologous methods. The timing of reconstruction, one- or two-stage prosthesis reconstruction, and type of autologous reconstruction differ in published reports. It is important to consider the cost analysis for different breast reconstruction methods when developing public health care systems. Reconstruction with DIEP flap and other autologous alternatives demand a longer time in the operating room, longer hospital stay, and are associated with higher rates of early complications.[9,19-21] Consequently, DIEP flap reconstructions are far more expensive in the short run than implants. However, previous works have used a retrospective design.

Therefore, here we use a prospective randomized approach that aims to assess the short-time complications and costs and to evaluate patient satisfaction among patients randomized to breast reconstruction with either EP or DIEP flap. This cohort will be studied over time, and subsequent studies will report the medium- and long-term findings, thereby informing Swedish national guidelines.

Material and methods

Subjects

Between April 2012 and January 2018, 135 patients with prior unilateral mastectomy, but no RT, were referred to our clinic for secondary breast reconstruction (Figure 1). All patients were asked to participate in our prospective randomized study. Twenty-eight patients declined, as they wished to undergo an EP reconstruction. Of the remaining patients, nine had insufficient abdominal donor tissue for a DIEP flap reconstruction. One had earlier abdominal liposuction, and one a previous abdominoplasty and, therefore, were unsuitable for DIEP flap. Two patients were not appropriate for EP due to pronounced scars on the chest, and additional shoulder disability. One patient was excluded due to her warfarin treatment for atrial fibrillation. One patient did not want an abdominal scar, and one patient wanted a reconstruction without further delay, which in our unit meant an EP reconstruction according to our standard routine.

The 91 remaining patients were included in our study for breast reconstruction with either EP or DIEP flap. However, one patient had a recurrence of breast cancer after inclusion but before randomization. Forty patients were eventually randomized to EP and 50 to DIEP flap. In the EP group, four patients chose to withdraw since they wanted to have a DIEP flap reconstruction. Three patients changed their minds about surgery, and one did not meet the weight criteria at the time for surgery. One patient, randomized to EP, had a recurrence of her breast cancer, one patient wished to be reconstructed at her local hospital, and one patient was operated by a surgeon who was not a member of the study team. In the DIEP flap group, three patients withdrew from the study as they changed their minds and wanted an EP according to our standard procedure. Two patients changed their minds about reconstruction and abstained further surgery, and one did not meet the weight criteria at the time for surgery. Hence, the EP group consists of 29 patients and the DIEP flap group of 44 patients. For all these patients, a digital case report form (CRF) was created aimed at collecting relevant data from each participant. Demographic and clinical data included age at surgery, BMI, abdominal scars from previous surgery, smoking habits, parity, concurrent diseases, and chemotherapy. The included perioperative and postoperative parameters were: anesthesia time, surgery time, days in the hospital, day surgery, and

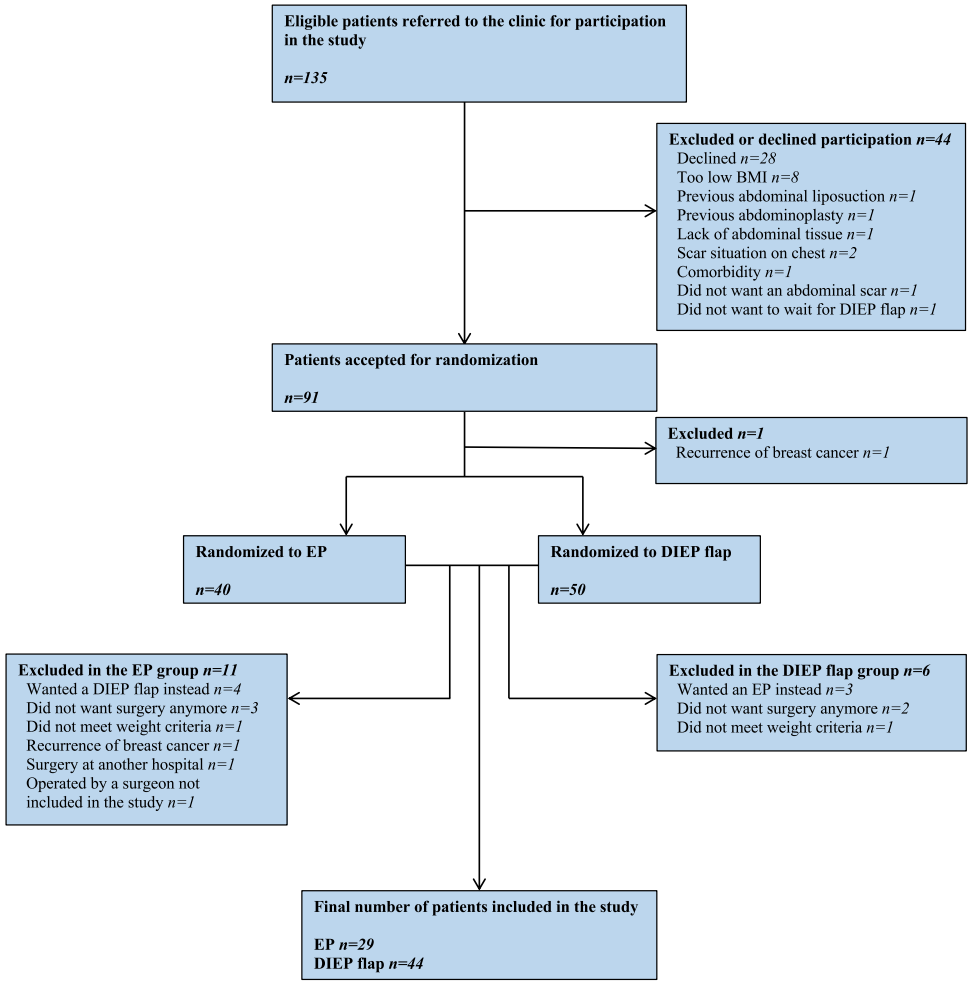

Figure 1 Flow chart for the study illustrating inclusion and exclusion of subjects. EP, expander prosthesis; DIEP, deep inferior epigastric perforator.

out-patient consulting visits. In two patients, the surgery time and anesthesia time were not recorded in the operating records, and were treated as missing data. For six patients in the EP group, a contralateral breast reduction was performed in the same session, but the time to perform this procedure was not included in the time measurements.

Patient satisfaction and quality of life were evaluated preoperatively using the validated BREAST-Q questionnaire. All patients included in our study received one questionnaire preoperatively and one postoperatively. The results were transformed with the Q-Score software. In our study, we used the BREAST-Q Preoperative Reconstructive Module and the BREAST-Q Postoperative Reconstructive Module.

This article is reported in accordance with the STROBE guidelines. The EP used in this study was a MENTOR® Contour Profile Becker-35 and the breast implant used for prosthesis exchange was a MENTOR® Contour Profile Gel 312.

Health care cost

Health care costs were calculated based on rates in Swedish crowns from the Southern Health Care Region for Plastic and Reconstructive Surgery according to the 2018 calendar year.[22] Rates were converted to Euro prior to statistical analysis. Included in the rates were admission to hospital, doctor assessment at admission, doctor assessment for

each hospitalized day, number of hospital days, anesthesia time, surgery time, and surgery time for reoperation when needed, day surgery in case of EP, postoperative consulting visits to doctor and other health care workers, all within the first 30 postoperative days. Surgery time was measured from incision to last suture and anesthesia time from induction to extubation. Consulting visits included visits to a plastic surgeon, nurse, or assistant nurse. Health care costs were calculated with the help of a medical economist at Lund University, Sweden.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS) software version 25.0. A p-value < 0.05 was considered to indicate a significant difference. P-values were calculated with the Mann–Whitney U test, Student's t-test, and the paired Student's t-test. For calculation of statistical differences of costs, Student's t-test was used with bootstrapping. Confidence intervals were checked with the bootstrapping confidence intervals to assess if the results from Student's t-test were credible. The use of Student's t-test for analyzing differences in health care costs has been advocated in the literature, although the costs are typically non-normally distributed.[23,24] Chi-square test or Fisher's exact test was used for categorical data.

Results

Twenty-nine patients were randomized to reconstruction with EP and 44 to DIEP flap. The mean age at surgery was 56 years (range= 36–70) in the EP group and 52 years (range= 34–70) in the DIEP flap group. Patient demographics and clinical data are displayed in Table 1. The two groups had compatible demographic variables, apart from parity. Parity was higher in patients reconstructed with DIEP flaps. There was no significant difference in regard to age and BMI between the groups.

Patient satisfaction and quality of life evaluated with the BREAST-Q Preoperative Reconstruction Module were also compatible between the groups, except the scores for the physical well-being of the chest and abdomen, which were lower in the EP group ($p = 0.04$ and $p = 0.04$; Table 2). The mean time from breast reconstruction surgery to completed BREAST-Q postoperative forms was 63 months. BREAST-Q postoperative results showed that satisfaction with breasts was significantly higher in patients who had undergone reconstruction with DIEP flap compared with EP (Table 3). Compared with BREAST-Q preoperative responses, both EP and DIEP flap reconstructed patients had higher postoperative patient satisfaction with breasts and higher psychosocial and sexual well-being. A decrease in patient satisfaction was noted in the DIEP flap group for the well-being of the abdomen after surgery. No difference was found for the well-being of the chest prior to and after surgery within the groups (Table 4). Seventy-one patients (97%) responded to the preoperative questionnaire, and 70 patients (96%) responded to the postoperative questionnaire.

Peri- and postoperative data, including consultation visits, are shown in Table 5. Anesthesia time and surgery time were significantly longer for DIEP flap surgery. There were 11 patients who required reoperations after DIEP flap reconstruction and one after EP reconstruction. One patient reconstructed with a DIEP flap required two reoperations. The number of postoperative consulting visits was significantly higher in patients reconstructed with an EP ($p = 0.03$).

Complications

Within the first 30 postoperative days, there were two complications (2/29) in the EP group. One patient suffered from deep venous thrombosis and the other required prosthesis exchange due to retraction of the filling port. Complications occurred in 16 patients (16/44) in the DIEP flap group, and the diversity of the complications is shown in Table 6. Two patients had both donor sites and flap complications. No flaps were lost. The complication rate was significantly higher in the DIEP flap group compared with the EP group ($p < 0.01$).

Costs

Health care consumption within 30 days was markedly higher in the DIEP flap group. Costs for consulting visits to the doctor were significantly higher in the EP group. Table 7 presents specifications of costs and comparison of costs between the EP and DIEP flap groups.

Discussion

PRO was evaluated with BREAST-Q in this study. We report higher satisfaction with breasts in patients who underwent DIEP flap reconstructions compared with EP. This result is in agreement with previous studies comparing autologous and implant reconstructions.[3,16,17] BREAST-Q scores were higher, but not significantly, for satisfaction with the outcome and sexual well-being in the DIEP group. Liu et al. presented greater satisfaction in all BREAST-Q scales for autologous breast reconstruction, apart from the well-being of the chest. The response rate in their study was 62%, compared with the 96% reported here. Furthermore, time from surgery to completed questionnaires was not reported.[16] Both response rate and follow-up time might influence BREAST-Q results and hypothetically contribute to differences in reported results.

The main purpose of undergoing breast reconstruction is to improve life quality and body satisfaction. Based on our findings, this is true for both EP and DIEP flap reconstructions. In addition, significantly lower scores for the physical well-being of the abdomen in the autologous reconstructed group were noted in our study and in the work of Santosa et al.[3] For obvious reasons, the process of choosing breast reconstruction method will mainly focus on the outcome of the breasts. Autologous reconstruction results in breasts that look and feel more natural and are, therefore, considered the gold standard. The reports of lower satisfaction concerning the abdomen post-surgery highlight an area in

Table 1 Patient demographics and clinical characteristics.

	All ($n=73$)	EP ($n=29$)	DIEP flap ($n=44$)	p-value
Age at surgery (mean)	53.7 ± 9.4 (34-70)	55.8 ± 8.9 (36-70)	52.3 ± 10(34-70)	0.13[a]
BMI (mean)	25.7 ± 2.9 (19.0-33.0)	25.1 ± 3.1(19.0-30.8)	26.1 ± 2.7 (20.5-33.0)	0.15[a]
Smokers (n)				
Never smoker	45 (62)	16 (55)	29 (66)	0.36[b]
Former smoker	22 (30)	11 (38)	11 (25)	0.24[b]
Stopped before surgery	6 (8)	2 (7)	4 (9)	0.74[b]
Abdominal scars (n)	31 (42)	13 (45)	18 (41)	0.74[b]
Open surgery	22 (30)	9 (31)	13 (30)	0.89[b]
Laparoscopic surgery	5 (7)	2 (7)	3 (7)	1[c]
Open and laparoscopic surgery	4 (5)	2 (7)	2 (4)	1[c]
Parity (n)				
Nulliparity	8 (11)	6 (21)	2 (4)	0.05[c]
Parity	65 (89)	23 (79)	42 (95)	0.05[c]
Chemotherapy (n)	38 (52)	13 (45)	25 (57)	0.32[b]
Concurrent diseases (n)				
Hypertension	16 (22)	7 (24)	9 (20)	0.71[b]
Type I diabetes	1 (1)	1 (3)	0	0.4[c]
Rheumatoid arthritis	2 (3)	2 (7)	0	0.15[c]
APC resistance	1 (1)	0	1 (2)	1[c]
Addison's disease	1 (1)	0	1 (2)	1[c]

Description of patient-specific data obtained from medical journals prior to the breast reconstruction surgery. Expander prosthesis (EP) group and deep inferior epigastric perforator (DIEP) flap group are presented separately and statistical analysis is illustrated with a p-value. Statistical tests used were [a]Student's t-test.
[b] chi^2 test.
[c] Fisher's exact test. Age and BMI are presented with means ± standard deviation, and minimum and maximum values in parentheses. Numbers are presented with percentages in parentheses.

Table 2. Preoperative patient satisfaction measured with BREAST-Q.

BREAST-Q	EP ($n=29$)	DIEP flap ($n=42$)	p-value
Satisfaction with Breasts	42.7 ± 14.2	39.9 ± 18.3	0.49
Psychosocial Well-being	48.8 ± 16.0	53.8 ± 19.2	0.25
Physical Well-being of Chest	73.8 ± 13.2	81.3 ± 15.3	0.04
Physical Well-being of Abdomen	83.6 ± 14.1	89.6 ± 10.6	0.04
Sexual Well-being	39.0 ± 14.1	41.8 ± 18.6	0.51

Score from 0 to 100. A higher score indicates a more satisfied patient. Values are presented as means ± standard deviation. Student's t-test was used for statistical analysis. EP=expander prosthesis; DIEP=deep inferior epigastric perforator.

Table 3 Postoperative patient satisfaction measured with BREAST-Q.

BREAST-Q	EP ($n=28$)	DIEP flap ($n=42$)	p-value
Satisfaction with Breasts	63.4 ± 11.8	72.1 ± 17.7	0.03
Satisfaction with Outcome	79.4 ± 14.2	82.3 ± 21.4	0.55
Psychosocial Well-being	78.8 ± 20.1	79.1 ± 21.5	0.95
Sexual Well-being	58.4 ± 23.1	67.1 ± 28.1	0.19
Physical Well-being of Chest	72.0 ± 21.5	79.6 ± 21.1	0.09
Physical Well-being of Abdomen	n/a	81.0 ± 15.3	
Satisfaction with Nipples	65.4 ± 21.8	67.7 ± 24.9	0.76
Satisfaction with Information	68.5 ± 17.4	72.3 ± 20.2	0.42
Satisfaction with Surgeon	91.8 ± 13.2	89.3 ± 18.4	0.57
Satisfaction with Medical Staff	96.9 ± 9.7	91.3 ± 17.3	0.09
Satisfaction with Office Staff	95.6 ± 10.9	95.6 ± 11.6	0.91

Score from 0 to 100. A higher score indicates a more satisfied patient. Values are presented as means ± standard deviation. Student's t-test was used for statistical analysis. EP=expander prosthesis; DIEP=deep inferior epigastric perforator; n/a=not applicable.

Table 4 Comparison of preoperative and postoperative BREAST-Q results.

BREAST-Q Scales	Pre-op.	Post-op.	*p*-value
Satisfaction with Breasts			
EP	42.7 ± 14.2	63.4 ± 11.8	<0.01
DIEP flap	39.9 ± 18.3	72.1 ± 17.7	<0.01
Psychosocial Well-being			
EP	48.8 ± 16.0	78.8 ± 20.1	<0.01
DIEP flap	53.8 ± 19.2	79.1 ± 21.5	<0.01
Physical Well-being of Chest			
EP	73.8 ± 13.2	72.0 ± 21.5	0.74
DIEP flap	81.3 ± 15.3	79.6 ± 21.1	0.66
Physical Well-being of Abdomen			
EP	83.6 ± 14.1	n/a	
DIEP flap	89.6 ± 10.6	81.0 ± 15.3	0.02
Sexual Well-being			
EP	39.0 ± 14.1	58.4 ± 23.1	<0.01
DIEP flap	41.8 ± 18.6	67.1 ± 28.1	<0.01

Score from 0 to 100. A higher score indicates a more satisfied patient. Values are presented as means ± standard deviation. Paired Student's *t*-test was used for statistical analysis. EP=expander prosthesis; DIEP=deep inferior epigastric perforator; n/a=not applicable.

Table 5 Peri- and postoperative parameters.

	EP ($n=29$)	DIEP flap ($n=44$)	*p*-value
Hospital stay, days (mean)	1.66 ± 1.78	5.86 ± 1.27	<0.01[a]
	(0-6)	(4-10)	
Anesthesia time, minutes (mean)	103 ± 24.3	333 ± 71.8	<0.01[a]
	(66-163)	(200-607)	
Missing (*n*)	5 (17)	0	
Surgery time, minutes (mean)	45 ± 10	225 ± 72	<0.01[a]
	(26-67)	(123-475)	
Missing (*n*)	1 (3)	0	
Day surgery (*n* of surgeries)	12 (41)	0	<0.01[b]
Contralateral reduction (*n*)	6 (20)	0	
Reoperation time, minutes (mean)	19 ± 0	86 ± 66	0.11[a]
	(0-19)	(30-221)	
Missing (*n*)	0	1 (2)	
Reoperation in general anesthesia (*n* of surgeries)	1	11	0.02[b]
Reoperation in local anesthesia (*n* of surgeries)	0	3	0.27[b]
Consulting visits <30 days (mean)	3.1 ± 1.7	2.3 ± 1.6	0.03[a]
	(1-9)	(0-6)	
Doctor	0.9 ± 0.7	0.4 ± 0.7	<0.01[a]
	(0-3)	(0-3)	
Nurse	1.1 ± 1.4	1.1 ± 1.4	0.92[a]
	(0-6)	(0-5)	
Assistant nurse	1 ± 1	0.8 ± 1	0.25[a]
	(0-4)	(0-4)	

Parameters regarding the hospital stay, initial breast reconstruction surgery, reoperation and consulting visits for the expander prosthesis (EP) group and deep inferior epigastric perforator (DIEP) flap group.
Statistical analysis is presented with a *p*-value <0.05 stating statistical significance. Statistical tests used were [a]Mann-Whitney U test and [b]Fisher's exact test. Mean values are presented with standard deviation, and minimum and maximum values in parentheses. Numbers are presented with means percentages in parentheses.

need of improvement and should be discussed with patients in the decision-making process.

This study compares early complications after breast reconstruction with EP and DIEP flap. The literature presents an early complication rate of 9-22% after breast reconstruction with implants, including both one and two stages.[19,25,26] A low complication rate of 2/29 was found in this study, which supports that reconstruction with EP is a low-invasive and initially safe method.

The most common complications reported in the literature after DIEP flap reconstructions are venous congestion, fat or skin necrosis, and hematoma.[19,27,28] The reconstruction method is more resource consuming and has higher rates of complications in the initial period; in this

Table 6 Complications in the DIEP flap group <30 days.

Patient	Arterial stop	Venous stasis	Hematoma flap	Necrosis flap <2 cm	Hematoma donor site	Infection donor site	Seroma donor site	Necrosis donor site
1	x	x	x					
2			x				x	
3		x						
4						x		
5			x					
6		x			X			
7		x						
8					X			
9	x							
10		x						
11						x		
12				x				
13						x		
14		x	x					
15						x		x
16						x		x

A presentation of each patients in the DIEP flap reconstructed group who suffered from complications. Patients 2 and 6 had both flap and donor site complications.

study, 16 of 44 patients experienced complications. There is only one previous study presenting a higher percentage of early complications for DIEP flaps. The authors, Thorarinsson et al., reported a 50% complication rate after DIEP flap reconstructions. The high complication rate was explained by a broad inclusion of complications and that some surgeries were performed by less experienced microsurgeons.[19] In our study, all complications within 30 days were included, implying that some patients had more than one complication (Table 6). Duraes et al. reported an early complication rate of 31% and Mioton et al. of 22% after free flap breast reconstruction. Regarding reoperation, in general anesthesia, the numbers reported from these studies were 8% versus 20%.[8,25] In our study, we had 11 patients (11/44) who required reoperation in general anesthesia and three (3/44) in local anesthesia. The reoperation rate is similar to the report from another Swedish study, but higher compared with some other studies.[8,19,25] Reoperations requiring general anesthesia were often a result of venous stasis in the DIEP flaps (Table 6). Currently, if there is any doubt that the venous outflow is suboptimal, an additional venous coupling is made during the DIEP flap procedure.

Clearly, we report higher numbers of microvascular complications and length of stay for DIEP flap reconstructions compared with most specialist centers. In reflection of these results, the Enhanced Recovery after Surgery (ERAS) pathway may be implemented to optimize postoperative results.[29] The pathway comprises evidence-based recommendations specific to breast reconstruction surgery and has been proven successful in a previous study.[30] At our center, both microvascular complications and length of stay have decreased since the beginning of this study, mostly due to higher microsurgeon experience and enhanced perioperative care.

A comparison of early health care costs in this study concluded that breast reconstruction with EP is almost three times cheaper than with DIEP flap in the short term. Apart from our study, there is only one report in the literature presenting calculations on early health care costs. In a retrospective study, Damen et al. calculated short- and medium-term costs (intramural and extramural), comparing EP and DIEP flap reconstructions within a public hospital. Intramural costs include the actual hospital care and extramural concerns costs, such as sick leave and transportation. In the short-term, intramural costs for unilateral DIEP flap were greater than with one-stage implant reconstruction, whereas there was no difference compared with unilateral two-stage implant reconstruction. The cost difference decreased over time but did not level out completely during the mean follow-up time of six years.[31]

Cost-effectiveness analysis is a useful method to assess costs, and has been used to assess breast reconstruction methods.[15,32] Matros et al. created a model with BREAST-Q as the effectiveness measure and concluded unilateral DIEP flaps to have higher breast health-related quality-adjusted life years than unilateral implants.[15] Contrary to absolute costs as reported in this present study, cost-effectiveness analysis, though partly based on probability, presents an interpretation of health care costs in relation to its impact on society. Moreover, attempts have been made to conclude both intramural costs and cost-effectiveness in relation to breast reconstruction. Studies from the United States have calculated costs based on a federal health insurance company's fees as a third-party payer, but the information was evidently difficult to interpret from the perspective of a public health care system.[32-34] Although there are limitations and fundamental differences in the literature evaluating costs between the implant and autologous breast reconstruction, there is a tendency toward an agreement that the long-term benefits of breast reconstruction with autologous tissue, preferably DIEP flap, as the cost gap diminishes with time.

The inclusion of patients was a challenge in the setting up of this prospective randomized study. Participation in the

Table 7 Cost specification and comparison between EP and DIEP flap.

Costs in Euro (€)	EP ($n=29$) mean ± SD	DIEP flap ($n=44$) mean ± SD	p-value
Total costs	3839 ± 1327 (1694-6532)	9187 ± 2465 (5956-18 082)	<0.01
Breast tissue expander, EP (1071)	1071 ± 0 (1071-1071)	n/a	
Breast implant[a] (383)	13 ± 71 (0-383)	n/a	
Ward admission (76)	45 ± 38 (0-76)	81 ± 19 (76-152)	<0.01
Admission, doctor assessment (186)	109 ± 93 (0-186)	199 ± 47 (186-372)	<0.01
Inpatient days (436 per day)	721 ± 766 (0-2614)	2732 ± 955 (1743-7406)	<0.01
Inpatient days, doctor assessment (210 per day)	347 ± 368 (0-1257)	1314 ± 459 (838-3562)	<0.01
Outpatient visit, doctor (266 per visit)	238 ± 179 (0-798)	97 ± 173 (0-798)	<0.01
Outpatient visit, nurse/under nurse (48 per visit)	102 ± 74 (0-380)	91 ± 65 (0-238)	0.51
Cost surgeon, day surgery (310 per surgery)	128 ± 155 (0-310)	0	<0.01
Cost surgeon time (5 per min)	200 ± 73 (0-312)	1148 ± 467 (573-3050)	<0.01
Operation assistance (10 per min)	865 ± 442 (0-1629)	3511 ± 1030 (1998-7863)	<0.01

Values in parentheses in the EP and DIEP flap columns represent minimum and maximum values. EP=expander prosthesis; DIEP=deep inferior epigastric perforator; n/a=not applicable. The statistical test used was Student's t-test.
[a] = Breast implant Mentor® Contour Profile Gel™ (CPG) 312 was used in a prosthesis exchange.

present study was the only way for women without RT to be reconstructed with a DIEP flap. Subjects set to DIEP flap but randomized to an EP opted to withdraw from the study.

Strengths of this study include its prospective design and the randomization of patients. A PubMed search indicates that this is the first randomized study in the field. The sample groups turned out to be compatible, and complications were clearly documented. Another strength is that all operations, including EP, were performed by three experienced microsurgeons. In the microsurgical reconstructions, often two of them worked together with an ensuing mean surgery time of 3 h and 45 min. In addition, all patients shared the same perioperative hospital routines, and there was a consistency in the collection of data.

Our analysis did not include extramural data. Because of the short-time frame of the study (30 days), these costs would not have had a crucial impact on the cost difference.

Conclusion

We conclude that breast reconstruction with DIEP flap demands more time and greater resources in a 30-day perspective than EP. The complication rate of DIEP flap is also higher than that of EP. There is a substantial short-term cost-benefit to opt for EP. Breast reconstruction improves the quality of life, and patients undergoing DIEP flap reconstructions are more satisfied with their breasts. Selection of the breast reconstruction method should be entirely based not only on risk and costs, but also on patient satisfaction, individual characteristics, and patient wishes. The present cohort will be studied systematically over time, and results concerning the need for complementary surgery, costs, esthetics, and the PRO will be reported in future works.

Ethics

The study was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 2012/187).

Conflict of interest

None.

Financial disclosure

None.

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Paper II

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ORIGINAL PAPER

Breast softness in patients randomised to postmastectomy breast reconstruction with an expander prosthesis or DIEP flap

Linda Tallroth[1] · Håkan Brorson[1] · Nathalie Mobargha[1] · Patrik Velander[1] · Stina Klasson[1] · Magnus Becker[1]

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Abstract

Background Objectively measured breast softness in reconstructed breasts and its relation to patients' subjective satisfaction with breast softness has not yet been investigated. The aim of this study was to evaluate breast softness in patients 1 year following delayed breast reconstruction with an expander prosthesis (EP) or deep inferior epigastric perforator (DIEP) flap, using objective and subjective methods.

Methods Seventy-three patients were randomised to breast reconstruction with an EP or DIEP flap between 2012 and 2018. Of these, 69 completed objective evaluation at a mean of 25 (standard deviation, SD 9.4) months following breast reconstruction. Objective evaluation included measurements of breast volume, jugulum-nipple distance, clavicular-submammary fold distance, ptosis and Baker scale grading. Breast softness was assessed with applanation tonometry. Subjective evaluation was performed using the BREAST-Q questionnaire.

Results Objectively, DIEP flaps were significantly softer than EP breast reconstructions. Non-operated contralateral breasts were significantly softer compared with reconstructed breasts. In the subjective evaluation, the median score on the question (labelled 1.h) "How satisfied or dissatisfied have you been with the softness of your reconstructed breast (s)?" was higher in the DIEP flap group corresponding to greater satisfaction in this group. A fair correlation was found between the applanation tonometry and the patient-reported satisfaction with the reconstructed breast's softness ($r_s = 0.37$).

Conclusions In terms of breast softness, breast reconstructions with DIEP flaps result in more satisfied patients. Concerning applanation tonometry as an objective tool for softness assessment, future studies on interobserver agreement are warranted. Level of evidence: Level I, therapeutic study

Keywords Breast reconstruction · Expander prosthesis · Deep inferior epigastric perforator (DIEP) flap · Applanation tonometry · Softness · BREAST-Q

Introduction

Following modern breast cancer treatment, patients are offered breast reconstruction to mitigate the negative outcomes of a mastectomy. Breast reconstruction after mastectomy has demonstrated increased patient satisfaction and quality of life (QOL) [1]. The goal is to reconstruct a new breast with a natural appearance. The evaluation of outcomes following breast reconstruction guides future surgical development and provides valuable information to patients in their decision-making process. Consequently, the validated patient-reported outcome measurement BREAST-Q emerged [2]. BREAST-Q was developed through qualitative research as well as a literature review, in order to capture the patient's perspective in relation to breast surgery [3, 4].

One question in the BREAST-Q Postoperative Reconstructive Module concerns the softness of the reconstructed breast. Hence, the degree of breast softness influences patient satisfaction. In previous reports, objective evaluation of softness has been addressed in the context of capsular contracture [5–13]. Capsular contracture is one of the major complications that may follow implant-based breast reconstruction, resulting in a harder breast. Applanation tonometry is a method used for assessment of breast softness and

Stina Klasson and Magnus Becker are joint senior authors.

✉ Linda Tallroth
linda.tallroth@med.lu.se

[1] Plastic and Reconstructive Surgery, Skåne University Hospital, Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden

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capsular contracture and was introduced by Moore [14]. It is performed by placing a tonometer with a certain weight on the breast, generating a force. The imprint area read from the tonometer is used to estimate the intramammary pressure through the formula Pressure = Force/Area [14]. Apart from investigating capsular contracture, applanation tonometry has been used for symmetrical comparison of two autologous breast reconstruction methods [15]. A more popular method that includes a breast softness assessment is the Baker classification scale, developed for diagnosis of capsular contracture. It is a four-grade scale and grades III–IV correspond to a symptomatic hard breast defined as showing capsular contracture [16]. The Baker scale is based on a combination of clinical palpation and breast appearance and is thus dependent on the examiner's experience and subjective assessment [17].

There are various breast reconstruction methods available today, comprising implant and autologous alternatives. To our knowledge, no investigation comparing breast softness following autologous or implant-based reconstruction has yet been performed. In addition, the association between the reconstructed autologous breast and the contralateral healthy breast is unknown. Our hypothesis is that autologous breast reconstruction using the deep inferior epigastric perforator (DIEP) flap results in softer breasts compared to reconstruction using an expander prosthesis (EP), resulting in patients with the DIEP flap reconstruction being more satisfied in terms of breast softness.

The primary aim of this study was to compare breast softness measured with applanation tonometry in patients randomised to unilateral breast reconstruction with an EP or DIEP flap. Comparison of reconstructed breasts with contralateral breasts was a secondary aim. A third aim was to investigate the relationship between tonometry measurements and the BREAST-Q question "How satisfied or dissatisfied have you been with the softness of your reconstructed breast (s)?".

Material and methods

Study design

The patients included in this study are enrolled in a randomised study conducted at our clinic [18]. Briefly, between 2012 and 2018, 73 patients who had undergone modified radical mastectomy were randomised to delayed breast reconstruction with an EP or DIEP flap. Study participation gave non-irradiated breast cancer patients the possibility to be reconstructed with a DIEP flap. At that time, the national guidelines suggested DIEP flaps should be offered only to patients who had previously undergone radiation therapy (RT) to the breast. A description of the randomisation process, including inclusion and exclusion criteria and reasons for participant drop out, was presented in our previous report [18]. Implant breast reconstruction is low-invasive, and since the development of the EP with a detachable port, often only one operation is required. The EP used in this study was a Siltex Mentor® Contour Profile Becker-35, Cohesive I (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08,933, USA). In contrast, breast reconstruction with autologous abdomen-based tissue, as with the DIEP flap, is a more extensive and technical operation. The DIEP flap has gained increased popularity over recent decades and is currently the gold standard in autologous breast reconstruction internationally and at our clinic.

Patients

Patient characteristics and follow-up times are presented in Table 1. The mean age at follow-up was 54 (standard deviation, SD 9.4) years. Of the 73 patients included in the randomised study, 69 completed objective examination at a mean of 25 (SD 9.4) months following breast reconstruction. Four patients were not evaluated. Two patients were waiting for a nipple reconstruction, one for a second opinion and one cancelled several follow-up appointments. Patient data was collected from medical journals and subsequently transferred to a document and coded. Informed and written consent was collected before the initial breast reconstruction procedure.

Contralateral surgery and prosthesis exchange

Patients were offered contralateral breast surgery to achieve symmetrical results. Thirty-one patients had contralateral surgery at a mean of 18 (SD 8.0) months prior follow-up. In the EP group, comprising 28 patients, contralateral surgery was performed on 15 patients, whereof nine were reduction mammaplasties and six were mastopexies. Of the 41 patients in the DIEP group, 15 underwent reduction mammaplasties and one a mastopexy.

Six patients in the EP group had a prosthesis exchange before the objective evaluation. One patient received a Mentor® Siltex Round, Moderate Plus Profile, Cohesive I (Johnson & Johnson Medical Ltd, New Brunswick, NJ, 08,933, USA), three changed to a Mentor® CPG 312, Moderate Plus Projection, Cohesive III (Johnson & Johnson Medical Ltd, New Brunswick, NJ, 08,933, USA), and two to a Mentor® CPG 313, High Projection, Cohesive III (Johnson & Johnson Medical Ltd, New Brunswick, NJ, 08,933, USA). Two exchanges were the result of capsular contracture (6 and 24 months following primary breast reconstruction), one of asymmetry and one was due to discomfort. Removal of the detachable port caused leakage in two EPs, requiring an exchange. Also, one patient had a revisional contralateral

Table 1 Patient characteristics, time between breast surgery procedure and follow-up (mean ± SD, range in parenthesis) and BREAST-Q softness question (median, 1q and 3q) for all patients and by breast reconstruction method

	All patients n = 69	EP n = 28	DIEP flap n = 41	p-value[b]
Age (years)	54 ± 9.4	56 ± 9.0	53 ± 9.5	0.20
BMI (kg/m^2)	26 ± 2.9	25 ± 3.1	26 ± 2.7	0.23
Breast reconstruction to follow-up (months)	25 ± 9.4 (11–56)	25 ± 9.8 (12–56)	25 ± 9.3 (11–50)	0.96
Contralateral surgery to follow-up (months)	18 ± 8.0 (2–36)	15 ± 5.0 (4–25)	21 ± 9.5 (2–36)	0.06
Breast reconstruction to completed BREAST-Q (months)	24 ± 10 (8–56)	26 ± 11 (11–56)	24 ± 9.3 (8–50)	0.44
BREAST-Q question 1.h[a] "How satisfied or dissatisfied have you been with the softness of your reconstructed breast (s)?"	3 (3, 4)	3 (3, 3)	4 (3, 4)	**< 0.01**[c]

[a]The question belongs to the BREAST-Q Reconstruction Postoperative Module Version 1.0 and the response options range from "very dissatisfied" (1) to "very satisfied (4)"

[b]Student's t-test

[c]Chi^2-test

Abbreviations: *SD*, standard deviation; *1q*, lower quartile; *3q*, upper quartile; *BMI*, body mass index; *EP*, expander prosthesis; *DIEP*, deep inferior epigastric perforator

P-values < 0.05 were considered significant and are in bold

surgery due to volume asymmetry resulting in augmentation with a Mentor® Siltex Round, Moderate Profile, Cohesive I (Johnson & Johnson Medical Ltd, New Brunswick, NJ, 08,933, USA).

Objective examinations

All measurements were performed at the plastic surgery outpatient clinic. Two registered nurses, experienced in breast reconstruction, conducted the examinations according to a study-specific protocol (Appendix). First, measurements were taken with the patient in a sitting position. Breast volumes were determined using plastic breast cups designed by a former plastic surgeon at our clinic (Emballageform AB, Limhamn, Sweden) [19]. Jugulum-nipple distance, clavicular-submammary fold distance and ptosis were assessed with a tape measure. Jugulum-nipple distance measurements were not made in 10 patients who had not chosen to undergo nipple reconstruction. Also, grading according to the Baker classification scale was performed [16].

Applanation tonometry was assessed with the patient in the supine position. A round, plexiglass disc engraved with a circular scale in millimetres was used [7, 15]. The disc had a weight of 280 g. After moistening the disc with 70% ethanol, it was placed on the highest part of the breast. From the breast contact area, two perpendicular diameters were identified with the engraved scale and labelled A and B. In accordance with previous studies, the imprint area was calculated according to the formula Area = πAB/4 as the shape of the breast imprint corresponds to that of an ellipse [15]. However, the tonometer area is dependent on the breast volume. To prevent differences in breast volume affecting the comparisons, fractional areas were calculated by dividing the breast area of interest by the sum of the reconstructed and the contralateral breast areas, similar to previous studies [8, 9]. The higher the fractional area, the softer the breast.

BREAST-Q

The BREAST-Q Postoperative Reconstruction Module Version 1.0 was given to all patients in connection with the objective evaluation. The module is comprised of QOL domains (Psychosocial Well-being, Sexual Well-being and Physical Well-being) and Satisfaction domains (Satisfaction with Breasts, Satisfaction with nipples, Satisfaction with abdomen, Satisfaction with Outcome and Satisfaction with Care) [2]. Satisfaction with Breasts includes 18 questions which are answered using a 4-point Likert scale: very dissatisfied (1), somewhat dissatisfied (2), somewhat satisfied (3) and very satisfied (4). One patient in the DIEP flap group did not answer the question "How satisfied or dissatisfied have you been with the softness of your reconstructed breast (s)?" Another patient reconstructed with a DIEP flap did not return the questionnaire. The breast reconstruction was performed at a mean of 24 (SD 10) months prior to completing the BREAST-Q, presented in Table 1.

Statistical analysis

Parametric and non-parametric tests were used for statistical analysis. Data was presented as mean and SD or median and quartiles when appropriate. Group comparisons were

conducted with the Student's t-test or Mann–Whitney U-test for unpaired samples and the paired t-test or Wilcoxon signed-rank test for paired samples. A chi^2-test was used for ordinal data. Spearman's rank correlation was used for measuring the association between two variables. A p-value below 0.05 indicated a significant difference. Statistical Package for Social Sciences version 26 (IBM Corp. Armonk, NY: IBM Corp. Released 2019) was used for statistical analysis.

Results

Objective examinations

Age and body mass index did not differ between the EP and the DIEP flap groups. The number of months between breast reconstruction and follow-up, contralateral surgery and follow-up, and breast reconstruction and BREAST-Q completion were comparable between the two groups (Table 1).

Breast volume, jugulum-nipple distance, clavicle-submammary fold distance and ptosis were measured on the reconstructed and the contralateral breasts, and ratios were calculated (Table 2). A ratio of 1 equalled symmetry. Breast volumes were somewhat larger in the DIEP flap group. Mean volume ratios were 0.94 and 1.01 in the EP and DIEP flap groups respectively; however, there was no significant difference between the ratios. Jugulum-nipple distance and ptosis ratios, but not clavicular-submammary fold distance, differed significantly between the reconstructed groups, with mean ratios closer to 1 in the DIEP flap group.

All breasts were evaluated according to the Baker scale. No breasts were graded as III or IV.

Breast softness comparisons of EP and DIEP flaps assessed with applanation tonometry are presented in Table 3. The fractional areas were significantly larger in the DIEP flap reconstructed breasts. In both the EP and DIEP flap groups, the tonometric and the fractional areas were significantly larger in the contralateral breasts compared with the reconstructed ones (Table 4). Divided into groups by type of contralateral surgery, contralateral breast reductions but not mastopexies remained significantly larger for all patients ($p_{reduction} < 0.01$ and $p_{mastopexy} = 0.06$). There were no significant differences between contralateral breast reductions nor mastopexies when compared with the paired EP or the paired DIEP flap reconstructed breasts (Table 5). Tonometric data on the reconstructed breasts were missing from two patients in the EP group.

BREAST-Q softness

The median response to the BREAST-Q question "How satisfied or dissatisfied have you been with the softness of

Table 2 Objective measurements of the reconstructed breasts and the contralateral breasts for all patients and by breast reconstruction method

Mean ± *SD*	All patients n = 69			EP n = 28			DIEP flap n = 41			p-value[b]
	RB	CB	Ratio (RB/CB)	RB	CB	Ratio (RB/CB)	RB	CB	Ratio (RB/CB)	
Breast volume (ml)	471 ± 181	486 ± 187	0.98 ± 0.17	408 ± 139	441 ± 164	0.94 ± 0.11	514 ± 195	517 ± 196	1.01 ± 0.19	0.09
Jugulum-nipple[a] (cm)	23.4 ± 2.21	24.3 ± 2.51	0.97 ± 0.06	22.0 ± 1.55	23.5 ± 2.56	0.94 ± 0.07	24.5 ± 2.05	24.9 ± 2.34	0.99 ± 0.04	**< 0.01**
Clavicular-submammary fold (cm)	31.2 ± 3.36	33.6 ± 4.28	0.93 ± 0.09	29.4 ± 2.78	32.4 ± 3.87	0.91 ± 0.07	32.4 ± 3.18	34.5 ± 4.39	0.95 ± 0.09	0.08
Ptosis (cm)	1.0 ± 1.1	2.3 ± 1.6	0.6 ± 0.6	0.1 ± 0.3	2.1 ± 1.5	0.1 ± 0.3	1.6 ± 1.1	2.5 ± 1.7	0.8 ± 0.7	**< 0.01**

[a]Jugulum-nipple distance measurements were not obtained from the 10 patients without nipple reconstructions

[b]Student's t-test was used for comparison of ratios between EP and DIEP flap groups

Abbreviations: *SD*, standard deviation; *EP*, expander prosthesis; *DIEP*, deep inferior epigastric perforator; *RB*, reconstructed breast; *CB*, contralateral breast

P-values < 0.05 were considered significant and are in bold

Table 3 Comparisons of breast softness assessed with applanation tonometry between the EP and DIEP flap groups

	EP n = 28[a]	DIEP flap n = 41	p-value[c]
Fractional area[b] *Mean ± SD*			
Reconstructed breasts	0.36 ± 0.12	0.47 ± 0.06	**< 0.01**
All contralateral breasts	0.64 ± 0.12	0.53 ± 0.06	**< 0.01**

[a]Tonometric data from the reconstructed breast were missing from two patients in the EP group

[b]Fractional area = breast area of interest divided by the sum of the reconstructed and contralateral breast areas

[c]Student's t-test

Abbreviations: *SD*, standard deviation; *EP*, expander prosthesis; *DIEP*, deep inferior epigastric perforator; *RB*, reconstructed breast; *CB*, contralateral breast

P-values < 0.05 were considered significant and are in bold

your reconstructed breast (s)?" was 3 (lower quartile, upper quartile; 3, 3) in the EP group, corresponding to "somewhat satisfied", and 4 (lower quartile, upper quartile; 3, 4) in the DIEP flap group, corresponding to "very satisfied". The DIEP flap group was significantly more satisfied with the softness of their reconstructed breasts in the group comparison ($p < 0.01$) (Table 1). A fair positive correlation was found between the areas analysed with tonometry in the reconstructed breasts and the BREAST-Q question responses ($r_s = 0.37$, $p < 0.01$) [20].

Discussion

To our knowledge, this is the first report investigating breast softness following breast reconstruction with an EP or DIEP flaps. In this study, the DIEP flap group had significantly softer breast reconstructions and higher patient-reported satisfaction with breast softness compared with the EP group. A fair correlation was found between the objective measurements and the patient satisfaction regarding breast softness. Objectively, the non-operated contralateral breasts were significantly softer compared with the breast reconstructions.

Factors determining the final surgical results require further investigation, and therefore softness was chosen to be the focus of this study. As expected, we found DIEP flaps to be softer than an EP. The EP is placed in a submuscular pocket closed with sutures and filled with saline to adopt a projection. The enclosed cavity, together with a high degree of filling, results in a harder breast. In contrast, the DIEP flap consists of abdominal fat and is attached to the chest mainly through intracutaneous sutures enabling a softer composition. As the DIEP flap is softer and more similar to a natural contralateral breast, we were not surprised to find patients were more satisfied in this group. Previous studies have concluded that patients with autologous reconstructed breasts are more satisfied with their breasts than patients with implant-based reconstructions [21, 22]. Liu et al. reported a significantly higher score for "Satisfaction with Breasts" when comparing patients with abdomen-based autologous breast reconstructions and implant-based [22]. Since breast softness is included in the "Satisfaction with Breasts" domain, we believe our finding is in accordance with the aforementioned report. Thus, the degree of correlation between the objective measure and the patient-reported satisfaction regarding softness was interpreted only as fair in this study. Similar weak correlations have been reported in previous reports, thereby illustrating the complexity of measuring patient-reported outcomes [23, 24]. Patient satisfaction is most likely influenced by many different factors, for example the current psychosocial situation, in addition to the objective outcome.

A harder breast in terms of a breast reconstruction or augmentation is most likely a cause of capsular contracture formation, a common complication in breasts with implants [25]. The implant surface and anatomical placement affect the likelihood of capsular contracture. In a study by Handel et al., polyurethane foam-coated implants had a decreased risk for capsular contracture compared with textured and smooth surfaced implants. However, the reports comparing

Table 4 Comparisons of breast softness between the reconstructed and contralateral breasts for all patients and by breast reconstruction method

	All patients n = 69[a]		p-value[c]	EP n = 28[a]		p-value[c]	DIEP flap n = 41		p-value[c]
Mean ± SD	RB	CB		RB	CB		RB	CB	
Tonometric areas (cm^2)	50.3 ± 20.2	64.5 ± 19.5	**< 0.01**	32.5 ± 11.4	59.6 ± 24.3	**< 0.01**	61.6 ± 16.0	67.8 ± 14.8	**< 0.01**
Fractional areas[b]	0.43 ± 0.11	0.57 ± 0.11	**< 0.01**	0.36 ± 0.12	0.64 ± 0.12	**< 0.01**	0.47 ± 0.06	0.53 ± 0.06	**< 0.01**

[a]Tonometric data from the reconstructed breast were missing from two patients in the EP group

[b]Fractional area = breast area of interest divided by the sum of the reconstructed and contralateral breast areas

[c]Paired t-test for pairwise comparisons between the reconstructed (RB) and the contralateral breast (CB)

Abbreviations: *SD*, standard deviation; *EP*, expander prosthesis; *DIEP*, deep inferior epigastric perforator; *RB*, reconstructed breast; *CB*, contralateral breast

P-values < 0.05 were considered significant and are in bold

Table 5 Comparisons of breast softness in reconstructed and contralateral breasts divided into groups by prevalence and type of contralateral surgery and by breast reconstruction method

Fractional area[b], *Median (1q, 3q)*	All patients[a]	p-value[c]	EP[a]	p-value[c]	DIEP flap	p-value[c]
Non-operated contralateral, n	38/38		13/38		25/38	
RB	0.45 (0.34, 0.49)	**<0.01**	0.32 (0.27, 0.37)	**<0.01**	0.48 (0.44, 0.51)	0.05
CB	0.55 (0.51, 0.66)		0.68 (0.63, 0.73)		0.53 (0.49, 0.56)	
Operated contralateral, n	31/31		15/31		16/31	
RB	0.43 (0.33, 0.49)	**<0.01**	0.33 (0.30, 0.47)	**0.01**	0.46 (0.42, 0.50)	0.05
CB	0.57 (0.51, 0.67)		0.67 (0.53, 0.70)		0.54 (0.50, 0.58)	
Reduction, n	24/24		9/24		15/24	
RB	0.44 (0.34, 0.50)	**<0.01**	0.34 (0.30, 0.44)	0.09	0.46 (0.41, 0.50)	0.07
CB	0.56 (0.50, 0.67)		0.66 (0.56, 0.70)		0.54 (0.50, 0.59)	
Mastopexy, n	7/7		6/7		1/7	
RB	0.33 (0.30, 0.49)	0.06	0.33 (0.28, 0.50)	0.07	0.47	
CB	0.67 (0.51, 0.70)		0.67 (0.50, 0.72)		0.53	

[a]Values missing from two patients reconstructed with an EP

[b]Fractional area = breast area of interest divided by the sum of the reconstructed and contralateral breast areas

[c]Wilcoxon signed-rank test

Abbreviations: *1q*, lower quartile; *3q*, upper quartile; *EP*, expander prosthesis; *DIEP*, deep inferior epigastric perforator; *RB*, reconstructed breast; *CB*, contralateral breast

P-values < 0.05 were considered significant and are in bold

capsular contracture following textured and smooth implant insertions are conflicting [6, 9, 25, 26]. Placement of the implant in the submuscular position was found to decrease the risk of capsular contracture in another report [27]. Moreover, RT as well as breast reconstruction, when compared with augmentation, increased the risk for capsular contracture [13, 25, 28]. In this study, the EP used had a textured surface, all implants were placed in the submuscular position and no patients underwent RT. Nonetheless, two of the six prosthesis exchanges were due to capsular contracture, and no breasts were assessed as Baker grades III or IV at the objective examinations.

Based on the findings from the objective evaluations, a DIEP flap, overall, was more symmetrical with its contralateral breast compared with an EP. Symmetry in breasts reconstructed with pedicled or free TRAM flaps has been evaluated by Edsander-Nord et al. using objective methods [15]. They report a higher level of symmetry in free TRAM flap reconstructed breasts, most pronounced for breast volume and softness [15]. Similar to this study, the free autologous method provided the most symmetrical results. In our analysis however, breast volume was the only measurement that did not differ between the EP and DIEP flap groups, probably as a result of symmetrising contralateral surgery. Although it is possible to improve volume symmetry with surgery, other aspects such as ptosis are more difficult to correct. In the past, symmetry after breast surgery has been objectively evaluated with various modalities. Volumetric symmetry after breast reconstruction has been studied using magnetic resonance imaging and three-dimensional imaging [24, 29]. Software programmes like breast cancer conservation treatment cosmetic results (BCCT.core) and the breast analysing tool (BAT®) have been developed and improved for breast symmetry assessment [30–32]. The BCCT.core and BAT® calculate asymmetry parameters in digital photographs, and in addition the BCCT.core assesses skin colour and scar visibility [30, 31]. Yet none of these software programmes has been validated for breast reconstruction.

Natural breasts are composed of fat, and glandular and ductal tissue whereas a DIEP flap consists of abdominal fat. Hence, one could expect a natural breast to be firmer. However, our findings indicate the opposite, except in the group with operated contralateral breasts, in which no difference was found. With a mean age of 54 (SD 9.4) years at follow-up, a plausible explanation might be the changes in the breast composition that occur in older women. During menopause, the breast undergoes involution of ductal and glandular tissues. With age the amount of breast fat decreases and supporting Cooper ligaments relax, resulting in a looser and softer breast composition [33].

A strength of this study is its randomised and prospective design and the high participation rate as only four patients did not complete objective evaluations. To mitigate measurement variability, the evaluations were performed by one of two nurses experienced in breast reconstruction. The use of

the validated BREAST-Q questionnaire is also a strength, although we chose to use only one question.

A limitation is that no interobserver agreement was tested for the objective examinations. A recently published study reported low interobserver agreement for grading capsular contracture according to the Baker scale, emphasising the importance of this matter [17]. In order to strengthen the role of applanation tonometry as an objective breast softness measurement tool, an assessment of the interobserver agreement is warranted. Additionally, the broad time interval between breast reconstruction and follow-up could have had an impact on our findings as a breast reconstruction changes over time.

Conclusions

In regard to breast softness, this study reports DIEP flaps to be objectively softer than an EP and to give higher patient-reported satisfaction. The fair correlation found between the two measures suggests that there are factors other than those objectively measured that influence patient-reported satisfaction. However, further investigation is warranted for evaluation of the interobserver agreement regarding applanation tonometry.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00238-021-01835-z.

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Declarations

Ethical approval The procedures were in accordance with the Declaration of Helsinski of 1964 and its most recent revision in 2013. The study was approved by the Regional Ethical Review Board in Lund, Sweden (ref no. 2012/187).

Patient consent All participants were asked to participate in the study and gave their written informed consent if they wanted to participate.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest Linda Tallroth, Håkan Brorson, Nathalie Mobargha, Patrik Velander, Stina Klasson and Magnus Becker declare no conflict of interest.

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Paper III

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ARTICLE

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Assessment of local tissue water in breasts following breast reconstruction with an expander prosthesis or DIEP flap

Linda Tallroth[a,b], Håkan Brorson[a,b], Nathalie Mobargha[a,b], Patrik Velander[a,b], Stina Klasson[a,b] and Magnus Becker[a,b]

[a]Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden; [b]Plastic and Reconstructive Surgery, Skåne University Hospital, Malmö, Sweden

ABSTRACT

The role of breast oedema in breast reconstruction is unknown. Therefore, our aim was to investigate local tissue water (LTW) and breast oedema-related symptoms in breasts reconstructed with either an expander prosthesis (EP) or with a deep inferior epigastric perforator (DIEP) flap at a minimum of one year postoperatively. Sixty-eight patients randomised to breast reconstruction with an EP or DIEP flap completed follow-up. Objective evaluation was performed at a mean of 25 (standard deviation, SD 9.5) months following breast reconstruction, and included measurements of breast volume and LTW with the MoistureMeterD® instrument. The patients completed the BREAST-Q questionnaire pre- and postoperatively. No significant differences in LTW were found when comparing EP and DIEP flap reconstructed breasts. The reconstructed breasts had an increase in LTW compared with the non-operated contralateral breasts. The BREAST-Q responses related to breast oedema symptoms were overall low and the median responses ranged from 1 to 2. A score of 1 indicated that symptoms were experienced 'None of the time'. Our findings indicate that mastectomy followed by breast reconstruction inflicts damage on the lymphatic system, shown as an increase in LTW. However, no breast oedema-related symptoms were reported in the BREAST-Q questionnaire, and therefore, we consider our objective results to be below a potential threshold for symptomatic breast oedema. A threshold for clinical indication of breast oedema remains to be defined.

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Breast reconstruction; expander prosthesis; deep inferior epigastric perforator (DIEP) flap; MoistureMeterD®; BREAST-Q

Background

Breast surgery procedures give rise to temporary or persistent oedema in the skin and underlying tissue. Damage to the lymphatic vascular system during breast cancer surgery may lead to arm lymphoedema, a well-documented condition associated with impaired wound healing, risk of infection and a negative impact on patient-reported quality of life (QOL) [1–4]. Similarly, breast oedema following breast surgery causes local discomfort and pain and an overall worsened QOL [5,6]. In comparison, however, breast oedema has received little focus in literature [7].

Previous studies have mainly focused on breast oedema as a result of breast-conservation surgery (BCS) and treatment [3,5,6,8,9]. Risk factors for the development of breast oedema were found to encompass axillary lymph node dissection, sentinel lymph node biopsy and high body mass index (BMI) [6,9]. Radiation therapy (RT) also increased the risk [3,6,10].

Several methods have been used to investigate breast oedema. Subjective evaluation with clinical examination and self-reported questionnaires, as well as a number of objective approaches have been studied in the past [3,5,6,8,11,12]. The objective methods used were high-frequency ultrasound, bioelectrical impedance analysis, and tissue dielectric constant (TDC) measurements [3,8,12]. The MoistureMeterD® (MoistureMeterD®, Delfin Technologies Ltd, Kuopio, Finland) is a device measuring TDC and has been validated for assessment of oedema in biological tissues and is suitable for early detection of lymphoedema [13–15]. However, no standardised methods for measurement or a definition of breast oedema have yet been agreed [7,16].

Breast reconstruction is an established procedure facilitating higher QOL for breast cancer survivors [17]. Nonetheless, a breast reconstruction involves tissues already traumatised by previous cancer surgery. Hypothetically, a breast reconstruction would inflict additional damage to the breast's lymphatic circulation, resulting in postoperative oedema. Breast oedema in breast reconstruction has previously been assessed by Greenhowe *et al.* using the MoistureMeterD® Compact [12]. The authors reported increased tissue water content in autologous immediate reconstructed breasts up to three months postoperatively [12]. Based on our literature search, this is the only report published on breast oedema from the perspective of breast reconstructions. Consequently, breast oedema in relation to breast reconstruction methods and prevalence over time is unknown.

The aim of this randomised study was therefore to objectively investigate local tissue water (LTW) in breasts reconstructed with either an expander prosthesis (EP) or a deep inferior epigastric perforator (DIEP) flap, and compare with the contralateral breasts.

CONTACT Linda Tallroth linda.tallroth@med.lu.se Lund University, Lund, Sweden

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Another aim was to compare the results with specific BREAST-Q questions corresponding to breast oedema-related symptoms.

Material and methods

Study design

Between 2012 and 2018, 135 patients with unilateral mastectomy and no previous RT were refereed to our clinic for delayed breast reconstruction. All eligible patients were asked to participate in the study and randomised to breast reconstruction with either an EP or DIEP flap. At that time, participating in the study was the only way for these patients to be reconstructed with a DIEP flap. According to the national guidelines, DIEP flap breast reconstruction was offered only to patients with previous RT to the breast. After exclusion, 73 patients remained. Of these, 29 were reconstructed with an EP and 44 with a DIEP flap. The study details are described in our previously published study [18]. Written informed consent was collected from all patients prior to breast reconstruction surgery. Patient data and dates for follow-up were collected from study protocols and medical journals. The collected data were transferred to a document and coded before analysis to ensure confidentiality.

Patients included in the study were reconstructed with either an EP or a DIEP flap. An EP is a silicon implant with an inner fillable lumen connected to a subcutaneously placed detachable port. The EP is filled with saline *via* the port lumen. The EP used in this study was a Siltex Mentor® Contour Profile Becker-35, Cohesive II (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08933, USA) and in all cases it was placed in the submuscular position. A DIEP flap surgery is a more extensive breast reconstruction method and includes transferring of autologous tissue from the abdomen to the chest as well as use of a microsurgical technique.

Patients and contralateral surgery

This study was approved by the Regional Ethical Review Board in Lund (ref no. 2012/187). Written informed consent was collected from all participating patients. The procedures were in accordance with the Declaration of Helsinki of 1964 and its most recent revision in 2013.

Sixty-eight of 73 patients completed follow-up at the outpatient clinic, 27 patients were reconstructed with EP and 41 with DIEP flaps. Of the five remaining patients, two were waiting for a nipple reconstruction. One patient was waiting for a second opinion, one patient cancelled her appointment several times, and TDC assessment was not completed in one patient. The mean age at breast reconstruction was 54 (standard deviation, SD 9.4) years. A mean of 25 (SD 9.5) months passed between the breast reconstruction and the follow-up (Table 1).

Of the 68 participating patients, 31 underwent symmetrising contralateral surgery. Twenty-four were reduction mammaplasties and seven were mastopexies. In the EP group, 15 patients had contralateral breast surgery, of which nine were reductions and six mastopexies. Of the 41 patients reconstructed with DIEP flaps, 16 had contralateral breast surgery and all but one was reductions. Contralateral surgery was performed at a mean of 18 (SD 8.1) months prior to follow-up. One patient had a contralateral breast reduction mammaplasty prior to the breast reconstruction. One patient had a breast augmentation two years after a mastopexy in the contralateral breast. The implant used was a Mentor® Siltex Round, Moderate Profile, Cohesive I (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08933, USA).

Table 1. Patient characteristics, treatment factors and times to follow-up listed for all patients ($n = 68$) and by breast reconstruction method (EP $n = 27$ and DIEP flap $n = 41$).

	All patients	EP	DIEP flap	*p* Value[a]
Mean ± SD (range)				
Age (years)	54 ± 9.4	56 ± 9.0	53 ± 9.5	0.26
BMI (kg/m^2)	26 ± 3.8	25 ± 2.9	26 ± 2.7	0.37
Volume breast (ml)				
RB	474 ± 180	414 ± 139	514 ± 195	**0.02**
CB	489 ± 186	448 ± 163	517 ± 196	0.14
Arm lymphoedema	7 (10.3%)	1 (3.7%)	6 (14.6%)	0.23[c]
Treatment factors				
Chemotherapy	39 (57.4%)	13 (48.1%)	26 (63.4%)	0.21[b]
Endocrine therapy	47 (69.1%)	19 (70.4%)	28 (68.3%)	0.86[b]
Immune therapy	11(16.2%)	4 (14.8%)	7 (17.1%)	0.81[b]
Axillary operation				
ALND	16 (23.5%)	3 (11.1%)	13 (31.7%)	0.06[a]
SLNB	51 (75%)	23 (85.2%)	28 (68.3%)	
No	1 (1.5%)	1 (3.7%)	0	
Time to follow-up (months)				
Breast reconstruction to follow-up	25 ± 9.5 (11–56)	25 ± 10 (12–56)	25 ± 9.3 (11–50)	0.95
Contralateral surgery to follow-up	18 ± 8.1 (2–36)	15 ± 5.0 (4–25)	21 ± 9.5 (2–36)	0.06
Breast reconstruction to completed BREAST-Q	25 ± 10 (8–55)	26 ± 11 (11–55)	24 ± 9.3 (8–50)	0.42

[a]Student's *t*-test.
[b]Chi^2-test.
[c]Fisher's exact test.
SD: Standard deviation; BMI: Body mass index; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator; RB: Reconstructed breast; CB: Contralateral breast; ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy.
p Values < 0.05 were considered significant and is in bold.

Between breast reconstruction surgery and follow-up, six patients reconstructed with an EP had a prosthesis exchange. Of the new breast prostheses inserted, one was a Mentor® Siltex Round, Moderate Plus Profile, Cohesive I (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08933, USA), three were Mentor® CPG 312, Moderate Plus Profile, Cohesive III (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08933, USA) and two were Mentor® CPG 313, High Projection, Cohesive III (Johnson & Johnson Medical Ltd, New Brunswick, New Jersey 08933, USA).

Objective examinations

All examinations were performed at the plastic surgery outpatient clinic. Before examination, nipple reconstruction and tattoo on the reconstructed breast had to be completed. One of two registered nurses performed the measurements according to a study-specific protocol (Supplementary Appendix). Breast volumes were assessed with plastic breast cups, with the patient in the sitting position [19]. TDC measurements were taken with the patient in the supine position. The breasts were divided into quadrants (medial upper, medial lower, lateral lower, lateral upper). In each quadrant, a point of measurement was marked at a distance of 3–5 cm from the areola border. If there was no areola, an estimation was made. Each point was measured three times using the MoistureMeterD® device and then averaged as recommended by a previous study [14]. The M25 probe was selected, providing a measurement depth of 5 mm.

TDC methodology

The MoistureMeterD® is a non-invasive and water-specific instrument. Placed on the skin surface, the coaxial probe transmits an

ultra-high-frequency electromagnetic wave of 300 MHz to the subcutaneous fat. Data received from the electromagnetic energy reflected back, generates the TDC, which is directly proportional to the tissue water content [13].

Four probes are accessible to the instrument, each measuring different depths of the tissue. With an increasing depth, the TDC values will be lower as a result of less water content in the deeper more fat-rich tissues [20].

BREAST-Q

Prior to the breast reconstruction and at the follow-up, all patients were instructed to complete the BREAST-Q Reconstruction Preoperative and Postoperative Module Version 1.0. The BREAST-Q questionnaire, designed to investigate patient satisfaction and QOL, consists of QOL domains (Psychosocial Well-being, Sexual Well-being and Physical Well-being) and Satisfaction domains (Satisfaction with Breasts, Satisfaction with Nipples, Satisfaction with Abdomen, Satisfaction with Outcome and Satisfaction with Care) [21]. In the Physical Well-being domain, there are seven questions that correspond to self-reported symptoms experienced by patients with breast oedema [5,6]. These questions are the same in the preoperative (labelled 3.i, 3.j, 3.k, 3.l, 3.m, 3.o and 3.p) and postoperative questionnaire (labelled 6.i, 6.j, 6.k, 6.l, 6.m, 6.o and 6.p) and were selected for analysis. The response options were 'None of the time' (1), 'A little of the time' (2), 'Some of the time' (3), 'Most of the time from' (4) and 'All of the time' (5). The mean time between breast reconstruction and completed BREAST-Q was 25 (SD 10) months (Table 1). Two patients in the DIEP flap group did not complete the preoperative questionnaire. In the DIEP flap group, one patient did not return the postoperative questionnaire and eight did not respond to the questions evaluated in this study. In the EP group, two patients did not respond to these questions.

Statistical analysis

Data was presented as mean and SD for parametric data and as median and quartiles (1q, 3q) for non-parametric data. Non-paired data were calculated with the Student's t-test or Mann–Whitney U-test, and for paired data the Paired t-test or Wilcoxon signed-ranks test were used. Ordinal data was tested with the Chi^2-test or Fisher's exact test. *P*-values below 0.05 were considered to indicate a significant difference. Statistical Package for Social Sciences version 26 (IBM Corp. Armonk, NY: IBM Corp. Released 2019) was used for statistical analysis.

Results

Patient characteristics and follow-up

A description of the patients and time between breast surgery and follow-up are given in Table 1. Age, BMI, treatment factors and follow-up times were comparable between the EP and DIEP flap groups. The reconstructed breasts were significantly larger in the DIEP flap group compared with the EP group.

TDC in breast reconstructions

Table 2 presents TDC measurements in breasts reconstructed with EP and DIEP flaps. No differences were found between the groups in any quadrant when tested for absolute values and ratios ($p_{absolute}$=0.78, p_{ratio}=0.26). Separated into groups by contralateral surgery, no significant differences in ratios between EP and DIEP flap breasts were observed ($p = 0.19$, 0.87, respectively). No significant differences were found between the TDC ratios or the absolute TDC values of the reconstructed breast when separating the patients into groups by chemotherapy, endocrine and immune therapy, type of axillary operation and presence of arm lymphoedema.

TDC in patients with non-operated contralateral breast

Comparisons of absolute TDC values in the group of patients with non-operated contralateral breasts are displayed in Table 3. Reconstructed breasts had significantly higher TDC values in all quadrants compared with the contralateral breasts ($p < 0.01$). On further separation of the patients using the reconstruction method, the EP group had significantly higher TDC values in all quadrants but the lateral upper quadrant. Similarly, DIEP flaps had significantly higher TDC values in all quadrants but the medial upper quadrant.

TDC in patients with operated contralateral breast

Absolute TDC values, presented as quadrant means in Tables 4 and 5, were significantly higher in all reconstructed breasts, apart from the medial upper quadrant compared with all operated contralateral breasts ($p < 0.01$). Divided into groups by type of contralateral surgery, the differences in TDC values were more pronounced in relation to contralateral breast reductions. The mean TDC values were comparable between the EP reconstructed breasts and the corresponding operated contralateral breasts. However, when comparing DIEP flap with the corresponding

Table 2. Comparisons of absolute TDC values and ratios in breasts reconstructed with EP or DIEP flaps, among all patients and in groups by prevalence of contralateral surgery.

	Absolute values			*Ratios (reconstructed/contralateral breast)*		
	EP	DIEP flap	*p* Value[a]	EP	DIEP flap	*p* Value[a]
TDC Median (1q, 3q)						
All reconstructed breasts $n = 68$	27	41		27	41	
Mean value quadrants	29.3 (25.5, 31.3)	28.6 (26.0, 31.4)	0.78	1.13 (1.06, 1.19)	1.09 (1.03, 1.15)	0.26
Patients with non-operated contralateral breasts $n = 37$	12	25		12	25	
Mean value quadrants	29.5 (27.4, 32.9)	28.7 (27.4, 30.7)	0.43	1.16 (1.04, 1.27)	1.07 (1.07, 1.16)	0.19
Patients with contralateral surgery $n = 31$ (reduction/mastopexy)	15 (9/6[b])	16 (15/1)		15 (9/6[b])	16 (15/1)	
Mean value quadrants	27.4 (23.7, 31.2)	27.8 (25.6, 43.2)	0.24	1.09 (1.09, 1.17)	1.11 (1.11, 1.14)	0.87

[a]Mann–Whitney U-test.
[b]One patient had a breast augmentation two years after mastopexy in the contralateral breast.
TDC: Tissue dialectic constant; 1q: Lower quartile; 3q: Upper quartile; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator.

Table 3. Comparisons of absolute TDC values in reconstructed breasts and non-operated contralateral breasts.

	Reconstructed breast	Non-operated contralateral breast	*p* Value[a]
TDC Median (1q, 3q)			
EP and DIEP flap, *n*			37
Mean value quadrants	28.9 (27.5, 30.8)	26.5 (25.1, 28.4)	**<0.01**
EP, n			12
Mean value quadrants	29.5 (27.4, 32.9)	26.4 (25.1, 28.9)	**<0.01**
DIEP flap, n			25
Mean value quadrants	28.7 (27.4, 30.7)	26.5 (25.1, 28.2)	**<0.01**

[a]Wilcoxon signed-rank test.
TDC: Tissue dialectic constant; 1q: Lower quartile; 3q: Upper quartile; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator.
p-values < 0.05 were considered significant and are in bold.

Table 4. Comparisons of absolute TDC values in reconstructed breasts and operated contralateral breasts.

	Reconstructed breast	Operated contralateral breast	*p* Value[a]
TDC Median (1q, 3q)			
EP and DIEP flap, n			31
Mean value quadrants	27.4 (24.8, 31.9)	25.9 (23.4, 29.3)	**<0.01**
EP, n			15[b]
Mean value quadrants	27.4 (23.7, 31.2)	25.6 (23.4, 27.7)	0.06
DIEP flap, n			16
Mean value quadrants	27.8 (25.6, 34.2)	26.7 (22.9, 29.6)	**<0.01**

[a]Wilcoxon signed-rank test.
[b]One patient had a breast augmentation two years after mastopexy in the contralateral breast.
Abbreviations: TDC: Tissue dialectic constant; 1q: Lower quartile; 3q: Upper quartile; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator.
p-values <0.05 were considered significant and are in bold.

Table 5. Comparisons of absolute TDC values in reconstructed breasts and contralateral breasts after reduction mammaplasty or mastopexy.

	Reconstructed breast	Reduction mammaplasty	*p* Value[a]	Reconstructed breast	Mastopexy	*p* Value[a]
TDC Median (1q, 3q)						
EP and DIEP flap, n			24			7
Mean value quadrants	27.8 (25.6, 33.0)	26.1 (23.4, 29.2)	**<0.01**	24.8 (20.4, 31.5)	25.5 (18.3, 30.0)	0.24
EP, n			9			6[b]
Mean value quadrants	27.4 (24.6, 30.6)	25.9 (23.7, 27.1)	0.14	27.3 (20.0, 32.3)	25.6 (19.9, 30.8)	0.25
DIEP flap, n			15			1
Mean value quadrants	28.2 (25.7, 34.3)	27.5 (22.7, 29.6)	**<0.01**	24.8 (24.8, 24.8)	24.8 (24.8, 24.8)	

[a]Wilcoxon signed-rank test.
[b]One patient had a breast augmentation two years after mastopexy in the contralateral breast.
Abbreviations: TDC: Tissue dialectic constant; 1q: Lower quartile; 3q: Upper quartile; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator.
p-values <0.05 were considered significant and are bolded.

operated contralateral breasts, significantly higher TDC values were seen in all quadrants but the medial lower.

BREAST-Q

The BREAST-Q questions analysed are presented in Table 6. The question 3/6.k '*Nagging feeling in your breast area*' received a significantly higher score postoperatively in the DIEP flap group. The remaining questions were comparable. The median pre- and postoperative responses ranged from 1 to 2 in both groups.

Discussion

To our knowledge, this is the first report investigating LTW in delayed breast reconstruction. No significant differences were observed comparing the two breast reconstruction methods regarding LTW or breast oedema-related symptoms assessed with the BREAST-Q questionnaire. However, reconstructed breasts had a higher amount of LTW compared with breasts that had not been exposed to previous surgery. Our findings indicate that reconstructed breasts have a remaining increase in LTW at a mean of two years postoperatively compared with non-operated breasts.

Breast oedema is a condition related to breast cancer treatment and has received little focus in the past, especially in terms of breast reconstruction. One could presume DIEP flap reconstructed breasts to have an increase in LTW during the initial postoperative period. Tissue injury initiates an acute inflammatory response, subsequently leading to the transfer of intravascular fluids to the interstitial space [22,23]. The inflammatory response will be higher the more extensive the surgery, and thus, the response will be greater in a DIEP flap breast reconstruction than in EP [24]. In addition, transferring of a DIEP flap includes separation of the flap from its adjacent tissues, inevitably damaging the lymphatic circulation. An imbalance between excess interstitial fluids and an impaired lymphatic drainage will result in tissue oedema [25]. The hypothesis is supported by Greenhowe *et al.*, who report an increased tissue water content in autologous breast reconstruction during the first three months following surgery compared with the contralateral breasts [12]. Although a difference in LTW might have been present at an earlier stage also in this study, our results indicate that LTW in EP and DIEP flaps are comparable in the longer-term perspective.

Table 6. Comparison of pre- and postoperative BREAST-Q responses regarding questions comprising breast oedema-related symptoms for all patients ($n = 68$) and by breast reconstruction method (EP $n = 27$ and DIEP flap $n = 41$).

	All patients			EP			DIEP flap		
Median (1q, 3q)	Preop	Postop	*p* Value[a]	Preop	Postop	*p* Value[a]	Preop	Postop	*p* Value[a]
Question 3/6.i "Tightness in your breast area?"	1 (1, 2)	2 (1, 2)	0.83	2 (1, 3)	2 (1, 2)	0.81	1 (1, 2)	1 (1, 2)	0.45
Question 3/6.j "Pulling in your breast area?"	2 (1, 2)	1 (1, 2)	0.12	2 (1, 3)	2 (1, 2)	0.08	2 (1, 2)	1 (1, 2)	0.46
Question 3/6.k "Nagging feeling in your breast area?"	1 (1, 1)	1 (1, 2)	**0.04**	1 (1, 2)	1 (1, 2)	0.74	1 (1, 1)	1 (1, 2)	**0.01**
Question 3/6.l "Tenderness in your breast area?"	1 (1, 2)	1 (1, 2)	0.56	1 (1, 2)	1 (1, 2)	0.87	1 (1, 2)	1 (1, 2)	0.21
Question 3/6.m "Sharp pains in your breast area?"	1 (1, 1)	1 (1, 1)	0.25	1 (1, 1)	1 (1, 1)	0.91	1 (1, 1)	1 (1, 1)	0.10
Question 3/6.o "Aching feeling in your breast area?"	1 (1, 1)	1 (1, 1)	0.93	1 (1, 2)	1 (1, 1)	0.36	1 (1, 1)	1 (1, 1)	0.10
Question 3/6.p "Throbbing feeling in your breast area?"	1 (1, 1)	1 (1, 1)	0.21	1 (1, 1)	1 (1, 1)	0.23	1 (1, 1)	1 (1, 1)	0.52

The questions belong to the BREAST-Q Reconstruction Preoperative (question 3) and Postoperative (question 6) Module Version 1.0 and are preceded by 'In the past two weeks, how often have you experienced:' The response options range from 1–5 where 1 corresponds to 'None of the time' and 5 to 'All of the time'.
[a]Wilcoxon signed-rank test.
1q: Lower quartile; 3q: Upper quartile; EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator.
p-values <0.05 were considered significant and are bolded.

In order to relate our objective findings with the patients' perceptions, we selected BREAST-Q questions corresponding to breast oedema-related symptoms. Pain, heaviness, swelling and tensed skin in the breast have previously been reported in the literature [5,6,26]. The patients in this study did not report any breast oedema-related symptoms pre- or postoperatively, as indicated by the median BREAST-Q responses ranging from 1 to 2. However, the BREAST-Q questionnaire was not created for analysis of separate questions [27]. The questions we selected have not been validated for breast oedema assessment. Fortunately, a patient-reported questionnaire for breast oedema was recently presented and validated in a study by Verbelen *et al.* [26]. The questionnaire focuses on patients following BCS, similar to most studies published on breast oedema [5,6,26]. A breast oedema-specific questionnaire may be useful in future studies for assessing breasts following both breast reconstruction and BCS.

In this study, operated breasts had higher LTW compared with non-operated breasts. Similar findings have been presented previously in both short-term and long-term assessments [12,28–30]. The aforementioned study by Greenhowe *et al.*, reported increased tissue water content in the operated breasts during the three first postoperative months [12]. Two other studies investigated the lymphatic function following breast surgery with lymphoscintigraphy [28,29]. Perbeck *et al.* found a higher radiotracer clearance in breasts operated for benign tumours compared with healthy breasts two to five years postoperatively. The high clearance rate was initially interpreted as increased lymph flow, a theory that was later questioned and instead proposed to be a result of dermal backflow [28,31]. Similarly, a higher radiotracer clearance was found postoperatively in breasts that had undergone reduction mammaplasty compared with preoperatively [29]. Both studies indicated a worsened lymphatic function in breasts following surgery. Moreover, they suggested the lack of clinical findings of breast oedema to be due to a residual reserve capacity for the lymphatic circulation [28,29]. In this study, without any reported breast oedema-related symptoms, we propose that the lymphatic reserve capacity in the reconstructed breasts has not yet been exceeded. Subsequently, our objective TDC results are considered to fall below a potential symptomatic threshold for breast oedema.

Currently, no diagnostic threshold for breast cancer-related breast oedema is in place. In an attempt to create a diagnosis threshold for breast cancer-related arm lymphoedema, Mayrovitz *et al.* assessed TDC in the ventral forearms [15]. They suggested a TDC ratio above 1.20 to indicate subclinical lymphoedema. To increase the sensitivity, a threshold ratio of 1.165 was also discussed [15]. In our study, the EP/non-operated contralateral breast ratio comes very close to the subclinical oedema threshold (TDC ratio = 1.16), although no symptoms of oedema were reported. However, breast oedema ratios may be different and not comparable with that of the forearms. This hypothesis was strengthened by Mayrovitz et al. in a more recent study suggesting different TDC thresholds for different anatomical locations [32]. Further investigations are warranted.

There are some limitations of this study. Due to the absence of a clear definition of breast oedema, multiple assessment methods have been used in previous studies, thus limiting the interpretation of our objective findings [7]. Also, this study has a wide follow-up interval between breast reconstruction and objective examination, potentially affecting the results. In a future study, it would be of interest to establish a TDC ratio threshold for breast oedema diagnosis. In the presence of such a threshold, TDC measurements could be performed to assess breast oedema routinely at an out-patient clinic. Moreover, a translation of the Dutch breast oedema questionnaire could enable the use of a validated patient-reported diagnostic tool [26].

A strength of this study was its randomised prospective study design. To optimise the conditions for reliable data collection, all measurements were taken by one of two nurses. The MoistureMeterD® Compact was recently reported to be a reliable tool with high intra- and inter-rater reliabilities [33].

Conclusion

In conclusion, there were no differences in LTW between the EP and the DIEP flap breast reconstructions. However, the significant increase in LTW in reconstructed breasts compared with non-operated contralateral breasts indicates lymphatic damage measurable up to a mean of two years after surgery. However, the patients did not report any breast oedema-related symptoms, suggesting our objective findings fall below a potential symptomatic breast oedema threshold. Establishing a diagnostic breast oedema threshold for TDC ratios is warranted and could be the

aim of a future study. Finally, the use of a breast oedema-specific questionnaire would be of value in the future.

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ORCID

Linda Tallroth http://orcid.org/0000-0002-3469-9361
Håkan Brorson http://orcid.org/0000-0001-9968-6062

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Paper IV

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ARTICLE

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Evaluation of an assessment scale for aesthetic outcome in breast reconstructions based on digital photos in both 2D and 3D format

Linda Tallroth[a,b], Nathalie Mobargha[c], Patrik Velander[a,b], Stina Klasson[a,b] and Magnus Becker[a,b]

[a]Department of Plastic and Reconstructive Surgery, Skåne University Hospital, Malmö, Sweden; [b]Department of Clinical Sciences in Malmö, Lund University, Sweden; [c]Department of Reconstructive Plastic Surgery, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

The aesthetic outcome is crucial in a breast reconstruction. Our aim was to evaluate the intra- and interrater reliability of an aesthetic outcome assessment scale with digital photos of breast reconstructions in two-dimensional (2D) and three-dimensional (3D) format. Thirty-three women with delayed breast reconstructions, consecutively participating in a five-year follow-up between November 2019 and June 2021, were included in the study. Of these, 14 were reconstructed with an expander prosthesis (EP) and 19 with a deep inferior epigastric perforator (DIEP) flap. Photos of the breasts were assessed in 2D and 3D format by expert, layman and patient panels. Data were analysed with the weighted kappa (wk) statistics. The intrarater agreements were moderate to substantial, with wk between 0.66 and 0.73 for the panels. Within the panels, the interrater agreements were 0.46–0.62. Moderate agreements were found between the matched 2D and 3D format photos (wk 0.62–0.66). The patient panel graded scar appearance worse in 3D compared with 2D format. In all panels, there was a tendency towards DIEP flap reconstructions receiving higher aesthetic outcome grades compared with EP. Thus, the aesthetic outcome assessment scale demonstrated acceptable agreements between the individual panellists and within the panels. Scars captured in 3D format may provide a greater resemblance to the reality compared with 2D. Implications for clinics remain to be further studied.

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Aesthetics; expander prosthesis; DIEP flap

Background

In Sweden in 2020, 2405 women with breast cancer and no remote metastases underwent mastectomy [1]. Mastectomy has a negative impact on women's body image and quality of life and thus, a breast reconstruction is offered to mitigate these effects [2]. A breast reconstruction may be implant-based, created from autologous tissue, or potentially a combination of the two. Individual patient characteristics and patient preferences will guide the choice of breast reconstruction method and influence the result. A satisfactory aesthetic result together with a good functional outcome are essential in a breast reconstruction. Yet there is no agreement on how best to evaluate the aesthetic outcome.

The aesthetic outcome after a breast reconstruction is often evaluated with photos using an assessment scale. A variety of assessment scales have been reported [3–9]. The most common assessment scale used for professional assessment has been a four-point scale [10]. In previous reports, the number and size of panels recruited to evaluate the aesthetic outcome have differed and the agreements have in many cases been poor or have not been addressed [5–7,11]. In addition, measurement of aesthetic outcome with panel assessment has received criticism as it is time-consuming [12]. However, subjectivity is crucial for evaluating outcomes in plastic surgery as it may provide information that is not explored by objective measures. To this day, there is no gold standard assessment scale for evaluation of breast reconstructions. In a review article from 2015, the scale reported by Visser et al. was considered the most preferable as it demonstrated high validity [4,10]. It was, however, limited by a wide range of intra- and interrater agreements [4]. An assessment scale that is reliable between assessors with similar experiences and can identify differences over time is desirable. Therefore, the main aim of this study was to evaluate the reliability of an assessment scale for aesthetic outcome in breast reconstructions. A secondary aim was to compare the aesthetic outcome following expander prosthesis (EP) breast reconstructions with deep inferior epigastric perforator (DIEP) flap breast reconstructions.

Material and methods

Patients

Thirty-four consecutive patients who had undergone unilateral delayed breast reconstruction between October 2012 and November 2016 were selected for participation in this study. The patients had been randomised to breast reconstruction with either an EP or a DIEP flap, and participated in a prospective five-year follow-up [13]. The study was approved by the Ethical Review Board in Sweden Dnr 2012/187 and Dnr 2021-00555.

Photo session

Photography of the patients was performed by a professional medical photographer or by the first author, in a hospital photo studio with standardised lightning. A two-dimensional (2D)

CONTACT Linda Tallroth linda.tallroth@med.lu.se Jan Waldenströms gata 18, 214 28 Malmö, Sweden

camera and a three-dimensional (3D) camera were used for documentation of the breasts. The photos in 2D format were taken with a single-lens reflex digital camera (Nikon Corporation, Tokyo, Japan). The lens used during photography was a NIKKOR lens with constant f/2.8 aperture and focal length of 24–70 mm (Nikon Corporation, Tokyo, Japan). The 3D camera system, 3dMD trio system (3dMD LLC, Atlanta, GA), had 12 fixed cameras. Of these 12 cameras, four were mounted frontally and four on both sides. Prior to each 3D photo session, the 3dMD trio system was calibrated. Subsequently, photos were taken from three angles, resulting in a photo possible to be viewed as a 3D photo in the 3dMD Vultus (version 2.2.024) program. The program enables the viewer to rotate the 3D photo, zoom in on details and conduct measurements, but was not used by the panellists in this study.

Aesthetic outcome assessment scale

The assessment scale used in this study was a modification of the scale reported by Visser et al. [4]. The five items—breast size, shape, symmetry, scar appearance and nipple areolar complex (NAC)—were graded using a five-point Likert scale. The five-point Likert scale ranged from very bad (1) to very good (5). The item size was graded from much smaller [1], equal [3] to much larger [5], compared with the non-reconstructed breast, different from the scale by Visser et al. The option "Cannot be evaluated" was added as a modification in the absence of a NAC. The overall aesthetic outcome was assessed using a ten-point Likert scale, very bad (1) to very good (10).

Panels

Three types of panellists were recruited for this study. Plastic surgeons and breast surgeons participated as experts. Only consultant and senior consultant physicians were invited. Laymen with varying degrees of medical knowledge were invited to join the layman panels. Twelve patients were invited to join a patient panel. Their participation included assessment of their own breast reconstruction.

Data collection

The study data were managed and collected using Research Electronic Data capture (REDcap) tools hosted at Lund University [14,15]. REDcap is a web-based platform which we used to facilitate the photo assessments. The study was performed in two phases. In the first phase, 48 sets of photos accompanied by the assessment scale were included. The same breast reconstruction appeared on two sets of photos. There were four photos per set in 2D format and five per set in 3D format (Figure 1(A–D)). The sets were arranged in a randomised order. Laterality was noted but not reconstruction type. To facilitate a high response rate, the assessments could be completed at any time. The panellists were not informed in advance that the same reconstruction appeared twice, nor that two different camera modalities were used. All panellists were asked to perform the assessment twice, a minimum of three weeks apart. They were also asked to record the time it took to perform the assessment. An expert and a layman panel assessed the photos in the study's first phase and a reliability analysis was conducted. In the second phase of the study, all breast reconstructions apart from two were replaced by new breast reconstructions. Twelve breast reconstructions were included, and in total there were 24 sets of photos. An expert, a layman and a patient panel assessed the breast reconstructions in the second phase. The assessment was performed twice by the patients and once by the other panels.

Statistical analysis

Statistical Package for Social Sciences version 27 (IBM Corp. Armonk, NY: IBM Corp. Released 2020) was used for statistical analysis. Intrarater and interrater agreements were calculated with the weighted kappa (wκ) and were presented as median, minimum and maximum values. The wκ was used for a reliability analysis of the assessment of digital photos in 2D format with the corresponding assessments in 3D format. Interrater reliability was presented as the median of the individually pairwise calculated kappa values. Level of agreement was interpreted as poor below 0.00, slight 0.00–0.20, fair 0.21–0.40, moderate 0.41–0.60, substantial 0.61–0.80, and almost perfect 0.81–1.00 [16]. A *p*-value below 0.05 was considered statistically significant.

Results

Patient characteristics

Thirty-four patients completed the photography as a part of the prospective follow-up. One patient was excluded as she had undergone a contralateral breast reconstruction due to breast cancer. Thus, 33 patients were included. The photo sessions were performed between November 2019 and June 2021 at a mean of 66 (standard deviation, SD 11) months after breast reconstruction. The median age at breast reconstruction was 55 (SD 10) years. Of the included patients, 14 breasts were reconstructed with an EP and 19 with a DIEP flap.

Panel characteristics

Eleven plastic surgeons and two breast surgeons participated in the expert panel in the first phase of the study. Of these, eight were men and five were women. The age within the panel ranged from 38 to 68 years. Eleven of them performed the assessment twice. In the second phase, none of the four expert panellists had been involved in the care of the patients. The layman panel comprised of nine panellists of which four were men and five were women. Their ages ranged from 20 to 58 years. One member of the panel was a senior consultant physician working within a non-surgical specialty, two were intern physicians, and one was a medical student. The other laymen did not have any previous medical knowledge.

The median time for performing the assessment in the first phase was 60 (40–120) min for the experts and 50 (35–120) min for the laymen.

Reliability analysis

Distribution on the Likert scale

The distributions of the panels' gradings per item are shown in Tables 1–2. The expert and layman assessments are from the first phase of the study and the patient panel assessment from the second phase. Grades 4 and 5 were the most frequent for symmetry; however, grade 2 was the most common grade in the layman panel assessment of photos in 3D format. Regarding scar appearance, grade 4 was the most frequent grade in the expert and layman panels. However, photos in 2D format were most frequently assessed as grade 5 and photos in 3D format as grade 2 by the patient panel.

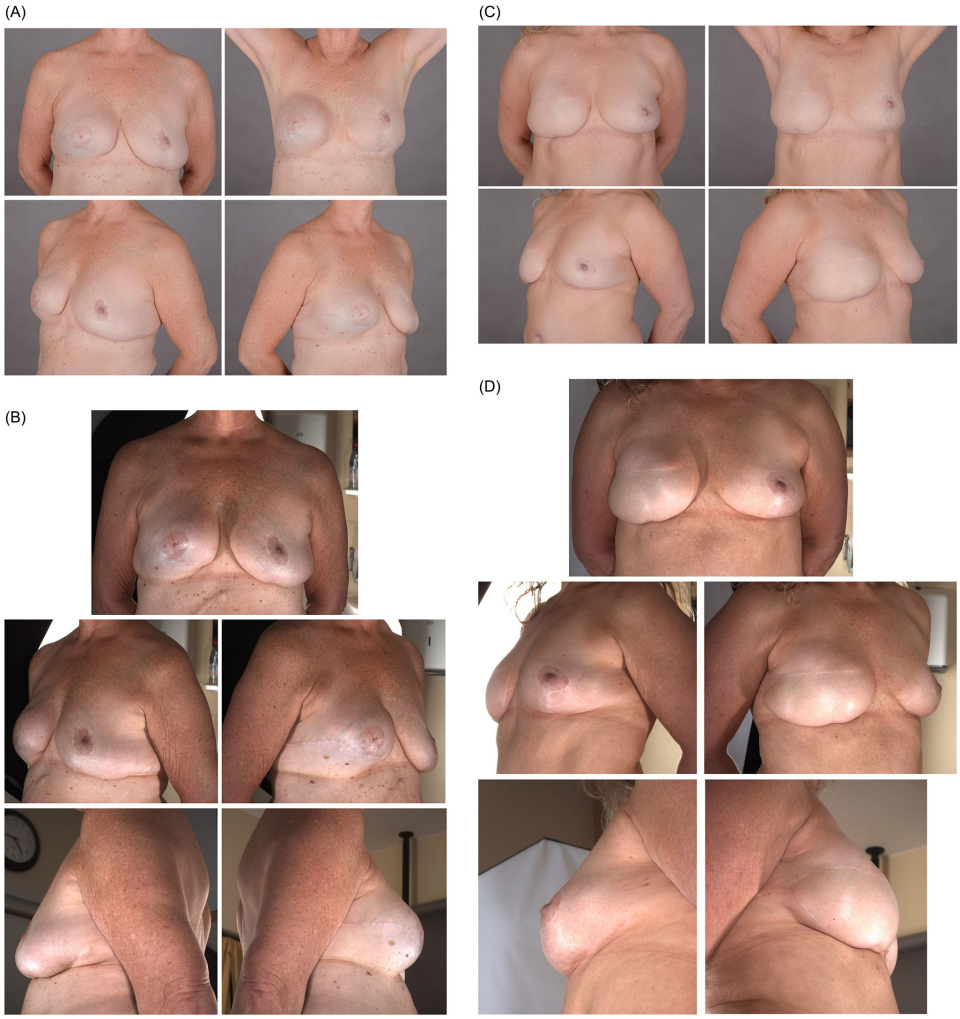

Figure 1. Examples of postoperative photographs evaluated in the study. (A) An expander prosthesis (EP) breast reconstruction in two-dimensional (2 D) format and in (B) three-dimensional (3 D) format. (C) A deep inferior epigastric perforator (DIEP) flap breast reconstruction in 2 D format and in (D) 3 D format.

Reliability for repeated assessments

In the expert panel, the intrarater agreements were moderate to substantial with a median wκ of 0.70 (0.62 – 0.75) for photos in 2D format and 0.67 (0.54 – 0.80) for photos in 3D format. In the layman panel, the agreements were moderate to substantial. The median wκ was 0.70 (0.58 – 0.74) and 0.66 (0.60 – 0.69) for the respective photo format. The patient panel had a median wκ of 0.73 (0.50 – 0.89) and 0.72 (0.29 – 0.83) respectively, assessed in the second phase of the study. The intrarater agreements are summarised in Table 3.

Reliability for assessment within panels

The interrater agreements were moderate in the expert and the layman panels. In the expert panel ($n = 13$), the median wκ was 0.60 (0.36 – 0.74) for photos in 2D format and 0.55 (0.35 – 0.77) for photos in 3D format. In the layman panel ($n = 9$), the assessments resulted in a median wκ of 0.62 (0.44 – 0.73) and 0.57 (0.38 – 0.67) for photos in 2D and 3D format respectively. The agreements in the patient panel ($n = 12$) were somewhat lower with a median wκ of 0.46 (0.19 – 0.73) for photos in 2D format and 0.48 (0.04 – 0.73) for photos in 3D format. The interrater agreements are presented in Table 4.

Table 1. Frequency distribution of panels' grading from the panels' first assessments separated by photo format for size, shape, symmetry, scar appearance and nipple areolar complex.

Item	n	Likert scale grades *n* (%) 1	2	3	4	5	Total *n* (%)
Size							
2 D format							
Expert	13	10 (4.3)	62 (27.0)	**103 (44.8)**	53 (23.0)	1 (0.4)	229 (99.6)
Layman	9	19 (9.2)	49 (23.7)	**105 (50.7)**	33 (15.9)	1 (0.5)	207 (100)
Patient	12	12 (8.3)	42 (29.2)	**69 (47.9)**	15 (10.4)	4 (2.8)	142 (98.6)
3 D format							
Expert	13	12 (5.2)	66 (28.7)	**96 (41.7)**	55 (23.9)	1 (0.4)	230 (100)
Layman	9	28 (13.5)	51 (24.6)	**92 (44.4)**	35 (16.9)	206 (99.5)	207 (100)
Patient	12	14 (9.7)	46 (31.9)	**73 (50.7)**	9 (6.3)	2 (1.4)	144 (100)
Shape							
2 D format							
Expert	13	8 (3.5)	44 (19.1)	31 (13.5)	**101 (43.9)**	46 (20.0)	230 (100)
Layman	9	5 (2.4)	42 (20.3)	26 (12.6)	53 (25.6)	**81 (39.1)**	207 (100)
Patient	12	9 (6.3)	19 (13.2)	16 (11.1)	**57 (39.6)**	42 (29.2)	143 (99.3)
3 D format							
Expert	13	15 (6.5)	50 (21.7)	42 (18.3)	**92 (40.0)**	31 (13.5)	230 (100)
Layman	9	18 (8.7)	45 (21.7)	25 (12.1)	56 (27.1)	**63 (30.4)**	207 (100)
Patient	12	12 (8.3)	26 (18.1)	16 (11.1)	**45 (31.3)**	43 (29.9)	142 (98.6)
Symmetry							
2 D format							
Expert	13	10 (4.3)	53 (23.0)	32 (13.9)	**91 (39.6)**	43 (18.7)	229 (99.6)
Layman	9	7 (3.4)	48 (23.2)	26 (12.6)	49 (23.7)	**76 (36.7)**	206 (99.5)
Patient	12	9 (6.3)	14 (9.7)	16 (11.1)	51 (35.4)	**54 (37.5)**	144 (100)
3 D format							
Expert	13	16 (7.0)	59 (25.7)	34 (14.8)	**89 (38.7)**	30 (13.0)	228 (99.1)
Layman	9	20 (9.7)	**56 (27.1)**	30 (14.5)	50 (24.2)	51 (24.6)	207 (100)
Patient	12	7 (4.9)	34 (23.6)	13 (9.0)	41 (28.5)	**49 (34.0)**	144 (100)
Scar appearance							
2 D format							
Expert	13	0	22 (9.6)	45 (19.6)	**130 (56.5)**	31 (13.5)	228 (99.1)
Layman	9	1 (0.5)	27 (13.0)	46 (22.2)	**77 (37.2)**	54 (26.1)	205 (99.0)
Patient	12	6 (4.2)	19 (13.2)	16 (11.1)	42 (29.2)	**60 (41.7)**	143 (99.3)
3 D format							
Expert	13	7 (3.0)	49 (21.3)	60 (26.1)	**93 (40.4)**	17 (7.4)	226 (98.3)
Layman	9	9 (4.3)	56 (27.1)	53 (25.6)	**65 (31.4)**	22 (10.6)	205 (99.0)
Patient	12	14 (9.7)	**38 (26.4)**	20 (13.9)	34 (23.6)	35 (24.3)	141 (97.9)
NAC							
2 D format							
Expert	13	9 (3.9)	40 (17.4)	58 (25.2)	**72 (31.3)**	20 (8.7)	199 (86.5)
Layman	9	11 (5.3)	38 (18.4)	35 (16.9)	**56 (27.1)**	35 (16.9)	175 (84.5)
Patient	12	7 (4.9)	24 (16.7)	18 (12.5)	**42 (29.2)**	35 (24.3)	126 (87.5)
3 D format							
Expert	13	7 (3.0)	51 (22.2)	39 (17.0)	**82 (35.7)**	19 (8.3)	198 (86.1)
Layman	9	10 (4.8)	33 (15.9)	38 (18.4)	**62 (30.0)**	26 (12.6)	169 (81.6)
Patient	12	8 (5.6)	25 (17.4)	12 (8.3)	**43 (29.9)**	41 (28.5)	129 (89.6)

The expert and layman assessments are from the first phase of the study and the patient panel assessment from the second phase. The Likert scale grade with highest frequency per panel and item is in bold.
2 D: Two dimensional; 3 D: Three dimensional; NAC: Nipple areolar complex.

Table 2. Frequency distribution of panels' grading from the panels' first assessments separated by photo format for the overall aesthetic outcome.

Item	n	Likert scale grades *n* (%) 1	2	3	4	5	6	7	8	9	10	Total *n* (%)
Overall aesthetic outcome												
2 D format												
Expert	13	0	6 (2.6)	16 (7.0)	13 (5.7)	18 (7.8)	23 (10.0)	41 (18.7)	**57 (24.8)**	41 (17.8)	15 (6.5)	230 (100)
Layman	9	0	4 (1.9)	14 (6.8)	11 (5.3)	18 (8.7)	25 (12.1)	36 (17.4)	**42 (20.3)**	39 (18.8)	18 (8.7)	207 (100)
Patient	12	5 (3.5)	5 (3.5)	9 (6.3)	7 (4.9)	9 (6.3)	13 (9.0)	18 (12.5)	23 (16.0)	**30 (20.8)**	25 (17.4)	144 (100)
3 D format												
Expert	13	6 (2.6)	5 (2.2)	27 (11.7)	18 (7.8)	21 (9.1)	32 (13.9)	37 (16.1)	**52 (22.6)**	23 (10.0)	9 (3.9)	230 (100)
Layman	9	2 (1.0)	10 (4.8)	25 (21.1)	21 (10.1)	17 (8.2)	26 (12.6)	27 (13.0)	**36 (17.4)**	**36 (17.4)**	7 (3.4)	207 (100)
Patient	12	6 (4.2)	7 (4.9)	11 (7.6)	8 (5.6)	20 (13.9)	11 (7.6)	9 (6.3)	**28 (19.4)**	21 (14.6)	23 (16.0)	144 (100)

The expert and layman assessments are from the first phase of the study and the patient panel assessment from the second phase. The Likert scale grade with highest frequency per panel is in bold.
2 D: Two dimensional; 3 D: Three dimensional.

Table 3. Intrarater agreements with weighted kappa (κw) values.

Photo format	Expert panel $n = 11$	Layman panel $n = 7$	Patient panel $n = 12$
2 D	0.70 (0.62 – 0.75)	0.70 (0.58 – 0.74)	0.73 (0.50 – 0.89)
3 D	0.67 (0.54 – 0.80)	0.66 (0.60 – 0.69)	0.72 (0.29 – 0.83)

The patient panel's agreements were calculated based on ratings from the second phase of the study. Agreements are presented in median with minimum and maximum values in parenthesis.
Interpretations of wκ values: 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate 0.61–0.80 substantial, >0.80 almost perfect [17].
2 D: Two dimensional; 3 D: Three dimensional.

Table 4. Interrater agreements with weighted kappa (κw) values.

Photo format	Expert panel $n = 13$	Layman panel $n = 9$	Patient panel $n = 12$
2 D	0.60 (0.36 – 0.74)	0.62 (0.44 – 0.73)	0.46 (0.19 – 0.73)
3 D	0.55 (0.35 – 0.77)	0.57 (0.38 – 0.67)	0.48 (0.04 – 0.73)

The patient panel agreements were calculated based on ratings from the second phase of the study. Agreements are presented in median with minimum and maximum values in parenthesis.
Interpretations of wκ values: 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate 0.61-0.80 substantial, >0.80 almost perfect [17].
2 D: Two dimensional; 3 D: Three dimensional.

Table 5. Intrarater agreements with weighted kappa (κw) between assessments in 2 D format with the corresponding in 3 D format.

Reconstruction method	Expert panel $n = 13$	Layman panel $n = 9$	Patient panel $n = 12$
All	0.64 (0.33 – 0.78)	0.62 (0.46 – 0.73)	0.66 (0.25 – 0.77)
EP	0.55 (0.27 – 0.71)	0.56 (0.34 – 0.67)	0.57 (0.19 – 0.69)
DIEP flap	0.63 (0.32 – 0.83)	0.61 (0.43 – 0.80)	0.63 (0.13 – 0.86)

The patient panel's agreements were calculated based on ratings from the second phase of the study. Agreements are presented in median with minimum and maximum values in parenthesis.
Interpretations of wκ values: 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate 0.61–0.80 substantial, >0.80 almost perfect [17].
EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator; 2 D: Two dimensional; 3 D: Three dimensional.

Digital photos in 2D and 3D format

Intrarater agreements were calculated on the matched assessments of photos in 2D and 3D format. The median wκ was moderate in all panels. The median wκ was 0.64 (0.33 – 0.78) in the expert panel, 0.62 (0.46 – 0.73) in the layman panel, and 0.66 (0.25 – 0.77) in the patient panel. Separated by reconstruction method, the median wκ values were somewhat higher in assessments of DIEP flaps. The results are presented in Table 5.

Aesthetic outcome

The aesthetic outcome results are presented in Table 6. The results presented are from the second phase of the study. In all panels, there was a general tendency towards higher grades for DIEP flap breast reconstructions compared with EP. The tendency was more pronounced for the overall aesthetic outcome regarding photos in 3D format. In comparison of the panels, laymen gave the lowest median grades for overall aesthetic outcome. An in-depth review of the patients receiving lower overall outcome scores, less than or equal to 6.5, by the expert panels in phase one and two illustrated potential negative factors such as previous prosthesis exchanges ($n = 3$), increased body mass index (BMI) with more than four units ($n = 1$) and early reoperations due to complications ($n = 2$).

Table 6. Aesthetic outcome scores per item and photo format assessed by three panels.

	Aesthetic outcome scores Median (range)					
Panel	Size	Shape	Symmetry	Scar	NAC	Overall
Expert						
2 D format	3 (2–5)	4 (1–5)	4 (1–5)	4 (2–5)	4 (1–5)	8 (2–10)
EP	3 (2–4)	3.5 (1–5)	3.5 (1–5)	4 (2–5)	3 (1–5)	7 (2–10)
DIEP flap	3 (2–5)	5 (4–5)	5 (4–5)	5 (2–5)	4 (2–5)	9 (7–10)
3 D format	3 (2–5)	4 (1–5)	4 (1–5)	4 (2–5)	4 (1–5)	7.5 (2–10)
EP	3 (2–4)	3.5 (1–5)	3.5 (1–5)	3 (2–5)	3 (1–5)	6 (2–10)
DIEP flap	3 (2–5)	5 (4–5)	5 (3–5)	4 (2–5)	4 (4–5)	9 (7–10)
Layman						
2 D format	3 (1–4)	4 (1–5)	4 (1–5)	3 (1–5)	4 (1–5)	7 (1–10)
EP	2 (1–4)	4 (1–5)	4 (1–5)	3 (2–5)	3 (1–5)	6 (1–10)
DIEP flap	3 (2–4)	4.5 (3–5)	4 (3–5)	3 (1–5)	4 (3–5)	8 (6–10)
3 D format	3 (1–4)	4 (1–5)	4 (1–5)	3 (1–5)	4 (1–5)	7 (2–9)
EP	2 (1–4)	3 (1–5)	3 (1–5)	3 (1–5)	3 (1–5)	5 (2–9)
DIEP flap	3 (2–4)	5 (4–5)	5 (4–5)	3 (1–4)	4 (3–5)	8 (2–9)
Patient						
2 D format	3 (1–5)	4 (1–5)	4 (1–5)	4 (1–5)	4 (1–5)	8 (1–10)
EP	2 (1–4)	4 (1–5)	4 (1–5)	4 (1–5)	3 (1–5)	7 (1–10)
DIEP flap	3 (2–5)	4 (2–5)	4 (2–5)	4 (1–5)	4 (1–5)	9 (2–10)
3 D format	3 (1–5)	4 (1–5)	4 (1–5)	3 (1–5)	4 (1–5)	7.5 (1–10)
EP	2 (1–4)	3 (1–5)	3 (1–5)	3 (1–5)	3 (1–5)	5 (1–10)
DIEP flap	3 (2–5)	5 (2–5)	5 (2–5)	4 (1–5)	4 (2–5)	8.5 (3–10)

On the 5-point rating scale, 1 equal very bad and 5 very good regarding items shape, symmetry, scar appearance and NAC. For the item size, 1 equal much smaller than the natural breast, 3 the same size as the natural breast and 5 much larger than the natural breast. Overall aesthetic outcome was rated on a 10-point scale on which 1 equal very bad and 10 very good.
EP: Expander prosthesis; DIEP: Deep inferior epigastric perforator; 2 D: Two dimensional; 3 D: Three dimensional; NAC: Nipple areolar complex.

Discussion

In this study, we report on the reliability of an aesthetic outcome assessment scale used for breast reconstructions. Median agreements were moderate to substantial for repeated assessments in expert, layman and patient panels. Between members of the same panel, somewhat lower median agreements were found, with the lowest values in the patient panel. In a comparison of matched photos in 2D and 3D format, moderate to substantial median agreements were demonstrated.

In the context of breast reconstructions, repeated evaluations are essential to identify changes postoperatively. For example, weight changes and implant disfiguration may alter the aesthetic result over time. Based on the findings from this study, the assessment scale demonstrated acceptable reproducibility. Compared with a study by Veiga et al., the agreements in our report were high. They presented intrarater agreements between 0.12 and 1 for photo evaluations of autologous breast reconstructions at three different time points [17]. The wide agreement range presented could be explained by the scale used. It may be difficult for panellists to distinguish between adjacent grades in the presence of a scale with ten grades. However, our findings concurred with the intrarater agreements reported by Godden et al. ranging from 0.4 to 0.7, using a five-point scale [18].

The use of aesthetic outcome assessment scales has been questioned, partly as a result of the high variability of interrater agreements reported in the literature. In the past, different statistical analysis methods have been used, which complicates comparisons between studies [3,5,19]. Moreover, in some studies, reliability was not analysed [6,7]. Results from this study reflect moderate agreements, similar to some previous studies [5,19]. Lindegren et al. and Gahm et al. used the wκ and consequently, their results can be compared with ours [5,19]. Meanwhile, Visser et al. and Liu et al. used a different analysis method, the intraclass

correlation, and presented higher agreements [3,4]. We found the lowest agreements in the patient panel, indicating that there may be a heterogenicity within this panel. Plausibly, the patient's own reconstruction experience and result influences the perception of other breasts. Supposedly, a satisfied patient will assess other breast reconstructions more favourably. Although we opt for high agreements, some variability is to be expected as aesthetics are perceived differently between individuals.

The agreements between the matched assessments of photos in 2D and 3D format, together with similar intrarater agreements between the two, suggest a comparable use of the photo formats. A similar result was reported in a study evaluating cleft, lip and palate patients using 2D and 3D photos. The difference between the interrater agreements of the 2D and 3D photos was small, 0.56 and 0.62, respectively [20]. We used a 3D camera system aiming for more realistic and detailed photos compared with the standard digital photos in 2D format. Our hypothesis was that the panels would grade photos in 3D format worse due to greater enhancement of scars and skin surface irregularities. We did not find a general tendency confirming this hypothesis. Interestingly, compared with the photos in 2D format, the photos in 3D format were assessed with lower grades concerning scar appearance by the patient panel. This result may be explained by scar appearance being an important outcome for patients, and therefore assessed more critically. Also, patients may have unrealistic expectations concerning the final scar appearance. This is further supported by the findings in the study by Lindegren et al. in which patients were less satisfied with the DIEP flap donor scar compared with experts [5]. Photos in 3D format may provide a better reflection of the reality. By using photos in 3D format when informing patients preoperatively, more realistic expectations may be achieved. In the process of choosing the reconstruction method it is crucial that the patient is well-informed, with awareness of the possible aesthetic outcomes, as this may increase the postoperative satisfaction. In addition, a future perspective would be to evaluate the reliability between outpatient clinic assessments and 3D photo assessments.

Although a low number of patients were included in this study, the results tended to be in favour of the DIEP flap breast reconstructions due to the better aesthetic outcome. Superior aesthetic outcome in autologous reconstruction compared with implant-based reconstructions has been reported previously [21–23]. The difference in aesthetic outcome between the reconstruction methods may increase with time as autologous reconstructions tend to be stable over time, unlike implants. Thus, other treatments and patient characteristics may influence the aesthetic outcome. Radiation therapy had a negative effect on the overall aesthetic outcome in a study by Huis et al. [6]. In addition, higher BMI and reoperations due to complications have also been reported to negatively affect aesthetics [21]. An in-depth review of our study material supports these results as some of the patients with low overall aesthetic outcome had been through reoperations due to complications, and in one case had a large increase in BMI. However, these associations must be confirmed in a larger body of material.

In concordance with previous studies, we acknowledge that the use of an assessment scale for aesthetic evaluation of breast reconstructions is time-consuming. To facilitate a high number of participating panellists, we used REDcap, which provided a more flexible way to evaluate the photos. Although there is a considerable advantage to using an electronic platform that can be accessed easily, a drawback is the possible influence of external factors. Strengths of this study are that the patients were randomised to breast reconstruction with an EP or a DIEP flap and that they were included consecutively. The panels were blinded to the reconstruction method and all reconstructions were assessed twice; in 2D and 3D format. The long follow-up time provided evaluation of breast reconstructions that were somewhat stable in their appearances. A weakness of the study is that the reliability analysis for the patient panel was based on different photos to those used with the expert and layman panels. The low number of patients included in this study is another weakness. Moreover, it is important to consider the drawback of not being able to rotate the 3D photos. This feature may have led to different results.

Conclusion

The result from this study suggested that continued use of the assessment scale in breast reconstructions could be recommended. A possible value of assessing scar appearance with photos in 3D format was found. A comparison between clinical assessments in the outpatient clinic and assessment of 3D photos is yet to be performed.

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ORCID

Linda Tallroth http://orcid.org/0000-0002-3469-9361

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Linda Tallroth, MD
Department of Clinical Sciences Malmö,
Faculty of Medicine, Lund University, Lund, Sweden

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