Breast reconstructive surgery: Risk factors for complications and health-related quality of life

- Clinical studies

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"Every body and every thing conspire to make me as contented as possible in it; yet I have seen too much of the vanity of human affairs, to expect felicity from the splendid scenes of public life. I am still determined to be cheerful and to be happy, in whatever situation I may be; for I have also learnt, from experience, that the greater part of our happiness or misery depends upon our dispositions, and not upon our circumstances. We carry the seeds of the one or the other about with us, in our minds, wheresoever we go"

-Martha Washington

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ABSTRACT

Background: Breast cancer is the most common form of cancer in women worldwide. Although the incidence is increasing, the mortality rate is not. This results in a growing number of breast cancer survivors, and thereby in increasing demand for breast reconstructions. Complications after breast reconstructive surgery are common and can be caused by a wide range of factors, such as the reconstructive method, perioperative factors and patient-related factors. As the principal aim of breast reconstruction is to reverse the mastectomy deformity and restore body image and health-related quality of life (HR-QoL), traditional clinical outcome measures, such as medical or surgical complications, do not suffice assessing the values of different reconstruction methods for the patient.

There are no established guidelines on choosing the best reconstruction method for the individual patient. However, patient perspectives and experiences are important when choosing the reconstructive method, and HR-QoL needs to be investigated in a systematic way when comparing different reconstruction methods.

Aim: The aim of this thesis was to evaluate postoperative complications, to find independent risk factors for complications and compare HR-QoL between breast reconstruction patients, and with the general population.

Method: The four retrospective studies were based on a large database of breast reconstructions between the years 2003 and 2009 at the Department of Plastic Surgery, Sahlgrenska University Hospital, and the results of HR-QoL questionnaires from patients surgically treated with breast reconstruction during this time.

Results: Paper I states the importance of a systematic and meticulous registration of complications in comparisons of different methods. The study revealed high complication rates with all of the methods, and the spectrum of complications was related to the operation method, where the DIEP group had the highest rate. The pattern of occurrence of complications ranged between early and late time points.

Paper II shows the perioperative factors of duration of surgery and blood loss during surgery as independent risk factors for several postoperative complications, both early and late.

Paper III shows several patient-related factors and adjuvant therapy as independent risk factors for complications, such as BMI, smoking, and radiotherapy.

Paper IV shows that patients reconstructed with a DIEP flap are more satisfied with their reconstruction and overall outcome than patients in the other groups.

Conclusion: Complications after breast reconstructive surgery are common and can be caused by many different factors. Patients reconstructed with a DIEP flap are more satisfied with their reconstruction than patients reconstructed with other methods. To maximize patient satisfaction, DIEP flaps should be more widely available, and complications rate after this type of surgery should be minimized.

Keywords: breast cancer, breast reconstruction, surgical complications, health-related quality of life, perioperative risk factors, patient-related risk factors, DIEP flap, latissimus dorsi flap, lateral thoracodorsal flap, breast implants

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Bröstcancer är den vanligaste cancerformen hos världens kvinnor, incidensen ökar, men dödligheten är stabil. Detta resulterar i ett växande antal patienter som har överlevt sin bröstcancer, och därmed en ökad efterfrågan på bröstrekonstruktioner. Komplikationer efter bröstrekonstruktion är vanliga och kan orsakas av ett flertal faktorer, såsom den rekonstruktiva metoden, perioperativa faktorer och patientrelaterade faktorer. Eftersom det huvudsakliga syftet med bröstrekonstruktion är att återskapa bröstformen, förbättra självbilden och normalisera hälsorelaterad livskvalitet, är traditionella kliniska mått, såsom medicinska eller kirurgiska komplikationer, otillräckliga för att bedöma värdet av olika rekonstruktionsmetoder för patienten. Patientens perspektiv är mycket viktigt inför val av metod och hälsorelaterad livskvalitet behöver utvärderas på ett systematiskt sätt, vid jämförelse av olika rekonstruktionsmetoder.

Syfte: Syftet med denna avhandling är att utvärdera och jämföra komplikationer vid bröstrekonstruktiv kirurgi, hitta oberoende riskfaktorer för postoperativa komplikationer och jämföra hälsorelaterad livskvalitet mellan de fyra vanligaste rekonstruktionsmetoderna som används vid Verksamhetsområde plastikkirurgi, Sahlgrenska Universitetssjukhuset i Göteborg.

Metod: Data för denna avhandling har hämtats från en specialframtagen databas för bröstrekonstruktioner utförda mellan 2003 till 2009, och resultaten för den hälsorelaterade livskvaliteten från inskickade frågeformulär från patienter som opererats under studietiden.

Resultat: Den första studien fastställer vikten av en systematisk och noggrann registrering av komplikationer vid jämförelse av olika rekonstruktionsmetoder. Studien visade höga komplikationsfrekvenser för alla metoder, och spektrumet av komplikationer var relaterat till den rekonstruktiva metoden. Mönstret för komplikationer varierade mellan tidiga och sena tidpunkter.

Den andra studien visade att två perioperativa faktorer, operationstid och blodförlust under operation, är oberoende riskfaktorer för flera postoperativa komplikationer, både tidiga och sena.

Den tredje studien visade att flera patientrelaterade faktorer var oberoende riskfaktorer för komplikationer, såsom BMI, rökning och strålbehandling.

Den fjärde studien undersökte hälsorelaterad livskvalitet efter bröstrekonstruktion. Studien beskriver att patienter som rekonstruerats med DIEP lambå är mer nöjda med känslan av sitt bröst och det generella resultatet än patienter som är opererade med andra metoder.

Slutsatser: Komplikationer efter bröstrekonstruktioner är vanliga och kan orsakas av många olika faktorer. Patienter, rekonstruerade med DIEP lambå är mer nöjda med sin rekonstruktion än patienter rekonstruerade med andra metoder. För att maximera vinsten i hälsorelatedad livskvalitet, bör DIEP lambåer vara mer tillgängliga, och komplikationer efter denna typ av kirurgi bör minimeras.

Nyckelord: bröstcancer, bröstrekonstruktion, postoperativa komplikationer, hälsorelaterad livskvalitet, peroperativa riskfaktorer, patientrelaterade riskfaktorer, DIEP lambå, latissimus dorsi lambå, implantatrekonstruktion, bröstimplantat

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SAMANTEKT Á ÍSLENSKU

Bakgrunnur: Brjóstakrabbamein er algengasta krabbamein meðal kvenna í heiminum. Nýgengi eykst, en dánartíðni í hinum vestræna heimi helst stöðug. Þetta leiðir til vaxandi fjölda eftirlifandi sjúklinga, og þar með aukinnar eftirspurnar eftir brjóstauppbyggingum. Fylgikvillar eftir brjóstauppbyggingar eru algengir og geta stafað af ýmsum orsökum, t.d. þeirri aðferð sem notuð er við uppbygginguna, af skurðtæknilegum þáttum og persónubundnum þáttum. Þar sem megintilgangur brjóstauppbyggingar er að endurheimta lögun brjóstsins, bæta sjálfsmynd og heilsutengd lífsgæði, er viðhorf sjúklingsins mikilvæg við val á uppbyggingaraðferð. Heilsutengd lífsgæði þarf að mæla á kerfisbundinn hátt við samanburð á aðferðum til brjóstauppbygginga.

Markmið: Markmið þessarar ritgerðar er að meta og bera saman fylgikvilla brjóstauppbygginga, finna sjálfstæða áhættuþætti fyrir fylgikvilla og bera saman heilsutengd lífsgæði milli fjögurra algengustu brjóstauppbyggingaraðferða sem notaðar eru við Lýtalækningadeild Sahlgrenska háskólasjúkrahússins í Gautaborg.

Aðferðir: Gögnum var safnað í sérhannaðan gagnagrunn fyrir allar brjóstauppbyggingar framkvæmdar á árunum 2003 til 2009. Heilsutengd lífsgæði voru mæld með viðurkenndum spurningalistum.

Niðurstöður: Fyrsta rannsóknin varpar ljósi á mikilvægi kerfisbundinnar og nákvæmrar skráningar á fylgikvillum við samanburð á uppbyggingaraðferðum. Rannsóknin sýndi háa tíðni fylgikvilla, að tegund þeirra tengdist uppbyggingaraðferðinni og að mynstur þeirra var ólíkt hvort sem um var að ræða snemma eða seint í uppbyggingarferlinu.

Önnur rannsóknin sýndi að tveir skurðtæknilegir þættir, blóðtap og skurðtími eru sjálfstæðir áhættuþættir fyrir marga fylgikvilla, bæði snemm- og seinkomna.

Þriðja rannsóknin sýndi ákveðna persónubundna þætti sem sjálfstæða áhættuþætti fyrir fylgikvilla, svo sem þyngdarstuðul (BMI), reykingar, og geislameðferð.

Fjórða rannsóknin bar saman heilsutengd lífsgæði milli mismunandi uppbyggingaraðferða. Hún sýndi að sjúklingar sem fengið hafa

uppbyggingu með DIEP flipa eru ánægðari með uppbygginguna en aðrir hópar.

Ályktanir: Fylgikvillar eftir brjóstauppbyggingu eru algengir og geta stafað af mörgum þáttum. Til að hámarka ávinning í heilsutengdum lífsgæðum ættu DIEP flipar verða aðgengilegri vinna skal markvisst að því að halda fylgikvillum í lágmarki.

Leitarorð: brjóstakrabbamein, brjóstauppbygging, fylgikvillar eftir aðgerð, heilsutengd lífsgæði, skurðtæknilegir áhættuþættir, sjúklingatengdir áhættuþættir, DIEP flipi, latissimus dorsi flipi, lateral thoracodorsal flipi, brjóstauppbygging með brjóstapúðum.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Thorarinsson, A., Fröjd, V., Kölby, L., Lewin, R., Molinder, N., Lundberg, J., Elander, A., Mark, H. *A systematic comparison of the incidence of various complications in different delayed breast reconstruction methods.* **Journal of Plastic Surgery and Hand Surgery.** 2015; 50(1): 25-34.

II. Thorarinsson, A., Fröjd, V., Kölby, L., Modin, A., Lewin, R., Elander, A., Mark, H. *Blood loss and duration of surgery are independent risk factors for complications after breast reconstruction.* **Journal of Plastic Surgery and Hand Surgery.** 2017; doi: 10.1080/2000656X.2016.1272462. [Epub ahead of print].

III. Thorarinsson, A., Fröjd, V., Kölby, L., Lidén, M., Elander, A., Mark, H. *Patient determinants as independent risk factors for postoperative complications of breast reconstruction.* **Manuscript accepted in Gland Surgery.**

IV. Thorarinsson, A., Fröjd, V., Kölby, L., Ljungdal, J., Taft, C., Mark, H. *Long-term health-related quality of life after breast reconstruction: Comparing four different methods of reconstruction.* **Manuscript accepted in Plastic and Reconstructive Surgery, Global Open.**

CONTENT

ABBREVIATIONS

Ais	Aromatase inhibitors
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
BRCA	Breast cancer susceptibility gene
CC	Creative commons
CI	Confidence interval
DI	Direct implant
DIEP	Deep inferior epigastric artery perforator
DVT	Deep vein thrombosis
EQ-5D	EuroQol five dimensions questionnaire
EXP	Expander / implant
HR-QoL	Health-related quality of life
LD	Latissimus dorsi
LSD	Least significant difference
LTDF	Lateral thoracodorsal flap
NAC	Nipple/areola complex
OR	Odds ratio
PGWB	The Psychological General Well-Being Index

PROM	Patient reported outcome measure
PRS	Plastic and Reconstructive Surgery journal
SD	Standard deviation
SF-36	Short form 36 health survey
SPSS	Statistical Package for the Social Sciences
TRAM	Transverse rectus abdominis muscle
VAS	Visual analogue scale

DEFINITIONS IN SHORT

Dependent variable	A variable whose value depends on that of another variable.
Domain of PROM	The condition, skills or abilities being measured by a questionnaire or PROM.
Independent variable	A variable whose variation does not depend on that of another variable.
Latent variable	An underlying construct that is not measured directly but rather through several items in a PROM measure reflecting that construct.
Rasch measurements	A statistical method of measurements of latent traits, like attitude or ability. Used in scoring of the Breast-Q questionnaire.
Reliability	The overall consistency of a measure. The degree to which test scores are consistent from one test administration to the next.
Type I error	The incorrect rejection of a true null hypothesis; false positive results.
Validity	The extent to which a concept, conclusion or measurement corresponds accurately to the real world.

1 INTRODUCTION

Breast cancer

Breast cancer is the most common invasive cancer in women. It accounts for 22.9% of all invasive cancers in the female population.[1,2] Most cases of breast cancer are sporadic, however, approximately 2-3% of breast cancers are genetic, caused by the breast cancer genes BRCA1 and 2.[3,4] Certain gene mutations associated with breast cancer are more common among certain geographic or ethnic groups, such as Ashkenazi Jews and people of Icelandic, Norwegian and Dutch ancestry.[5]

The incidence and mortality of breast cancer is increasing in developing countries, although in Europe and North America the mortality rate is stable or slightly decreasing.[6-10] In Sweden, the incidence has more than doubled since 1958, when the cancer registry of the National Board of Health and Welfare started.[11] As treatment modalities have improved, about 90% of women in the USA survive for at least five years after the diagnosis,[12] which increases demand for breast reconstructions.[13,14] Breast reconstructions are therefore becoming more frequent,[15,16] and in Gothenburg, Sweden, approximately 40% of women undergo breast reconstruction after mastectomy.[17]

A third of women treated with mastectomy have persistent psychosocial morbidity, with reduced self-esteem, insomnia, increased anxiety, depression, disturbed body image and/or sexual problems.[18-21] Both primary and secondary breast reconstructions benefit the patient in terms of increased self-esteem and health-related quality of life (HR-QoL) compared with no reconstruction.[22-25]

Different methods are used for breast reconstruction, and the preferred method varies between centres and surgeons. At Sahlgrenska University Hospital, Gothenburg, five different surgical treatments have mainly been used: (1) deep inferior epigastric perforator flap (DIEP),[26] (2) latissimus dorsi flap (LD),[27] (3) lateral thoracodorsal flap with silicone implant (LTDF),[28] (4) tissue expander with a secondary silicone implant (EXP),[29] and, when soft tissue permits (5) direct

augmentation with silicone implant (DI), however, this method was abandoned after 2009.

Breast cancer treatment

Surgery

Surgery is always a part of treatment for breast cancer. The American surgeon William Halsted performed the first radical mastectomy in 1892, and proved this method to be the best treatment of breast cancer at the time. Halsted's report from 1894, which summarized the outcome for the first 50 cases, showed better results than any previously published data. The axillary lymph nodes and both the pectoralis major and minor were excised *en bloc*, and the defect was reconstructed with a skin transplant (Figure 1). It should be noted that when Halsted began the radical mastectomy era, breast cancer was basically incurable. Radical mastectomy, therefore, became the therapy of choice. Nevertheless, some women refused this treatment due to the postoperative deformation of the chest.

Radical mastectomies were carried out until the 1970s. As late as 1972, it was used to treat 47.9% of breast cancer patients in the USA. It would later gave way for modified radical mastectomy and, later, breast conserving therapy.[30]

In the early 1930s, the modified radical mastectomy was introduced. The pectoralis major was spared, but all the skin was excised, and the defect was still reconstructed with a skin graft. In the 1950s and later on, many studies compared the results of radical mastectomy and modified radical mastectomy, and found no difference in cure rates. Later research showed no difference in cure rates between modified radical mastectomy and lumpectomy with radiotherapy, thus paving the way for breast-conserving therapy. [28]

In Europe and the USA, as in Gothenburg, about half of the patients diagnosed with breast cancer choose breast-conserving therapy with lumpectomy and radiotherapy.[17]

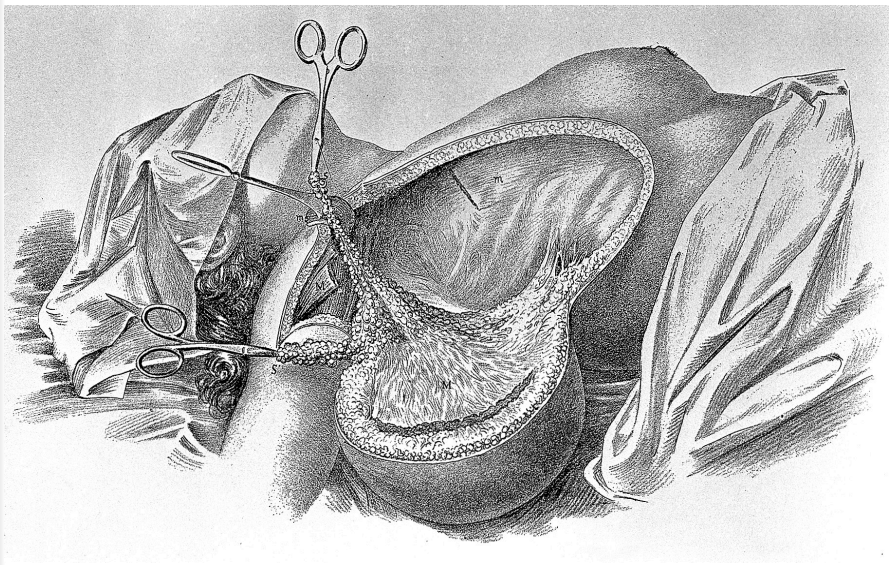

Figure 1: A Halsted mastectomy[a]

Adjuvant therapy

The use of cytotoxic chemotherapy is common, in both the early and late stages of breast cancer. Despite better understanding of the use of adjuvant treatment in the early stages, the treatment of metastatic disease has not come as far. However, while being incurable, metastatic disease is often sensitive to chemotherapy, especially early in the disease process.

Radiotherapy after breast cancer is comparable to surgery in that it is a local treatment. It is used together with breast-conserving surgery to limit the surgical defect or if the tumour is large or of an aggressive nature. The target of radiotherapy is the breast area, with or without the thoracic wall, and/or the axillary lymph nodes. Radiotherapy significantly decreases the risk for local and regional recurrence especially in patients with tumours that are liable to reoccur.[31,32]

[a] *Author: William Stewart Halsted. From: http://wellcomeimages.org/ indexplus/image /L0004968.html. Licence: CC-BY 4.0*

Breast cancer cells can have receptors for hormones, such as oestrogen or progesterone. Oestrogen binds to these receptors stimulating cell proliferation. If the receptors are blocked or the levels of oestrogen are minimized, cancer growth may be slowed down or even stopped. Two types of medication are used as adjuvant hormone therapy: oestrogen receptor blockers (tamoxifen) and aromatase inhibitors (AIs). Tamoxifen inhibits oestrogen receptors in cancer cells,[33] while AIs block the capability of the aromatase enzyme to produce oestrogen and is more commonly used in postmenopausal women.[34]

Breast reconstructions

Flaps

The first documented breast reconstruction was conducted in 1895, when Vincent Czerny, professor of surgery in Heidelberg, Germany, transplanted a large lipoma to the thoracic wall, replacing the mastectomized breast. Breast reconstructions were avoided for a long time because of Halsted's opposition. He argued that breast cancer was a regional entity, and if breast reconstruction was done it would be a "violation of the local control of the disease."[35-37] Several techniques were introduced during the first half of last century using "walking" tube flaps, either from the contralateral breast or the abdomen. Sir Harold Gilles used a flap from the abdomen when performing his first breast reconstruction in 1942. However, the technique was associated with multiple procedures, extensive donor site morbidity, and occasional flap failures.[35,36]

The latissimus dorsi flap

In 1979, the LD flap was introduced for single stage reconstruction of mastectomy defects.[27,38] During the procedure, the patient is first placed in the lateral decubitus position. Incisions are made round a skin island in the back. Then, the entire latissimus dorsi muscle is

dissected free from its origin at the iliac spine and the vertebrae, while the humeral attachments of the muscle are left intact along with its thoracodorsal vessels and nerve. Some surgeons dissect the thoracodorsal nerve and divide it in order to decrease the risk for breast animation postoperatively. A tunnel is made from the mastectomy scar to the axilla and the flap is then transferred to the front. The patient is then turned to the supine position and the breast is reconstructed in combination with a silicone implant (Figure 2).

The LD flap remains a workhorse flap in reconstructive breast surgery, despite the incidence of donor-site morbidity.[27,39]

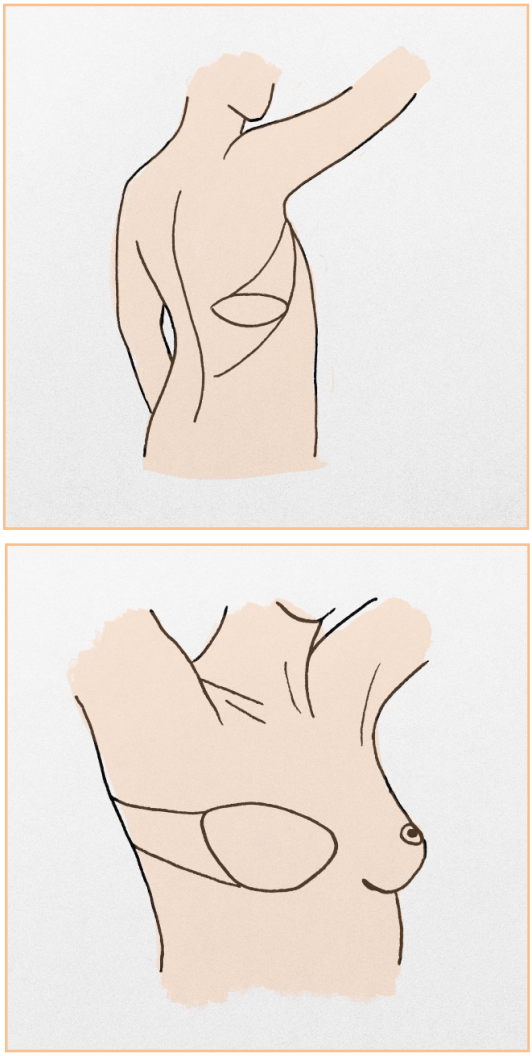

Figure 2: The latissimus dorsi flap

The lateral thoracodorsal flap

The LTDF was first published in 1986 in the Plastic and Reconstructive Surgery (PRS) journal.[28] The flap can be used in both primary and secondary breast reconstruction with or without an implant. It is considered a one stage procedure, with an implant after mastectomy, but can also be used to reconstruct lateral defects of breasts after large lumpectomies without an implant.[40,41] The flap is designed laterally of the mastectomy area, with its inferior border a few centimetres under the new inframammary fold. The flap is then raised, making sure the deep muscle fascia is included in the flap, and is rotated from a horizontal to a vertical position, thereby adding the tissue of the flap to the mastectomy site. A pocket is then dissected under the pectoralis major muscle, which is released from its inferior attachment. Finally, an implant is placed under the muscle (Figure 3).

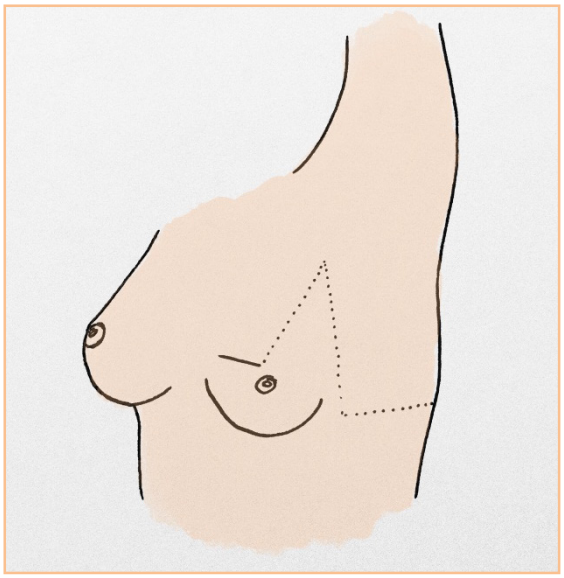

Figure 3: The thoracodorsal flap

The TRAM flap

The pedicled TRAM flap was introduced in 1982.[42] It is widely used and remains a workhorse flap for autologous breast reconstructions in many centres.[35] During the procedure, all skin and fat from the umbilicus to the pubis bone is dissected free from the muscle fascia, except for one side of the rectus abdominis muscle, where the perforating vessels enter the subcutaneous tissue from the epigastrica profunda through the muscle. The rectus abdominis is divided inferiorly and the muscle is dissected free from the deep muscle fascia.

This way, the muscle acts as a pedicle for the flap tissue. The flap is then tunnelled to the breast area and shaped as a breast.

Refinements of the TRAM flap lead to the development of the muscle sparing free TRAM, in which a small segment of the rectus abdominis muscle is included in the flap, the vessels are cut and a microsurgical anastomosis is carried out at the recipient site.[43]

The DIEP flap

Later, the DIEP flap was introduced, in which no muscle is included and the motor nerves to the rectus abdominis muscle are retained.[44,45]

A DIEP flap procedure involves two surgical teams. One team opens the mastectomy scar, identifies rib III or IV, resects the rib cartilage and isolates the mammaria interna vessels. The other team dissects the perforator through the rectus abdominis muscle, and follows the deep inferior epigastrica profunda vessels down to the inguinal area. The vessels are then ligated, the flap is usually rotated 180° and the vessels are microsurgically anastomosed to the mammaria vessels. The tissue is then shaped to the new breast (Figure 4).

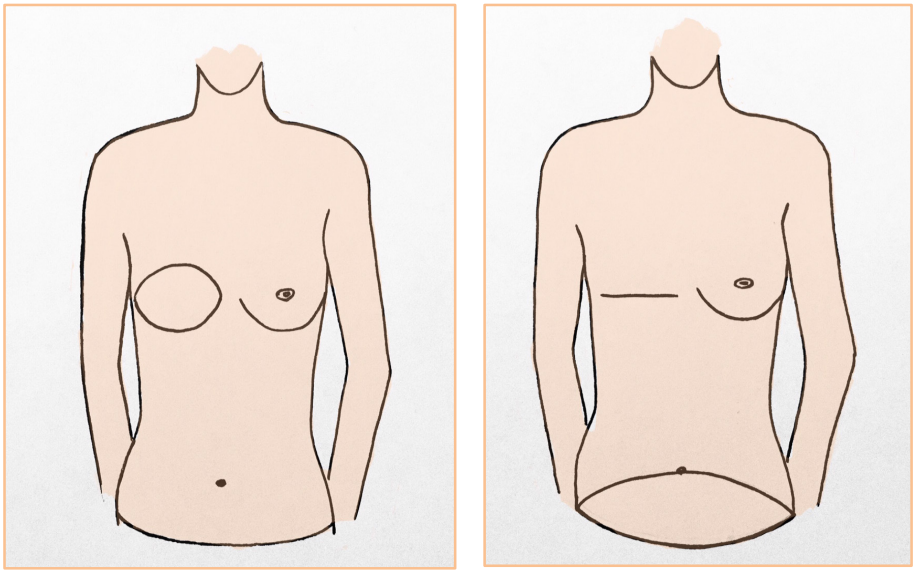

Figure 4: The DIEP flap

Studies have shown that DIEP flaps have slightly higher risk of flap necrosis compared with the TRAM flaps, but the TRAM flaps have higher risk of abdominal complications.[46] Reports state that patients receiving a DIEP reconstruction, are more satisfied compared with patients receiving an implant based reconstruction.[47,48]

Other flaps (TFL, SGAP, IGAP, TUG flap)

Several other free flaps have been introduced for breast reconstruction. The tensor fascia lata (TFL),[49] superior gluteal flap (SGAP),[50] inferior gluteal flap (IGAP),[51] transverse upper gracillis flap (TUG)[52] and Reuben´s flap are examples.[36] These flaps are not as widely used due to the need for complicated positioning of the patient during the surgery. For unilateral reconstructions, the donor sites for these flaps are not symmetrical and can therefore cause deformities.

Breast reconstructions – Implants

The first attempts to perform autologous breast reconstructions were associated with difficulties and often caused considerable donor-site morbidity. As a result, there has been substantial interest in synthetic materials that could be used for breast reconstruction.

Prosthetic materials have many advantages and have a long history. Many different materials have been adopted, but few have gained popularity. Robert Gersuny, an Austrian surgeon, was the first who tried to augment a breast with paraffin in 1889.[37] Other examples of materials that have been used are petroleum jelly, vegetable oils, lanolin, ivory, ox cartilage, ground rubber, terylene wool, gutta-percha, polyethylene chips, polyethylene tape, silastic rubber, polyurethane foam sponges, beeswax, glass balls, teflon- silicone prosthesis and Ivalon gauzes.[36] These materials frequently cause an immunological reaction, and serious complications, such as lung emboli, skin necrosis, chronic infections and extensive scar tissue.[37]

The silicone implant was first introduced by Cronin and Gerow in 1961 and was first used for breast augmentation in 1962. However, silicone implants did not achieve early popularity for breast reconstructions since most breast cancer patients had a defect after a

Halsted radical mastectomy.[36] The first generation of implants in the 1960s had a thick and durable untextured shell and high viscosity gel. Many patients found these implants inflexible. In the second generation implants, introduced in the 1980s, the shell was thinner and softer and the silicone gel had lower viscosity. Because of the softness, a shorter incision was possible and the augmented breast was soft. However, if the implant ruptured, the gel leaked out causing granuloma formation and foreign body immunological reactions. Therefore, the third generation of implants had a thicker shell again, and higher gel viscosity.[37]

Breast reconstructions with implants were initially performed as a one-stage procedure. This changed in the early 1990s when tissue expanders were introduced. This gave opportunity for both primary and secondary breast reconstruction with more flexibility to choose the size and shape of the reconstructed breast. However, in this major advantage lies a significant weakness; an expander reconstruction is always a two-stage procedure.

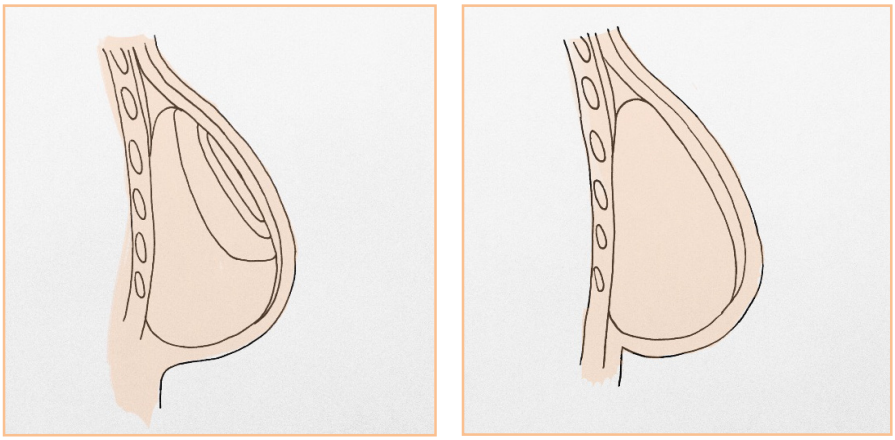

Figure 5: An expander and an implant

Implant reconstruction with an expander followed by a permanent implant is the most common method for breast reconstruction at the Department of Plastic Surgery, Sahlgrenska. In the first stage, an incision in the mastectomy scar is made, a pocket under the pectoralis major muscle is dissected and the origin of the muscle inferiorly and the lowest quarter of the sternal attachment is released. The low height tissue expander is then inserted and gradually filled with saline during

the following weeks. After a three-month waiting period, the expander is replaced with a permanent implant (Figure 5).

Complications after breast reconstruction

Complications after breast reconstruction are common, consume considerable resources every year[53-62] and affect the patient's emotional well-being and level of satisfaction.[57,63-66] Many suffer from possibly avoidable complications. Patient satisfaction and health-related quality of life are frequent parameters in outcome measurement in plastic surgery. This emphasizes the importance of efforts to identify and reduce the possible risks for complications.

The risk for complications can be related to several factors. The surgical method itself is of importance since different methods have different spectra of complications.[67] The selection of patients is also of importance where certain patient characteristics (e.g. age, smoking habits, obesity, and adjuvant cancer therapy) must be considered.[54,58,68-72] Once the individualized choice of reconstruction method is made, the surgical procedure must be optimized with respect to perioperative factors such as the duration of surgery, blood loss and skills of the surgeon.

The choice of method as a risk factor for complications

In order to better understand and compare the frequency of different complications between different breast reconstruction methods, it is important to use the same definitions of complications. However, there is a need for studies that systematically investigate and compare the incidence of complications in different reconstruction methods where the same definitions for complications are used. Studies on the frequency of complications after breast reconstruction have mostly compared inadequate numbers of surgical methods and included limited numbers of patients.[45,55,57,73-89]

Perioperative factors

Studies show that prolonged duration of surgery is a risk factor for tissue expander loss,[90,91] increases risk for unplanned admission after ambulatory plastic surgery[92] and has a high correlation with other complications, such as fat necrosis, skin necrosis and infection.[93,94] Other studies have failed to show a relationship between duration of surgery and hematoma,[95] or other postoperative complications, such as wound complications, flap failure, thromboembolism or respiratory complications.[96-99] On the other hand, a study by Rambachan and co-workers shows that the duration of surgery, measured in 30 minute intervals, is an independent risk factor for complications but that it does not affect mortality.[94]

Studies of blood loss in the field of plastic surgery are few. Regarding breast reconstruction, one study shows no correlation between several patient characteristics and blood loss.[93] However, another study, analysing the relationship between perioperative blood transfusion and complications, finds a strong correlation, but blood loss is not directly studied.[75]

It has been established that more experienced surgeons have lower complication rates, both in plastic surgery and in other specialities.[100-102]

Patient-related factors

Several studies have examined the relationship between patient characteristics and complications,[54,58,69-72] but the results are not conclusive.

Radiotherapy has been shown to adversely affect outcomes after an implant-based reconstruction, with increased late failure rates,[57,68,103] poor aesthetic results, loss of symmetry,[104-106] capsular contraction and infection, even with the latest generation of implants and modern radiotherapy.[57,61,68,85,103,105,107-113] However, the results from studies on radiotherapy and autologous reconstructions are more conflicting. Certain studies find that radiotherapy of a breast reconstructed with a DIEP or a TRAM flap has no effect,[114,115] while others show a

considerable negative effect on the final results.[113,116-121] Reconstruction with autologous tissue in an irradiated patient does not seem to increase the risk for adverse events.[47]

Studies on the effect of chemotherapy on complications after delayed reconstructions are scarce, and not in agreement. On one hand, adjuvant chemotherapy is reported to be associated with a higher rate of complications and reconstruction failure than radiotherapy,[109] and another study shows a trend towards more complications in TRAM flaps in patients who have had chemotherapy.[53] A third study shows an association between preoperative chemotherapy and infection during expansion.[122] On the other hand, several other studies show no association between adjuvant chemotherapy and adverse events after breast reconstruction.[82,103,123] Preoperative chemotherapy has also been shown to decrease satisfaction with breast(s), measured with the Breast-Q questionnaire.[100]

There is no general agreement on whether adjuvant hormone therapy increases the risk for complications or not. Some studies show an association with overall complications,[124] especially capsular contraction,[107,125] while other studies have shown no such association.[109,126-129]

It is well established that high BMI increases the risk for surgical complications and overall morbidity. This is true for both the donor and recipient sites, for both implant and autologous reconstruction, for immediate and late reconstruction and for the use of an acellular dermal matrix.[77,80,84,90,122,130-135] A high BMI also has an association with adverse effect on body image after prophylactic mastectomy with immediate breast reconstruction.[136] While general satisfaction is not decreased in obese patients undergoing an implant based breast reconstruction, they have less aesthetic satisfaction. This difference is not seen in patients undergoing autologous reconstruction.[136-138]

It is well established that smoking can have a detrimental effect on free flap breast reconstruction,[45,58,59,72,87,139,140] even if some studies have failed to find this relationship.[43,56,141,142] The same seems to be true for implant based reconstructions,[71,82,88,107,143,144] even if not all studies confirm the findings.[122]

Numerous studies show no relationship between age and risk for complications,[43,45,72,96,141,142,145-149] while some other studies show that elderly patients have increased risks.[71,90,143]

Diabetes has been associated with postoperative complications after autologous reconstruction; however, the results after implant-based breast reconstruction are more conflicting.[47,122,150,151] Noninsulin-dependent diabetes is associated with surgical complications, both in autologous and implant reconstructions. Insulin-dependent diabetes is associated with medical and overall complications.[169] However, other studies have failed to find any association between diabetes and any postoperative complications.[152]

Other patient-related factors

Patients with renal disease seem to be prone to postoperative complications in plastic surgery.[151,153] Very little has been written on the relationship between a history of DVT and postoperative complications, but one study shows an increased risk for thrombosis after free flap surgery in hypercoagulative patients and a very low salvage rate of the flaps.[154] Some studies have shown a connection between silicone implants and several rheumatic- and neurologic diseases[155]; however, most studies have shown the opposite.[156-159]

Health-related quality of life

Science has always focused on measurable variables such as mortality and morbidity. With better technology, researchers have been able to measure objective variables with greater precision. This has led to considerable advances in treatment options for different diseases.[160]

However, traditional measures have still not been able to measure important subjective psychological experiences, such as satisfaction with life, social relations, security, commitment and interests in the future.[161] Traditional measurements are also insufficient at evaluating very common diseases like most mental illnesses.[161] The relationship

between medical, objective measurements and subjective experiences are often weak or non-existent.[162]

Modern medical care can consume almost unlimited resources. The demand for prioritizing different treatments or examinations is increasing, and resources need to be allocated where they benefit as many people as possible.[163] For this to become reality, traditional, objective measurements are inadequate.[160]

The conditions for measurements of HR-QoL are:

- A well-defined concept or phenomenon to be investigated
- A group of patients or other subjects of interest
- A HR-QoL instrument to measure the concept of interest[164]

There is a vast number of instruments for measuring HR-QoL, which can be classified into either generic or disease-specific.[165,166] The generic ones, such as the SF-36, are aimed at a wide range of patients regardless of age or health status, and are intended to be relevant to the general population.[167] However, they are insensitive when studying subgroups or how certain conditions change over time. The specific ones are oriented towards a specific disease or treatment and can more precisely measure conditions of smaller groups where a general instrument would not show significant change.[168-170] On the other hand, the disease-specific questionnaires cannot measure general health in a large population of people.

If the intention is to draw conclusions for a larger group than only the group answering the questionnaire, the instrument needs to be sensitive, reliable and valid.[171]

Although life-saving interventions sometimes occur in reconstructive plastic surgery, the primary goal is to improve the patients' quality of life. It is relatively easy to measure certain variables, such as amount of breast tissue surgically removed or relapse of skin tumours in the face, but it also is essential to measure changes in HR-QoL when evaluating the results of a given treatment.[172]

All HR-QoL questionnaires are composed of multiple questions that are selected by a validity process. None of the individual items can directly measure the variable of interest. Therefore, no single HR-QoL instrument can be the *best* instrument in all situations. This is particularly true in plastic surgery.

Questionnaires

General information on PROMs

Psychometrics is the discipline in psychology that deals with design, administration and interpretation of quantitative tests for the measurement of psychological variables.[173] Psychometrics use patient-reported outcome measures (PROMs) as an instrument for measuring the subject of interest.

PROMs are a broad concept, which may include terms such as fatigue, depression or pain or physical symptoms like nausea and vomiting.[174,175] A PROM consists of one or more items. An item is a question whose answer is the manifestation of an underlying variable or construct,[174] which is of interest for the researchers. Several items reflecting one construct are often used to increase reliability. Scales are then constructed from the responses of the collection of items. They are intended to reveal the level of an underlying variable, which is not readily observable by direct questions.[176] A questionnaire can consist of several scales and items (Figure 6).

Each question in an HR-QoL questionnaire is an expression for each item. Some of these items can be simple assessments of HR-QoL related issues, such as a physical symptom. Other HR-QoL concepts of interest are more complex, and frequently it is necessary to use several items, which in combination can shed light on the concept of interest, the so-called latent variable. The latent variable is a construct that cannot be directly measured by a single observable variable or item. It is rather indirectly measured with multiple items in a multi-item scale.[177]

Some psychological aspects of HR-QoL have a definite, explicit, and universally agreed definition. Example of this is stress, which manifests in both physiological and psychological symptoms. Other psychological aspects can be argumentative, and it may even be debated whether the psychological concept really exists as a separate concept or entity that can be measured. An example of this can be measurements of a fulfilling life or the perceived degree of autonomy in life.

Difficulties in collecting data and getting patients to answer questionnaires are common in clinical trials.[178] Bias in the results of the PROM may arise due to missing data, either because the responders skip certain questions or do not follow the instructions given by the researchers.[166] If the missing data is systematic, e.g. many responders omit the same question, the results of the PROM cannot be representative of the entire group, but only of the group that answers the question. The consequences are, that the results of the study cannot be considered reliable. However, if the missing data can be considered as entirely random, then the analyses performed on the data may not be biased, but are dependent on the number of responses.

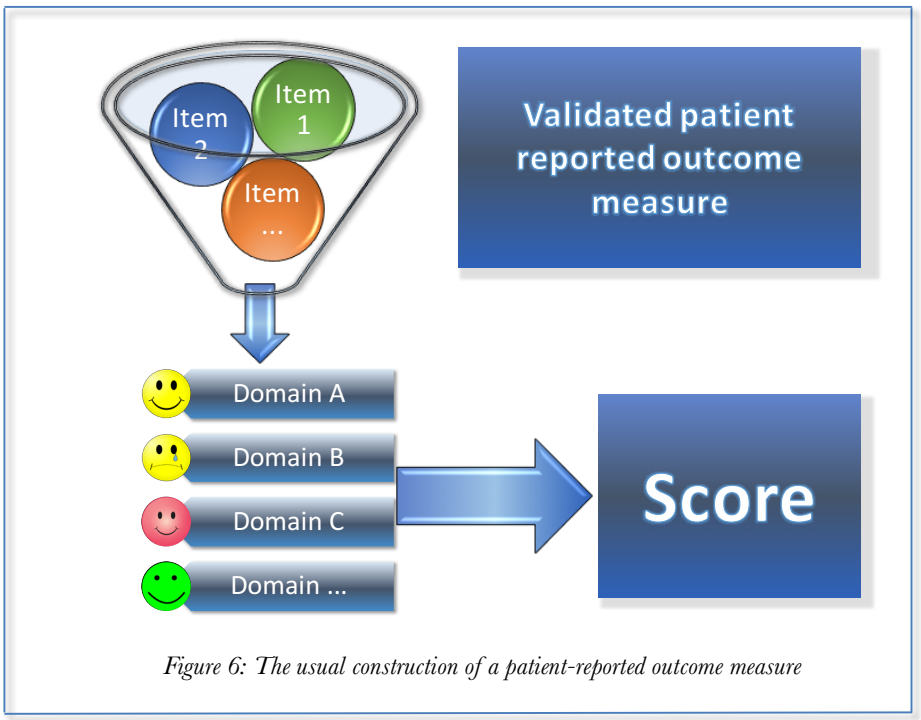

Figure 6: The usual construction of a patient-reported outcome measure

If the group of responders is large enough, there is the possibility of discovering minimal changes in the average level of HR-QoL; miniscule changes that are of little relevance to the individual patient.[166] If, however, the group of responders is small, there have to be considerable changes in the PROM to be able to obtain statistically significant results.[179]

SF-36

The SF-36 is a *Short-Form health questionnaire* constructed of 36 items. The 36 items are brought together in 8 functional health and well-being domains (Figure 7). The scales are then aggregated into two summary measures of *Physical health* and *Mental health*. Each item belongs to only one scale. Three of the domains (*PF*, *RP*, and *BP*)

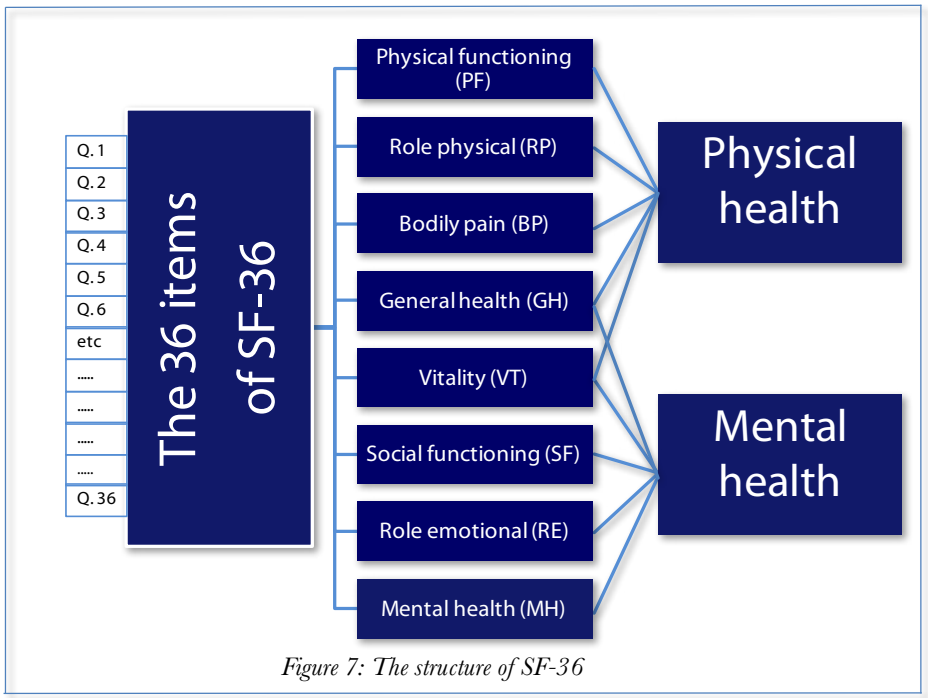

Figure 7: The structure of SF-36

correlate highly with the physical health and contribute the most to the *Physical Component Summary (PCS)* scale. Three of the domains (*SF*, *RE* and *MH*) highly correlate with mental health and contribute the most to the *Mental Component Summary (MCS)* scale. Two of the scales (*GH* and *VT*) have a good correlation with both *PCS* and *MCS*.[167,180] SF-36 is a generic PROM, intended for large populations.[181]

EuroQol five dimensions questionnaire (EQ-5D)

The primary objective in the development of EQ-5D was to develop a scale that would be general and not specific to a certain disease.[182] It consists of five general questions: *mobility*, *self-care*, *usual activities*,

pain/discomfort and *anxiety/depression*. Each question has three levels: no problem, some problem or a significant problem. On the second page of the questionnaire is a 20 cm vertical, visual analogue scale (VAS) where at the top is "best imaginable health state" and at the bottom is "worst imaginable health state." The VAS scale gives quantitative information that can be used as a measure of health outcome for the responders.

The EQ-5D has been extensively used in both general populations and patient samples. Since three levels are used for each dimension, the scale has been criticized for "ceiling effects," i.e. not being able to measure small differences in health states or in patients with mild conditions. As a response to this criticism, the new, more detailed scale has been designed with five levels; having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problems.[183]

The EQ-5D has been used for breast cancer patients.[184] It is infrequently used as a single scale, but usually in combination with other more specific PROM scales.

The Psychological General Well-Being Index (PGWB)

PGWB measures the subjective perception of psychological general well-being and psychological symptoms. It is used to assess psychological well-being and quality of life in large groups and patients with chronic diseases. It is composed of 22 items and includes six dimensions: *anxiety*, *depressed mood*, *positive well-being*, *self-control*, *general health* and *vitality*.[185] A Swedish version has been developed,[186] and values for the general population are available. Analysis of general populations has shown that women have a lower score than men.[187]

The PGWB is considered to be useful to assess the differences between different types of treatment. However, it does not detect clinically meaningful differences in well-being as sensitively as a disease-specific PROM. Therefore, it is often appropriate to use the PGWB in combination with other specific questionnaires.[185]

The Breast-Q

Pusic et al. published a review article in 2007 examining 223 PROMs in plastic surgery and showed that only 7 of them met criteria of psychometric evidence for use in patients having breast surgery.[188] One of the modules of the Breast-Q questionnaires was specially developed and validated using a meticulous methodology with focus groups, expert panels, patient interviews, and detailed literature reviews to evaluate outcome after breast reconstruction. This includes the use of Rasch measurement methods and building scales from the perspective of psychometric analyses.[189,190]

In the development of Breast-Q, the aim was to construct a model which could capture the entire reconstructive process and obtain a representative picture of the patient's whole experience, both in terms of the effect on HR-QoL and satisfaction with the results (Figure 8).[191,192]

The Breast-Q is built on two underlying themes: HR-QoL and patient satisfaction. Each of these have the subthemes of *physical*, *psychosocial* and *sexual well-being*, and *satisfaction with care*, *satisfaction with breasts* and

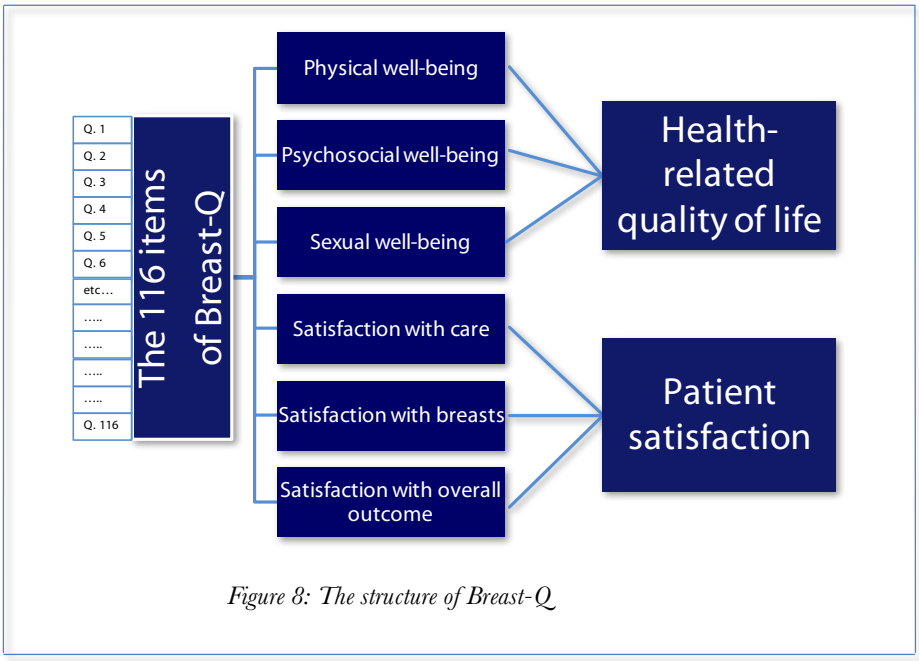

Figure 8: The structure of Breast-Q

satisfaction with overall outcome.[193] The Breast-Q questionnaire scales are developed from the subthemes.[194] It is not necessary to use all the scales of Breast-Q at once. There is the possibility of using one or a few of the scales, for example if the focus is on measuring the quality of care provided by the office staff.[191]

2 AIMS

The aims of this thesis are:

1. To systematically examine complications after breast reconstruction with regard to each of the reconstructive methods used.

2. To find independent perioperative risk factors for complications.

3. To find independent patient-related risk factors for complications.

4. To examine the effect of breast reconstruction on health related quality of life

3 PATIENTS AND METHODS

Study samples

A list of all patients who had undergone any type of breast reconstruction was obtained using the Operätt (C&S Healthcare Software AB, Mölndal, Sweden) software, which is the planning and database management application of the Dept. of Plastic Surgery´s operation theatres at Sahlgrenska University Hospital. The study period started from the year 2003, since that year Sahlgrenska began using electronic medical records that were easily accessible by the researchers. The end of 2009 was chosen as the end point, since from 2010 onwards a prospective randomized study on the four most common methods of breast reconstruction has been running.

In the next step, a FileMaker database (Filemaker Inc., Santa Clara, CA) was designed, which aimed to capture the entire reconstructive process from first referral to last follow-up visit. Numerous variables were collected for each patient (Table 1). A relatively large number of patients in the database had only undergone cosmetic corrections, reconstruction of the nipple/areola complex (NAC), or were lacking follow-up data for more than 30 days and were therefore excluded.

Data on the parameters of interest was then extracted from the database. The inclusion and exclusion criteria were not identical between the studies; therefore, there is a difference in the number of patients in each study even if they come from the same pool.

In Paper I, the study group was patients receiving first-time reconstruction with one of the 5 most common methods of delayed reconstruction used at the Department during the study time. This gave a total of 685 patients.

As the method of DI was abandoned during the study period, it was decided for Paper II and III to omit this group and only use the more common methods of DIEP, LD, LTDF, and EXP. This gave a total of 623 patients.

Data collection		
Name	Date of first referral	Pharmaceutical used
Social security number	Surgeon making first assessment	ASA
Address	ASA classification	Anticoagulants
Age	Previous diseases	Adjuvant hormone therapy
Smoking	Heredity for breast cancer	Corticosteroids
BMI	Bleeding disorder	Breast cancer surgery
Length	Diabetes	Sector resection
Weight	Rheumatic disease	Mastectomy
Chemotherapy	Lung disease	Direct reconstruction
Radiotherapy	Heart disease	Contralateral breast
Previous reconstruction	Renal disease	Mastopexy
Breast reconstruction method	Liver disease	Breast reduction
DIEP flap	Hypothyroidism	Breast augmentation
Latissimus dorsi flap	Neurologic disease	Other
Lateral thoracodorsal flap	DVT or lung embolus	Early follow up (< 30 days)
Expander / implant	First operation	Date
Direct implant	Date	Surgeon making assessment
Other	Surgeon	Reoperation
Late follow-up	Assistent 1	Signs of infection
Same factors as early follow-up	Assistent 2	Antibiotics administered
Dogears	Duration of surgery	Bacterial culture taken
PAD	Operation codes	Complication of mammilla
Scar problems	Antibiotic prophylaxis	Fat necrosis
Implant replacement	Blood loss during surgery	Skin necrosis
Questionnaires	Drains	Wound rupture
SF-36	Implant (kind of implant)	Hematoma
EQ-5D	Transexam acid adm.	Seroma
PGWB	Desmopressin adm.	Pneumonia
Breast-Q	Reoperation	Pneumothorax
Follow-up time in months	Days of admittance	Blood transfusion
Date of first operation	Second operation	DVT or lung embolus
Last follow-up visit	Same factors as first operation	Local of complication
Included in study	Third operation	Surgical treatment for complications
Yes / no	(etc.)	Implant event

Table 1: Data collection for the database

In the analysis of satisfaction and HR-QoL, it was decided *not* to exclude patients who had previously been reconstructed. Therefore, there are a total of 685 patients in Paper IV. That this number of patients is the same as in Paper I is purely coincidental.

Patient data, from the first referral to last follow-up visit, were collected from the medical softwares Melior (Siemens Health Care, Upplands Väsby, Sweden) and Operätt.

Data extraction, Paper I

Paper I was a retrospective single-centre study of patients with breast cancer who had undergone unilateral mastectomy and who were surgically treated with unilateral breast reconstruction procedures at the Department between 2003 and 2009.

The inclusion criteria were first-time unilateral reconstruction with one of five different methods of delayed breast reconstruction: (1) DIEP, (2) LD, (3) LTDF, (4) EXP, and (5) DI; and the availability of data on at least 30 days of follow-up (Table 2).

Inclusion criteria:	
First time delayed reconstruction with:	DIEP flap
	Latissimus dorsi flap
	Lateral thoracodorsal flap
	Expander with secondary implant
	Direct implant
Exclusion criteria:	
Data from follow up < 30 days	

Table 2: Inclusion and exclusion criteria, Paper I

Exclusion criteria were data from a follow-up time of less than 30 days, if the patient was still under treatment or if only procedures other than first time reconstruction had been performed.

Table 3 displays the data extraction for Paper I.

Paper I	
Demography	Main procedure
Age	Duration of surgery
BMI	Blood loss during surgery
Smoking	Hospital stay
Chemotherapy	Total number of procedure
Radiotherapy	Total duration of surgery
Previous reconstruction	Total hospital stay
Pharmaceutical used	Complications
Concurrent diseases	Early
Follow-up time	Late

Table 3: Data extraction, Paper I

Early complications	Definition
Overall complications	All events of registered complications
Signs of infection	Induration, redness, wound discharge, pus, and/or systemic signs of infection
Administration of antibiotics	Postoperative antibiotics administered during follow-up of ≤ 30 days
Overall local complications	Fat necrosis, skin necrosis, hematoma, seroma and wound rupture combined
Fat necrosis	Non-infectious firmness, redness, or non-infectious discharge from wound
Skin necrosis	Necrosis of skin of flap or recipient site of reconstruction
Hematoma	Localized collection of blood in donor or recipient site, regardless of need for reoperation
Seroma	Collection of serous fluid in donor or recipient site
Wound rupture	Opening of surgical wound without an infectious cause or skin necrosis
Resurgery	Postoperative surgical procedures to treat complications during follow-up ≤ 30 days
Late complications	**Definition**
Same as early complications	*Same definitions, but with onset > 30 days*
Scars in need of treatment	Need for silicone compression dressings, steroid injection, or scar revision
Dog-ears	When diagnosis was recorded in the patient's medical record
Resurgery	Surgical procedures to treat complications or secondary cosmetic corrections

Table 4: Registered complications and their definitions, Paper I - IV

Reconstruction of the NAC was not specifically registered since not all patients requested this procedure. In the EXP group, the first and second procedures were compiled for all perioperative and follow-up parameters. Follow-up parameters and complications encountered were divided into early (≤30 days after surgery) and late (>30 days after surgery). Registered complications and definitions are displayed in Table 4.

Data extraction, Papers II and III

As the method of DI was omitted for Paper II and III, the number of patients enrolled to the study was lower than that in Paper I. This also resulted in slightly different demographic variables for the *overall* group compared to Paper I; these variables were, of course, the same for each method group.

Inclusion and exclusion criteria, registration of pharmaceuticals and concurrent diseases was the same as in Paper I. Definitions of complications were the same as in Paper I and follow-up parameters and complications encountered were registered in the same way.

Additionally, perioperative parameters registered were the name of the surgeon, duration of surgery (measured from the first incision to the last stitch) and blood loss during surgery (volume of blood in the suction system and the weight of gauzes used).

Study sample and data extraction, Paper IV

Table 5 displays the data extraction for Paper IV. The same demographical factors as for Papers I-III were collected. Registration of pharmaceuticals and concurrent diseases were the same as in Paper I.

Paper IV	
Demography	
Reconstruction method	Years from primary surgery
Age	Follow-up time
BMI	ASA Classification
Smoking	Complications
Chemotherapy	Early
Radiotherapy	Late

Table 5: Data extraction, Paper IV

Only patients who responded to the HR-

QoL questionnaires were enrolled. Exclusion criteria were the same as in Paper I-III.

Additionally, the number of years from primary reconstructive procedure to submitted questionnaires, follow up-time in months from first referral to last follow-up visit and scores of The American Society of Anaesthesiologists (ASA) physical status classification system were collected.[195]

Statistics

Statistics of Paper I

Patient and perioperative data were treated as independent variables. Statistical analyses were performed with SPSS (IBM, Armonk, NY) in all of the papers of this thesis. For the continuous scale parameters (BMI, follow-up times, blood loss during surgery, duration of surgery and hospital stay) the Kruskal-Wallis and Mann-Whitney U-tests were used. Age was tested with one-way ANOVA with a post-hoc LSD test. For statistics with dichotomous variables, logistic regression adjusted to the reconstruction method was used. For tests comparing all the different method groups together, p-values and area under the curve (AUC) values are presented. Results of comparisons between two groups are presented with odds ratio (OR), 95% confidence intervals (CI), and p-values. Any p-values less than 0.05 were considered statistically significant in all of the papers of this thesis.

Statistics of Paper II and III

Logistic regression was used to study the association between the independent possible risk factors and the dependent outcome parameters (the postoperative complications). As the reconstruction methods varied significantly in terms of the duration of surgery, blood loss during surgery and the incidence of postoperative complications, all models were adjusted to the reconstructive method. This means that the reconstructive method itself was not a factor that could bias the

results of the statistical analysis. To establish whether the patient-related factors, experience of the surgeon, the duration of the surgery or perioperative blood loss had an independent effect on the outcome factors, a multivariate logistic regression with adjustment for patient demographic parameters acting as confounding factors was performed. This means that all demographic factors that acted as confounding factors were statistically adjusted for and do not bias the results of the statistical analysis. Relationships between independent variables (i.e., possible risk factors) and dependent (outcome) variables are presented with OR, 95% CI and p-values.

Statistics of Paper IV

The demographic factors and questionnaire answers were compared between the four surgical methods as independent variables. To evaluate the response rate and representativeness of the questionnaire's responders, the four groups of surgical methods were also compared separately between responders and non-responders as independent variables.

Normality of distribution was tested with Kolmogorov-Smirnov´s test. None of the demography variables and questionnaire answers were normally distributed. Accordingly, the Kruskal-Wallis test with *post hoc* pairwise comparisons and adjustment of significance levels was used. For dichotomous variables (history of smoking, chemotherapy, radiotherapy, early and late complications and need for re-surgery) the Chi square test was used. For response analysis the Mann-Whitney U test was used.

Results of comparison between the groups are presented with median and minimum and maximum values.

The results of the SF-36, EQ-5D and PGWB were analysed according to the instructions from their respective manuals and interpretation guides.[185,196,197] Raw data from the Breast-Q questionnaire was transformed into a summary score for each scale, ranging from 0 to 100, corresponding to "very dissatisfied" to "very satisfied,"[193] using the Q-score software, which constructs scale scores from individual answers from each patient.[194,198,199]

Ethical permission

Approval from the Gothenburg Ethical Committee was obtained before the studies were initiated (No. 043-08).

4 RESULTS

Summary of results, Paper I

Demography

A total of 685 patients undergoing first time reconstruction with DIEP, LD, LTDF, EXP or DI, and with existing data on at least 30 days of follow up were identified. The demographic results of Paper I are displayed in Table 6.

	All groups (N=685)	DIEP (n=104)	LD (n=113)	LTDF (n=103)	EXP (n=303)	DI (n=62)	p-values
Follow up-time in months: mean ± SD	30.2 ± 19.5	31.2 ± 20.0	32.2 ± 19.1	31.0 ± 23.0	28.8 ± 18.8	30.5 ± 16.7	n.s.
Age in years: mean ± SD	56.4 ± 9.2	54.2 ± 7.2	55.3 ± 9.0	61.2 ± 8.1	55.7 ± 9.1	57.4 ± 11.6	<0.001
BMI: mean ± SD	25.2 ± 3.8	26.0 ± 3.3	25.1 ± 3.8	25.6 ± 4.8	24.8 ± 3.6	25.1 ± 4.1	0.009
Smoking	20.3%	16.0%	21.4%	24.4%	20.0%	20.8%	n.s.
Chemotherapy	43.7%	66.7%	59.8%	36.7%	35.4%	26.7%	<0.001
Radiotherapy	42.5%	82.7%	89.4%	30.5%	16.2%	31.1%	<0.001
Pharmaceuticals							
Hormone therapy	55.3%	63.5%	60.2%	45.6%	56.4%	43.5%	0.024
Acetylsalicylic acid	4.7%	1.0%	2.7%	7.8%	5.3%	6.5%	n.s.
Corticosteroids	0.7%	1.0%	1.8%	1.0%	0.0%	1.6%	n.s.
Anticoagulants	0.7%	0.0 %	1.8%	1.0%	0.7%	0.0%	n.s.
Concurrent diseases							
Diabetes	2.9 %	1.9%	2.7%	4.9%	3.0%	1.6%	n.s.
Hypothyroidism	11.1%	13.5%	13.3%	15.5%	8.6%	8.1%	n.s.
Cardiovascual disease	3.9%	2.9%	1.8%	6.8%	4.6%	1.6%	n.s.
History of thromboembolism	1.2%	1.0%	0,0%	3.9%	0.7%	1.6%	n.s.
Coagulopathy	1.6%	0.0%	2.7%	1.0%	2.0%	1.6%	n.s.
Rheumatic disease	5.4%	1.9%	6.2%	6.8%	5.3%	8.1%	n.s.
Neurologic disease	1.9%	1.0%	3.5%	1.9%	2.0%	0.0%	n.s.
Renal disease	1.8%	1.0%	1.8%	0.0%	2.6%	1.6%	n.s.
Liver disease	1.0%	0.0 %	0.9%	2.9%	1.0%	0.0%	n.s.
Lung disease	3.2%	1.9%	4.4%	4.9%	3.0%	1.6%	n.s.

Table 6: Summary of demographic parameters, pharmaceuticals, and concurrent diseases for the overall group and for each method

Early complications

Early complications and differences between methods are presented in detail in Figure 9 and in Paper I. The DIEP group had the highest rate of early complications, including local complications such as fat necrosis, compared to all other groups. Postoperative antibiotics were administered more frequently in the DIEP group as a consequence of these local events; however, the signs of infection were not significantly more frequent in the DIEP group. Accordingly, the DIEP group had the most incidences of resurgery for complications.

Early overall complications

Early complications affected 30.5% of all patients. There were significant differences between the groups ($p<0.001$, AUC 0.620). The DIEP group had the highest rate at 50.0%, which was significantly higher than all other groups.

Early antibiotics administered

Early postoperative antibiotics were administered to 16.5% of all patients. There were significant differences between the groups ($p=0.013$, AUC 0.586). The DIEP group had the highest rate at 27.9%, which was significantly higher than in the LD group (14.2%, $p=0.014$) and the EXP group (13.2%, $p=0.001$).

Early overall local complications

Early local complications (fat necrosis, skin necrosis, wound rupture, hematoma and seroma accumulated) affected 16.8% of all patients. There were significant differences between the groups ($p<0.001$, AUC 0.698). The DIEP group had the highest rate, at 35.6%, which was significantly higher than in the LD group (20.4%, $p<0.013$), the EXP group (7.3%, $p<0.001$) and the DI group (12.9%, $p=0.002$).

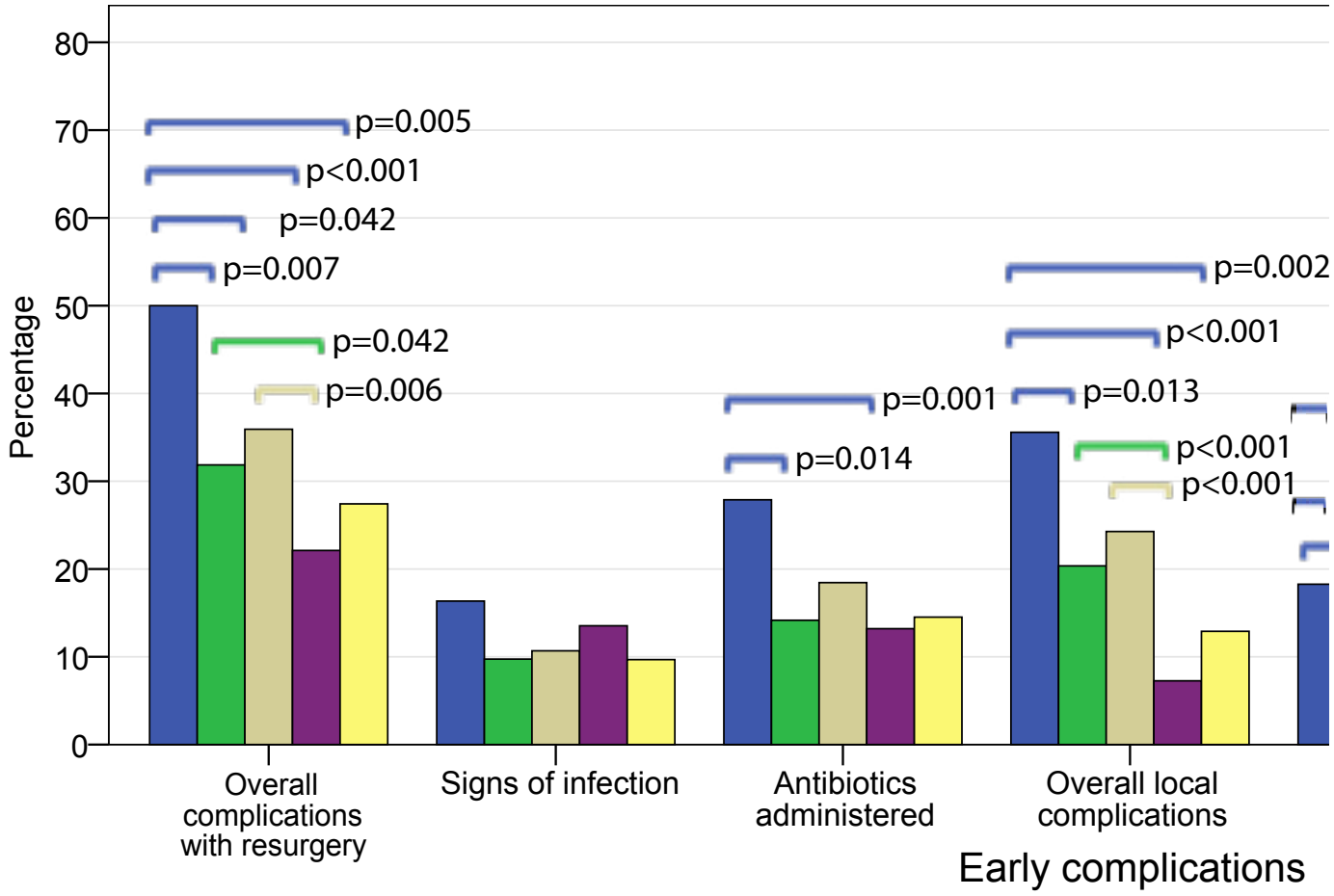

Figure 9: Early complication rates and reoperations (≤30 days) for the five groups. Horizontal brackets show statistically significant differen difference is given adjacent to the horizontal brackets

Early surgery for complications

There was surgical intervention due to early complications in 12.4% of all patients. There were significant differences between the groups ($p<0.001$, AUC 0.672). The DIEP group had the highest rate at 26.9%, which was significantly higher than in the LD group (7.1%, $p<0.001$) and the EXP group (6.9%, $p<0.001$).

Late complications

Late complications and differences between methods are presented in detail in Figure 10 and in Paper I. The pattern of late complications was considerably different from early complications. The DIEP and EXP groups had the lowest rate of both overall late complications and resurgery for complications and cosmetic corrections, while the other methods had a significantly higher rate. The LTDF and DI groups in particular had high rates of revision surgery.

Late overall complications

Late overall complications and need for surgical corrections affected 54.7% of all patients. There were significant differences between the groups ($p<0.001$, AUC 0.625). The LTDF group had the highest rate at 74.8%, which was significantly higher than in the DIEP (46.2%, $p<0.001$) and the EXP (44.9%, $p<0.001$) groups.

Late overall local complications

Late overall local complications (fat necrosis, skin necrosis, wound rupture, hematoma and seroma accumulated) affected 5.3% of all patients. There were significant differences between the groups ($p=0.009$, AUC 0.666). The DIEP group had the highest rate at 11.5%, which was significantly higher than in the LD (3.5%, $p=0.033$), the EXP group (3.3%, $p=0.041$) and the DI groups (1.6%, $p=0.049$).

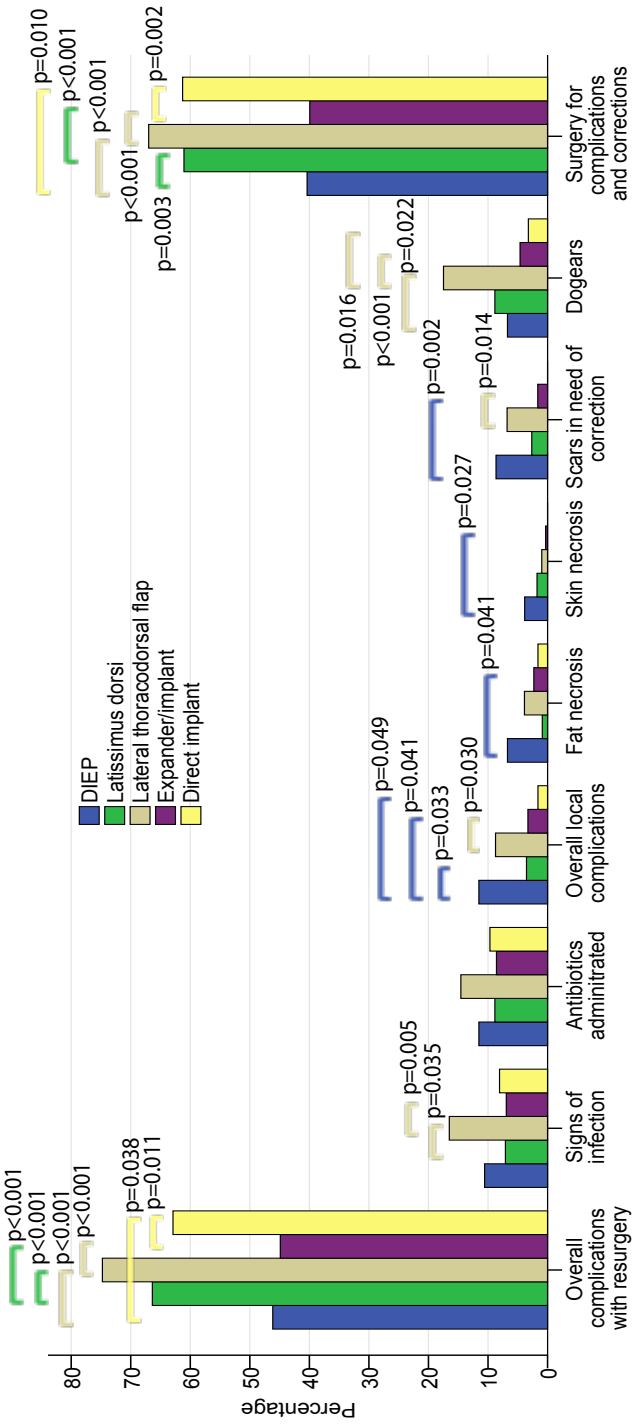

Figure 10: Late complication rates and reoperations (> 30 days) for the five groups. Horizontal brackets show statistically significant differences between groups, where the colour indicates the group with higher value. The p-value for the difference is given adjacent to the horizontal bracket

Secondary corrective surgery

Late surgical intervention, due to complications or secondary cosmetic corrections, were performed in 49.5% of all patients. There were significant differences between the groups ($p<0.001$, AUC 0.617). The LTDF group had the highest rate at 67.0%, which was significantly higher than in the EXP (39.9%, $p<0.001$) and the DIEP groups (40.4%, $p<0.001$).

Implant related complications

Implant related complications are presented in Table 7. In summary, the frequency of implant extraction and implant rupture is generally low, as is capsular contraction. This is considering that a relatively large number of the patients had a history of radiotherapy.

	All groups (N=581)		Latissimus dorsi (n=113)		Thoracodorsal flap (n=103)		Expander / implant (n=303)		Direct implant (n=62)	
Total implant related event	166	28.6%	34	30.1%	36	35.0%	73	24.1%	23	37.1%
N extraction of implant (%)	20	3.4%	2	1.8%	5	4.9%	6	2.0%	7	11.3%
N capsular contraction (%)	124	21.3%	27	23.9%	27	26.2%	54	17.8%	16	25.8%
N wound rupture with implant exposure (%)	12	2.1%	2	1.8%	4	3.9%	5	1.7%	1	1.6%
N diagnosed implant rupture (%)	2	0.3%	1	0.9%	0	0.0%	1	0.3%	0	0.0%%
N implant dislocation (%)	9	1.5%	2	1.8%	0	0.0%	7	2.3%	0	0.0%%

Table 7: Summary of all implant-related events for the groups with implant-based reconstructions, both in numbers and percentage

Implant-related complications affected 29.6% of all patients with an implant-based reconstruction. There were significant differences between the groups ($p=0.014$, AUC 0.580). Intergroup comparison showed that the DI group had the highest rates of implant related events at 37.1%, which was significantly higher than the EXP group (24.1%, $p=0.036$). The LTDF group (39.6%) had a significantly higher rate than the EXP group ($p=0.004$). In the LD group, 32.4% of the patients were affected.

More detailed results of the intergroup comparison (OR and 95% CI), are found in Paper I.

Summary of results, Paper II and III

A total of 623 patients undergoing reconstruction with DIEP, LD, LTDF or EXP and existing data on at least 30 days of follow up were identified. The demographic parameters are displayed in Table 8.

Demography	Overall (n=623)	DIEP (n=104)	LD (n=113)	LTDF (n=103)
Follow up time (months ± SD)	30.2 ± 19.5	31.2 ± 20.0	32.2 ± 19.1	31.0 ± 23.0
Age (years ± SD)	56.3 ± 8.9	54.2 ± 7.2	55.3 ± 9.0	61.2 ± 8.1
Age (range)	31-83	37-71	31-76	43-80
BMI (mean ± SD)	26.0 ± 3.3	25.1 ± 3.8	25.6 ± 4.8	24.8 ± 3.6
BMI (range)	17.7-38.7	19.3-35.1	18.4-34.6	18.5-37.6
Smoking	20.2%	16.0%	21.4%	24.4%
Previous chemotherapy	45.4%%	66.7%	59.8%	36.7%
Previous radiotherapy	43.6%%	82.7%	89.4%	30.5%
Hormone therapy	56.5%%	63.5%	60.2%	45.6%

Table 8: Demography, overall group and each method, Paper II and III

Blood loss as an independent risk factor for complications

Table 9 shows the association between the amount of blood loss and the risks for postoperative complications. The univariate model shows an association between increased blood loss in 10-ml increments and increased risk for numerous early and late complications. The multivariate model, adjusted for the reconstructive method and for all demographic factors acting as confounding factors, shows that for each 10-ml of blood loss during the procedure, the risk for overall early complications (OR 1.019, p=0.017), early seroma (OR 1.016, p=0.037), early resurgery for complications (OR 1.019, p=0.010), late overall complications (OR 1.019, p=0.024) and late fat

Blood loss (10-ml steps)	Univariate models		Adjusted for confounding factors*	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
Early complications				
Overall complications (n=192)	1.022 (1.013-1.030)	<0.001	1.019 (1.003-1.036)	0.017
Signs of infection (n=80)	1.008 (1.000-1.016)	0.040	1.008 (0.997-1.019)	0.157
Antibiotics administration (n=104)	1.008 (1.000-1.016)	0.040	1.004 (0.995-1.014)	0.374
Local overall complications (n=107)	1.010 (1.002-1.018)	0.018	1.002 (0.992-1.012)	0.715
Fat necrosis (n=26)	1.025 (1.012-1.038)	<0.001	1.013 (0.997-1.029)	0.125
Skin necrosis (n=41)	1.010 (1.001-1.018)	0.032	1.004 (0.991-1.017)	0.565
Hematoma (n=26)	1.005 (0.996-1.015)	0.277	1.007 (0.988-1.026)	0.484
Seroma (n=40)	1.010 (1.001-1.020)	0.024	1.016 (1.001-1.032)	0.037
Wound rupture (n=9)	1.007 (0.994-1.020)	0.302	n.a.**	
Resurgery for complications(n=76)	1.023 (1.014-1.033)	<0.001	1.019 (1.001-1.037)	0.039
Late complications				
Overall complications (n=336)	1.002 (0.995-1.008)	0.567	1.006 (0.995-1.016)	0.320
Signs of infection (n=57)	1.006 (0.998-1.014)	0.115	1.004 (0.993-1.015)	0.473
Antibiotics administration (n=63)	1.005 (0.997-1.013)	0.213	1.004 (0.993-1.015)	0.502
Local overall complications (n=35)	1.016 (1.004-1.027)	0.007	1.019 (1.003-1.036)	0.024
Fat necrosis (n=19)	1.018 (1.004-1.031)	0.011	1.023 (1.002-1.044)	0.031
Skin necrosis (n=8)	1.007 (0.994-1.020)	0.306	n.a.**	
Hematoma (n=2)	0.994 (0.898-1.100)	0.905	n.a.**	
Wound rupture (n=9)	1.006 (0.991-1.021)	0.434	n.a.**	
Seroma (n=4)	0.993 (0.944-1.046)	0.802	n.a.**	
Scar problems (n=24)	1.005 (0.995-1.015)	0.339	0.982 (0.949-1.017)	0.305
Dogears (n=49)	1.002 (0.992-1.012)	0.729	1.001 (0.988-1.015)	0.839
Resurgery/Cosmetic corrections (n=301)	1.001 (0.995-1.007)	0.793	1.006 (0.996-1.017)	0.251

*age, BMI, smoking, diabetes, corticosteroids, adjuvant hormonal therapy, chemotherapy, radiotherapy and reconstruction method

**Due to low occurrance frequency, early wound rupture, late skin necrosis, late hematoma, late wound rupture and late seroma were not applicable for multivariate analysis.

Table 9: Blood loss as an independent risk factor for complications

necrosis (OR 1.023, p=0.031) all increased. Thus, for example, the risk for encountering any early complication increased by 1.9% for each 10-ml of blood loss during the surgical procedure (Figure 11). As a result, significant blood loss during a procedure can explain why there is a substantial increase in the risk for an early overall complication.

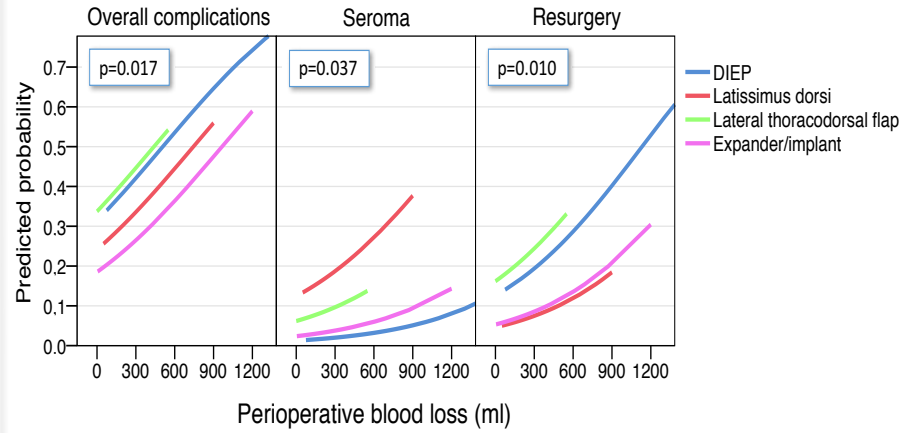

Figure 11: Risk model, perioperative blood loss, early complications

Duration of surgery as an independent risk factor for complications

Table 10 shows the association between the duration of surgery and the risks for postoperative complications. The univariate model shows a clear association between increased duration of surgery in 10-minute increments and increased risk for numerous early and late complications. The multivariate model, adjusted for the reconstructive method and all demographic factors acting as confounding factors, shows that for each 10-minute increase in duration of surgery, the risk for overall early complications increased (OR 1.052, p=0.019). Thus, the risk for encountering any early complication increased by 5.2% for each 10 minute increase in the duration of surgery (Figure 12). As a result, a long duration of surgery can explain a substantial increase of the risk for any early complication.

Duration of surgery (10-min steps)	Univariate models		Adjusted for confounding factors*	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
Early complications				
Overall complications (n=192)	1.040 (1.026-1.056)	<0.001	1.052 (1.008-1.097)	0.019
Signs of infection (n=80)	1.020 (1.002-1.038)	0.027	1.050 (0.990-1.114)	0.107
Antibiotics administration (n=104)	1.030 (1.014-1.047)	<0.001	1.019 (0.967-1.074)	0.477
Local overall complications (n=107)	1.042 (1.026-1.059)	<0.001	1.018 (0.967-1.071)	0.504
Fat necrosis (n=26)	1.085 (1.057-1.114)	<0.001	1.038 (0.962-1.121)	0.338
Skin necrosis (n=41)	1.059 (1.037-1.081)	<0.001	1.048 (0.982-1.117)	0.156
Hematoma (n=26)	1.011 (0.981-1.042)	0.483	0.913 (0.814-1.025)	0.125
Seroma (n=40)	1.014 (0.990-1.039)	0.252	1.049 (0.954-1.152)	0.324
Wound rupture (n=9)	1.035 (0.993-1.078)	0.102	n.a.**	
Resurgery for complications(n=76)	1.041 (1.024-1.059)	<0.001	1.008 (0.954-1.066)	0.771
Late complications				
Overall complications (n=336)	0.994 (0.981-1.007)	0.357	0.994 (0.952-1.039)	0.799
Signs of infection (n=57)	1.012 (0.991-1.033)	0.269	1.026 (0.958-1.099)	0.463
Antibiotics administration (n=63)	1.014 (0.994-1.034)	0.173	1.036 (0.968-1.109)	0.304
Local overall complications (n=35)	1.036 (1.013-1.059)	0.002	1.008 (0.937-1.085)	0.823
Fat necrosis (n=19)	1.043 (1.014-1.073)	0.003	1.015 (0.928-1.111)	0.742
Skin necrosis (n=8)	1.053 (1.012-1.095)	0.010	n.a.**	
Hematoma (n=2)	0.733 (0.463-1.162)	0.187	n.a.**	
Wound rupture (n=9)	0.971 (0.868-1.085)	0.601	n.a.**	
Seroma (n=4)	1.007 (0.955.1.060)	0.808	n.a.**	
Scar problems (n=24)	1.035 (1.008-1.064)	0.012	1.009 (0.928-1.098)	0.830
Dogears (n=49)	1.003 (0.978-1.027)	0.839	1.054 (0.972-1.142)	0.203
Resurgery/Cosmetic corrections (n=301)	0.992 (0.978-1.005)	0.219	0.985 (0.943-1.030)	0.513

*age, BMI, smoking, diabetes, glucocorticoids, adjuvant hormonal therapy, chemotherapy, radiotherapy and reconstruction method

**Due to low occurrance frequency, early wound rupture, late hematoma, late skin necrosis, late wound rupture and late seroma were not applicable for multivariate analysis.

Table 10: Duration of surgery as an independent risk factor for complications

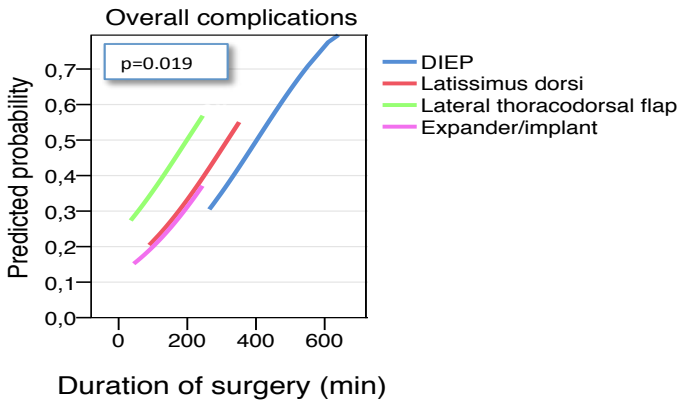

Figure 12: Risk model, duration of surgery, and early overall complications

Patient-related factors as independent risk factors for complications

Early complications

Table 11 displays in detail the statistically significant associations between the patient-related factors and early complications. In the multivariate model, the patient factor related to highest number of early complications was smoking, with increased BMI and a history of radiotherapy coming in second and third, respectively. Age seemed to be a protective factor against the development of early seroma.

Early overall complications				
	Univariate model		Multivariate model	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
BMI	1.08 (1.03-1.14)	0.002	1.07 (1.01-1.13)	0.017
Smoking	1.65 (1.07-2.54)	0.023	2.05 (1.25-3.37)	0.005
Radiotherapy	1.87 (1.32-2.65)	<0.001	n.s.	n.s.
Early signs of infection				
BMI	1.08 (1.01-1.16)	0.018	n.s.	n.s.
Early administration of antibiotics				
BMI	1.13 (1.06-1.20)	<0.001	1.10 (1.04-1.18)	0.002
Smoking	1.84 (1.11-3.03)	0.017	2.10 (1.19-3.71)	0.010
Hormone therapy	1.56 (1.01-2.43)	0.046	n.s.	n.s.
Radiotherapy	1.77 (1.15-2.73)	0.009	2.03 (1.24-3.30)	0.005
Early overall local complications				
Smoking	2.28 (1.40-3.72)	0.001	2.77 (1.61-4.75)	<0.001
Radiotherapy	3.20 (2.04-5.01)	<0.001	2.03 (1.09-3.75)	0.025
Early skin necrosis				
Smoking	2.70 (1.36-5.33)	0.004	3.64 (1.67-7.93)	0.001
Radiotherapy	3.13 (1.55 - 6.30)	0.001	n.s.	n.s.
Early fat necrosis				
BMI	1.22 (1.10-1.36)	<0.001	n.s.	n.s.
Smoking	3.00 (1.29-6.95)	0.010	n.s.	n.s.
Radiotherapy	7.29 (2.47-21.51)	<0.001	n.s.	n.s.
Early hematoma				
Smoking	3.52 (1.48-8.36)	0.004	n.s.	n.s.
Early seroma				
Age	0.96 (0.93-1.00)	0.030	0.95 (0.92-0.99)	0.016
Radiotherapy	2.18 (1.12-4.24)	0.022	n.s.	n.s.
Early resurgery				
BMI	1.11 (1.04-1.19)	0.003	1.09 (1.01-1.17)	0.029
Radiotherapy	1.73 (1.05-2.83)	0.031	n.s.	n.s.

Table 11: Statistically significant associations between patient-related factors and early complications. Univariate and multivariate models. n.s.=non-significant

Independent risk factors combined

BMI (OR 1.07, p=0.017) and smoking (OR 2.05, p=0.005) were independent patient-related risk factors for overall early complications. Thus, the risk for encountering overall early complications rose by 7% for each unit of BMI increase, and the risk increased over 200% if the patient was a smoker. When both risk factors were combined, the mean predicted probability was 230% higher for smokers with a BMI of 30 compared to non-smokers with a BMI of 20. The patients in the expander group had the greatest increase at 3.8-fold for the combination of high BMI and being a smoker (Figure 13).

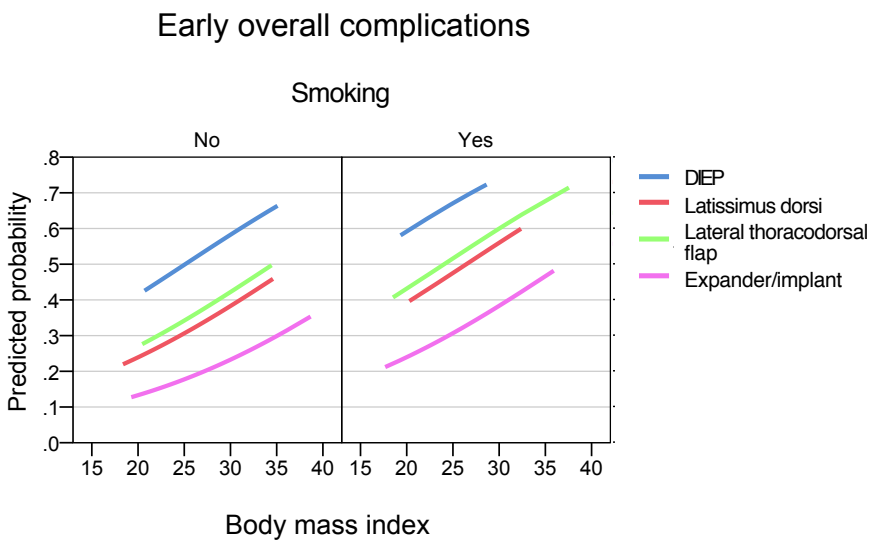

Figure 13: Smoking and BMI combined as risk factors for early overall complications

Smoking (OR 2.77, p<0.0001) and radiotherapy (OR 2.03, p=0.025) were independent patient-related risk factors for early local complications. Thus, the risk for encountering early local complications rose by 277% if the patient was a smoker, and the risk increased by over 200% if the patient had been irradiated. The predicted probability for all methods increased a mean 3.6-fold for smokers who had undergone radiotherapy compared to patients who

were neither smokers nor had undergone radiotherapy. The patients in the expander group had the greatest increase of 4.6-fold for the combination of smoking and radiotherapy (Figure 14).

When BMI (OR 1.10, p=0.002) was added as a third risk factor to smoking and radiotherapy, the association with early administration of

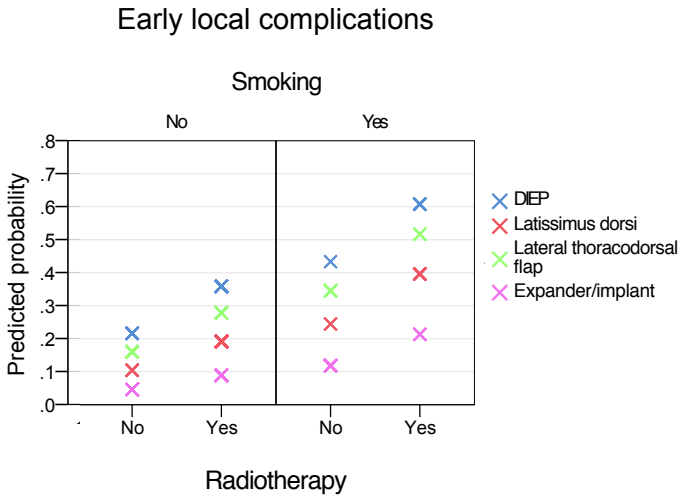

Figure 14: Smoking and radiotherapy combined as risk factors for early local complications

antibiotics rose manifold. A smoking, irradiated patient with a BMI of 30 had a 7.2-fold risk for early administration of antibiotics than a non-smoking, non-irradiated patient with a BMI of 20 (Figure 15).

Hypothyroidism, cardiovascular disease, coagulopathy, renal disease, liver disease and lung disease had no statistically significant relationship to any of the complications registered.

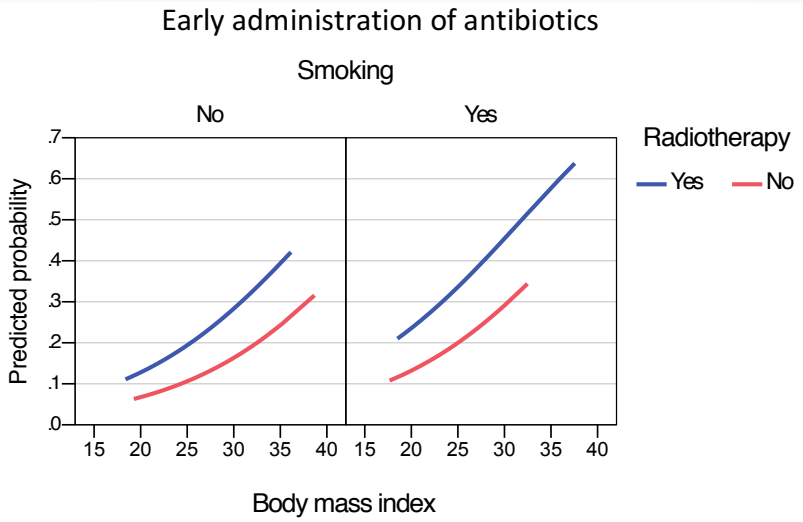

Figure 15: BMI, smoking and radiotherapy combined as risk factors for early administration of antibiotics, all groups combined

Late complications

Table 12 displays in detail the associations between the statistically significant patient-related factors and late complications. In the multivariate model, the patient factors related to the highest number of the subgroups of late complications were high BMI (late overall complications, late signs of infection, late administration of antibiotics and late fat necrosis) and history of radiotherapy (late overall complications, late administration of antibiotics, late overall local complications and late fat necrosis). Smoking was only associated with late resurgery.

Late overall complications				
	Univariate model		Multivariate model	
	OR (95 % CI)	p-value	OR (95 % CI)	p -value
BMI	1.06 (1.01-1.12)	0.014	1.06 (1.00-1.11)	0.042
Rheumatic disease	2.27 (1.03-4.99)	0.041	n.s.	n.s.
Radiotherapy	1.79 (1.29-2.49)	<0.0001	1.66 (1.01-2.74)	0.046
Late signs of infection				
BMI	1.19 (1.10-1.28)	<0.0001	1.18 (1.09-1.28)	<0.001
Late administration of antibiotics				
BMI	1.13 (1.05-1.21)	0.001	1.11 (1.03-1.20)	0.007
Acetylsalicylic acid	3.93 (1.65-9.33)	0.002	6.08 (2.29-16.11)	<0.001
Radiotherapy	1.72 (1.01-2.93)	0.046	1.89 (1.04-3.42)	0.037
Late overall local complications				
Metabolic disease	2.47 (1.08-5.67)	0.033	n.s.	n.s.
Radiotherapy	3.31 (1.56-7.06)	0.002	3.79 (1.54-9.33)	0.004
Late skin necrosis				
Radiotherapy	9.27 (1.13-75.82)	0.038	n.s.	n.s.
Late fat necrosis				
BMI	1.20 (1.08-1.35)	0.001	1.18 (1.05-1.33)	0.005
Radiotherapy	3.48 (1.23-9.90)	0.019	3.37 (1.17-9.70)	0.024
Late hematoma				
Age (years)	1.21 (1.00-1.46)	0.046	n.s.	n.s.
Diabetes	33.5 (2.01-557.09)	0.014	n.s.	n.s.
Late seroma				
Metabolic disease	7.97 (1.11-57.50)	0.039	n.s.	n.s.
Late wound rupture				
Age	1.13 (1.026-1.21)	0.009	n.s.	n.s.
Radiotherapy	9.27 (1.13-75.82)	0.038	n.s.	n.s.
Late resurgery				
Smoking	1.92 (1.25-2.94)	0.003	1.88 (1.21-2.92)	0.005
Reumatic disease	2.46 (1.15-5.29)	0.021	2.44 (1.07-5.57)	0.033
Radiotherapy	1.55 (1.12-2.14)	0.008	n.s.	n.s.

Table 12: Statistically significant associations between patient-related factors and late complications. Univariate and multivariate models. n.s.=non-significant

Independent risk factors combined

BMI (OR 1.06, p=0.042) and a history of radiotherapy (OR 1.66, p=0.046) were independent patient-related risk factors for late overall complications. Thus, the risk of encountering overall late complications rose by 6% for each unit of BMI increase, and the risk rose by 66% if the patient was irradiated. When both risk factors were combined, an irradiated patient with a BMI of 30 had a 2.3-fold higher risk for late overall complications compared with a non-irradiated patient with a BMI of 20 (Figure 16).

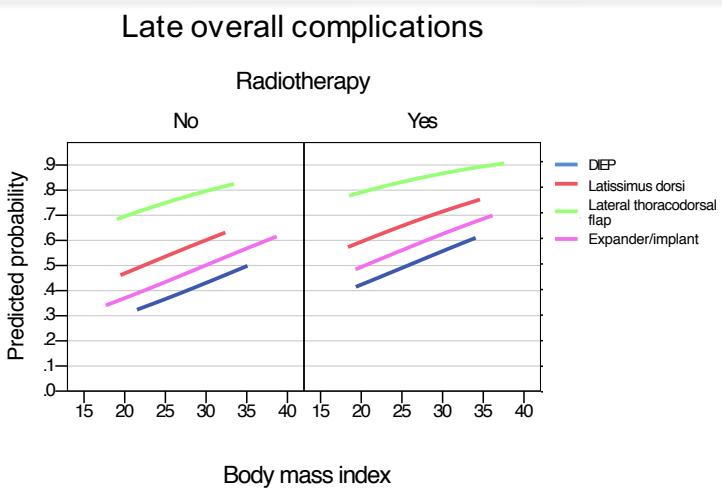

Figure 16: Radiotherapy and BMI as risk factors for late overall complications

The patient-related factors of smoking (OR 1.88, p=0.005) and rheumatic disease (OR 2.44, p=0.033) were independent risk factors for late resurgery. Thus, the risk for encountering late resurgery was 88% higher if the patient was a smoker, and 244% higher if the patient had rheumatic disease. A smoking patient with a history of rheumatic disease had an over 3-fold higher risk for late resurgery compared to that in a non-smoking patient without rheumatic disease (Figure 17).

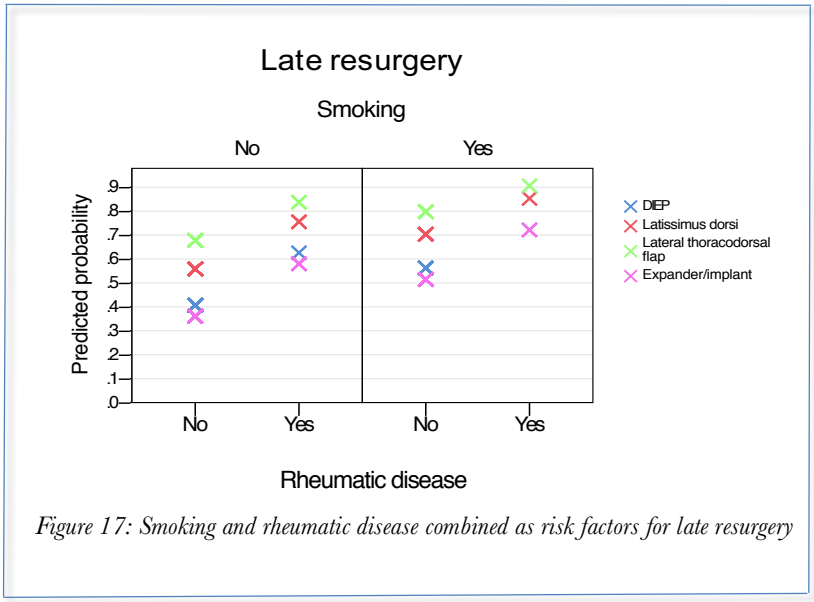

Figure 17: Smoking and rheumatic disease combined as risk factors for late resurgery

BMI (OR 1.18, p=0.005), and radiotherapy (OR 3.37, p=0.024) were independent patient-related risk factors for late fat necrosis. Thus, the risk for encountering late fat necrosis rose by 18% for each unit of increased BMI, and the risk increased by 337% if the patient was irradiated. An irradiated patient with a BMI of 30 had a 16.4-fold higher risk for late fat necrosis than a non-irradiated patient with BMI of 20 (Figure 18).

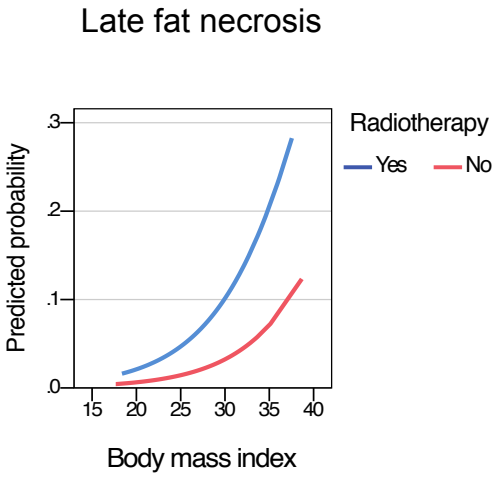

Figure 18: BMI and radiotherapy combined for late fat necrosis

Summary of results, Paper IV

Patient selection and demography

Figure 19 shows the patient selection for the study of Paper IV. A total of 685 patients undergoing reconstruction with DIEP, LD, LTDF or EXP and having existing data on at least 30 days of follow up were identified. Three hundred forty one patients were excluded according to the exclusion criteria. A total of 459 patients responded to the questionnaires (67.0%) with no significant differences between the groups (p=0.338).

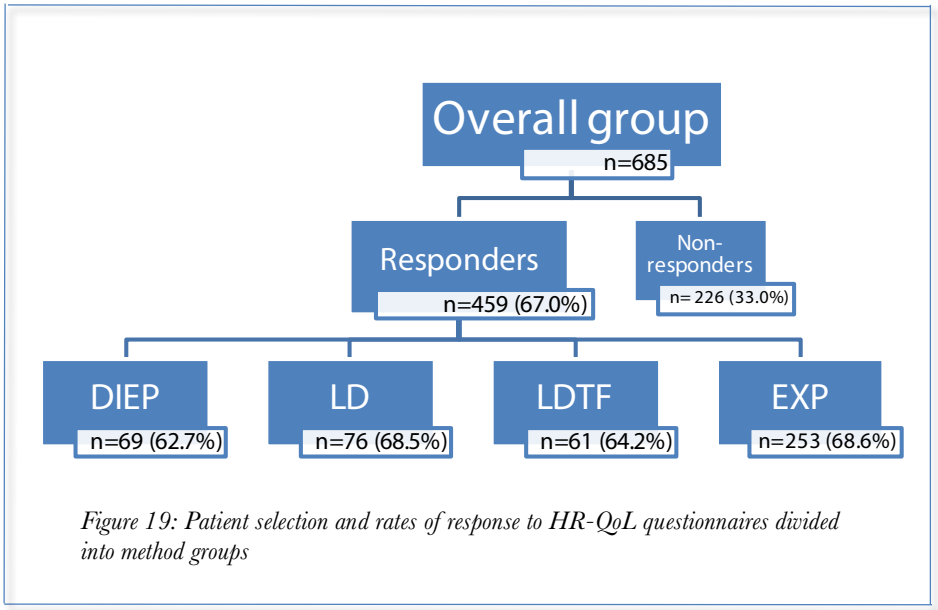

Figure 19: Patient selection and rates of response to HR-QoL questionnaires divided into method groups

Table 13 displays demographic data for the overall group and for each method of reconstruction. There were significant differences between the groups regarding BMI, age at the time of surgery, follow-up time, years since primary surgery to submission of questionnaire answers, chemotherapy and radiotherapy.

Results of SF-36: Comparison between study groups

The detailed results of SF-36 results and comparison between the four method groups are displayed in Figure 20. There were significant differences between groups in the *vitality* domain, where patients in the DIEP group had a lower score than the LTDF (p=0.019) and EXP (p=0.022) groups.

Results of SF-36: Overall group compared to normal population

Figure 21 displays the results from the comparison between the overall study group (all methods) and 930 age-matched women from the Swedish general population. Patients in the study group had a significantly higher score in the domain of *physical functioning* (p<0.001). The age- matched normal population had higher scores in the domains of *general health* (p<0.001), *vitality* (p<0.001), *social functioning* (p=0.013), *mental health* (p<0.001) and the *mental component summary* (p<0.001).

Demography	Overall (n=685)	DIEP (n=110)	LD (n=111)	LTDF (n=95)	Exp (n=369)	Sign.
BMI: median (min - max)	24.6 (19.0-40.2)	25.9 (19.3-35.1)	25.3 (19.5-34.6)	25.9 (19.0-40.2)	24.0 (19.3-37.0)	p = 0.001
Age at time of surgery: median (min-max)	58 (29-83)	54 (39-71)	57 (34-76)	62 (46-78)	58 (29-83)	p < 0.001
Follow-up time in months: median (min - max)	28.2 (0-107)	25.8 (0-79)	25.4 (6-99)	25.9 (0-98)	32.1 (4-107)	p = 0.032
Years since primary op to questionnaire: median (min - max)	5 (0-9)	5.5 (0-8)	5 (0-9)	6 (0-8)	5 (0-9)	p < 0.001
ASA: median (min - max)	1 (1-3)	1 (1-2)	1 (1-3)	1 (1-2)	1 (1-2)	p = 0.519
Smoking: n/n of known (%)	21.3%	15.3%	26.5%	23.0%	21.0%	p = 0.275
Chemotherapy: n/n of known (%)	43.4%	66.7%	57.3%	34.8%	34.2%	p < 0.001
Radiotherapy: n/n of known (%)	40.9%	66.7%	88.3%	19.8%	17.6%	p < 0.001

Table 13: Demography, Paper IV. Statistically significant results are in red

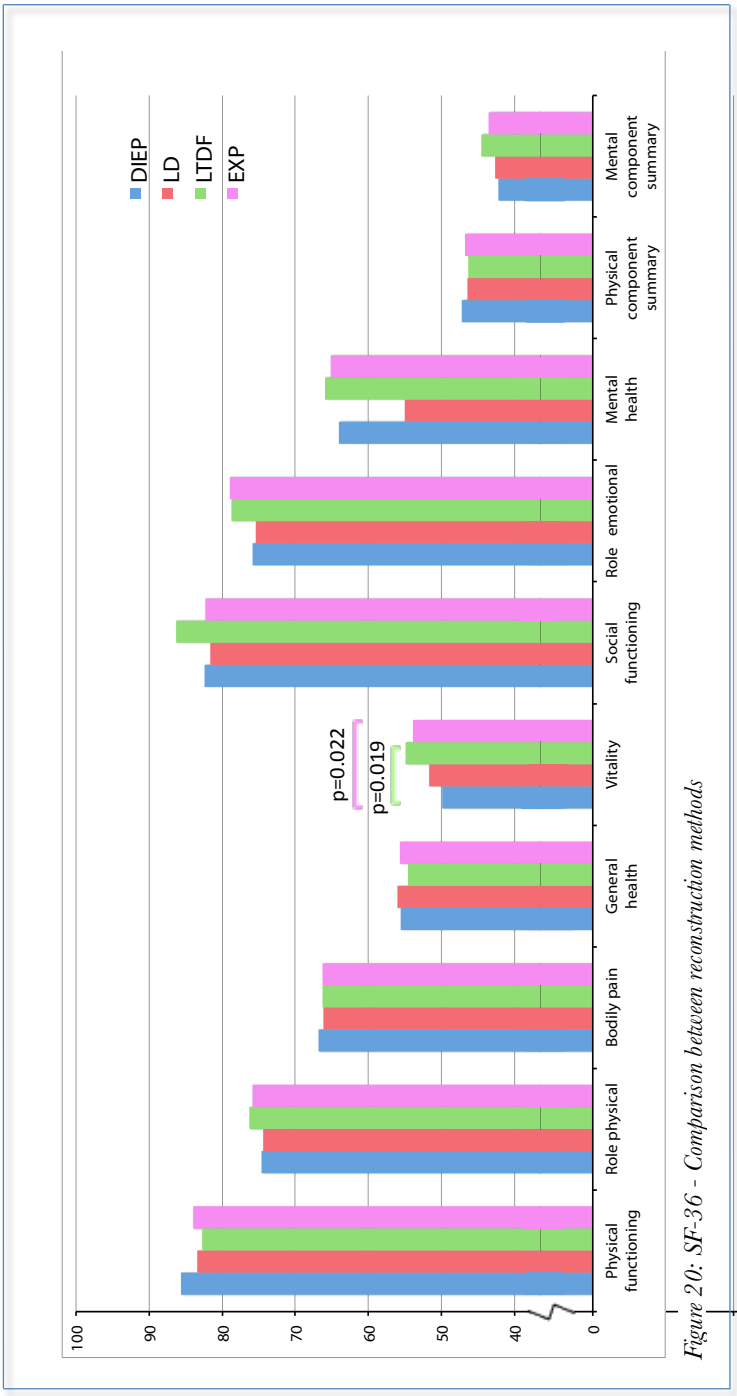

Figure 20: SF-36 - Comparison between reconstruction methods

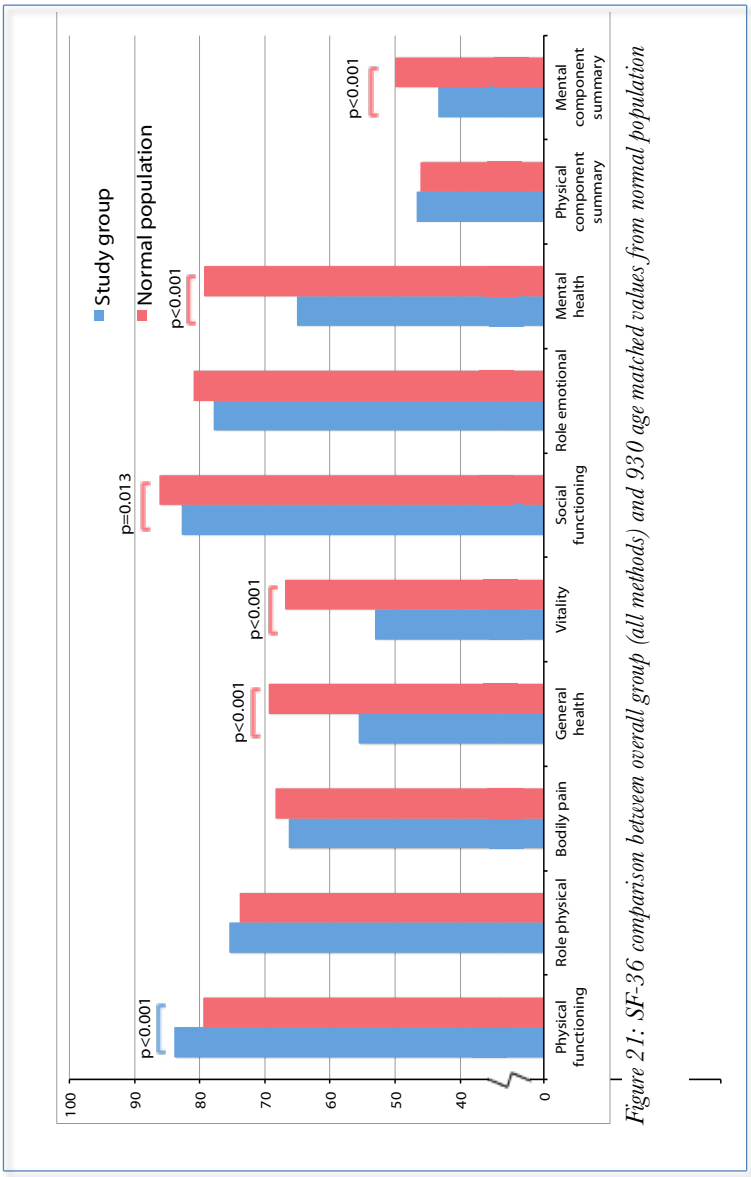

Figure 21: SF-36 comparison between overall group (all methods) and 930 age matched values from normal population

Results of SF-36: Each group

When each subgroup of the four reconstruction methods was compared with the general population, all methods had significantly lower scores in the domains of *general health*, *vitality*, *mental health* and the *mental component summary* (all p-values <0.001).

The DIEP group had a significantly higher score in the domain of *physical functioning* (p<0.041) than the general population. The difference was not statistically significant among the other three groups.

EQ-5D – comparison between groups

There were no significant differences between the subgroups of the four reconstruction methods, neither among the descriptive items nor the VAS scale.

PGWB – comparison between groups

There were no significant differences in the *global score* between the subgroups of the four reconstruction methods. There were also no significant differences between the subgroups in each of the domains of *anxiety*, *depressed mood*, *positive well-being*, *self-control*, *general health* and *vitality*.

Breast-Q, comparison between study groups

The detailed results of the comparison between the reconstruction method groups are displayed in Figure 22. There were significant differences between the groups regarding the Breast-Q scale of *satisfaction with breasts* (p<0.001); the DIEP group had a higher score compared to the other groups. Regarding the scale of *satisfaction with outcome*, the DIEP group also had a higher score compared with that of the LTDF and EXP groups.

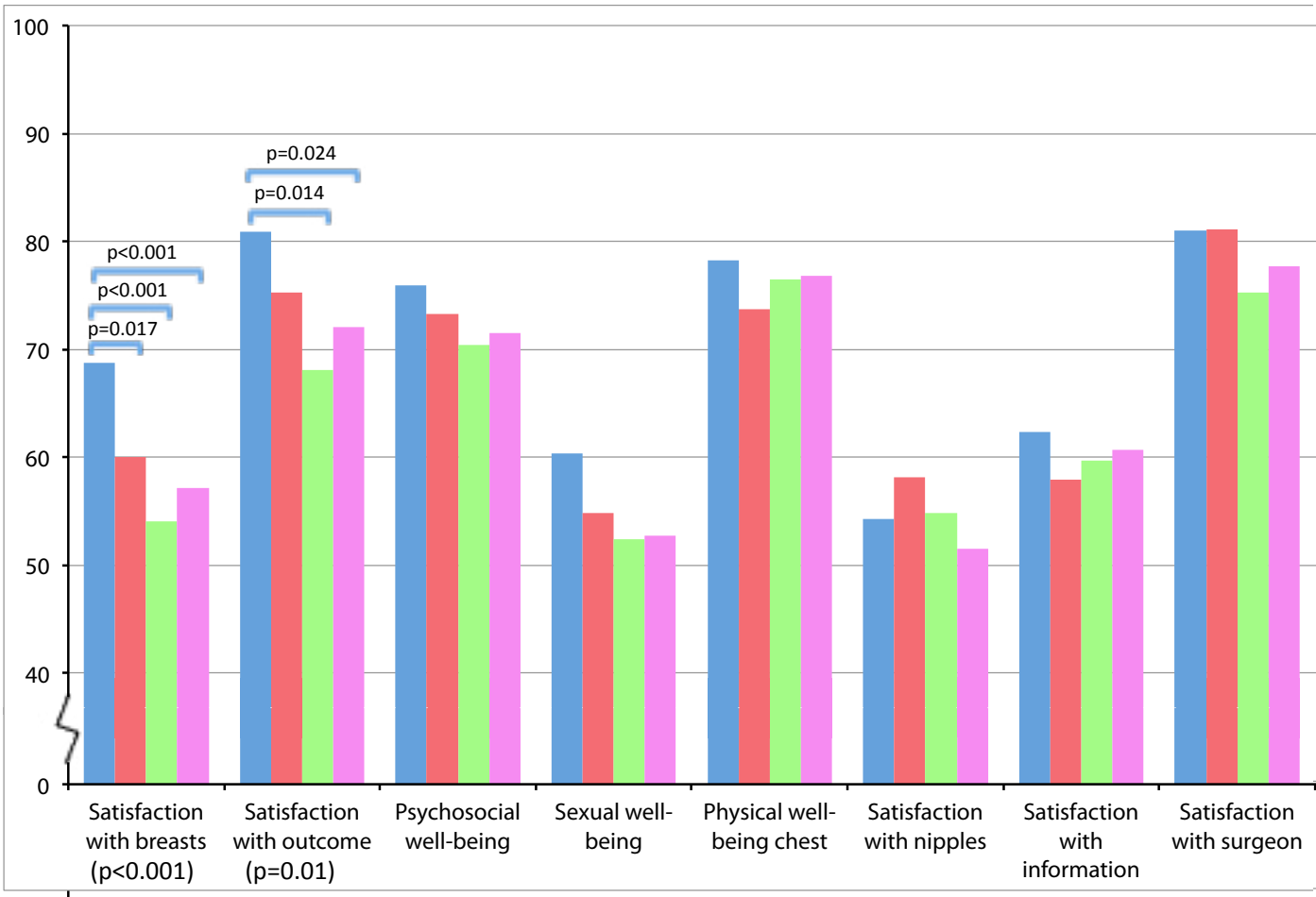

Figure 22: Breast-Q comparison between the reconstruction methods. P-values under the domain of satisfaction with breasts *and* satisfaction with *together. Horizontal brackets show statistically significant differences between groups, where the colour indicates the group with higher value. The p-valu brackets*

There was a trend for the DIEP group to have a higher score than the other groups in the domains of *psychosocial well-being*, *sexual well-being*, *physical well-being chest* and *satisfaction with information*, *medical staff* and *office staff*, but the difference did not reach statistical significance.

Response analysis

Table 14 shows the demographic parameters for all groups, separated into responders and non-responders. There were no significant differences in the overall group between responders and non-responders regarding BMI, ASA classification, history of radiotherapy, early complication rate and early and late re-surgery. There were significant differences in age at time of surgery showing the responders were older than the non-responders (p=0.001). The follow-up time was shorter in the responders group than the non-responders group (p=0.009). The non-responder group had higher frequencies of smoking (p<0.001) and more frequent history of chemotherapy (p=0.004). Additionally, the responders had a higher late complication rate (p=0.045).

All groups	Respondents (n=419)	Non-respondents (n=266)	p-value
BMI: median (min - max)	24.8 (18.2 - 40.2)	24.4 (17.7 - 37.0)	0.368
Age at time of surgery: median (min - max)	58 (29 - 77)	55 (31 - 83)	0.001
Follow up time in months: median (min - max)	28.0 (0 - 107)	30.9 (0 - 106)	0.009
ASA: median (min-max)	1 (1 - 3)	1 (1 - 2)	0.528
Smoking: n/n of known* (%)	75/510 (14.7%)	53/167 (31.7%)	<0.001
Chemotherapy: n/n of known* (%)	186/480 (38.8%)	104/206 (50.7%)	0.004
Radiotherapy: n/n of known* (%)	172/476 (36.1%)	91/209 (43.5%)	0.067
Early complications rate	126/419 (30.1%)	95/266 (35.71%)	0.124
Early resurgery rate	21/419 (5.0%)	23/266 (8.6%)	0.059
Late complications rate	154/419 (36.8%)	78/266 (29.3%)	0.045
Late resurgery rate	54/419 (12.9%)	34/266 (12.8%)	0.968

Table 14: Response analysis. Comparison between responders and non-responders. Significant differences are in red

5 DISCUSSION

General issues

Breast cancer comprises 22.9% of all invasive cancers in women making it the most common invasive cancer.[1,2] The incidence is increasing, affecting increasingly younger women. Mortality in developing countries is also increasing, although, in western Europe and the US, survival is maintained or is slightly increasing.[8]

In Sweden, the incidence of breast cancer has more than doubled since the National Board of Health and Welfare's Cancer Registry started in the fifties,[11] resulting in an increasing number of breast cancer survivors. Breast reconstruction after mastectomy is therefore becoming more frequent.[13,14] About 40% of women in Gothenburg, who have undergone mastectomy due to breast cancer request breast reconstruction.[17]

Surgery is still the primary treatment for breast cancer, but adjuvant therapy is frequently used to improve survival rates, with radiotherapy, chemotherapy, and hormone therapy being the most common.[200]

A third of women treated with mastectomy experience persistent psychosocial morbidity, with reduced self-esteem, insomnia, increased anxiety, depression, disturbed body image, and/or sexual problems.[18-21] Both primary and secondary breast reconstruction, after mastectomy, have been shown to enhance self-esteem and quality of life compared to the absence of any reconstruction.[22-25]

The principal aim of breast reconstruction is to reverse the deformity created by mastectomy.[201] However, even if this is accomplished, the larger aim should be to normalize the body image, the HR-QoL, and to satisfy patients with the results of the reconstruction. Consequently, the patient's expectations are always the key to a successful breast reconstruction.

Many methods for breast reconstruction have been introduced, and all have their advantages and disadvantages. Implant-based reconstructions are generally seen as fast and reliable, but they have a distinct range of complications (especially late complications), while

autologous reconstructions are more expensive, but have the obvious advantage of only using the patients´ own tissue. The method of choice depends on anatomical factors, concurrent morbidity, requests of the patient, and the preferences of the surgeon. Many reports provide descriptions and recommendations for different reconstructive methods.[26,27,202-206] However, no consensus or generally accepted guidelines exist on the method of choice for each individual patient. Most studies in the plastic surgery literature evaluate only a single method or compare two different methods.[54-58,71,76,103,107,207,208]

Complications after breast reconstruction are common, and many patients are exposed to avoidable complications.[53-58,209] Several studies have suggested that complications significantly affect patient satisfaction and emotional well-being.[57,63,64,210,211]

For a complete understanding of the methods for breast reconstruction, the research has to include:

- Clear description of the method, including all surgical steps to achieve reproducible results
- The definitions and evaluations of both medical and surgical postoperative complications
- Evaluation of aesthetic results and patient satisfaction
- Health-related economics; how different methods provide a health-related benefit regarding long-term cost
- The outcome in terms of HR-QoL, with the use of generally accepted HR-QoL instruments and questionnaires

The present thesis meets several of these requirements. Firstly, the approach to each of the four reconstructive methods has been comprehensively described[26-29] and all surgeons at the department have had thorough training in all of the methods, except the operations involving microsurgery. Secondly, the analysis of all complications with the same definitions is carried out in Paper I. Thirdly, the measurements of changes in HR-QoL have been carried out by applying both generic (SF-36, EQ-5D, and PGWB) and specific (the Breast-Q) questionnaires, commonly used to measure HR-QoL. The SF-36 is one of the most frequently used instruments for assessing general health, and is designed for a large population of patients. [167]

Breast-Q is widely used in measuring the effect of breast reconstruction on satisfaction and HR-QoL.[194] In SF-36, the results are compared with age-matched data from the Swedish general population.

Unfortunately, preoperative data could not be obtained before the start of these studies, so comparisons before and after surgery could not be made. Additionally, assessments of aesthetic results have not been carried out in the present thesis. There have been many attempts at assessing aesthetic results by using photographs,[212-215] but so far there is no general agreement on the methodology, and the published studies are based on weak scientific data. The only measurements on aesthetic results in this thesis are indirect measurements collected using the Breast-Q's domains, which include *satisfaction with breasts* and *satisfaction with overall outcome*, where only the patient does the assessment.

Additionally, there is no attempt made to estimate the cost of each of the methods studied. That aspect was considered as out of the scope of this thesis.

Accordingly, the aim of the present thesis was to examine the frequency of complications, to find independent risk factors for complications among perioperative and patient-related factors, and to examine differences in HR-QoL between women having undergone breast reconstruction and the general population, as well as differences between the reconstructive methods used.

Patient selection, study design, and statistics

All studies in this thesis are retrospective analyses, with all of its associated flaws. In the registration of variables in a retrospective study, missing values are unavoidable. Furthermore, data collection is never as thorough, and the data of the studies are dependent on the record-keeping of others at an earlier time point, some of whom were not a part of the research projects.

In Paper II, the results show that many complications are statistically significant in the univariate regression analysis, possibly suggesting some false-positive results. Statistically significant outcome variables are reduced when all applicable confounding factors are adjusted for; however, it is possible that more factors would become statistically significant if the patient population had been even larger.

In Papers II and III, the entire data was studied using both univariate and multivariate regression analysis, not separately for each paper. This means that all possible confounding factors were accounted for and it rules out the possibility that a certain confounding factor in one of the papers is the real cause for the results in the other paper. Nevertheless, it was decided that the results should be presented in two separate original articles due to the vastness of the dataset.

Complications and comparison of methods

The results of Paper I show that all reconstructive methods have high complication rates. All methods had a higher frequency of complications than previously described in the literature. The overall incidence of early complications for DIEP was as high as 50%, which is considerably higher than has been reported in other studies.[43,46,56,73,78,79,207,216,217]

One possible explanation may have been differences in the definitions of complications and their detailed registration. Generally, there is no widely accepted way of defining and registering complications in a uniform way and there is large variation in how this is carried out in different studies. In this thesis, both relatively minor (but undesirable) postoperative outcomes and serious events were included as complications.

Another explanation for the high complication rates in the DIEP group may have been that during the study period DIEP reconstructions were a relatively novel method in Sweden, and the reconstructions were performed by microsurgeons at the beginning of their microsurgical learning curve. A study has been published indicating improvement of complications in this group of patients during the study period,[207] but the registration of complications in that paper is completely different than in Paper I.

The analysis in Paper I shows that the DIEP group had a generally higher BMI than the other groups. It is known that obesity causes a higher frequency of complications compared to rates in normal weight individuals,[218] which could also explain the higher frequency of complications in the DIEP group. The results of this thesis show that

BMI is one of the key patient-related factors that affect postoperative complications.

There were also considerable differences in complications between the LTDF and EXP groups, particularly regarding the higher incidence of early local complications, such as skin necrosis in the LTDF group, which was not seen in the expander group. An explanation for the difference may be the generally higher BMI in patients in the LTDF group than in patients in the EXP group. Additionally, patients in the LTDF group had a significantly higher rate of radiotherapy than in the EXP group, which also could be a cause of the LTDF group's higher rates of postoperative complications.[219-221]

A considerable number of patients in the implant reconstruction groups had received radiotherapy; from 16.2% in the EXP group to 89.4% in the LD group. The risk of capsular contracture has been reported to be high in irradiated implant-based reconstructions, which can lead to poor cosmetic results, pain,[57,61,68,104,110,111,202] increased risk of infection and subsequent implant extraction.[57,103] On the other hand, in comparison with other studies,[107,117,222] the rate of capsular contraction in this study was relatively low.

The search for independent risk factors for complications

In Paper II, it was established that both blood loss during surgery and duration of surgery were independent risk factors for postoperative complications. Long duration of surgery has been found to be an independent risk factor for thromboembolism, hematoma, and persistent pain in other specialities;[223,224] however, several studies in the field of plastic surgery have failed to find a relationship between the duration and postoperative complications.[225-227] Nevertheless, the results of Paper II are in agreement with other studies, showing prolonged duration of surgery as a risk factor for breast expander loss,[90,91] wound infection[228] and flap failure.[93,94,229] Regarding blood loss, Lymperopoulos et al. did not find a significant correlation between several patient characteristics and blood loss, but did find a high correlation between the duration of surgery and complications.[93] The results of this thesis are to a certain degree also in line with two other

studies, where a relationship between the need for transfusion and complications was evident, but at the same time showed no significant correlation between blood loss and various patient characteristics.[75,93]

The results of Paper II also demonstrate that in addition to keeping surgery duration to a minimum, meticulous surgical technique to minimize blood loss is important.

The factors of blood loss and duration of surgery are highly associated with the increased skill of the surgeons. It is well established that the experience of the surgeon is associated with a low frequency of complications.[101,230,231] However, in Paper II, no correlation was seen between the experiences of the eight surgeons (resident, consultant without extensive experience, consultant with extensive experience). There could be several explanations for these results. Firstly, the accurate methodology of registering all postoperative occurrences as complications gives no room for grading the severity of each complication. More experienced surgeons may have had complications of a milder degree than less experienced surgeons. Secondly, more experienced surgeons may have operated on patients for whom the preconditions for successful results were more complicated. Thirdly, there is a certain bias in the distribution of cases between the surgeons, in which only two of them carried out all of the microsurgical reconstructions besides the other methods, while the others only performed the non-microsurgical reconstructions. Furthermore, in the study, no attempt was made to evaluate if there were differences in the cosmetic results between more and less experienced surgeons.

In the study of Paper III, we also found that smoking, increased BMI and a history of radiotherapy were closely associated with several postoperative complications, both early and late, irrespective of reconstruction method. Interestingly, smoking was associated with several early complications (early overall complications, early administration of antibiotics, early overall local complications and early skin necrosis), but only one late complication (late resurgery). Increased BMI affected both early complications (early overall complications, early administration of antibiotics and early resurgery) and late complications (late overall complications, late signs of infection, late administration of antibiotics and late fat necrosis). A history of radiotherapy, on the other hand, generally affects late complications (late overall complications, late administration of antibiotics, late

overall local complications and late fat necrosis), but also has some effect on early complications (early administration of antibiotics and early overall local complications). Additionally, when the different independent risk factors were combined, the risks increased significantly.

The same significant independent risk factors found in Paper III have been previously identified, both in plastic surgery and in other surgical specialities.[71,72,91,100,128,132,152,218,232] However, the advantage of the study of Paper III is the evaluation of four different reconstruction methods with the same criteria for complications. This is the first study on a large group of patients where the association between an extensive collection of patient-related factors and meticulously registered postoperative complications was studied using the same definition of complications applied to all reconstruction methods, showing that the increases in risk were independent of the method. The large number of patients also allows adjustment for all confounding factors, providing independent risk factors and the construction of the solid risk models as seen in Figs 14-19. Consequently, the statistically significant associations are true associations, unbiased by operation method or patient determinants acting as confounding factors in the model.

Also of interest are the negative findings of Paper III. Hormone and chemotherapy seemed not to affect complication rates after breast reconstruction, which is in agreement with most other studies,[53,82,103] but in conflict with a study by Tallet, stating that chemotherapy is a risk factor for complications.[109] Additionally, age seems to not have an association with postoperative complications, besides a protective effect against early seroma. History of chemotherapy, adjuvant hormone therapy, and concurrent morbidity (diabetes, hypothyroidism, cardiovascular disease, history of thromboembolism, coagulopathy, rheumatic disease, neurologic disease, renal disease, liver disease, or lung disease) had no association with any of the registered complications.

Radiotherapy for breast cancer is still one of the most effective treatments to increase survival for many types of breast cancer.[31,32] Radiotherapy inevitably damages the tissue, and as long as the modus of radiotherapy is unchanged, a post-radiation breast reconstruction will be more challenging. Most studies find that radiotherapy in an implant-based reconstruction increases complications and late failure

rates. The results of the study of Paper III show as well that history of radiotherapy doubles the risk for any local complications and the results of increased risk are in line with similar studies.[57,61,68,85,103-112,116,118,120]

The aim of a successful breast reconstruction is to make the patient satisfied with the breast, even though it is never of the same quality or sensation compared to before the mastectomy or the contralateral healthy breast. One of the key elements in patient satisfaction is safety during the procedure. As noted before, it is well established that postoperative complications influence patient satisfaction.[57,63,64] Therefore it is essential to minimize risks during the surgical procedure. In order to make an individual assessment of each patient, Paper III contains important information on deciding the best reconstruction method.

Ethical considerations

The obviously increased risk associated with smoking and high BMI posits the question of whether health care providers should demand that the patients cease smoking and adapt to normal BMI before surgery. Even if high BMI and smoking can be a relative contraindication for surgery, the question can be raised of whether it can be considered discriminatory to deny certain patients breast reconstruction. It is quite simple to require that patients cease smoking before surgery because of the availability of various nicotine substitutes. However, there is lack of research on the effect of these substitutes on flap survival or wound infections after implant reconstructions, for example. Additionally, in the present thesis, the results indicate that the risks for complications increase with each unit of BMI. There does not seem to be any "cut-off" values, neither at the low end, nor at the top end. To decide the upper limit is, according to this thesis' results, arbitrary.

Health-related quality of life

As the principal aim of breast reconstruction is to reverse the deformity, created by mastectomy, and restore body image and HR-QoL, traditional clinical outcome measures, such as medical or surgical complications, do not suffice in assessing the value of different reconstruction methods for each individual patient. There are no established guidelines on choosing the best reconstruction method. However, patient perspectives and experiences are important when choosing a method, and HR-QoL needs to be investigated in a systematic way when comparing the advantages of different reconstruction methods.

There are two study designs, in which PROMs are applied: cross-sectional studies, and follow-up studies.

Cross-sectional studies collect data which represent a certain degree of HR-QoL in a certain group of patients.[166] The results of the PROM can then be compared with the known average score in the general population. As an example, in Paper IV in this thesis, the SF-36 responses of the study group were compared to 930 age-matched controls from the Swedish general population.

On the other hand, there are follow-up studies, in which measurements with the same PROMs are carried out twice or more during a certain period of time.[166,177,233] The follow-up study can also be used as a cross-sectional study at a certain moment of time, but is mostly used to evaluate changes after a specific intervention.

In this thesis, the four PROMs (SF-36, EQ-5D, PGWB, and Breast-Q) are used as a cross-sectional instrument in the reconstruction groups, in which HR-QoL is compared between four groups undergoing breast reconstruction with different methods. Breast-Q has both a preoperative and a postoperative module, and it can therefore be used as a follow-up instrument. Unfortunately, Breast-Q had not yet been developed when the patients of the study group had their surgery. Furthermore, Breast-Q values for a normal population do not exist to the best of the author's knowledge. Obtaining these values can be a basis for further research.

There are two main findings in Paper IV. Firstly, there were no significant differences in most of the domains of the HR-QoL

instruments, suggesting that none of the reconstruction methods were unquestionably superior to the others. Secondly, the only differences between the groups were found in the most specific of the instruments, the Breast-Q (with the exception of the *vitality* domain of SF-36). The patients in the DIEP group were more satisfied than the other groups in the Breast-Q domains *satisfaction with breasts* and *satisfaction with outcome*. The domain *satisfaction with breasts*, measures the perception of the breast appearance, and comprises the patient´s opinion on size, symmetry, and softness of the breast. The domain *satisfaction with outcome*, measures the overall sense of satisfaction with the outcome after undergoing breast reconstruction.[234] The patients that underwent DIEP were more satisfied with their reconstruction; this is especially interesting, given that the patients in this group had a higher frequency of complications than the patients in the other groups,[67] and it is known that postoperative complications tend to decrease satisfaction with the outcome of breast reconstruction.[57,63,64,210,211] The results of the present thesis therefore do not agree with those of previous studies.

The high *satisfaction with breasts* in the DIEP group is, however, in line with previous studies reporting similarly high rates of satisfaction in this group of patients.[235-241] Liu et al. compared autologous microsurgical reconstruction to expander/implant reconstruction, and showed similar results as in Paper IV using Breast-Q, however, only two methods were compared.[241] Another study by Yueh and co-workers, which also shows autologous reconstruction to be superior to implant-based reconstruction, compared as many methods as in Paper IV, but used other outcome measures,[238] whereas most studies only evaluate DIEP as a single method without comparing it to any other methods,[45,145,211,216,239,242,243] or comparing it only to the pedicled TRAM flap.[244-247]

All groups scored similarly on the SF-36, EQ-5D, and PGWB, with the exception that the LTDF and EXP groups had a higher score than the DIEP group in the *vitality* domain of the SF-36. This is puzzling and it might be interpreted as a Type 1 error, especially as there are no significant differences in the *vitality* domain of the PGWB. The reason for the inability of the instruments to detect significant differences is that the instruments are probably too generic and not specific enough for this group of patients.

Additionally, it would have been interesting to have preoperative HR-QoL data for the groups to be able see whether breast reconstruction has a positive effect on HR-QoL or not.

On analysis of the representativeness of the responders group compared to the non-responders group, small differences were found in age, follow-up time, smoking, history of chemotherapy and late complication rate. Smoking and history of chemotherapy are factors that can negatively affect the surgical results. It is possible that they cause a non-response bias, whereby a group of patients exposed to complications do not wish to answer the questionnaires because of dissatisfaction with the results. The shorter follow-up time of the responders and higher rate of late complications suggest that patients who were still actively thinking about their breast reconstruction were more likely to respond to the questionnaires.

The advantages of Paper IV are its relatively good response rate and well-validated generic and specific patient-reported outcome measures. The study also includes a greater number of patients compared to that of other studies evaluating patient satisfaction after breast reconstruction,[24,237,239] and is based on the registration of consecutive patients during a relatively long period of time.

However, Paper IV has some limitations. A noticeable limitation is the fact that it does not contain baseline data on HR-QoL before breast reconstruction. The Breast-Q has modules for both preoperative and postoperative evaluation,[248] but no values for a normal population. Since only non-validated specific questionnaires were in use at the time, and the Breast-Q had not been developed, baseline data on this group of patients was not available. Nevertheless, postoperative patient-reported outcome measurements, alone, do provide valuable insights into HR-QoL and patient satisfaction after breast reconstruction and can be efficiently utilized to compare reconstruction methods. To get a more comprehensive picture, a prospective study with randomized selection of reconstruction method, using both the preoperative and postoperative questionnaires, would be appropriate.

The emphasis an individual patient places on the outcome factor *satisfaction with breasts* versus the other outcome factors, such as length of recovery or complication rates, needs to be discussed with the patient and is an important factor to consider when deciding on the most suitable method of breast reconstruction.

It is unclear how to interpret the fact that all the reconstruction groups score equally, or even higher than the normal population in the physical function domain, but, on the other hand, have a lower score in the mental health domains. Even if breast cancer is rather common, the reference population is probably mostly healthy, having a distribution of physical and psychological conditions similar to the general population. With this in mind, it probably is the long-term consequences of the diagnosis of breast cancer that causes the poorer mental health. An uncomplicated interpretation of the results is that after full treatment for breast cancer, the patients may completely recover physically, but never completely recover mentally.

The number of patients in Paper IV is larger than other studies evaluating patient satisfaction after breast reconstruction[24,237,239] and is based on the registration of consecutive patients during several years. The results generally show a trend towards superior HR-QoL and patient satisfaction in the DIEP group, and it is not unlikely that an even larger sample of patients would show additional significant differences. In Sweden, there is a lifetime guarantee on breast reconstructions performed in the public funded health care system. Therefore, it is possible that the implant patients need additional corrections in the future. However, it takes a DIEP patient 1.7 procedures until completion, and many of the 0.7 operations are because of early complications. In the present thesis, there is no analysis carried out on if there generally is shorter time since the implant patients have been in the office discussing results, satisfaction or late complications, compared with the DIEP group. Analysis of this could indicate whether the implant patients are still considering their reconstruction or not.

6 CONCLUSIONS

1. The frequency of complications is high with all the four methods studied, with higher frequencies than in most other studies. It is unclear if the reason is the detailed registration of complications, and that all occurrences were considered adverse events, or if the frequency is truly higher.
2. The perioperative factors of blood loss during surgery and duration of surgery are independent risk factors for postoperative complications in breast reconstruction, without possible confounding factors being the true reason for the association.
3. The patient-related factors that also are independent risk factors for complications in breast reconstruction are previously known and they increase the risk significantly when they are combined.
4. The DIEP group were more satisfied according to the Breast-Q´s domains, *satisfaction with breasts* and *satisfaction with outcome*, than the other groups, even though the patients in this group had higher frequency of complications compared to the patients in all of the other groups.

7 FUTURE PERSPECTIVES

To get a more comprehensive picture of the operation methods, a prospective study with randomized selection of reconstruction methods using both the preoperative and postoperative questionnaires would be appropriate. Since 2010, a prospective, randomized study has been conducted at the Department of Plastic Surgery, Sahlgrenska University Hospital, where irradiated patients are randomized to either a DIEP, or an LD, and non-irradiated patients are randomized to either LTDF or EXP. At present, the patients of the study have already undergone their surgery. Data on early complications has been collected and the data is now under analysis. Data on late complications are continuously collected, but complete data with as long follow-up time as in this thesis is several years ahead.

When data from the prospective study will be analysed, it is important to compare the factors of blood loss and duration of surgery with the results of this thesis to evaluate if blood loss, duration of surgery and the frequency of complications has decreased. If that is the fact, there is even more evidence to conclude that blood loss and duration of surgery are important factors for decreasing complication frequency in the DIEP group.

In general, implant based reconstructions have a shorter duration of surgery but a larger number of reoperations. One surgical procedure has a fixed cost in terms of disposables, instruments, cost of implants, more inactive time in the operation theatre (changing from one patient to the next), and longer convalescence time. The LD, LTDF, and DI methods are planned as one-stage reconstructions, but the results of Paper I and II reveal that this is simply not correct. The actual mean number of procedures for LD, LDTF, and DI is 2.0, 2.0, and 1.9, respectively. Thus, in this patient population, the LD, LTDF, and DI are really two stage reconstruction methods. The same value for EXP is 2.5, which is a two-stage method from the beginning, and the DIEP, with all its complications, is only 1.7. When choosing the reconstructive method, this fact needs to be explained to the patients and taken into consideration in the decision-making on which methods should be offered to the patients.

There is a compelling need to study the *total* cost of the DIEP reconstructions compared to the implant based reconstructions. It is not impossible that a DIEP flap, which often is considered a much more expensive reconstruction method than implant based reconstructions, could in the long run be the most cost effective.

As long as the tissue damage of radiotherapy will not change fundamentally, the transfer of non-irradiated tissue to the breast area will be necessary, for a high quality breast reconstruction to be made. The tissue transfer approach automatically causes the reconstructive procedure to be more extensive surgery than the simple removal of the breast. The introduction of novel, individually designed, medical treatment may possibly decrease the frequency of radiation, which can help in the attempts to make breast reconstruction a less extensive surgery.

Breast-Q, which today seems to be the best instrument to measure HR-QoL and satisfaction shows, without a doubt, that DIEP patients are more satisfied with their reconstruction than patients in the other groups, even if this group is more exposed to complications, especially early complications. It is interesting to speculate which effect it would have if it was possible to significantly reduce complications in this group of patients. Is it possible that *vitality* would not be significantly lower in the SF-36? Would it be possible that DIEP patients would have a higher score in more domains than just *satisfaction with breast*s and *satisfaction with overall outcome* in the Breast-Q? If these were the results, there would be an even clearer picture pointing in the direction that for patients to get the highest gain in HR-QoL, a DIEP should be chosen. If this is the fact, the analysis of data from the prospective study should reveal it.

The study design of this thesis is a single-centre study with patients of eight surgeons. It is well accepted that surgeons have certain preferences in the choice of method for breast reconstruction. In the group of patients studied in this thesis, several of the surgeons performing the LD, LTDF, and EXP operations were not involved in the microsurgical DIEP procedures. This could have biased both choice of method, and have effects on the patients' satisfaction with the outcome. In possible future research, including patients from several clinics and more surgeons could help minimize potential confounding

effects of the clinic where the reconstructions take place and the surgeon performing the procedure.

Another aspect of implant reconstructions is that no one knows the real lifetime of the newest generation of silicone implants, which did not exist in the market, until about 15 years ago; therefore, no patients have had them longer than that. Even though, until now, there have not been any notable quality problems, it is unknown what will happen in 20 or 40 years. It is not impossible that tissue engineering can contribute with products that make silicone implants obsolete, but that also means that patients with implants have to have at least one additional surgical procedure, creating a filling under the skin to restore the breast shape.

All results combined indicate that a DIEP reconstruction with duration of surgery and blood loss kept to a minimum, in a non-irradiated, non-smoking, healthy patient with a normal BMI, has the best chance to result in an optimal quality of life after mastectomy and breast reconstruction.

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