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BREAST RECONSTRUCTION WITH BIOLOGICAL GRAFT

CLINICAL OUTCOMES IN THE SETTING OF BREAST CANCER TREATMENT

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BREAST RECONSTRUCTION WITH BIOLOGICAL GRAFT: CLINICAL OUTCOMES IN THE SETTING OF BREAST CANCER TREATMENT

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Ladies and gentlemen, I am now locked up in a handcuff that has taken a British mechanic five years to make. I do not know whether I am going to get out of it or not, but I can assure you I am going to do my best.

-HARRY HOUDINI, LONDON HIPPODROME,
SAINT PATRICK´S DAY 1904

POPULAR SCIENCE SUMMARY OF THE THESIS

Treatment for breast cancer can roughly be divided into two categories; local treatment (surgery and radiotherapy) and systemic treatment (chemotherapy, hormone therapy, targeted therapy, and immunotherapy).

Most women with breast cancer will have surgery as part of their treatment, and there are two ways to surgically remove cancer in the breast: to remove only part of the beast (*breast conserving surgery*) or to remove the entire breast (*mastectomy*).

For women having the entire breast removed, several options to reconstruct the breast are available. A breast reconstruction is a surgical procedure aiming to restore the shape and contour of the breast, and can be performed at the time of breast cancer surgery (*immediate reconstruction*) or at a later time (*delayed reconstruction*).

In broad terms, there are two ways to reconstruct the breast; The surgeon can use tissue transplanted from another part of the body where there is a surplus of tissue, often belly or back (*Autologous or "flap" reconstruction*), or use silicone implants or expander implants filled with salt water (*implant reconstruction*).

Regardless of what type of reconstructive method that is used (autologous or implant based), restoring the breast commonly involves several surgical operations to achieve a satisfactory result. While the aim is to create a silhouette similar to the breast before mastectomy, re-creating the exact shape is difficult and can seldom be fully achieved.

Meshes are commonly applied in surgical procedures where there is a need for repairing a tissue weakness. A surgical mesh refers to a flexible thin flat sheet, and can be made from biological tissue (*acellular dermal matrix or ADM*) or from synthetic materials. In breast reconstructions, the mesh is sewn to the chest wall to provide a hammock-like support, (like an “internal bra”) for the implant, essentially making the chest-muscle space larger, allowing a permanent full-sized breast implant to be inserted without the use of an expander implant. Surgical meshes for use in breast reconstructions, are promoted by the manufacturers for allowing single-step breast reconstructions, and for creating a more natural-looking breast.

The purpose of this thesis was to study if the use of a surgical mesh could reduce the number of surgical procedures for women with breast cancer having an implant-based breast reconstruction (IBBR). A further aim was to evaluate if using a mesh with this kind of surgery would improve health-related quality of life (factors that are part of a person´s health), as well as improve cosmetic results as viewed by the patient and the surgeons.

We found that using a mesh in implant-based breast reconstructions (IBBR) did not reduce the number of surgical procedures or improve health-related quality of life, compared to the same surgery without a mesh. In addition, we found that the mesh was associated with more surgical complications, such as delayed wound healing, compared to doing the surgery without a mesh.

In conclusion, findings from this thesis did not provide support that using a mesh, improves the results for women with breast cancer having an implant-based breast reconstructions–after mastectomy.

ABSTRACT

The overall aim of this thesis was to investigate the use of acellular dermal matrix (ADM) in implant-based breast reconstructions (IBBR) in the setting of breast cancer treatment. ADM refers to a surgical mesh developed from human or animal skin, and was initially applied in surgeries where soft tissue was deficient (e.g., hernia repair and treatment of burns). In the past few years, there has been a substantial increase in demand of ADM products for use in IBBR, and in many institutions ADM is a cornerstone in these procedures. The rationale for applying ADM in IBBR was initially two-fold: provide soft tissue coverage with implant support, and convert two-stage surgeries into one-stage procedures. In doing so, aesthetic outcomes after IBBR were said to improve, and breast reconstructions with implants would potentially require fewer overall procedures.

In this context, the randomized trial this thesis is based upon, was initiated to evaluate the use of a biological mesh (xenograft) in IBBR. In the trial, women with breast cancer planned for mastectomy and immediate IBBR, were *randomly allocated to either IBBR with ADM or to IBBR without ADM.*

Due to emerging reports concerning a potential relationship between ADM and harm, the short-term (complications within six months) safety of ADM-assisted IBBR was investigated. In **study I**, we found ADM not to be associated with an increased risk of reconstructive failure, compared to conventional IBBR without ADM, but linked to more surgical adverse events requiring reoperations.

We further explored whether using ADM would translate into improved health-related quality of life (HRQOL), by means of superior aesthetic outcomes as viewed by the patient, compared to conventional IBBR without ADM. In **study II**, we found a tendency of improved aesthetic outcomes favoring ADM-assisted IBBR, compared to conventional IBBR without ADM, measured at six months after reconstruction. However, the differences were minor, and we were unable to confirm any advantages of ADM with respect to HRQOL and self-perceived aesthetics. In **study III**, HRQOL and patient-reported aesthetic outcomes were also assessed, but with a two-year follow-up. Again, we failed to find an advantage of ADM-augmented IBBR with regard to patient-perceived aesthetics or HRQOL.

With implant-based breast reconstructions regularly involving additional surgeries, the primary trial endpoint was presented in **study III**, i.e., comparing reoperation rates between IBBR with and without ADM. The outcome of this study revealed that ADM-assisted IBBR, compared to conventional IBBR without ADM, did not reduce the number of reoperations within a follow-up time of two years. In **study IV**, we evaluated whether IBBR augmented with ADM would improve aesthetics, measured as physician-reported scores at two years. Results from this study did not support a benefit of using ADM in IBBR.

In summary, outcomes from this randomized trial performed in a breast cancer setting indicated ADM being associated with increased risk for complications compared to IBBR without ADM. We were unable to confirm the proposed benefit for acellular dermal matrix in reducing the number of surgical procedures, or improving health-related quality of life and patient-reported aesthetic outcomes, when used in immediate implant-based breast reconstructions.

LIST OF SCIENTIFIC PAPERS

I. Lohmander F, Lagergren J, Roy PG, Johansson H, Brandberg Y, Eriksen C, Jan Frisell. **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**. *Annals of Surgery*. 2019;269(5):836-41.

II. Lohmander F, Lagergren J, Johansson H, Roy PG, Frisell J, Brandberg Y. **Quality of life and patient satisfaction after implant-based breast reconstruction with or without acellular dermal matrix: randomized clinical trial.** *British Journal of Surgery Open.* 2020;4(5):811-20.

III. Lohmander F, Lagergren J, Johansson H, Roy PG, Brandberg Y, Frisell J. **Effect of immediate implant-based breast reconstruction after Mastectomy With and Without Acellular Dermal Matrix Among Women With Breast Cancer: A Randomized Clinical Trial.** *JAMA Netw Open,* 2021;4(10):e2127806.

IV. Lohmander F, Johansson H, Roy PG, Brandberg Y, Frisell J, Lagergren J. **Aesthetic outcomes following implant-based immediate breast reconstruction with biological graft – Physician-reported results from a randomized study.** *In manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

ADM	Acellular dermal matrix
AE	Adverse event
AI	Aromatase inhibitor
ALND	Axillary lymph node dissection
BCS	Breast conserving surgery
BMI	Body mass index
CC	Capsular contracture
CI	Confidence interval
CMF	Cyclophosphamide, Methotrexate and Fluorouracil
DCIS	Ductal carcinoma in situ
DIEP	Deep inferior epigastric perforator
DTI	Direct-to-implant
EBCTCG	Early Breast Cancer Trialists' Collaborate Group
ER	Estrogen receptor
FDA	The US Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
HIC	High-income countries
HRQOL	Health-related quality of life
ICC	Intraclass correlation coefficient
IBBR	Implant based breast reconstruction
IMF	Inframammary fold
LD	Latissimus dorsi
LMIC	Low and middle-income countries
MCID	Minimal clinically important differences
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MROCS	Mastectomy Reconstruction Outcomes Consortium Study
NAC	Nipple areola complex

NACT	Neoadjuvant chemotherapy
NSM	Nipple sparing mastectomy
OBS	Oncoplastic breast surgery
pCR	Pathological complete remission
PgR	Progesterone receptor
PMM	Pectoralis major muscle
PMRT	Post mastectomy radiotherapy
PROM	Patient reported outcome measures
QOL	Quality of life
QLG	Quality of Life Group
RCT	Randomized controlled trial
RT	Radiotherapy
SAE	Serious adverse event
SNB	Sentinel node biopsy
SSM	Skin sparing mastectomy
TE	Tissue expander
WHO	World Health Organization

1 PREFACE

The foundation for my thesis relies on a single study: a randomized clinical trial that was conducted in Sweden and the United Kingdom between April 24, 2014, and May 10, 2017.

When the trial was initiated, enthusiasm and support for using biological grafts in breast reconstructions with implants were high. Early adopters labelled it a “game changer” for implant-based breast reconstructions (IBBR), predicting superior aesthetic outcomes as well as more single-stage reconstructions. Manufacturers commonly referred to the products as a tool in the field of ´regenerative medicine´, referring to the meshes suggested ability of reinforcing soft tissue by re-vascularization. At the same time, several reports had also emerged concerning an increased risk for harm when acellular dermal matrix matrix (ADM) was applied in IBBR.

It was in this context, that this thesis was written.

Fredrik Lohmander, Stockholm 2021

2 INTRODUCTION

2.1 RECONSTRUCTION OF THE BREAST– A HISTORICAL PERSPECTIVE

Attempts at a breast reconstruction was described as early as 1896 by the Italian surgeon Iginio Tansini, where a pedicled latissimus dorsi myocutaneous flap was rotated to the mastectomy defect[1]. Despite this innovative endeavor, the effort was soon forgotten, and the following years only saw occasional attempts, with restoration of breast by many considered a "luxury operation with limited indications". Sir Harold Gilles (a pioneer in sex assignment surgery) described a method of using a tubed abdominal flap, developed in 1919, with results published in 1942[2]. These surgical procedures were extensive and commonly necessitated numerous staged surgeries over several months, not only resulting in significant scars, but in frequent flap failures, and "neither surgeon nor patient would recommend them"[2].

The Swedish surgeon Hans Holmström was one of the early pioneers in the era of free tissue transfer, when in 1979, he used tissue from a abdominoplasty as a ´free flap´ for a breast reconstruction[3]. While further advancements in the microsurgical field have led to a number of other variations of ´free flap´ procedures, the Deep Inferior Epigastric Perforator (DIEP) flap has remained first choice in autologous breast reconstructions.

The modern era of implant-based breast reconstructions originated with the first procedure described in 1962, where a sponge-like device of foam was inserted subcutaneously after a nipple-sparing mastectomy for benign disease, to recreate a breast[4]. Results from the first IBBR for malignant breast disease after a radical mastectomy were published in 1971, where a fixed volume implant was placed subcutaneously after a traditional skin reducing mastectomy and an axillary lymph node dissection (ALND)[5]. While these procedures had the intention of recreating a breast mound, there was limited focus on aesthetic outcomes. This approach would continue for the remainder of the decade.

In 1982, Radovan presented a model of tissue expansion[6]. This allowed for a gradual expansion of skin (and muscle) in patients lacking tissue after mastectomy, but required staged surgery, with a subsequent exchange to a permanent implant as a second procedure. Hilton Becker later introduced a dual-chamber expander implant, combining a silicone compartment with an expandable lumen of saline, initiating the single-stage expander technique[7]. However,

the long-term results with implants were unpredictable, and cosmetics commonly deteriorated over time as the implants aged[8].

In an effort to lower complications, the 1990´s saw a change from the subcutaneous implant position to full muscle coverage[9]. Covering the implant with well vascularized muscle decreased postoperative complications, such as skin necrosis and implant extrusion in presence of thin skin flaps[10]. However, aesthetic outcomes commonly deteriorated with time, and created functional issues such as pain and muscle spasms, harming physical activity[11]. Nevertheless, in the following years and today, variations of the sub-muscular technique have been standard method when performing IBBR´s.

Painting depicting a mastectomy procedure with students from the University of Pennsylvania observing. By Thomas Eakins in 1889.

3 LITERATURE REVIEW

"Exploration is the physical expression of the Intellectual Passion"

Apsley Cherry-Garrard (1886-1959)

The Worst Journey in the World: Antarctica, 1920-1913, Penguin Classics, 2006

3.1 BREAST CANCER EPIDEMILOGY

Breast cancer represents 1 in 4 cancers diagnosed among women globally, annually affecting some 1.38 billion patients worldwide (**Figure 1 and 2**)[12]. Annual incidence varies across regions, being higher at >80 per 100,000 women in high-income countries (HIC), and comparably low at <40 per 100,000 in low and middle-income countries (LMIC)[13]. However, available evidence suggests that breast cancer is increasing in emerging economies such as sub-Saharan Africa, were lifestyle changes, improved diagnostic procedures, and underlying tumor biology seem to be contributing factors, along with an aging population[14-16].

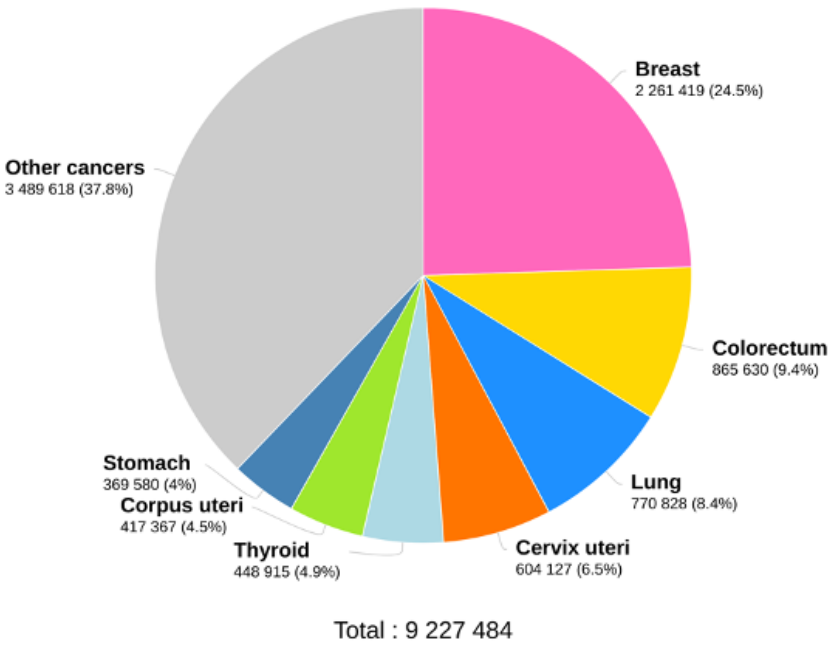

***Figure 1**. Global estimated cancer incidence (total number of diagnosis) among women of all ages in 2020. (Globocan 2020, IARC. Non-melanoma skin cancer excluded)*

Over the last decades, the incidence of breast cancer has increased, with a three-fold increase reported between 1980 and 2010, and with an annual increase of a 3.1%[17]. The reasons for this can likely be attributed to better detection via screening programs, an ageing population in the world, and improvements when reporting data. Globally, 641 000 individuals received the diagnosis in 1980, versus 2.1 million in 2018[13]. In Sweden, 8400 women were diagnosed in 2012, versus 8453 women receiving a breast cancer diagnosis in 2020[18]. This is compared to 2000 women being diagnosed with breast cancer in Sweden in 1960.

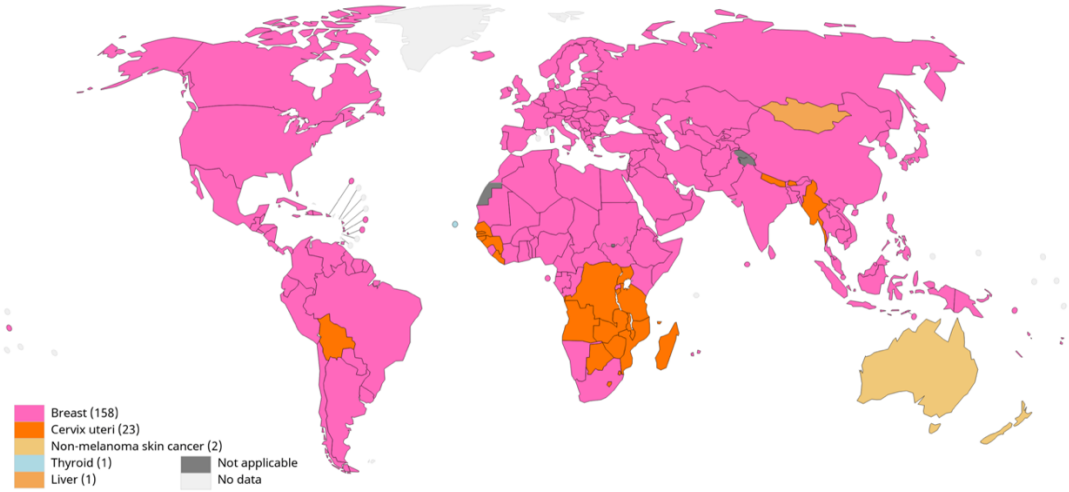

***Figure 2**. Top female cancer per country, estimated age-standardized incidence rates (World) in 2020, females, all ages. (Globocan 2020, IARC).*

The survival rates for breast cancer have seen a substantial improvement, with an increase in breast cancer survival seen in all HIC during the three last decades[13]. This can likely be attributed to improved access to healthcare, implementation of screening mammography, life-style factors, as well as advancements in systemic therapies[19]. In the USA, the rate of breast cancer death decreased by 37% between 1989 to 2012, and in Sweden, the overall 5-year survival rate for women diagnosed with breast cancer is today over 80%[20-22].

However, there are growing inequalities and disparities in the global burden of breast cancer. E.g., there continues to be differences between countries in Europe, with worse survival reported in eastern and southern Europe, with more breast cancer deaths occurring (**Figure 3**) in LMIC compared to HIC[12, 23]. With a low awareness and absence of programs for early detection, coupled with a lack of facilities for timely diagnosis and safe surgical treatment, many women in sub-Saharan Africa present with late stage-disease[14, 24]. Several studies have reported a low awareness of breast cancer, not only in the general population, but also among

health-care professionals[25]. Results from a meta-analysis in 2016 revealed that a majority of breast cancer patients in sub-Saharan Africa (73%) were diagnosed at stages III/ IV[14].

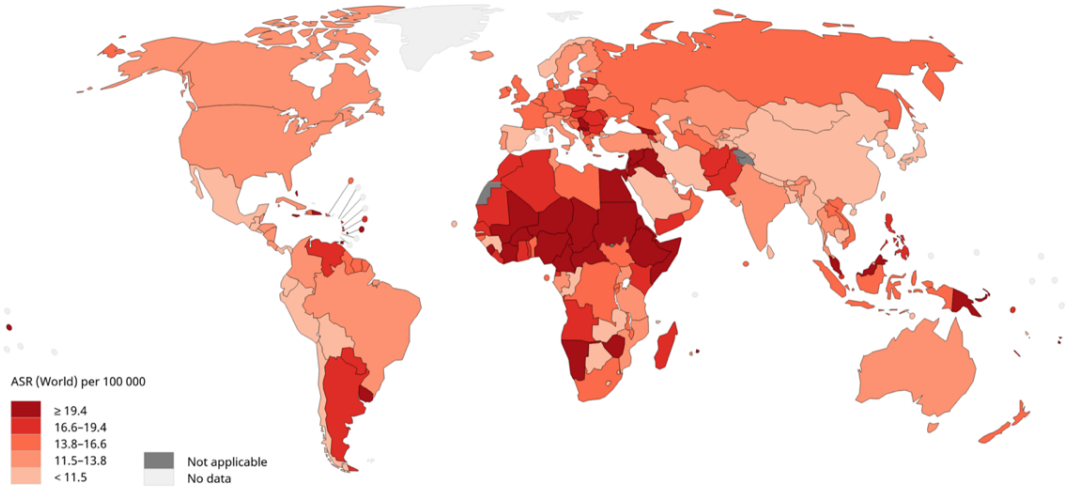

Figure 3. *Estimated age-standardized mortality rates (World) in 2020, breast cancer, all ages. (Globocan 2020, IARC).*

To address the issue of imbalance of mortality rates from common conditions needing surgery (such as breast cancer) being disproportionately higher in LMIC, the Lancet Commission for Global Surgery was launched in 2014. Findings from this report concluded that surgical conditions have been unrecognized and neglected in LMIC, and proposed a set of key policy messages to combat this increasing problem, such as investing in surgical services and improve access to safe and affordable surgical care[24]. The commission further concluded that surgery is an "indivisible and indispensable part of health care".

From photo by Fredrik Lohmander 2018

3.2 CLASSIFICATION OF TUMORS AND BIOMARKERS

3.2.1 TNM classification

The TNM staging system classifies the amount and spread of tumors, with ´T´ referring to the size and extent of the tumor; ´N´ referring to any regional lymph node metastasis; and ´M´ describing the presence of distant metastasis. The system was developed as a tool for physicians by the American Joint Committee on Cancer in 1977. With the introduction of biomarkers in cancer treatment, the system has evolved and been modified. In breast cancer, the system classifies the disease in four stages, with stages being associated with survival. In Sweden the 5-year overall survival in stage 0-1 disease is nearly 100%; roughly 80% for stage II, 60% in stadium III, and stage IV being around 20%. The overall 5-year breast cancer survival rate in Sweden is close to 83%, with breast cancer[20, 21].

3.2.2 Histological grade and type

Tumor grade, according to the World Health Organization (WHO) classification system (initially described in 1957), is a fundamental prognostic factor for treatment recommendations[26, 27]. The the morphological features of cancer cells is the basis for the overall scoring (I-III), (Nottingham histological grading). There are several histological types of breast cancers, with the most common subtypes being invasive ductal carcinoma and lobular cancers[28].

3.2.3 Biomarkers

Biomarkers form a pillar in clinical decision making by providing *prognostic* information (to differentiate patients having better outcomes from those with worse outcomes) and by *predicting* a response (whether a specific intervention is likely to be beneficial or not) to specific therapies.

Routinely tested biomarkers are the *Oestrogen receptor (ER), Progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2),* and *proliferation marker Ki67*. They are all included in the Swedish guidelines for breast cancer[29].

The majority of invasive breast cancers (up to 80-85%) express the ER receptor (i.e., tumors sensitive to endocrine treatment). A positive ER status is associated with beneficial tumor response after endocrine treatment as it reduces the risk of recurrence[30]. The ER receptor blocker Tamoxifen, discovered in 1962 by the chemist Dora Richardson[31], is on the WHO

List of Essential Medicines, and was a game changer in the treatment of breast cancer[30, 31]. Tamoxifen reduces recurrence rates by nearly 50% (RR 0.53 at four years and RR 0.68 during years 5-9) and breast cancer specific mortality by 30% during the first 15 years (RR 0.71 years 0-4, 0.66 years 5-9, 0.68 years 10-14)[32].

The nuclear protein Ki67 (reported as a value between 0 and 100%) is expressed on proliferating tumor cells, reflecting the proportion of dividing cancer cells. Due to a considerable variability between observers, as well as disparities between laboratories, cut-off values to discriminate between high, intermediate, and low proliferating tumors, varies widely[33, 34]. With the introduction of digital image analysis as well as assistance from machine learning (AI), reliability and reproducibility when determining Ki67 is expected to improve[35, 36].

The HER2, is a tyrosine kinase receptor located on the cell surface, expressed in about 15-20% of all breast cancers. The HER2 is a predictive biomarker for therapeutic tumor response, and the gene expression of HER2 is associated with a more aggressive tumor biology, and worse overall survival[37].

3.2.4 Molecular breast cancer subtypes

With advancements in histopathological diagnostics and gene expression analysis, breast cancer is today regarded as heterogenous disease that includes several groups of tumors, each with different biological characteristics. Since Perou et al. initially identified four distinct groups of molecular patterns[38], these four clusters have today been translated to include surrogate subtypes (determined by hormone receptors, HER2 status, and proliferations markers), resulting in five distinct intrinsic tumor subtypes[39]:

- *Luminal A*: The most common molecular subtype (60-70%). Characterized by a low proliferative activity measured by Ki67, ER and PgR positive, HER2 negative.
- *Luminal B-like HER2 neg*: Characterized by a high proliferation measured by Ki67, a negative HER2 expression, and a positive ER and PgR status. Accounts for 10-20% of breast cancers.
- *Luminal B-like HER2 pos*: Same biomarkers as above, with additional HER2 expression.
- *HER2-positive non-luminal*: Characterized by negative ER and PgR expression, a high proliferation, and HER2 expression. Approximately 15% of breast cancers.

- *Triple-negative (TNBC)*. Lack of ER, PgR and HER2 expression. Commonly high proliferating tumors.

The classification of breast cancer into molecular subtypes has become clinically important when setting up treatment plans, with treatments today being tailored to the individual patient[38]. Treatment plans according to this classification are incorporated into international clinical guidelines[40].

3.3 DIAGNOSTIC PROCEDURES AND SCREENING

3.3.1 Breast cancer screening

Since 1986, the National Board of Health and Welfare in Sweden recommends mammography screening every 18-24 months for women between the ages of 40 and 74 years[41]. Early detection is often mentioned as an important element in determining cancer outcomes[42]. Nevertheless, the impact of mammography screening on breast cancer mortality continues to be a topic of discussion, where reported benefits are contrasted against potential harms such as overdiagnosis and overtreatment[43, 44]. A trend towards a more personalized screening aimed at specific risk groups, is seen internationally[45].

3.3.2 Triple assessment and the multidisciplinary approach

Clinical examination, *diagnostic imaging* (mammography, ultrasound, MRI), and *fine needle aspiration* (FNA), or *core biopsy*, are cornerstones in breast cancer diagnostics. With a sensitivity and specificity close to a 100%, the triple diagnostic assessment has been the ´gold standard´ in breast cancer care[46]. Treatment for breast cancer today requires input from several specialties, including surgeons, oncologists, radiologists, pathologists, and nurses. Envisioned in the 1970´s, aiming to improve breast cancer care, this multidisciplinary team approach revolutionized breast treatment[47]. Multidisciplinary meetings (MDT´s) not only serve as the base for decision-making, but also involves what specialties to utilize, and in what order. According to Swedish guidelines, all breast cancer patients should be discussed pre- and post-operatively at an MDT[29].

3.4 BREAST CANCER TREATMENT – THE SHORT VERSION

3.4.1 Surgical treatment

Since the ancient Egyptians and Hippocrates described the existence of tumors located in the breast, surgery has been a central component in the treatment of breast cancer. The radical mastectomy, first described by William Halsted in 1894, was a mutilating surgical procedure, completely removing the underlying pectoralis major muscle, accompanied by a thorough clearance of the ipsilateral axillary lymph nodes[48]. Despite sometimes serious complications, this radical breast amputation was standard surgical approach until the mid 1970´s, when awareness that failures in treatment were commonly related to the occurrence of occult systemic disease, rather than insufficient local treatment[49]. Since then, the modified version of the radical mastectomy (sparing the pectoralis major muscle) has been the standard method of mastectomy [50]. At the time of this shift, there was concern among surgeons that an adequate axillary dissection could not be achieved without excision of the pectoralis major muscle (**Figure 4**)[51].

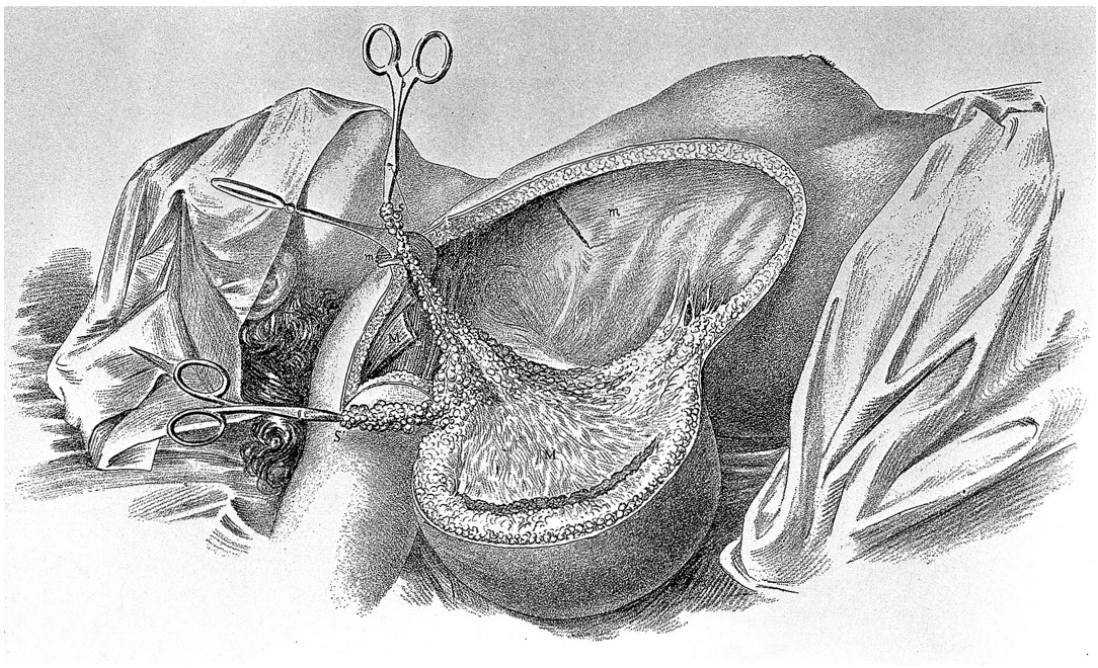

Illustration in the paper "Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January 1894", published by William Halsted in Annals of Surgery 1894.

Recent years has seen a steady decline in the mastectomy rate in favor of breast conservation surgery (BCS)[20]. Several randomized trials with more than 20 years of follow-up, have indisputably shown that BCS followed by adjuvant radiotherapy is equal to mastectomy regarding breast cancer survival[52]. The decline in mastectomy rates can be attributed to an increased use of chemotherapy in a neoadjuvant setting, allowing for smaller resected volumes, as well as increased uptake of 'oncoplastic breast surgery', permitting resections of larger tumors, without compromising on margins or cosmetics, thus avoiding mastectomies[53, 54]. Current guidelines concerning tumor margins, with "no tumor cells on ink" have possibly added to this development[55, 56].

Interestingly, there is data from several cohort studies suggesting that BCS followed by RT can have survival benefits over mastectomy[57-59]. Reasons for these reported survival benefits after BCS versus mastectomy is a current matter of discussion, where selection bias and radiotherapy have been suggested as possible explanations[57, 60].

Multifocal tumors are not a contraindication for BCS, provided clear margins have been achieved[61]. The most common and often overriding principle when assessing surgical options (BCS versus mastectomy), is anticipating the breast volume needing to be resected versus the volume of the breast[53].

3.4.1.1 ´Oncoplastic surgery´

The term 'oncoplastic breast surgery' (OBS), refers to the integration of oncologic surgery with techniques from the field of reconstructive and cosmetic breast surgery. The concept originated with the idea of avoiding a mastectomy by means of larger tumor excisions and a simultaneous partial breast reconstruction. The principle was later stretched to include the concept of 'seamless breast cancer surgery', by also incorporating immediate reconstruction of the breast at the time of mastectomy[53, 62]. Various descriptions and classifications for OBS have been introduced over the years, but no real consensus on how to define the term exist. Most of the OBS definitions originate from the work of Clough et al[53, 63, 64]. A recent attempt to define the term was made by Chatterjee et al[65].

3.4.1.2 Nipple-sparing mastectomy

Over the years, the mastectomy technique progressed from a "tissue-eliminating" to a "tissue-saving" approach. The skin-sparing and nipple sparing mastectomy (NSM) has perhaps been the most influential factor in the advancement of modern breast reconstructive outcomes. There is data supporting that preservation of the nipple-areola complex has health benefits for women undergoing IBBR[66]. Since the terminal breast ducts are possibly left behind when preserving the NAC, potentially leading to higher risk for local recurrence, oncological safety of NSM has been a topic of discussion[67, 68]. However, current results suggest that NSM is an oncologically safe approach, provided patients are properly selected (depending on the size and location of the tumor, in relation to the NAC)[69-71].

3.4.1.3 Surgical treatment of the axilla

ALND has been a pillar of breast cancer surgery[51]. ALND maintained regional control in the axilla and identified lymph node metastasis[72]. However, since introduction of the sentinel node concept in 1994, to accurately stage lymph nodes with less surgical morbidity, management of the axilla with ALND as a diagnostic procedure, has gradually been shifting towards less extensive surgery[73-75]. This notion has now been extended to evaluate the role of ALND as a therapeutic procedure in node-positive tumors as well, and there are currently several clinical trials under way assessing this topic[76].

Two randomized trials (ACOSOG Z0011 and IBCSG 23-01) revealed that if limited axillary metastatic disease were left behind (without ALND), this did not compromise the oncological safety in selected patients[77, 78]. In women with a maximum of 2 macro-metastatic lymph nodes, having BCS followed by adjuvant radiotherapy, it is today considered safe in some institutions to avoid ALND[79]. It is worth mentioning here that patients treated with mastectomy are underrepresented in the current data on omitting ALND in node-positive patients[80]. The ongoing Swedish SENOMAC trial, a multicenter randomized trial evaluating the benefit of ALND in sentinel-node positive patients, also includes patients treated with mastectomy receiving adjuvant RT[76]. Current evidence also suggests that ALND can be omitted following detection of micro-metastasis in 1-2 sentinel nodes, in clinically node negative patients[78]. Previous data have shown that ALND decreases the risk of local axillary recurrences (associated with survival benefits) (**Figure 4**)[81].

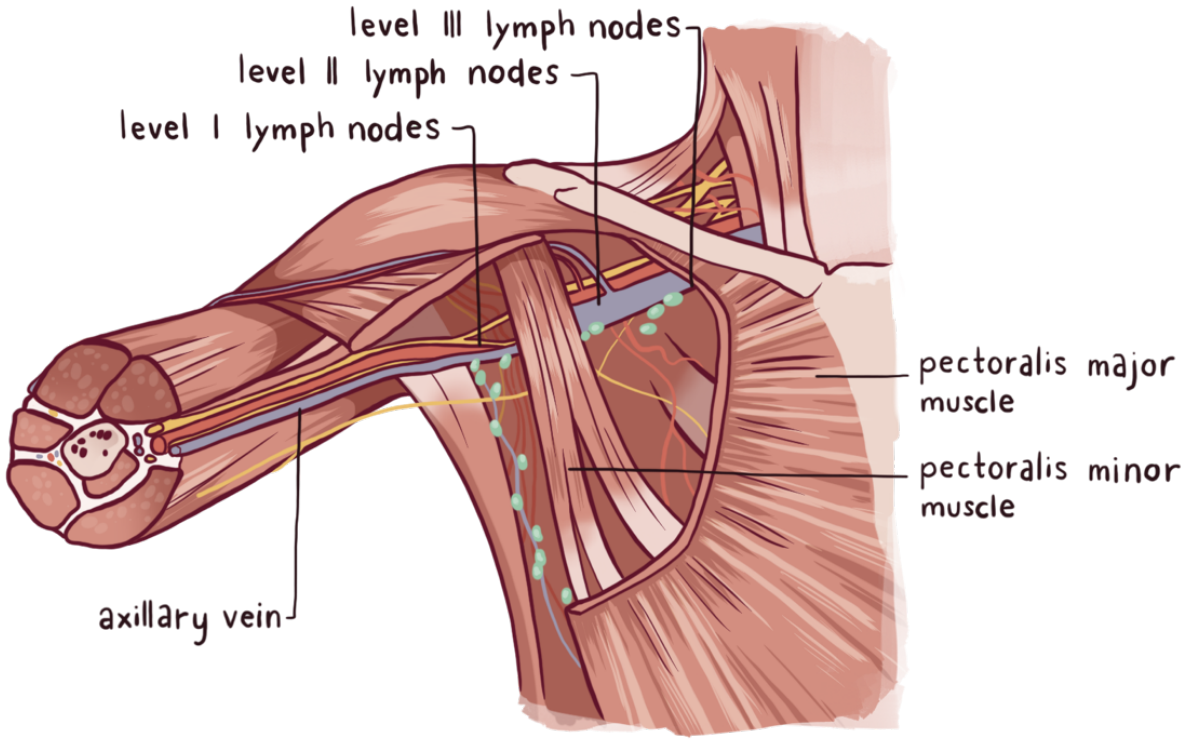

Figure 4. *Illustration of the axillary region. ©Linn Lohmander.*

In patients with a pre-operatively staged clinically free axilla, extirpation of 1-3 sentinel lymph nodes is today standard method for axillary staging, carrying a high sensitivity and detection rate, as well as a low arm morbidity[82-84].

In patients treated with neo-adjuvant radiotherapy (NACT), sentinel node biopsy (SNB) after chemotherapy is now considered a safe and standard method in many countries[85]. With extirpation of at least two sentinel nodes (and the use of dual detection using blue dye and scintigraphy), the false negative rate is comparable to SNB performed before chemotherapy[86]. There is an added benefit of performing SNB after NACT in patients having had their tumors down-staged after NACT. In these patients, where a potentially positive SNB status (with a clinically negative axilla) before NACT, is converted to a node negative SNB status after treatment (in 40% to 50% of patients with HER2+ and triple-negative breast cancer), ALND and adjuvant RT can be omitted. This would lead to less morbidity without increased risk of local recurrence in the axilla, provided at least three lymph nodes are removed[87, 88]. In patients with a confirmed macro-metastasis in the axilla before start of NACT, ALND is still performed[87]. A further development in assessing a node positive axilla prior to NACT is to target the lymph node with charcoal before NACT, for a more targeted axillary dissection[89].

3.4.2 Chemotherapy

Chemotherapy has been fundamental in the treatment of breast cancer since its introduction in the 1960´s, when combining *Cyclophosphamide, Methotrexate and Fluorouracil (CMF)* showed a reduction of breast cancer mortality at 20 years by almost 25%, compared to no chemotherapy[90]. A large meta-analysis on individual patient data from 123 randomised trials in 2012, by the Early Breast Cancer Trialists' Collaborate Group (EBCTCG), showed a 16% relative risk reduction of recurrence, and decreased the relative mortality risk by 21% (absolute risk reduction at 10 years 6.5%) when anthracyclines was added[91]. With the addition of anthracyclines and taxanes to the treatment, breast cancer mortality has been further improved[91].

Data from an overview of several randomized trials has shown that chemotherapy given as an adjuvant regimen extends recurrence-free and breast cancer-specific survival[92, 93]. With alterations in sequence and intensity of the chemotherapy regimens (such as increasing the dose or shortening treatment intervals), outcomes have been shown to be further improved[94, 95]. This is supported by recent data from a meta-analysis of the EBCTCG in 2019[96].

Chemotherapy is, however, associated with various degrees of toxicity. Most side-effects are of relatively mild character, such as fatigue, nausea and mucositis, whereas others can be more severe, potentially leading to treatment-related mortality[97].

Initially, the primary indication for giving adjuvant chemotherapy was a node-positive disease. However, with advancement of biomarkers to better predict and assess risk of relapse and sensitivity to chemotherapy before treatment, evaluating indications for chemotherapy has become more complex[95].

NACT, the concept of administering chemotherapy before surgery and not after, was long used for downsizing locally advanced cancers in the breast and axilla, and as such, increase operability for tumors initially considered inoperable[98]. The current rationale for NACT is that it enables adjustment of the treatment in case of poor response, and at the same time provide monitoring and in-vivo evaluation of the treatment effects, with the possibility of prospectively adapting the treatment regimen[99]. The shift from being an adjuvant treatment, to frequently being administered in the pre-operative setting, has in many institutions been practice-changing[90, 93].

Today, some guidelines state that neoadjuvant chemotherapy can be used whenever adjuvant chemotherapy is considered, based on tumor biology (such as molecular subtypes, tumor size, lymph node status, and comorbidity) from a core biopsy. Other guidelines are aimed to improve and predict the survival outcome, though several randomized trials have demonstrated equivalent risk of breast cancer specific and overall survival for pre- or post-operative delivery of chemotherapy[93].

Nevertheless, the fundamental difference and potential benefit compared to the adjuvant treatment option, is the ability to monitor tumor-response during therapy. Perhaps more importantly, there is today good evidence supporting that a pathologic complete response (pCR), i.e., the absence of residual invasive cancer on hematoxylin and eosin evaluation, is a prognostic marker for more favorable outcomes, particularly in patients with HER2 positive and triple negative tumor biology[100]. For patients with operable tumors of more than 2 cm, and a triple negative or HER2 positive tumor biology, current Swedish guidelines, as well as the St. Gallen consensus recommend NACT[29, 85].

Current data suggests that the same chemotherapy treatment given before or after surgery results in the same risk for distant relapse, as well as breast cancer specific and overall survival[93]. Nonetheless, data from 10 randomized trials, evaluated by EBCTCG, showed that the possibility of performing BCS increased from 49% to 65%[93]. The proportion of patients treated with NACT ranges between 7% and 27% internationally, with 9% of Swedish breast cancer patients receiving pre-operative chemotherapy in 2019[21, 101]. Whether pCR after NACT translates to a survival benefit is a current topic of discussion[101].

3.4.3 Targeted treatment: Anti-HER2 therapy

The discovery of Trastuzumab, a monoclonal antibody introduced in the year 2000, revolutionized breast cancer treatment[37, 102]. Trastuzumab binds to the HER2-receptor and reduces tumor proliferation by impairing the HER2 signaling. Since 2006, it is available for treatment of primary breast cancer. There is now evidence supporting that treatment with Trastuzumab combined with chemotherapy, leads to a 34% relative improvement in overall survival in HER2-positive breast cancer patients[103].

3.4.4 Radiotherapy

The national guidelines for adjuvant radiotherapy following breast cancer surgery, are based on a number of variables, including tumor extent, axillary lymph node status, and the type of surgery. Radiotherapy is recommended following breast conserving surgery, with the aim of eliminating residual (microscopic) disease, hence reducing risk of local recurrence as well as improving breast cancer-specific survival[104].

Results from the EBCTCG follow-up analysis in 2011, revealed a significant reduction of local recurrence with RT and an increase in breast cancer specific survival after 15 years for all age groups[104]. The absolute risk reduction for local recurrence after BCS, was 15.7% over 10 years, and an absolute reduction of breast cancer death of 3.8% over 15 years[104]. For breast cancer with node-positive disease (macro metastasis), the absolute risk-reduction is even more noticeable, with an absolute reduction of 10-year risk for recurrence of 21.2%[104]. After BCS, local RT focuses on the remaining breast tissue, chest wall, as well as the breast skin, while locoregional RT involves axillary lymph nodes, and supra- and infraclavicular areas as well.

In women having mastectomy, with node-positive axillary status, the risk of breast cancer recurrence is also reduced with adjuvant RT[105, 106]. The absolute benefit of post-mastectomy radiotherapy (PMRT) was 10.6% and 8.1% for 10-year breast cancer recurrence and 20-year specific breast cancer survival respectively, according to a meta-analysis from the EBCTCG in 2014[106]. This trial also showed that women having mastectomy with axillary dissection with node negative disease, did not have the same benefit of PMRT (radiotherapy of the chest wall) regarding risk for loco-regional recurrence at 10 years (RR 1.06, 95% CI 0.89 – 1.55)[106].

According to the Swedish national guidelines, adjuvant RT to regional lymph nodes combined with local RT, is recommended regardless of whether BCS or mastectomy is performed, in the presence of node-positive disease[29]. The Swedish guidelines also recommend PMRT to the chest wall if tumor extent is more than 5 cm, or in the case of multi focal disease[20, 29, 104, 107]. For smaller, hormone receptor positive breast cancers in women over 70 years, RT can be omitted[108]. International recommendations differ in women having had axillary clearance with 1-3 positive lymph nodes, and the meta-analysis from the EBCTCG in 2014 did not reveal a clear risk reduction for loco-regional recurrence after 10 years, or for breast cancer mortality at 20 years following adjuvant RT to the chest wall for women treated with mastectomy and axillary clearance[106].

In the presence of micro metastases, and in women with 1 positive node and advantageous cancer biology (Luminal A), adjuvant RT is not suggested in Sweden[20, 29]. The dose of RT and number of fractions given has been decreasing over time, resulting in shorter treatment duration of adjuvant RT[109].

RT has been shown to carry long term complications, with risk of developing other malignancies such as angiosarcoma and lung cancer, as well as cardiac disease[110]. To reduce the risk of overtreatment, models to better predict the individual response to RT are being evaluated[111].

The application of intraoperative radiotherapy, as opposed to whole-breast external breast radiation, has been evaluated in several studies, but its use has not been unanimously supported by the scientific community, and the method is not implemented in Swedish treatment guidelines[112].

3.5 BREAST RECONSTRUCTION OPTIONS TODAY

In broad terms, three different modalities of breast reconstruction are available following mastectomy, each of which can be done at the time of mastectomy (immediate reconstruction), or performed as a delayed procedure.

I. Implant-based breast reconstruction (with or without using a tissue expander).
II. Pedicled flaps with or without an implant. Commonly a myocutaneous latissimus dorsi (LD) flap.
III. Transfer of non-pedicled tissue (without harvesting muscle) to the recipient site (internal mammary vessels) by way of a microvascular anastomosis based on the deep inferior epigastric perforator vessels (DIEP)[113]. Other, less frequently used alternatives, are free flaps using buttock or thigh fat.

The timing and choice of reconstruction method is dependent on a number of variables, such patient preferences, body habitus, as well as breast cancer stage and tumor biology. Additional factors such as patient-received information, treatment setting (i.e., whether adjuvant RT is anticipated) and surgeon´s preferences influence decision-making[114].

According to Swedish and international guidelines, women treated for breast cancer should be informed about the availability of breast reconstruction as part of their treatment plan[115-119]. The proportion of women undergoing immediate breast reconstruction in Sweden varies widely, with numbers below 1% to more than 30% being reported[21]. Variations in patient-reported information and involvement in the surgical decision-making process have been suggested as important factors for this variability[120].

3.5.1.1 DIEP flap reconstruction

Autologous reconstruction with DIEP flap is commonly performed in a delayed setting in Sweden, either following immediate IBBR (if surgical complications or unsatisfactory results after IBBR), or as a planned procedure after a mastectomy without an immediate IBBR. National guidelines recommend delayed reconstructions with free flap techniques to be performed at least two years after completion of breast cancer treatment (as many recurrences occurring within this time frame), and are primarily offered to irradiated patients[121]. DIEP flaps for immediate breast reconstructions are applied less frequently in Sweden, but occasionally offered to selected patients planned for risk-reducing surgery.

3.5.1.2 Pedicled Latissimus dorsi (LD) flap

Due to its relative simplicity, versatility, and robust blood supply, the pedicled LD myocutaneous flap was long regarded as the ´workhorse´ in breast reconstructions, particularly in the United Kingdom[122]. In selected patients, extensive tissue harvest can enable an entirely autologous reconstruction without an implant (´extended LD´), but a more common strategy is the ´implant-assisted LD´ for additional volume. With advancements in microvascular techniques, enabling fasciocutaneous flaps to be raised without utilizing muscles for blood supply, the LD flap has seen a decline in the immediate setting[123]. The LD can also result in donor-site morbidity such as muscle weakness[124]. However, applied as a delayed reconstruction in irradiated patients with limited tissue surplus for a ´free flap´ procedure, the technique is a viable option, as well as a useful approach for repairing extensive tissue defects following surgery for local recurrences[125].

3.5.2 Implant-based breast reconstruction

Microsurgical techniques for free tissue transfer in breast reconstructions have become more refined and efficient, and there are reports suggesting that autologous tissue is a more sustainable option for women considering breast reconstruction, with lower risk of surgical maintenance in the long run[126, 127]. Despite this, implant-based methods are more often used,

particularly in the immediate setting. Implant-based reconstructions have increased compared to autologous-based modalities in the United States, where patient driven decisions, as well as economic incentives likely have contributed to increased rates of bilateral mastectomies for unilateral cancers[128, 129]. A similar trend is seen in the United Kingdom[123].

Broadly, two ways of placing the implant have been used; the subcutaneous implant placement, i.e., placing the implant directly under the remaining skin and subcutaneous tissue following mastectomy, or using muscle to cover the implant. With full muscle coverage, the implant is covered by the pectoralis major, anterior rectus fascia and commonly by an advancement flap of serratus anterior for lateral tissue coverage. Combinations of these two methods have also been applied.

3.5.3 ADM-assisted implant-based breast reconstruction

When ADM, a detergent-washed and decellularized dermal xeno- or allograft, was introduced for implant-based breast reconstructions in 2005, the underlying concept was that by combining the benefits of the subcutaneous and submuscular techniques, cosmetic outcomes would improve, and possibly allow for more one-stage surgeries[130].

After its introduction, ADM quickly gained approval, and several benefits were reported in the literature, including decreased need for tissue expanders (permitting one-stage procedures), improvement in aesthetic outcomes, and less need for revision surgery[131, 132]. In particular, the ability of performing IBBR using fixed-volume implants, instead of tissue expanders, was described as one of the main potential benefits[133].

A search in PubMed for papers published between 2005 and 2021 reporting on outcomes of IBBR with ADM, yields 840 articles. Of these, 10 RCT´s compared different types of

The following search terms were used for the PubMed search; *(("acellular dermis" [MeSH] OR "biocompatible materials" [MeSH] OR veritas [tiab] OR flexhd [tiab] OR dermamatrix [tiab] OR surgimend [tiab] OR alloderm [tiab] OR strattice [tiab] OR acellular derm* [tiab] OR adm [tiab]) AND (plastic surg* [tiab] OR "surgery, plastic" [MeSH] OR "mammaplasty" [MeSH] or mammaplast* [tiab] or mammoplast* [tiab] or breast reconstruction* [tiab]) AND (prosthe* [tiab] OR expander* [tiab] OR implant* [tiab] OR "tissue expansion devices" [MeSH] OR "breast Implants" [MeSH]) AND ("breast" [MeSH] or breast* [tiab]))*

biological meshes, but only one trial compared IBBR with a mesh versus IBBR without a mesh[134].

Despite ADM´s high cost (approximately US$2000 per mesh) and lack of evidence supporting mentioned benefits, its use has in many institutions become common practice. Today, IBBR supported with a mesh (biological or synthetic) has now become the most commonly used reconstruction method in the UK, and is applied in over half of the IBBR´s performed annually in the USA[129, 135]. A 2015 review noted that 84% of the American Society of Plastic Surgery members used ADM in breast reconstruction[136]. Interestingly, The US Food and Drug Administration (FDA) has not approved the use for ADM in breast reconstructions, and this use of the product is regarded as off-label[137-139]. ADM is, however, approved for other reconstructive purposes, such as repair for abdominal hernias[138]. Meshes come in both a biological and synthetic form, and are marketed by a number of different manufacturers[140, 141].

With the current practise trend of supporting the implant with meshes, the subcutaneous implant placement has seen a revival, leading to an increase in publications describing the benefits of the method and the products[142-144]. However, with most reports based on retrospective case series, the potential benefit of this technique cannot be evaluated[145].

3.5.3.1 ADM-assisted IBBR and harm

The role of ADM, and its potential to cause harm, has been a matter of debate, with higher rates of skin necrosis and implant loss reported, compared to IBBR without ADM[134, 146].

An RCT from The Netherlands published in 2017 evaluating both therapeutic and risk-reducing surgeries, revealed ADM-assisted IBBR being associated with a higher risk for surgical complications leading to reconstructive failure, compared with traditional two-staged IBBR using full muscle coverage[134].

As a consequence of the higher complication rate, the trial was closed early due to concerns of safety. The trial included smokers, a known risk factor in standard IBBR[147]. Further, a review concluded that the evidence supporting the use of ADM is inadequate, and that *´the method should be regarded as an experimental surgical technique until firmer scientific proof was recognized'*[146]. A temporary pause on using ADM (Strattice™) in IBBR by health authorities in France following high rates of surgical complications, added concerns regarding safety[148].

In contrast, results from the iBRA-study, a prospective multicentre cohort study conducted in the UK revealing short-term safety results after different types of breast reconstructions, did

not show higher rates of implant loss for ADM-assisted IBBR[149]. It is worth noting, that interpretation of many studies is complicated by a lack of uniform standards for reporting surgical complications[150, 151].

Since the introduction of biological meshes (ADM), several synthetic meshes have arrived on the market, with results from an RCT suggesting a lower risk for complications compared to biological meshes, including less seroma formation[152].

3.5.4 Radiotherapy in the setting of implant-based reconstructions

Although improvements in radiotherapy techniques have increased treatment tolerance, with less severe complications seen today than in the past decades, irradiated implants clearly fare worse than those not irradiated, and with few exceptions, PMRT negatively affects outcomes after IBBR[153, 154] [155, 156].

Capsular contracture (CC), the most frequent complication, is a dense fibrous tissue, encapsulating and constricting the implant[157]. CC impairs aesthetics and creates discomfort, potentially impairing health-related quality of life (HRQOL) for women undergoing IBBR. Over time, the effects of CC can progress, resulting in implant displacement and lack of softness, and with few exceptions, necessitating surgical revisions, and at times conversion to autologous procedures[157-164]. Revision surgery such as capsulotomy (with or without implant exchange), usually resolves or mitigates the problem associated with CC, but does not prevent its recurrence[158, 165] [166-168].

With indications for PMRT extended over the years, the proportion of women receiving adjuvant RT after IBBR has increased. This has complicated the timing and choice of a breast reconstruction[107, 169]. The US National Cancer Database reported an increase between 2004 and 2013 from 13% to 33% of women receiving adjuvant RT following IBBR[170, 171]. In Sweden, the proportion of women with 1-3 positive nodes receiving PMRT has increased from 67% in 2012 to 84% in 2019[21].

A fourfold increase in risk for surgical complications in the presence of RT, was reported in a meta-analysis including 1105 women undergoing IBBR, and with risk of implant failure in the context of RT in up to 37% of patients reported in the literature[157, 160, 172-174].

A large Swedish retrospective cohort study that included 725 patients from four hospitals, revealed a 5-year implant failure rate at 10% in the non-irradiated IBBR group, versus 25%

risk of implant loss in the presence of PMRT and IBBR[158]. Of the non-irradiated patients, 44% had at least one unplanned surgery versus 59% in the patients receiving adjuvant RT[158].

A retrospective cohort study reported that in the presence of adjuvant RT, IBBR was associated with a three-fold (95% CI 1.20-7.75, p = 0.019) higher odds of an unplanned reoperation compared to reconstruction with autologous tissue[175]. It is here worth mentioning that adjuvant radiation following immediate reconstruction with autologous tissue also carries a risk of post-operative complications such as fat necrosis, contractures of the flap, and flap failure, leading to deformity also requiring revision surgery[176]. There are conflicting reports whether a tissue expander or a fixed volume implant is preferable in the presence of irradiation[163, 164].

Whether immediate IBBR should be performed when adjuvant RT is anticipated, considering the higher risk for surgical complications, is a topic of discussion, with some authors questioning the concept due to ethical issues[177]. There is no international common consensus whether IBBR should be recommended in the setting of adjuvant RT[178]. At our institutions where currently about 40% of the patients receive PMRT, IBBR is not a contraindication per se if adjuvant radiotherapy is anticipated, provided the patient is informed of the higher risk for post-operative complications, including the likelihood of further revision procedures and risk of implant loss[20, 179].

In contrast to radiotherapy, neither neoadjuvant nor adjuvant chemotherapy seem to be linked with increased risk for adverse outcomes in patients undergoing immediate implant-based or immediate autologous breast reconstruction[180].

3.5.5 Reoperations in breast reconstructions

After the initial breast reconstruction, many patients will have additional procedures[165]. Additional procedures can be seen as *anticipated*, i.e., replacing a tissue expander to a fixed-volume implant, a contralateral mammoplasty for symmetry, or reconstruction of the nipple areolar complex to complete the breast façade. Some reconstructions entail *unanticipated* revisional procedures, due to complications such as hematoma or flap failure, or more long-term complications (i.e., capsular contracture), or require reoperations for repairing abdominal hernia at the donor site following ´free flap´ surgery.

Several studies have examined reoperations on a larger scale following breast reconstructions, but long-term estimations are lacking, and reports on reoperation rates vary. Many studies are also predominantly single-surgeon/institution-based, or limited to one reconstructive modality,

making for limited generalizability and comparison between reconstructive modalities difficult. In addition, as long-term complications in IBBR, such as CC, commonly progresses over time, variations in follow-up times complicates interpretation of the results[165, 181-184].

Recent data from the Mastectomy Reconstruction Outcomes Consortium Study (MROCS), a large prospective cohort study, showed that almost half of women undergoing implant-based procedures required surgical revision within two years after the initial reconstruction[126, 181]. For one-stage reconstructions, the reoperation rate was 33%, with an average number of reoperations ranging from 1.4 procedures in direct-to-implant (DTI) procedures, to 2.4 in tissue-expander/implant reconstructions. A retrospective cohort study evaluated secondary procedures after immediate reconstruction, revealing that 88% had at least one further surgical procedure (across all reconstructive modalities) following the initial reconstruction[165].

Reports on reoperations rates following ADM-assisted procedures are limited, but for DTI procedures (with ADM) revision rates of 21% at five years, and 20% for tissue/ expander procedures have been reported[185].

High reoperation rates in IBBR are particularly evident in the presence of adjuvant radiotherapy[158, 165] [166-168]. Results from a recent retrospective cohort study of over 3000 women having immediate IBBR, showed that the incidence of unanticipated surgeries increased by 56% for implant patients in the setting of radiation, compared to patients not receiving radiation (HR: 1.56; CI: 1.32-1.84)[186].

Data regarding revision rates in autologous based breast reconstructions also varies, with some studies suggesting autologous procedures have a short-term rate equal to IBBR, whereas others reveal that patients undergoing autologous reconstructions are subject to higher revision rates compared to implant procedures[126, 187]. However, outcomes indicate that rates of additional surgeries for implant-based procedures increase with time, as revisions for capsular contracture remain at risk for a longer time compared to flap-based procedures[165, 187].

In summary, in reconstructive breast surgery, *irrespective of reconstructive modality*, a substantial portion of patients will require multiple procedures for completion, including reoperations for surgical complications as well as refinements for aesthetic reasons, to achieve and maintain satisfactory results over time[181, 185, 186] [126].

3.6 HEALTH-RELATED QUALITY OF LIFE

HRQOL is today considered an important variable, and an integral part of health care outcomes monitored by policy makers, researchers and health care practitioners[188]. Using HRQOL as an endpoint is regularly required in prospective clinical studies[189].

With an aging general population, advancements in treatments and early cancer detection, the number of long-term survivors (more than 5 years) increases[12]. This has further strengthened the need for evaluating new treatments using patient-reported outcome measures (PROM´s). Some authors advocate that HRQOL should, alongside survival, be regarded as a hard end-point when designing and evaluating cancer trial outcomes[190]. The FDA has emphasized the necessity for measuring outcomes from the view of the patient by defining patient reported outcomes (PROs) as a "*measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else*)"[191].

Consecutive reviews of the clinicaltrials.gov registry showed an increase in the use of PROM´s (generic and disease specific questionnaires) from 14% to 27% between 2004 and 2013, and a more recent review of the Australia and New Zealand clinical trial registry also noticed a substantial increase over time in the proportion of PROM´s registered in clinical trials[192-194].

It is generally agreed upon that HRQOL is a dynamic, multidimensional concept, encompassing both physical, emotional and social aspects, and that it is a subjective measure[195]. However, there is less consensus on how to find a widely accepted definition, and how to properly capture an individual´s or a group´s perceived physical or mental health[195]. In order to detect and estimate potential effects of medical and surgical treatments on an individual´s HRQOL in clinical trials, validated and standardized questionnaires should be used[196].

Treatment for breast cancer can expose women to physical changes, with chemotherapy, radiotherapy and surgery, all being associated with an increased risk of poor body image[197]. Many women must also handle the long-term effects on HRQOL after treatments[197]. Because of this, the *quality* of survivorship becomes more important, and having instruments to quantify the quality of survivorship has become a goal in breast cancer treatment[198].

Generic instruments (questionnaires) aim to measure an individual´s general HRQOL, and should have certain psychometric properties including: *reliability* (reproducible results when circumstances remain the same), *sensitivity* (detect differences between groups of patients), and *responsiveness* (detect differences within a patient over time). Generic instruments (such as SF-36) are not designed to evaluate a specific type of intervention, such as the impact of specific cancer therapies or new surgical methods[198-200].

To assess what features influence quality of life (QoL) for cancer patients, and raise awareness of physicians about HRQOL in the treatment of cancer, *The European Organization for Research and Treatment* (EORTC) Quality of Life Group (QLG) developed a framework of questionnaires to measure HRQOL among cancer patients in clinical trials[201]. An essential part of EORTC´s concept, was that a core questionnaire (*QLQC30*) would be supplemented by additional components to give more details relevant to specific patient populations[198]. The *EORTC QLQC30,* developed in 1987, is a generic validated questionnaire, and one of the most used tools globally for evaluating outcomes in clinical cancer trials[201]. To specifically measure HRQOL outcomes during and after breast cancer treatment, EORTC later developed the disease specific questionnaire EORTC *QLQ-BR23* to complement the C30[198].

While there is evidence that women having BCS have better HRQOL than those having a mastectomy, many women still undergo mastectomy, especially a higher proportion of young women (45-50%), compared to older (35%)[202]. Available data suggest that a breast reconstruction after mastectomy can improve HRQOL, by restoring body image and reducing stress associated with mastectomy[203].

The EORTC QLG group further developed a validated instrument to be used in conjunction with *QLQC30* (cancer) and *QLQ-BR23* (breast cancer) for measuring the effect on HRQOL and satisfaction after breast reconstruction (today *QLQ-BRECON23*)[204].

Another commonly used instrument to evaluate HRQOL after breast surgery and breast reconstruction is Breast-Q™. This questionnaire was developed by Pusic and collaborators at Memorial Sloan-Kettering Cancer Center, and was initially aimed at evaluating cosmetic outcomes after breast augmentation, and reduction mammoplasties. The instrument is now an internationally validated tool for measuring aesthetic results after breast reconstruction[205].

Cartoon by Marty Bucella featured in Wall Street Journal.
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The increased use of HRQOL as an outcome measure has underscored the need for more practical instruments when interpreting aggregated HRQOL scores. Because p-values as a measure of statistical significance, does not necessarily indicate that a change in HRQOL resulting from an intervention is meaningful to the patient, the concept of minimal clinically important differences (MCID) was introduced. MCID can be viewed as benchmark for researchers evaluating effectiveness in clinical trials, and help communicate significant outcomes to clinicians when applying the trial results[206]. A common definition of MCID is: '*the smallest difference in score in the outcome of interest that patients perceive as important (either beneficial or harmful), and which would lead the patient or clinician to consider a change in the management'*[207].

4 AIMS OF THIS THESIS

This thesis was based on the same clinical trial, with the overall purpose of evaluating clinical outcomes after immediate IBBR augmented with ADM in a setting of breast cancer treatment.

More specifically, the aims were to:

I. To investigate whether application of ADM in immediate IBBR would result in overall fewer surgical procedures (reoperations), compared to IBBR without ADM, measured over the course of two years (**Paper III)**.
II. To investigate whether the use of ADM in immediate IBBR increased surgical complications in the early postoperative course (six months), compared to IBBR without ADM (**Paper I).**
III. To investigate whether there were any differences in HRQOL and patient reported satisfaction with aesthetic outcomes, between immediate IBBR with ADM and IBBR without ADM (**Paper II and III**).
IV. To assess aesthetic outcomes two years after ADM-assisted immediate IBBR measured by physicians evaluating post-operative photos (**Paper IV**).

5 PATIENTS AND METHODS

"Tell me and I forget. Teach me and I remember. Involve me and I learn."

- Benjamin Franklin

5.1 STUDY SETTING AND PARTICIPANTS

The setting for this trial was breast cancer treatment, with potential participants identified by local investigators and enrolled from Sweden and United Kingdom. Four of the five trial sites were high-volume units, annually handling approximately 400-500 cases of primary breast cancer cases. All patients were pre- and postoperatively discussed at multi-disciplinary meetings.

Participants eligible for inclusion were women with a confirmed invasive or pre-invasive breast cancer, planned for mastectomy, who for wished an immediate reconstruction with an implant. Participants were randomized to either immediate IBBR with ADM in combination with partial muscle coverage in the ADM-group, or to immediate IBBR without ADM, using complete muscular coverage of the implant in the control group. Allocation to treatment was done in units of six, using a computer-based randomization module. The process was stratified between participating centers for equal balance between treatment arms. Each participant was assigned a unique case number, recorded in a screening log kept locally. Physicians recruiting patients did not have access to screening log. *The study was open label with both surgeons and patients being informed about the allocation result before the surgical procedure.*

Exclusion criteria included previous radiotherapy to the breast (anticipated need for adjuvant radiotherapy did not exclude patients), neo-adjuvant treatment with chemotherapy, smoking, body mass index ≤30 kg/ m^2, and a predicted implant size <200 ml or >600 ml.

Written informed consent was obtained from all participants prior to any study-related procedures. The study protocol was approved by the central ethical review board in Stockholm (registration number: 2012/1173-31/1). A separate ethical approval was obtained for the study center in the UK (IRAS project ID: 150240).

5.2 SURGICAL METHODS

5.2.1 Implant-based breast reconstruction (IBBR)

Preoperatively, breast dimensions were marked, with base perimeter and volume of breast used as guide for implant selection. Choice of skin incision was based on the amount of skin redundancy as well as on tumor location. All patients underwent a skin- or nipple-sparing mastectomy and the subsequent reconstruction was performed by either a breast or plastic surgeon, experienced with IBBR and familiar with the technique of ADM. A permanent expander- and fixed-volume implant could be applied in both groups. This intra-operative decision on the type of implant, was based on clinical judgment after evaluating tissue viability, and whether the sub-muscular pocket was large enough to accommodate a fixed-volume implant (in the control group). In both groups a temporary sizer was used when appropriate, to determine size and dimensions of the final implant in an effort to optimize the match between the skin envelope and implant volume.

In the control group (IBBR without ADM), the PMM, serratus anterior muscle and, when needed, rectus fascia was raised after mastectomy, allowing for an implant pocket with complete muscular coverage of expander or fixed-volume implant.

Becker 35 expander implant illustrating the inner saline filled

5.2.2 ADM-assisted IBBR

Following completion of mastectomy, a temporary sizer was commonly used, to determine whether expander or permanent implant should be applied. The inferolateral origin of PMM was elevated off the chest wall along the infra-mammary fold (IMF), leaving the pectoralis minor, serratus anterior, and rectus abdominis muscles untouched. The mesh was then attached to the inferior portion of the PMM, and as such, working as an extension of the PMM, forming a hammock or "internal bra", creating an implant pocket (**Figure 5 and 6**). The method of covering the implant with both ADM and muscle, is sometimes referred to as the dual-plane technique.

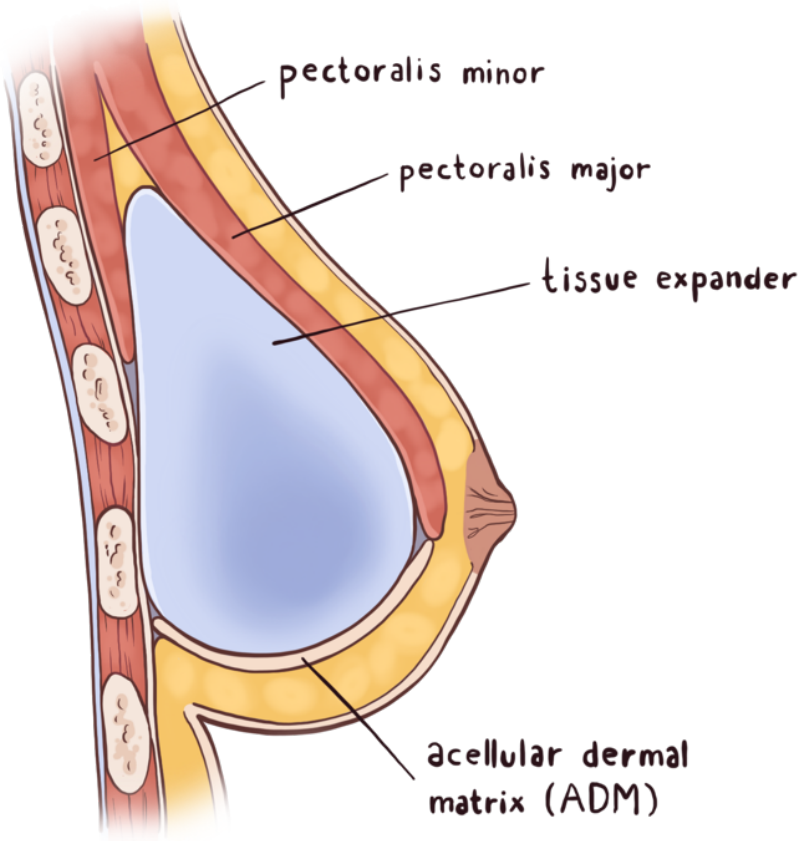


Figure 5. *Illustration of ADM-assisted implant-based breast reconstruction with dual-plane technique. ©Linn Lohmander*

Hygienic rules applying to prosthetic surgery was followed. All patients received implants made by Mentor© (Santa Barbara, California, USA) or Allergan™ (Dublin, Ireland).

All participants received two drains, one in the implant cavity and one subcutaneously. For the ADM group, drains remained in place until output was <30 ml per 24 h for two days in a row, but remained a maximum of 14 days. For the control group, drains were removed when output was <50 ml per 24 h. One dose of preoperatively prophylactic antibiotic (1g Cloxacillin i.v.) was given to all patients, followed by three doses within 24 h postoperatively. Tissue expansion started around three weeks postoperatively according to standard practice routines.

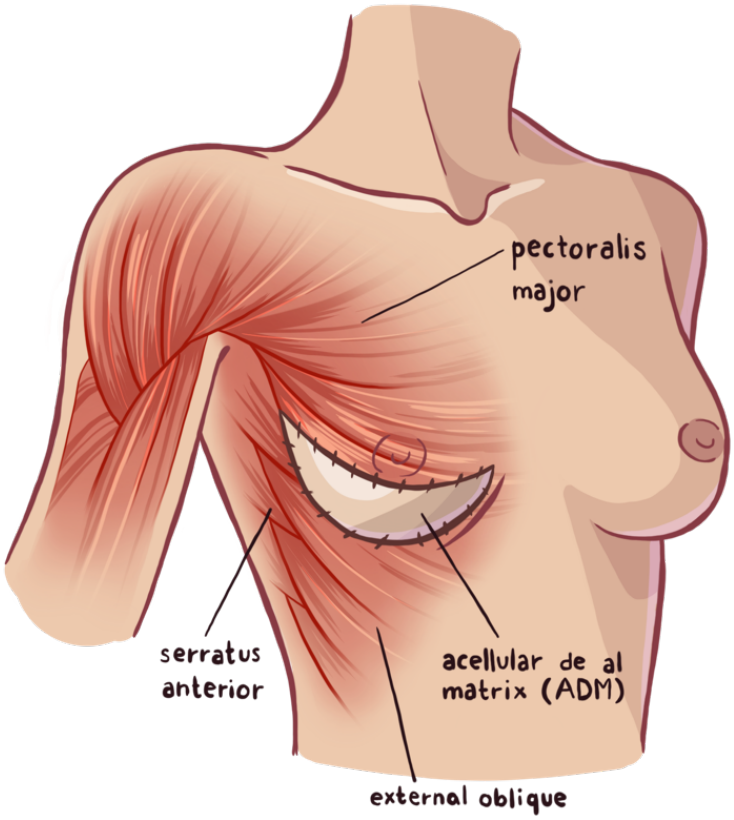


Figure 6. *Illustration of ADM-assisted implant-based breast reconstruction with dual-plane technique. © Linn Lohmander.*

5.3 STUDY DESIGN

In a randomized study design, subjects are randomly allocated into treatment groups. This minimizes or eliminates *selection bias*, i.e., the preference of giving a specific treatment to specific subjects, and *confounding*, where underlying differences in the treatment groups characteristics might influence outcomes.

By letting chance determine which type of breast reconstruction the patient received, any known (and unknown) differences (confounders) between patients who received the intervention (IBBR with ADM), and those who did not receive it (IBBR without ADM), were balanced out in the two groups. This effectively leads to the groups of study patients being (roughly) equal in terms of risk factors, regardless of whether those risk factors have been assessed before the study or not. A randomized study design can also permit the application of *blinding* (*masking*), i.e., concealing the nature of the treatment from patients and physicians, provided this is practically feasible. In this trial it was not possible to conceal the type of treatment to the surgeons.

Randomized studies contrast to *observational studies*, where even if an association with an outcome after intervention remains statistically and clinically relevant (after adjusting for confounders), any remaining associations could reflect residual group differences that were not possible to assess before the study began or adjust for when analyzing results. In non-randomized observational studies, potential confounders and biases can be significant, so outcomes revealing small differences in treatment benefits (or harm), should be interpreted with caution. Still, observational studies may reveal treatment effects provided they are well

designed and large enough[208-210]. RCT´s are considered to be ´hypothesis testing´, whereas observational studies are ´hypothesis generating´.

As there are inherent obstacles in setting up and performing RCT´s in surgical settings, such as lack of resources, recruitment issues, and increasing bureaucratic burdens, evaluations of prospective patient databases have been promoted as a source for evaluating safety and efficacy of new treatments[211]. In the 1960´s, when the concept of RCT´s became more formalized in clinical settings, the study design initially received varied reviews[212] and at times weak support. The double blind RCT by Cobb et al in 1957, evaluating the established practice of ligating the internal mammary arteries in patients with angina pectoris, received initial skepticism and critique, but the surgical method was later abandoned[213]. Moreover, it was not until the 1970´s that the FDA required RCT´s before approving new pharmaceuticals[214]. As evidence-based medicine gained support, RCT´s became the "Gold standard" to evaluate efficacy of treatments in medical science[215].

5.4 OUTCOMES STUDIED

As incidence of revision surgery is a reasonably objective measure of surgical interventions needed to attain acceptable aesthetics in implant-based reconstructions, it functioned as a good primary endpoint in this study. A surgical procedure in the study was defined as any subsequent surgical procedure including, but not limited to the following:

I. *Reoperation caused by complications (including implant removal or evacuation of hematoma or seroma) or due to cosmetic reasons, or implant exchange for other reasons.*
II. *Contralateral procedures such as a reduction mammoplasty or augmentation. Capsulectomy or capsulotomy.*
III. *Any secondary autologous reconstruction.*

The primary endpoint in this trial was to compare the total number of surgical breast procedures between IBBR with ADM and IBBR without ADM at 24 months. The secondary endpoints in the trial were

- To compare the difference in complication rates between the two study groups.
- Measure HRQOL, using questionnaires EORTC QLQ-C30, EORTC-BR23, and EORTC-BRR26.

- Compare aesthetic outcome between the two study groups, based on evaluation from pre- and postoperative photos by external observers (breast/plastic surgeons).

5.4.1 Postoperative surgical complications

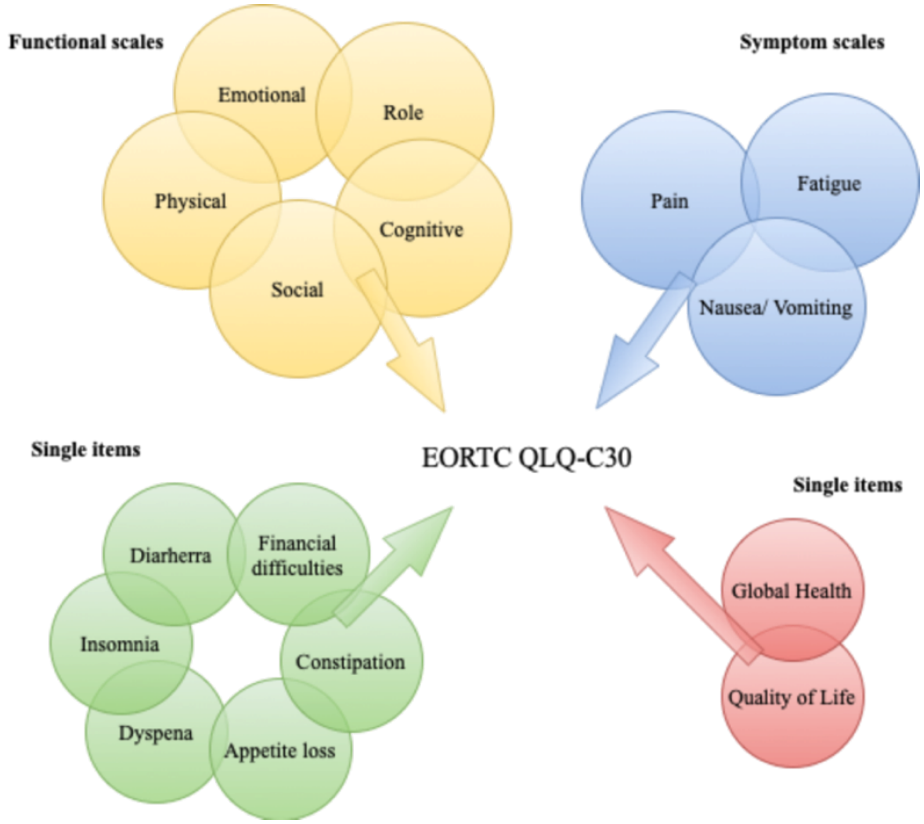
While a number of attempts have been made to define surgical complications, there is an absence of a common definition and lack of consensus on how to classify and rank adverse events (AE) in the surgical literature[145, 216, 217]. This makes evaluation of outcomes after surgical procedures difficult, and without consistent methodology, there is room for subjective interpretations, and results between studies can be difficult to compare. The terminology in the literature to classify and report negative outcomes in pharmaceutical trials uses the terms *minor, moderate, major, or severe* AE. However, as these terms carry a certain subjectiveness in the surgical setting, some authors have suggested they be discarded when grading surgical complications[151].

In this thesis, *reoperations* for complications were defined as procedures requiring general anesthesia, such as evacuation of hematoma, wound debridement with or without re-entering of implant cavity, or implant removal. Seromas were only recorded if aspirated (in an out-patient setting). A serious adverse event (SAE) was defined as any occurrence resulting in a persistent or significant disability or incapacity, a life-threatening event, or death.

5.4.2 Health-related quality of life

In this trial, HRQOL outcomes were measured at baseline (before randomization), and at six and 24 months, using the three validated instruments developed by the EORTC group:

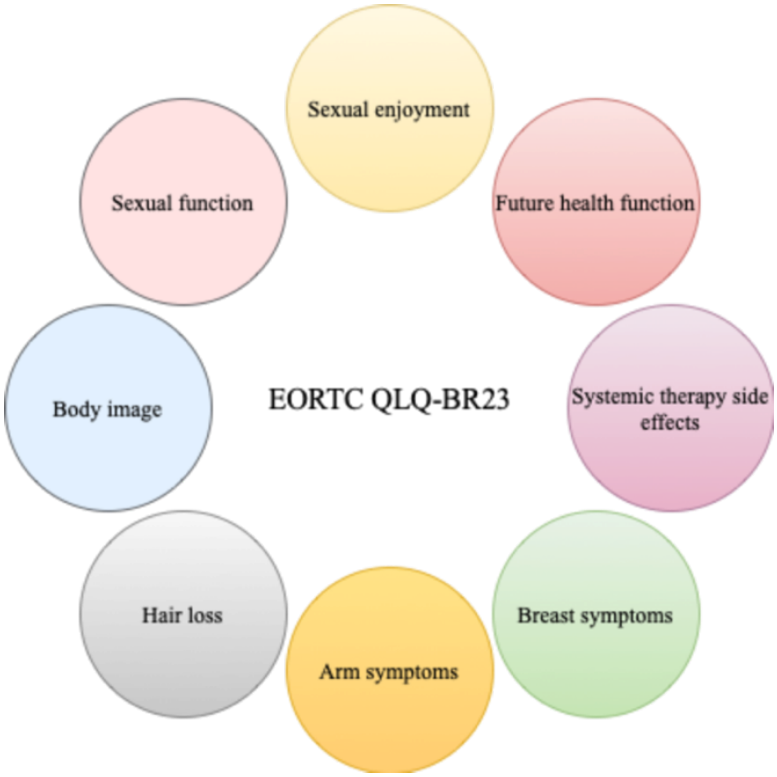
EORTC QLQC30, the generic questionnaire consisting of 30 items (questions) comprising five function scales: physical, emotional, social, role, and cognitive; and three symptom scales: fatigue, nausea/vomiting, and pain. Six single items are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Two items assess global health and overall quality of life. Most items are responded to on a four-point scale ranging from 1 (not at all) to 4 (very much). The two items assessing global health and overall quality of life are responded to in seven categories ranging from 1 (very poor) to 7 (excellent).



Framework for the generic questionnaire QLQ-C30.

EORTC QLQ-BR23, the breast cancer specific module, containing 23 questions, forming five multi-item scales assessing disease symptoms such as arm and breast symptoms, side-effects of treatment, body image and sexual functioning[198]. In addition, sexual enjoyment, hair loss

and future perspectives are measured by single items. The response format is the same as for the generic questionnaire.



Framework for the Breast cancer specific questionnaire QLQ-BR23

*EORTC QLQ-BRR26 (*today *BRECON 23*), a questionnaire measuring satisfaction with the breast reconstruction, consisting of 26 items (scores ranging from 1 ('Not at all') to 4 ('A lot') forming seven scales: disease treatment/surgery related symptoms, problems finding a well-fitting bra, sexuality, cosmetic outcome breast, cosmetic outcome donor site, satisfaction with reconstructed nipple, and problems with losing the nipple. The questionnaire was validated and tested for reliability in a set of breast cancer patients after breast reconstruction. The Swedish version was a part of the development of this questionnaire[199, 204, 218].

For **study II**, questionnaires were administered at baseline (before randomization) and at six months post reconstruction. The breast reconstruction specific questionnaire *QLQ-BRR26* was administered at six months post reconstruction, and not at baseline.

5.4.3 Physician-reported aesthetic outcomes

Aesthetic outcomes were evaluated by external observers. Photographs taken two years after reconstruction were independently evaluated by four surgeons (3 breast surgeons and one plastic surgeon). *Shape, position of infra-mammary fold and nipple-areola complex* of the reconstructed breast, and *symmetry* between the breasts, were assessed. The four panel participants were blinded to the allocation of treatment and encouraged to rate the four parameters on a Likert scale from 1 to 5 (5 representing the best possible outcome), with descriptions corresponding to each separate score. In addition, they were asked to give an *overall rating* including both breasts, also from 1 to 5. All available photos at two years were put into a PowerPoint presentation, and shown in random order without information on adverse events, or whether any additional surgical revisions had been performed.

Correlation and the inter-observer agreement were assessed, with validity calculated by the correlation between total score and overall rating of the aesthetic outcome, as described by Visser et al[219].

5.5 STATISTICAL METHODS

The calculation of the trial sample size was made with respect to the primary trial endpoint. We estimated a reoperation rate of 60% in the control group (IBBR without ADM) and projected that with the application of ADM, reoperation rates would be reduced by half (30%) in the study group (IBBR with ADM), observed over the course of 24 months from the primary procedure. This assumption was based on ADM in immediate IBBR permitting more single-stage procedures.

To detect a statistical difference between the two groups, we calculated that a total number of 98 patients was needed, when a significance level of 5% and power in the study (*the probability of getting a significant result when some effect is really present*) was set to 80%. Sample size calculations were performed using normal approximation with continuity correction. To account for a loss to follow-up, we intended to recruit a total of 120 patients in the trial. Descriptive statistics such as means, standard deviations, counts and percentages were used to depict patient demographics and outcomes.

In **study I**, the difference in complications, a secondary study endpoint, between the two groups were measured as the difference in proportions together with 95% confidence intervals (*the range that is likely to include the true value or the precision of the estimate*). Differences between the groups were tested using Fishers' exact test, and adverse events

expressed as complications per breast. Confidence intervals were calculated according to Newcombe's method[220].

In **study II**, the aim was to evaluate whether ADM-assisted IBBR resulted in higher patient-reported HRQOL, a secondary endpoint in the trial. The differences between treatment arms were assessed and tested with linear regression models, with the subscale items categorized as dependent variables, and allocation group as independent variables. The outcomes from these models were presented as mean differences together with 95% confidence intervals, and the calculation of p-values (*the probability that random fluctuations can produce an observed effect*) using Wald tests[221]. We presented the differences between the two groups as mean values, unadjusted at baseline measurement, and adjusted for baseline at the six months measurement.

Data from the questionnaires were analysed according to the user instructions provided by the EORTC group[222]. The standard EORTC scoring algorithm was applied, converting scores linearly to ranges of 0 to 100. For calculation of clinically relevant differences, the method developed by Osoba et al was applied, with scores between 5 to 9 interpreted as small, 10 to 19 as moderate and ≥ 20 as large differences[223].

In **study III,** the primary trial endpoint, as well as outcomes from HRQOL, a secondary study endpoint was presented. We presented the differences in complications between the two groups as differences in percentages (together with a 95% confidence interval). Differences were tested using Pearson´s Chi-squared test for categorical data, or Fisher's exact test when appropriate. Descriptive statistics such as means, standard deviations, counts and percentages were used to describe patient demographics and outcomes.

Differences between treatment arms for HRQOL variables were estimated and tested using linear regression models, with sub-scales labeled as dependent variables, and allocation group as an independent variable. Results from these models were showed as mean differences (MD) with 99% confidence intervals. P-values were calculated according to Wald tests[221]. To account for multiple testing (*Type I error inflation*) the significance-level was set to 0.01.

Similar to study II, results from the EORTC questionnaires were analyzed according to the user manual[222]. Clinically relevant differences were determined as follows: 5 to 9 as small, 10 to 19 as moderate and ≥ 20 as large differences.

In **study IV**, the aim was to evaluate cosmetic outcomes based on post-operative photos evaluated by four surgeons. This was a secondary trial endpoint. We assessed interobserver agreement between surgeons, using the intraclass correlation coefficient (ICC). The ICC constant (single measurement) was estimated using a two-way random effects model. Differences between groups was estimated using linear regression models. Results from these models are presented as mean group differences together with 95% confidence intervals. Reported p-values refer to Wald tests.

For calculation of *minimal clinically important differences (MCID)*, we used the method developed by Osoba et al, where clinically relevant differences were interpreted in terms as small (5 to 9), moderate (10 to 19) and large (≥ 20) differences when assessed by the EORTC instruments[223].

STATA version 15 and SPSS version 25 were used for all analyses.

6 RESULTS

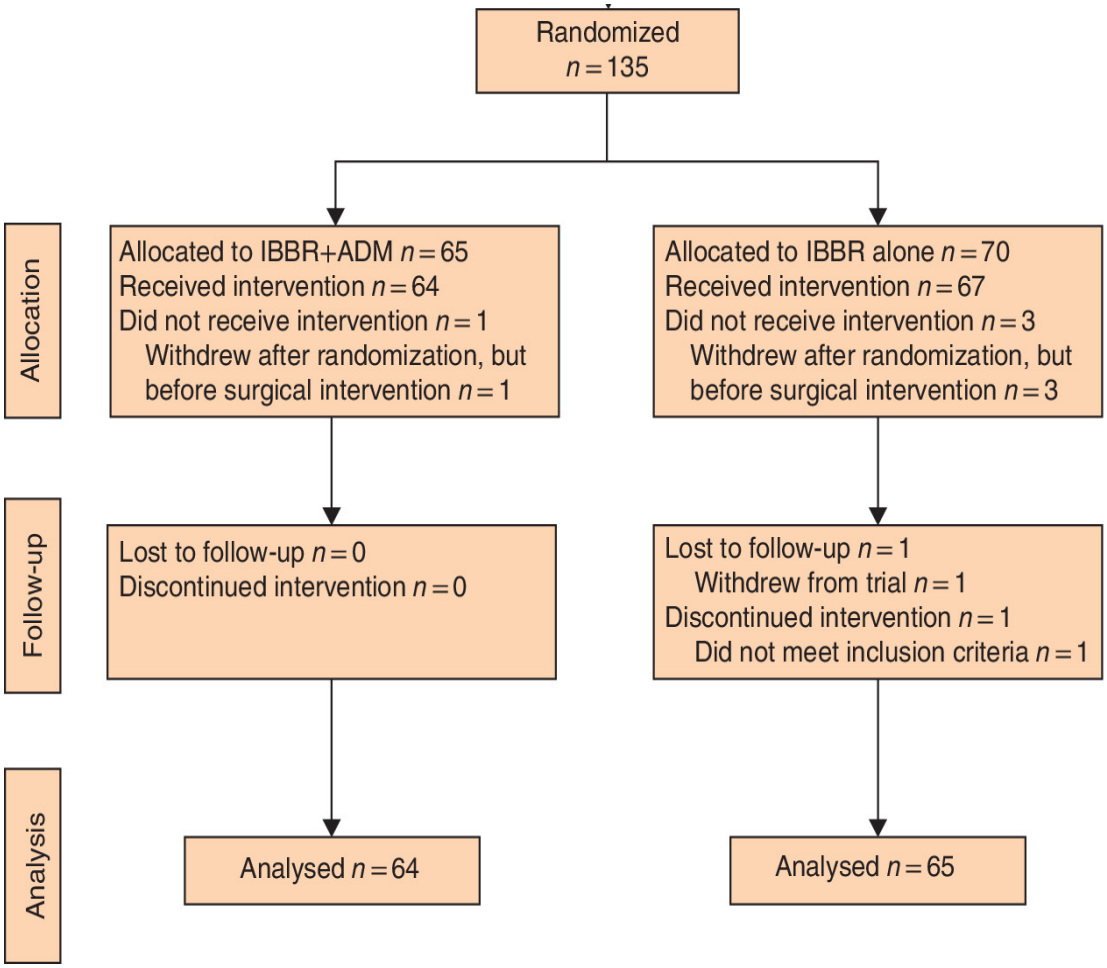
"To see what is in front of one´s nose needs a constant struggle."

-George Orwell (1903-1950)

In Front of Your Nose, 1946

6.1 TRIAL PROFILE AND PATIENT DEMOGRAPHICS

The first patient was enrolled in this trial on April 24, 2014. At the completion of trial inclusion on May10, 2017, 135 participants had been consented and randomized to undergo either immediate IBBR with ADM and partial muscle coverage (n=65), or IBBR with complete muscle coverage of implant (n=70). Four patients (one in the ADM-group and three in the control group) chose to leave the trial shortly after randomization, but before surgery (stating preference for other reconstructive methods). One patient in the control group (IBBR without ADM) was withdrawn from study after surgery after not meeting inclusion criteria. One additional patient in the control group having bilateral reconstruction was excluded shortly after surgery preferring both her implants to be removed. Consequently, 129 participants were available for analysis (**Trial profile**), 64 in the study group, and 65 in the control, at the close of trial. Both groups exhibited similar baseline demographics (**Table 1**), with a mean age of 50.4 (SD 9.5) and a mean-body mass index of 23.4 kg/m^2 (SD 2.7).



Trial profile

Table 1. Baseline characteristics

	IBBR with ADM (n=64)	**IBBR without ADM (n=65)**	**p-value****
Patient demographic data			
Age [years] (SD)	51.8 (9.5)	49.1 (9.4)	
Body-mass index [kg/m^2] (SD)	23.6 (2.6)	23.0 (2.7)	
Invasive ductal cancer [n]	32 (50%)	28 (43%)	
Invasive lobular cancer	13 (20%)	14 (22%)	
DCIS	17 (27%)	23 (35%)	
Paget´s disease of the breast	2 (3%)	0	
Treatment related variables			
Axillary surgery	64 (100%)	63 (97%)	
Sentinel node only	52 (81%)	57 (88%)	
Axillary lymph node clearance*	12 (19%)	6 (9%)	
Nipple sparing mastectomy	26 (40%)	32 (51%)	
Mastectomy weight [g] (SD)	358.4 (161.5)	342.4 (156.9)	
Adjuvant radiotherapy	29 (45%)	35 (54%)	
Adjuvant chemotherapy	33 (52%)	30 (46%)	
Allocation related variables††			
Direct-to-implant†	39 (61%)	11 (17%)	< 0.001
Implant volume [ml] (SD)	313.6 (66.6)	255.9 (46.9)	< 0.001
Expander volume [ml] (SD)	445.2 (94.4)	383.6 (83.2)	< 0.001
Intraoperative filling volume [ml] (SD)	149.8 (64.3)	112.1 (51.8)	< 0.001

*Data expressed as mean (SD) or number (%) unless otherwise stated. IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix. DCIS=ductal carcinoma in situ. *With or without previous sentinel node. † Fixed-volume implant at time of mastectomy.*
*** t-test for continuous variables and Fishers exact test for categorical variables.*
†† Variables dependent on allocation group.

6.2 STUDY I

Results from **study I** showed that immediate IBBR with ADM conveyed a risk of reconstructive failure equal to conventional IBBR without ADM, but was linked to significantly more post-operative wound healing problems. Complications in the ADM-group were mostly related to a compromised skin circulation, requiring a reoperation (p = 0.013), with 26 (41%) patients in the ADM group having at least one adverse event, compared to 18 (28%) in the control group (difference 0.13, 95% CI, -0.03 to 0.28, p = 0.140, (**Table 2**).

Four (6%) patients in each group had a surgical complication resulting in loss of implant. In the group without ADM, all implant losses were led by a deep wound infection needing in-hospital treatment with intravenous antibiotics. In the ADM group, six (9.4%) patients, compared to none in the control group (p = 0.013), experienced wound healing complications correlated to compromised skin circulation (**Table 2**). Four of these six complications necessitated an implant-exchange, either to a smaller fixed volume implant, or to a deflated expander implant.

Outcomes from **study I** contrasted with data from another RCT conducted in the Netherlands that revealed a significantly higher risk for reconstructive failure in the ADM group compared to two-stage IBBR without ADM[134].

Results from **study I** indicated that ADM was associated with increased postoperative complications requiring reoperations, but not linked to higher risk of implant loss when ADM was applied in small to medium breasts volumes. The conclusion was to carefully assess the mastectomy flap viability when one-stage reconstructions with ADM are planned.

	Allocated treatment: (%)		P-value[#]	Difference in proportions (95% confidence interval)[d]
	IBBR with ADM (n=64)	**IBBR without ADM (n=65)**		
Adverse events (AE):				
1. Skin blisters /wound dehiscence/ exposure of ADM or implant	6 (9)	0 (0)	0·013	
2. Redness without infection	1 (2)	0 (0)	0·496	
3. Nipple necrosis	2 (3)	3 (5)	1·000	
4. Infection in-hospital treatment	4 (6)	4 (6)	1·000	
5. Seroma	14 (22)	8 (12)	0·167	
6. Infection out-patient treatment	9 (14)	4 (6)	0·155	
Patients with any[a] AE (1-6):	26 (41)	18 (28)	0·140	0·13 (-0·03 to 0·28)
Reoperations:				
7. Open evacuation of hematoma	2 (3)	1 (2)	0·619	
8. Re-excision after mastectomy	1 (2)	2 (3)	1·000	
9. Re-entry of implant cavity	4 (6)	0 (0)	0·058	
10. Implant removal	4 (6)	4 (6)	1·000	
Patients with any[b] reoperation (7-10):	11 (17)	7 (11)	0·321	0·06 (-0·06 to 0·19)
Any[c] complication (1-10):	29 (45)	19 (29)	0·070	0·16 (-0·01 to 0·32)

[#]Fisher's exact test.
[a] Number of patients with at least one AE.
[b] Number of patients with at least one reoperation.
[c] Number of patients with at least one AE or reoperation.
[d] B versus A. Confidence intervals according to Newcombe's Method 10.

Table 2. *Postoperative complication at 6 months*

6.3 STUDY II

The aim was to evaluate HRQOL and aesthetic outcomes from the view of the patient, measured six months after IBBR with ADM. At baseline before surgery, and at six months post-operatively, we found no statistically significant between-group differences measured with the questionnaires QLQ-C30 and QLQ-BR23. Equally, we were not able to prove that patients valued ADM-assisted IBBR better in terms of aesthetics (measured with the breast reconstruction-specific QLQ-BRR26), compared to the group having a reconstruction without ADM.

However, we did notice some clinically relevant group differences[224]. Two subscale-items, satisfaction with ´cosmetic outcome´ (p = 0.041), and ´problems finding a well-fitting bra´ (p = 0.038), produced higher satisfaction scores for the ADM-assisted IBBR group compared to IBBR without ADM (**Table 3**).

Similarly, the HRQOL data from the Dutch study did not reveal any statistically significant or clinically relevant group differences between one-stage IBBR with ADM, compared to two-stage IBBR without ADM[225]. It is worth noting that the study from the Netherlands used

	Control (n = 65)	ADM (n = 64)	Mean difference	95% CI of difference	P-value
EORTC QLQ-BRR26					
Domain					
Disease treatment/ surgery related symptoms	11 (8)	8 (9)	-2.65	-8.01, 2.71	0.335
Problems finding a well-fitting bra	40 (9)	27 (9)	-13.21^{M}	-25.54, -0.89	0.038
Sexuality	40 (8)	37 (10)	-2.35	-12.41, 7.70	0.647
Cosmetic outcome breast	56 (8)	64 (9)	8.66^{S}	0.46, 16.86	0.041
Cosmetic outcome donor site	N/O	N/O	N/O	N/O	
Satisfaction with reconstructed nipple	50 (37)	65 (46)	15.21^{M}	0.59, 29.84	0.048
Problems with losing the nipple	35 (40)	41 (32)	5.96^{S}	-11.07, 22.98	0.496

Table 3. Patient reported mean values (range 0-100) at 6 months for the breast reconstruction specific EORTC-BRR26 questionnaire. Number of missing responses for each sub-scale in parenthesis.
A higher score indicates higher satisfaction for ´Satisfaction with reconstructed nipple and ´Cosmetic outcome of breast`, for all other domains a lower score indicates higher satisfaction.
^{S} = Small clinical difference, ^{M} = Moderate clinical difference (Osoba 1998)

Breast-Q™ questionnaires along with the questionnaire EQ-5D to evaluate HRQOL, making comparisons to this study difficult.

6.4 STUDY III

In this study the primary trial endpoint was assessed. I.e., we wanted to evaluate whether ADM-assisted IBBR would reduce the number of re-operations compared to traditional IBBR without ADM, measured at 2 years. As a secondary outcome in this study, we also measured whether the use of ADM would improve HRQOL and aesthetic results evaluated as patient-reported outcomes.

At two years after mastectomy with a concomitant implant-based breast reconstruction, nine patients (14%) in the experimental arm (ADM group) had the implant removed, four of these in conjunction with the reconstruction. Another four implants were removed following implant exchange with revision (capsulotomy). Two of these following a deep wound infection, and two due removed because of persistent seroma with chronic skin redness (without infection signs). All four of these patients had previous adjuvant radiotherapy. One further patient had the implant removed due to local cancer recurrence.

In the group without ADM, 7 (11%) patients had the implant removed. Four of these seven reconstructive failures were due to a complicated postoperative surgical course following the initial reconstruction. The remaining three had the implant removed due to patient preferences, with all three later converted to a secondary reconstruction (one with two-stage expander-implant and two with autologous tissue.

In the group reconstructed with ADM, 31 patients (48%) went through at least one reoperation on the ipsilateral side, versus 35 (54%) in the control group ($p = 0.539$) (**Table 4**). Corresponding number of reoperations for the contralateral side were 34 (53%) versus 31 (48%) respectively ($p = 0.537$).

Table 4. Number of reoperations and procedures per patient and study arm performed under general anesthesia on the ipsilateral and contralateral breast at 24 months

Ipsilateral side	Number of reoperations	IBBR with ADM (n=64)	IBBR without ADM (n=65)	Difference in percentages and 95% CI	p-value
	1	21 (33%)	28 43%)		
	2	9 (14%)	6 (9%)		
	3	1 (2%)	1 (2%)		
Subtotal procedures per study arm (primary trial endpoint)		42	43		
Number of patients with no procedure on ipsilateral side		33 (52%)	30 (46%)		
Number of patients with any procedure on ipsilateral side		31 (48%)	35 (54%)	-5.4 (-22.6 to 11.8)	0.539
Contralateral side					
	1	31 (48%)	25 (38%)		
	2	2 (3%)	5 (8%)		
	3	1 (2%)	1 (2%)		
Subtotal procedures per study arm (primary trial endpoint)		38	38		
Number of patients with no procedure on contralateral side		30 (47%	34 (52)		
Number of patients with any procedure on contralateral side		34 (53%)	31 (48%)	5.4 (-11.7 to 22.7)	0.537
Total ipsi- and contralateral procedures per study arm (primary trial endpoint)		80	81		

IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix

As for the number of anesthetic events, we also noticed a near equal distribution between the two groups, with 44 patients (69%) having at least one anesthetic event in the ADM group, versus 43 (66%) in the control group (p = 0.753) (**Table 5**). Two patients in the ADM group, and three patients in the control group had a risk-reducing mastectomy on the contralateral side. These five prophylactic surgeries were included in our final analysis.

Table 5. Number of anaesthetic events per patient and study arm performed under general anesthesia at 24 months

Anaesthetic events per patient	IBBR with ADM (n=64)	IBBR without ADM (n=65)		
1	30	29		
2	11	11		
3	3	3		
Total anaesthetic events per study arm	61	60		
Number of patients with no event	20 (31%)	22 (34%)		
Number of patients with any event	44 (69%)	43 (66%)	2.6 (-13.6 to 18.8)	0.753

HRQOL, the secondary outcome measure in this study, was evaluated with three validated questionnaires: QLQ-C30, QLQ-BR23, and QLQ-BRR26. At two years after reconstruction, we were not able to detect any statistically significant differences between the groups (**Figure 4**)

As for the breast reconstruction specific questionnaire (QLQ-BRR26), the subscale item (question) *´cosmetic outcome´* yielded a mean score of 68 (SD=23) for the ADM group and 60 (SD=24) for the control group, with a mean difference of 8 (99% CI: -5 to 20, p = 0.111, (**Figure 7**), corresponding to a small clinical difference[223]. The question *´Problems finding a well-fitting bra´*, also resulted in scores slightly favoring the ADM-group, with a mean score of 19 (SD=25) and 31 (SD=32) respectively, and a mean difference of -13 (99% CI: -28 to -3, p = 0.038, **Figure 7**). This corresponded to a moderate clinical difference[223]. No other domains resulted in a statistically or clinically significant difference between the groups.

Figure 7. Health-Related Quality of Life (HRQOL). Mean differences between implant-based breast reconstruction with and without use of an acellular dermal matrix measured at 24 months.

6.5 STUDY IV

This study aimed to assess cosmetic outcomes from the view of the physician, based on post-operative photos at 2 years after reconstruction. The group differences for all five cosmetic scales appeared to be in favour of the ADM-group, but this difference did not reach a statistical significance (**Table 6**).

For the five cosmetic parameters evaluated by the panel participants, the mean group differences ranged from 0.03 (95% CI: -0.26 to 0.31, p = 0.86) to 0.39 (95% CI: 0.06 to 0.71, p = 0.02).

Table 6. Differences between treatment arms in surgeon's mean assessment of cosmetic outcome. Results based on the patients' mean scores from 4 different surgeons. Unadjusted MD´s estimated using linear regression models

	Mean (SD)			
Cosmetic parameter	IBBR without ADM	IBBR with ADM	MD[a] (95%CI[b])	P
Shape (n = 85)	3.48 (0.76)	3.87 (0.75)	0.39 (0.06 to 0.71)	0.02
IMF** (n = 85)	4.18 (0.64)	4.20 (0.66)	0.03 (-0.26 to 0.31)	0.86
NAC* (n = 68)	3.82 (0.70)	3.95 (0.81)	0.13 (-0.24 to 0.49)	0.49
Symmetry (n = 84)	3.39 (0.74)	3.49 (0.83)	0.10 (-0.24 to 0.44)	0.57
Total (n = 84)	3.47 (0.73)	3.70 (0.73)	0.22 (-0.09 to 0.54)	0.16

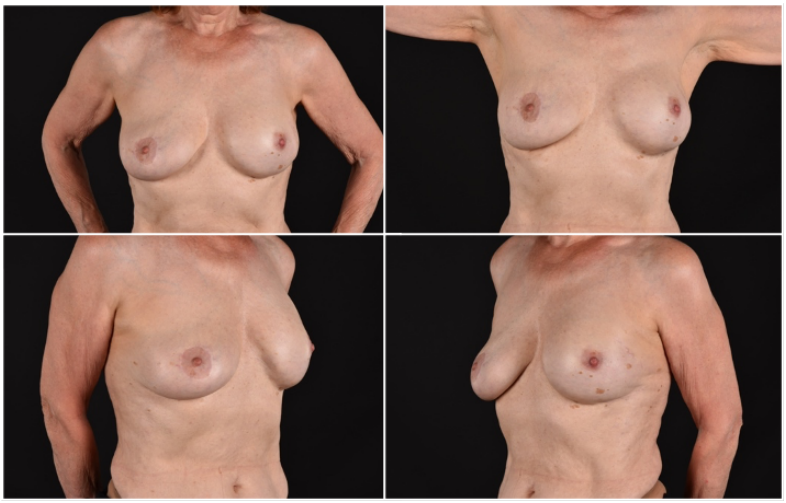
[a] *Mean difference*
[b] *Confidence interval*
[*] *Nipple Areola Complex*
[**] *Infra Mammary Fold*

Agreement between panel participants (the interobserver correlation) was judged as "poor to moderate", measured with the intraclass correlation coefficient (ICC), with values ranging from 0.32 (95% CI: 0.14 to 0.50) to 0.39 (95% CI: 0.14 to 0.60) for the five cosmetic areas (**Table 7**) [226].

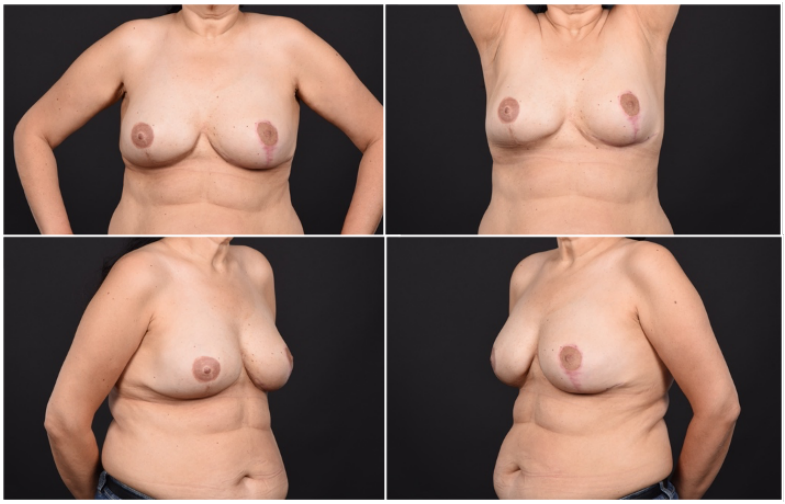
Table 7. Interobserver correlation between four independent and blinded surgeons based on 5 cosmetic grading scales.

Cosmetic parameter	ICC[a]	Interpretation[b]
Shape (n = 85)	0.33 (0.14 to 0.51)	Poor to moderate
IMF* (n = 85)	0.32 (0.14 to 0.50)	Poor to moderate
NAC** (n = 68)	0.35 (0.13 to 0.54)	Poor to moderate
Symmetry (n= 84)	0.38 (0.12 to 0.59)	Poor to moderate
Total (n = 84)	0.39 (0.14 to 0.60)	Poor to moderate

[a]*Intraclass correlation coefficient of absolute agreement (single measurement) estimated using a two-way random effects model.*
[b]*Benchmark scale by Koo and Li (2015)*
**Infra Mammary Fold*
***Nipple Areola Complex*



Picture 1. IBBR *without* ADM (left side) and a contralateral reduction mammoplasty at 24 months post reconstruction



Picture 2. IBBR *with* ADM (right side) and a contralateral reduction mammoplasty at 24 months post reconstruction.

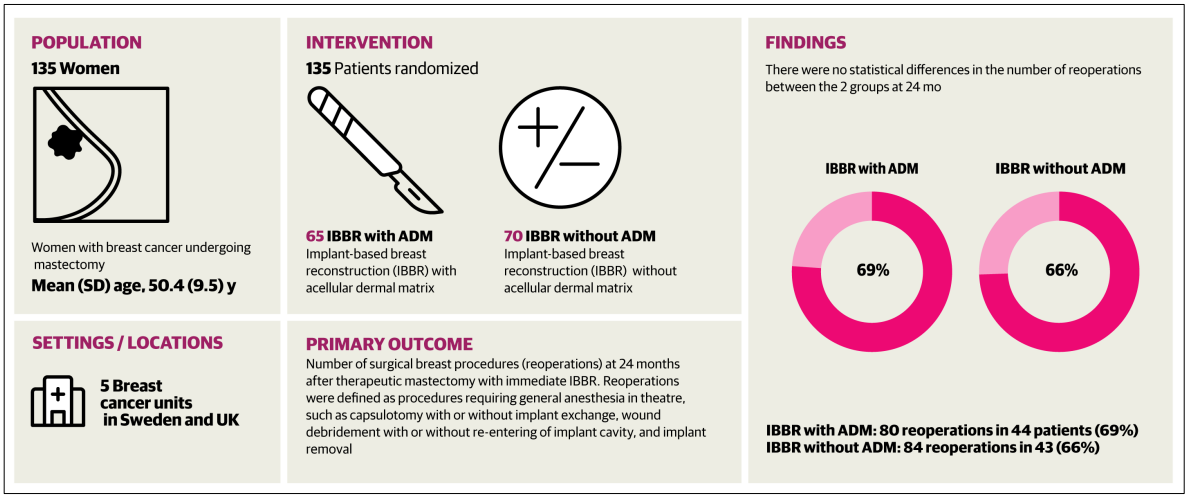
7 DISCUSSION

"Surgery is based on science, knowledge, experience,
strong opinions, and magical thinking – in unknown proportions."

-Unknown

This PhD thesis aimed at investigating whether the use of a biological graft in immediate implant-based breast reconstruction (IBBR) would benefit women having IBBR in a setting of breast cancer care. Two variations of IBBR performed at the time of mastectomy were compared in a randomized trial: *IBBR with acellular dermal matrix (ADM) and IBBR without ADM.* The hypothesis to be tested was whether the use ADM in IBBR, would result in fewer surgical procedures over the two years after reconstruction, compared to the traditional method of IBBR without ADM. Secondly, we investigated the harms of ADM, reported as post-operative surgical complications occurring within six months after reconstruction. Finally, we evaluated if health-related quality of life (HRQOL) and aesthetic outcomes, measured as patient-reported outcome measures (PROMs), would improve when IBBR was augmented with ADM, compared to the traditional method of IBBR. In addition, aesthetic outcomes measured as physician-reported scores were presented.

In **study I**, immediate IBBR with ADM was associated with risk of reconstructive failure comparable to IBBR without ADM, but ADM was linked to more to surgical complications entailing a reoperation. In **study II**, we found that IBBR with ADM was not better in terms of higher levels of HRQOL or patient-reported aesthetic outcomes, compared to IBBR without ADM, measured at six months after reconstruction. In **study III**, we found that immediate IBBR with ADM did not result in less reoperations, or improved patient-reported aesthetic outcomes over a 24 months follow-up, compared to IBBR without ADM. **Study IV** presented aesthetic outcomes assessed by external observers from postoperative photos, showing that application of ADM in IBBR did not yield improved aesthetic outcomes compared to IBBR without ADM, measured at two years after reconstruction.



Visual abstract of **study III**

7.1 COMPLICATIONS AND FAILURES

When biological meshes were introduced on the market for use in IBBR around 2005, enthusiasm for the products were high, and the inherent limitations of using implants to reconstruct the breast were hoped to be lessened[227]. With the initial reports of improved aesthetic outcomes, increased ability of performing more single-stage surgeries, with fewer reoperations, ADM would also ease the surgical load for women undergoing implant-based breast reconstructions. However, despite its subsequent widespread use, clear and low-risk-of-bias evidence substantiating ADMs stated advantages remains scarce[146, 225].

When this study was initiated in 2014, no data from randomized trials had been reported. Since then, the number of papers describing outcomes after ADM-assisted breast reconstructions has increased substantially. However, only one RCT comparing IBBR with and without ADM, has to date been conducted. This RCT revealed that one-stage ADM-assisted IBBR was associated with markedly more adverse outcomes compared to conventional two-staged IBBR, and no RCT had evaluated ADM-assisted IBBR in the setting of breast cancer treatment[134].

While the hypothesis in this thesis was that ADM would yield more single-stage procedures, current data at the time regarding the safety profile of ADM´s, encouraged a more practical study design. The published RCT from the Netherlands had largely examined the viability of one-stage procedures, by requiring implants with fixed-volumes in the ADM arm[134]. However, thin and poorly vascularised mastectomy skin flaps have been described as risk factors for surgical complications in IBBR, particularly in the presence of biological

grafts[228]. As the implant volume cannot be adapted in single-stage procedures with fixed volume implants (risking strain on skin and wound), DTI procedures are inherently less "forgiving". Having the option of applying expander implants in the whole cohort of patients, offered an "escape-route" in this present trial, while at the same time ensuring safety, should flap quality be judged as uncertain.

Due to reports of ADM-assisted IBBR possibly increasing the risk for harm (specifically adverse events occurring in the early post-operative course), we evaluated whether early post-operative surgical complications (occurring within 6 months after reconstruction) were more common after IBBR with ADM compared to IBBR without. In **study I**, the six patients having a complicated postoperative course with compromised skin circulation and necrosis, all had an ADM-assisted reconstruction. These complications were primarily treated conservatively, but frequently progressed, and ultimately required a salvage procedure such as exchange to a smaller implant. Whether it indicated an adverse reaction to the mesh, or signifies a problem of using a subcutaneous implant position, can neither be confirmed nor denied.

The contrasting outcomes between **study I** and the RCT from the Netherlands regarding implant failure, might partially be explained by different study designs. While our study permitted the use tissue expanders in both treatment arms, the trial from the Netherlands tested the potential of using ADM only with permanent fixed-volume implants, and comparing it with a control group having two-stage IBBR[134]. Though outcomes in **study I** did not reveal ADM as an independent risk factor for implant failure, it remains uncertain whether a biological mesh in one-stage procedures is an additional complicating element, as no randomized trials have compared direct-to-implant procedures with and without ADM.

Results from a recent retrospective cohort study evaluated immediate ADM-assisted direct-to-implant procedures (Strattice™). Outcomes from this study showed that one of five patients experienced delayed wound healing, and 13% had a postoperative complication requiring implant removal[228].

In the USA, where a substantial part of IBBR´s are performed with the aid of ADMs, many of these reconstructions are two-stage procedures[229]. Moreover, several studies have suggested an increased risk for adverse events in ADM-assisted implant reconstructions, with several authors suggesting a careful patient selection, especially when one-stage reconstructions with ADM are considered[134].

"If I knew where I'd lost the sponge, it wouldn't be lost, now, would it?"

Originally published in the The New Yorker 1995. Reprinted with permission by license from CartoonStock.

7.2 ELECTIVE PROCEDURES IN BREAST RECONSTRUCTIONS

When examining reoperation rates in *elective* reconstructive breast surgery, it is important to bear in mind how fundamentally personal the nature of these decisions can be to the patient. In contrast to interventions for postoperative complications, such as evacuation of a hematoma, or exploration of a free flap with venous congestion, a capsulotomy with implant exchange, or fat grafting for volume deficit, could be considered medically unnecessary procedures.

Patients presenting similar complaints regarding shape or symmetry after a breast reconstruction, can have vastly different views of the importance of the issue and the thresholds for pursuing further modifications. In that sense, how we manage a patient´s request for further surgery can affect revision rates, and depending on the comfort level of the patient and surgical preconditions, physicians may choose to combine several surgeries under one anesthetic event, or perform them on separate occasions.

A more thorough understanding of patient-reported data on the incentives for choosing (or forgoing) reoperations might add to/improve the shared decision-making process[230]. Informing patients regarding the average number of expected interventions to achieve satisfactory results following breast reconstructions, is therefore critical in setting realistic expectations, and can help patients make informed decisions when contemplating a breast reconstruction.

Several retrospective studies have evaluated the decision-process in women contemplating a breast reconstruction. In those studies, the knowledge about the pros and cons of a breast reconstruction have been found to be limited[231, 232]. A prospective cross-sectional survey found that much of the deficit in the decision course, was due to women undergoing a breast reconstruction in spite of having predilections more in line with undergoing a mastectomy only[114].

In this thesis, outcomes from **study III** revealed that two-thirds of the patients in both groups had an anesthetic event following the index operation, including events for postoperative complications. These results are similar with outcomes from the Mastectomy Reconstruction Outcomes Consortium Study (MROCS), revealing that 67% of patients across all reconstructive modalities experienced a reoperation, including surgical complications, and also similar to outcomes from other studies[165, 181, 185, 186]. The Brighter study, currently being conducted in the UK, aims to explore long term clinical and patient-reported outcomes following breast reconstruction with both autologous and implant-based procedures[233].

In theory, one-stage reconstructions present an opportunity of restoring the breast in one procedure. In this trial, with two-thirds of the patients in the ADM group having a planned single-stage reconstruction, this would intuitively have converted to fewer surgeries. However, additional contralateral surgeries for symmetry present a second chance to simultaneously revise the ipsilateral reconstructed breast during the same anesthetic event. This might have contributed to leveling out the reoperation rates between the groups.

In contrast to results from **study III**, were a substantial proportion of patients in both groups had contralateral procedures for symmetry, the BRIOS study revealed a discrepancy in the number of contralateral balancing procedures. Thirteen (21%) of 62 patients in the two-stage group had contralateral surgery for symmetry, whereas no contralateral balancing procedures were reported in the ADM group. This finding might add information in explaining that patients

seem more prone to undergo contralateral balancing procedures when second-stage surgery is scheduled.

Because additional and unplanned surgeries can be associated with higher co-morbidity, loss of income, sick-leave, and repeated hospital visits, potentially impairing HRQOL, reoperations have been proposed as an important quality indicator in general and orthopaedic surgery[186, 187, 234-236].

7.3 AESTHETICS AND HEALTH-RELATED QUALITY OF LIFE AFTER BREAST RECONSTRUCTION

Breast reconstruction after mastectomy has the potential to improve a person´s HRQOL[237, 238]. While **study II** revealed *clinically relevant differences* in favour of the ADM group (at six months post reconstruction), the differences were *small*, and pertained to only two of the 29 domains. As the majority of cosmetic items showed no significant difference between treatments at 6 months, we concluded that these moderate group differences should be interpreted with caution. These differences could also be influenced by the fact that a higher proportion reconstructed with ADM, had one-stage procedures. Similar results were noted in **study III**, were a minor advantage for a couple of domains in the ADM group was seen, while the remainder of the domains showed no differences between the treatment arms two years after a unilateral breast reconstruction.

Outcomes from **studies II** and **III** are comparable to results from The BRIOS and MROC studies[181, 225]. While both studies used different questionnaires (SF-36 and Breast-Q™) to evaluate HRQOLF and patient-reported aesthetic outcomes, none of the studies could identify any improvements in patient-reported outcomes when augmenting IBBR with a biological mesh[137, 225].

Scores for the reconstruction-specific module BRR26 in **study II** and **III**, were similar to results from a study assessing psychosocial outcomes for women with increased hereditary risk for breast cancer having risk-reducing mastectomy and IBBR without ADM[239]. This study used EORTC-BRR26 to evaluate patient-perceived aesthetics[239]. However, there are no other published papers having evaluated outcomes after breast reconstructions using this tool, making it difficult to put the results from **study II** and **III** into a broader context. The questionnaire EORTC QLQ-BRR26 was tested for reliability in 2014 and 2017[199]. When presenting MCID scores in **study II** and **III**, the method by Osoba et al was used[223].

The notion of minimal clinically important differences (MICD) interpreting PROM scores to make them more meaningful is appealing[206]. However, MCID is not an absolute measure, and since its introduction, numerous definitions of the terminology have been introduced, each with different calculation methods. Estimations of MCID may also vary depending on the clinical context, the study population, and if the patient´s condition is improving or deteriorating, or if measuring at group- or individual level. As an example, MCID might be different for a woman of 35 years with breast cancer, compared to a woman of 75 years, and although a change from ´poor´ to ´average´ in a patient´s condition might seem like an improvement to the health provider, ´average´ might not be an acceptable condition to the patient.

Because the term MCID emphasizes the *clinical* aspect (rather than the patients' *experience*), some authors have argued the "C" to be removed from MCID to focus on the minimal important difference (MID)[207].

7.4 AESTHETIC OUTCOMES AFTER BREAST RECONSTRUCTION – PHYSICIANS VIEW

Who decides if a breast reconstruction is successful or not? Aesthetic outcomes after breast reconstructions have traditionally been evaluated by the profession, and several methods have been used to try and quantify aesthetic results[134, 219, 240]. While evaluation of aesthetic outcomes ultimately should derive from the patient, issues on whether an elective reoperation is reasonable (and realistic) to pursue, is commonly discussed at our institutions, and centered on pre-and postoperative photos. Without references, patients might be equally happy with the surgery, regardless of the reconstructive method. Hence, based on their collective references, physicians assessing photos might value improved aesthetic results differently from patients.

Several retrospective cohort studies have reported improved aesthetic results when IBBR is augmented with ADM, relying on evaluations from external observers to assess outcomes, including one study using three-dimensional imaging as basis for evaluation[229, 241-244].

In **study IV**, aesthetic outcomes evaluated by external observers from postoperative photos, did not differ between the two groups at two years post reconstruction. These results were also in agreement with outcomes from the RCT by Dikmans et al (BRIOS), where one-stage ADM-assisted IBBR was not superior in terms of aesthetic results measured by external observers (including lay people) evaluating blinded photos[225].

Results from **study III** showed that more than half of the patients in both groups had a reoperation (**Table 4**). This could partly explain why aesthetic results did not differ between

the groups, as revisions for aesthetic reasons possibly evens out any underlying group differences. For the same reasons, it is possible that ADM´s potential aesthetic benefits would become more evident in a setting of bilateral IBBR. However, **study IV** revealed a poor to moderate consensus between the observers, which impeded the chances to draw conclusions from the comparison between the groups from the surgeon´s perspective. Why surgeons given identical information come to different judgements is unclear. One reason why people come to different conclusions despite having access to the same information, could be explained by the variability of error, or what can be defined as ´noise´[245]. I.e., that common variability across individuals influence decision-making and how humans generally evaluate outcomes. An additional and contributing reason is bias[245].

Kamuli Mission Hospital, Uganda. Photo by Philip Unwin 2016

In the context above, it is worth mentioning that no ´gold standard´ exists of what constitutes an ´ideal´ breast shape, and consensus between physicians whether additional surgery is indicated can vary from poor to good.

8 STRENGHTS AND LIMITATIONS

The randomized controlled study design that this thesis is based upon, were selection bias and confounding are minimized, remains the best possible method to establish safety and efficacy of a therapeutic intervention.

There are examples of surgical procedures discontinued or re-examined after being re-evaluated in RCT´s (having been previously assessed in non-randomized studies), such as lung-volume reduction surgery in patients with emphysema, carotid endarterectomy in certain patient groups, and extracranial to intracranial bypass to reduce the risk of stroke[246-248]. Other surgical interventions such as knee arthroscopic surgery and reconstruction for acute cruciate ligament tears (ACL), continue to be practiced, despite several RCTs showing weak evidence for a benefit in patients with knee osteoarthritis and young active adults with ACL tear, respectively[249, 250].

While this thesis did not provide evidence that biological grafts improve outcomes in breast reconstruction with implants, there are limitations that should to be addressed. Firstly, evaluating procedure-based interventions is difficult, and randomized trials in surgical disciplines are associated with several practical and methodological challenges[251]. In contrast to pharmaceutical trials which can be standardized and endpoints readily defined, surgery commonly consists of several interacting components that cannot be separated, such as the surgeon(s), anaesthesia team, nursing team, as well as the pre- and postoperative care[252]. Components that, within themselves, also tend to vary[253]. As non-randomized studies are easier to undertake than RCT´s in the surgical field, several established interventions have been widely adopted without having been evaluated in low-risk-of-bias studies, such as heart, liver, kidney, and lung transplantations.

Learning curves for a surgical procedure, where surgeons gain skills, also carries a challenge. Previous experience, as well as inherent skills, naturally varies between surgeons. The ideal that surgeons should attain the same performance is not realistic, and a certain variability in performance is to be expected[254]. When this trial started recruiting participants in 2014, the experience among surgeons of performing ADM-assisted IBBR in Sweden was limited. For this reason, one could criticize this trial for carrying an imbalance of expertise, that potentially could have favored the established comparator (IBBR without ADM), when evaluating a new surgical intervention (IBBR with ADM). A more thorough experience with the ADM technique

might have favored outcomes for the experimental group with ADM. In that sense, a consequence of an "early RCT" would be that we have evaluated a surgical technique that is not fully refined. Subsequent study outcomes could then reflect stages of development and learning, and not the effect of the surgical procedure itself.

Another limitation in this trial was the absence of masking. While concealing the intervention to the surgeon was not possible, masking allocation group to the patient could have been feasible, albeit with a number of practical challenges during the follow-up visits in the out-patient clinic. However, treatment allocation was not revealed to the participant until after completion of the baseline HRQOL questionnaires. As expectations can be a factor in the patient's satisfaction after a procedure, a placebo effect could have influenced satisfaction with aesthetic results[255].

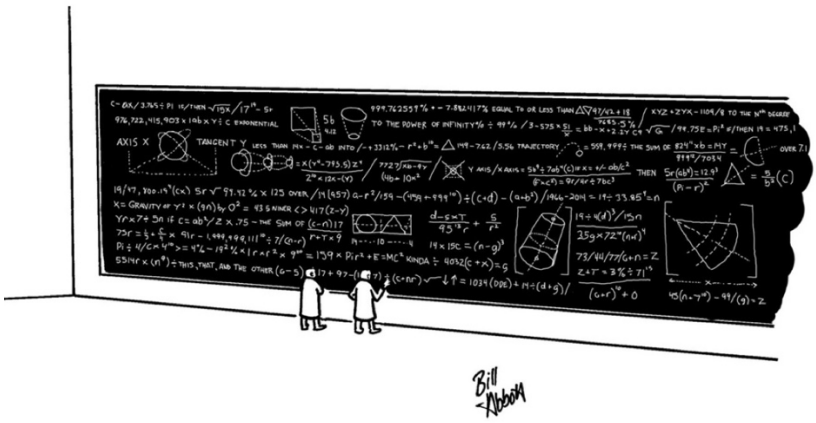
In this trial, the surgical technique of enlarging the subpectoral implant pocket by way of extending the pectoralis major muscle with a mesh (dual plane technique), is rapidly being replaced by the prepectoral method[256]. Although robust evidence of the benefits of the prepectoral implant placement is lacking, one cannot rule out that the role of ADM in prepectoral reconstruction could be different than in the dual plane technique, making our results difficult to generalize, and our results can therefore not necessarily be extrapolated to the prepectoral method. In the light of this, the reconstructive method (applied in the ADM group) in this trial, could be seen as less up-to-date.

A further possible limitation is that we evaluated one specific mesh (*Strattice™, Acelity™, Branchburg, NJ, USA*). Since this trial started, the market for surgical meshes aimed at breast reconstructions have expanded considerably, today including a number of different biological grafts, as well as synthetic meshes. It is known that ADMs and synthetic meshes can vary significantly in their source, level of sterility, biomechanical properties, and preparation methods prior to clinical application[141, 152, 257].

Notably, the US Food and Drug Administration (FDA) recently completed an analysis of patient-level data from real-world use of ADM´s, suggesting that certain meshes have a higher risk-profile than others[258]. While we did not observe any overt signs of reactions to the mesh in the present trial, the causative role of the specific product studied in the increased incidence of complications that was noted in **study I**, can neither be verified nor rejected.

In addition, the tissue expanders applied in this trial are designed to work as permanent implants. However, with contralateral procedures frequently being performed, these expanders are commonly exchanged to fixed volume implants as a second stage surgery. The lack of a clear definitions of what defined *anticipated* and *unanticipated* surgeries can confounds these results.

Lastly, with hopes originally set high for ADM to improve on the traditional technique of performing IBBR, the hypothesis that ADM would have an effect on reoperation rates may have been overly confident. However, when designing this trial, data on ADM and reoperation rates was not available. With radiotherapy being a known predictor for additional surgical revisions, this trial was also underpowered to explore whether radiotherapy influenced outcomes.



"I was just looking for a simple yes or no."

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9 ETHICAL CONSIDERATIONS

"Comparison is the thief of joy"

- C.S Lewis (and others)

Written informed consent was attained from all participants prior to study start in the trial. Each patient was assigned a unique case number that was recorded in a log kept locally, and personal data was deidentified on all postoperative photos. Participants were also told they had the option to withdraw from any study-related activities at any point in time, should they wish to do so.

While this thesis did not aim to elaborate on the question of whether women should be offered an immediate implant-based breast reconstruction in the setting of radiotherapy, it might be relevant to add a brief view on the matter in this section. The following four fundamental principles constitute ethics in medicine: *Beneficence* (act for the benefit of the patient), *nonmaleficence* (do no harm), *autonomy* (right to make informed decisions), and *justice* (appropriate and fair distribution of scarce health-care resources). The first two principles can be traced back to Hippocrates "*to help and do no harm*," whereas the last two evolved later. On that basis, a fundamental question one could ask then, is whether the *potential benefit* of the procedure (implant-based breast reconstruction in a setting of adjuvant radiotherapy), outweighs the *potential harm* that the same procedure could lead to[259]?

An interesting finding from the BRIOS study was that the higher complication rates seen in the ADM group did not appear to affect patient satisfaction[225]. Furthermore, a majority of the patients who experienced reconstructive failure in that study, had a delayed secondary reconstruction. One way to interpret these findings could be that patients having a breast reconstruction are equally content with the final result irrespective of how the reconstruction is accomplished? By the same token, a similar conclusion could be drawn from the National Mastectomy and Breast Reconstruction Audit, where short-term complications following implant-based reconstructions did not seem to change HRQOL in the long term[260].

In addition, an important outcome from a Swedish cohort study revealed that although overall satisfaction was lower among women having irradiated implants, the majority of patients receiving adjuvant radiotherapy after IBBR still recommended the procedure to other women in the same setting[158].

According to Swedish guidelines and the British National Institute for Health and Care Excellence (NICE), the proportion of women receiving immediate breast reconstructions is considered a quality indicator in breast cancer treatment, and the European Society of Breast Cancer Specialists (EUSOMA) has set 40% as a minimum proportion of patients that should receive immediate breast reconstruction[21, 117, 261].

Nevertheless, one could argue whether immediate breast reconstructions should be a quality measure in breast cancer treatment? Since utilization of breast reconstructions also depends on the patient's candidacy for the surgical procedure, as well as personal choices, having immediate IBBR as a quality metric might be an oversimplification. Instead of solely focusing on the rates of (immediate) breast reconstructions, ensuring that the patient who wishes (and is able to undergo) a reconstruction, receives transparent information regarding risks and benefits in shared decision-making, might be a more transparent measure?

From photo by Fredrik Lohmander 2015

10 CONCLUSIONS AND FUTURE PERSPECTIVES

10.1 CONCLUSION

In conclusion, outcomes from this thesis based on a randomized trial, were unable to confirm any of the proposed benefits for women having implant-based breast reconstructions (IBBR) with acellular dermal matrix (ADM) in the setting of breast cancer treatment. The potential value of using ADM in IBBR needs to be further evaluated in prospective clinical studies.

10.1.1 Study specific conclusions

I. The addition of ADM to IBBR, increased the risk for adverse surgical outcomes such as dealyed wound healing in the early postoperative course, compared to IBBR with complete submuscular implant coverage without ADM. The risk of reconstructive failure after ADM-assisted IBBR was equal to IBBR without ADM.

II. Applying ADM in IBBR, did not reduce the overall number of reoperations compared to IBBR without ADM.

III. At two years after IBBR with and without ADM, no significant differences were detected between the two groups, concerning HRQOL, measured with three validated questionnaires (QLQ-C30, QLQ-BR23, and QLQ-BRR26). Nor was ADM superior in terms of patient-reported aesthetic outcomes.

IV. ADM-assisted IBBR, did not yield better aesthetics based on physician-reported results assessed from post-operative photos, compared to IBBR without ADM. There was a poor to moderate agreement between the four panel participants.

10.2 FUTURE PERSPECTIVES

While this thesis, to some extent, has cast light on the use of IBBR in the setting of breast cancer treatment, several questions remain.

From Halsted's radical surgery of removing the breast en bloc with the pectoralis muscle, breast cancer surgery has de-escalated to involve significantly smaller resections. With further advancements in tumor downstaging, along with better tools to more accurately and reliably evaluate treatment effects, breast-conservation surgery (BCS) will likely continue to increase.

One question to ask then, is whether surgery in the future can be omitted in some patients having a pathological complete response (pCR) following neoadjuvant therapy? Similarly, it is not inconceivable to think that ultimately, breast cancer surgery in selected patients will shift from being a therapeutic procedure to a diagnostic tool. Until such a time however, histological assessment of the removed specimen will remain at the center of effective treatment. On this basis, reconstructive breast surgery will likely focus more on surgical techniques to improve aesthetic outcomes after *BCS*. E.g., by volume *displacement* (mammoplasties), or by volume *replacement*, such as the use of local pedicled perforator flaps.

Nevertheless, many women will still require a mastectomy. The re-emergence of the *prepectoral technique* (with or without a mesh) for IBBR is rapidly gaining popularity. With no muscle dissection required (preserving chest wall function), the method of placing the implant in a subcutaneous position is intuitively appealing. While a number of benefits have been proposed, such as reduced animation deformity, decreased operating time, and aesthetic enhancements, the technique is yet to be evaluated in clinical trials, particularly in a setting of breast cancer treatment. Furthermore, the pre-pectoral method necessitates a thorough intraoperative assessment of skin circulation, requiring strict patient selection, particularly if adjuvant radiotherapy is anticipated, and future prospective studies are needed to evaluate the technique.

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