Mesh-based Immediate Breast Reconstruction

Complications and long-term results

Håkan Hallberg, MD

Department of Plastic Surgery

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2019

Cover illustration: L'architettura. About 1570. Giambologna (1529-1608). Museo Nazionale del Bargello. Florence, Italy. Photo: Emma Hansson

Mesh-based Immediate Breast Reconstruction

hakan.p.hallberg@vgregion.se

ISBN 978-91-7833-263-2 (PRINT)
ISBN 978-91-7833-264-9 (PDF)

Printed in Gothenburg, Sweden 2019
Printed by BrandFactory

To my family

ABSTRACT

There are few high-quality studies evaluating use of meshes in implant-based immediate breast reconstruction (IBR). This thesis analyzed current evidence of matrices and compared outcomes from the use of biological or synthetic meshes and traditional muscle-covered implants. The comparisons examined short- and long-term complications and corrections, predictors of complications, and patient satisfaction and quality of life (QOL). Manuscript I describes a systematic review and meta-analysis specifically assessing differences in outcomes between reconstructions with and without matrices. Manuscript II presents the results of reconstruction using a synthetic mesh [TIGR®; $n = 49$ patients (65 breasts)]. Manuscript III compares reconstruction outcomes using a biological mesh [Surgisis®; $n = 71$ (116 breasts)] with those from a traditional muscle-covered technique ($n = 90$; 132 breasts) regarding complications and health-related QOL. Manuscript IV compared outcomes from use of either a synthetic mesh (TIGR®; $n = 49$) or a biological mesh (Surgisis®; $n = 53$) regarding long-term patient satisfaction and health-related QOL. All patients were followed between 17 and 162 months.

Meta-analysis revealed a possible increased risk of infection upon use of an acelullar dermal matrix (ADM), but not with synthetic meshes. The result must be interpreted with caution due to severe limitations in the included studies. Additionally, the results suggested that IBR with a synthetic mesh can be performed with a relatively low complication rate. The overall complication rate was higher using biological mesh as compared to muscle-covered implants; however, no significant difference was noted in implant loss rates between the groups. Predictors of complications were mainly patient-related, although high complication rates were associated with the use of tissue expanders, especially in patients with a history of irradiation. Furthermore, long-term patient satisfaction and QOL were similar when using a synthetic, biologic or no mesh, except for complications that affected patient satisfaction with the outcome. Our findings suggest that biological and synthetic meshes provide similar long-term quality of life.

Keywords: immediate breast reconstruction, plastic surgery, acelullar dermal matrix, mesh, quality of life

ISBN 978-91-7833-263-2 (PRINT)
ISBN 978-91-7833-264-9 (PDF)

SAMMANFATTNING PÅ SVENSKA

Då kvinnobröst tas bort på grund av cancer eller ökad risk för cancer återskapas ofta bröstet med protes i samma operation, detta kallas för direktrekonstruktion. Det finns olika kirurgiska tekniker för att återskapa (rekonstruera) bröst. Under senare år har det blivit mycket vanligt att använda ett nät tillsammans med protesen. Trots att det nu är vanligt är det vetenskapliga stödet för nätanvändning svagt och studier är därför angelägna. Syftet med detta projekt är att undersöka om användningen av nät är säker och vilket nät patienterna tycker ger bäst resultat.

Totalt har 210 kvinnor som genomgått direktrekonstruktion deltagit i studierna. Kvinnorna har rekonstruerats med antingen syntetisk nät, biologiskt nät eller traditionell muskeltäckt protes. De har följts under en period på mellan 1,5 och 13,5 år, kontrollerats noga på mottagningen och svarat på enkäter om vad de tycker om bröstrekonstruktionen.

I det första delprojektet visades att det vetenskapliga stödet för nät är mycket svagt och att det finns få bra studier på området. I det andra delprojektet visades att det förefaller säkert, i ett två årsperspektiv, att använda ett syntetiskt nät. I det tredje delprojektet visades att det kan vara mer komplikationer då biologiska nät används än vid traditionell muskeltäckt teknik. Riskfaktorer för komplikationer inkluderar rökning, övervikt och strålning. Patienterna som rekonstruerats med de två metoderna var lika nöjda med sina bröst enligt enkäterna. I delarbete fyra visades att patienter som opererats med biologiskt och syntetiskt nät förefaller vara lika nöjda med sina bröst på lång sikt.

Tillsammans har dessa studier visat att ur komplikationssynpunkt förefaller det vara säkert att använda nät vid bröstrekonstruktion. Kvinnor som har direktrekonstruerats med olika tekniker förfaller lika nöjda och har liknande livskvalitet.

LIST OF PAPERS

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

I. **Hallberg H**, Rafnsdottir S, Selvaggi G, Strandel A, Samuelsson O, Stadig I, Svanberg T, Hansson E, Lewin R. Benefits and risks with acellular dermal matrix (ADM) and mesh support in immediate breast reconstruction: a systematic review and meta-analysis. *Journal of Plastic Surgery and Hand Surgery* 2018; 52(3):130-147.

II. **Hallberg H**, Lewin R, Elander A, Hansson E. TIGR® matrix surgical mesh – a two-year follow-up study and complication analysis in 65 immediate breast reconstructions. *Journal of Plastic Surgery and Hand Surgery* 2018; 52(4):253-258.

III. **Hallberg H**, Lewin R, Bhatti Søfteland M, Widmark-Jensen E, Kogler U, Lundberg J, Hansson E. Complications, long-term outcome and quality of life following Surgisis® and muscle-covered implants in immediate breast reconstruction: a case-control study with a 6-year follow-up. *European Journal of Plastic Surgery* 2018 https://doi.org/10.1007/s00238-018-1444-x Open access.

IV. **Hallberg H**, Elander E, Kölby L, Hansson E. A biological or a synthetic mesh in immediate breast reconstruction? A cohort-study of long-term Health Related Quality of Life (HrQoL). *Submitted*.

CONTENT

ABBREVIATIONS

ADM	Acellular dermal matrix
ALCL	Anaplastic Large T-Cell Lymphoma
ATM	Ataxia telangiectasia mutated gene
BCT	Breast conserving therapy
BRCA	BReast CAncer susceptibility gene
BMRT	Before mastectomy radio therapy
PMRT	Post mastectomy radio therapy
CHECK2	Checkpoint kinase 2
CI	Confidence interval
CPM	Contralateral prophylactic mastectomy
DBR	Delayed breast reconstruction
DCIS	Ductal cancer in situ
DTI	Direct-to-implant
IBR	Immediate breast reconstruction
HrQoL	Health related Quality of Life
LR	Local recurrence
NAC	Nipple areola complex
NSM	Nipple-sparing mastectomy
NSSM	Non Skin-Sparing mastectomy

MRM	Modified radical mastectomy
OR	Odds ratio
OS	Overall survival
PALB2	Partner and localizer of BRCA2
PTEN	Phosphatase and tensin homolog
PRO	Patient reported outcome
PROM	Patient reported outcome measure
QoL	Quality of Life
RR	Relative risk
SSM	Skin-sparing mastectomy
TE	Tissue expander
TNBC	Triple-negative breast cancer
TP53	Tumor protein P53
TRAM	Transverse rectus abdominis myocutaneous
VAS	Visual analogue scale

1 INTRODUCTION

1.1 BREAST CANCER

Breast cancer is the most common type of cancer among women in Sweden. In 2016, nearly 9000 cases were diagnosed, with one in 10 women at risk of developing breast cancer before the age of 75. Breast cancer is a multifactorial disease where heritage and environment play a part. Additionally, female hormones, both premenopausal and postmenopausal, represent important risk factors [1].

Advances in diagnosis and treatment have improved patient prognosis, with the relative 10-year overall survival (OS) rate currently 86% [2]. As a consequence of better treatment and survival, the demand for either immediate or delayed breast reconstruction has increased, with those having an increased hereditary risk of breast cancer frequently requesting immediate breast reconstruction (IBR) [1].

1.2 SUBCUTANEOUS AND NIPPLE-SPARING MASTECTOMY

Recent advances in the pathophysiological understanding of breast cancer have radically changed surgical approaches from previous wide, clear surgical margins to the current *no ink on tumour* concept [3]. *No ink on tumour* is considered an oncologically safe surgical treatment for invasive breast cancer, where a 2-mm clear margin combined with whole-breast radiation therapy is considered safe for *ductal cancer in situ* (DCIS) [4]. This has led to less aggressive surgery and an increased proportion of breast-conserving therapy (BCT), often involving oncoplastic techniques, to obtain good aesthetic results. However, there still remain indications that might require a mastectomy [1]:

- for oncologic reasons if the tumour is large or multicentric;
- in cases where the patient previously received radiation therapy and BCT and further radiotherapy are not options;
- in small breasts, where BCT would render an unacceptable aesthetic result;
- in patients that wish to avoid postoperative radiation; and

- for prophylactic reasons in patients harbouring a cancer-specific genetic mutation or at high risk of developing breast cancer.

For patients needing a mastectomy, all women should be informed about the possibility of IBR [1].

1.2.1 THERAPEUTIC MASTECTOMY

A therapeutic mastectomy can either be done as a simple (total) mastectomy, with excision of the gland and excessive skin, or as a skin-sparing (subcutaneous) mastectomy (SSM) combined with immediate reconstruction and with or without preservation of the nipple–areola complex (NAC) [i.e., nipple-sparing mastectomy (NSM)].

The first therapeutic mastectomy with implant-based reconstruction was performed in 1971 [5]. In cases of SSM, the operation consists of removing all breast tissue, often with an elliptical incision around the NAC, which is also removed. If the tumour is superficially located, the skin overlying it is often also removed, followed by dissection between the subcutaneous fat layer and the breast tissue. This layer is not always distinct in the breast, with previous results suggesting that some breast tissue will consistently be retained on the flaps, regardless surgical technique and especially if the flaps are >5-mm thick [6]. In a cadaver study by Goldman and Goldwyn [7], performance of a subcutaneous mastectomy through a submammary incision revealed residual glandular tissue in 42% of the cases (n = 12).

It was previously feared that preserving the NAC would not be oncologically safe and could increase the risk of complications. A meta-analysis in 2010, comparing preservation of skin or not, indicated no difference in local recurrence (LR) rate between NSSM and NSM [8], although there were no randomized controlled studies included in that review. A more recent study from 2016 included >150 000 patients diagnosed with breast cancer between 1988 and 2013 (median follow-up: 7.9 years) and showed that NSM was not associated with worse OS than SSM [hazard ratio (HR): 0.86; 95% confidence interval (CI): 0.52–1.42] [9]. However, among the limitations of the study were its inclusion of only patients with unilateral mastectomy and that lack of important data, including family history and genetic mutation status. In a review from 2015, 20 studies totalling 5594 patients evaluated outcomes of therapeutic NSM versus SSM and/or modified radical mastectomy, with

findings of no adverse oncologic outcomes of NSM in carefully selected women with early stage breast cancer [10]. Although the literature suggests that NSM is an oncologically safe procedure, indications and contraindications remain debatable. In a consensus report from 2018 [11], evaluation of the available literature and a panel discussion concluded that NSM is a safe procedure when performed by specialists selecting the right patients and techniques; however, contraindications were addressed regarding NAC preservation. The findings of report emphasized the need for standardization of NSM and IBR, as well as randomized trials and recommendations to register and evaluate patient-reported outcomes (PROs).

The techniques used for NSM are similar to those described above, except for sparing the NAC and using different incisions. The type of mastectomy (conventional or skin- and/or nipple-sparing) depends upon breast shape and volume, tumour localization in the breast, the distance from the sternal notch to the NAC, and patient preference.

1.2.2 PROPHYLACTIC MASTECTOMY

According to Swedish guidelines [1], an investigation for suspected hereditary breast or ovarian cancer should be initiated in the following cases:

- breast cancer diagnosed at <40-years old;
- breast cancer diagnosed at <50-years old and with at least one first- or second-degree relative diagnosed with breast cancer;
- breast cancer diagnosed at <60-years old and at least two first- or second-degree relatives diagnosed with breast cancer;
- triple-negative breast cancer diagnosed at <60-years old;
- male breast cancer, regardless of age at diagnosis;
- ovarian or tubarian cancer or peritoneal carcinomatosis diagnosis, regardless of age; and
- the presence of other hereditary syndromes associated with breast or ovarian cancer.

In all patients where a prophylactic mastectomy might be relevant, the decision is made by the patient together with a multidisciplinary team (MDT) comprising a breast surgeon and a plastic surgeon and, in some cases, an oncologist/geneticist.

In an article from the Lancet in 1990 [12], data indicated that inherited breast cancer involved mutation(s) located on chromosome 17q21, with this work representing the starting point for current knowledge concerning hereditary breast cancer. There are a number of known mutations, with those in *BReast CAncer susceptibility gene 1* (*BRCA1*; chromosome 17q) and *BRCA2*; chromosome 13q) the most common and associated with the highest risk of developing breast cancer. Patients with *BRCA1* or *BRCA2* mutations are diagnosed with breast cancer earlier (median: 45 years) as compared with the normal population, where the age at diagnosis is 63 years [2]. Other less common mutations, such as those in *TP53*, *phosphatase and tensin homolog*, *partner and localizer of BRCA2* (*PALB2*), *ataxia telangiectasia mutated gene*, and *checkpoint kinase 2* (*CHEK2*), are also associated with an increased risk of breast cancer. However, there are mutations that remain unknown in families with a history of developing breast cancer. Some of the most common mutations are listed in Table 1.

Table 1. Common mutations related to breast cancer and their associated risk.

Gene	Lifetime risk	Ovarian cancer risk	Risk for contralateral breast cancer	Associated cancers
BRCA1	High (50–80%)	30–60%	Increased	
BRCA2	High (50–80%)	10–25%	Increased	Prostatic, pancreatic
PALB2	Medium - high (14–35%)	Evidence lacking	Unknown	
TP53	High	No evident risk		Li-Fraumeni syndrome*
CHEK2	Medium (20–25%)	No increased risk		Elevated risk for colorectal cancer

**Associated with a high risk of developing a number of malignancies, including paediatric cancer.*

In the absence of an identified mutation, the risk for developing breast cancer can be estimated using the *BOADICEA* model (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), a web-based program that calculates the risk for breast and ovarian cancer based on family history [13].

In a review published in 2018 [14], surgical outcomes involving patients harbouring *BRCA1/2*, *TP53*, and *PALB2* mutation revealed that:

- BCT and mastectomy outcomes displayed equivalent OS in BRCA1/2 carriers at a 15-year follow-up, although after 15 years, the risk for LR was higher in the BCT group as compared with the mastectomy group (23.5% vs. 5.5%);
- BCT outcomes in BRCA1/2 carriers versus non-carriers showed equivalent OS, although BRCA carriers had a significantly increased risk of LR and a relative risk of 1.151 (median follow-up: ≥7 years);
- no impaired OS was found in BRCA1/2 carriers due to radiotherapy;
- one study showed that contralateral prophylactic mastectomy (CPM) reduced the risk of metachronous contralateral breast cancer but did not affect the OS, whereas another meta-analysis demonstrated a decrease in all-cause mortality;
- in BRCA1/2 carriers without breast cancer, bilateral prophylactic mastectomy reduced the risk of breast cancer by >95%, with one meta-analysis showing reduced breast cancer-specific mortality and another showing no difference in all-cause mortality; and
- although absolute risk of breast cancer in patients harboring a TP53 is unknown, mastectomy is recommended for both healthy carriers and those with breast cancer, whereas BCT is not recommended due to a higher susceptibility to radiation-induced DNA damage and risk for subsequent radiation-induced cancer (angiosarcoma).

Similar findings were reported in a review by Ludwig et al. [15] evaluating data examining the effect of prophylactic oophorectomy and concluding that both risk-reducing mastectomy and oophorectomy reduced the risk of both breast and ovarian cancers. Moreover, improvements in ovarian cancer related and all-cause mortality were reported in association with oophorectomy (moderate quality data) but not in mastectomy (very low quality data) [15].

A large prospective study involving 3722 patients with information concerning oophorectomy status and followed either until breast cancer diagnosis, prophylactic mastectomy, or death [16] revealed no significant difference in

annual incidence of breast cancer in all patients, regardless of having undergone prophylactic oophorectomy (yes: 1.9%; no: 1.6%). After stratification according to *BRCA1* or *BRCA2* mutation, annual incidence changed to 1.7% and 1.5%, respectively, and after stratifying for age at diagnosis, no association was found between oophorectomy and *BRCA1* mutation in patients aged <50 years, although a significant reduction in breast cancer was observed in patients harbouring a *BRCA2* mutation and aged <50-years but not in patients aged >50 years ($p = 0.007$). Despite no differences in overall effect of prophylactic oophorectomy on breast cancer, their findings based on ovarian cancer onset were that prophylactic oophorectomy should be recommended at age 35 for *BRCA1* carriers and age 40 for *BRCA2* carriers.

In a Swedish national survey from 2011 and including 223 women undergoing bilateral prophylactic mastectomy at eight different hospitals between 1995 and 2005 [17], no primary breast cancer was found during a median follow-up of 6.6 years. All patients had a history of high risk of breast cancer without prior breast malignancy, and risk calculations performed using BOADICEA [13] on 204 patients revealed that ~12 incidences of breast cancer were expected in the absence of bilateral prophylactic mastectomy.

The alternative to surgery in patients without cancer is screening for early detection of a malignancy. Swedish guidelines recommend that women harbouring a *BRCA1/2* mutation begin screening starting at age 25 and continuing until age ~74 and receiving mammogram and magnetic resonance tomography (MRT) examinations from ages 25 to ~55 [1]. For patients with a moderately increased risk (>20%), onset of screening starts at 5 years before the first onset of breast cancer according to family history or no later than age 40.

1.3 IMMEDIATE IMPLANTE BASED BREAST RECONSTRUCTION (IBR)

1.3.1 INDICATIONS AND CONTRAINDICATIONS OF IBR

Swedish guidelines require that all patients receiving a planned mastectomy be informed that immediate reconstruction is an option, and that the decision regarding the procedure will be made at an MDT conference [1].

Absolute contraindications for IBR include locally advanced breast cancer, inflammatory breast cancer, and mental instability or an inability to understand the impact of the reconstruction, risks, and complications. Relative contraindications include obesity (body mass index (BMI) > 30), active smoking, and/or a comorbidity that could affect healing or risks that might extend surgery time. Additionally, irradiation is associated with higher risks for complications, especially for implant-based reconstructions, and should be avoided [1, 18].

1.3.2 QUALITY OF LIFE (QOL) ASSOCIATED WITH IBR

From an historical point of view, evaluations of breast reconstruction have mainly focused on surgical outcomes, with less attention given to patient opinion on the result. Data from the literature are inconsistent about the effect of an immediate reconstruction as compared with a simple mastectomy without reconstruction on QOL. A review by Lee et al. [19] found that seven of 11 studies reported no significant difference in QOL between those reconstructed immediately and those receiving simple mastectomy only, with three studies reporting better QOL, and one reporting worse QOL. The majority of the studies used generic instruments; however, the five studies using specific instruments for breast cancer (Breast-Q and EORTC QLQ BR-23) showed no difference or worse outcomes in QOL when an IBR was performed.

Regarding body image, nine of 16 studies found no significant differences between IBR and mastectomy alone, and seven studies reported better body image following IBR, with only one study reporting use of a breast cancer-specific instrument [19].

Regarding sexuality and sexual function, seven of 12 studies found no difference between women undergoing reconstruction and women undergoing mastectomy without reconstruction. Three studies reported improved outcomes, and two reported poorer outcomes in sexual function following IBR. Only two of the studies reported using instruments specific for breast cancer [19].

In contrast to the review from 2009 [19], a previous study comparing the QOL of 92 patients receiving immediate reconstruction as compared with 45 patients receiving mastectomy alone found that women with successful reconstruction reported significant improvements in the appearance of their chest/breasts ($p = 0.003$) and better psychosocial ($p = 0.008$) and sexual ($p = 0.007$) feelings as compared with patients receiving mastectomy alone according to Breast-Q results[20]. Additionally, the reconstructed patients reported improved physical function ($p = 0.012$) and experienced fewer limitations and pain ($p = 0.007$). RAND-36 measurements of the same patients showed significant differences in physical functioning and pain, with the reconstructed patients scoring better. The study concluded that the patients benefitted from breast reconstruction following mastectomy, although the study was very limited and had scientific flaws. Moreover, outcomes from those with complications, including radiotherapy, were not presented.

PROs can vary in the event of serious complications. A study from 2015 reported the results of a 10- and 20-year follow-up of 621 patients with a history of breast cancer who underwent CPM [21]. Of these, 403 patients underwent IBR, with most of the patients reporting stable long-term satisfaction (79%); however, patients with unplanned re-operations were significantly less satisfied and less likely to choose CPM again. Moreover, the group undergoing CPM without immediate reconstruction reported higher satisfaction (90%; $p = 0.0001$) relative to those receiving immediate reconstruction; however, both groups reported that they would definitely choose CPM again (80% in the reconstruction group vs. 91% in the group without reconstruction) [21].

A recent study investigating the accuracy of patient predictions of future well-being after IBR found that both patients with IBR and those receiving a mastectomy without reconstruction misjudged their own outcomes at 12-months post-surgery [22]. Patients undergoing a mastectomy without reconstruction underestimated their future well-being according to all Breast-Q domains, and those undergoing reconstruction generally overestimated the future outcomes associated with satisfaction with their breasts-unclothed, sexual attractiveness-clothed, and sexual attractiveness-unclothed.

1.3.3 IMPLANTS AND EXPANDERS IN IBR

The first silicone implant was invented by Dr. Tomas Cronin and initially tested on a dog, followed by use in a female patient [5, 23]. The production of breast implants has since become more strictly regulated [24, 25].

ONE- OR TWO-STAGE IBR?

An implant-based IBR can be performed as a one- or two-stage procedure. A one-stage reconstruction involves insertion of a permanent implant or permanent tissue expander (TE) in connection with the mastectomy. A two-stage procedure involves insertion of a temporary TE at the mastectomy site, followed by its replacement with a permanent implant after expansion and a specific time period.

The choice between performing a direct-to-implant (DTI) IBR or a two-stage operation with a tissue expander (TE) and subsequent insertion of a permanent implant depends upon a number of factors. The advantages of a DTI include fewer operations, especially if an NSM is performed, and shorter reconstruction time, although there might be risks of additional complications as compared with a two-stage reconstruction.

A meta-analysis from 2016 analysing outcomes between one- and two-stage implant-based reconstructions reported a statistically significant ($p = 0.02$) increase in the risk for implant loss and a significantly higher risk for total complications ($p = 0.03$) in the one-stage group as compared with the two-stage group[26]. Additionally, comparison of NSM with non-NSM indicated a significantly higher risk ($p = 0.01$) for both implant loss and total complications in the one-stage group; however, comparison of one-stage NSM with two-stage NSM showed no significant differences for any complication. There was no information concerning the use of meshes.

Only three studies have reported aesthetic outcomes based on evaluations performed using different panels, with no significant differences found between one- and two-stage reconstructions. However, the one-stage group had lower total costs, despite higher costs associated with complications. The study concluded that one-stage reconstruction is comparable with two-stage reconstruction in patients with NSM, despite the higher cost of complications, but that controlled studies are required to draw solid conclusions [26].

A review from 2015 of 10 retrospective cohort studies, two prospective cohort studies, and one prospective randomized trial including >5000 patients showed no significant differences in risk for hematoma, seroma, infection, or capsular

contracture between one- and two-stage reconstruction [27]. However, the risks of flap necrosis [odds ratio (OR): 1.43; CI: 1.09–1.86) and re-operation due to complications (OR: 1.25; CI: 1.02–1.53) were higher in the DTI group. Additionally, 11 studies reported implant-loss rates exhibiting a significantly increased risk in the DTI group (OR: 1.87). The authors noted study limitations, including bias in selecting DTI or TE, and the fact that subgroup analysis could not be performed regarding the use of acellular dermal matrix (ADM), irradiation, and chemotherapy due to lack of data. Moreover, they stressed the need for data concerning PROs and QOL [27].

In a recent prospective multicentre study of 99 patients who underwent DTI and 1328 patients operated on with TE and later exchanged to a permanent implant[28], no significant differences were found in complications. PROs assessed with a panel of questionnaires, including use of the Breast-Q with baseline data from the time of surgery and follow-up after 2 years revealed no significant differences in satisfaction with breasts, psychosocial well-being, physical well-being, except for sexual well-being, were DTI scored better [28].

DTI was the standard procedure for early implant-based breast reconstruction; however, the use of expanders increased along with increased demand for IBR. The introduction of ADM resulted in another increase in DTI use due to reports that ADM might improve results and decrease complications [29]. A multicentre study (11 centres and 1427 patients) compared 2-year complication rates and PROs for DTI compared with TE, with results indicating that there were more complications in the DTI group (32.3% vs. 26.2%), although the differences were not statistically significant. PROs measured preoperatively and after 2 years showed that patients in the DTI group scored significantly better for sexual well-being, but otherwise no differences were found. Reconstructive failures were excluded from the analysis [28].

Traditional muscle-covered IBR

Tissue that remains following a mastectomy is often very thin and vulnerable due to decreased blood supply. Moreover, the space under the flaps is wide and increases the risk of implant movement, especially laterally, and rippling of the overlaying skin. To address this issue, additional tissue allowing coverage with a layer of muscle is needed. Traditional surgical techniques aimed to achieve complete coverage over the implant by opening the major pectoral muscle in the direction of the muscle fibre, thereby creating a pocket comprising the major pectoral muscle and the lateral serratus muscle (Figure 1) [30].

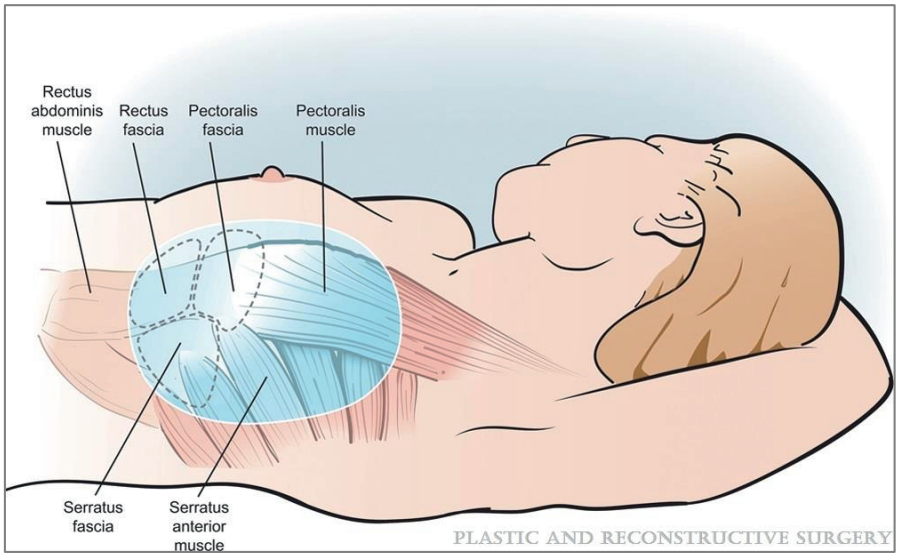

Figure 1. Complete muscle coverage (implant pocket represented in blue color). Copyright: Wolters Kluwer: 2016, Cordeiro et al., Two-stage Implant-based Breast Reconstruction: An Evolution of the Conceptual and Technical Approach over a Two-Decade Period, Plastic and Reconstructive Surgery, 138(1), p 1-11. Https://journals.lww.com/plasreconsurg/pages/default.aspx.

Disadvantages of these procedures include the difficulty of DTI due to the lack of expansion, especially in larger breasts. Even when a TE is used, the expansion of the lower pole can result in a flattened appearance and a less successful aesthetic result. Currently, the preferred technique involves dual-plane dissection, where the major pectoral muscle is released from the inferior attachment and medially at the sternum, and a pocket is created between the thoracic wall and the serratus muscle in order to prevent lateral movement of the implant (Figure 2). The main advantage of this technique is improved lower-pole expansion, which provides a more naturally shaped breast, whereas the main disadvantage is the risk of pectoral-muscle retraction, which would result in less coverage in the lower pole. In both cases, either an implant or TE is introduced in the newly created pocket.

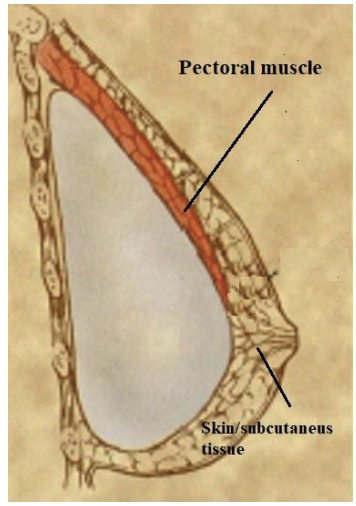

Figure 2. Partial muscle coverage, dual plane. Copyright: Wolters Kluwer: 2006 Tebbetsl., Dual Plane Breast Augmentation: Optimizing Implant-Soft-Tissue Relationships in a wide Range of Breast Types, Plastic and Reconstructive Surgery, 118(7), p 81-98. Https://journals.lww.com/plasreconsurg/pages/default.aspx.

Alternative lower-pole coverage: dermal sling and meshes

These techniques sometimes involve problems with implant positioning and a lack of tissue in the lower pole in the case of dual-plane muscle coverage, with accompanying increased risks of implant exposure and a sub-optimally defined submammary fold. The introduction of ADMs and synthetic meshes and their use in breast reconstruction offered a potential resolution to many of the shortcomings associated with muscle coverage. The surgical technique is similar to that for the dual-plane procedure; however, to achieve coverage of the lower pole of the breast, the matrix or mesh is sutured to the submammary fold and to the lower part of the pectoral muscle and laterally to the chest wall, without raising the serratus muscle. The result is a more complete coverage of the implant and the creation of an ´internal bra´.

In the case of a larger and ptotic breast, the inferior portion of the skin envelope, with or without preservation of the NAC, can be de-epithelialized and used to cover the lower pole of the breast (Figure 3-4). The skin is subsequently sutured to the lower part of the pectoral muscle, as described

above. Using patient-derived tissue has the advantage of no extra cost and minimized risk for foreign body reaction, which can be an issue with biological and synthetic meshes. Additionally, this method allows NAC preservation in large and ptotic breasts, where disadvantages include smaller breast size in most cases [30, 31].

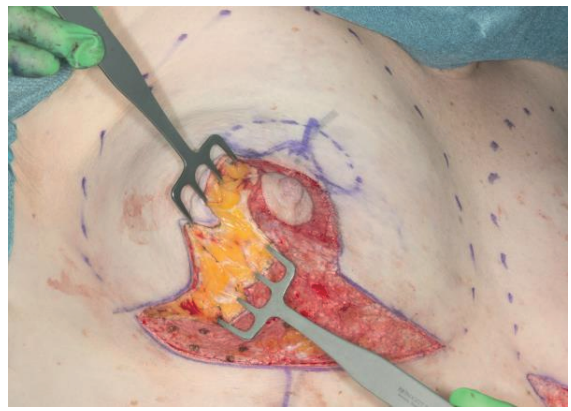

Figure 3. Dermal sling, with preserving of the NAC, incision. With permission from Journal of Plastic, Reconstruction & Aesthetic Surgery: Lewin et al., Immediate breast reconstruction with a wise pattern mastectomy and NAC-sparing McKissock vertical pedicle dermal flap, 2018, 71(10), p 1432-1439

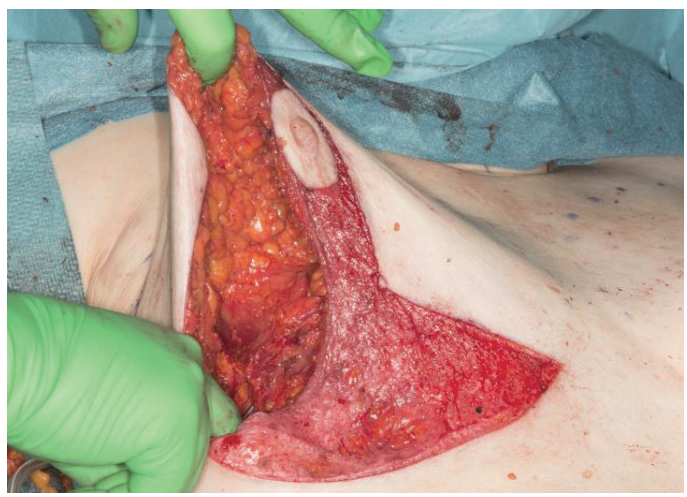

Figure 4. Dermal sling, with preserving of the NAC, flap raised. With permission from Journal of Plastic, Reconstruction & Aesthetic Surgery: Lewin et al.,

Immediate breast reconstruction with a wise pattern mastectomy and NAC-sparing McKissock vertical pedicle dermal flap, 2018, 71(10), p 1432-1439

1.3.4 MESHES USED IN IBR

The first study citing the use of allograft dermis in aesthetic breast surgery to reduce rippling in 34 patients with breast implants was published[32]. Apart from one patient suffering an infection and another developing a capsular contraction, no complications were noted, and patients reported a high degree of satisfaction [32].

The first use of mesh in an IBR was presented by Breuing and Warren [33]. Bilateral mastectomy and immediate reconstruction were performed in 10 patients and using an allograft, Alloderm® (LifeCell Corporation, Woodlands, TX, USA) to cover the lower/lateral part of the breast. The allograft eliminated the need for a TE and provided an option for single-stage reconstruction with an implant, with one complication involving suture-line ischemia during the follow-up period (6–12 months) reported.

Numerous studies have since been published reporting varying results and a number of mesh-specific advantages [34], as follows:

- a decreased or eliminated need for expanders;
- reduced post-operative pain;
- decreased operation time;
- increased initial-fill volumes of the expander;
- fewer expansions;
- precise control over the lateral and inframammary folds;
- increased ability to use more of the mastectomy skin flaps;
- faster completion of the reconstruction;
- improved lower-pole expansion;
- decreased incidence of capsular contraction;
- fewer capsular modifications at second-stage surgery; and
- improved aesthetic outcome.

In a review by Nguyen et al. [34], the proposed advantages were addressed, and consistent support for decreased incidence of capsular contraction was found, although following limited long-term follow-up. All other proposed advantages were considered mostly anecdotal [34].

BIOLOGICAL MESHES: ADM

Biological meshes include those derived from human dermal tissue [i.e., ADM; e.g., Alloderm®, Allomax®, FlexHD®, and Dermacell®) and those derived from non-human sources, such as xenografts from pig skin, pig bowel submucosa, or pericardium from veal (e.g., Strattice®, Surgisis®, and Veritas®).

ADM from human tissue is not approved for use in Sweden but represents the most used mesh in the United States. In nearly 90 000 annual IBRs performed in the United States, an ADM (mostly Alloderm®) was used in the majority of cases [35]. All biologic meshes are processed using different techniques in order to remove donor cells and potential pathogens while retaining other structures. The meshes can either be sterile or aseptic, with differences in mesh sourcing and processing evidently unimportant [35]. In randomized trials performed by Mendenhall et al. [36, 37] comparing Alloderm® and Dermamatrix®, the biological ADMs that had been processed differently showed no significant differences in complications [36, 37]. There are few studies comparing human- and xenograft-derived ADM [35].

SYNTHETIC MESHES

The use of synthetic meshes has become more common in recent years due to the high costs of and unclear evidence associated with the use of biologic meshes [34]. Synthetic meshes can be either absorbable (TIGR® Matrix, SERI® scaffold, and Vicryl®) or permanent (TiLOOP® bra, ULTRAPRO®, Surgimesh-PET®, and Gore® DualMesh). Meyer Ganz et al. [38] compared IBR between a group with a complete submuscular pocket (46 breasts) and a group with a partial submuscular pocket in combination with a Vicryl® mesh (115 breasts), findings no significant difference in early complications at a 90-day follow-up (4.4% vs. 11.6%, respectively). Moreover, at a 5-year follow-up, early and late complications were similar. with 41.3% in the total submuscular group and 33.9% in the Vicryl® mesh group. However, there were significantly fewer surgical revisions necessary in the mesh group (8.9%) as compared with 21.7% in the non-mesh group ($p = 0.05$).

Dieterich et al. [39] retrospectively compared IBR with and without permanent TiLOOP® in order to evaluate differences in QOL with a validated instrument Breast-Q [40]. The results indicated no significant differences in complications across the entire study group (90 patients), with an overall complication rate of 21.1%. Comparison of QOL outcomes showed no differences in Breast-Q results between the groups.

BIOLOGIC VERSUS SYNTHETIC MESHES

There are relatively few studies comparing outcomes associated with the use of biological and synthetic meshes. In one prospective randomized trial, Gschwantler-Kaulich et al. [41] compared use of an ADM (Protexa®) with that of TiLOOP®, with an initial report of higher incidence of severe complications, including implant loss ($p < 0.0001$), in the Protexa® group. Due to the small sample size ($n = 48$), this statement was later corrected to a non-significant but increased risk for implant loss in the Protexa® group ($p = 0.068$)[42]. This study was subsequently criticized by Potter et al. [43] for their lack of a primary end point, definition of complications, and use of validated specific QOL instruments.

1.3.5 COMPLICATIONS IN IMPLANT-BASED IBR

EARLY COMPLICATIONS

Complications following IBR are evaluated at both short- and long-term periods. Most authors define early complications as events within 30 days, although these are often loosely defined in many articles, thereby making it difficult to compare incidences between different studies. Early complications are often divided into minor complications, such as seroma, hematoma, minor necrosis or infections, and others not needing any surgery or hospitalization but merely local treatment or medication, whereas major complications are mostly defined as events that either have serious consequences involving failure of the reconstruction or major medical events that require hospitalization with surgery and/or medication.

A study by Arver et al. [17] of 223 patients receiving bilateral IBR with either autologous reconstruction, DTI, or TE/implant (TE/I) at eight centres reported that 52% of patients experienced one or more complications, the most common of which was partial skin necrosis in 29.9%, followed by wound infection (17.0%), blood loss requiring transfusion (9.0%; 67% in the autologous group and 9% in the implant groups), hematoma (8.1%), seroma (7.6%), and wound rupture (3.6%). Serious non-breast-related complications occurred in 3% of patients, with implant loss of 10%. Similar complication rates were reported in a study of 269 women, where 64% indicated one or more complications within 1 year of surgery [44], and the majority of complications occurring within 1 month after surgery. Neither of these articles addressed the eventual impact of irradiation or mesh use on the development of a complication.

In a study evaluating the effect of radiation on IBR, Eriksson et al.[18] showed that radiation administered before reconstruction resulted in a reconstruction-failure rate of 25%, whereas patients receiving radiation postoperatively displayed a reconstruction-failure rate of 15% relative to a 6% rate in non-irradiated patients.

In a review by Basta et al. [27], 13 studies with a total of 5216 patients and comparing complications between DTI with TE/I reconstructions revealed higher risks of flap necrosis (OR: 1.43; p = 0.0.1), implant loss (OR: 1.87; p = 0.04), and re-operation due to complication in the DTI group (OR: 1.25; p = 0.04) (Tables 2 and 3).

Table 2. Studies included in the meta-analysis. *

Reference	Design	LOE	Two-Stage	DTI	Total	Timing	Follow-Up (mo)
Pinsolle et al., 2006[21]	R-COH	III	27	38	65	Immediate	84.0
Breuing and Colwell, 2007[27]	R-COH	III	14	30	44	Immediate*	18.9
Mitchem et al., 2008[28]	P-COH	II	34	5	39	Immediate	NR
Plant et al., 2009[29]	R-COH	III	10	14	24	Immediate	NR
Hvilsom et al., 2011[18]	P-COH	II	149	40	189	Immediate	46.8
Petersen et al., 2012[31]	R-COH	III	81	127	208	Immediate	44.4
Roostaeian et al., 2012[32]	R-COH	III	87	62	149	Immediate	14.0
Kim et al. (in press)[34]	R-COH	III	40	23	63	Immediate	22.4
Lardi et al., 2014[35]	R-COH	III	90	110	200	Immediate	22.2
Susarla et al., 2015[37]	R-COH	III	416	166	582	Immediate	NR
Eriksen et al., 2012[30]	P-RCT	I	20	20	40	Immediate	42
Colwell et al., 2014[33]	R-COH	III	185	286	471	Immediate	26.0
Gfrerer et al., 2015[36]	R-COH	III	1264	1878	3142	Immediate	86.9
Total	—	—	2417	2799	5216	—	40.8 (SD, 26.8)

LOE, level of evidence; DTI, direct to implant; R-COH, retrospective cohort; P-COH, prospective cohort; P-RCT, prospective, randomized, controlled trial; NR, not reported.
*Four delayed reconstructions excluded from analysis.

PLASTIC AND RECONSTRUCTIVE SURGERY

**Copyright: Wolters Kluwer: 2018, Basta et al., A systematic Review and Head-to Head Meta-analysis of outcomes following Direct-to-Implant versus Conventional Two-stage Implant Reconstruction, Plastic and Reconstructive Surgery, 136(6), p 1139.*
Https://journals.lww.com/plasreconsurg/pages/default.aspx.

*Table 3. Comparison of complications observed between DTI and TE reconstruction according to a meta-analysis. **

Outcome	*n* (*N*)	Incidence (%)		OR (95% CI)	*p*	I^2 (%)
		DTI (95% CI)	Two-Stage (95% CI)			
Implant infection	11 (5129)	7.8 (3.7–12.0)	7.4 (2.7–12.1)	1.08 (0.68–1.72)	0.74	38
Seroma	7 (1675)	6.8 (2.5–11.0)	7.1 (3.1–11.1)	0.95 (0.57–1.60)	0.85	0
Hematoma	7 (1700)	4.3 (0.3–8.3)	5.2 (−1.0–12.4)	0.96 (0.49–1.89)	0.90	0
Flap necrosis	9 (4900)	8.6 (1.9–15.4)	6.7 (2.7–10.6)	1.43 (1.09–1.86)	0.01	51
Contracture	5 (647)	13.5 (−5.1–32.3)	13.8 (0.3–27.2)	0.90 (0.44–1.85)	0.77	0
Reoperation	9 (4432)	17.9 (5.0–30.8)	14.1 (6.2–22.1)	1.25 (1.02–1.53)	0.04	43
Implant loss	11 (1683)	14.4 (7.3–21.4)	8.7 (2.0–15.4)	1.87 (1.05–3.34)	0.04	33

n (*N*), no. of studies (no. of patients) for each outcome; DTI, direct-to-implant; *F*, interstudy heterogeneity. PLASTIC AND RECONSTRUCTIVE SURGERY

**Copyright: Wolters Kluwer: 2018, Basta et al., A systematic Review and Head-to Head Meta-analysis of outcomes following Direct-to-Implant versus Conventional Two-stage Implant Reconstruction, Plastic and Reconstructive Surgery, 136(6), p 1139.*
Https://journals.lww.com/plasreconsurg/pages/default.aspx

Because complications often are reported as occurring with 30-days post-surgery, there might be a risk that total complication rates are underestimated. In a study of 903 IBRs, Hansen et al. [45] showed that the overall complication rates at day 30 at 5.9%, which increased to 18.9% at the 1-year follow-up. Additionally, implant-loss rate also increased from 2.3% to 13.2%. Moreover, univariate analysis revealed that patients reporting a complication at 1-year post-surgery were significantly older, experienced additional comorbidities, and had a higher BMI as compared with patients reporting no complications.

LATE COMPLICATIONS

Some complications appear later after primary surgery, with capsular contraction an example of one that can develop years after the initial breast reconstruction. Capsular contraction is a complication reportedly caused by local excessive formation of collagen due to a foreign body reaction [46]. The exact mechanism remains unclear; however, one theory is that it is caused by a complex combination of bacterial contamination in the implant pocket, which stimulates inflammation and leads fibroblast proliferation and collagen deposition and contracture [47, 48], thereby resulting in a firm and sometimes painful breast. The grade of capsular contraction is traditionally classified using the Baker classification system [49], which was originally intended for augmentation mammoplasty and represents a subjective evaluation of breast firmness by a physician. Spear and Baker [50] modified this system to allow a

more accurate description in the context of breast reconstruction, with the modified system including Grades I through IV:

- Grade I, a normal breast;
- Grade II, a mild contraction with no symptoms;
- Grade III, a moderate capsular contracture, where the implant can be palpated easily and might be visible or distorted; and
- Grade IV, severe firmness with significant distortion and pain/tenderness.

The surface of the implant plays a major role in elevated risk of developing capsular contraction. A meta-analysis [51] reported an OR of 0.19 (CI: 0.07–0.052) in favour of textured implants as compared with smooth implants. Implant surfaces have been altered over time, and recent nanotechnology/microtechnology has improved implant interactions with surrounding tissue in order to reduce the risk of capsular contraction, although no clinical long-term follow-up studies have been performed [47].

The incidence of capsular contraction varies in the literature from a low percentage to ~30% [52], with this representing the most common overall indication for re-operation among patients with breast implants. Handel et al. [53] reported that the cumulative risk for developing capsular contraction increases by the time the implant is in place according to Kaplan–Meier analysis [data derived from a mean follow-up of 37.4 months (range: 0–280)]. In contrast to Barnsley et al. [51] they [53]reported no differences observed in contracture incidence between smooth and textured implants, but noted a decreased incidence with polyurethane foam-covered implants.

BREAST-IMPLANT-ASSOCIATED CANCER

In 2006, the results of a long-term epidemiologic study with an average follow-up time of 18 years involving women with cosmetic breast implants showed no increased risk of breast or other cancers [54]. In 1995, a case report of three patients with cutaneous T-cell lymphoma and breast implants indicated possible associations between breast implants in young females and cancer onset, although the causality was unknown [55]. Another study not long after the case report identified T cell lymphoma in the proximity of an implant [56]. Jong et al. [57] described patients with breast implants and diagnosed with anaplastic large T-cell lymphoma (ALCL) in the breast and suggested a possible association with the implants. A subsequent report described 56 cases

diagnosed in New Zeeland and Australia between 2007 and 2018 [58]. The evidence for an association between ALCL and breast implants is now well established, and the World Health Organization classified breast-implant-associated ALCL (BIA-ALCL) as a new entity in 2016[59]. BIA-ALCL onset usually presents as a seroma formation between the implant and the surrounding fibrous capsule, with the median interval from primary surgery to onset of the lymphoma ~10 years [59]. The exact incidence in Sweden is not known but is generally considered low (i.e., ~10 cases have been diagnosed since 2016). Due to the low incidence of BIA-ALCL, its diagnosis and treatment have varied among different centres worldwide. The National Comprehensive Cancer Network published guidelines for the diagnosis and management of BIA-ALCL in a consensus meeting in 2017 [60].

RISK FACTORS FOR COMPLICATIONS

The causes of IBR-related complications are multifactorial and include those that are patient-, surgery, and treatment-related [61].

Patient-related risk factors

Several patient-related factors, such as smoking, BMI, and advanced age, increase the risk for IBR-related complications. Song et al. [62] measured cerebral blood flow by quantitative MRT in 15 healthy men (age <45 year), revealing a significant decrease in blood flow after smoking [7.3% ($p = 0.024$)]. In two studies of >10 000 patients, the ORs for implant loss or skin necrosis in active smokers was 4.0 and 3.55, respectively (Table 4) [63, 64]. Additionally, Lardi et al. [65] showed that the risk for implant loss or skin necrosis/infection doubled in patients presenting a BMI >30 (Table 4), and Eriksson et al. [18] reported an increased risk for implant loss in patients presenting a BMI >25 (HR: 2.01; $p = 0.002$). Furthermore, Fischer et al. [63] and Jimenez-Puente et al. [66] found patients aged >50 were at an increased risk for implant loss/reconstructive failure (Table 4).

Table 4. Reports of patient-related risk factors associated with IBR.

Risk factor:	**Fischer et al. (*n* = 9305)[63]**	**Jiménez-Puente et al. (*n* = 112) [66]**	**Lardi et al. (*n* = 149)[65]**	**Gfrerer et al. (*n* = 3142)[64]**	
Outcome	Implant loss	Reconstructive failure	Any complication	Skin necrosis	Infection
Age (y)	>55; (OR: 2.0; CI: 1.3–3.2; p = 0.004)	>50; (OR: 3.02; CI: 1.19–7.67; p = 0.02)	NR	OR=1.01 (p=.0556)	OR=1.02 (p=0.092)
BMI (k/m²) >30	OR: 1.7; CI: 1.1–2.7; p = 0.03	NR	OR: 2.16; CI: 1.07–4.33; p = 0.0308	OR=2.12 (p=<0.01)	OR=1.7 (p<0.05)
Active smoker	OR: 4.0; CI: 2.5–6.4; p = 0.001	NR	Mastectomy weight >600 g or BMI >30 kg/m^2	OR=3.55 (p<0.01)	OR=0.63 (p=0.380

Surgery related risk factors

IBR-related complications are often related to thin mastectomy flaps and impaired blood circulation. Surgery related risk factors for complications have been identified and are presented below.

Surgeon experience

Studies show that surgeon experience can affect the risk for complications. Eriksson et al. [18] performed multivariate analysis, revealing that the risk for reconstruction failure increased for reconstructive surgeons with <5 years of experience (HR: 3.62; CI: 1.61–8.12; p = 0.002). Additionally, Gfrerer et al. [64] analysed the importance of surgeons, revealing a significant variation in the risk for skin necrosis among surgical oncologists, with ORs varying between 0.69 and 2.98. Reconstructive teams were analysed according to number of performed procedures (ranges: <150, 150–300, and >300), with multivariate analysis showing an increased rate of infections in the group with the least experience (OR: 2.48; p < 0.05).

IBR versus delayed breast reconstruction (DBR)

There are few randomized trials comparing complications between IBR and DBR. A previous study [67] of >17 000 patients and comparing wound complications following IBR and DBR (with IBR defined as surgery within 7 days of mastectomy and DBR as a mastectomy without IBR within >7 days of surgery) indicated that for IBR, the incidence of surgical-site infection was significantly higher (8.9%) as compared with 3.3% in the DBR group. By contrast, surgical-site infections were similar between IBR and DBR in an autologous reconstruction group (9.8% vs. 13.9%). Additionally, surgical-site infections and non-infectious wound complications were higher in secondary implant reconstructions receiving adjuvant radiotherapy relative to autologous reconstruction, where no increased rates were observed. These results suggested that some high-risk patients might benefit from DBR or autologous reconstruction to reduce the risk of serious complications [67].

One-stage (DTI) versus two-stage (TE/I) breast reconstruction

Srinivasa et al. [28] compared DTI and TE/I groups, showing no significant differences in the rates of complications, which occurred in the range of 26.2% to 32.3% of the time while reconstructive failure occurred from 7.4% to 8.1% of the time. Additionally, ADM was more frequently used in the DTI group (92.9%) as compared with the TE/I group (51.7%), and radiation was more common in the TE/I group. Regression analysis showed significant complications associated with BMI, age, smoking status, laterality, lymph node management, and radiation.

Incision for breast reconstruction

Incision and implant type can affect the risk of developing complications. A systematic review comparing one-stage reconstruction (DTI) with two-stage reconstruction (TE) and using a Wise pattern incision showed an increased risk for overall complications in the DTI group as compared with the TE group (30.3% vs. 20.3%) [68].

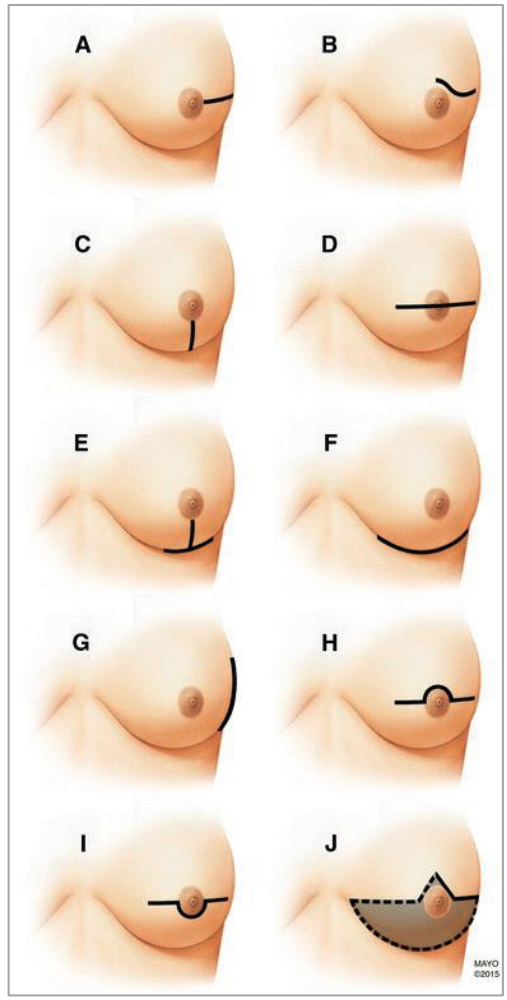

Figure 5. Examples of incision used in immediate breast reconstruction. Wise pattern with and without saving NAC, E and J.
Reprinted by permission from Springer Nature: Current Surgery Reports, Nipple-Sparing Mastectomy: To Spare or Not to Spare, Akiko et al., 2016

Treatment-related risk factors

Preoperative and postoperative radiotherapy

Preoperative or postoperative radiation is associated with a higher risk of complications, although the literature shows large heterogeneity in the size of the increased risk. A study from Sweden of 725 patients operated on at four hospitals evaluated irradiation and PRO measures, finding a reconstructive-failure rate of 6% in non-irradiated patients (NoRT) as compared with 25% for those receiving irradiation before mastectomy (BMRT) and 15% in patients receiving irradiation postoperatively (PMRT)[18]. The median follow-up was 43 months, and estimation of the 5-year failure rate revealed a 10.4% risk in the NoRT group, a 28.2% risk in the BMRT group, and a 25.2% risk in the PMRT group, with no report of the eventual impact of mesh use[18]. Similar findings were reported from a single-centre study of 210 patients (265 breasts)[69], where PMRT showed an increased rate of expander infection as compared with NoRT (20% vs. 2.6%; $p = 0.001$) and expander removal (26% vs. 8.3%; $p = 0.007$), with the overall failure rates for both expander use and later exchange to a permanent implant of 26.1% (BMRT), 21.2% (PMRT), and 6.2% (NoRT).

In a large database study analysing data from 4781 patients who underwent mastectomy combined with radiotherapy and breast reconstruction (IBR or DBR), the overall complication rate associated with IBR was 45.3% as compared with 30.8% with autologous reconstruction, with reconstruction-failure rates of 29.4% and 4.3%, respectively[70]. Among the study limitations were that it only included patients using insurance and lacked information concerning race/ethnicity, BMI, smoking status, prior surgery, and surgery preference. Moreover, the study did not include information about the use of meshes; however, the authors concluded that their analyses offered insight into the morbidity of irradiated patients undergoing varies types of breast reconstruction.

A recent prospective multicentre study of 622 irradiated and 1625 non-irradiated patients showed that at a 2-year follow-up, 38.9% of IBR patients had experienced at least one complication in the irradiated group as compared with 25.6% of those undergoing autologous reconstruction and irradiation, whereas 28.3% of the non-irradiated group experienced a complication[71]. Additionally, Laporta et al. [72] performed a multivariate analysis based on 288 patients receiving a mixture of autologous and implant-based NSM, with BMRT patients showing an increased risk of complications (OR: 10.14; CI: 3.99–27.01; $p < 0.001$).

1.3.6 AUTOLOGOUS IBR

Autologous breast reconstruction was first reported in 1895, with Vincenz Czerny describing transfer of a lumbar lipoma to a breast as a substitute after a lumpectomy [23, 73].

THE LATISSIMUS DORSI FLAP

In 1896, the first breast reconstruction using the latissimus dorsi myocutaneous flap was described by the Italian surgeon Iginio Tansini [74]. This method did not gain interest until Olivari 'rediscovered' the flap and deemed it safe and suitable for treating irradiation damage or addressing recurrence following mastectomy [75]. Subsequent development of the method resulted in its frequent use as both a pedicle flap for breast reconstruction, as well as other types of reconstructions in the area, and as a free flap for other reconstructive procedures.

ABDOMINAL FLAPS

From the early 1900s to the late 1970s, different tubed flaps were tested for breast reconstruction. However, flaps from the abdomen gained wider interest after Mathes and Bostwick [76] first described use of the rectus abdominis myocutaneous flap for reconstruction of the abdominal wall, with its later use for breast reconstruction. Additionally, Holmström [77] described a novel technique involving use of a rectus abdominis myocutaneous free flap with microvascular anastomosis for breast reconstruction. This method was derived from observations of abdominoplasty procedures, which confirmed that elevation of an abdominal flap on isolated vessels did not compromise tissue viability. Hartrampf et al. [78] later described a technique using a transverse rectus abdominis myocutaneous (TRAM) flap in breast reconstruction. The work of Holmström [77] offered a foundation for later work by Taylor [79] describing muscle-saving technique, where the flap comprised the lower part of the rectus abdominis muscle and preserved the periumbilical rectus abdominis perforators. Later, the deep inferior epigastric perforator (DIEP) flap was invented by Allen and Treece [80] in an attempt to preserve the rectus abdominis muscle, with this technique currently used following subsequent modifications.

OTHER AUTOLOGOUS RECONSTRUCTION METHODS

Other methods in addition to those using the latissimus dorsi and TRAM/DIEP flaps have been developed. The first free gluteal myocutaneous flap for use in breast reconstruction was described by Fujino [81], with other flap variations subsequently developed [23, 82].

2 AIMS

The aims of this thesis were as follows:

- Analyze differences in cancer recurrence, oncologic treatment, health-related quality of life, complications, and aesthetic outcomes between the use of a matrix or no matrix (I);

- Examine short-term complications (<30 days) and predictors of complications following breast reconstruction using a TIGR® Matrix Surgical Mesh combined with a tissue expander/implant (TE/I) or a direct-to-implant (DTI) (II);

- Compare short- and long-term (>90 days) complications and predictors of complications, as well as long-term patient quality of life and satisfaction, following immediate TE/I-based breast reconstruction using a Surgisis® matrix and a traditional muscle-cover technique (III); and

- Compare patient quality of life and satisfaction following immediate breast reconstruction (IBR) using a biological mesh (Surgisis®) or a synthetic mesh (TIGR®) (IV).

3 PATIENTS AND METHODS

3.1 STUDY DESIGN

Study I was a systematic review and meta-analysis, study II was a case-series study, study III was a case-control study, and study IV was a cross-sectional study between two cohorts from studies II and III.

3.2 EVALUATION METHODS AND DATA COLLECTION

3.2.1 SYSTEMATIC REVIEW AND META-ANALYSIS (I)

A systematic review is a research technique that qualitatively summarises the results of multiple studies in order to generate the highest grade of evidence, whereas a meta-analysis quantitatively synthesizes the studies using statistical methods [83]. Inclusion criteria for our study were defined according to PICO (Patient, Intervention, Comparison, and Outcome) and designed in accordance with the aims of the study.

Patients:

- One- or two-stage IBR in women with hereditary risk of developing breast cancer or diagnosed with breast cancer and either having received or not received radiation treatment.

Intervention:

- Breast reconstruction with a biologic mesh or a synthetic mesh.

Control:

- Breast reconstruction without a mesh.

Outcome:

- HrQoL
- Breast cancer recurrence and associated mortality
- Aesthetic outcome
- Complications (e.g., implant loss or infections)
- Capsular contraction
- Delayed neo-adjuvant therapy due to complications

For the meta-analysis, we included all randomised and non-randomised controlled trials and either case series with >200 patients reconstructed using a biologic mesh, AlloDerm® or those with >20 patients reconstructed using any other ADMs or matrices/meshes.

For study I, systematic searches were performed in May 2016 of PubMed, Embase, the Cochrane Library, the Centre for Reviews and Dissemination database, and the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and the Norwegian Knowledge Centre for the Health Services. Additionally, the lists of references in relevant manuscripts were scrutinised for relevant studies. Searches were conducted using a controlled vocabulary and words taken from titles and abstracts. The search was limited to studies in English, Swedish, Danish, and Norwegian and to articles published from 2005 to 2016. Literature searches, study selection, and abstract assessment were performed separately by two different researchers, and any disagreements were resolved in consensus. All authors read the selected articles independently, and a consensus meeting determined which articles should be included in the assessment.

The included studies were critically appraised using a checklist for the assessment of cohort studies [84] modified from that used by the SBU by the Centre for Health Technology Assessment at Sahlgrenska University Hospital. The appraisal addressed directness (external validity), risk of bias (internal validity), and precision using a three-level scale. Data were extracted by at least two authors per outcome.

The certainty of evidence across studies was assessed by all authors and rated separately for all outcomes according to the GRADE system (Grading Recommendation Assessment Development and Evaluation) [85] as high ⊕⊕⊕⊕, moderate ⊕⊕⊕, low ⊕⊕, or very low ⊕ quality:

- High: "Further research is highly unlikely to change our confidence in the estimate of the effect."
- Moderate: "Further research is likely to have an important impact on our confidence in the estimate of the effect and might change the estimate."
- Low: "Further research is very likely to have an important impact on our confidence in the estimate of the effect and likely to change the estimate."
- Very low: "Any estimate of the effect is very uncertain."

3.2.2 CLINICAL EVALUATION (II–IV)

For studies II through IV, patients were clinically evaluated at 1-week and 3- and 12-months post-operatively and thereafter based on need. We used a clinical case report form to ensure standardization of patient evaluation for all complications.

The registered demographic variables included age, preoperative BMI (the ratio of the body mass in kilograms and the square of the height in meters), and smoking status. The registered clinical details included comorbidities, laterality, reason for mastectomy, type of mastectomy, specimen weight (using scales with an accuracy of 0.01 kg), implant type and size, perioperative inflation volume in millilitres, receipt of preoperative or postoperative radiotherapy, and complications.

Determinations of which complications to register were based on previous studies [86] and divided into major complications, including implant loss (e.g., implant exposure, mesh exposure, implant loss, and infection leading to implant loss), mastectomy skin flap epidermolysis/necrosis requiring revision, NAC epidermolysis/necrosis requiring revision, thrombosis, and embolism, and minor complications, including seroma requiring aspiration, hematoma requiring re-operation, type IV delayed hypersensitivity reactions (i.e., "red breast"), epidermolysis not requiring revision, minimal wound rupture/necrosis not requiring revision, and infections not leading to implant loss.

Infection was graded from 1 to 4, as previously described [87], where grade 1 indicates wound exudate, grade 2 indicates redness, swelling, heat, and exudate, grade 3 indicates redness, swelling, heat, and purulent drainage or induration, and grade 4 indicates fever and/or sepsis. All re-operations and corrections were registered during long-term follow-up.

3.2.3 QUALITY OF LIFE-QUESTIONNAIRES

Historically, outcome reports on breast surgery focused on surgical techniques, complications, and aesthetic outcomes and often used non-validated methods, with less emphasis on patient reported outcomes, PROs. In recent decades, HrQoL has become an important measurement used to evaluate the results of different surgical procedures [88]. HrQol can be measured based on different dimensions, including general health and physical, mental, and psychosocial well-being. The instruments used to evaluate these parameters can be either generic, such as the SF-36 survey instrument [89] and the hospital anxiety and depression scale (HADS) [90], or disease-specific, such as the Breast-Q [40].

All included questionnaires were delivered by post to the patients and controls along with an explanatory letter and a return envelope. A reminder was delivered after 2 weeks to those who had not returned the questionnaire.

BREAST-Q (II–IV)

Patient satisfaction and well-being were measured using the Swedish version of the postoperative reconstruction module of BREAST-Q [40, 91]. BREAST-Q was developed to measure QOL in breast patients and has been validated [40, 91], with translation to Swedish performed according to guidelines for the linguistic validation of PRO instruments [92]. Only domains relevant to the aims of the studies were analysed, including the following (Figure 6).

- QOL domains: 1) psychosocial well-being; 2) sexual well-being; and 3a) physical well-being (chest and upper body)
- Satisfaction domains: 1) satisfaction with breasts, and 5) satisfaction with outcome.

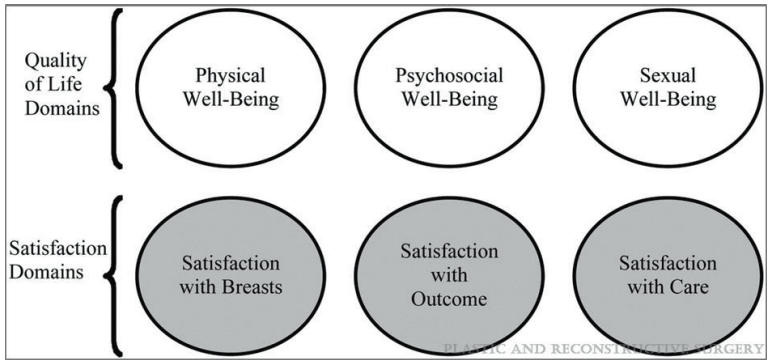

Figure 6. Breast-Q domains and sub-domains.

Copyright: Wolters Kluwer: 2009, Pusic et al., A systematic Review and Head-to Head Meta-analysis of outcomes following Direct-to-Implant versus Conventional Two-stage Implant Reconstruction, Plastic and Reconstructive Surgery, 124(2), p 345-353. Https://journals.lww.com/plasreconsurg/pages/default.aspx.

EUROQOL FIVE-DIMENSION QUESTIONNAIRE WITH THREE LEVELS (EQ-5D-3L) (IV)

The EQ-5D-3L comprises a five-dimension, three-level scale that measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A global score, where 1 indicates “perfect health” and 0 “death”, is calculated from the answers. A visual analogue scale (VAS) was included for the patient to evaluated his/her current health state from 0 (“worst imaginable”) to 100 (“best imaginable”). The EQ-5D-3L was initially developed for economic and clinical evaluation of health care, but has since been used to evaluate breast reconstruction [93] and validated for the Swedish language [94] (Figure 7).

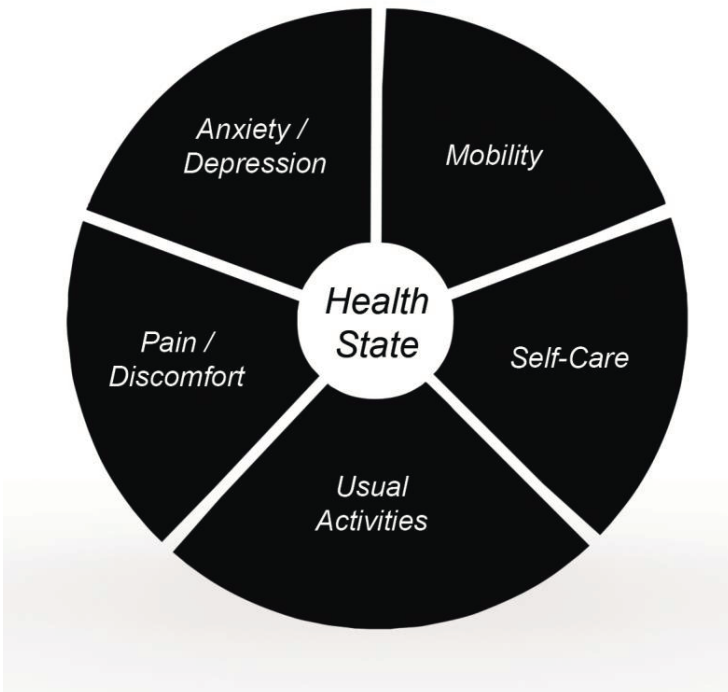

Figure 7. EQ-5D domains. (Niclas Löfgren*)*

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

The HADS instrument measures anxiety experienced during the previous week and comprises 14 questions (seven covering anxiety and seven covering depression). Each question is scored from 0 (“never, no intensity”) to 3 (“every day, very intense”), and for each scale, a total score is calculated. A total score of ≤7 is judged as no depression or anxiety, a score between 8 and 9 suggests that depression or anxiety might be present, and a score >9 indicates that the presence of depression or anxiety is plausible. The instrument has been used to evaluate breast reconstruction [95, 96] and translated to Swedish [97] Figure 8).

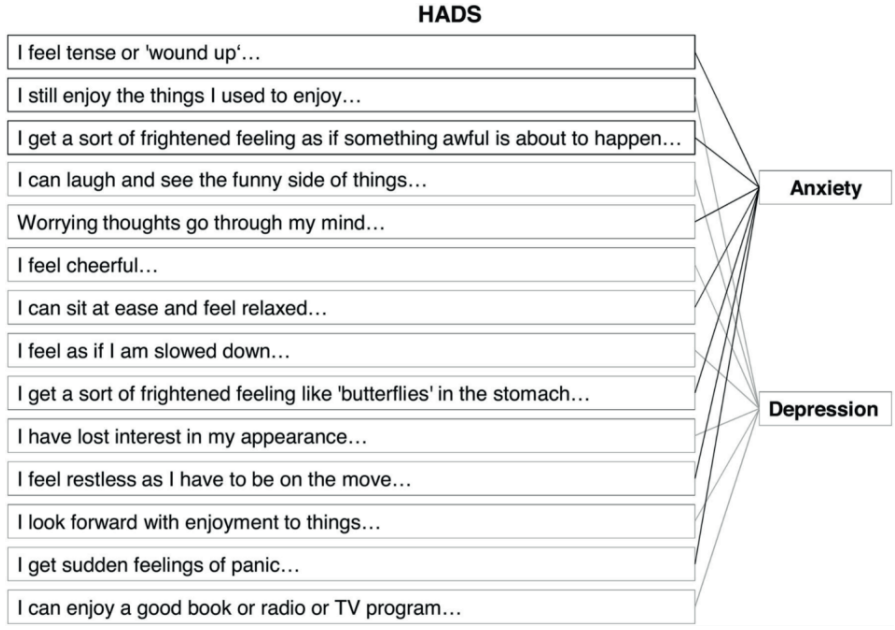

Figure 8. The HADS questions. Amonn, K; Stortecky, S, Quality of life in high-risk patients: comparison of transcatheter aortic valve implantation with surgical aortic valve replacement, Eur J Cardiothorac Surg. 2012;43(1):34-42. By permission of Oxford University Press.

3.3 STUDY PARTICIPANTS

3.3.1 INTERVENTION GROUPS (II-IV)

Criteria for inclusion in one of the intervention groups included age ≥18 years and indications for a unilateral or bilateral mastectomy, either for oncologic or prophylactic reasons, and IBR. The exclusion criterion was the inability to provide informed consent. Indications and operation techniques were discussed at an MDT conference in all cases. In cases were postoperative radiation was anticipated, late autologous reconstruction was recommended to the patient rather than IBR.

The cohorts were operated on consecutively during different time intervals. From 2005 to 2014, patients were operated on with Surgisis ® (III and IV), and from 2015 to 2016, patients were operated on with TIGR® Matrix Surgical Mesh (II and IV).

3.3.2 CONTROL GROUPS (III, IV)

For the control group for study III, we recruited patients undergoing a technique involving muscle coverage and no mesh between 2005 and 2014. Inclusion and exclusion criteria were the same as those described for the intervention groups. For study IV, we compared two intervention groups that included patients operated on with synthetic (II) and biological (III) meshes.

3.4 INTERVENTIONS: SURGICAL METHODS

3.4.1 MESH-ASSISTED RECONSTRUCTION (II–IV)

Patients were marked preoperatively in a sitting position, with the anatomical boundaries of the breast, as well as those of the planned implant pocket and incision pattern, identified. In cases of a ptotic breast, a Wise pattern skin resection was performed; however, most cases received a sub mammary incision. In cases where previous surgery had been performed, modified skin patterns were used according to previous scars. A breast surgeon performed NSM or SSM accordingly.

A plastic surgeon performed reconstruction. The inferior-lateral and -medial attachments on the sternum of the pectoralis muscle were released and the muscle was lifted in order to create a retro-pectoral pocket. The mesh was sutured to the inferior border of the pectoral muscle superiorly, to the chest inferiorly, and to the serratus fascia laterally using 2-0 Maxon® (Covidien, Dublin, Ireland) (Figure 9). A sizer was used to determine implant size, and an anatomical TE (CPX; Mentor Worldwide, LLC, Santa Barbara, CA, USA) or a permanent anatomical silicone implant (DTI; CPG; Mentor Worldwide, LLC) was placed into the pocket. When a TE was used, it was partially inflated with saline in order to achieve a tensionless closure.

Two suction drains were used for each breast (one sub-pectoral and one subcutaneous), with the drains kept in place until the output was <30 mL/24 h. Prophylactic perioperative and postoperative antibiotics (cloxacillin; or clindamycin in case of allergy) were administered until drain removal. The amount of bleeding was estimated by the anaesthetist nurse in millilitres based on the amount of blood present in the compresses. The patients were admitted to the hospital for 48 h postoperatively, and TEs were exchanged for a permanent implant at 3 to 6 months after the first operation.

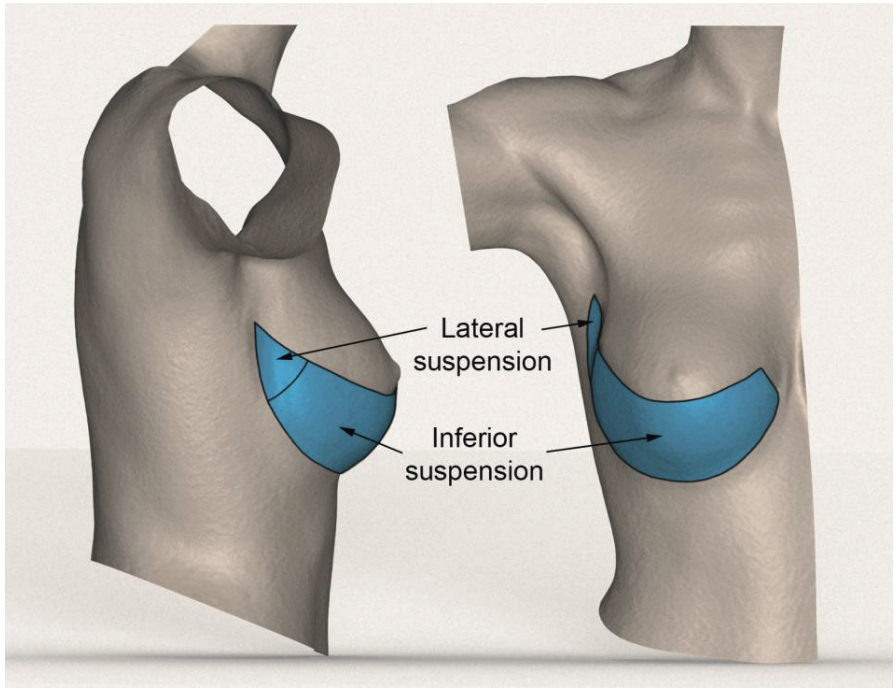

Figure 9. Schematic view of mesh insertion. (Niclas Löfgren)

TIGR® Matrix Surgical Mesh (Novus Scientific, Uppsala, Sweden) was used in studies II and IV (Figure 10). This represents a synthetic, long-term, absorbable, macroporous mesh knitted from two types of fibres: a fast-degrading copolymer between glycolide and trimethylene carbonate and a slow-degrading copolymer between lactic and trimethylene carbonate. The slow-degrading region of the mesh maintains its strength for 6 to 9 months and is completely resorbed after ~3 years, whereas the fast-degrading region provides additional strength during the healing phase and is gradually absorbed during the first 4-months post-surgery, thereby making the mesh softer and more flexible. Both regions of the mesh are degraded by hydrolysis into small molecules that are excreted from the body [98]. TIGR® Mesh has be used for multiple surgical techniques, including those involving hernia surgery [99] and for bra-implant-based breast reconstruction [100, 101].

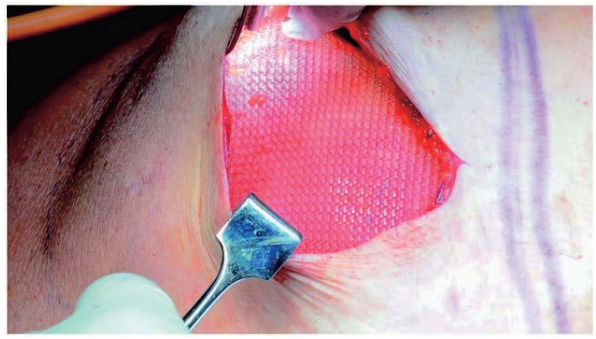

Figure 10. TIGR® Mesh

Surgisis® mesh (Cook, Inc., West Lafayette, IN, USA) was used in studies III and IV (Figure 11). This represents a sterile, biological, porcine-derived dried matrix comprising multi-layered, non-cross-linked collagen (types I, III, and V), gylcosamingylcans, proteoglycans, glycoproteins, and growth factors. This mesh is produced from small-intestine submucosa, is biodegradable, and works as an acellular scaffold that is subsequently incorporated and neovascularized in animal models and humans [102-106].

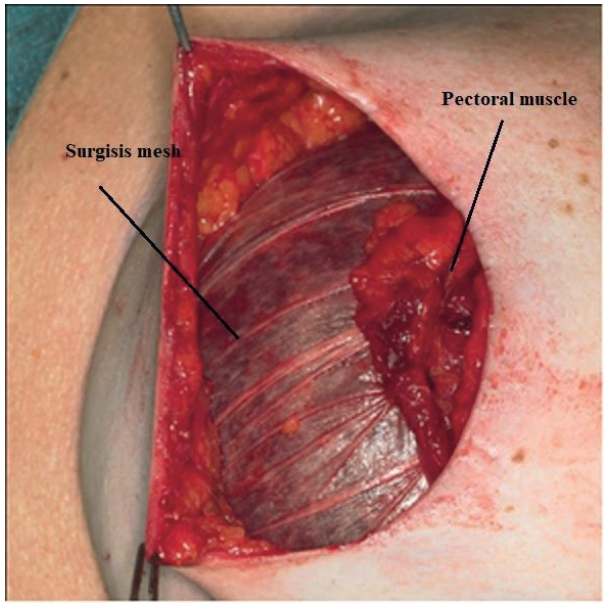

Figure 11. Surgisis® mesh.

3.4.2 TRADITIONAL MUSCLE-COVERAGE TECHNIQUE (III)

In cases were the traditional muscle-coverage technique was used, the operation was performed as described, but a mesh was not used. When the major pectoral muscle was raised, the serratus muscle was raised accordingly and used to cover most of the upper and lateral aspects of the TE/I.

3.5 STATISTICAL METHODS

In study I, extracted data were pooled in meta-analyses, when possible, that were performed using Review Manager (RevMan v5.3; Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration, 2014). We applied a random-effects model, with the effect estimate expressed as risk ratios (RRs) with 95% CIs. The individual studies and the pooled estimates were presented graphically using forest plots. Statistical heterogeneity was examined using the Chi-squared test and I-squared characteristics.

In studies II through IV, categorical variables were represented as numbers and percentages, and continuous variables were represented as means and standard deviations, medians, and ranges. All tests were two-tailed, and a $p < 0.05$ was considered statistically significant. All analyses were performed with SAS software (v9.4; SAS, Cary, NC, USA).

In study II, analyses were performed at the breast level and not at the patient level; therefore, generalized estimating equation models were used to predict minor and major complications during the entire study and within the first 30 days. Calculations were adjusted according to within-individual correlations with a Poisson distribution and log-link function with robust error variances [107]. The analyses returned RRs with 95% CIs and p-values, and probability curves were generated in order to illustrate statistically significant predictors.

In study III, differences between two groups were evaluated using Fisher's exact test for dichotomous variables, the Chi-squared test for non-ordered categorical variables, and the Mann–Whitney *U* test for continuous variables. Relationships between two ordered categorical variables were tested using the Mantel–Haenszel Chi-squared test. Prediction of complications using baseline-characteristic variables was performed using logistic regression, resulting in ORs and 95% CIs presented with their associated p-values. The area under the receiver operating characteristic curve (AUC) was used to generate

goodness-of-fit statistics and probability plots for graphical presentation. For continuous variables with an AUC >0.70, the cut-off maximising both sensitivity and specificity was identified, and a dichotomised variable based on this cut-off was analysed using logistic regression. All analyses were performed separately for permanent implants and TEs.

In studies III and IV, HrQoL data were analysed in a similar manner, and scores from the questionnaires were calculated according to their respective manuals. For tests between two groups, Fisher's exact test was used for dichotomous variables, and the Mann-Whitney *U* test was used for continuous variables. Relationships between two continuous variables were described and tested according to Spearman's rank correlation. The adjusted analysis of tests between biological and synthetic mesh groups with respect to different Breast-Q domains was performed using logistic regression, with each group representing a dependent variable, and each domain at the time representing the main-effect variable. Variables were adjusted for age, BMI, unilateral/bilateral surgery, and radiation.

3.6 ETHICS

All procedures were performed in accordance with the Helsinki Declaration of 1964, as revised, and Good Clinical Practice guidelines. Prior to 2017, permission to create a register of patients was obtained in accordance with the Swedish Privacy Protection Law. Since 2018, personal data have been treated in accordance with the General Data Protection Regulation. The studies were reviewed and approved by the Regional Ethical Committee (043-08).

4 RESULTS

4.1 META-ANALYSIS OF BENEFITS AND RISKS WITH ADM AND MESHES (I)

Fifty-one articles were included in the systematic review. The search and selection process is summarized in Figure 12.

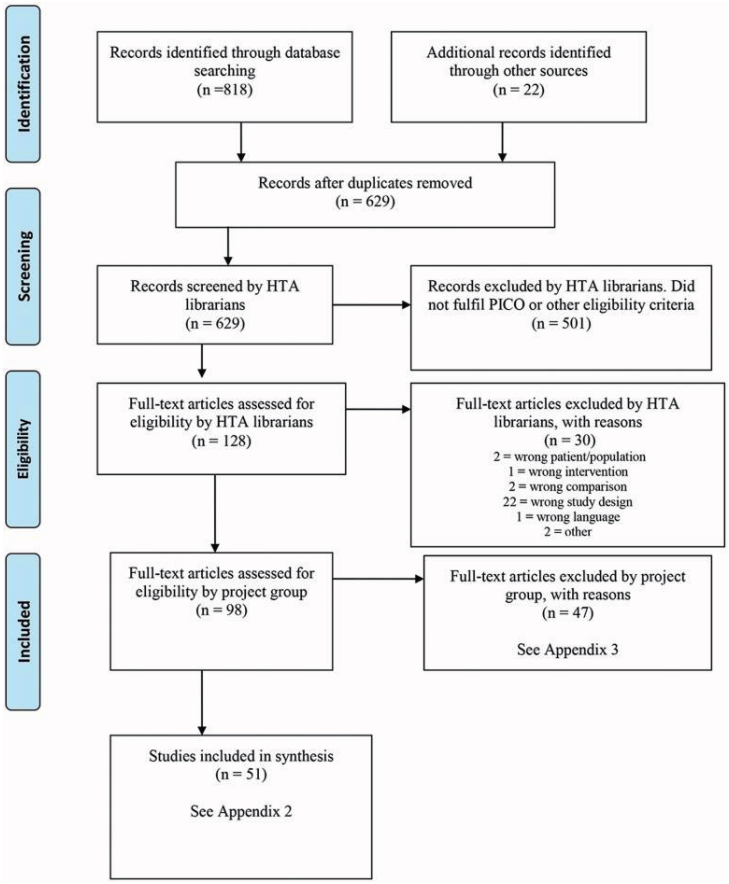

Figure 12. Overview of the process involved in determining the manuscripts included in Study I. Reprinted with permission from Taylor & Francis.

Overall complications were reported in 10 cohort studies and 18 case series. Pooled data from the 10 cohort studies showed an RR of 1.31 (CI: 0.94–1.81), but all studies reported severe limitations. The 18 case series reported overall complication rates ranging from 4% to 41%, with a low certainty of evidence (Grade II).

Implant loss was reported in all of the included studies. Twenty-one case series and 16 cohort studies used in the analysis reported severe limitations, and meta-analysis of studies using ADM demonstrated a high heterogeneity, with an RR of 1.02 (CI: 0.65–1.58). Case series reported implant loss rates ranging from 0% to 17%, and it was uncertain whether there were small or no differences in implant loss rates between IBR with or without the use of a mesh. The certainty of evidence was very low (Grade I).

Twenty case series and 21 cohort studies reported infections, although all of these studies also reported severe limitations. A meta-analysis showed an increased risk of infection when ADM was used [RR = 1.61 (CI: 1.20–2.15)], whereas meta-analysis concerning the use of a synthetic mesh showed no difference as compared with the use of no mesh. The included case series reported infection rates ranging from 0% to 17%. Due to study limitations, it was unclear whether the use of meshes increased the risk of infection. The certainty of evidence was very low (Grade I).

Only five case series and five cohort studies reported results concerning capsular contracture, with all of these studies also reporting severe limitations. Three cohort studies reported on the use of ADM, and two reported on the use of synthetic mesh. The meta-analysis showed a relative RR of 0.55 (CI: 0.38–1.69) comparing ADM versus no ADM, and the case series showed capsular contraction rates ranging from 0.4% to 13%. It was uncertain whether ADM versus no ADM decreased the risk of developing a capsular contraction in IBR. The certainty of evidence was very low (Grade I).

Three studies reported aesthetic outcomes, with all of them using non-validated methods and reporting contradictory results. None of the studies reported patient-reported outcomes, and it was uncertain what the degree of differences was in aesthetic outcomes using ADM as compared with no ADM. The certainty of evidence was very low (Grade I).

None of the studies reported complications specifically associated with radiotherapy in patients reconstructed with or without the use of meshes; therefore, a proper sub-analysis could not be performed.

None of the studies reported HrQoL outcomes or recurrence of breast cancer.

One study reported a delay in adjuvant therapy for 7 of 27 (26%) patients due to complications from breast reconstruction. The certainty of evidence was very low (Grade I).

4.2 PARTICIPANTS AND CONTROLS IN STUDY II-IV

Between 49 and 71 patients (65–132 reconstructions) were included in the different intervention groups, and 90 patients (132 reconstructions) were included in the control group (Table 5). The subjects were followed between 17 and 162 months.

Table 5. Overview of patients in studies II–IV.

	Study II, TIGR®	**Study III, Surgisis®**	**Study III, Controls**	**Study IV, Surgisis®**	**Study IV, TIGR®**
Study type	Case series	Cohort		Cohort	
No. of patients	49	71	90	53	41
No. of breasts	65	116	132	n/a	n/a
Missing follow-up	0	0	9*	(see Table 8)	(see Table 8)
Surgical intervention	TIGR® + permanent implant or expander	Surgisis + permanent implant or expander	Muscle-covered permanent implant or expander	Surgisis® + permanent implant or expander	TIGR® + permanent implant or expander

**Deceased from breast or ovarian cancer.*

.

4.3 EARLY COMPLICATIONS (<30 DAYS) (II-IV)

In study II evaluating the use of synthetic mesh (TIGR®), the overall 30-day complication rate (breast-level) was 23.1%, including four major complications (6.2%) and 11 minor complications (16.9%). Details are provided in Table 6.

Table 6. Early breast-level (studies II and III) and patient-level complications (study IV).

Study	II	III/ Surgisis	III/ Control	IV/Surgisis ®	IV/TIGR®
				No. of Responders	No. of Responders
No. of breasts/ patients	65/49	116/71	132/90	53 (53/71)	41 (41/49)
Early complications (<30 days)					
Overall	15/65 (23.1%)	26/116 (22.4%)	27/132 (20.4%)	19 (35.8%)	12 29.3%)
Major complications	4(6.2%)	13/116 (11.2%)	15/132 (11.3%)	8(15.1%)	3(7.3%)
Implant loss	2(3.1%)	13 (11.2%)**	15(11.3%)**	8(15.1%)	2(4.9%)
Pulmonary embolism	1(1.5%)*	0	0	0	1* (2.4%)
Reoperation due to hematoma	1(1.5%)*	0	0	0	*
Minor complications	11(16.9 %)	14(12.1%)	12(9.1%)	11(20.7%)	8(19.5%)

** One patient had booth a pulmonary embolus and underwent reoperation due to a hematoma.*

***One patient in the Surgisis® group and three patients in the control group who were reconstructed bilaterally lost implants on both sides.*

In study III, the biological mesh group (Surgisis®) showed overall complication rates of 37% per patient and 22.4% per breast, both which were higher, but not statistically significantly, then rates in the muscle-covered control group [27% (per patient) and 20.4% (per breast); p = 0.24] (Table 6).

The overall implant loss rate per breast was 11% in both the synthetic mesh group and the muscle-covered controls and 17% versus 13% at the patient level, respectively. There was a higher, but not significant, risk for any complication in the TE group operated on with Surgisis® as compared with that in the implant group (p = 0.056) (Figure 13).

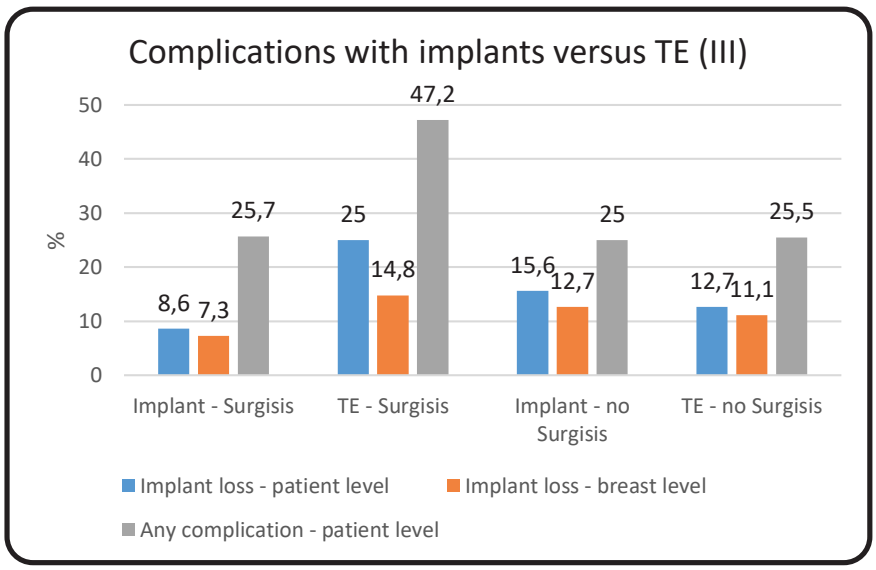

Figure 13. Complications in the biological mesh group and in muscle-covered controls. Complications are shown separately for implants and TEs.

4.4 LONG-TERM COMPLICATIONS/SURGICAL CORRECTIONS (II-IV)

In study II evaluating the use of synthetic mesh (TIGR®), four minor surgical complications occurred and 10 minor aesthetic corrections were performed, with no implant losses occurring after day 30. There were two cases of capsular contraction (Baker II) not requiring surgical intervention during the follow-up period (Table 7).

Study	II TIGR®	III/ Surgisis	III/ Control	IV/Surgisis ®	IV/TIGR®
				No. of Responders	No. of Responders
No. of breasts/patients	65/49	116/71	132/90	53 (53/71)	41 (41/49)
Late events (>30 days)	21.5%	29.3%	26.5%	58.5%	19.5%
Events needing surgery:	10/65 (15.3%)	34/116 (29.3%)	31/117 (26.5%)	31/53 (58.5)%)	8/41(19.5%)
Lipofilling (e.g., due to rippling)	7/65(10.7%)	17/116 (14.6%)	15/117 (12.8%)***	17(32.1%)	6(14.6%)
Minor skin correction	3/65(4.6%)	5/116 (4.3%)	4/117(3.4%)	5(9.4%)	2(4.9%)
Capsular contracture	2/65(3.1%) ****	4/116 (3.4%)	2/117(1.7%)	3(5.6%)†	****
Correction of implant position	0	7/116 (6.0%)	8/117(6.8%)	6/53(11.3%)	0
Other surgical intervention	0	1/116 (0.9%)**	2/117(1.7%)	n/a	n/a
Minor complications (no surgery)	2/65(3.1%)	n/a	n/a	n/a	n/a

*** Implant removal due to relapse*
**** Nine (9) patients diseased from breast or ovarian cancer.*
***** Baker grade II in two cases, not needing surgery.*
†One patient needed bilateral operation and is counted as one as this is evaluated as per-patient.

Table 7. Late breast-level (studies II and III) and patient-level (study IV) complications/surgical corrections.

In study III, rates of capsular contraction during median follow-up was slightly higher in the biologic mesh group Surgisis®; 4.2% as compared with that in the control group, 2.5% per patient (3.4% vs. 1.7% per breast). Minor surgical corrections (mainly lipofilling) were performed in 29.3% of cases in the Surgisis® group and 26,5% of cases in the control group (Table 7).

4.5 PREDICTORS OF COMPLICATIONS (II-III)

In the synthetic mesh group (TIGR®) in study II, predictors for developing a complication within 30 days were age >51 years, BMI >24.5, and resection weight >361 g. There was also a 3-fold increased risk of complication when a Wise pattern incision was used (Figure 14).

Predictors of developing any complication in the biological mesh group (Surgisis®) in study III were found to be BMI and radiation. Separate evaluation of DTI and TE in the implant subgroup revealed that the only statistically significant predictor of developing any complication was an elevated BMI. In the TE subgroup, the use of Surgisis® versus no Surgisis® was a predictor of complications, and radiation was a risk factor for implant loss, with the frequency of implant/TE loss higher in irradiated Surgisis® patients than in non-irradiated Surgisis® patients (40% vs. 11%, respectively) (Figure 14).

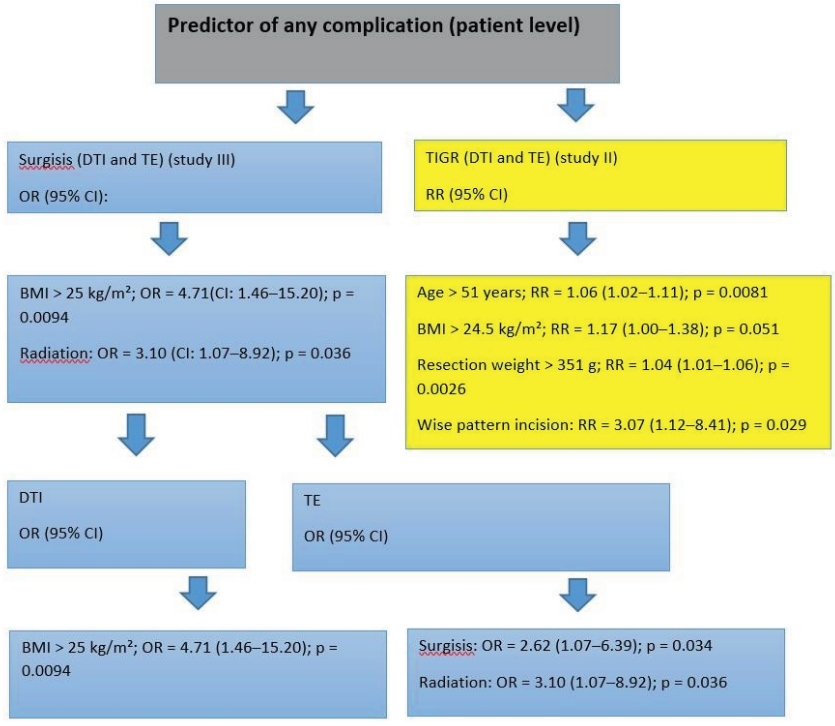

Figure 14. Predictors for complication in study II and III.

4.6 RESPONSES TO QUESTIONNAIRES

In patients operated on with synthetic mesh (TIGR®), the first round of questionnaires was sent a median of 74 months (range: 43–162 months) after the operation, whereas in patients operated on with biologic mesh (Surgisis®), questionnaires were sent a median of 68 months (range: 43–158 months) after the operation. The controls received the questionnaires a median of 100 months (range: 44–162 months) after the operation. Response rates ranged from 68% to 84% across studies (Table 8).

Table 8. Response rate to questionnaires in study III-IV

	Study II, TIGR®	**Study III, Surgisis®**	**Study III, Controls**	**Study IV, Surgisis®**	**Study IV, TIGR®**
Questionnaires	—	Breast-Q	Breast-Q	Breast-Q, HAD, EQ5D	Breast-Q, HAD, EQ5D
Responders	—	49/71(69%)	55/81(68%)	53/71(75%)	41/49(84%)
Non-responders	—	22/71(31%)	22/81(32%)	18/71(25%)	8/49(16%)

In study IV, the overall per-patient complication rates were 35.8% versus 29.3%, and the implant loss rate was 15.1% versus 4.9% in the Surgisis and TIGR groups, respectively (Table 6). Figure 15 shows information associated with responders versus non-responders. Of the patients answering the questionnaires in study IV, 58.5% in the Surgisis group underwent surgical corrections (lipofilling, skin corrections, and/or corrections due to capsular contracture) as compared with 19.5% in the TIGR® group (Table 7).

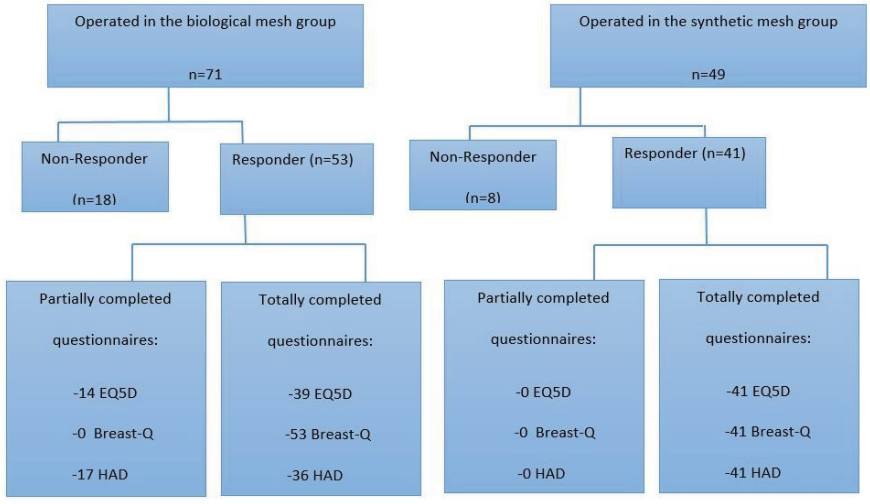

Figure 15. Responders vs. non-responders in study IV

4.7 PATIENT REPORTED OUTCOMES AND QUALITY OF LIFE (III, IV)

Comparison of the biological mesh group with the synthetic mesh group (study III) revealed no statistically significant difference in ether of the domains according to Breast-Q (Figure 16).

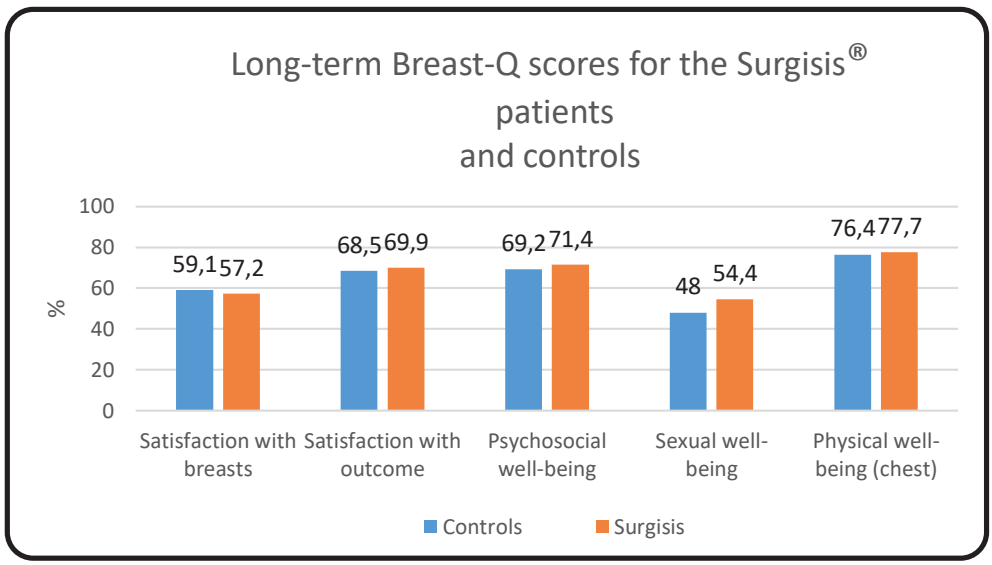

Figure 16. Breast-Q scores in the biological mesh group and the muscle covered controls.

In study IV, the biological mesh group (Surgisis®) was compared with the synthetic mesh group (TIGR®), revealing no statistically significant difference between ether of the domains according to Breast-Q (Figure 17) or HAD/EQ5D (Figure 18)

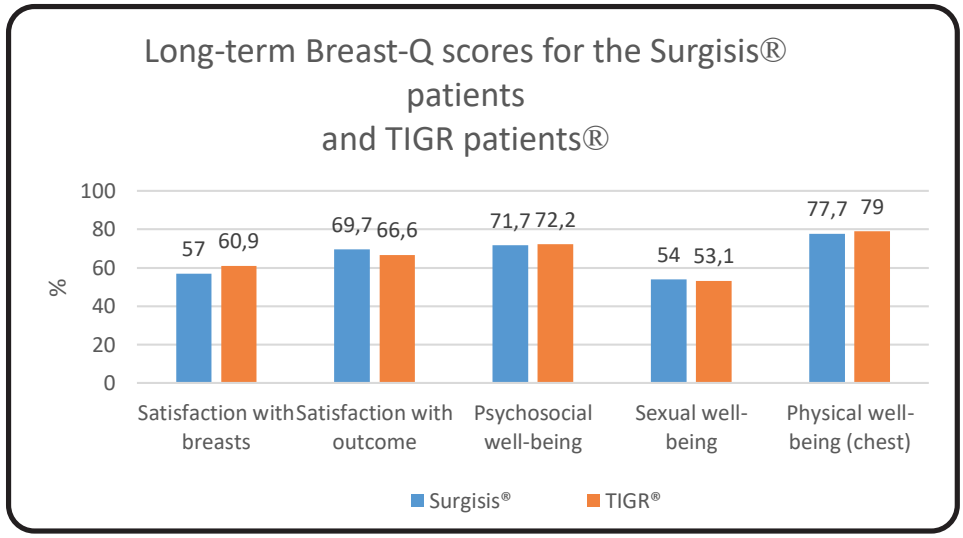

Figure 17. Breast-q scores for the synthetic mesh group and the biological mesh group.

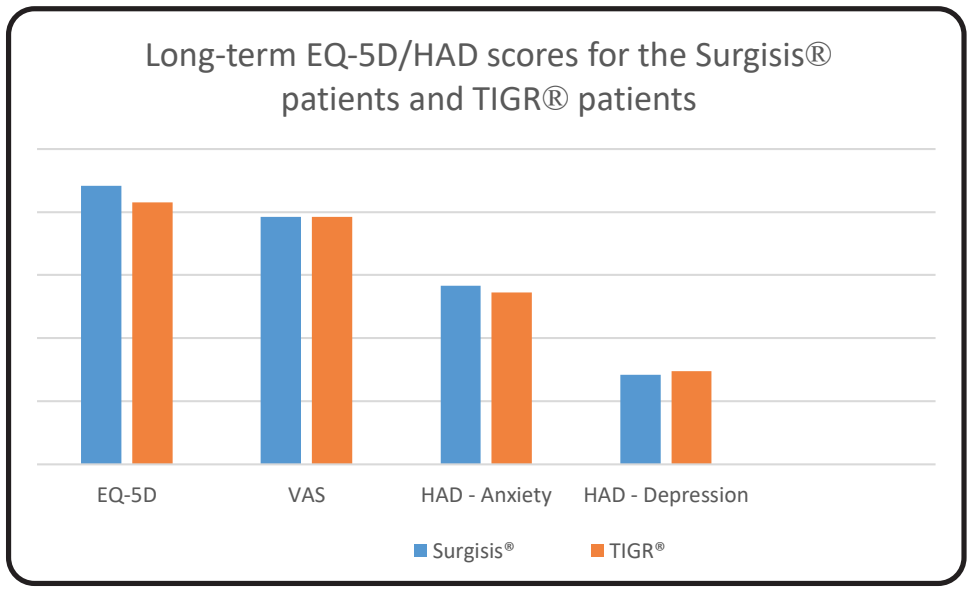

Figure 18. EQ-5D and HAD-scores for the synthetic mesh group and the biological mesh group.

However, adjustment of the analysis for complications indicated that the biological mesh group with a higher complication rate (Table 7) scored significantly lower than the synthetic mesh group in terms of patient satisfaction with surgical outcome (p = 0.024). No statistically significant differences were found according to the other Breast-Q domains (Figure 19).

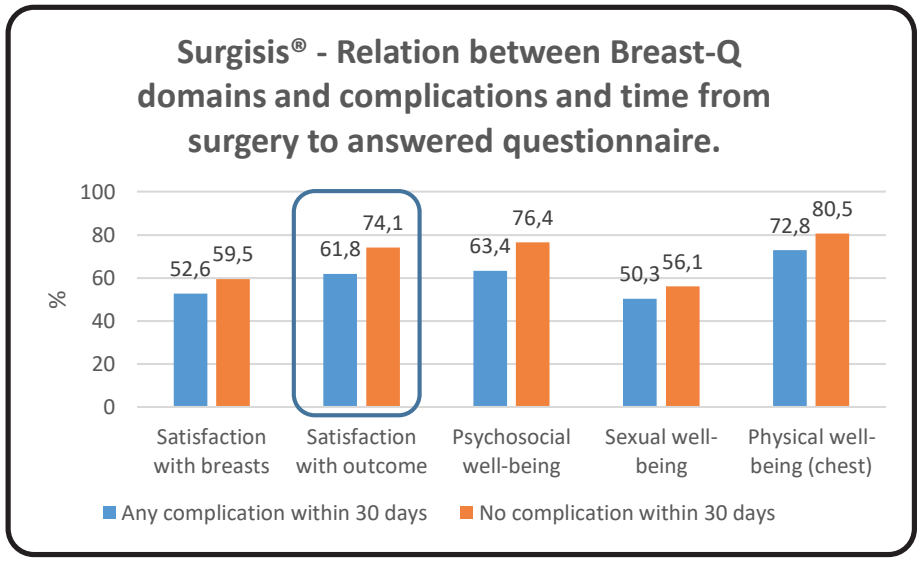

Figure 19. Surgisis® - Relation between Breast-Q domains and complications and time from surgery to answered questionnaire.

5 DISCUSSION

5.1 CONSIDERATIONS REGARDING THE RESULTS

5.1.1 COMPLICATIONS INVOLVING MESH-BASED IBR

There are a number of uncertainties that need to be considered when interpreting complication rates. These include the lack of consensus regarding how to define, diagnose, and report complications, and results reported as per breast or per patient also differ between reports. This makes comparison between different studies problematic. Additionally, variation in follow-up time is an important factor when complications are reported, as rates tend to increase along with time [45]. From this perspective, a common strength of the studies used in this analysis is that they involved longer follow-up periods (rang: 17–162 months).

IMPLANT LOSS ACCORDING TO THE USE OF MESH

The most significant breast-related complication in IBR is reconstructive failure or implant loss. Previous studies suggest that meshes/matrices might increase the risk of implant loss. Two reviews [108, 109] reported a 3- to 4-fold increased risk of implant loss when using mesh as compared with traditional muscle-covered techniques. On the other hand, a recent randomized controlled multicenter study [110] comparing results obtained using porcine ADM (Strattice®; n = 64) with those from traditional muscle coverage (n = 65) showed no difference in implant loss at a 6-month follow-up (6% in both groups). Our results agreed with those findings, as we found an implant loss of 3.1% after a median follow-up of 23 months (range: 17–24) for patients undergoing IBR involving a synthetic mesh (study II), with no difference in implant loss between the biological mesh group and the traditional muscle-covered groups (11% in both groups; study III).

Earlier reports on meshes/matrices[108, 109] reported higher incidences of implant loss as compared with more recent reports [110]. One explanation for this could be the learning curve associated with the use of meshes/matrices, as well as the necessity for technique development. The impact of surgeon experience on outcomes was previously addressed by Eriksson et al.[18] and

indicated that worse outcomes were reported in relation to surgeons with <5 years of experience relative to those with >5 years of experience. Similarly, Barber et al.[111] reported that the implant loss rate ranged from 0% to 40% depending on surgeon experience. Although the difference was not statistically significant (p = 0.051), other indicators suggested that surgeon experience is a determinant of complication rates. In this thesis, we did not analyze the impact of surgeon experience; however, the implant loss rate of 11% in the earliest mesh cohort (study III; when meshes were first introduced in the clinic) as compared with 3% in the most recent mesh cohort (study II) might suggest the importance of experience.

In summary, previous findings suggest that the implant loss rates presented here are considered acceptable and do not indicate an increased risk associated with the use of meshes. Additionally, the data indicated similar outcomes from the use of synthetic and biologic meshes, at least in short-term outcome. However, comparisons of implant loss rates between different studies are difficult due to the different confounders between different studies.

OVERALL COMPLICATION RATES ACCORDING TO THE USE OF MESH

The overall complication rates were consistent between early and more recent reports concerning the use of meshes/matrix[108-110]. Meta-analyses indicated an increased risk of complications when meshes/matrices are used as compared with when they are not used [RR = 2.8 (CI: 1.76–44.5) [108] and OR = 4.00 (CI: 2.33–6.88) [109]]. Additionally, Lomander et al. [110] reported a higher per-patient overall complication rate in the ADM group relative to that in the control group (41% vs. 29%, respectively), with a similar trend observed in in the present thesis. In study III, there was a higher overall per-patient complication rate in the mesh group (Surgisis®) relative to that in the control group (37% vs. 27%; p = 0.0056); however, when comparison of per-breast complication rates revealed similar rates between groups (22.4% vs. 20.4%, respectively). In study II, the overall early complication rates were in line with those in study III (23.1%) but with a somewhat lower risk of major complications (6.2%; 3.1% of which were breast related).

The overall complication rate reported in different studies ranged from low to high. This might be explained by that variation in how each study defined and reported complications. For example, the rates would different significantly depending on their being reported per breast or per patient, as shown in this

thesis. The two breasts of a given patient cannot be considered independent of each other according to the risk profile of that patient for certain complications. Therefore, inadequate notification of how the rates were reported can result in a flawed interpretation of the results.

In summary, the overall complication rates presented in this thesis are in agreement with previously reported findings[110] and were similar in operations with and without the use of mesh.

COMPLICATIONS ASSOCIATED WITH THE USE OF SYNTHETIC OR BIOLOGICAL MESHES

There are few comparisons of complication rates between the use of biological or synthetic meshes in the literature. In a prospective, randomized trial by Gschwantler et al.[41], they found no significant difference in overall complication rates between biological (Protexa) and synthetic (TiLoop) groups; however, the risk of a severe complication leading to reconstructive failure was initially reported as highly significant in the biological mesh group (30% vs. 8%; $p < 0.0001$), although this was later corrected to a non-significant difference[42]. That study was later criticized for its study design [43].

Similarly, the analysis performed in this thesis suggested that use of a synthetic mesh might result in less serious complications relative to use of a biologic mesh (studies II and III). Meta-analysis of study I revealed that the risk of infection was statistically higher in the biological mesh group than in the synthetic mesh group [RR = 1.61 (CI: 1.20–2.15)]; however, these results should be interpreted with caution due to the low quality of included studies. Overall, the data suggest a possibly higher risk of serious complications in reconstructions using biological rather than synthetic meshes.

LONG-TERM COMPLICATIONS ACCORDING TO THE USE OF MESH

A Swedish national survey [17] reported that 52% of patients that had undergone IBR experienced at least one postoperative complication, with 64% resulting in re-operation (median follow-up: 6.6 years). However, that study did not report whether meshes were used. Clarke-Pearson et al. [112] compared IBR with DTI and ADM with TE/I without a mesh and reported a revision rate of 20% in both groups.

The long-term revision rates reported in this thesis (studies II and III) were 15.3% in the TIGR® group and 29.3% and 26.5% in Surgisis® and control groups respectively, with most of the surgical corrections qualifying as minor procedures (e.g., lipofilling, implant position correction and surplus skin).

CAPSULAR CONTRACTURE ACCORDING TO THE USE OF MESH

Previous studies suggested that the use of biological ADM might prevent capsular contracture [113-115]. However, we were unable to confirm this according to the studies analyzed, as the frequency of capsular contracture was higher in the mesh group than in muscle-covered controls (study III). In study I, the meta-analysis showed no significant difference in the incidence of capsular contraction with or without biologic meshes [RR = 0.55 (CI: 0.38–1.69)].

There are no studies reporting the effect of synthetic meshes on the occurrence of capsular contracture; however, in the cohort analyzed for this thesis, this incidence was very low (study II). Generally, incidences of capsular contracture increase over time, with Salzberg et al reporting that capsular contractions can occur up to 2-years postoperatively according to a cohort followed for 13 years [114]. The follow-up in study II was only 17 months in some cases, suggesting that longer-follow up periods are needed to investigate the effect of synthetic meshes on the formation of capsular contracture.

FACTORS AFFECTING COMPLICATIONS

Irradiation

Previous studies show that both preoperative and postoperative irradiation increases the risk of complications associated with IBR [69, 71, 111]. A multivariate analysis by Eriksson et al. [18] indicated that preoperative radiotherapy had an HR of 9.28 ($p < 0.01$), and postoperative radiation had an HR of 3.08 ($p < 0.01$) associated with the risk of reconstructive failure. Similarly, Spear[116] reported that irradiation increased the complication risk 11 fold for IBR involving human ADM (Alloderm).

Our findings showing a 3-fold increased risk [OR = 3.10 (CI:1.07-8.92; p = 0.036)] for complications in the Surgisis® TE/I group receiving radiation (study III) agreed with those of previous studies. Moreover, we found that the

complication frequency was considerably higher in patients reconstructed with TIGR® and having a history of irradiation (study II). Notably, irradiation has a long-term effect on tissue, with subsequent effects on implants possibly manifesting at a later time; therefore, the negative effect of irradiation might be underestimated in the included studies [18]. It remains unclear what role the mesh/matrix might have on complication rates associated with irradiation[117]. A review by Clemens et al. [117] concluded that *´use of ADM for implant-based breast reconstruction does not appear to increase or decrease the risk of complications´*, with this suggesting that in the context of irradiation, the presence or absence of mesh might be of little importance concerning the complication rate.

DTI versus TE/I

A proposed advantage of meshes/matrices is that IBR can be performed as a DTI reconstruction, thereby avoiding the use of TEs and staged reconstruction [34]. The risk of complications associated with DTI versus TE/I varies in the literature. Srinivasa et al. [28] reported higher complication rates in the DTI group; however, after adjusting for baseline characteristics, an equal risk of complications between the two groups was found. By contrast, a review by Basta et al. [27] concluded that there was a higher risk for both flap necrosis and implant loss when a DTI was performed. In a randomized controlled trial by Dikmans et al. [118]one-stage IBR with ADM was associated with significantly higher risk per breast of surgical complications. Major adverse events occurred in 29% in the one-stage IBR with ADM group and in five (5%) in the two-stage IBR group. The risk for implant loss was higher in the one-stage IBR group, with an OR at 8.80(CI:8.24–9.40; $p<0{\cdot}001$).

Regarding the use of meshes/matrix in one- and two-stage reconstruction, respectively, Azouz et al. [119] found that use of human ADM (Alloderm RTU) increased the complication frequency associated with a staged reconstruction with a TE (40.5% vs. 28.2%; $p = 0.037$). A similar result was observed in study III, where the complication frequency was higher in the TE group than in the implant group ($p = 0.0056$). However, it remains unclear whether the risk is greater when meshes and matrices are used in connection with TEs.

In summary, there are conflicting results in current literature comparing outcomes in IBR involving DTI versus TE/I. In one randomized trial[118] in this area, there was a significant increased risk in the DTI group, but the choice of whether to perform DTI or TE/I is often made based on patient

characteristics and local traditions at the clinic. This introduction of bias into the process of selecting a surgical method could be one explanation for the divergent results.

Study III included more patients operated on with TE/I. One reason is that at the time of this study, the policy at the clinic was not to perform NSM. Moreover, in many cases, the remaining skin envelope was not sufficient for a DTI reconstruction, thereby resulting in a TE/I reconstruction being chosen. Another explanation might be that Surgisis® material is thin relative to that of dermis-derived meshes; therefore, it is plausible that Surgisis® material is mechanistically inadequate for forming contacts with the overlapping flap in a manner similar to a stiffer mesh, resulting in its early degradation prior to initial integration.

Patient-related factors

Patient-related factors play a role in the risk of complications. Several studies report that BMI [18, 63, 65, 112], smoking status [63, 64, 112], the amount of resected breast tissue [65, 120], and age [63, 66] are risk factors for complications associated with IBR. Similar findings were reported in the present analysis, with smoking being an exclusion criterion for breast reconstruction in Sweden and, therefore, not investigated. it was not determined whether patient-related factors have a synergistic effect along with the use of meshes/matrixes concerning the risk of complications.

5.1.2 PATIENT SATISFACTION WITH MESH-BASED IBR

POPULATION NORMS

Surgeries were performed in a similar manor, except for the use of ADM/mesh versus no ADM/mesh in studies II, III and IV. However, the results in those studies might have been affected by factors other than the surgical technique used.

Unfortunately, normative values for Breast-Q in a Swedish population are missing; thereby precluding comparison. Mundy et al. reported normative values for an American population of 1201 women [121]; therefore, we used this data and Breast-Q scores from two other studies [122, 123] for comparison with our results from studies III and IV (Figure 20).

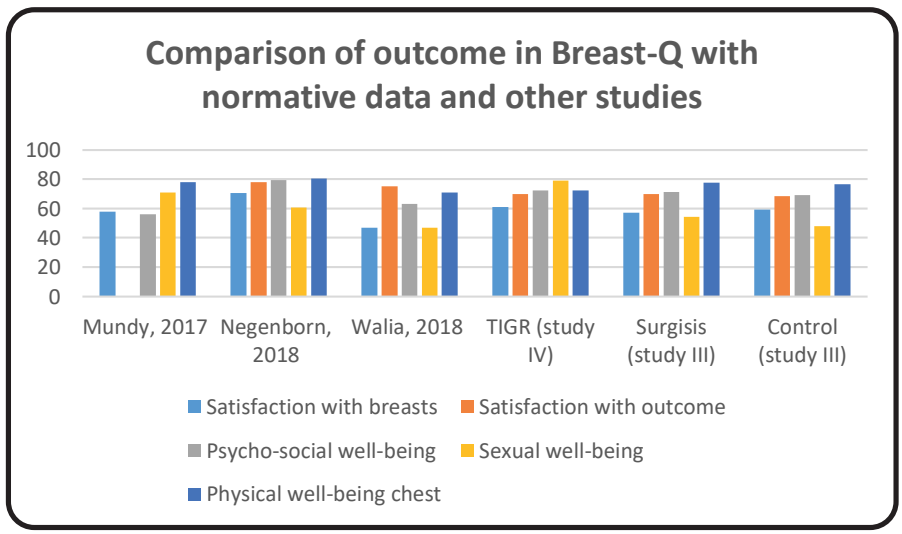

Figure 20. Comparison of results with Breast-Q normative data.

Kouwenberg [93] used EQ-5D to assess outcomes from IBR, irrespective of surgical technique (n = 103), finding a mean EQ-5D score of 0.851 ± 0.17. Additionally, Fernandez-Delgado [95] reported scores for HADS-anxiety (3.99) and HADS-depression (2.90) following analysis of 153 patients undergoing IBR. Comparison of these results with our data (Figure 21) indicated that our findings agreed with previous results associated with measurement using EQ-5D, HADS, and its subdomains.

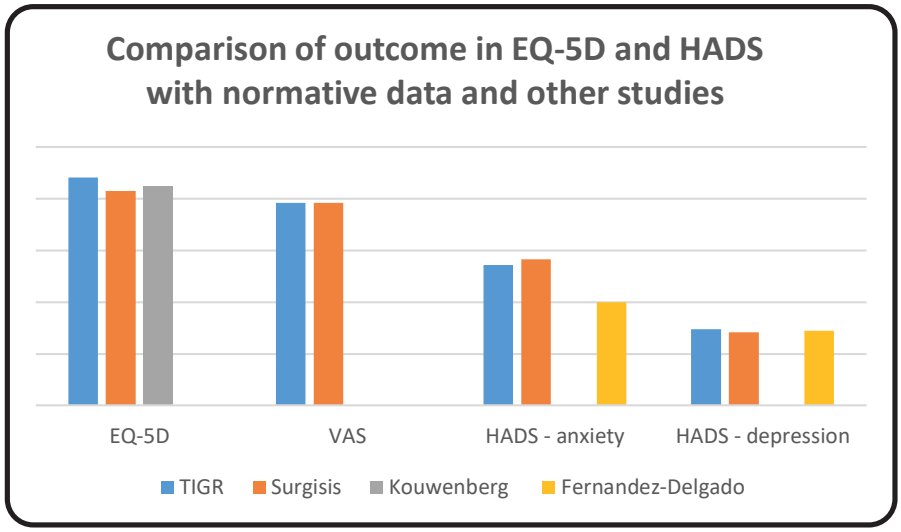

Figure 21. Comparison of results with HADS/EQ-5D normative data

We observed no significant differences in the reported Breast-Q scores between groups in studies III and IV, except for those reporting a complication and resulting in a significantly lower score involving *satisfaction with outcome*. A previous study reported a similar finding from patients experiencing complications [18]. Our results were comparable in most Breast-Q, EQ-5D, and HADS domains, indicating small differences between reconstructed populations and those not undergoing reconstruction.

These findings suggest no differences in the outcome regarding the timing of implant-based reconstruction or the use of ADM/meshes. However, it is also possible that the instruments used to detect differences in such outcomes are currently inadequate.

5.2 METHODOLOGICAL ISSUES: STRENGTHS AND LIMITATIONS

5.2.1 METHODOLOGICAL ISSUES REGARDING SYSTEMATIC REVIEW AND META-ANALYSIS (I)

The strengths of a systematic review and/or a meta-analysis are that these techniques offer a more objective appraisal of the evidence and increased statistical power, as they summarize the results of all available studies [124]. The validity of these techniques is dependent upon the scientific quality of the different steps of the review process. To minimize the risk of bias, we employed a rigorous protocol and the PRISMA statement guidelines [125] in this thesis. Additionally, to ensure adequate quality in every step, a high competence level in the individuals involved in each step (e.g., professional librarians, breast surgeons, plastic surgeons, and experts in meta-analysis statistics) was confirmed.

Nevertheless, the quality of such an analysis is susceptible to the quality of the included studies. Despite the use of rigorous eligibility criteria, the methodological quality of the available studies was generally low, with these studies often including small sample sizes and suboptimal research designs. Additionally, many involved a risk of reporting bias, as well as unclear inclusion and exclusion criteria, the complications included, and how they were diagnosed. Moreover, many studies failed to separately report data for irradiated and non-irradiated patients. As a result, some of the reported outcomes and the estimated size effect might be questionable; therefore, the results of our assessment of study heterogeneity could represent characteristics associated with these potential shortcomings.

Meta-analysis results are also susceptible to the statistical methods used to analyze the data. A statistical shortcoming in this thesis was that most of the studies reported a number of patients, breasts, and complications but not how many patients experienced bilateral complications. Moreover, patient characteristics were frequently unspecified; therefore, the meta-analysis had to be performed based on complication per breast (aggregate data) rather than complications per individual (individual participant data).

Briefly, a meta-analysis is highly dependent on the quality of the included studies. With the rigorous methodology applied in study I, the results should

reflect the best evidence currently available; however, the quality of the evidence was low.

5.2.2 CONSIDERATIONS REGARDING THE MEASUREMENT OF QOL (III, IV)

Since the 1990s [126], HrQoL has become an increasingly important outcome measurement in many fields, including cancer treatment and reconstructive surgery. This measurement encompasses not only the length of survival and frequency of complications but also the impact on patient QOL and perspective [126, 127]. Evaluating HrQoL requires consideration of a number of factors, some of which are discussed in this section.

Minimal important difference (MID)

The MID is the smallest difference in an HrQoL score and that patients perceive as beneficial. The value is often related to 50% of the baseline standard deviation in subscale scores and in an effect size of 0.5, although there is no consensus on how MID should be determined [128]. Moreover, there are no MID-related data for Breast-Q reconstruction; however, a study on the augmentation module in Breast-Q [128] demonstrated that the mean MIDs for the different subscales of that particular module include the following: satisfaction with breasts, 8 (range: 7–8); psychosocial well-being, 10 (range: 8–11); sexual well-being, 10 (range: 9–10); and physical well-being, 7 (range: 2–11). For the HADS, MIDs only exist for patients that have survived respiratory failure [129]. For that group, the MID was ~2.5 for both the anxiety and the depression modules. For the EQ-5D-3L, the MID for patients that underwent glioma surgery ranged from 0.13 to 0.15 [130]; however, these MIDs might not be relevant in the setting of breast reconstruction (our patient sample), but could give an indication of what range of differences are needed to detect a clinically significant difference. The differences between the Surgisis® and muscle-covered implant groups (study III) and the synthetic and biological mesh groups (study IV) were much smaller than the previously published MIDs (Figure 16, 17, 18).

In clinical research, a $p < 0.05$ is often used to indicate a statistical difference and to dichotomize between the presence or absence of a “treatment effect”; however, a p-value indicates a statistical probability and does not necessarily imply a clinically significant difference [131]. In this thesis, statistical tests were used to compare clinical differences in complication rates (studies II and III) and HrQoL (studies III and IV), with no differences detected between the

groups (Figure 16, 17, 18 and Table 6, 7). The statistical tests together with the small differences in absolute scores (likely smaller than the MIDs) might indicate that there were truly no differences in HrQoL between the groups.

Response shift

Schwartz and Sprangers[132] defined response shift as "a change in the meaning of one's self-evaluation of a target construct as a result of: (a) a change in the respondent's internal standards of measurement (i.e., scale recalibration); (b) a change in the respondent's values (i.e., the importance of component domains constituting the target construct); or (c) a redefinition of the target construct (i.e., reconceptualization)". A more easily understandable definition of response shift was proposed by Rapkin et al. [133]. "QOL response shift may best be understood as an epiphenomenon: individuals' ratings of QOL can respond to changes in illness, treatment, and other life events in atypical (e.g., statistically different from some expected value) ways or in ways that do not gibe with external observation. Changes in QOL appraisal may be able to account for these discrepancies"[133].

HrQoL scores can be incorrectly interpreted if response shift is not taken into account [134]. This is particularly relevant when evaluating a mixture of therapeutic and prophylactic mastectomies. A response shift was reported early after diagnosis among breast cancer patients [135], and HrQoL in disease-free breast cancer patients 5 years after treatment were comparable to that in healthy women [136]. On the other hand, response shift has never been studied in patients undergoing prophylactic mastectomy and reconstruction.

In summary, response shift would have been used if we had included baseline values in the different populations; however, given that a long period of time had elapsed since surgery in our cohorts, response shift likely would have had a minimal effect on the HrQoL results, but might have hide treatment effects[135].

Regression to the mean

The questionnaire results are interpreted at the group level; therefore, it is unclear whether subgroups in the cohorts benefitted more or less from the treatment. Additionally, a previous study noted that patients can adapt to a given state before a change in life (regression to the mean [137]), which can make interpretation of results difficult. One example is that a group of breast

cancer patients followed for 5 years adapted to their status over time, with their response comparable in many aspects to those from the general population [136].

Missing data and attrition bias

Missing data can affect the result of questionnaire responses, as there might be systematic differences between patients answering the questions and those who do not, thereby potentially introducing selection bias. A higher frequency of missing data increases the risk of bias in result interpretation, and a previous study suggested that a loss of <5% of responses would likely result in minimal bias, whereas a loss of >20% could potentially harm the validity of the results [138].

In study III, the questionnaire response rates were 69% and 68% for the Surgisis® and control groups, respectively, whereas the study IV response rates were 76% and 84%; biological and synthetic mesh groups, respectively). In study IV, all responders answered the Breast-Q questionnaire in both groups; however, in the biological mesh (Surgisis®) group, 14/53 and 17/53 questionnaires were incomplete for EQ-5D and HADS, respectively. In this group, nine patients had died at follow-up (Table 6); therefore, this exceeded the 20% threshold and potentially threatened the validity of the results. However, all of the patients that had experienced complications answered the questionnaires, suggesting that the questionnaires were not answered only by those patients satisfied with their outcome (study IV). Nevertheless, it is possible that the missing data could have introduced bias that affected the comparison between groups (studies III and IV).

Relevance of the HrQoL instruments used

The main objective of using HrQoL instruments as an outcome measurement in clinical studies is to collect evidence related to the results from the patient's perspective. To ensure accuracy, such instruments need to be scientifically validated and tested for reliability. A previous study [139] recommended minimum standards for patient-reported outcome measurements according to patient-centered outcomes. Additionally, the instrument needs to be relevant to the research question posed. The instruments used in this thesis meet the recommended requirements for HrQoL instruments in regard to their validity, reliability, interpretability.

To ensure that the instruments were relevant to the research question, this thesis employed one disease-specific instrument, designed especially to capture patient perspective on breast reconstruction, and two generic instruments, previously used in different populations. It is difficult to use generic instruments to evaluate a specific treatment modality, and there is often no evidence confirming their validity for use to evaluate breast reconstruction (i.e., they are responsive and sensitive to changes after surgery [140]). Nevertheless, generic instruments remain the most used instruments in reconstructive surgery, and a combination of generic and specific instruments is likely the optimal way to evaluate HrQoL following breast reconstruction [140]. Therefore, we believe that the use of a combination of generic and disease-specific instruments in this thesis was relevant to the research questions being addressed.

Data analysis

There is no consensus on how HrQoL should be statistically analyzed, which makes comparison between different studies difficult [141]. In this thesis, a clear research hypothesis was formulated when HrQoL was included, and only domains of interest were included in the analysis. This limed the number of statistical analyses and potentially reduced the risk for a type 1 error. Moreover, we adjusted for variables, such as age, BMI, unilateral/bilateral surgery, and radiation treatment, potentially affecting the surgical outcome (study IV). One limitation was that missing data were not handled in the statistical models.

5.2.3 CONSIDERATIONS REGARDING STUDY DESIGN, SAMPLING, POWER, AND REPRESENTATIVENESS

Meshes and matrices have been used in clinical practice since 2005 and are currently used in the majority of implant-based breast reconstructions in the United States [34]. Therefore, studies II through IV allowed comparisons of surgical effectiveness research, as they focused on evaluating clinical treatments currently used on the general population [142].

In these studies, outcome measurements were based principally on the patients and providers being considered as stakeholders, suggesting that the goal was to identify the best available treatment for the patients in order to improve the quality of care, proficiency, and information received by the patients [143]. One strength of the studies was that they were originally designed to monitor the quality of mesh and matrix use in our clinic. Therefore, prospective collection of the clinical data was standardized, enabling the data to be aggregated, and IBR methods to be compared over a period of 13 years. Additionally, the drop-out rate was low, allowing data to potentially be retrieved during long-term follow-up from almost the entire cohorts for both studies II and III.

Another strength of these studies involved the long follow-up time, which is particularly important when complications are reported. A previous study [45] reported low complication rates of 5.9% at day 30, whereas the rate increased to 18.9% at 1 year. In the studies analyzed for this thesis, patients were followed for a minimum of 17 months and up to 162 months.

Methodological weaknesses associated with data collection from a clinical setting include variations in how clinical practices represent certain data, including surgeon learning curves when different meshes are used, small variations in surgical technique, and patient selection. However, relatively few surgeons have performed immediate reconstructions over the 13-year period of the included studies, during which time senior surgeons have consistently trained new surgeons joining the team. We believe that the effect of variations in clinical practice is likely minimal in the present cohorts, although variations in clinical practice might have introduced bias into the interpretations of the results. Furthermore, the evaluation of specific clinical practices might have diminished the risk of performance bias possibly existing had the patients been randomized according to the use of different meshes. Unfortunately, surgeons

cannot be blinded to what mesh they use; therefore, employment of a randomization process would have likely been nullified by the personal preference of the surgeon.

In clinical research, the ideal study design for comparing treatment effects involves sampling by randomization; however, the study design used for this thesis precluded randomization. In studies II through IV, a consecutive sampling technique was used, where all consecutive patients fulfilling the inclusion criteria were included in a certain cohort. Additionally, the surgical methods used were determined according to the current clinical practice used by the department. Nevertheless, employment of a random-sampling technique might have strengthened our studies.

A clear weakness of consecutive sampling is that the sample size became arbitrary, which might have underpowered the studies, with the small sample sizes potentially precluding the option of rejecting the null hypothesis [144]. Therefore, it is possible that the lack of differences observed between the use of Surgisis® and muscle-covered implants in study III and between synthetic and biological meshes in study IV could be explained by the sample sizes being too small to allow the detection of differences. Nevertheless, the small differences in the real scores calculated between the groups (Figure 16, 17, 18) might suggest that the lack of differences observed between the groups was not a result of a type II error.

Another weakness of small cohorts is that they might not be representative of the overall population needing IBR, and that minor differences in the cohorts might cause bias. In this thesis, this might be relevant in the comparison of the cohorts between studies III and IV; however, there were no differences in demographic factors or the reasons for surgery between the cohorts, except for there being more bilateral cases in the biological mesh cohort as compared with the synthetic mesh cohort in study IV. Therefore, these characteristics suggest that that the cohorts might be representative of the population needing IBR, regardless of sample size.

6 CONCLUSIONS

This thesis investigated the different aspects of mesh- and ADM-assisted IBR, with the main conclusions as follows:

- Meta-analysis revealed the possibility of an increased risk of infections associated with the use of ADM but not when synthetic meshes are used. This result should be interpreted with caution due to severe limitations with the majority of the included studies.

- IBR combined with a synthetic mesh (TIGR®) can be performed with expectations of a relatively low risk of short-term complications. Although later complications mostly involved issues requiring minor corrections for aesthetic reasons, a longer follow-up period is needed to establish risks of capsular contracture associated with synthetic meshes.

- The overall complication rate was higher when a biological mesh (Surgisis®) was used as compared with muscle-covered implants, although no significant difference was noted in implant loss rates between the groups. Predictors of complication were mainly patient related. Notably, a high complication rate associated with TE reconstruction was found, especially in patients with a history of irradiation.

- Long-term patient satisfaction and QOL were similar between those undergoing IBR involving Surgisis® or muscle-covered implants.

- There were few differences in reported QOL between patients undergoing IBR involving a synthetic or biologic mesh, with the occurrence of complications being a determining factor of patient satisfaction with the surgical outcome. This might suggest that the use of biological or synthetic meshes provides similar long-term QOL.

7 FUTURE PERSPECTIVES

The benefits of using meshes and matrices in IBR remain unclear, although this thesis concluded that the risks associated with their use seem to be comparable with traditional muscle covered reconstructions. However, this does not imply that they ensure superior outcomes relative to traditional muscle-covered techniques. Long-term benefits concerning capsular contracture rates and patient QOL could not be verified in this thesis. Moreover, it remains unclear whether biological meshes are superior to synthetic meshes in any aspect.

Any benefits of a given technique need to be analyzed relative to the costs. Biological meshes add a considerable material cost to IBR, whereas synthetic meshes are considerably more cost-effective. To clarify the beneficial or detrimental role of meshes and matrices in IBR, long-term health-specific economic studies and analyses involving comparisons with other reconstructive options are necessary.

Randomized controlled trials are necessary to further elucidate whether biological and synthetic meshes provide different outcomes. Meshes have only been used since 2005; therefore, the current extent of long-term follow-up is capped at ≤14 years, thereby limiting the ability to critically assess long-term outcomes.

Because relatively few studies of high scientific quality have been conducted on the use of meshes, studies concerning patient selection, surgical techniques, and the choice of implant type remain important in order to ensure appropriate application of meshes in breast reconstruction.

ACKNOWLEDGEMENTS

I wish to express gratitude to all those involved in my personal and professional success, including the following people.

Emma Hansson My principle supervisor and friend who, with seemingly endless enthusiasm and patience, helped me overcome all obstacles to finish this thesis. This would not have been possible without you.

Anna Elander The head of our department, my colleague for many years, and co-supervisor for this thesis. Without your personal and professional support, I likely would not have been able to complete this work.

Lars Kölby My co-supervisor and the person encouraging my ambition toward scientific research in our clinic, as well as his ability to share funny stories from the countryside from which we both originated.

Ann Chatrin Edvinsson Our breast nurse in outpatient clinic, who keeps the breast team running. We could not have managed without you.

Yngve Hessman My mentor in general surgery, the person who initiated my interest in plastic surgery, and a primary reason for my being in the plastic surgery department.

Clas Lossing My friend and former colleague, who taught me the principals of plastic surgery and is among the most generous people I know.

Rikard Lewin Former colleague and friend in the breast team, with whom I have discussed various things in the breast reconstruction area over the years.

All of the co-workers that contributed to this thesis: Rikard Lewin, Jonas Lundberg, Madiha Bhatti Søfteland, Emmelie Widmark-Jensen, Ulrika Kogler, Svanheidur Rafnsdottir, Gennaro Selvaggi, Annika Strandell, Ola Samuelsson, Ida Stadig, and Therese Svanberg.

My thanks to **Anna Paganini** for her help in making this thesis readable and her willingness to consistently provide help whenever a Microsoft product encouraged me to give up.

Niclas Löfgren and Åsa Bell Thank´s for help with photos and illustrations.

Christina Sahlin My friend and former colleague, whose knowledge of medicine and other areas I respect highly.

Aldina Pivodic Our excellent statistician, whose help with the sometimes incomprehensible world of statistics was indespensible.

My thanks to **all of my colleagues**, past and present, in the General Surgery Department in Skövde and the Plastic Surgery Department in Göteborg.

My thanks to **all of the staff**, past and present, of the ward, outpatient clinic, and the operating theatre for their support over the years.

Sven My father, whose age has not slowed him and who continues to support me and my family.

In memory of my mother, **Anna-Lisa,** who unfortunately left us when she was too young year, but meant the world to me.

My sister Yvonne and her family for their friendship and for all our shared experiences over the years.

Anna-Lena My beloved wife, who has always supported me and taken such good care of our family and anyone else needing help. I love you.

My beloved children, Simon and Ida, of whom I am very proud.

Mikael Plith and his wife Ulrika My friend, with whom I have shared many hours studying, listening to music, and discussing the meaning of life.

Anna-Märta Leijon and in memory of her husband Jerker My friends, who ensured that I always had something to eat during my study period and with whom I have been trained in gracile movements.

Benny and Inga-Lill Lindblad My friends for many years back and with whom my wife and I have spent many unforgettable moments.

All other friends Those not mentioned here but certainly not forgotten, and who have meant a great deal to me.

Funding

The studies associated with this thesis were financed by grants from the Swedish state under the agreement between the Swedish government and the country councils [the ALF-agreement (ALFGBG-724171)]. Financing was

also received from the Percy Falk foundation for research into prostate and breast cancer and Göteborgs Läkarsällskap (GLS).

REFERENCES

1. *Bröstcancer. Nationellt vårdprogram*. 2018.
2. Socialstyrelsen. *Socialstyrelsen - statistik*. 2016; Available from: http://www.socialstyrelsen.se/statistik/statistikefteramne/cancer.
3. Nayyar, A., K.K. Gallagher, and K.P. McGuire, *Definition and Management of Positive Margins for Invasive Breast Cancer.* Surg Clin North Am, 2018. **98**(4): p. 761-771.
4. Morrow, M., et al., *Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ.* Pract Radiat Oncol, 2016. **6**(5): p. 287-295.
5. Snyderman, R.K. and R.H. Guthrie, *Reconstruction of the female breast following radical mastectomy.* Plast Reconstr Surg, 1971. **47**(6): p. 565-7.
6. Torresan, R.Z., et al., *Evaluation of residual glandular tissue after skin-sparing mastectomies.* Ann Surg Oncol, 2005. **12**(12): p. 1037-44.
7. Goldman, L.D. and R.M. Goldwyn, *Some anatomical considerations of subcutaneous mastectomy.* Plast Reconstr Surg, 1973. **51**(5): p. 501-5.
8. Lanitis, S., et al., *Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies.* Ann Surg, 2010. **251**(4): p. 632-9.
9. Kurian, A.W., et al., *Equivalent survival after nipple-sparing compared to non-nipple-sparing mastectomy: data from California, 1988-2013.* Breast Cancer Res Treat, 2016. **160**(2): p. 333-338.
10. De La Cruz, L., et al., *Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple-Areolar Recurrence in the Setting of Nipple-Sparing Mastectomy: A Meta-Analysis and Systematic Review.* Ann Surg Oncol, 2015. **22**(10): p. 3241-9.
11. Weber, W.P., et al., *Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy.* Breast Cancer Res Treat, 2018.
12. Hall, J.M., et al., *Linkage of early-onset familial breast cancer to chromosome 17q21.* Science, 1990. **250**(4988): p. 1684-9.
13. Antoniou, A.C., et al., *The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions.* Br J Cancer, 2008. **98**(8): p. 1457-66.
14. Song, C.V., et al., *Surgery for BRCA, TP53 and PALB2: a literature review.* Ecancermedicalscience, 2018. **12**: p. 863.

15. Ludwig, K.K., et al., *Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review.* Am J Surg, 2016. **212**(4): p. 660-669.
16. Kotsopoulos, J., et al., *Bilateral Oophorectomy and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers.* J Natl Cancer Inst, 2017. **109**(1).
17. Arver, B., et al., *Bilateral prophylactic mastectomy in Swedish women at high risk of breast cancer: a national survey.* Ann Surg, 2011. **253**(6): p. 1147-54.
18. Eriksson, M., et al., *Radiotherapy in implant-based immediate breast reconstruction: risk factors, surgical outcomes, and patient-reported outcome measures in a large Swedish multicenter cohort.* Breast Cancer Res Treat, 2013. **142**(3): p. 591-601.
19. Lee, C., C. Sunu, and M. Pignone, *Patient-reported outcomes of breast reconstruction after mastectomy: a systematic review.* J Am Coll Surg, 2009. **209**(1): p. 123-33.
20. Eltahir, Y., et al., *Quality-of-life outcomes between mastectomy alone and breast reconstruction: comparison of patient-reported BREAST-Q and other health-related quality-of-life measures.* Plast Reconstr Surg, 2013. **132**(2): p. 201e-209e.
21. Boughey, J.C., et al., *Impact of reconstruction and reoperation on long-term patient-reported satisfaction after contralateral prophylactic mastectomy.* Ann Surg Oncol, 2015. **22**(2): p. 401-8.
22. Lee, C.N., et al., *Accuracy of Predictions of Patients With Breast Cancer of Future Well-being After Immediate Breast Reconstruction.* JAMA Surg, 2018. **153**(4): p. e176112.
23. Champaneria, M.C., et al., *The evolution of breast reconstruction: a historical perspective.* World J Surg, 2012. **36**(4): p. 730-42.
24. FDA, *Regulatory history of Breast Implants in U.S.*
25. EU, *Rådets direktiv 93/42/EEG av den 14 juni 1993 om medicintekniska produkter* in *93/42/EEG*.
26. Lee, K.T. and G.H. Mun, *Comparison of one-stage vs two-stage prosthesis-based breast reconstruction: a systematic review and meta-analysis.* Am J Surg, 2016. **212**(2): p. 336-44.
27. Basta, M.N., et al., *A Systematic Review and Head-to-Head Meta-Analysis of Outcomes following Direct-to-Implant versus Conventional Two-Stage Implant Reconstruction.* Plast Reconstr Surg, 2015. **136**(6): p. 1135-44.
28. Srinivasa, D.R., et al., *Direct-to-Implant versus Two-Stage Tissue Expander/Implant Reconstruction: 2-Year Risks and Patient-Reported Outcomes from a Prospective, Multicenter Study.* Plast Reconstr Surg, 2017. **140**(5): p. 869-877.
29. Topol, B.M., et al., *Immediate single-stage breast reconstruction using implants and human acellular dermal tissue matrix with*

adjustment of the lower pole of the breast to reduce unwanted lift. Ann Plast Surg, 2008. **61**(5): p. 494-9.
30. Lewin, R., et al., *Immediate breast reconstruction with a wise pattern mastectomy and NAC-sparing McKissock vertical bipedicle dermal flap.* J Plast Reconstr Aesthet Surg, 2018. **71**(10): p. 1432-1439.
31. Hansson, E., *Breast reconstruction with a dermal sling: a systematicreview of surgical modifications.* Journal of Plastic Surgery and Hand Surgery, 2018.
32. Duncan, D.I., *Correction of implant rippling using allograft dermis.* Aesthet Surg J, 2001. **21**(1): p. 81-4.
33. Breuing, K.H. and S.M. Warren, *Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings.* Ann Plast Surg, 2005. **55**(3): p. 232-9.
34. JoAnna Nguyen, T., J.N. Carey, and A.K. Wong, *Use of human acellular dermal matrix in implant- based breast reconstruction: evaluating the evidence.* J Plast Reconstr Aesthet Surg, 2011. **64**(12): p. 1553-61.
35. Kim, J.Y.S. and A.S. Mlodinow, *What's New in Acellular Dermal Matrix and Soft-Tissue Support for Prosthetic Breast Reconstruction.* Plast Reconstr Surg, 2017. **140**(5S Advances in Breast Reconstruction): p. 30S-43S.
36. Mendenhall, S.D., et al., *The BREASTrial: stage I. Outcomes from the time of tissue expander and acellular dermal matrix placement to definitive reconstruction.* Plast Reconstr Surg, 2015. **135**(1): p. 29e-42e.
37. Mendenhall, S.D., et al., *The BREASTrial Stage II: ADM Breast Reconstruction Outcomes from Definitive Reconstruction to 3 Months Postoperative.* Plast Reconstr Surg Glob Open, 2017. **5**(1): p. e1209.
38. Meyer Ganz, O., et al., *Risks and benefits of using an absorbable mesh in one-stage immediate breast reconstruction: a comparative study.* Plast Reconstr Surg, 2015. **135**(3): p. 498e-507e.
39. Dieterich, M., et al., *Patient-Reported Outcomes in Implant-Based Breast Reconstruction Alone or in Combination with a Titanium-Coated Polypropylene Mesh - A Detailed Analysis of the BREAST-Q and Overview of the Literature.* Geburtshilfe Frauenheilkd, 2015. **75**(7): p. 692-701.
40. Pusic, A.L., et al., *Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q.* Plast Reconstr Surg, 2009. **124**(2): p. 345-53.
41. Gschwantler-Kaulich, D., et al., *Mesh versus acellular dermal matrix in immediate implant-based breast reconstruction - A prospective randomized trial.* Eur J Surg Oncol, 2016. **42**(5): p. 665-71.
42. Gschwantler-Kaulich, D., et al., *Corrigendum to "Mesh versus acellular dermal matrix in immediate implant-based breast*

reconstruction - A prospective randomized trial" [Eur J Surg Oncol 42 (5) (2016) 665-671]. Eur J Surg Oncol, 2017. **43**(7): p. 1380-1381.
43. Potter, S., et al., *Response to: Gschwantler-Kaulich et al (2016) Mesh versus acellular dermal matrix in immediate implant-based breast reconstruction - A prospective randomized trial doi:10.1016/j.ejso.2016.02.007.* Eur J Surg Oncol, 2016. **42**(11): p. 1767-1768.
44. Barton, M.B., et al., *Complications following bilateral prophylactic mastectomy.* J Natl Cancer Inst Monogr, 2005(35): p. 61-6.
45. Hansen, N., et al., *Evaluating Mastectomy Skin Flap Necrosis in the Extended Breast Reconstruction Risk Assessment Score for 1-Year Prediction of Prosthetic Reconstruction Outcomes.* J Am Coll Surg, 2018. **227**(1): p. 96-104.
46. Wolfram, D., et al., *Cellular and molecular composition of fibrous capsules formed around silicone breast implants with special focus on local immune reactions.* J Autoimmun, 2004. **23**(1): p. 81-91.
47. Kang, S.H., et al., *Current Approaches Including Novel Nano/Microtechniques to Reduce Silicone Implant-Induced Contracture with Adverse Immune Responses.* Int J Mol Sci, 2018. **19**(4).
48. Headon, H., A. Kasem, and K. Mokbel, *Capsular Contracture after Breast Augmentation: An Update for Clinical Practice.* Arch Plast Surg, 2015. **42**(5): p. 532-43.
49. Baker, S., *The theory of natural capsular contracture around breast implants and how to prevent it.* Aesthetic Plast Surg, 1980. **357**(4).
50. Spear, S.L. and J.L. Baker, Jr., *Classification of capsular contracture after prosthetic breast reconstruction.* Plast Reconstr Surg, 1995. **96**(5): p. 1119-23; discussion 1124.
51. Barnsley, G.P., L.J. Sigurdson, and S.E. Barnsley, *Textured surface breast implants in the prevention of capsular contracture among breast augmentation patients: a meta-analysis of randomized controlled trials.* Plast Reconstr Surg, 2006. **117**(7): p. 2182-90.
52. Araco, A., et al., *Capsular contractures: a systematic review.* Plast Reconstr Surg, 2009. **124**(6): p. 1808-19.
53. Handel, N., et al., *A long-term study of outcomes, complications, and patient satisfaction with breast implants.* Plast Reconstr Surg, 2006. **117**(3): p. 757-67; discussion 768-72.
54. McLaughlin, J.K., et al., *Long-term cancer risk among Swedish women with cosmetic breast implants: an update of a nationwide study.* J Natl Cancer Inst, 2006. **98**(8): p. 557-60.
55. Duvic, M., et al., *Cutaneous T-cell lymphoma in association with silicone breast implants.* J Am Acad Dermatol, 1995. **32**(6): p. 939-42.

56. Keech, J.A., Jr. and B.J. Creech, *Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant.* Plast Reconstr Surg, 1997. **100**(2): p. 554-5.
57. de Jong, D., et al., *Anaplastic large-cell lymphoma in women with breast implants.* JAMA, 2008. **300**(17): p. 2030-5.
58. Chacko, A. and T. Lloyd, *Breast implant-associated anaplastic large cell lymphoma: a pictorial review.* Insights Imaging, 2018.
59. Swerdlow, S.H., et al., *The 2016 revision of the World Health Organization classification of lymphoid neoplasms.* Blood, 2016. **127**(20): p. 2375-90.
60. Clemens, M.W. and S.M. Horwitz, *NCCN Consensus Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma.* Aesthet Surg J, 2017. **37**(3): p. 285-289.
61. Fischer, J.P., et al., *Complications and morbidity following breast reconstruction--a review of 16,063 cases from the 2005-2010 NSQIP datasets.* J Plast Surg Hand Surg, 2014. **48**(2): p. 104-14.
62. Song, Y., et al., *Evaluation of cerebral blood flow change after cigarette smoking using quantitative MRA.* PLoS One, 2017. **12**(9): p. e0184551.
63. Fischer, J.P., et al., *Peri-operative risk factors associated with early tissue expander (TE) loss following immediate breast reconstruction (IBR): a review of 9305 patients from the 2005-2010 ACS-NSQIP datasets.* J Plast Reconstr Aesthet Surg, 2013. **66**(11): p. 1504-12.
64. Gfrerer, L., et al., *Assessment of patient factors, surgeons, and surgeon teams in immediate implant-based breast reconstruction outcomes.* Plast Reconstr Surg, 2015. **135**(2): p. 245e-52e.
65. Lardi, A.M., et al., *Immediate breast reconstruction with acellular dermal matrix: factors affecting outcome.* J Plast Reconstr Aesthet Surg, 2014. **67**(8): p. 1098-105.
66. Jimenez-Puente, A., et al., *Complications in immediate breast reconstruction after mastectomy.* Int J Technol Assess Health Care, 2011. **27**(4): p. 298-304.
67. Olsen, M.A., et al., *Comparison of Wound Complications After Immediate, Delayed, and Secondary Breast Reconstruction Procedures.* JAMA Surg, 2017. **152**(9): p. e172338.
68. Corban, J., et al., *A systematic review of complications associated with direct implants vs. tissue expanders following Wise pattern skin-sparing mastectomy.* J Plast Reconstr Aesthet Surg, 2017. **70**(9): p. 1191-1199.
69. Kearney, A.M., M.S. Brown, and H.T. Soltanian, *Timing of radiation and outcomes in implant-based breast reconstruction.* J Plast Reconstr Aesthet Surg, 2015. **68**(12): p. 1719-26.

70. Chetta, M.D., et al., *Reconstruction of the Irradiated Breast: A National Claims-Based Assessment of Postoperative Morbidity.* Plast Reconstr Surg, 2017. **139**(4): p. 783-792.
71. Jagsi, R., et al., *Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction.* J Natl Cancer Inst, 2018. **110**(2).
72. Laporta, R., et al., *Breast reconstruction following nipple-sparing mastectomy: clinical outcomes and risk factors related complications.* J Plast Surg Hand Surg, 2017. **51**(6): p. 427-435.
73. Czerny, V., *Plastischer ersatz der brustdruse durch ein lipom.* 1895.
74. Maxwell, G.P., *Iginio Tansini and the origin of the latissimus dorsi musculocutaneous flap.* Plast Reconstr Surg, 1980. **65**(5): p. 686-92.
75. Olivari, N., *The latissimus flap.* Br J Plast Surg, 1976. **29**(2): p. 126-8.
76. Mathes, S.J. and J. Bostwick, 3rd, *A rectus abdominis myocutaneous flap to reconstruct abdominal wall defects.* Br J Plast Surg, 1977. **30**(4): p. 282-3.
77. Holmstrom, H., *The free abdominoplasty flap and its use in breast reconstruction. An experimental study and clinical case report.* Scand J Plast Reconstr Surg, 1979. **13**(3): p. 423-27.
78. Hartrampf, C.R., M. Scheflan, and P.W. Black, *Breast reconstruction with a transverse abdominal island flap.* Plast Reconstr Surg, 1982. **69**(2): p. 216-25.
79. Taylor, G.I., R. Corlett, and J.B. Boyd, *The extended deep inferior epigastric flap: a clinical technique.* Plast Reconstr Surg, 1983. **72**(6): p. 751-65.
80. Allen, R.J. and P. Treece, *Deep inferior epigastric perforator flap for breast reconstruction.* Ann Plast Surg, 1994. **32**(1): p. 32-8.
81. Fujino, T., T. Harashina, and K. Enomoto, *Primary breast reconstruction after a standard radical mastectomy by a free flap transfer. Case report.* Plast Reconstr Surg, 1976. **58**(3): p. 371-4.
82. Teymouri, H., et al., *Breast reconstruction with autologous tissue following mastectomy.* Hippokratia, 2006. **10**(4): p. 153-62.
83. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Syst Rev, 2015. **4**: p. 1.
84. *Assessment of methods in health care*. 2017, Stockholm: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)
85. Atkins, D., et al., *Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group.* BMC Health Serv Res, 2004. **4**(1): p. 38.
86. Hunsicker, L.M., et al., *Short-Term Complications Associated With Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction.* Ann Plast Surg, 2016.

87. Lewin, R., et al., *A randomized prospective study of prophylactic cloxacillin in breast reduction surgery.* Ann Plast Surg, 2015. **74**(1): p. 17-21.
88. Zhong, T. and A.L. Pusic, *Future of outcomes research in plastic surgery.* Clin Plast Surg, 2013. **40**(2): p. 351-7.
89. Ware, J.E., Jr., *SF-36 health survey update.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3130-9.
90. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
91. Cano, S.J., et al., *The BREAST-Q: further validation in independent clinical samples.* Plast Reconstr Surg, 2012. **129**(2): p. 293-302.
92. Sousa, V.D. and W. Rojjanasrirat, *Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-friendly guideline.* J Eval Clin Pract, 2011. **17**(2): p. 268-74.
93. Kouwenberg, C.A.E., et al., *"The validity of the EQ-5D-5L in measuring quality of life benefits of breast reconstruction".* J Plast Reconstr Aesthet Surg, 2018.
94. Burstrom, K., et al., *Swedish experience-based value sets for EQ-5D health states.* Qual Life Res, 2014. **23**(2): p. 431-42.
95. Fernandez-Delgado, J., et al., *Satisfaction with and psychological impact of immediate and deferred breast reconstruction.* Ann Oncol, 2008. **19**(8): p. 1430-4.
96. Al-Ghazal, S.K., L. Fallowfield, and R.W. Blamey, *Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction.* Eur J Cancer, 2000. **36**(15): p. 1938-43.
97. Saboonchi, F., et al., *Examination of the construct validity of the Swedish version of Hospital Anxiety and Depression Scale in breast cancer patients.* Qual Life Res, 2013. **22**(10): p. 2849-56.
98. Hjort, H., et al., *Three-year results from a preclinical implantation study of a long-term resorbable surgical mesh with time-dependent mechanical characteristics.* Hernia, 2012. **16**(2): p. 191-7.
99. Soderback, H., et al., *Prophylactic Resorbable Synthetic Mesh to Prevent Wound Dehiscence and Incisional Hernia in High High-risk Laparotomy: A Pilot Study of Using TIGR Matrix Mesh.* Front Surg, 2016. **3**: p. 28.
100. Sharma, S., et al., *De novo experience of resorbable woven mesh in immediate breast reconstruction post-mastectomy.* European Journal of Plastic Surgery, 2016.
101. Becker, H. and J. Lind, *The use of synthetic mesh in reconstructive, revision, and cosmetic breast surgery.* Aesthetic Plast Surg, 2013. **37**: p. 914-921.

102. Chan, J.C., et al., *A clinically relevant in vivo model for the assessment of scaffold efficacy in abdominal wall reconstruction.* J Tissue Eng, 2017. **8**: p. 2041731416686532.
103. Rice, R.D., et al., *Comparison of Surgisis, AlloDerm, and Vicryl Woven Mesh grafts for abdominal wall defect repair in an animal model.* Aesthetic Plast Surg, 2010. **34**(3): p. 290-6.
104. Madani, A., et al., *Biologic mesh for repair of ventral hernias in contaminated fields: long-term clinical and patient-reported outcomes.* Surg Endosc, 2017. **31**(2): p. 861-871.
105. Luo, X., et al., *In vitro evaluation of decellularized ECM-derived surgical scaffold biomaterials.* J Biomed Mater Res B Appl Biomater, 2017. **105**(3): p. 585-593.
106. Memon, H.U., et al., *Comparison of graft-reinforced repairs and suture repair using a novel biomechanical test.* Int Urogynecol J, 2016. **27**(1): p. 47-53.
107. Zou, G., *A modified poisson regression approach to prospective studies with binary data.* Am J Epidemiol, 2004. **159**(7): p. 702-6.
108. Kim, J.Y., et al., *A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction.* Plast Reconstr Surg, 2012. **129**(1): p. 28-41.
109. Ho, G., et al., *A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction.* Ann Plast Surg, 2012. **68**(4): p. 346-56.
110. Lohmander, F., et al., *Implant Based Breast Reconstruction With Acellular Dermal Matrix: Safety Data From an Open-label, Multicenter, Randomized, Controlled Trial in the Setting of Breast Cancer Treatment.* Ann Surg, 2018.
111. Barber, M.D., et al., *Outcome of the use of acellular-dermal matrix to assist implant-based breast reconstruction in a single centre.* Eur J Surg Oncol, 2015. **41**(1): p. 100-5.
112. Clarke-Pearson, E.M., et al., *Revisions in Implant-Based Breast Reconstruction: How Does Direct-to-Implant Measure Up?* Plast Reconstr Surg, 2016. **137**(6): p. 1690-9.
113. Basu, C.B. and L. Jeffers, *The role of acellular dermal matrices in capsular contracture: a review of the evidence.* Plast Reconstr Surg, 2012. **130**(5 Suppl 2): p. 118S-24S.
114. Salzberg, C.A., et al., *Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience.* Plast Reconstr Surg, 2016. **138**(2): p. 329-37.
115. Vardanian, A.J., et al., *Comparison of implant-based immediate breast reconstruction with and without acellular dermal matrix.* Plast Reconstr Surg, 2011. **128**(5): p. 403e-410e.
116. Spear, S.L., et al., *Acellular dermis-assisted breast reconstruction.* Aesthetic Plast Surg, 2008. **32**(3): p. 418-25.

117. Clemens, M.W. and S.J. Kronowitz, *Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review.* Plast Reconstr Surg, 2012. **130**(5 Suppl 2): p. 27S-34S.
118. Dikmans, R.E., et al., *Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial.* Lancet Oncol, 2017. **18**(2): p. 251-258.
119. Azouz, V., S. Lopez, and D.S. Wagner, *Surgeon-Controlled Comparison of Direct-to-Implant and 2-Stage Tissue Expander-Implant Immediate Breast Reconstruction Outcomes.* Ann Plast Surg, 2018. **80**(3): p. 212-216.
120. Di Candia, M., et al., *Experience with the Wise mammaplasty skin resection pattern in skin-sparing mastectomy and immediate breast reconstruction for large breast volumes.* Int J Surg, 2011. **9**(1): p. 41-5.
121. Mundy, L.R., et al., *Breast Cancer and Reconstruction: Normative Data for Interpreting the BREAST-Q.* Plast Reconstr Surg, 2017. **139**(5): p. 1046e-1055e.
122. Negenborn, V.L., et al., *Patient-reported Outcomes after ADM-assisted Implant-based Breast Reconstruction: A Cross-sectional Study.* Plast Reconstr Surg Glob Open, 2018. **6**(2): p. e1654.
123. Walia, G.S., et al., *Prepectoral Versus Subpectoral Tissue Expander Placement: A Clinical and Quality of Life Outcomes Study.* Plast Reconstr Surg Glob Open, 2018. **6**(4): p. e1731.
124. Noble, J.H., Jr., *Meta-analysis: Methods, strengths, weaknesses, and political uses.* J Lab Clin Med, 2006. **147**(1): p. 7-20.
125. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* BMJ, 2009. **339**: p. b2535.
126. Cella, D.F., *Methods and problems in measuring quality of life.* Support Care Cancer, 1995. **3**(1): p. 11-22.
127. Cano, S.J., A. Klassen, and A.L. Pusic, *The science behind quality-of-life measurement: a primer for plastic surgeons.* Plast Reconstr Surg, 2009. **123**(3): p. 98e-106e.
128. Cano, S.J., et al., *Interpreting clinical differences in BREAST-Q scores: minimal important difference.* Plast Reconstr Surg, 2014. **134**(1): p. 173e-175e.
129. Chan, K.S., et al., *Distribution-based estimates of minimal important difference for hospital anxiety and depression scale and impact of event scale-revised in survivors of acute respiratory failure.* Gen Hosp Psychiatry, 2016. **42**: p. 32-5.
130. Sagberg, L.M., A.S. Jakola, and O. Solheim, *Quality of life assessed with EQ-5D in patients undergoing glioma surgery: what is the*

responsiveness and minimal clinically important difference? Qual Life Res, 2014. **23**(5): p. 1427-34.
131. Nuzzo, R., *Scientific method: statistical errors.* Nature, 2014. **506**(7487): p. 150-2.
132. Schwartz, C.E. and M.A. Sprangers, *Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research.* Soc Sci Med, 1999. **48**(11): p. 1531-48.
133. Rapkin, B.D. and C.E. Schwartz, *Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift.* Health Qual Life Outcomes, 2004. **2**: p. 14.
134. Barclay-Goddard, R., J.D. Epstein, and N.E. Mayo, *Response shift: a brief overview and proposed research priorities.* Qual Life Res, 2009. **18**(3): p. 335-46.
135. Dabakuyo, T.S., et al., *Response shift effects on measuring post-operative quality of life among breast cancer patients: a multicenter cohort study.* Qual Life Res, 2013. **22**(1): p. 1-11.
136. Schmidt, M.E., J. Wiskemann, and K. Steindorf, *Quality of life, problems, and needs of disease-free breast cancer survivors 5 years after diagnosis.* Qual Life Res, 2018.
137. Yu, R. and L. Chen, *The need to control for regression to the mean in social psychology studies.* Front Psychol, 2014. **5**: p. 1574.
138. Schulz, K.F. and D.A. Grimes, *Sample size slippages in randomised trials: exclusions and the lost and wayward.* Lancet, 2002. **359**(9308): p. 781-5.
139. Reeve, B.B., et al., *ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research.* Qual Life Res, 2013. **22**(8): p. 1889-905.
140. Korus, L.J., et al., *Patient-reported outcome measures in reconstructive breast surgery: is there a role for generic measures?* Plast Reconstr Surg, 2015. **135**(3): p. 479e-490e.
141. Bottomley, A., et al., *Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards.* Lancet Oncol, 2016. **17**(11): p. e510-e514.
142. Sox, H.C. and S.N. Goodman, *The methods of comparative effectiveness research.* Annu Rev Public Health, 2012. **33**: p. 425-45.
143. O'Connor, D.P. and M.R. Brinker, *Challenges in outcome measurement: clinical research perspective.* Clin Orthop Relat Res, 2013. **471**(11): p. 3496-503.
144. Greene, T., *Randomized controlled trials 5: Determining the sample size and power for clinical trials and cohort studies.* Methods Mol Biol, 2015. **1281**: p. 225-47.