Biological and synthetic mesh in breast reconstructive surgery

PhD thesis | 2020

Mette Eline Brunbjerg

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UNIVERSITY
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Department of Plastic and Breast Surgery
Aarhus University Hospital

Supervisors

Main supervisor

Tine Engberg Damsgaard, MD, PhD, MRBS, Professor

Consultant Plastic Surgeon

Department of Clinical Medicine, Aarhus University

Department of Plastic Surgery and Burns Treatment, Rigshospitalet and University of Copenhagen, Denmark

Co-supervisors

Peer Christiansen, MD, DMSc, Professor

Consultant Breast Surgeon

Department of Plastic and Breast Surgery, Aarhus University Hospital, Aarhus, Denmark

Jens Overgaard, MD, DMSc, Professor

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Assessment Committee

Anders Bonde Jensen, MD, PhD, Professor (Chairman of the Assessment Committee)

Consultant Oncologist

Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Lisbet Rosenkrantz Hölmich, MD, DMSc, Professor

Consultant Plastic Surgeon

Department of Plastic Surgery, Herlev Hospital, Herlev, Denmark

Emma Hansson, MD, PhD, Associate Professor

Consultant Plastic Surgeon

Department of Plastic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

Tine Engberg Damsgaard, MD, PhD, MRBS, Professor (main supervisor, non-voting member)

Consultant Plastic Surgeon

Department of Clinical medicine, Aarhus University

Department of Plastic Surgery and Burns Treatment, Rigshospitalet and University of Copenhagen, Denmark

Preface

The present thesis is based on the following three manuscripts:

I

One- versus two-stage immediate implant-based breast reconstruction. A cohort study on cost and patient reported outcome measures.
Submitted July 2020

II

Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study.
Submitted June 2020

III

Reinforcement of the abdominal wall with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.
Submitted July 2020

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The Faculty of Health Science, Aarhus University; the Danish Cancer Society [R130-A8304-15-S38]; Novo Nordisk foundation [NNF13OC0007477]; Foundation of Jacob and Olga Madsen; the Danish Medical Association's Research Fund; AP Møller Foundation; LifeCell Corporation (Branchburg, NJ, USA); the Korning Foundation; Foundation of the Kjaersgaard Family, Sunds; King Christian X Foundation; Architect Holger Hjortenberg and wife Dagmar Hjortenbergs Foundation; A. V. Lykfeldt and wife's Legacy, Kurt Bønnelycke and wife Mrs. Grethe Bønnelyckes Foundation, and Doctors insurance Association of 1891. Furthermore, LifeCell Corporation (Branchburg, NJ, USA) provided acellular dermal matrix (Strattice™) for use in the studies.

None of the above mentioned had any involvement in the study design, data analysis or interpretation of the results.

Abbreviations

A	Answer
ADM	Acellular Dermal Matrix
BIS	Body Image Scale
BMI	Body Mass Index
BR	Breast reconstruction
BRA Score	Breast Reconstruction Risk Assessment Score
CONSORT	Consolidated Standards of Reporting Trials
CT	Computerized Tomography
DBCG	Danish Breast Cancer Group
DCIS	Ductal carcinoma in situ
DIEP	Deep Inferior Epigastric Perforator
DRG	Diagnosis related group
HrQoL	Health related Quality of Life
iBRA	implant Breast Reconstruction Evaluation
IDEAL	Idea, Development, Exploration, Assessment, and Long-term
LD	Latissimus Dorsi
N	Number
NS	Not significant
PPBCT	Persistent pain after breast cancer treatment
PRO	Patient Reported Outcome
PROMs	Patient Reported Outcome Measures
Q	Question
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized controlled trial
RR	Relative Risk
SNOSE	Sequentially Numbered Opaque Sealed Envelopes
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TAP	Thoracodorsal Artery Perforator
TRAM	Transverse Rectus Abdominis Musculocutaneous
TUG	Transverse Upper Gracilis
VAS	Visual Analogue Scale
Y/N	yes/no

Contents

Background

Breast cancer and surgical treatment

Breast cancer is the most frequent cancer among women worldwide and the second leading course of cancer-related death among women in Northern Europe, United Kingdom and Northern America only preceded by lung cancer (1). Overall, women in the Western world have a life-time breast cancer risk of around 10% to 12% (2) and in Denmark, the incidence of female breast cancer is increasing while the mortality is decreasing (3). This results in more women living for a considerable number of years with the late-effects of breast cancer treatment.

Hereditary and genetic factors account for 5% to 10% of breast cancer cases, but risk factors related to menarche, reproduction, exogenous hormone intake, nutrition etc. are mainly responsible for developing breast cancer (1). Risk prediction models aid in identifying women harboring a high risk of developing breast cancer among whom, individualized surveillance and prevention through adequate intervention can reduce breast cancer incidence (2). Risk reducing therapy may be medical or surgical and an increasing number of women undergoes prophylactic mastectomy (4). Currently, neither chemoprevention nor prevention by radiation therapy is recommended in Denmark.

Surgical treatment of early breast cancer and precursors of breast cancer can be performed as a breast conserving procedure or as a mastectomy, and when indicated also removal of one or more lymph nodes in (5-7). The surgical treatment is in some cases preceded by neoadjuvant therapy and/or followed by adjuvant therapy such as chemotherapy, radiation therapy and antihormonal therapy depending of the tumor characteristics (7). The international trend goes toward a decreasing mastectomy rate and increasing rate of breast conserving procedures (8).

In appropriate cases, oncoplastic principles for tumor resection can be used with the advantage of achieving a better health related quality of life (HrQoL) compared to patients undergoing traditional breast conserving procedures (9). Furthermore, the skin-sparing, or if possible, nipple-sparing, technique for mastectomy is performed when appropriate thereby providing the best prerequisites for a breast reconstruction (BR) (10, 11).

A multidisciplinary collaboration including surgical oncologists, oncologists, radiologists, plastic surgeons, and physiotherapists is needed for optimal treatment and rehabilitation for patients suffering from breast cancer or in high risk of developing breast cancer.

Risk reducing mastectomy

Risk reducing mastectomy (often skin- or nipple sparing) can be performed in the case of high risk for developing breast cancer. Women undergoing bilateral prophylactic mastectomy experience improvements in satisfaction with breasts and psychosocial well-being after successful immediate BR (12). Decreasing anxiety but also a negative impact on body image and sexuality has been reported by others

(13). In the case of contralateral prophylactic mastectomy after unilateral breast cancer without hereditary disposition the proposed advantage is higher satisfaction with breasts (14) but not necessarily gained quality of life (QoL) compared to surveillance (15).

Breast cancer treatment and morbidity

Long-term late-effects after breast cancer treatment is associated with decreased HrQoL and may include chronic pain, sensory disturbances, restricted mobility of the arm/shoulder, and lymphedema (16). Pain after treatment for breast cancer is not a static problem and can both regress or progress with time (17). Furthermore, reduced mobility of the shoulder is a frequent long-term outcome, associated not only to axillary surgery and radiation therapy, but also the extent of the breast surgical procedure (18). Upper limb morbidity is sought limited by early rehabilitation focused on mobilization (19) as exercise and stretching has been shown to be effective for improving shoulder mobility and reduce pain located to the upper limb after breast cancer surgery (20).

Breast reconstruction – an integrated part of breast cancer treatment and rehabilitation

Being diagnosed with breast cancer or facing a high risk for developing breast cancer and as a consequence undergo mastectomy or breast conserving surgery, may leave the women with a feeling of demolishing of her body integrity and loss of femininity (21). Approximately 40% of Danish women treated with mastectomy for breast cancer chose to undergo a breast reconstructive procedure (22). Women opt for a BR in order to feel and look normal, to improve self-image, to avoid limitations associated with wearing a prosthesis and due to other individual reasons (23, 24). Furthermore, the literature suggests that BR after mastectomy result in higher satisfaction with appearance and that patients fare better physically, psychosocially and sexually and experience less pain and limitations than women with mastectomy alone and have a feeling of overcoming cancer (24-26).

A considerable number of women undergoing mastectomy does, however, not opt for BR. It has been suggested, that the reasons for this is fear of possibly masking cancer recurrence and concerns about risks with additional surgery (24). However, the overall survival of women undergoing BR is not different from women undergoing mastectomy alone and likewise, the breast cancer recurrence rate does not differ and BR does not result in delay of detection of recurrence (27, 28). Therefore, BR is an integrated part of breast cancer care and rehabilitation (7).

Patients opting for BR is a heterogenous group. Some have just been diagnosed with cancer, some have lived with the knowledge of increased risk for developing breast cancer for years, and some have already undergone mastectomy and now opt for a delayed BR. When women facing mastectomy needs to decide whether to undergo BR or not, the decision is based upon how they predict their future well-being with or without a breast reconstructive procedure. The literature suggests that patients having mastectomy with immediate reconstruction generally overestimate their future well-being, and patients having

mastectomy without reconstruction generally underestimate their future well-being, and that misprediction is associated with greater regret but not with satisfaction with decisions (29). This emphasizes the need for a thorough and individualized discussion with the patient on what to expect especially regarding numbness, pain, scarring, aesthetic outcome, long-term outcome, etc. to provide the best possibly foundation for shared decision-making about BR.

Breast reconstruction – timing, trends, and techniques

When counselling the patient in their breast reconstructive pathway, several factors should be considered. Patient wishes and expectations, concerns about donor-site morbidity, considerations regarding the postoperative course, physical factors e.g. size and shape of the breasts, the amount and quality of tissue available for autologous BR, comorbidity, and whether adjuvant therapy is warranted. Using the BRA Score risk calculator for assessment of complication risk for different BR modalities may be helpful when informing the patient (30).

Breast reconstruction can be performed as an immediate procedure at the same time as the mastectomy, or as a delayed procedure after the mastectomy and any relevant oncologic treatment. It has been suggested, that patients who undergo immediate reconstruction fare best as anxiety and depression is lower but body image, self-esteem, and satisfaction are higher compared to patients undergoing delayed BR (31), but the literature is not unambiguous. Breast cancer patients have been shown to have different starting points before BR. Patients aiming for immediate BR report higher satisfaction with breasts, better body image, psychosocial well-being, and sexual well-being compared to patients aiming for delayed BR (32, 33). However, in a prospective longitudinal study Metcalfe et al. demonstrated no difference between the immediate and delayed group regarding QoL, body image, and psychological distress one year after BR (33). Overall, there might be an advantage in using the immediate BR approach if feasible, but further investigation, including baseline psychological testing, is needed to elucidate this subject (34).

Breast reconstruction can be performed with the use of an implant, autologous tissue, or a combination as described below. An increasing number of women undergo BR, and an increasing proportion is performed as immediate procedures (35). In particular implant-based BR is increasing, and far more implant-based than autologous reconstructions are performed. Actually, the incidence of autologous procedures has been slightly decreasing (8, 36, 37).

Implant-based breast reconstruction

Implant-based BR can be performed as a two-stage procedure or as a one-stage procedure. The implant can be placed completely under the pectoral muscle, partially submuscularly, or subcutaneously (38). Patients previously irradiated or planned for postmastectomy radiation therapy are not optimal candidates (39, 40) even though there is a recent trend in the US towards increasing use of implant-based BR in the setting of postmastectomy radiotherapy (41). Furthermore, the results of a Danish multicenter randomized

clinical trial regarding delayed-immediate BR in early breast cancer patients treated with mastectomy and adjuvant loco-regional radiation therapy is awaited with interest (42). In this study patients will be randomized to either delayed-immediate BR with insertion of a silicone implant and adjuvant radiation therapy or to delayed implant-based BR.

The two-stage procedure entails a course, where a temporary expander is inserted under total muscle coverage, consisting of the pectoralis major muscle, the serratus anterior muscle or its fascia, and the anterior rectus sheath, or partially muscle cover by the pectoralis major muscle with the use of acellular dermal matrix (ADM) to cover the inferior part of the implant. The expander is inflated with saline several times over the next months and three to six months after the final implant volume has been achieved, the expander is exchanged to a fixed size silicone implant. The gradual expansion of muscle and skin allows for a possibly lager implant size than the one-stage approach.

The one-stage procedure consists of a fixed-size silicone implant most often inserted under partly muscle coverage by the pectoralis major muscle and a piece of ADM or synthetic mesh to cover and support the inferior part of the implant. As the two-stage approach can be used in both the immediate and delayed setting, the one-stage approach is mostly performed as an immediate BR following skin- or nipple sparing mastectomy.

The literature suggest that the one-stage approach entails a higher risk of complications as infection, necrosis and implant loss compared to the two-stage approach (43-45). But the overall advantage with the one-stage approach is the reduced need for outpatient visits for expander fillings and the possibility to avoid a second operation in general anesthesia for exchange of the expander to silicone implant. The risk of capsular contracture (Spear-Baker classification for implant-based breast reconstructions grade III-IV (46)) has been reported higher for two-stage BR (8,2% (47),10% (48), 19,4% (49) and even higher in the case of irradiated tissue), than for one-stage BR (1,5% (50), 1,9% (51) and 2,4% (52)). The aesthetic result has been reported higher when breast reconstruction was performed with the use of ADM (49, 53) but in a randomized controlled trial (RCT) comparing ADM assisted one-stage BR with submuscular two-stage expander-to implant BR there was no significant difference between the two groups regarding satisfaction with the breast or the overall outcome (54).

Autologous breast reconstruction

Autologous BR uses the patient's own tissue and can be performed with either a pedicled flap relying on the native blood supply or with a free flap, where blood vessels are discontinued and microvascular anastomoses is performed with the tissue in a new anatomical location. The flap can consist of muscle, subcutaneous tissue and skin or various combinations thereof. Furthermore, the tissue can originate from nearby as e.g. abdomen as the Transverse Rectus Abdominis Musculocutaneous flap (TRAM) or the Deep Inferior Epigastric artery Perforator flap (DIEP), from the back as the Latissimus Dorsi flap (LD) or the Thoracodorsal Artery Perforator Flap (TAP Flap), or from a more distant location as e.g. the Transverse Upper Gracilis flap (TUG) (38).

Autologous BR is preferable when radiation therapy is indicated after surgery (41). The surgical procedures are time consuming compared to implant-based BR and, in the case of free tissue transfer, surgeons with microsurgical skills are needed. Patients undergoing BR with autologous tissue report better outcome regarding psychosocial and sexual well-being and satisfaction with the overall outcome and reconstructed breast compared with patients undergoing implant-based BR (55-58).

The TRAM flap will be discussed here in details, as this technique is used in study III. The TRAM flap has been extensively used in autologous BR (59). However, over the past three decades the DIEP flap has gained enormous popularity over the TRAM flap (60). The advantage of DIEP flaps over TRAM flaps is the preservation of muscle tissue and possibly nerves at the donor-site, but yet no unambiguous evidence has been presented that favor one technique over the other (61, 62). The pedicled TRAM flap consists of the rectus muscle and abdominal subcutaneous tissue and skin based on the superior epigastric artery. Abdominal donor-site morbidity as bulging or herniation (63) or abdominal discomfort (64) has been reported since the flap was introduced four decades ago (65, 66). Different techniques have been used to alleviate the abdominal wall weakness as direct suture of the remaining rectus fascia, using the adjacent fascial, or reinforcement with synthetic mesh or dermal transplants (67). Especially synthetic mesh has been used for many years for reinforcement of the abdominal donor-site. Different incidences are reported for development of abdominal laxity ranging from 1.5% to 5.9% hernia (68-71) and 2.3% to 10% bulge (64, 69, 70) after reinforcement with synthetic mesh. With the introduction of acellular dermal matrices (described below) these materials were sought used to obtain a dynamic abdominal wall reconstruction and decrease donor-site morbidity. However, results were variable depending on the nature of the reinforcing matrix. More than 25% risk of bulging and herniation has been reported when using Alloderm™ (human ADM) for reinforcement of the abdominal wall (72) in contrast to no herniation or bulging after reinforcement of the abdominal donor-site with the porcine non-crosslinked ADM Strattice™ (73).

The concept of acellular dermal matrix

A range of acellular dermal matrices (ADM) are available. They are derived from either human cadaveric dermis or animal dermis. These products undergo processes that eliminates all cellular elements and antigenic components from the tissue leaving only the intact extracellular matrix. When the ADM product is implanted the tissue will undergo remodeling including angiogenesis, host cell infiltration, mitogenesis, and deposition and organization of new host extracellular matrix. Component growth factors as vascular endothelial growth factor, basic fibroblast growth factor, and transforming growth factor beta are released during scaffold degradation and exert their biologic effects as they are dissociated from their binding proteins and activated (74). In this way the matrix provides a scaffold, promoting integration of the connective tissue, thus being revascularized and repopulated by the patient's own cells. The biological response after implantation of a biological mesh may vary depending of the processing techniques used for production (75). Some ADM products undergo chemical crosslinking to improve the tensile strength and make the collagen of the biologic mesh less prone to degradation in vivo. The literature suggest that

the non-crosslinked ADM products show earlier cell infiltration, extracellular matrix deposition, scaffold degradation and neovascularization compared with crosslinked materials (76) and that the use of crosslinked ADM products can possibly lead to limited tissue integration and chronic inflammation resulting in surgical site infection and morbidity (77).

In the studies included in the present PhD project, a porcine, non-crosslinked ADM named Strattice™ was used (Figure 1).

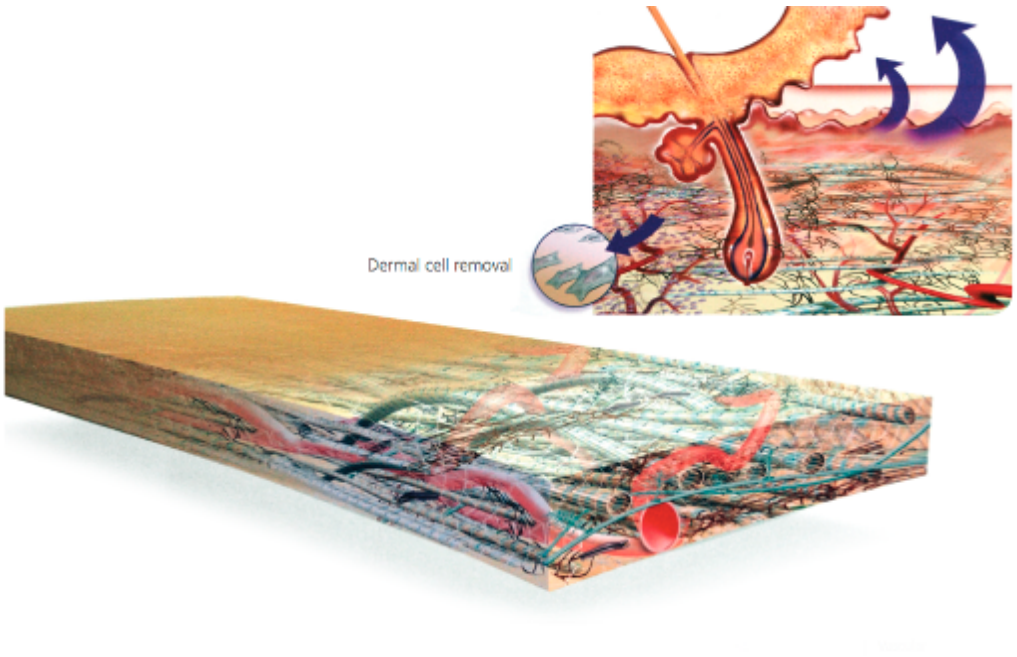

Figure 1. Illustration of Strattice™ (porcine non-crosslinked ADM).

Indications for application of acellular dermal matrices

ADM was first introduced for the treatment of full-thickness burns in 1995 (78), and in 2001 the first use in breast surgery for reducing visible rippling of breast implants was published by Duncan (79). In 2005-06 Breuing and Salzberg (80, 81) were the first to publish the use of ADM for immediate implant-based breast reconstruction following skin-sparing mastectomy thereby demonstrating the advantage of potentially performing the breast reconstruction in a single stage. In 2007 Bindingnavele et al. introduced the use of ADM in tissue expander breast reconstruction, suggesting that this would decrease the postoperative pain and allow a faster expansion course (82). The advantages of using ADM in breast reconstruction has been stated as improved control of the inframammary fold position (83) and better lower pole projection (84) compared to the traditional submuscular expander-to-implant technique. Furthermore, some suggest that breast reconstruction with ADM results in decreased development of capsular contracture, even when the

patient has to undergo radiation therapy (49, 51). Seroma has, on the other hand, been associated with the use of biological meshes (85, 86).

Besides the extensive use in breast reconstruction, ADM products have also been used with success in e.g. oculofacial plastic and reconstructive surgery (87), for dura repair (88), thoracic wall reconstruction (89), and abdominal hernia repair (72, 90). ADM has been preferred in the repair of contaminated surgical hernia where synthetic mesh repair was not favorable (91, 92), but recent literature suggest no advantage of biological mesh use and there is a need for further research to elucidate this area (93).

Surgical mesh evolution

The development of meshes is closely related to treatment of hernias. The first meshes were handmade silver filigrees developed in 1900 by the Germans Witzel and Goepel (94). Metal meshes further developed to stainless steel meshes (95), but their use resulted in abdominal stiffness and patient discomfort. Therefore, they have been replaced by more soft 'plastic' meshes (96). A whole range of meshes exist classified according to the composition type of materials. First generation meshes were mostly non-absorbable based on polypropylene. Usher developed the wowen Marlex mesh (97) and further refined it to the knitted polypropylene mesh. Also, absorbable meshes as "Vicryl®" made of polyglactin is a first-generation mesh. Second generation meshes combined materials, for example an absorbable and non-absorbable material. Third generation meshes are biological meshes made from dermis (ADM) or e.g. intestine or pericardium (98).

When a surgical mesh is implanted and lacks appropriate biocompatibility the body responds by encapsulating the foreign system leading to the formation of a stiff scar which may results in poor tissue incorporation, causing hernia recurrence or infection of the mesh (98) and eventually may result in contracture and chronic pain (91). The ideal mesh has not yet been developed, but efforts are made to improve biocompatibility and thereby develop a mesh that can be incorporated with minimum of foreign body response and inflammation. Coating with for example collagen or titanium or use of nanofiber technology to mimic the extracellular matrix seem promising (98).

Surgical innovation – evidence-based plastic surgery

Integration of the highest level evidence and clinical expertise and patient values into clinical decision making, defines evidence-based plastic surgery (99). This emphasizes the need for evaluating surgical interventions through research studies with outcomes as safety, long term results, costs, and patient satisfaction evaluated by reported outcome measures (PROMs). When new techniques are considered implemented, a health technology assessment can be performed as for example for immediate breast reconstruction with or without the use of ADM (100). The assessment is based upon existing evidence preferable on a high level in accordance with the methodologic hierarchy with case reports at the bottom and randomized controlled trials (RCTs) at the top (101). Where evaluation of pharmacological treatment is

based on RCTs, the evaluation of medical devices may be more complicated, as not all clinical questions can be answered with an RCT (99). In surgical innovation, the IDEAL recommendations can be used as a stepwise framework for evaluating e.g. surgical operations and medical devices. The recommendations were first published isn 2009 and has since been developed and is an excellent intuitive guide describing the stages of surgical innovation: Idea, Development, Exploration, Assessment, and Long-term Study (102, 103).

Finally, health economics with regard to a given treatment modality has to be considered when allocating limited health care resources. Different perspectives can be applied, including the patient, the hospital, and the societal perspective and for allocating health care resources, there is consensus that a broader societal perspective is of most relevance (104). Advanced economic evaluations as cost-utility studies measure the health improvement in quality-adjusted life years (QALYs) and the results are expressed as cost per QALY gained. But whether a treatment modality is cost-effective and will be implemented is a multifactorial decision (105).

For the following sections study number relates to the below listed studies.

Study I

One- versus two-stage immediate implant-based breast reconstruction. A cohort study on cost and patient reported outcome measures.

Study II

Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study.

Study III

Reinforcement of the abdominal wall with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.

Aims and hypotheses

Study I

Aim

The aim was to compare immediate implant-based BR using the ADM assisted one-stage approach with the two-stage expander-to-implant approach regarding costs and patient reported outcome (PRO).

Hypothesis

The hypothesis was that BR with the ADM assisted one-stage approach was less costly and evaluated superior by PROMs in comparison with the two-stage approach.

Study II

Aim

The aim was to compare immediate implant-based BR using the ADM assisted one-stage approach with the two-stage expander-to-implant approach regarding postoperative complications, number of aesthetic corrective procedures, and aesthetic outcome.

Hypothesis

The hypothesis was that BR with the ADM assisted one-stage approach resulted in fewer complications, fewer aesthetic corrective procedures, and a superior aesthetic outcome in comparison with the two-stage approach.

Study III

Aim

The aim was to compare donor-site morbidity after reinforcement of the abdominal wall with either synthetic mesh (Prolene®) or porcine non-crosslinked ADM (Strattice™) with regard to development of bulging or hernia, abdominal muscle strength, postoperative complications, and abdominal pain.

Hypothesis

The hypothesis was that after breast reconstruction with the pedicled TRAM flap, reinforcement with ADM in comparison with synthetic mesh results in less bulging and hernia at the abdominal donor-site and less abdominal discomfort.

Methods – study I and II

Design

Observational single-centre cohort study. Follow-up time was 24 months.

Participants

All women admitted for immediate, implant-based BR following skin-sparing mastectomy at the Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark over a period of 40 months were eligible study participants. Patients were diagnosed with either ductal carcinoma in situ (DCIS), breast cancer, or were considered high risk for developing breast cancer. Exclusion criteria were mastectomy weight > 600 g, age less than 18 years, smoking less than four weeks prior to surgery, and patients not able to understand enough Danish to comprehend the given information and to complete the study questionnaire. The patients in the two-stage group had to be able to achieve two-year follow-up visit after BR.

Recruitment

In December 2012 the one-stage approach was implemented as a standard care for immediate implant-based BR following skin-sparing mastectomy. All eligible patients were offered participation in the one-stage group and inclusion continued consecutively until 21 patients were included. The two-stage cohort was established retrospectively as illustrated in Figure 2.

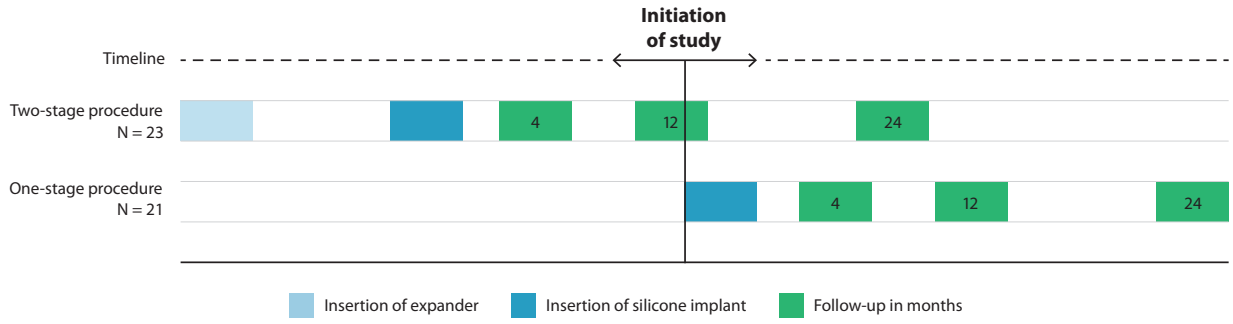

Figure 2. Timeline of study inclusion.

By using diagnosis- and procedure-related codes, patients were identified that had undergone immediate implant-based BR following skin-sparing mastectomy with the two-stage expander-to-implant technique. Patient records were examined, and patients that fulfilled the inclusion criteria were identified and

consecutively offered participation in the two-stage group. Inclusion continued *retrospectively* until 23 patients were included (Figure 3).

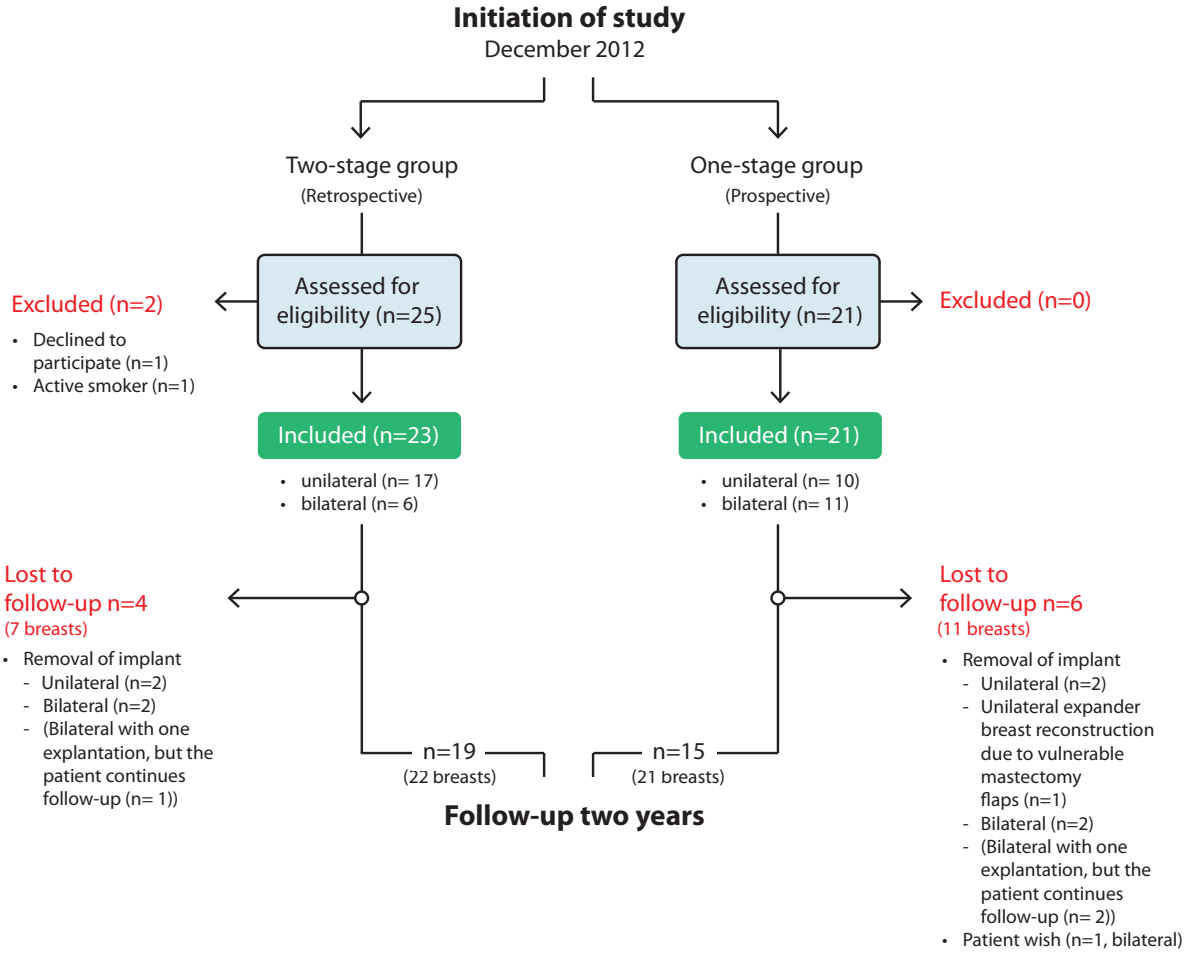

Figure 3. Flowchart of study participants. Prospectively included one-stage group and retrospectively included two-stage group.

Ethical considerations and data management

The study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent before surgery. The Ethics Committee of the Central Region of Denmark (1-10-72-572-12) and The Danish Data Protection Agency (1-16-02-6-13) approved this study and it was submitted in ClinicalTrials.gov (NCT04209010). Study data was managed using REDCap electronic data capture tools hosted at Department of Clinical Medicine, Aarhus University.

Data

Participants were informed and interviewed before initiating the breast reconstructive trajectory if the patient was included in the prospective one-stage group after study start December 1st, 2012. If the patient was included retrospectively in the two-stage group, information and interview took place at the earliest possibly timepoint after December 1st, 2012 whether it would be before exchange to silicone implant or at follow-up visits. Patients underwent clinical examination 4, 12-, and 24 months after insertion of the silicone implant. All performed by the investigator (Figure 4). Furthermore, patients completed a study-specific questionnaire at 12- and 24-month follow-up. Data regarding postoperative complications and cost variables were obtained from patient records at follow-up visits.

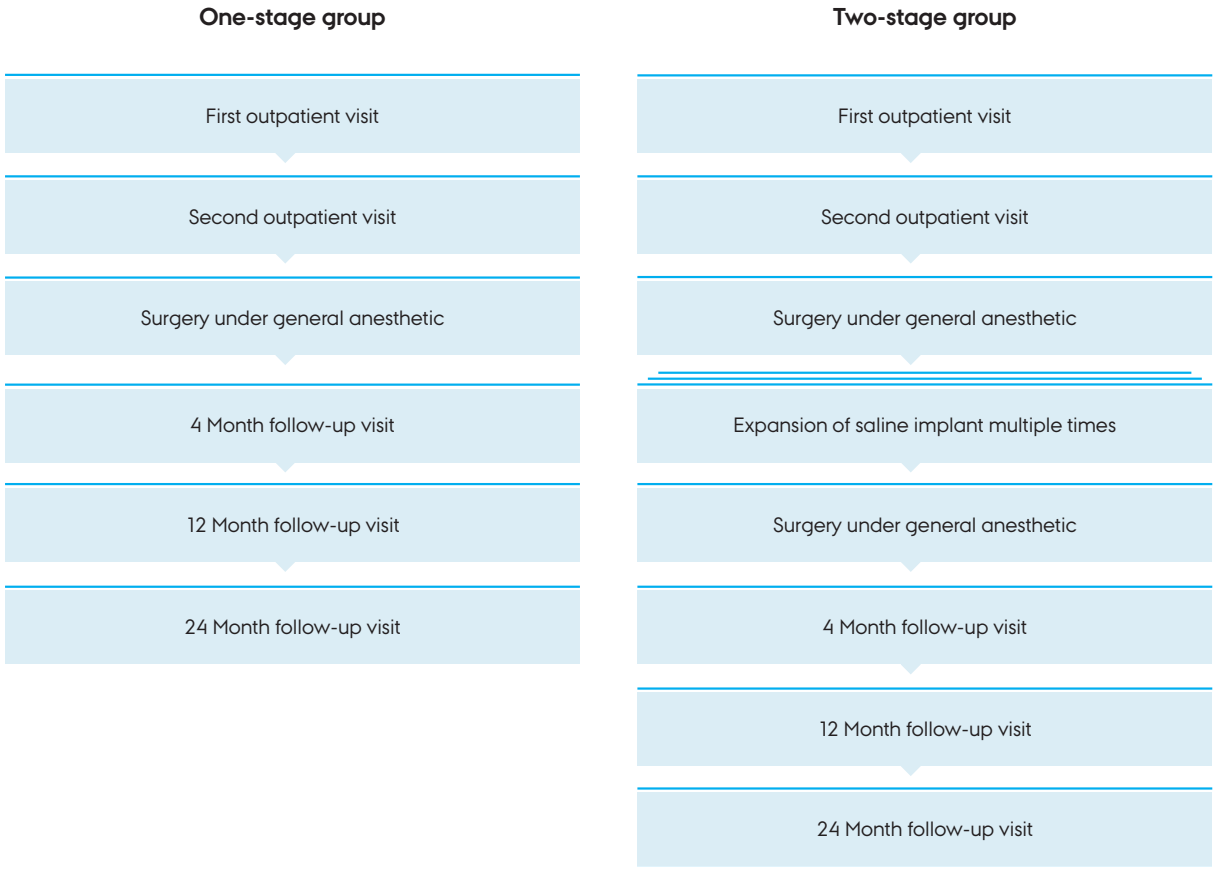

Figure 4. Illustration of the breast reconstructive treatment trajectory for study participants.

Intervention

All patients underwent immediate BR after skin-sparing mastectomy. The one-stage group had the fixed size silicone implant inserted in the subpectoral plane with ADM covering the inferolateral part as an extension of the pectoralis major muscle sutured to the inframammary fold. The two-stage group had an expander inserted under total muscle cover consisting of the pectoralis major muscle, the serratus anterior muscle or its fascia, and the anterior rectus sheath. Postoperatively the expander was inflated several times in the outpatient clinic and three to six months after the final expansion volume was achieved, the expander was changed to a fixed sized implant (Figure 5).

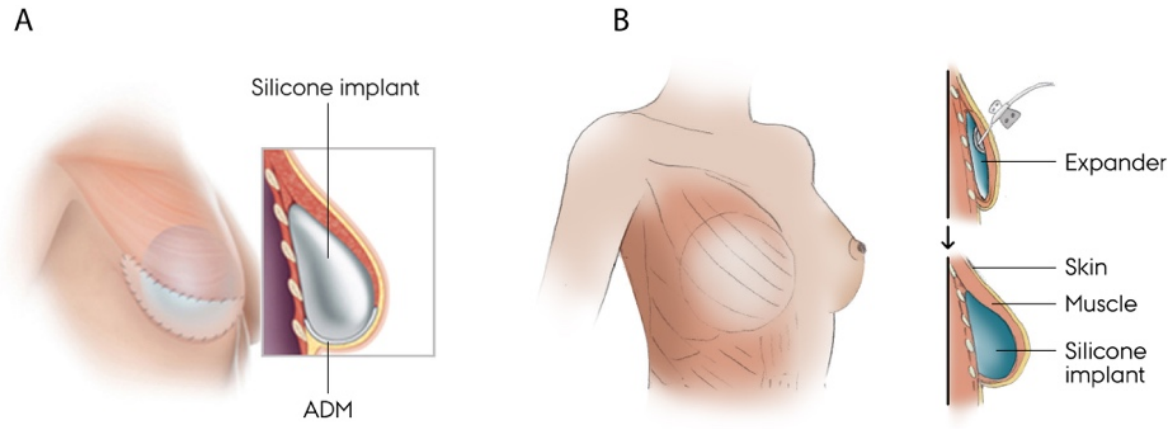

Figure 5. A. ADM assisted one-stage BR. B. Expander-to-implant two-stage BR.

Sample size

The primary endpoint “reduction in surgery time” was used for power calculation on as the duration of surgery was considered to have a significant impact on overall costs. Duration of surgery time for bilateral BR with the two-stage technique was estimated to 300 minutes, based on own experience. The minimum relevant difference the study was aiming to achieve was 60 minutes reduction in surgery time using the one-stage technique (106). Significance level was set to 5% and power to 80% and it was calculated that 16 patients were needed in each treatment group. Originally 20 patients were planned in each group, but late secondary review of patients revealed, that one patient had been excluded by mistake from the one-stage group due to conversion to expander-based BR because of vulnerable mastectomy flaps and another three patients were excluded due to removal of implant before inclusion started in the two-stage group. By allocating these patients to their correct study group the result was 21 patients in the one-stage group and 23 patients in the two-stage group.

> The remaining method section and methodological considerations are described separately for study I and study II.

Outcomes study I

Primary endpoint

Cost reported for bilateral and unilateral BR in the two treatment arms were the primary outcome. The following variables were included: 1) Cost of silicone implants, sizers, expanders and sheets of ADM (Strattice pliable 8x16 cm) in €. 2) Duration of the breast reconstructive procedure in minutes. In case of unilateral BR with contralateral breast surgery in the same intervention, the duration of the breast reconstructive procedure was estimated by a senior consultant (TD). 3) Number of outpatient visits for expansions in patients who underwent a two-stage procedure. 4) Number of interventions to address seroma. 5) Number of surgical interventions to address complications. In case several procedures were performed at one operation it only counted for one intervention. 6) Number of surgical interventions to address aesthetic outcome. In case of unilateral BR with contralateral breast surgery at the same time as the breast reconstructive procedure, the contralateral procedure counted for one aesthetic intervention. However, in case different procedures e.g. fat grafting and correction of skin was performed in the same intervention it counted for only one intervention. 7) Duration of hospitalization in days and estimated costs in € and 8) duration of sick leave reported by patients (days before work was resumed). Data was obtained for a two-year period after insertion of the final-size silicone implant.

Secondary endpoints

Body Image Scale (BIS)

Body image was evaluated using Hopwoods Body Image Scale (BIS) (107) at 12- and 24-month follow-up. The scale consists of 10 items answered with reference to the past week. Items include evaluation of femininity, physical and sexual attractiveness, self-consciousness, satisfaction with body and scars. Each question has four options for rating body image: “not at all” (score 0), “a little” (score 1), “quite a bit” (score 2), and “very much” (score 3). The 10 item scores were summed to produce an overall score for each patient, ranging from 0 to 30. 0 represented no symptom/distress and higher scores represented increasing symptoms/distress (see Supplementary material 1.2, page 79).

Patient reported outcome measures (PROMs)

Patients fulfilled a study specific questionnaire regarding health status, pain, quality of life (QoL), sensory disturbance, and functional sequalae at 12- and 24-month follow-up consisting of items answered at with regard to the breast and items answered with regard to the patient. Some of the questions were answered on a Likert scale and were dichotomized prior to analysis as elaborated in the description of questions found in Supplementary material 1.3, page 80.

Statistical methods

Descriptive statistics were applied for patients' demographics with stating mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test.

The continuous outcome was analyzed using a simple linear regression model, or mixed regression model wherever it was necessary to adjust for the repeated measurements at the patient level (either repeated over time or observations at the breast level), in which case Kenward-Roger approximation as used to adjust for the degrees of freedom due to small sample size.

The dichotomous outcome was analyzed using a generalized linear model with log-link function and in case of repeated measurements, the IDs were used as clusters. As a special case, for the PRO data at breast level, the two breasts were assumed to be coming from two different patients. Therefore, a new ID variable was created at the breast level and used as clusters in the model to adjust for the repeated measurements. The significance level was set to 0.05.

Methodological considerations for study I

Study design

The prospective cohort design makes it possibly to study the predefined outcomes of interest over a long time and measure changes. However, with a longer follow-up time the risk of loss to follow-up increases and this may reduce internal validity. The predefined and consecutively obtained outcome measures allows for high completeness and high quality of data. The prospective cohort study design gives a better ability to infer causality compared to retrospective studies or cross-sectional studies. But attention should be drawn to identifying confounding factors before making unambiguous conclusions. Disadvantages include that the prospective cohort design is time consuming as a considerable time is used for enrollment of study participants followed by managing and maintaining the follow-up times for every patient. The present study was not exclusively prospective as a retrospective enrollment of the two-stage group was performed resulting in missing data from 4- and 12-month follow-up visit in this treatment group.

The small sample size in this study was a limitation resulting in large confidence intervals making it difficult to draw conclusions.

Blinding of the intervention was for obvious reasons not possible in the present study. This could potentially result in biased reporting from patients and investigator, as one method of breast reconstruction could be perceived as advantageous over the other.

This study was conducted as a single-centre study. There are many advantages with this design e.g. it is logistically easy, the data collection is simple and the study population is typically quite homogenous compared to multi-centre studies. But the single-centre design potentially may result in limited external validity of the study as interventions tested in a single, clinical setting is not necessarily generalizable (108). The ultimate recommendation following a single-centre study may therefore be, that investigation of the intervention should be performed in a larger multi-centre setting.

The study participants of the present study are thought to be representative of the patients aiming for immediate implant-based breast reconstruction. But differences in local setup may play a role for cost analysis, decreasing the external validity.

The two-year follow-up time was chosen as this was the estimated period in which the costs of the two treatment methods would vary and furthermore, to get an appropriate follow-up time of PROMs.

For transparent reporting the STROBE guidelines for reporting observational cohort study were used (109).

Cost

When surgical procedures are performed, resources (personnel, equipment, facilities, time, and materials) are utilized. To determine which procedure is most effective for a given outcome, competing interventions

must be compared in terms of costs and outcomes such as, complications, patient satisfaction, and functional/psychological morbidity (110). This type of analysis assumes that the outcomes of the two procedures are equal.

The aim of the present study was not to perform a cost-benefit-, cost-utility- or cost-effectiveness analysis. Performing these analyses demand a large setup preferable with RCT comparing the two treatment arms, in depth knowledge about economical evaluation methods, and another timeframe. However, we sought to provide a simple cost analysis by reporting the direct costs / resources associated with the two treatment methods. Furthermore, it was the aim to assess the outcome from the patient and the hospital perspective by discussing the related costs associated with treatment.

The definition of cost is 'any use of a resource', and all costs must be in the same unit, usually monetary value (105). It has been emphasized that in reporting costs, it is important to report the physical quantities of resources consumed or released by the surgical treatments separately form their prices, as users of the analysis in another setting is thereby able to draw their own conclusions (104). Obtaining accurate cost data is often difficult and can limit the generalizability (105).

The present study did not succeed to put a monetary value on all cost variables, even though relevant health care authorities were consulted. This may impede a straightforward interpretation of the cost analysis.

When implementing new techniques, the initial literature at hand is sparse. Thus, initiating this study in 2012 the literature regarding cost analysis comparing one-stage BR with ADM with the two-stage method was also limited (111, 112). Consequently, a state-of-the-art economic analysis based on large patient populations was not feasible.

When the literature is interpreted, it is important to know which societal preconditions form the basis for the research. The US health care system is for example driven by private insurances as opposed to the Canadian system or the system in most European countries, where there is a universal national health care insurance program (113). This could potentially play a role for reimbursing health care providers and the availability of certain surgical procedures.

PROMs

Body image

In the present study Hopwoods BIS was used for measuring body image. The scale is constructed in collaboration with the European Organization for Research and Treatment of Cancer (EORTS) Quality of Life Study Group and tested in a sample of cancer patients, revised and tested in breast cancer patients (107). The BIS was developed for use in trials where the main need was to make comparisons between patient groups. It is validated for use in cancer patients, has high reliability, good clinical validity, and is sensitive to changes. There has not yet been determined a threshold of clinical score for body image

disturbance (114). The scale has not undergone a formal validation in a Danish population but has been forward and backward translated and has previously been used at our institution (55, 115).

Questionnaire

A study specific questionnaire was used to obtain information regarding health status, QoL, pain, sensory disturbances, and functional sequelae.

Over time the use of instruments to measure PRO has evolved from ad hoc measures in study specific questionnaires to formally developed, standardized and validated questionnaires, as they are more likely to assess the outcome of interest and makes it possibly to compare between studies (116). Efforts have been undertaken to develop a core set of outcomes based on issues important for both patients and health-care professionals (117) and three questionnaires have been identified as meeting the criterias for recommended use of PROMs in a breast reconstructive patient population. BREAST-Q, BRECON-31 and EORTC QLQ-BRECON23 (118). Though, the latter has only been validated for patients undergoing breast reconstruction for cancer and ductal carcinoma in situ and not for risk reducing purpose (119). Since 2009 the use of BREAST-Q for obtaining PRO in breast reconstructive research has been rapidly increasing and it is currently the most often used tool (120). Unfortunately, this questionnaire was not available in a validated Danish version at study start.

The questionnaire used in this study was based on previously used questionnaires at our institution based on EORTC QOL BR-23 and SF36 (55, 56).

Outcomes study II

Primary endpoint

Postoperative complications reported per breast.

Explantation was defined as either ***implant exchange,*** defined as removal of the device implanted at the initial surgery and exchange to an expander, or ***loss of implant,*** resulting in failure of the initial implant-based BR.

Major complications (requiring surgical intervention) included hematoma, infection requiring explantation, and skin flap necrosis.

Minor complications included cellulitis/wound infection requiring treatment with antibiotics and seroma requiring intervention.

Secondary endpoints

Aesthetic corrective procedures

Aesthetic corrective procedures were defined as number of surgical procedures performed in general anesthesia with the aim of achieving a better aesthetic outcome. Nipple-areola reconstruction or surgery due to postoperative complications were not included in this analysis. In case of unilateral BR contralateral symmetrization procedures was also considered an aesthetic correction. Results were provided for two-year follow-up data.

Aesthetic result reported by patient and investigator

The patients completed a study specific questionnaire consisting of items evaluated *per breast* ("satisfaction with appearance of the reconstructed breast with clothes", "satisfaction with appearance of the reconstructed breast without clothes", and "overall satisfaction with the BR") and items evaluated at *patient level* ("satisfaction with symmetry regarding breast size" and "satisfaction with symmetry regarding breast shape"). A seven-point Likert scale for answering were used ranging from very dissatisfied (score 1) to very satisfied (score 7). Score evaluating satisfaction with appearance of the reconstructed breast with/without clothes and scores evaluating symmetry were summed into a total score ranging from 2-14. Higher scores represented greater aesthetic satisfaction.

The investigator assessed the aesthetic outcome in regard to "overall aesthetic result of BR with clothes" and "overall aesthetic result of BR without clothes" (reported per breast) and "symmetry regarding breast size" and "symmetry regarding breast shape" (reported per patient). Assessment was scored into four categories ('excellent' score 4, 'good' score 3, 'fair' score 2, and 'poor' score 1). This was summed into a total score, range 2-8. Higher scores represented greater aesthetic satisfaction.

Investigator obtained an objective measurement of symmetry by measuring suprasternal notch to nipple (SSN:N) distance and nipple to inframammary fold (N:IMF) distance. Symmetry was described as difference in cm between measurements of right and left side. Lower score represented a better symmetry between breasts.

Furthermore, investigator assessed the degree of capsular contracture according to the Spear-Baker classification for implant-based breast reconstructions (46). Results were provided for two-year follow-up data.

Statistical methods

Descriptive statistics were applied for patients' demographics giving mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test. For the continuous outcome the arms were compared using t-test for two means or were analyzed using a simple linear regression model. A multiple linear regression was used to adjust for BMI etc. Mixed regression model was used wherever it was necessary to adjust for the repeated measurements at the patient level (observations at the breast level), in which case Kenward-Roger approximation as used to adjust for the degrees of freedom due to small sample size.

The dichotomous outcome was analyzed using a generalized linear model with identity-link function and in case of repeated measurements, the IDs were used as clusters. The outcome "number of aesthetic corrections" were analyzed using a Poisson regression model. The significance level was set to 0.05.

Methodological considerations for study II

Study design

The same methodological considerations that were done for study I applies to study II.
Please see page 17.

Complications

The most severe complication was explantation. In this study this incident was further subdivided into loss of implant (failure of the initiated implant-based breast reconstruction) or implant exchange (removal of the implanted silicone implant and insertion of an expander) as the outcome was different. Further complications were subdivided in two categories. Major complications resulting in surgical intervention and minor complications, not resulting in surgical intervention. This approach was previously used at our institution (56).

Aesthetic corrective procedures

This included all surgical procedures performed with the patient in general anesthesia and was provided at patient level. Contralateral symmetrization was also perceived as an intervention with aesthetics as the overall goal. The aim was to estimate how many procedures was needed to obtain a satisfying aesthetic outcome, and therefore every procedure counted. If for example a skin reduction as well as fat grafting was performed, it counted for two procedures even though it was performed under the same surgical intervention. This endpoint was chosen as it is of great interest whether one approach results in more correction procedures than the other. This is important knowledge for a solid foundered information to patients aiming for a breast reconstruction.

Aesthetic result reported by patient and investigator

Patients completed a study specific questionnaire developed from previously used questionnaires used at our institution (55, 56), as no validated Danish instrument evaluating patient satisfaction with the aesthetic result after BR was available at study start. Items for analysis were chosen to enable comparison between patient and investigator assessment even though they did not use the same scale. In this study no baseline measurement of satisfaction with aesthetic result or symmetry was obtained. Though, it would have been of great interest to observe the longitudinal changes from before surgery to two years after surgery.

Different methods have been used to evaluate symmetry of breasts as e.g. 3D imaging (121, 122). This technique was not accessible in our setting and simple measurements with measuring tape was used as the investigator was accustomed to using this method. The literature suggests that the sternal notch to nipple ratio is correlated to patient-reported cosmesis, whereas other vertical and horizontal distance

measures are correlated to physician-reported cosmesis (123, 124). By using 0.5 cm difference between right and left measurements it was possibly to compare with symmetry data for preoperative measurements of breast cancer patients (124). The Spear-Baker classification for implant-based breast reconstructions (46) was chosen as instrument for measuring capsular contracture, as this was the most used instrument available and the investigator had previous experience with that.

Methods - Study III

Design

Randomized controlled trial (RTC) performed as a single-centre, double-blind (patient and investigator), prospective study, with two treatment groups, allocation ratio 1:1. Follow-up time was 24 months.

Participants

Eligible patients were all women undergoing autologous BR with the pedicled TRAM flap at Aarhus University Hospital during the inclusion period (January 2014 – November 2016). Exclusion criteria were smoking less than four weeks prior to surgery, age less than 18 years, and patients not able to understand enough Danish to comprehend the given information and to complete the study questionnaire.

Ethical considerations and data management

The study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent before surgery. The Ethics Committee of the Central Region of Denmark (1-10-72-10-13) and The Danish Data Protection Agency (1-16-02-7-13) approved this study and it was submitted in ClinicalTrials.gov (NCT02076724). Data were managed using REDCap electronic data capture tool hosted at Department of Clinical Medicine, Aarhus University.

Data

Participants were informed and interviewed before surgery and underwent clinical examination at follow-up visits 4, 12 and 24 months after surgery. All were performed by the investigator. Data regarding postoperative complications were obtained from patient records at 4-month follow-up.

Intervention

Patients were randomized to reinforcement of the abdominal donor-site with either synthetic mesh (Prolene®) or porcine non-crosslinked ADM (Strattice™) (Figure 6).

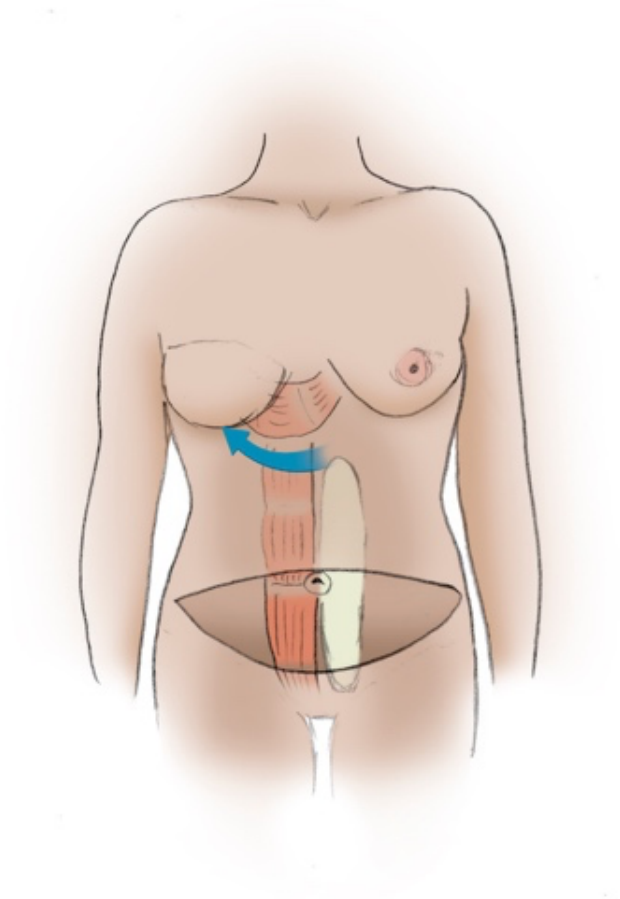

Figure 6. Illustration of the pedicled TRAM flap and reinforcement material at the abdominal donor-site.

Outcomes

Definition of bulge/hernia: bulge was defined as a visible protrusion of the abdominal wall, without a defect in the abdominal fascia; hernia was characterized as a protrusion of the abdominal wall with a defect in the abdominal fascia.

Primary endpoint

The primary end point was defined as CT-verified bulge or hernia at 24-month follow-up.

Secondary endpoints

Abdominal muscle strength

Measurements obtained using a fixated hand-held dynamometer before surgery and at 12- and 24-month follow-up. All measurements were performed by the investigator in the same standardized way using The PowerTrack IITM (JTech Medical Industries, Salt Lake City, USA). Measurements took place with the

patient in a supine position with legs straight and the arms along the body. The dynamometer was placed in a tripod, adjustable with belts, and placed below the xiphoid process (see Supplementary material 1.1, page 120). The patient was verbally instructed and performed a trial run to familiarize with the dynamometer. The patient was strongly encouraged to perform maximal effort at each trial. A resting period at 30 seconds was allowed between each test. The test was repeated until peak was clearly reached and the maximum score was chosen. Immediately after the last test the patient assessed pain during the exercise on a Visual Analogue Scale (VAS) instrument.

Donor-site complications

Complications were categorized as major (included hematoma, infection, and skin necrosis requiring surgical intervention) and minor (included cellulitis/wound infection requiring treatment with antibiotics and seroma requiring intervention). All complications were identified through review of patient records at 4-month follow-up visit.

Pain/discomfort

The investigator interviewed the patient regarding information of preoperative abdominal pain or discomfort. The postoperative assessment was obtained by the patients fulfilling a questionnaire regarding feeling of tightness of the abdominal wall and cutting /stabbing / shooting sensations located to the abdominal wall with reference to the past month. Furthermore, Dolotest® score was obtained at each follow-up visit. Dolotest® is a validated instrument measuring pain intensity and health related quality of life (HrQoL) in pain patients with reference to the past week (125) (see Supplementary material 1.2, page 121). The instrument consists of eight domains each evaluated on a VAS scale: 0 represents no problems and 100 represents worst possible problems (to what extent do you experience pain; problems with light physical activity; problems with more strenuous physical activity; problems doing your job; reduced energy and strength; low spirit; reduced social life; and problems sleeping). The developers' recommendation was followed in instruction of all patients. Calculation of a total score was performed by summating the eight scores (range 0-800). Higher scores representing worse pain related QoL.

Sample size

The minimum relevant difference the study was aiming for was a 6 % absolute reduction in bulging frequency between the synthetic mesh and the ADM group. Bulging frequency was estimated by following studies to 7% (126) and 10% (64) for reinforcement with synthetic mesh and 0% (73) for reinforcement with ADM. Significance level was set to 5% and power to 80% and it was calculated that 16 patients were needed in each treatment group but inclusion was terminated 16th November 2016 due to time limitation with regard to the ability to achieve two years of follow-up within the duration of the project.

Randomization

A permuted block design with blocks of 4 and 6 according to the SNOSE principles (127) was used to randomize patients. A researcher without involvement in the study prepared the allocation sequence and during surgery an instructed nurse performed the randomization.

Blinding

A standardized operation text was added to the patient record by the plastic surgeon, not revealing the nature of the reinforcement material applied for abdominal wall reconstruction. If a complication occurred that could be related to the use of reinforcement material and in all cases after two years of follow-up, the randomization was revealed. During the breast reconstructive pathway, the investigator did not participate and thus the patient, care providers, radiologist, and investigator were blinded for the intervention.

Statistical methods

Significance level was set to 0.05. The continuous outcome was analyzed using a mixed regression model to adjust for the repeated measurements at the patient level (repeated over time). Kenward-Roger approximation was used to adjust for the degrees of freedom due to small sample size. The dichotomous outcome was analyzed using a generalized linear model with log-link function and IDs as clusters. Dolotest® score were scaled up to eight questions for the two patients who answered only seven questions by multiplying their mean score by eight. Two sensitivity analysis were performed. One without the patient who had very high value at four months follow up and influencing the model result and another sensitivity analysis without the two patients who answered only seven questions. Abdominal strength measurements were adjusted for VAS score.

Methodological considerations for study III

Study design

A randomized clinical trial (RCT) may provide a higher level of evidence in clinical trials as the design decreases selection bias and minimizes confounding. But RCTs are time consuming and often costly to perform. Furthermore, several issues have to be addressed, as there is often inadequate reporting of these subjects in plastic surgery RCTs comparing surgical interventions (128).

The randomization was performed using the sequentially numbered opaque envelopes (SNOSE) principle, as this is an accessible and straightforward method of maintaining allocation concealment and does not require the use of specialized technology (127). The permuted block randomization was chosen in order to ensure balance in the trial after the enrollment of each block of patients in the case of not reaching the proposed number of study participants. All patients received the intervention they were allocated to, and randomization was concealed until 2 years after surgery. Thereby minimizing allocation bias. Review of demographics revealed that the treatment groups were similar at baseline with regard to important confounders as BMI, chemotherapy, and prior lower abdominal surgery with midline incision (for the risk of developing bulge or hernia). Thereby minimizing confounding bias.

The study participants are thought to be representative of the patients aiming for BR with the TRAM flap. The included patients are, however, not representative for other patient categories who may need a rectus muscle-based reconstruction (e.g. gender, age, or comorbidities). This may decrease the external validity.

The sample size might not have been large enough, and thereby the study might not have adequate power to draw conclusions of an effect of the intervention. Within the enrollment period, the number of patients referred to BR with the pedicled TRAM flap decreased, and enrollment was terminated to be able to obtain 24-month follow-up within the timeframe of the PhD study. This resulted in fewer study participants than originally planned.

The present study was double- blinded, as participants, caregivers, and outcome assessors were blinded to intervention assignment.

This study was conducted as a single-center study. The strengths and limitations associated with this study design have been discussed in the section “methodological considerations study I”.

For transparent reporting the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline was used (129).

Primary outcome was development of bulge or hernia at the abdominal donor-site. This endpoint was chosen as the literature suggest that this is still a problem despite numerous attempts to solve it. One very experienced radiologist examined all CT scans minimizing the bias of intra-observer evaluations. It is crucial to decrease donor-site morbidity, as a breast reconstruction should overall aim for the patient to

obtain an increase QoL. Furthermore, a substantial part of patients reinforced with a synthetic mesh, report symptoms as tightening across the abdomen (64). With the potential of obtaining a dynamic reconstruction of the abdominal wall with minimal donor-site morbidity in terms of bulging or herniation (73), the present study was initiated. Previous studies have suggested that bulge or hernia develops within the first two postoperative years (64, 126). Consequently, this was chosen as the follow-up time of this study.

Diagnosis of bulging or hernia

Assessment of abdominal wall weakness was assessed by the patients as their opinion is of utmost importance. Clinical examination was performed with the patient standing and in a supine position including Valsalva's maneuver to increase the intra-abdominal pressure and discover any bulges or hernias. Furthermore, an abdominal CT including Valsalva's maneuver (130) was performed to objectively verify the diagnosis.

Abdominal muscle strength measurement

Measurement of abdominal strength was obtained at baseline and at 12- and 24-month follow-up. Testing four months after surgery was not performed due to not stressing the newly operated field. Even though the isokinetic dynamometer is considered the gold standard for measuring muscle strength, it is not optimal in a clinical setting. Hand-held dynamometry has been shown to be a reliable and valid instrument in comparison with isokinetic dynamometry (131). Therefore, this instrument was chosen as it is easy to use in a clinical setting regarding accessibility, cost, and size. In this study the hand-held dynamometer was fixated with a tripod as it may be difficult for the tester to provide a counter pressure corresponding to the effort of the patient. This setup has been shown to increase reliability compared with a hand-held dynamometer fixated by the tester. The method has previously been used for the assessment of back extensor muscle strength (132).

In this study no information was obtained regarding the patients' subjective assessment of the abdominal muscle strength or difficulties as e.g. getting out of bed. This would have been relevant and could have been obtained by using e.g. BREAST-Q. However, this instrument was not validated in Danish when the study was initiated.

Abdominal pain and discomfort

A study specific questionnaire was used to obtain information regarding abdominal pain or tightening feeling as no validated Danish instrument was available at the time of study start. It would have been preferable to use BREAST-Q (133) for assessing this outcome at baseline and at follow-up as this would make it possible to compare directly with other studies using BREAST-Q and to normative data (134).

Dolotest® (125) was used to measure HrQoL and is validated in Danish. The instrument was chosen as it addresses the important impact of pain on daily life of the patient. Furthermore, it is easy to understand by the patient and fast to complete and has previously been used at our institution (135).

Summary of results

A brief summary of study results is included in this section. For further detail please see appendix with enclosed manuscripts.

Study I

Study population

23 patients (29 breasts) were included in the two-stage group, and 21 patients (32 breasts) were included in the one-stage group (Figure 3, page 12). There was no significant difference between the two treatment groups regarding demographics or clinical characteristics.

Cost

Materials for a one-stage procedure (Strattice™, sizer and silicone implant) was 2.6 times more expensive than materials for at two-stage procedure (expander, silicone implant and 2 sizers) with a difference at 1795 € for a unilateral procedure. The total duration of surgery was significantly longer (34%) for a unilateral two-stage BR than for a one-stage BR ($p=0.006$). For the bilateral cases there was no significant difference. Patients reconstructed with the two-stage method underwent in average 6 expansions. No significant difference between treatment groups were observed regarding surgical interventions to address complications, overall duration of hospital stay, or self-reported sick leave. But the one-stage group underwent more surgical interventions to address the aesthetic outcome. This was statistically significant comparing the unilateral treatment groups ($p<0.0001$).

Patient reported outcome

Overall, there was no statistically significant difference between treatment groups regarding any of the patient reported outcomes measures at 24-month follow-up. Patients felt to a large degree not restricted in their ability to perform physical activities and were able to use their arm on the reconstructed side as before BR. Most patients were mildly burdened by sensory disturbances, and 19%-32% described pain located to the reconstructed breast. Body image score was equally good in both treatment groups and 73% of patients in the one-stage group and 53% of patients in the two-stage group described an improved QoL compared to the time before BR (as recalled by the patients at follow-up visits after BR). All patients would recommend others in the same situation to undergo BR.

Study II

Study population

The information provided for study I also applies to study II. Please see page 30. Mastectomy specimen weight did not differ between treatment groups but patients in the two-stage group received significantly larger implants than patients in the one-stage group (p=0.001).

Complications

There was no significant difference between the two treatment groups regarding implant loss, implant exchange, or major complications.

The risk of implant exchange/implant loss was 13%/16% in the one-stage group and 7%/17% in the two-stage group, respectively. The majority of patients had no major complications, but the risk of at least one major complication was 28% in the one-stage group and 24% in the two-stage group. The risk of at least one minor complication was significantly higher in the two-stage group (41%) compared to the one-stage group (3%, p<0.0001). Most minor complications in the two-stage group were observed after insertion of the expander and not after exchange of the expander to the final silicone implant.

Aesthetic corrective procedures

The majority of patients in both treatment groups underwent at least one procedure (mean 1.8 in one-stage group, mean 1.5 in two-stage group) to obtain an acceptable aesthetic result. There was no significant difference between groups.

Aesthetic outcome

Overall, no significant differences were observed between groups regarding any of the outcome variables. Both patient and investigator were very satisfied with the aesthetic outcome and with symmetry regarding breast size and shape in both treatment groups. Measurements of suprasternal notch to nipple distance and nipple to inframammary fold distance confirmed that symmetry was achieved. Finally, no patients developed capsular contracture within two years of follow-up.

Study III

Development of bulge or hernia

At 24-month follow-up, abdominal donor-side hernia verified by CT was present in two patients (14%) in the ADM group but none in the synthetic mesh group.

The investigator observed no bulging at the donor-side at four-months follow-up, but a higher risk of bulging in the ADM group (51.7%) compared to the synthetic mesh group (20%) at 24-month follow-up, although this was not significant (RR 2.9, p=0.068). CT scan confirmed bulging at the donor-side in 35.7% of patients in the ADM group, but only in 6.7% of the synthetic mesh group (RR 5.4, p=0.109) at this timepoint. Both treatment groups had a 21-28% risk of bulging at the contralateral side (no-mesh side). This phenomenon was already present at four-month follow-up and did not change significantly through the study period. Two years after surgery more than 50% of patients observed abdominal bulging or hernia (not specified in laterality) with no statistically significant difference between treatment groups.

Abdominal muscle strength

No statistically significant difference in the mean dynamometer test result were observed between the groups at any time point (p=0.69) (Figure 7). Furthermore, comparing the 24-month follow-up result with baseline result, significant difference within the groups were not revealed. In the ADM group the difference was -12.2 (95% CI -25.8 - 1.4, p= 0.077), and in the synthetic mesh group the difference was -4.5 (95% CI -18.6 - 9.7, p= 0.519). Adjusting for VAS score did not change the conclusions.

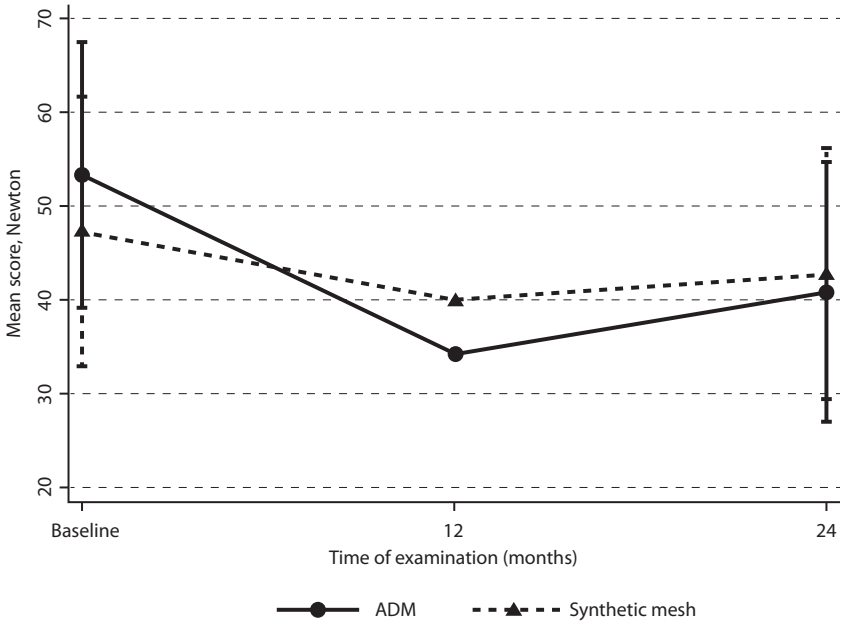

Figure 7. Abdominal muscle strength.

Donor-site complications

There was no statistically significant difference between treatment groups. Minor complications were only observed in the ADM group where one patient developed seroma and one patient developed cellulitis. Major complications (resulting in surgery) was observed in both treatment groups: one patient in the ADM group had an infection, and two patients in the synthetic mesh group experienced necrosis.

Pain and health-related QoL

In the present study, no statistically significant difference was observed between treatment groups at 24-month follow-up regarding feeling of abdominal tightness (RR 0.7, p= 0.376). Likewise, no statistically significant difference was observed between treatment groups at 24-month follow-up regarding feeling of cutting/stabbing/shooting sensations (RR 0.8, p= 0.583).

Dolotest® measuring health related quality of life related to pain did not differ statistically significant between treatment groups at any timepoint (p=0.65) (Figure 8). The synthetic mesh group demonstrated a significant decrease in HrQoL over time (increasing Dolotest® score) as the baseline Dolotest® score was 59 points less (95% CI: -117 - 2, p= 0.044) than the 24-month follow-up score. In the ADM group, the baseline Dolotest® score was 38 points less (95% CI -96 - 20, p= 0.197) than the 24-month follow-up score.

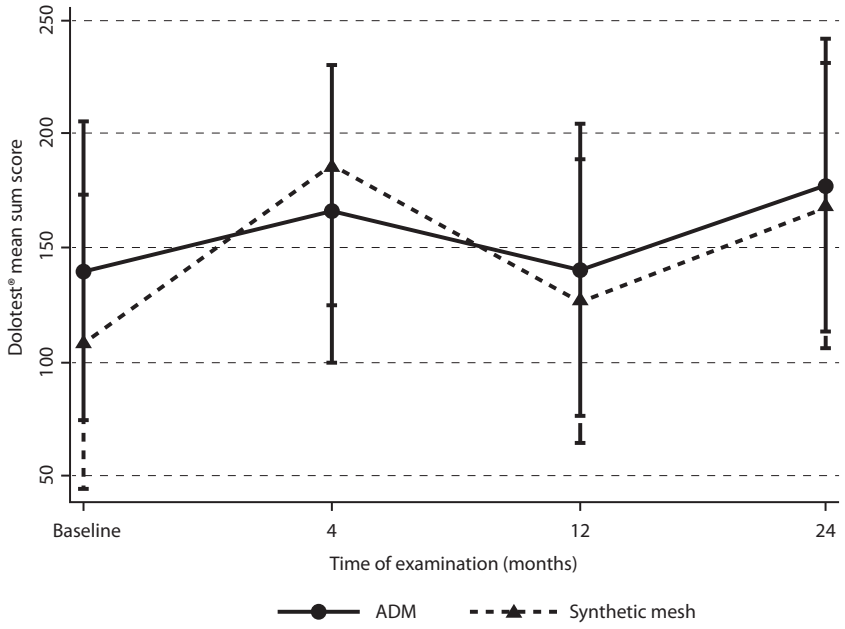

Figure 8. Dolotest® range 0-800. Higher score indicates decreasing HrQoL.

Discussion

Study I

Cost

Overall, in favor of the two-stage approach was reduced cost of materials and fewer interventions to address aesthetic outcome. In favor of the one-stage approach was the reduced need for outpatient clinic visits for expander fillings and a shorter total duration in minutes for the breast reconstructive procedures.

The longer overall duration of surgery for the two-stage group has been confirmed by others (136), and an explanation for at least some of the extra time used could be that adjustments of the implant pocket or revisions were often made in the same intervention as expander-to-implant exchange. The observation of more interventions in the one-stage group for aesthetic corrections compared to the two-stage group in this study is in accordance with this. The advantage of completing the BR in a single stage is lost seen from both the patient and the hospital's perspective, if a one-stage BR ultimately requires additional interventions to obtain an aesthetically satisfying result (137, 138). Previous studies have shown conflicting results regarding costs related to the benefits of the two different approaches to perform implant-based BR. A cost-utility analysis published in 2016 concluded that both with and without the cost of ADM included, the one-stage approach remained cost effective and had a psychological benefit compared to the two-stage approach (138). As opposed to this, Negenborn et al. concluded based on an RCT in 2019 that with increased costs and similar health outcomes, the ADM-assisted one-stage BR was not cost-effective relative to two-stage approach (136). The latter study was obviously not included in the recent review assessing cost-effectiveness studies in breast reconstructions (139). The review showed that the one-stage approach was the preferred method, because the costs of an obligate return to the operating room for the two-stage expander-to-implant group exceed the costs due to a higher revision rate because of complications in the one-stage group. Furthermore, the fewer operations resulted in gained quality adjusted life years (QALYs) in the one-stage group.

Despite the above mentioned, a major advantage of the one-stage approach is the avoidance of outpatient visits for expansions. The additional cost for utensils and outpatient clinic time may offset part of the cost of using ADM from the hospital's perspective. For the patient, there is a considerable advantage in avoiding expansions, as many indirect costs as sick leave from job, discomfort, risk for adverse events, and the psychological burden of not having completed the BR yet is associated with this.

Patient reported outcome

Overall, no statistically significant differences were observed between the treatment groups regarding pain, sensory disturbances, physical limitations, health status, QoL, and body image. It could be perceived as a very positive finding that the PRO was equally good regardless of which technique was used for BR. Not all

patients are suitable for one-stage BR due to e.g. vulnerable mastectomy flaps, or in case they desire a larger breast size and thereby opting for the two-stage method for BR.

The literature suggests that women undergoing immediate BR are “protected” from the body image disturbances normally associated with mastectomy (140), as these patients seem to preserve the perception of their body image from a preoperative evaluation to two years postoperatively. The present study unfortunately does not have baseline measurement of BIS, but at both 12- and 24-month follow-up patients in both treatment groups reported a good body image within the range of BIS score 5.6, range 0-30. The reported body image was better than previously reported for immediate unilateral two-stage BR by our institution, with a mean follow-up time at 3.8 years (BIS 16.4, SD 7.3) (55) but comparable with those found 1 year postoperatively for prophylactic mastectomy with BR (141).

The far majority of patients in the two-stage group and all patients in the one-stage group reported a good current overall health at 12- and 24-month follow-up. Results were comparable with other studies reporting very good health states after immediate BR with the techniques used in this study, though other instruments for measurement were used (136, 142). All patients not lost to follow-up due to patient wish or explantation, thought that BR was the right choice for them and would recommend BR to others in the same situation. This finding aligns with other studies with the same study populations (55, 143). But, as the answering patients were those with a successful BR, there is a risk of bias, as the patients were probably more minded to answer in a positive way compared to those with an unsuccessful or complicated BR treatment course.

The ratio of patients reporting improved health status and QoL compared to the time before BR was increasing from 12- to 24-month follow-up, though not significant. This study did not obtain a baseline measurement of health status or QoL, but the design of the two questions may be perceived as a then-test (baseline retrospective measurement) to capture changes in internal standards and adjust for response shift (144). Surviving a potentially life-threatening disease as breast cancer or going through a risk reduction procedure may be reflected in the patient’s assessment of health state and QoL. Thus, the improved QoL and general health may not be ascribed to the breast reconstructive procedure per se. More patients reported improved QoL compared to the time before BR at 24-month follow-up (73% and 53%) than previously reported for immediate BR at our institution with a mean follow-up time at 3.8 years (38.5%) (55).

Though some patients experienced pain and sensory disturbances, the far majority were able to use the arm at the reconstructed side at 24-month follow-up as before surgery, and patients generally experienced very few limitations in performing physical activities. Early mobilization and rehabilitation have been shown to play a significant role in reducing postoperative morbidity of the upper limb (19), and accordingly all patients were offered instruction by physiotherapist and began early mobilization of the upper limb after a standardized instruction. Two patients in the two-stage group underwent axillary dissection which is associated with upper limb morbidity (145), and these patients unfortunately developed lymphedema and were burdened by this in a varying grade.

Previous studies have not shown any association between immediate implant-based BR versus mastectomy alone and the development of chronic breast pain (146, 147). The presently reported frequency of pain located to the breast, arm, or shoulder at the reconstructed side two-years after BR aligns with literature (148).

Strengths and limitations

It strengthens the study that all BR was performed by only three experienced plastic surgeons and four breast oncology surgeons. The surgeons did not participate in the evaluation of outcomes. This was only performed by one independent investigator. The data completeness is high and there was a very small amount of missing values in questionnaire evaluations. Finally, a follow-up period at two years is considered to be appropriate for evaluating endpoints.

External validity may be compromised due to the single-center study design and the small sample size is a major limitation, as large confidence intervals makes it difficult to detect eventual differences between treatment groups. Furthermore, no baseline measurements were obtained for patient reported outcome, which would have been of great interest for longitudinal comparison. Many patients in the two-stage group did only attend 24-month follow-up visit resulting in missing values at 12-month follow-up due to the retrospective enrollment of patients in this treatment group.

It would have been very interesting to have done “intention to treat analysis” and include explanted patients in both the cost analysis and in evaluation by PROMs. These patients are expected to be "costly" both in terms of economics, as a second BR most often will be planned. Furthermore, these patients are supposed to experience decreased satisfaction with result with more pain, decreased ability to perform physical activities, decreased body image, etc.

The fact that putting a monetary value on all cost variables was not achieved is a limitation, as it makes it difficult to draw an unambiguous conclusion. Furthermore, discussions regarding what variables should be included in a cost analysis can always be made, but it would have been advantageous to include the number of outpatient visits in both groups. Finally, it would have been an advantage for comparison to other studies, if a validated questionnaire had been used.

Conclusion

The hypothesis was that BR with the ADM assisted one-stage approach was less costly and superior regarding the patient’s perception of their functional well-being and health status in comparison with the two-stage approach.

This study does not provide unambiguous results concerning costs associated with the two treatment methods. However, considering the equally good results in the two treatment groups regarding PRO and the possibly to avoid outpatient visits for expander fillings, the one-stage approach may be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

Study II

Complications

Overall no significant differences were observed between treatment groups regarding implant loss, implant exchange or major complications. But the risk of minor complications (seroma, cellulitis) were significantly larger in the two-stage group compared to the one-stage group.

Comparing with recent studies, the present study may have a higher incidence of complications. Potter et al. observed 8% implant loss 3 months after immediate implant-based BR with the use of ADM, where the majority (86%) were reconstructed as a one-stage procedure (149). Hillberg et al. reported 10.7% total explantation risk for ADM assisted one-stage BR (150). On the other hand, Dikmans et al. reported a total explantation risk for the one-stage group at 24%, somewhat lower but more comparable to the present findings of 29%. and. Regarding the two-stage group our total explantation risk at 24% was also larger than both Dikmans (4%) and Hillberg (0%).

The risk of major complications in the one-stage group of this study (28% risk of at least one complication) aligns well with results provided by others (45, 151), but for the two-stage group our results (24% risk of at least one complication) stands out as Hillberg et al. and Dikmans et al. reported an incidence of 5%-6% major complications in their two-stage groups. In the present study a significant difference was observed for the risk of at least one minor complication. Other studies find equal rates between the one-stage group and the two-stage group. Additionally, the risk of minor complications in this study (41%) is higher than found by Hillberg et al. (11.1%).

The two-stage group was introduced to a larger risk of adverse events due to the multiple expander fillings and the expander-to-implant exchange, and the observation of complications occurring to a larger degree in the expansion period than after exchange of implant has been reported by others (47). Furthermore, introducing a new surgical technique result in a learning curve, as experience is achieved. It has been suggested that complication rates after BR with ADM may be associated with the learning curve phenomenon (152), and this factor might be of importance in the present study leading to increased complication rates in the immediate BR group.

The results of two studies are awaited with interest. Lohmander et al. conducted an RCT comparing immediate implant-based BR with and without the use of ADM (Strattice). Six months safety data revealed no difference in proportion of implant loss but possibly a higher rate of surgical complications (153). They aimed at investigating the effect of ADM, as they allowed both one- and two-stage approaches in both groups, and their endpoints were the number of unplanned surgical breast procedures after the initial reconstruction, quality of life, aesthetics, and costs. Finally, the Multi Centre Canadian Acellular Dermal Matrix Trial (MCCAT) compares one-stage ADM-assisted and two-stage expander-to-implant reconstruction without ADM in regard to patient satisfaction and QoL, complication rates, aesthetic outcome, and also entails a cost-effectiveness analysis (154). It will be interesting to compare the results of the above-mentioned studies with the BRIOS study published by Negenborn et al. (54, 136, 155).

Aesthetic corrective procedures

To obtain a satisfying aesthetic result, the majority of patients in both treatment groups underwent at least one surgical procedure It was most often autologous fat grafting to the upper medial quadrant, skin reduction or contralateral symmetrization. Autologous fat grafting is considered a low risk intervention and has been shown to improve the cosmetic outcome after implant-based BR and alleviate pain (135, 156).

Aesthetic satisfaction, symmetry and capsular contracture

The opinion of the patients is of utmost importance and in this study satisfaction with the aesthetic result and breast symmetry was obtained from both the patients and the investigator. Furthermore, the response rate was very high in this study.

Overall no differences were observed between groups with regard to any of the outcomes. Both patients and investigator were very satisfied with the aesthetic outcome in both treatment groups. In other studies, the aesthetic result after ADM assisted implant-based BR has been rated significantly higher than BR without ADM (49, 53). These studies examined expander-based BR with and without ADM and furthermore, did not involve the patients in the aesthetic evaluation.

Although breast symmetry is not a major determinant of satisfaction with the BR, it is important (121). Breast asymmetry is a very common phenomenon. The proportions of patients in this study that obtained an acceptable symmetry of 0.5 cm or less difference in suprasternal notch to nipple measurement was in accordance with a normal population opting for BR (124).

In this study no patients developed capsular contracture within two years after BR. Previous studies have confirmed that the development of capsular contracture is progressive over several years (157), but it has also been suggested that in ADM assisted BR this complication develops within two years (51) and that the use of ADM is associated with a decreased capsular contracture rate (49, 50). But a recent review and meta-analysis concluded, that studies including this outcome had severe limitations and thereby the evidence level was low and no unambiguous conclusions could be made (158). In a meta-analysis by Liu et al. (52) from 2020 investigating only ADM assisted implant-based BR the conclusion was drawn, that ADM effectively reduces the incidence of capsular contracture but, like Hallberg et al. states, further high-quality studies are needed to elucidate this subject further (158).

Strengths and limitations

The strengths and limitations mentioned for study I regarding study design does also apply to this study. Please see page 36.

By using a study specific questionnaire, the comparison to other studies becomes more difficult, and for future studies it will be recommended to use a questionnaire validated for the breast reconstructive patient population. Furthermore, for comparison of patient and investigator assessed aesthetic outcome, using the same scale for assessment would have made interpretation simpler. No baseline measurement of satisfaction with breasts and symmetry was obtained. This would have been interesting for longitudinal comparison.

Conclusion

The hypothesis, that ADM assisted one-stage BR resulted in fewer complications and aesthetic corrective procedures could not be confirmed, as the two treatment approaches resulted in an equally risk of implant loss, implant exchange, and major complications. However, the two-stage group had significantly more minor complications compared to the one-stage group. With equally high satisfaction with the aesthetic result in the two treatment groups it is proposed, that the ADM assisted one-stage approach may be feasible and allows the patient to achieve an implant-based breast reconstruction with a minimum of surgeries and outpatient visits.

Study III

Development of bulge or hernia

In the present study the development of bulge and hernia at the abdominal donor-site has been investigated in its broadest sense by applying patient- as well as investigator assessment and in addition CT of the abdominal wall. The observation that more than 50% of patients in both treatment groups report abdominal bulging two years after surgery has, to our knowledge, not been reported by others. This is of concern, as the patient should not be bothered by abdominal discomfort in the exchange of a breast reconstruction. The frequency of bulging and hernia in the synthetic mesh group is comparable with the results by others (64, 71, 159). But the present study could not confirm the results found by Cicilioni et al. that did not report any bulging or hernia, within 10-20 months follow-up, after reinforcement of the abdominal wall with the same ADM product as used in this study (73). Even though there was no statically significant difference between treatment groups, there was a tendency for the ADM group to develop more bulging and herniation compared to the synthetic mesh group. It has previously been shown that the human ADM product Alloderm stretches after implantation and should therefore be inserted under tension (160). This is not thought to be the case in this study, as the two treatment groups experienced the same proportion of paradox bulging at the contralateral side, leading to the conclusion, that the reinforcement material might in some have been tightened too much perioperatively. Using crosslinked porcine ADM for reinforcement was not considered an alternative as these products has been shown to be encapsulated by scar tissue rather than being integrated in the host tissue and possibly lead to more complications (77, 161).

Abdominal muscle strength

In the present study, no significant difference between treatment groups was observed at any timepoints with regard to abdominal muscle strength. Furthermore, no statistically significant difference was observed within the groups comparing baseline measurement with two-year follow-up measurement. It was expected, that the muscle strength would decrease after surgery and then increase as the patient regains strength of the abdominal muscles or use adjacent muscles to compensate. This phenomenon has been shown by others (162), who observed a decrease in abdominal muscle strength, but after one year the

difference was no longer significant. As the patients did not undergo dynamometer testing at four-month follow-up, the present study may have passed the window of opportunity to observe a difference between groups. All patients were able to perform the dynamometer test at both 12- and 24-month follow-up leading to the conclusion, that they could do sit-ups. With the data obtained in this study it was not possible to elucidate whether the measurement of abdominal muscle strength reflect any the difficulties the patients experience in their daily life activities. This would could be a subject for further investigation.

Pain and health-related QoL

In this study no difference was observed between treatment groups regarding tightening sensation across the abdomen or cutting/stabbing/shooting sensations. Thereby the hypothesis that reinforcement using synthetic mesh leads to discomfort or pain due to the rigid properties of the material could not be verified. It was expected to observe a decreasing incidence of these symptoms related to time after surgery, but at two-year follow up more than 40% of patients report abdominal pain and discomfort within the past month. The literature suggests that even after several years 45-50% of patients undergoing BR with the pedicled TRAM flap report tightness in the abdomen (163). This is an occasionally reminder for the patient of the previously reconstructive surgery.

The two treatment groups did not significantly differ in regard to HrQoL measured by Dolotest®. In general, both groups had a low test score (high HrQoL) within the Dolotest® score range (0-800), leading to the conclusion, that both groups were to a large degree able to perform daily activities and continue their social life as before surgery. The synthetic mesh group demonstrated a significantly higher score (decreasing HrQoL) at 24-month follow-up compared to baseline, but this should be taken with some precautions as this group had a lower baseline score compared to the ADM group. Furthermore, several things can affect e.g. social life, mood, and sleeping disturbances besides abdominal pain. The data obtained in this study could not provide a basis for further elucidating this subject.

Strengths and limitations

The blinded and randomized study design strengthens the study. Furthermore, objective evaluation of the endpoints was applied when possible (CT scan, dynamometer) and one independent investigator did register all outcomes. A follow-up period at two years are thought to be appropriate for evaluating endpoints. Finally, a limited number of three experienced surgeons was involved in the breast reconstructive procedure.

The present study did not obtain the planned number of patients. In any case, it would have been an advantage to have an even larger study population. This would result in smaller confidence intervals and the possibility to adjust for factors as BMI, antihormone treatment, etc. The external validity may be compromised as the present study only represent fairly healthy women aiming for breast reconstruction and not patients in general in need for a rectus muscle-based reconstruction. It would have been preferable to use a validated questionnaire as e.g. BREAST-Q to elucidate patient reported outcome, as

satisfaction with abdomen, problems performing daily life activities, and QoL and to be able to compare results to other studies.

Conclusion

The present study did not demonstrate any statistically significant differences between treatment groups regarding risk of bulging or hernia, postoperative abdominal muscle strength, complications, pain, or HrQoL within two years of follow-up. Thereby the hypothesis that reinforcement with porcine non-crosslinked ADM is superior to reinforcement with synthetic mesh cannot be confirmed. Further research into methods for decreasing donor-side morbidity related to the TRAM flap or other rectus abdominis muscle-based flaps is needed. Finally, bulging and herniation seems to develop within the first postoperative year and for future studies aiming to investigate this endpoint 12 months is suggested to be the minimum time of follow-up.

Future aspects

While conducting this PhD study, experience has been obtained useful for future clinical studies. Especially regarding methodological considerations and the importance of solid and high-quality methods, instruments for measuring outcome of interest, and setup for conducting clinical studies have been recognized.

Inspiration regarding setup of a research group and regarding a systematic approach to the development of study design has been found by looking abroad where the UK based implant Breast Reconstruction Evaluation (iBRA) project based on a trainee-led research collaborative setup is very interesting (164). The stepwise investigations and preparations to determine the feasibility of a nationwide RCT investigating implant-based BR seems appropriate and imply pledges to deliver high-quality research concerning this issue. Step three out of four has recently been published discussing some of the barriers for conducting a large scale RCT (165). The next step is a pilot study to determine whether an RCT is possible to conduct. The concept of a National Trainee Research Collaborative is very interesting and may prove effective for delivery of high-quality multi-centre surgical research (166). This setup could also be perceived in Denmark, where it would allow for patients to be included in less time and permit greater generalizability of studies and furthermore stimulate or promote research in the field of plastic surgery.

As research is being conducted, a range of topics always arises that would be interesting to investigate. For instance, studies regarding materials and techniques for performing implant-based BR e.g. the pre-pectoral approach and long-term outcomes associated with this technique. How to minimize the complication rate of implant-based- and autologous BR and investigate whether complications cause delay of adjuvant therapy. If another reinforcement material or technique can minimize the abdominal long-term effects after rectus muscle-based reconstruction, as this technique is still an important part of the plastic surgeon's armamentarium even though the use for breast reconstruction is decreasing. Of special interest are investigations based on PRO data like satisfaction, expectations, body image, and quality of life (QoL) (23, 167, 168) and which factors influence these outcomes. Breast reconstruction is a voluntary option for women undergoing mastectomy and consequently the ultimate endpoint is QoL and an improved aesthetic outcome compared to mastectomy alone. How health care professionals can obtain information from the individual women and capture what is important for her and what expectations she has and compile this information into shared decision-making should be a goal for future research.

It has been hypothesized that complications, in particular infection, following immediate breast reconstruction after breast cancer is associated with increased risk of recurrence (169) even though several studies have not been able to confirm this (28, 170, 171). The literature is controversial, and no causal association has been identified. If an association exist between recurrence of breast cancer and postoperative infection or the extent of the surgical trauma, this would imply a change in how patients aiming for a breast reconstructive procedure will be guided and informed about the possibly consequences

of treatment. This subject would be of utmost interest to investigate but would demand a large cohort of patients undergoing breast reconstruction and prospectively collected data including long time follow-up.

Finally, it would be of great interest to further investigate the proposed protective effect of BR on lymphedema development (172). Such a study will also demand large cohorts prospectively followed for a long time and this emphasizes the urgent need for at national register of breast reconstructive procedures, which could possibly be facilitated by the Danish Breast Cancer Group (DBCG), making future research possible with large amounts of high-quality data.

Summary

The present PhD thesis investigates the potential benefits of ADM use in breast reconstructive procedures.

Study I and II investigates whether ADM assisted one-stage implant-based BR minimizes the risk of complications, costs, and surgical procedures and furthermore, improves the outcome evaluated by PROMs and evaluation of the aesthetic result compared to traditional two-stage expander-to-implant BR. Study results did not provide unambiguous results concerning costs associated with the two treatment methods. However, statistically significant more surgical interventions were performed in the one-stage group to obtain an aesthetical satisfying result. The two treatment groups reported equally good results in PROMs, and evaluation of the aesthetic results and symmetry were also comparable. Furthermore, no statistically significant difference was observed regarding implant loss, implant exchange, and major complications. However, the two-stage group had significantly more minor complications. In conclusion, it is proposed that the ADM assisted one-stage approach may be feasible for selected patients and allow the patients to achieve an implant-based breast reconstruction with a minimum of surgeries and outpatient visits. But the patients should be well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

Study III investigates whether the use of ADM for reinforcement of the abdominal donor-site after BR with the pedicled TRAM flap result in less bulging or herniation and decreased abdominal pain and discomfort compared to reinforcement with synthetic mesh. The study did not demonstrate any statistically significant differences between treatment groups regarding the risk of bulging or hernia, postoperative abdominal muscle strength, complications, pain, or HrQoL within two years of follow-up. In conclusion, the proposed advantages of ADM use for reinforcement of the abdominal donor-site could not be confirmed.

Further research, in a larger setting preferably including multiple centers and if possibly the RCT study design, is needed to further investigate the role of ADM in breast reconstructive procedures.

Dansk resumé

Denne PhD afhandling omhandler undersøgelser af potentielle fordele ved brug af ADM i brystrekonstruktive procedurer.

Studie I og II undersøgte hvorvidt et-stadie BR med brug af ADM minimerer risikoen for komplikationer, nedbringer omkostninger og antal af kirurgiske indgreb og der foruden forbedrer resultatet vedrørende patient rapporterede effektmål og tilfredshed med det æstetiske resultat sammenlignet med den traditionelle to-stadie expander-til-implantat BR. Resultaterne var ikke entydige vedrørende omkostninger forbundet med de to behandlingsmetoder. Imidlertid blev der udført statistisk signifikante flere kirurgiske indgreb i en-trins-gruppen for at opnå et æstetisk tilfredsstillende resultat. De to behandlingsgrupper rapporterede lige høje og gode resultater med hensyn til patient rapporterede effektmål, tilfredshed med BR og symmetri. Derudover blev der ikke observeret nogen statistisk signifikant forskel med hensyn til implantattab, udskiftning af implantat og større komplikationer, der krævede kirurgisk intervention. Patienter behandlet med to-stadie teknikken havde imidlertid signifikant flere mindre komplikationer, der dog ikke krævede kirurgisk intervention. Samlet set foreslås det, at et-stadie BR med brug af ADM kan være en mulighed for selekterede patienter og dermed give disse patienter mulighed for at opnå en implantatbaseret brystrekonstruktion med et minimum af operationer og ambulante behandlinger. Dog skal patienterne informeres om det potentielle behov for yderligere indgreb for at opnå et æstetisk tilfredsstillende resultat.

Studie III undersøgte om brugen af ADM til forstærkning af det abdominale donorsted efter BR med den stilkede TRAM lap resulterer i færre tilfælde af udbuling eller brok samt færre smerter og mindre ubehag sammenlignet med forstærkning af det abdominale donorsted med syntetisk net. Studiet påviste ikke nogen statistisk signifikante forskelle mellem behandlingsgrupperne med hensyn til risikoen for udbuling eller brok, postoperativ mavemuskel-styrke, komplikationer, smerter eller sundhedsrelateret livskvalitet inden for to år efter operationen. Således kunne de foreslåede fordele ved at anvende ADM til forstærkning af det abdominale donorsted efter brystrekonstruktion med den stilkede TRAM lap ikke bekræftes.

Yderligere forskning, i et større forskningsprojekt gerne med flere behandlingscentre og evt. ved brug af RCT studiedesign er nødvendig for yderligere at belyse den rolle ADM spiller i brystrekonstruktive procedurer.

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Appendix – overview

Manuscript I

Cost and Patient Reported Outcome Measures in immediate implant-based breast reconstruction. A cohort study using one- versus two-stage technique.

Supplementary material manuscript I

Co-authorship declaration

Manuscript II

Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study.

Co-authorship declaration

Manuscript III

Reinforcement of the abdominal wall with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.

Supplementary material manuscript III

Co-authorship declaration

Manuscript I

One- versus two-stage immediate implant-based breast reconstruction. A cohort study on cost and patient reported outcome measures.

One- versus two-stage immediate implant-based breast reconstruction. A cohort study on cost and patient reported outcome measures.

Mette Eline Brunbjerg, MD[1,3], Thomas Bo Jensen, MD, PhD[1], Jens Overgaard, MD, DMSc Professor[2], Peer Christiansen, MD, DMSc, Professor[1], Tine Engberg Damsgaard, MD, PhD, MRBS, Professor[3]

1 Department of Plastic and Breast Surgery, Aarhus University Hospital
2 Department of Experimental Clinical Oncology, Aarhus University Hospital
3 Department of Clinical Medicine, Aarhus University

Corresponding author:
Mette Eline Brunbjerg, MD
Department of Plastic and Breast Surgery
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
DK - 8200 Aarhus N.
Denmark
Telephone number: +45 60601470
E-mail: metteeline.brunbjerg@gmail.com

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Ethical statement
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The trial was conducted in accordance with the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Ethics Committee of the Central Region of Denmark (1-10-72-572-12) and informed consent was taken from all the patients.

Conflicts of Interest
MB reports grants from The Danish Cancer Society, grants from The Korning foundation, grants from Foundation of the Kjaersgaard Family, Sunds, grants from King Christian X foundation, grants from Foundation of Architect Holger Hjortenberg, grants and non-financial support from LifeCell Corporation (Branchburg, NJ, USA), during the conduct of the study. The other authors have no conflicts of interest to declare.

Abstract

Background

An increasingly number of breast reconstructive procedures is being performed leading to an awareness of improving the psychosocial and functional result and reduce costs associated with these procedures. One-stage implant-based breast reconstruction with acellular dermal matrix has potential advantages for the patient, but literature shows conflicting results regarding the cost-effectiveness of this approach compared to the two-stage expander-to-implant method. The patient's subjective assessment of the physical and psychosocial effects of breast reconstruction is extremely important. Therefore, the aim of the present study was to compare immediate implant-based BR using the one-stage approach with the two-stage expander-to-implant approach in a cost analysis and with regard to patient reported outcome measures.

Methods

The study was designed as an observational cohort study with 44 participants admitted for immediate implant-based breast reconstruction at Department of Plastic Surgery, Aarhus University Hospital, Denmark. 21 patients underwent breast reconstruction with a one-stage direct-to-implant technique using acellular dermal matrix and 23 patients underwent breast reconstruction with a two-stage expander-to-implant technique. Follow-up visits were planned 12 and 24 months after insertion of silicone implant. Follow-up time was 2 years.

Results:

Overall in favor of the one-stage group was a shorter duration of surgery and furthermore, the reduced need for outpatient visits (for in average 6 times of expansion) as well as for additional surgery for implant exchange. In favor of the two-stage approach was reduced cost of materials and fewer interventions to address the aesthetic outcome. Pain, sensory disturbances, physical limitations, health status, quality of life and body image were equally favorable between the two groups at two-year follow-up.

Conclusion

This study does not provide clear evidence for the cost-effectiveness of one method versus the other and further studies should be undertaken to investigate the cost-effectiveness of one-stage breast reconstruction with acellular dermal matrix or with synthetic meshes in comparison with the two-stage approach. Considering the equally good results in the two treatment groups regarding patient reported outcome measures the one-stage approach should be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

Introduction

Breast reconstructive techniques is constantly evolving aiming to offer the patients an aesthetically pleasing result and minimize short- and long-term complications. The overall goal is to relieve the psychosocial consequences following breast oncologic surgery and thereby contribute to improved quality of life (QoL). The trend goes towards an increasing rate of breast reconstructive procedures being performed in a younger population (1, 2) and this leads to an awareness of improving the psychosocial and functional result and reduce costs. The introduction of acellular dermal matrix (ADM) to obtain a one-stage immediate breast reconstruction (BR) (3, 4) gave the possibility to provide the patients with a breast reconstructive trajectory with a minimum of discomfort and outpatient visits and an excellent aesthetic result. Potentially, it could be cost effective, though ADM is expensive, due to the possibility of reducing expenses because of less operations and hospitalization days compared to the traditional two-stage expander-implant technique. The literature regarding this subject shows conflicting results. Some suggest that the use of ADM for immediate BR is cost advantageous compared with the two-stage approach and furthermore, that the use of ADM has clinical benefit for patients by allowing a one-stage procedure rather than two separate operations and results in fewer outpatient visits (5, 6). Another study has reported that the direct costs of one-stage implant-based BR with ADM were higher than those of two-stage BR, and that health outcomes did not differ between the groups (7)

The patient's subjective assessment of the aesthetic outcome and the physical and psychosocial effects of BR is extremely important as the overall objective by offering BR is to improve the patients QoL. Therefore, the aim of the present study was to compare immediate implant-based BR using the one-stage approach with ADM with the two-stage expander-to-implant approach regarding costs and patient reported outcome measures (PROMs).

We present the following article in accordance with the STROBE reporting checklist.

Materials and methods

Study design and participants

The present study was designed as an observational cohort study with 44 participants. Eligible patients were all women admitted for immediate, implant-based BR following skin-sparing mastectomy at the Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark over a period of 40 months. Patients were diagnosed with either breast cancer, ductal carcinoma in situ (DCIS) or were considered high risk for developing breast cancer. Inclusion criteria were mastectomy weight ≤ 600 g, patient older than 18 years, tobacco abstinence > 4 weeks prior to surgery, ability to complete the study questionnaire, and for the two-stage group; time to achieve two-year follow-up visit after BR. Follow-up visits were planned 12 and 24 months after insertion of silicone implant where patients completed a study-specific questionnaire regarding PROMs. Furthermore, a systematic review of patient records was performed to obtain information for cost analysis. Follow-up time was 24 months.

All participants gave written informed consent. The Ethics Committee of the Central Region of Denmark (1-10-72-572-12) approved this study and it was submitted in ClinicalTrials.gov (NCT04209010).

Recruitment

As the one-stage approach was implemented as a standard care for immediate implant-based BR following skin-sparing mastectomy, in December 2012, all eligible patients were offered participation in the one-stage group and inclusion continued consecutively until 21 patients were included. The two-stage cohort was established retrospectively. Patients that had undergone immediate implant-based BR following skin-sparing mastectomy with the two-stage expander-to-implant technique were identified using diagnosis- and procedure-related codes, records were examined and patients that fulfilled the inclusion criteria were identified and consecutively offered participation in the two-stage group. Inclusion continued retrospectively until 23 patients were included (see Supplementary material 1.1 "Timeline of study recruitment", page 79). The same study population has been used for the publication entitled "Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study" (manuscript submitted) where the outcome was postoperative complications, aesthetic correction procedures and aesthetic outcome.

Study size

Study size was determined upon power calculation on the primary endpoint "reduction in surgery time" as the duration of surgery was considered to have a significant impact on overall costs. Duration of surgery time for bilateral BR with the two-stage technique was, based on own experience, estimated to 300 minutes. The minimum relevant difference the study was aiming to achieve was 60 minutes reduction in surgery time using the one-stage technique (8). With a significance level at 5% and power on 80% it was calculated that 16 patients were needed in each treatment group. Originally 20 patients were planned in each group, but late secondary review of patients revealed, that one patient had been excluded by mistake from the one-stage group due to conversion to expander-based BR because of vulnerable mastectomy flaps and another three patients were excluded due to removal of implant before inclusion started in the two-stage group. Allocating these patients to their correct study group resulted in 21 patients in the one-stage group and 23 patients in the two-stage group.

Surgical techniques

In all cases the implant or expander was placed in a subpectoral plane.

The surgical technique for one-stage immediate BR using porcine acellular dermal matrix (Strattice™, LifeCell Corporation, Branchburg, NJ, USA) and fixed size silicone implant was as follows. Upon skin sparing mastectomy the pectoralis major muscle was elevated from the chest wall, the inferomedial attachment was divided, and an inflatable sizer used to determine the size of the implant taking the viability of mastectomy skin flaps into consideration. ADM was sutured to the inframammary fold at the chest wall. The fixed sized anatomical implant was inserted, and the cranial edge of the ADM was sutured to the caudal border of the pectoralis major muscle. Two suction drains were placed, draining the submuscular and subcutaneous pockets.

The surgical procedure for two-stage immediate BR using temporary expander implant and later exchange to fixed size silicone implant was as follows. After the skin sparing mastectomy, a submuscular pocket was created by elevating the pectoralis major muscle, the serratus anterior muscle or its fascia, and

the anterior rectus sheath. The latter in connection with the pectoralis major muscle. An inflatable sizer was used to estimate the expansion volume. Suction drains were placed, draining the submuscular and subcutaneous pockets and the expander was placed in the submuscular pocket. The first expansion was performed two weeks postoperatively and after that at weekly intervals, should no complications arise. Three to six months after the final expansion volume had been achieved the expander was changed to a fixed sized implant. The mastectomy scar was excised, the submuscular pocket was opened parallel to the muscle fibres of the pectoralis major muscle, the expander was removed and the necessary adjustments of the pocket were performed. An adjustable sizer was used to determine the size and the shape and dimensions of the pocket and the final size silicone implant was placed. One suction drain was used when deemed necessary. All patients received one prophylactic dose of antibiotic (Cefuroxim or Dicloxacillin) preoperatively and the one-stage group continued Cefuroxim for three days postoperatively. Drains were removed when output was less than 20 ml for two consecutive days.

Outcomes

The primary endpoint of the study was cost reported for bilateral and unilateral breast reconstructions in the two treatment arms. It was not possible to assign a monetary value on all variables, but the assumption was made that if e.g. number of interventions were higher in one group compared to the other, this would lead to increased costs. The following variables were included: 1) Cost of silicone implants, sizers, expanders and sheets of ADM (Strattice™ pliable 8x16 cm) in €. 2) Duration of the breast reconstructive procedure in minutes. In case of unilateral BR with contralateral breast surgery in the same intervention, the duration of the breast reconstructive procedure was estimated by a senior consultant (TD). 3) Number of outpatient visits for expansions in patients who underwent a two-stage procedure. 4) Number of interventions to address seroma. 5) Number of surgical interventions to address complications. In case several procedures were done during the same surgery it only counted for one intervention. 6) Number of surgical interventions to address aesthetic outcome. In case of unilateral BR with contralateral breast surgery at the same time as the breast reconstructive procedure, the contralateral procedure counted for one aesthetic intervention. 7) Duration of hospitalization in days and estimated costs in € and 8) duration of sick leave reported by patients (counted as days before work was resumed). These data were obtained for a two-year period after insertion of the final-size silicone implant. All second stage surgeries for the two-stage group were completed.

Secondary endpoints were PROMs including Hopwoods Body Image Scale (BIS) and a study specific questionnaire.

Body image was evaluated using Hopwoods BIS (9) at 12- and 24-months follow-up. The scale is validated for use in breast cancer patients and consists of 10 items answered with reference to the past week. The scale has high reliability, good clinical validity, and is sensitive to changes. Items include evaluation of femininity, self-consciousness, physical and sexual attractiveness, and satisfaction with body and scars. Each question has four options for rating body image: “not at all”(score 0), “a little” (score 1), “quite a bit” (score 2) and “very much” (score 3). The 10 item scores were summed to produce an overall

score for each patient, ranging from 0 to 30, with 0 representing no symptom/distress and higher scores representing increasing symptoms/distress (see Supplementary material 1.2, page 79).

Furthermore, the patients fulfilled a study specific questionnaire regarding health status, QoL, pain, sensory disturbance and functional sequalae at 12- and 24-month follow-up consisting of items answered at breast level and at patient level. Some of the questions were answered on a scale and were dichotomized prior to analysis as elaborated in the description of questions found in Supplementary material 1.3, page 80.

Bias

The funders (financial or the acellular dermal matrix supplier) did not participate in study design, data collection, data analysis, or interpretation and writing of the manuscript.

Statistical analysis

Descriptive statistics were used for patients' demographics with mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test.

For the cost analysis part, simple linear regression models were used and uni- and bilateral BR were compared separately between the treatment groups. BIS was analyzed using a mixed regression model due to repeated measurements using patient ID as random effect. Due to the small sample size, the Kenward Roger approximation method was used to calculate the degrees of freedom. The regression model assumptions were checked by visual inspection of the diagnostics plots such as QQ plot for the residuals and the scatter plot of residuals and the fitted values. If necessary, a log-transformed outcome was modelled.

PROMs reported at patient level with dichotomized outcomes were analyzed using generalized linear models with log-link function adjusting for repeated measurements by using patient ID as cluster. Regarding health-related limitation of activities the sum score was analyzed using a mixed model, adjusting for the repeated measurements and small sample size as described above.

The original outcomes of PROMs reported at breast level had flooring effect (except the question: Do you feel burdened by sensory disturbances in the area where you were operated?) i.e. many of the answers were "no pain" or similar to that. Therefore, all the outcomes were dichotomized as "no pain" or "yes, pain" (or similar). PROMs reported at breast level with binary outcome were analyzed using a generalized linear model with log-link function. By keeping the smaller sample size in mind, especially those with bilateral surgery, the two breasts were assumed to be coming from two different patients. Therefore, a new ID variable was created at the breast level, assuming that every breast reconstruction is from one individual, and used as clusters in the model to adjust for the repeated measurements.

The patient (in case of unilateral BR or bilateral BR with bilateral explantation) or the breast (in case of bilateral BR with unilateral explantation) was categorized as lost to follow-up if explantation occurred. Therefore, some patients did not have the opportunity to answer the questionnaire at follow-up visits and were thereby not randomly missing. This was the case for five patients (nine breasts) in the one-stage group and four patients (seven breasts) in the two-stage group (Figure 1).

Statistical analyses were performed using STATA® software IC16.1 (Stata Corporation, College Station, TX). Strobe guidelines for reporting observational cohort study were used.

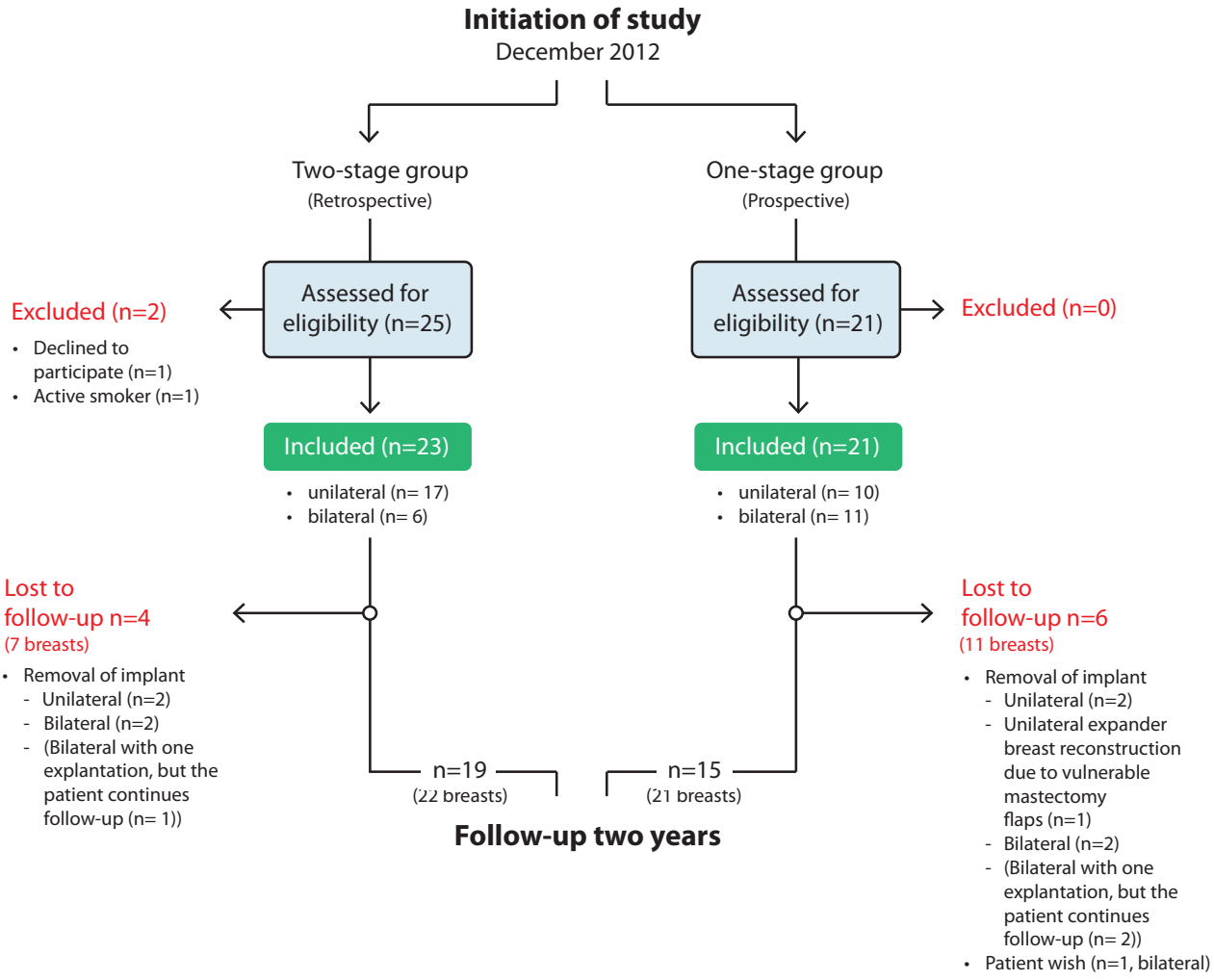

Figure 1. Flow chart of the study participants.

Results

44 patients were included in the study, 21 patients (32 breasts) in the one-stage group and 23 patients (29 breasts) in the two-stage group. 15 patients (21 breasts) in the one-stage group and 19 patients (22 breasts) in the two-stage group completed 24-months follow-up (Figure 1). The two groups did not differ significantly regarding demographics and clinical characteristics as summarized in Table 1.

Table 1. Baseline demographics and clinical characteristics.

	One-stage, Patient n=21	**Two-stage, Patient n=23**
Age (years), mean (SD)	48.3 (10.7)	42.7 (9.9)
BMI (kg/m$^{2)}$, mean (SD) †	23.1 (2.8)	24.7 (3.8)
Comorbidity †	7	3
Laterality of procedure		
Bilateral	11	6
Unilateral	10	17
Adjuvant therapy after surgery †		
Endocrine treatment	5	1
None	15	19
Axillary surgery †		
None	13	13
Sentinel node biopsy	7	5
Axillary dissection ‡	0	2
Indication for mastectomy †		
Cancer	3	0
DCIS	5	6
Prophylactic	14	14

BMI, body mass index; DCIS, ductal carcinoma in situ.

† Missing values one-stage group n=1, two-stage group n=3.

‡ Two patients in the two-stage group were diagnosed with DCIS but underwent axillary dissection due to micrometastasis in sentinel nodes.

Materials for a one-stage BR (silicone implant, Strattice™, sizer) was 2.6 times more expensive than materials for a two-stage BR (expander, silicone implant, sizer x 2) with a 1795 € difference in costs for a unilateral procedure (Table 2).

The one-stage procedure took longer time than the first operation for the two-stage procedure for both unilateral and bilateral cases. But when the duration of procedures in the two-stage group were summed, the overall surgery time of a unilateral two-stage procedure was 34% longer than a one-stage procedure (p=0.006). For the bilateral groups the overall two-stage procedure took 10% longer (p=0.348) time than the one-stage procedure.

Patients undergoing BR with the two-stage method underwent in average 6.3 (unilateral) and 5.9 (bilateral) expansions. There was no statistically significant difference in mean number of interventions to address seroma between the two treatment groups.

For the variable “surgical interventions to address complications” a flooring effect was observed. For the unilateral one-stage group seven of nine patients (78%) and 13 of 17 patients (76%) in the two-stage group did not undergo any surgeries due to complications. For the bilateral groups, six of 11 patients (55%) and four of six patients (67%) did not undergo any surgeries due to complications, respectively. By calculating mean number of interventions to address complications there were no significant difference between the two treatment groups for either unilateral BR nor bilateral BR.

Twelve of 15 patients (80%) (2 missing) in the unilateral two-stage group did not undergo further surgical procedures to address aesthetic outcome. With comparison to the one-stage group, where all 7 patients (100%) (3 missing) underwent at least one procedure to address aesthetic outcome, there was a statistically significant difference when comparing the means ($p<0.0001$). In the bilateral groups there was no significant difference between the mean number of interventions to address aesthetic outcome ($p=0.791$). By assuming that an intervention entails an expense the significant difference between the unilateral groups leads to the assumption that there are more expenses in the one-stage group.

Duration of overall hospital stay was the same for the two unilateral treatment groups (10 days) but two days longer for the bilateral one-stage patients (12 days) compared to the two-stage patients (10 days). There was no significant difference in self-reported sick leave between treatment arms.

Table 2. Costs reported per patient for unilateral and bilateral breast reconstructions.

	Unilateral				**Bilateral**			
	One-stage n=10	**Two-stage n=17**	**Comparison**	**p**	**One-stage n=11**	**Two-stage n=6**	**Comparison**	**p**
Total cost of materials (€) †	2.935	1.140			5.870	2.280		
Duration of operation (min) ‡								
First operation	136 (116 – 160)	95 (80 – 113)			225 (200 – 253)	151 (112 – 205)		
Second operation		83 (67 – 103)				93 (64 – 135)		
Overall	136 (116 – 160) M=1	183 (162 – 207) M=2	1.34 (1.10 – 1.65)	0.006*	225 (200 – 253)	247 (207 – 295) M=1	1.10 (0.89 – 1.36)	NS
Expansions §		6.3 (5.2 – 7.3) (range 3 – 11) M=2				5.9 (4.1 – 7.7) (range 4 – 8.5) M=1		
Interventions to address seroma §	0.11 (-0.28 – 0.51) M=1	0.24 (-0.05 – 0.52)	0.12 (-0.37 – 0.61)	NS	0 (-0.15 – 0.15)	0.17 (-0.04 – 0.37)	0.17 (-0.09 – 0.42)	NS
Surgical interventions to address complications §	0.56 (-0.002 – 1.11) M=1	0.29 (-0.11 – 0.7)	-0.26 (-0.95 – 0.43)	NS	1 (0.20 – 1.8)	0.5 (-0.59 – 1.59)	-0.5 (-1.85 – 0.85)	NS
Surgical interventions to address aesthetic outcome §	1.57 (1.05 – 2.09) M=3	0.27 (-0.09 – 0.62) M=2	-1.3 (-1.93 – 0.68)	<0.0001*	0.88 (0.28 – 1.47) M=3	0.75 (-0.09 – 1.59) M=2	-0.13 (-1.15 – 0.9)	NS
Duration of hospital stay (days) §								
First operation	10.4 (9.2 – 11.7)	6.9 (6.2 – 7.7)			12.1 (10.4 – 13.8)	7 (5.7 – 8.3)		
Second operation		3.2 (2.7 – 3.7)				2.6 (1.7 – 3.5)		
Overall	10.4 (9.2 – 11.7) M=1	10.1 (9.2 – 11.1) M=2	-0.3 (-1.9 – 1.3)	NS	12.1 (10.4 – 13.8)	9.6 (7 – 12.2) M=1	-2.5 (-5.6 – 0.6)	NS
Total cost for hospitalization, 470 € per day §	4909 (4330 – 5488) M=1	4763 (4314 – 5211) M=2	-146 (-879 – 587)	NS	5683 (4870 – 6495)	4512 (3306 – 5718) M=1	-1171 (-2625 – 283)	NS
Sick leave (days) §	40.5 (9.2 – 71.8) M=6	42.3 (23.4 – 61.2) M=6	1.8 (-34.8 – 38.3)	NS	62.6 (39.8 – 85.4) M=3	59.5 (13.9 – 105.1) M=4	-3.1 (-54.1 – 47.8)	NS

M=n indicates missing data=number, NS, not significant.

** statistically significant p value*

† one-stage group (silicone implant, Strattice™, sizer), two-stage group (expander, silicone implant, sizer x 2).

‡ Median (95% CI). Comparison with ratio of medians (95% CI, p) with reference to the one-stage group.

§ Mean (95% CI). Comparison with mean difference (95% CI, p) with reference to the one-stage group.

Regarding pain located to the operation field there was no significant difference between groups at 24-month follow-up (RR 1.67, p=0.354) (table 3). Nor was there any significant difference within the groups between 12- and 24- months follow-up. Patients were in general mildly burdened by sensory disturbances in the operation field as the means for the outcome (where the outcome is scaled from 1=minimum burden to 5=extreme burden) at 24 months were 1.52 (SD 1.12) and 1.33 (SD 1.09) for one- and two-stage group, respectively. There was no statistically significant difference between groups at 24-month follow-up (RR= 0.90, 95% CI 0.68 - 1.20, p= 0.482) or within groups between 12- and 24- months follow-up. Considering patient reported pain in the arm or shoulder on the operated side no statistically significant differences were observed within the groups between 12- and 24-month follow-up in either of the treatment groups. Even though more pain in the arm or shoulder was reported at 24-months follow-up in the two-stage group (32%) this was not statistically significant different from the one-stage group (14%, p=0.201). Regarding sensory disturbances in the arm or shoulder on the operated side there was no statistically significant difference reported within the groups between 12- and 24-month follow-up in either of the treatment groups or between groups at 24-month follow-up (RR 1.33, p=0.566).

One patient in the one-stage group reported lymphedema at 12-month follow-up and two patients in the two-stage group at 24-month follow-up. Both patients in the two-stage group underwent axillary dissection before unilateral BR.

All in the one-stage group (of 21 reported) and 82% (of 22 reported) in the two-stage group was able to use the arm on the operated side as before surgery at 24-month follow-up.

Table 3. PROMs reported at breast level. Pain, sensation disturbance, lymphoedema and arm function.

	One-stage N=32 †		**Two-stage N=29 †**		**RR**	**P**
Follow-up, months	12	24	12	24		
Have you felt pain in the area where you were operated? Yes ¶	6 (29%; 14% – 57%)	4 (19%; 8% – 47%)	2 (25%; 7 % – 84%)	7 (32%; 17% – 59%)	1.67 (0.56 – 4.94)	NS
Do you feel burdened by sensory disturbances in the area where you were operated? Yes ¶ Mean (SD)	18 (86%; 72% – 102%) 1.38 (0.97)	18 (86%; 72% – 102%) 1.52 (1.12)	4 (50%; 25% – 101%) 1.50 (1.85)	17 (77%; 61% – 97%) 1.33 (1.09)	0.90 (0.68 – 1.20)	NS
Have you felt pain in the arm or shoulder on the operated side? Yes ¶	3 (15%; 5% – 43%) M=12	3 (14%; 5% – 41%)	2 (25%; 7% – 84%)	7 (32%; 17% – 59%)	2.2 (0.65 – 7.60)	NS
Do you feel burdened by sensory disturbances in the arm or shoulder on the operated side? Yes ¶	3 (15%; 5% – 43%) M=12	5 (24%; 11% – 52%)	4 (57%; 30% – 109%)	7 (32%; 17% – 59%)	1.33 (0.50 – 3.60)	NS
Do you suffer from lymphedema in the arm or hand on the operated side? Yes (n)	1	0	0	2		
Are you able to use the arm on the operated side as before surgery? Yes ¶	15 (71%; 54% – 94%)	21	7 M=22	18 (82%; 67% – 100%)		

NS, not significant.

† Missing values one-stage group: n=11 at 12- and 24- months follow-up. Two-stage group: n=21 at 12-month follow-up and n=7 at 24-month follow-up. Exception from this is M=n that indicates missing data=number.

¶ N (proportion in %; 95% CI) and risk ratio (95% CI, p) for comparison of groups at 24-month follow-up with the one-stage group as reference.

Body image improved (BIS score reduction) in the one-stage group from 12 months (6.9) to 24 months follow-up (5.6), although this was not significant (difference -1.3 points; 95% CI -3.2 - 0.5, p=0.144) (table 4). In the two-stage group the mean BIS score was 5.6 at both 12- and 24- month follow-up with no significant difference (p=0.9888). Thereby, the reduction in mean BIS score from 12-months to 24-months follow-up were not statistically significant between the groups (p=0.446).

All patients were to a large degree unlimited in their ability to perform physical activities. In both treatment groups a mean score >8 (range 0-10) at 12- and 24 months follow-up. There was no statistically significant difference between groups at 24-months follow-up (p= 0.366).

Furthermore, all patients in the one-stage group and the far majority of patients in the two-stage group (83% and 95%) reported a good current overall health at 12 and 24-months follow-up. An increasing proportion of patients in both treatment groups report a better overall health status compared to the time of BR related to increasing time after surgery. The proportion of patients who report improved health was 27% (CI 0.56 – 2.85) larger in the one-stage group compared to the two-stage group at 24-month follow-up (p=0.568).

All patients, except for one patient in the one-stage group at 12-months follow-up, thought that BR was the right choice for them and at 24-month follow-up all patients would recommend others in the same situation to undergo BR.

An increasing number of patients in both treatment groups experienced an improved QoL from 12 to 24 months postoperatively, though not statistically significant. 53% of the patients in the two-stage group reported improved QoL at 24-months follow-up compared to 73% in the one-stage group (RR 0.7, p=0.222).

The use of painkillers was reduced from 13% at 12-months follow-up to 7% at 24-months follow-up in the one-stage group but increased from 33% to 37% in the two-stage group. These changes within the groups were not statistically significant. More patients in the two-stage group had used painkillers within the past month compared to patients in the one-stage group at 24-month follow-up, though not statistically significant (RR 5.5, p=0.096). At 24-month follow-up 20% in the one-stage group and 28% in the two-stage group report pain in other parts of the body than the operated area within the past month (p=0.614).

Table 4. PROMs reported at patient level.

	One-stage N=21 †		**Two-stage N=23 †**		**Comparison w.r.t. one-stage group**	**P**
Follow-up, months	12	24	12	24		
BIS § ‡	6.9 (4.1 – 9.7)	5.6 (2.8 – 8.4)	5.6 (2.3 – 8.9)	5.6 (3.1 – 8)	-0.01 (3.88 – 3.85)	NS
Health related limitation of activities + §	8.8 (7.9 – 9.7)	8.9 (8 – 9.8)	8.8 (7.8 – 9.9)	8.4 (7.5 – 9.1)	-0.5 (-1.75 – 0.66)	NS
How is your current overall health status? Good ¶	15	15	5 (83%; 58 – 120%)	18 (95%; 85% – 106%)		
How is your current overall health status compared to the time of BR? Improved ¶	5 (33%; 16% – 69%)	7 (47%; 27% – 81%)	1 (17%; 3% – 102%)	7 (37%; 20.% – 67%)	0.8 (0.4 – 1.8)	NS
Was breast reconstruction the right choice for you? Yes (n)	14	15	6	19		
With your current experience, would you recommend others to undergo breast reconstruction? Yes (n)	15	15	5	19		
How would you describe your current quality of life compared to the time before your breast reconstruction? Improved ¶	9 (60%; 40% – 91%)	11 (73%; 54% – 100%)	2 (33%; 11% – 105%)	10 (53%; 34 – 81%)	0.7 (0.4 – 1.2)	NS
Have you been taking painkillers within the past month? Yes ¶	2 (13%; 4% – 49%)	1 (7%; 1% – 46%)	2 (33%; 11% – 105%)	7 (37%; 20% – 67%)	5.5 (0.7 – 41.3)	NS
Pain elsewhere in the body? Yes ¶	4 (27%; 11% – 63%)	3 (20%; 7% – 56%)	0	5 (28%; 13% – 59%) M=5	1.39 (0.39 – 4.98)	NS

W.r.t., with reference to. NS, not significant. N, number.

† Missing values one-stage group: n=6 at 12- and 24- months follow-up. Two-stage group: n=17 at 12-month follow-up and n=4 at 24-month follow-up. Exception from this is M=n that indicates missing data=number.

‡ Body Image Scale range 0-30. 0 representing no symptom/distress and higher scores representing increasing symptoms/distress.

§ Mean (95% CI) and mean difference (95% CI, p) for comparison of groups at 24-month follow-up with reference to the one-stage group.

¶ N (proportion in %; 95% CI) and risk ratio (95% CI, p) for comparison of groups at 24-month follow-up with reference to the one-stage group.

+ Health related limitation of activities, range 0-10, higher scores representing more activities the patient can perform without any health-related limitations.

Discussion

The objective of this study was to compare two methods for immediate implant-based breast reconstruction in a cost analysis and furthermore, discuss the result in conjunction with the patient's subjective report of psychosocial and physical outcome measures. Overall in favor of the one-stage group was a shorter duration of surgery and furthermore, the reduced need for outpatient visits (for in average 6 times of expansion) as well as an additional surgery for implant exchange. In favor of the two-stage approach was reduced cost of materials due to the use of ADM in the one-stage group and fewer interventions to address the aesthetic outcome. However, pain, sensory disturbances, physical limitations, health status, QoL and body image were equally favorable between the two groups at two-year follow-up.

Sample size of this study was determined upon an expected decrease in duration of surgery on 60 minutes when using the one-stage approach. However, the reduction was 47 minutes in the unilateral group and 22 minutes in the bilateral group.

Healthcare cost can be calculated from different viewpoints including using reimbursement tariffs based on Diagnosis Related Groups (DRGs) using average costing. This may not reflect the actual costing as shown by others (5, 10) and in this publication the original variables as surgery time, number of additional surgeries and cost of materials were used. Several methods for calculating health care cost exist. A simple cost analysis is presented and result discussed from the patient and the hospital's point of view as the available data in this study did not allow for a cost benefit- or a cost-utility analysis.

Duration of surgery for the breast reconstructive procedure was longer in the two-stage group compared to the one-stage group (significant in the unilateral comparison) as found by others (7). During surgery for tissue expander–to-implant exchange adjustments such as implant pocket adjustments or revision of the inframammary fold, were often made and this could account for at least some of the extra time spent on surgery used in the two-stage group. This corresponds to the observation of more interventions for aesthetic corrections in the one-stage group compared to the two-stage group (significant in the unilateral comparison). If a one-stage BR ultimately requires additional interventions to obtain an aesthetically satisfying result, the advantage of completing the BR in a single stage is lost seen from both the patient and the hospital's perspective. This paradox has also been noted by others (10, 11). A major advantage of the one-stage approach is the possibility to avoid outpatient visits for expansion and the additional cost for outpatient clinic time and utensils may offset part of the cost of using ADM from the hospital's perspective. For the patient there is a huge advantage in avoiding expansions as there are also many indirect costs as sick leave from job, discomfort, risk for adverse events, and the psychological burden of not having completed the BR yet. In this study, no difference in hospitalization or sick leave was observed between the two treatment groups. Others report shorter length of stay at the hospital (5, 7, 12) and this may have changed to a shorter hospitalization period at our institution since this study was conducted.

It was expected that some patients would report pain located to the breast, arm, or shoulder at the reconstructed side two-years after BR. In the present study, the one-stage group reported less pain (19% and 14%) than the two-stage group (32% and 32%), although not significantly different. It has previously been shown that up to 20% of patients report persistent pain after breast cancer treatment (PPBCT)

located to the mastectomy scar or area of the missing breast (13). It has been suggested that BR increases the risk of chronic pain, but Klit et al. found no increased risk of persistent pain in patients having a reconstruction with an implant compared with mastectomy alone (odds ratio 0.82, p=0.33) (14). A recent meta-analysis confirmed this observation as there was no significant difference between the mean prevalence of surgically related chronic pain after mastectomy alone (35.6%) or after flap or implant-based BR (32.8%; p = 0.88) (15). In the present study most of the patients in both treatment groups felt burdened (although mildly burdened) by sensory disturbance located to the field of surgery and fewer felt burdened of sensory disturbances located to the arm or shoulder on the operated side. Despite pain and sensory disturbances, all patients in the one-stage group were able to use the arm at 24-month follow-up as before surgery compared to 82% in the two-stage group. None of the patients in the one-stage group, but two patients in the two-stage group underwent axillary dissection which is associated with upper limb morbidity (16). The two patients unfortunately developed lymphedema and were burdened by this in a varying grade. All patients were offered early instruction by physiotherapist and began mobilization of the upper limb after a standardized instruction for breast reconstructive patients. Early mobilization and rehabilitation has been shown to play a significant role in reducing postoperative morbidity of the upper limb (17).

In the present study patients reported a good body image (low BIS score) in both treatment groups at both 12- and 24- month follow-up (BIS 5.6, range 0-30). Body image score was lower (better body image) than previously reported for immediate unilateral two-stage BR by our institution, with a mean follow-up time at 3.8 years (16.4, SD 7.3) (18) but comparable with those found 1 year postoperatively for prophylactic mastectomies with BR (19). Atisha et al. observed a persistent good body image for immediate breast reconstructive patients from preoperatively to two years postoperatively suggesting that these women seem to have been “protected” from the body image disturbances normally associated with mastectomy (20).

All patients (not lost to follow-up due patient wish or explantation) thought that BR was the right choice for them and would recommend BR to others in the same situation. This is in accordance with other studies with the same study populations (12, 18). As the BR was successful for the answering patients, they are supposed to be more likely to answer in a positive way compared to those with an unsuccessful or complicated BR treatment course.

All patients in the one-stage group and the far majority of patients in the two-stage group reported a good current overall health at both follow-up visits. This was the dichotomized outcome of the choices: “excellent, very good and good” on a five-point scale with “bad” consisting of the choices: less well and bad. Results were comparable with other studies reporting very good health states after immediate BR with the techniques used in this study (7, 21)

In both treatment groups an increased ratio of patients (from 12- to 24-month follow-up) reported improved health status and QoL compared to the time before BR. In the present study no baseline measurement of health status or QoL was obtained and the design of the two questions may be perceived as a then-test (baseline retrospective measurement) to capture changes in internal standards and adjust for response shift (22). The patient’s assessment of an improved health state and QoL may reflect surviving a potentially life-threatening disease as breast cancer or a risk reduction. Thus, the improved QoL and

general health may not be ascribed to the breast reconstructive procedure per se. In the present study more patients reported improved QoL compared to the time before BR at 24-month follow-up (73% and 53%) than previously reported for immediate BR at our institution with a mean follow-up time at 3.8 years (38.5%) (18).

The strengths of this study were that the same three experienced plastic surgeons and four breast oncology surgeons performed all the breast reconstructive procedures and that the mastectomy procedure did not change during the study.

The conclusion to be drawn from the present study may be limited by the retrospective inclusion of the two-stage group as no baseline measurements of PROMs were obtained. Furthermore, the majority of patients in the two-stage group did not complete 12-month follow-up visit but only 24-month follow-up visit. Several additional variables would have been preferred in the cost analysis. For example, total number of outpatient visits for both treatment groups, duration of surgery for additional surgeries due to complications and aesthetic outcome, prize setting of operation time etc. Furthermore, this study did not take into consideration the additional cost for another BR in the case of complications leading to implant loss. At the time of study start no validated Danish questionnaire, as BREAST-Q, for use in patients undergoing breast reconstructive procedures was available. Therefore, a study specific questionnaire was used including questions previously used at our institution (18).

One-stage implant-based BR may entail advantages for the patient, but other, potentially more cost-effective, methods to obtain this has been suggested. The use of autologous dermal flaps to cover the inferior part of the implant in a similar manner than ADM, has been used for immediate one-stage BR of medium and large ptotic breasts (23) making it possibly to reduce costs compared to one-stage BR with the use of ADM (24). Although literature suggest that the risk for short-term complications is not higher than for other forms of implant-based BR, the evidence level for risk of long-term complications such as capsular contracture or PROMs and aesthetic outcome measures compared to other forms of implant-based BR is very limited (25). In 2019 Potter et al. found no statistically significant difference between complication rates of implant-based BR with biological mesh, dermal sling or synthetic mesh (26) and synthetic meshes might be a cost-effective alternative to ADM. It has been suggested that meshes as TiLOOP® and TIGR ® Matrix Surgical Mesh are safe, in terms om complications, and without any difference in long-term health-related QoL and patient satisfaction in use for one-stage BR compared to BR with the use of biological mesh (21, 27).

Conclusion

This study does not provide clear evidence for the cost-effectiveness of one method versus the other. Further studies should be undertaken to investigate the cost-effectiveness of one-stage BR with ADM or with synthetic meshes in comparison with the two-stage approach. Considering the equally good results in the two treatment groups regarding PROMs the one-stage approach should be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result.

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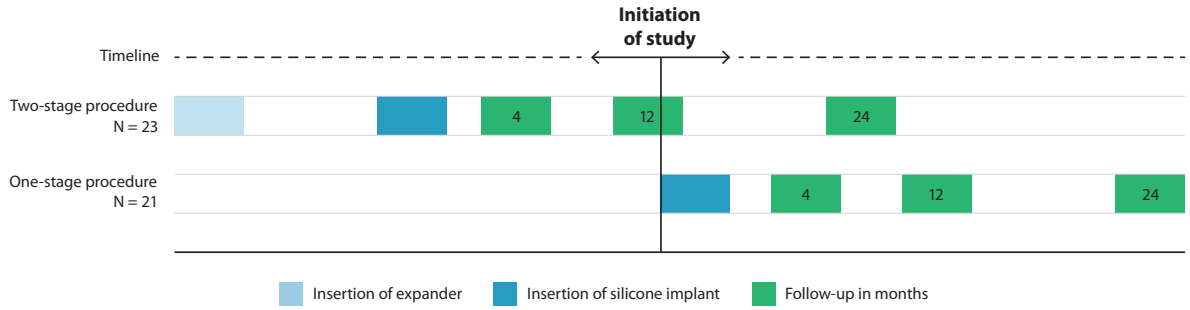
Supplementary material manuscript I

Supplementary material 1.1



Timeline of study recruitment

Supplementary material 1.2

BODY IMAGE SCALE

In this questionnaire you will be asked how you feel about your appearance, and about any changes that may have resulted from your disease or treatment. Please read each item carefully, and place a firm tick on the line alongside the reply which comes closest to the way you have been feeling about yourself, during the past week.

Name: _____ Date: _____

	Not at all	A little	Quite a bit	Very much
Have you been feeling self-conscious about your appearance?	.....	.....	.....	.....
Have you felt less physically attractive as a result of your disease or treatment?	.....	.....	.....	.....
Have you been dissatisfied with your appearance when dressed?	.....	.....	.....	.....
Have you been feeling less feminine/masculine as a result of your disease or treatment?	.....	.....	.....	.....
Did you find it difficult to look at yourself naked?	.....	.....	.....	.....
Have you been feeling less sexually attractive as a result of your disease or treatment?	.....	.....	.....	.....
Did you avoid people because of the way you felt about your appearance?	.....	.....	.....	.....
Have you been feeling the treatment has left your body less whole?	.....	.....	.....	.....
Have you felt dissatisfied with your body?	.....	.....	.....	.....
Have you been dissatisfied with the appearance of your scar?	.....	.....	.....	.....
	Not Applicable		.....	

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Supplementary material 1.3

Study specific questionnaire regarding PROMs

Questions regarding pain and long-term sequelae were answered at breast level as follows with reference to the past month.

Question (Q): Have you felt pain in the area where you were operated? Answer (A): Dichotomized so "yes"= pain few days a month, pain a few days a week, pain almost every day, pain several times a day, pain all the time, "no"= no pain.

Q: Do you feel burdened by sensory disturbances in the area where you were operated? A: Dichotomized so "no"= no sensory disturbance, "yes"= minimal, a little, somewhat, much, very much.

Q: Have you felt pain in the arm or shoulder on the operated side? A: Dichotomized so "yes"= pain few days a month, pain a few days a week, pain almost every day, pain several times a day, pain all the time, "no"= no pain.

Q: Do you feel burdened by sensory disturbances in the arm or shoulder on the operated side? A: Dichotomized so "no"= no sensory disturbance, "yes"= minimal, a little, somewhat, much, very much.

Q: Do you suffer from lymphedema in the arm or hand on the operated side? A: "yes"= much edema, some edema, only edema occasionally, "no"= no edema.

Q: Are you able to use the arm on the operated side as before surgery? A: Dichotomized so "yes"= yes, "no"= partly, no.

Questions answered at patient level were as follows.

Q: Have you felt pain anywhere else in the body (apart from the breast, arm or shoulder on the reconstructed side)? A: Dichotomized so "yes"= pain few days a month, pain a few days a week, pain almost every day, pain several times a day, pain all the time, "no"= no pain.

Q: Have you been taking painkillers within the past month? A: yes/no.

Q: How is your current overall health status? A: Dichotomized so "good"= excellent, very good, good, "bad"= less well, bad.

Q: How is your current overall health status compared to the time of BR? A: Dichotomized so "improved"= much better, slightly better, "unchanged/worse"= unchanged, slightly worse, much worse.

Health related limitations of activities

Q: Are you, due to your health, limited in the following activities? If so, how much? The item consists of 10 questions, each with three options for answering (A: not at all, little, very). The 10 questions represented a scale of how physically demanding activities were (a. Demanding activities, b. Easy activities, c. To lift or carry groceries, d. Walking several floors upstairs, e. Walking up a staircase, f. To bend or kneel, g. Walk more than 1 kilometer, h. Walk a few hundred meters, i. Walk 100 meters, j. Take a bath or put on clothes). Primarily it was assumed, that patients would be able to perform the activities from j. and up to a certain threshold on the scale. But review of data revealed, that some patients were able to perform some of the activities more challenging than after the first observed threshold on the scale from j. to a. This observation led to the decision of analyzing the number of activities the patient can do without any limitations. Answers were dichotomized so "1=no limitations" (A: not at all) and "0=limited to some degree" (A: little/very). Patients obtained a sum score, range 0-10, with higher scores representing more activities the patient can perform without any health-related limitations.

Q: With your current experience, would you recommend others to undergo breast reconstruction? A: Dichotomized so "yes"= yes, possibly, "no"= no, don't know.

Q: How would you describe your current quality of life compared to the time before your breast reconstruction? A: Dichotomized so "improved"=much better, slightly better, "unchanged/worse"=unchanged, slightly worse, much worse).

Q: Was breast reconstruction the right choice for you? A: Dichotomized so "yes"=absolutely, partly, "no"=not really, not at all.

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Mette Eline Brunbjerg

This declaration concerns the following article/manuscript:

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Authors:	Mette Eline Brunbjerg, Thomas Bo Jensen, Peer Christiansen, Jens Overgaard, Tine Engberg Damsgaard

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No ☒ Yes ☐ If yes, give details:

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Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study protocol was designed by the PhD student and main supervisor in collaboration. The detailed description of the study, setup of research facilities and organization of the study programme was primarily done by the PhD student.	
The acquisition, analysis, or interpretation of data:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has collected all data and interpreted all analyzes. Data analysis was carried out in collaboration with a statistician.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has prepared the first draft of the manuscript. This was discussed with the co-authors and adjusted accordingly.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
Submission of the manuscript was performed by the PhD student.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
7/8 2020	Mette Eline Brunbjerg	Mette Eline Brunbjerg
7/8 2020	Tine Engberg Damsgaard	Tine Engberg Damsgaard

Date: 8/8 - 2020

Mette Eline Brunbjerg

Signature of the PhD student

Manuscript II

One- versus two-stage immediate implant-based breast reconstruction. A cohort study on cost and patient reported outcome measures.

Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study.

Mette Eline Brunbjerg, MD[1,3], Thomas Bo Jensen, MD, PhD[1], Jens Overgaard, MD, DMSc Professor[2], Peer Christiansen, MD, DMSc, Professor[1], Tine Engberg Damsgaard, MD, PhD, MRBS, Professor[3]

1 Department of Plastic and Breast Surgery, Aarhus University Hospital
2 Department of Experimental Clinical Oncology, Aarhus University Hospital
3 Department of Clinical Medicine, Aarhus University

Corresponding author:
Mette Eline Brunbjerg, MD
Department of Plastic and Breast Surgery
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
DK - 8200 Aarhus N.
Denmark
Telephone number: +45 60601470
E-mail: metteeline.brunbjerg@gmail.com

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Acknowledgments
The authors wish to express their gratitude to the participating patients.

Ethical statement
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The trial was conducted in accordance with the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Ethics Committee of the Central Region of Denmark (1-10-72-572-12) and informed consent was taken from all the patients.

Conflicts of Interest
MB reports grants from The Danish Cancer Society, grants from The Korning foundation, grants from Foundation of the Kjaersgaard Family, Sunds, grants from King Christian X foundation, grants from Foundation of Architect Holger Hjortenberg, grants and non-financial support from LifeCell Corporation (Branchburg, NJ, USA), during the conduct of the study. The other authors have no conflicts of interest to declare.

Abstract

Background

The use of acellular dermal matrix in one-stage immediate implant-based breast reconstruction may offer advantages over the two-stage expander-to-implant technique, but literature shows conflicting results. The aim of the present study was to compare these two techniques for immediate implant-based breast reconstruction regarding postoperative complications, aesthetic correction procedures and aesthetic outcome.

Methods

The study was designed as an observational cohort study with 44 participants admitted for immediate implant-based breast reconstruction at Department of Plastic Surgery, Aarhus University Hospital, Denmark. 21 patients underwent breast reconstruction with a one-stage direct-to-implant technique using acellular dermal matrix and 23 patients underwent breast reconstruction with a two-stage expander-to-implant technique. Follow-up time was 2 years.

Results

The risk of implant loss was equal between groups; one-stage group 16% and two-stage group 17% whereas the risk of implant exchange (but not loss of breast reconstruction) was 13% in the one-stage group compared to 7% in the two-stage group. The risk of at least one major complication were equal between groups; 28% and 24% but the risk of at least one minor complication was significantly higher in the two-stage group (41%) compared to the one-stage group (3%). Number of aesthetic corrections were equally frequent in the two treatment groups (one-stage group 1.8, two-stage group 1.5). Patient and investigator assessed aesthetic outcome was very high in both groups as well as the degree of symmetry between breasts. No capsular contracture Baker grade 3 or 4 was observed.

Conclusion

The present study design sets limitations for drawing wide conclusions. This study did not reveal any significant differences between the two breast reconstructive techniques besides a higher risk of minor complications in the two-stage group, that did, however, not lead to a higher risk of implant loss. With equally high satisfaction with the aesthetic result and no significant difference in number of aesthetic corrections between the two groups we suggest, that the one-stage approach using acellular dermal matrix may be feasible and allows the patient to achieve an implant-based breast reconstruction with a minimum of surgeries and outpatient visits.

The study was registered in ClinicalTrials.gov (NCT04209010).

Introduction

Skin-sparing mastectomy provides optimal conditions for immediate reconstruction of an aesthetically satisfying breast. Even though autologous breast reconstruction (BR) has become very popular, some patients prefer less extensive surgery or are not candidates due to lack of tissue, co-morbidity or worries about donor-site morbidity. For those patients, an implant-based BR may be the obvious choice. The use of acellular dermal matrix (ADM) to obtain one-stage BR has revolutionized the concept of immediate implant-based BR after skin-sparing mastectomy (1). Attention has been drawn to advantages as improved control of inframammary fold position (2) and better lower pole projection (3) in comparison with the traditional two-stage expander to implant technique which can be associated with difficulties to achieve lower pole projection and ptosis (4). Furthermore, the two-stage method entails an extended course of treatment including multiple expansions and additional surgery for implant exchange. Despite more than two decades of research evaluating complications after implant-based BR with ADM the results are contradictory and level of evidence often low. It is often unclear which complications have been assessed and how they have been diagnosed, and also how and when capsular contracture and aesthetic outcome have been evaluated (5). Patients' perception of cosmetic outcome is a critical endpoint and the result of the BR should most likely be worth the effort and the struggles the women undergo in the BR treatment trajectory. Patients experiencing surgical complications after BR report suboptimal aesthetic outcome. This is reported to be more pronounced in patients undergoing implant-based BR compared to autologous reconstruction and BR after prophylactic mastectomy (6). This emphasizes the need for research regarding ways to decrease the complication rate and thereby improving the satisfaction with the BR.

The aim of the present study is to compare immediate implant-based BR using the one-stage technique with ADM with the two-stage expander to implant technique regarding postoperative complications, aesthetic correction procedures and aesthetic outcome.

We present the following article in accordance with the STROBE reporting checklist.

Materials and methods

Study design and participants

The present study was designed as an observational cohort study with 44 participants. Eligible patients were all women admitted for immediate, implant-based BR following skin-sparing mastectomy at the Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark over a period of 40 months. Patients were diagnosed with either breast cancer, ductal carcinoma in situ (DCIS) or were considered high risk for developing breast cancer. Inclusion criteria were mastectomy weight ≤ 600 g, patient older than 18 years, tobacco abstinence > 4 weeks prior to surgery (7), ability to complete the study questionnaire and for the two-stage group; time to achieve two-year follow-up visit after BR. Follow-up time was 24 months. Participants underwent clinical examination and completed a study-specific

questionnaire regarding aesthetic satisfaction with the result. Furthermore, a systematic review of patient records was performed to obtain information regarding complications.

All participants gave written informed consent. The trial was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Central Region of Denmark (1-10-72-572-12) approved this study and it was submitted in ClinicalTrials.gov (NCT04209010).

Recruitment

As the one-stage approach was implemented as a standard care for immediate implant-based BR following skin-sparing mastectomy, in december 2012, all eligible patients were offered participation in the one-stage group and inclusion continued consecutively until 21 patients were included. The two-stage cohort was established retrospectively. Patients that had undergone immediate implant-based BR following skin-sparing mastectomy with the two-stage expander to implant technique were identified using diagnosis- and procedure-related codes, records were examined and patients that fulfilled the inclusion criteria were identified and consecutively offered participation in the two-stage group. Inclusion continued retrospectively until 23 patients were included (Figure 1).

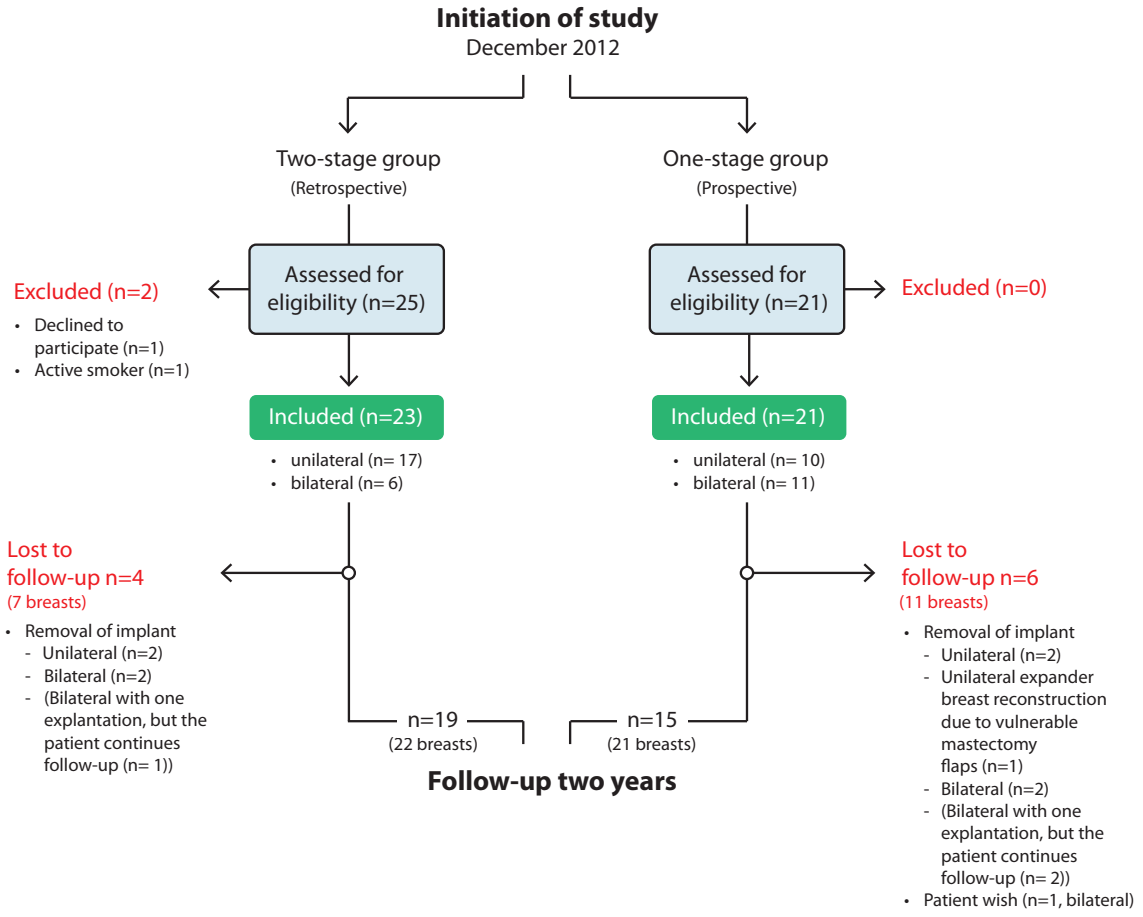


Figure 1. Flow diagram of the study participants.

Surgical techniques

In all cases the implant or expander was placed behind the pectoralis muscle.

The surgical technique for one-stage immediate BR using porcine acellular dermal matrix (ADM) (Strattice™, LifeCell Corporation, Branchburg, NJ, USA) and fixed size silicone implant was as follows. Upon skin sparing mastectomy the pectoralis major muscle was elevated from the chest wall, the inferomedial attachment was divided, and an inflatable sizer used to determine the size of the implant taking the viability of mastectomy skin flaps into consideration. ADM was sutured to the inframammary fold at the chest wall. The fixed sized anatomical implant was inserted, and the cranial edge of the ADM was sutured to the caudal border of the pectoralis major muscle. Two suction drains were placed, draining the submuscular and subcutaneous pockets.

The surgical procedure for two-stage immediate breast reconstruction using temporary expander implant and later exchange to fixed size silicone implant was as follows. After the skin sparing mastectomy, a submuscular pocket was created by elevating the pectoralis major muscle, the serratus anterior muscle or its fascia and the anterior rectus sheath. The latter in connection with the pectoralis major muscle. An inflatable sizer was used to estimate the expansion volume. Suction drains were placed, draining the submuscular and subcutaneous pockets and the expander was placed in the submuscular pocket. The first expansion was performed two weeks postoperatively and after that at weekly intervals, should no complications arise. Three to six months after the final expansion volume had been achieved the expander was changed to a fixed sized implant. The mastectomy scar was excised, the submuscular pocket was opened parallel to the muscle fibres of the pectoralis major muscle, the expander was removed and the necessary adjustments of the pocket were performed. An adjustable sizer was used to determine the size and the shape and dimensions of the pocket and the final size silicone implant was placed. One suction drain was used when deemed necessary. All patients received one prophylactic dose of antibiotic (Cefuroxim or Dicloxacillin) preoperatively and the one-stage group continued Cefuroxim for three days postoperatively. Drains were removed when output was less than 20 ml for two consecutive days.

Outcomes

Primary endpoint of the study was postoperative complications reported per breast. Explantation was defined as either ***loss of implant,*** and thereby failure of the initial implant-based BR, or as ***implant exchange*** defined as removal of the device implanted at the initial surgery and exchange to an expander. Major complications included hematoma requiring surgical intervention (within three days), infection requiring explantation (within three months) and mastectomy flap necrosis requiring flap revision (within four weeks). Minor complications included cellulitis/wound infection requiring treatment with antibiotics and seroma requiring intervention (within three months). For the two-stage group data regarding complications following the two operations were summated in the table but described in details in the result section.

Secondary endpoints were aesthetic correction procedures, patient and investigator assessed satisfaction with the aesthetic result of the BR, symmetry and capsular contracture. All outcomes were

provided for two-year follow-up data. Aesthetic correction procedures included all surgical procedures conducted in general anaesthesia with the aim of achieving a better aesthetic outcome for the patient. Thus, surgery due to postoperative complications was not included in this analysis. In case of unilateral BR contralateral symmetrization procedures was also considered an aesthetic correction. Patients completed a study specific questionnaire previously used in our department (8, 9) as no validated Danish instrument evaluating patient satisfaction with the aesthetic result after BR was available. The questionnaire consisted of items evaluated per breast ("satisfaction with appearance of the reconstructed breast with clothes", "satisfaction with appearance of the reconstructed breast without clothes" and "overall satisfaction with the BR") and items evaluated at patient level ("satisfaction with symmetry regarding breast size" and "satisfaction with symmetry regarding breast shape"). All items were answered on a seven-point Likert scale ranging from very dissatisfied (score 1) to very satisfied (score 7). Score evaluating satisfaction with appearance of the reconstructed breast with/without clothes and scores evaluating symmetry were summated into a total score ranging from 2-14 with higher scores representing greater aesthetic satisfaction. The investigator assessed the aesthetic outcome in regard to "overall aesthetic result of BR with clothes" and "overall aesthetic result of BR without clothes" (reported per breast) and "symmetry regarding breast size" and "symmetry regarding breast shape" (reported per patient). Assessment was scored into four categories ('excellent' score 4, 'good' score 3, 'fair' score 2, and 'poor' score 1). This was summated into a total score range 2-8 with higher scores representing greater aesthetic satisfaction. An objective measurement of symmetry was obtained by investigator measuring suprasternal notch to nipple (SSN:N) distance and nipple to inframammary fold (N:IMF) distance using a tape measure and recorded with an accuracy of 0.5 centimeters (cm). Measurements were obtained with the patient in a standardized standing position with the arms along the side of the body. Symmetry was described as difference in cm between measurements of right and left side. Lower score represented a better symmetry between breasts. Furthermore, investigator assessed the degree of capsular contracture according to the Spear-Baker classification for implant-based breast reconstructions (10).

Bias

The funders (financial or providing acellular dermal matrix) did not participate in study design, data collection, data analysis or interpretation or writing of the manuscript.

Study size

Study size was determined upon power calculation on the primary endpoint "reduction in surgery time" used for a publication in preparation. Originally 20 patients were planned in each group, but late secondary review of patients revealed, that one patient had been wrongly excluded from the one-stage group due to conversion to expander-based BR because of vulnerable mastectomy flaps and furthermore, three patients had been missed due to removal of implant before inclusion started in the two-stage group. Allocating these patients to their correct study group resulted in 21 patients in the one-stage group and 23 patients in the two-stage group.

Statistical analysis

Descriptive statistics were used for patients' demographics with stating mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test. For the categorical variables such as "major and minor complications" the groups were compared using Fisher's exact test for the independency of contingency table. For the dichotomized outcome on breast level such as "any major complication", the generalized linear model with identity-link function was used taking into account for repeated measurements for the same patient in case of bilateral BR. For the outcomes on breast level such as "loss of implant", the two groups were compared using test for two proportions. The risks (and 95% CI) and p-values for the comparison were reported. For the continuous outcome on patient level such as "symmetry", the two groups were compared using t-test, and for the outcome on the breast level such as "assessment of aesthetic outcome", a mixed model for repeated measurements were used. Due to sparse data, if the model could not converge, a simple linear regression model was used without correcting for the repeated measurements by being aware of resulting confidence intervals became wider. The outcome "number of aesthetic corrections" were analysed using a Poisson regression model and the mean number of aesthetic corrections (95% CI) and p-value comparing the groups were reported. Based on clinical experience it was decided to adjust for BMI and smoking in the analysis of postoperative complications. Missing data was described in tables and results and analyses were taking this into account.

Statistical analyses were performed using STATA® software IC16 (Stata Corporation, College Station, TX). Strobe guidelines for reporting observational cohort study were used.

Results

21 patients (32 breasts) were included in the one-stage group and 23 patients (29 breasts) were included in the two-stage group. 15 patients (21 breasts) in the one-stage group and 19 patients (22 breasts) in the two-stage group completed 24 months follow-up (Figure 1). The two treatment groups did not differ significantly regarding demographics and clinical characteristics as summarized in Table 1.

Table 1. Baseline demographics and clinical characteristics.

	One-stage, Patient n=21	**Two-stage, Patient n=23**
Age (years), mean (SD)	48.3 (10.7)	42.7 (9.9)
BMI (kg/m$^{2)}$, mean (SD) †	23.1 (2.8)	24.7 (3.8)
Comorbidity †	7	3
Never smoker	13	13
Former smoker	6	10
Smoker	2	0
Laterality of procedure		
Bilateral	11	6
Unilateral	10	17
Adjuvant therapy after surgery †		
Endocrine treatment	5	1
None	15	19
Axillary surgery †		
None	13	13
Sentinel node biopsy	7	5
Axillary dissection ‡	0	2
Indication for mastectomy †		
Cancer	3	0
DCIS	5	6
Prophylactic	14	14

BMI, body mass index; DCIS, ductal carcinoma in situ.

† Missing values one-stage group n=1, two-stage group n=3.

‡ Two patients in the two-stage group were diagnosed with DCIS but underwent axillary dissection due to micrometastasis in sentinel nodes.

Two patients in the one-stage group turned out to have smoked less than four weeks before surgery and analysis of the primary endpoint postoperative complications were adjusted for smoking. Mastectomy weight did not differ between the two groups, but there was a significant difference in final implant size (Table 2).

Table 2. Breast reconstruction descriptive data. Reported per reconstructed breast.

	One-stage, Breast n=32	**Two-stage, Breast n=29**	**P**
Mastectomy weight (g), mean (SD)	368 (113)	366 (127)	NS †
Final implant size (ml), mean (SD)	324 (66)	440 (138)	0.0001 † *
Expander data, mean (SD)			
Start volume, ml		95 (74)	
Number of expansions,		6.6 (1.9)	
Final expansion volume, ml		415 (118)	
Time from expander to final implant (days), median (iqr)		231 (91)	

Iqr, interquartile range; NS, not significant.

† Simple linear regression model

** Denotes statistical significance*

A breast reconstructed with the two-stage technique received a final implant approximately 100 ml larger than a breast reconstructed with the direct to implant technique. Patients in the two-stage group underwent expansion of the expander on average 6-7 times with approximately 50 ml each time and the median time from insertion of expander to exchange to final size implant was 231 days.

The risk of *implant loss* was equal between groups with 16% in the one-stage group compared to 17% in the two-stage group (Table 3). For the two-stage group four out of five implant loss took place after exchange of expander to final size implant. The risk of *implant exchange* was 13% in the one-stage group compared to 7% in the two-stage group. One patient (unilateral BR) in the one-stage group was converted from direct-to-implant BR to two-stage BR after re-excision of skin due to non-radical margins and thus not because of reconstructive complications and one patient in the two-stage group (bilateral BR) underwent implant exchange to smaller implants due to discomfort. Major complications, resulting in surgery, were equally frequent in the two treatment groups. In the direct-to-implant group the risk of at least one major complication were 28% (95% CI: 10% - 46%) compared to 24% (95% CI: 7% - 42%) in the two-stage group. Major complications were equally distributed after first (two partial flap necrosis and one infection) and second operation (four infections) in the two-stage group. The risk of at least one minor complication was significantly lower in the one-stage group 3% (95% CI: -3% - 9%) compared to the two-stage group 41% (95% CI: 21% - 61%). The majority of minor complications in the two-stage group were observed after insertion of the expander (five cellulitis and three seroma) and not after exchange of expander to final size implant (three cellulitis and one seroma). Adjustments for smoking and BMI did not change the results regarding complications.

Table 3. Postoperative complications. Reported per reconstructed breast.

	One-stage, Breast n=32	**Two-stage, Breast n=29**	**P**
Loss of implant, n (%; 95% CI)	5 (16%; 3% - 28%)	5 (17%; 4% - 31%)	0.86 †
Implant exchange, n (%; 95% CI)	4 (13%; 1% - 24%)	2 (7%; -2% - 16%)	0.46 †
Major None 1 complication 2 complications	 23 7 2	 22 7 0	 0.61 ‡
Minor None 1 complication 2 complications	 31 0 1	 17 12 0	 <0.0001 ‡*

† Test of two proportions

‡ Fisher's exact test

** Denotes statistical significance*

There was no difference between number of aesthetic corrections between the one-stage group; mean 1.8 (95% CI: 1.2 – 2.5) and the two-stage group; mean 1.5 (95% CI: 0.9 – 2, p=0.44). Most patients underwent at least one correction to get an acceptable aesthetic result and often more operations were needed. Aesthetic corrections were mostly autologous fat transplantation and symmetrization procedures. Only patients not explanted and thereby with the opportunity of receiving aesthetic corrections were included in the analysis.

Patients' satisfaction with appearance of the reconstructed breasts and the overall satisfaction with the breast reconstructions was generally very high within the range in both treatment groups (Table 4). Investigator assessment of the overall aesthetic result aligned well with the patient's assessment and was also very high in both treatment groups and there was no significant difference between the two groups. Due to lost to follow-up because of explantation analysis were performed at 21 breasts in the one-stage group and 22 breasts in the two-stage group.

Table 4. Assessment of aesthetic result and capsular contracture. Reported at breast level.

	One-stage, Breast n=21	**Two-stage, Breast n=22**	**P**
Patient: "Satisfaction with appearance of reconstructed breast with/without clothes" (range 2-14) Mean (CI)	12.4 (11.3 - 13.5)	12.6 (11.6-13.6)	NS †
Patient: "Overall satisfaction with the breast reconstruction" (range 1-7) Mean (CI)	6.2 (5.6 - 6.7)	6.2 (5.7 - 6.7)	NS †
Investigator: assessment of overall aesthetic result of BR with/without clothes (range 2-8) Mean (CI)	7.8 (7.5 - 8)	7.7 (7.5 - 7.9)	NS ‡
Baker grade III-IV	0	0	

NS, not significant.

† Mixed regression model.

‡ Linear regression model.

Assessment of symmetry was reported at patient level as symmetry requires two sides to compare (Table 5). Due to lost to follow-up because of explantation, analysis of patient and investigator assessed symmetry was performed at 15 patients in the one-stage group and 19 patients in the two-stage group. Both patients and investigator rated the symmetry very high within the range in both treatment groups without any significant difference. Measurements of SSN:N and N:IMF were only obtained if the nipple was reconstructed at the two-year follow-up visit. Therefore, analysis was performed with 12 patients in the one-stage group and 17 patients in the two-stage group. In both treatment groups there was less than 0.5 cm mean difference between left and right side in SSN:N and N:IMF measurements confirming to a very

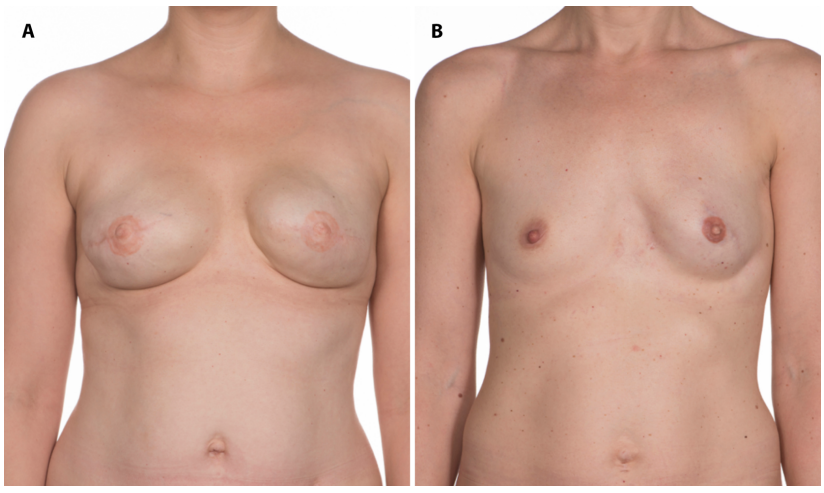
large degree symmetrical breasts (Table 5 and Figure 2). 67% (n=8) of patients in the one-stage group had a difference between sides at 0.5 cm or less in both SSN:N and N:IMF measurements. Whereas 53% (n=9) in the two-stage group had a difference between sides at 0.5 cm or less in SSN:N measurement and 59% (n=10) in N:IMF measurement. There was no significant difference between treatment groups. Significant capsular contracture, defined as Baker grade 3 or higher, was not observed in any of the treatment groups within two years of follow-up.

Table 5. Assessment of breast symmetry. Reported at patient level.

	One-stage	**Two-stage**	**P**
Patient: "Satisfaction with symmetry regarding breast size and breast shape" † (range 2-14) Mean (CI)	11.7 (10.1 - 13.2)	11.6 (10.3 - 13)	NS §
Investigator: "Assessment of symmetry regarding breast size and breast shape" † (range 2-8) Mean (CI)	7.4 (6.8 – 8)	6.8 (6 - 7.6)	NS §
SSN:N, cm ‡ Mean difference (CI)	-0.3 (-1.1 - 0.5)	0.4 (-0.1 - 0.8)	NS §
N:IMF, cm ‡ Mean difference (CI)	0 (-0.7 - 0.7)	-0.03 (-0.5 - 0.4)	NS §

SSN:N, suprasternal notch to nipple distance; N:IMF, nipple to inframammary fold distance.
† One-stage group n=15, two stage group n=19
‡ One-stage group n=12, two stage group n=17
§ T-test

Figure 2. Two years after breast reconstruction.



A. Bilateral one-stage breast reconstruction. B. Unilateral two-stage breast reconstruction (left).

Discussion

The present study was designed to compare two surgical techniques for implant-based breast reconstruction regarding postoperative complications, aesthetic correction procedures and aesthetic outcome. Overall, no major differences in outcome was found.

Most publications do not distinguish between loss of implant and implant exchange, as we did in the present study, and comparisons can be difficult. In our view, it makes sense to separate the two outcomes as the consequences are very different. Loss of implant is considered the most severe complication, as the BR has then failed. The present study revealed no significant difference in loss of implant between the one-stage and two-stage group (16% and 17% respectively). But the risks was higher than observed by e.g. Potter et al. in their prospective cohort study where a risk of 8% implant loss was observed 3 months after immediate implant based BR with the use of ADM, where the majority at 86% were reconstructed as a one-stage procedure (11). In contrast Dikmans et al. revealed similar total explantation risks in their one-stage group (24%), but a very limited risk of explantation in the two-stage group at 4% (12). Implant exchange may result in a prolonged course of breast reconstruction, but not in failure of the BR. In the present study, the risk of implant exchange was not significantly different between groups.

The risk of major complications as hematoma, infection and partial flap necrosis resulting in additional surgery was equal in the two treatment groups. The risk in the one-stage group is consistent with the risk of severe adverse events for the one-stage group at 29% observed by Dikmans et al. (12) and of early revision rate at 31% observed by Gdalevitch et al. (13), but higher than observed by Potter et al. in their prospective cohort study (11). Dikmans et al. found no difference between groups regarding mild to moderate adverse events (12). This result is contradictory to what was revealed in the present study, where the risk of at least one minor complication was significantly higher in the two-stage group than in the one-stage group (41% vs. 3%). The number of minor complications were higher after insertion of the expander than after insertion of the final size silicone implant. It is assumed that the risk for minor complications is associated with the minimal invasive procedure at each expansion.

A meta-analysis including studies comparing BR with and without the use of ADM revealed, that when ADM initially was used, the risk of seroma, infection and mastectomy flap necrosis increased and the risk of capsular contracture and implant malposition decreased. This did not result in a difference in explantation risk and total complications between the groups (14). There is, however, in the literature a range of reported total complication rates after BR with the use of ADM with the lowest reported 3,9% (15) and 8.6% (16). An explanation for the major and minor complication risks in the two-stage group of this study may be, that this group underwent two surgeries and multiple expansions, all of which present a risk of developing complications. Litterature suggest that increasing breast size increases the risk of complications (13, 17). In this study the two treatment groups had a mastectomy weight of approximately 370 g and this factor is not considered likely to influence the result.

Patient satisfaction with the result is crucial. Patients often undergo several surgical procedures and the end result should be worth the effort. Surgical corrections to optimize the aesthetic result of BR is most

often needed. In this study most patients underwent at least one surgical procedure consisting of mostly autologous fat grafting, but also skin reduction and contralateral reduction to achieve symmetry. Autologous fat grafting has been showed to improve the cosmetic outcome after implant based BR and furthermore alleviate pain (18, 19) and is considered to be a low risk intervention. In this study patients reported a very high overall satisfaction with the breast reconstruction regardless of which surgical approach was used. Likewise, both patients and investigator were very satisfied with the overall aesthetic result in both treatment groups. This result is contradictory to other studies where satisfaction with the aesthetic result of BR were higher when performed with the use of ADM (20, 21). An explanation for the very high satisfaction might be, that the reconstructive surgeons provided the patients with both orally and written detailed information prior to surgery to obtain a common understanding of the reconstructive course and expected outcome. Literature suggests this to be one of the main factors for a high satisfaction with the result of BR. Breast symmetry does also play an important role for satisfaction, but is not found to be a major determinant of outcome (22). Breast asymmetry is a common phenomenon and the proportions of patients in this study that obtained an acceptable symmetry of 0.5 cm or less difference in SSN:N measurement was in accordance with a normal population opting for BR (23). Absolut symmetry is not the ultimate goal and patients were informed of this prior to surgery in an attempt to manage patients' expectations.

Breasts reconstructed with the two-stage method received a significantly larger final implant than breasts reconstructed with the one-stage procedure. An explanation for this finding was that patients undergoing bilateral BR received larger implants due to patient request. This difference between groups was not reflected in assessment of satisfaction with the BR. It is suggested, that in general it is of less importance whether the reconstructed breast is larger or smaller than the former natural breast as long as symmetry is achieved. The gradual expansion of skin and muscle tissue in the two-stage group ultimately gives the possibility to insert larger implants with the tradeoff of more outpatient visits and an additional surgery under general anesthesia.

Capsular contracture may affect the aesthetic outcome and cause pain or discomfort. The phenomenon is observed to be a progressive condition but in BR with ADM, literature suggests that capsular contraction appears within a period of two years after BR (24). Furthermore, a comparison between immediate two-stage BR with and without ADM concluded, that the use of ADM was associated with less capsular contracture. Risk with/without ADM was 3.8% and 19.4% respectively (OR 0.18) (20). Research into the mechanisms of how ADM influences the development of capsular contracture is limited. In a recent study more myofibroblast and neovascularization were observed in the capsule of breasts reconstructed with biological mesh than in breasts reconstructed with synthetic mesh. Furthermore, collagen fibers seemed to be aligned in an irregular pattern with both parallel and vertical fibers (25). However, this difference in formation of capsular tissue was not reflected in the frequency of capsular contracture maybe due to a follow-up time of less than two years. In this study no capsular contraction grade III or IV was observed within two years follow-up in any of the treatment groups.

A limitation for this study is the small study population. Due to this, complications were pooled in only two groups as minor or major. It is a strength that all BR was performed by the same three experienced plastic surgeons and four breast oncology surgeons. They did not participate in the evaluation of the aesthetic result and there was only one independent investigator that did not participate in the surgical procedures. Introduction of a new surgical technique result in a learning curve as experience is achieved. It has previously been suggested that the learning curve may have influence on the complication rate after BR with ADM (26). This factor might be of importance in the present study. Two years follow-up time is thought to be an appropriate time for assessment of secondary endpoints.

An important prerequisite of a successful immediate BR is viable mastectomy skin flaps. This emphasizes that the collaboration between plastic- and breast surgeons is of pivotal importance. Imaging techniques, for instance laser-assisted indocyanine green angiography, can also potentially decrease complication rates. It is a useful technique to identify mastectomy skinflap areas with insufficient perfusion even though our institution did not find a beneficial effect on necrosis rates after implementing this technique (27).

Since this study was initiated, prepectoral breast reconstructive procedures ADM has been developed. It is a less invasive procedure and the advantages includes reduced pain and less animation deformities (28). The prepectoral approach may result in a secondary procedure with subcutaneous fat grafting to achieve a satisfying aesthetic result and furthermore, the expense of ADM may also be a factor to consider (29). Nipple-sparing mastectomy further enhances the cosmetic outcome and satisfaction with the BR (30).

Further research should be undertaken to investigate the cost effectiveness of the two treatment methods described in this study. ADM is expensive and the costs should be offset by fewer complications, better outcome or a lower burden on the health care system and the patient.

Conclusion

The present study design sets limitations for drawing wide conclusions. Since this study was initiated a randomized study has concluded, that that use of one-stage breast reconstruction with ADM should be considered carefully due to more early postoperative complications than after two-stage breast reconstruction (12). The present study did not reveal any significant differences between the two breast reconstructive techniques besides a higher risk of minor complications in the two-stage group, that did, however, not lead to a higher risk of implant loss. With equally high satisfaction with the aesthetic result and no significant difference in number of aesthetic corrections between the two groups, we find, based on this study, that the one-stage approach using ADM may be feasible and allows the patient to achieve an implant-based breast reconstruction with a minimum of surgeries and outpatient visits.

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Mette Eline Brunbjerg

This declaration concerns the following article/manuscript:

Title:	Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study.
Authors:	Mette Eline Brunbjerg, Thomas Bo Jensen, Jens Overgaard, Peer Christiansen, Tine Engberg Damsgaard

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Gland Surgery

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study protocol was designed by the PhD student and main supervisor in collaboration. The detailed description of the study, setup of research facilities and organization of the study programme was primarily done by the PhD student.	
The acquisition, analysis, or interpretation of data:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has collected all data and interpreted all analyzes. Data analysis was carried out in collaboration with a statistician.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has prepared the first draft of the manuscript. This was discussed with the co-authors and adjusted accordingly.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
Submission of the manuscript was performed by the PhD student.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
7/8 2020	Mette Eline Brunbjerg	Mette Eline Brunbjerg
7/8 2020	Tine Engberg Damsgaard	Tine Engberg Damsgaard

Date: 8/8 - 2020

Mette Eline Brunbjerg

Signature of the PhD student

Manuscript III

Reinforcement of the abdominal donor-site with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.

Reinforcement of the abdominal donor-site with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.

Mette Eline Brunbjerg, MD[1,3], Thomas Bo Jensen, MD, PhD[1], Peer Christiansen, MD, DMSc, Professor[1], Jens Overgaard, MD, DMSc Professor[2], Tine Engberg Damsgaard, MD, PhD, MRBS, Professor[3]

1 Department of Plastic and Breast Surgery, Aarhus University Hospital
2 Department of Experimental Clinical Oncology, Aarhus University Hospital
3 Department of Clinical Medicine, Aarhus University

Corresponding author:
Mette Eline Brunbjerg, MD
Department of Plastic and Breast Surgery
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
DK - 8200 Aarhus N.
Denmark
Telephone number: +45 60601470
E-mail: metteeline.brunbjerg@gmail.com

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Ethical statement
This study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent. The Ethics Committee of the Central Region of Denmark (1-10-72-10-13) and The Danish Data Protection Agency (1-16-02-7-13) approved this study and it was submitted in ClinicalTrials.gov (NCT02076724).

Conflicts of Interest
MB reports grants from The Danish Cancer Society [R130-A8304-15-S38], grants from Novo Nordisk foundation, grants from Foundation of Jacob and Olga Madsen, grants from The Danish Medical Association's Research Fund, grants from AP Møller foundation, grants and non-financial support from LifeCell Corporation (Branchburg, NJ, USA), during the conduct of the study. The other authors have no conflicts of interest to declare.

Abstract

Introduction

The pedicled transverse rectus abdominis musculocutaneous flap (p-TRAM) is a well-established option for autologous breast reconstruction (BR) but donor-site morbidity is still reported.
The aim of the present study was to compare donor-site morbidity after reinforcement of the abdominal wall regarding development of bulging or hernia, abdominal muscle strength, complications, and abdominal pain hypothesizing, that reinforcement with acellular dermal matrix (Strattice™) is superior to reinforcement with synthetic mesh (Prolene®).

Materials and methods

A randomized, prospective, double-blind study was conducted with 29 patients admitted for BR with the p-TRAM flap at Department of Plastic Surgery, AUH, Denmark, 2014-2016. Allocation rate 1:1. Follow-up at 4, 12, and 24 months.

Results

24 months postoperatively the computerized tomography (CT) verified bulging frequency was 35,7% in the ADM group and 6,7% in the synthetic mesh group (p=0.11). Two patients (14.3%) in the ADM group and no patients in the synthetic mesh group developed hernia. No significant difference between baseline and 2-year measurement of abdominal muscle strength was observed.

Conclusion

The present study did not demonstrate any statistically significant differences between treatment groups regarding risk of bulging or hernia, postoperative abdominal muscle strength, complications, pain or pain related QoL within two years of follow-up. Further research into methods for decreasing donor-side morbidity related to the use of rectus abdominis muscle based-flaps is needed. Finally, bulging and herniation seems to develop within the first postoperative year and for future studies aiming to investigate this endpoint 12 months is suggested to be the minimum time of follow-up.

Introduction

The transverse rectus abdominis musculocutaneous (TRAM) flap is an important option for autologous breast reconstruction (BR) (1) and other reconstructions such as coverage of inguinal defects (2) and reconstruction of the chest wall after re-recurrent breast cancer (3). The free TRAM flap was first described by Holmström in 1979 (4) and later introduced by Hartrampf et al. as a pedicled flap (5). Even though the flap is widely used, also with other skin islands, it may be associated with donor-site morbidity as abdominal bulge or hernia (6) and feeling of abdominal tightness (7). The abdominal weakness has been sought diminished by using different techniques such as direct suture of the remaining rectus fascia, using the adjacent fascial layers or reinforcement with synthetic mesh or dermal transplants (8). Synthetic mesh has been used for many years to reinforce the abdominal donor-site (9). However, there is a risk of infection and of development of foreign body reaction and chronic inflammation which may result in contracture and chronic pain (10). The introduction of biological meshes gave the possibility of an alternative reinforcement material to obtain a dynamic abdominal wall reconstruction and decrease donor-site morbidity. In a meta-analysis from 2011 Adetayo et al. found a frequency of bulging and herniation on more than 25% when using Alloderm for reinforcement of the abdominal wall (11). However, in 2012 Cicilioni et al. observed no bulging or herniation after reinforcement of the abdominal donor-site with the porcine non-crosslinked ADM Strattice™ (12). Reconstructing the fascial defect with porcine ADM may be promising and there is a lack of studies directly comparing abdominal wall reinforcement with either synthetic mesh or ADM.

Hypothesizing, that reinforcement with ADM results in less bulging at the abdominal donor-site and less abdominal discomfort compared to reinforcement with synthetic mesh the present randomized study was initiated. The aim was to compare donor-site morbidity after reinforcement of the abdominal wall with either synthetic mesh (Prolene®) or porcine non-crosslinked ADM (Strattice™) after breast reconstruction using the pedicled TRAM flap with regard to development of bulging or hernia, abdominal wall function, postoperative complications and abdominal pain.

Materials and methods

Study design and participants

The present study is a single-centre, double-blind (patient and investigator), prospective, randomized controlled trial with two groups, allocation ratio 1:1. All patients undergoing autologous BR with the pedicled TRAM flap at Aarhus University Hospital, Denmark during the inclusion period (January 2014 – November 2016) were offered inclusion in the study. Exclusion criteria were age less than 18 years, smoking less than four weeks prior to surgery and patients not able to understand enough Danish to comprehend the given information and to complete the study questionnaire. Data was obtained from patient records and participants underwent clinical examination before surgery and at follow up visits four, 12 and 24 months. All performed by the investigator. Follow-up time was 24 months.

Surgical techniques

Randomization was performed peroperatively and patients were allocated to reinforcement of the abdominal donor-site with either synthetic mesh (Prolene®) or ADM (Strattice™ Firm). The in-lay technique described by Cicilioni et al. (12) was used. The reinforcement material was trimmed and contoured to the width and length of the rectus muscle harvested and positioned between the anterior and posterior layers of the rectus fascia (Figure 1 A). The caudal edge of the reinforcement material was fixed to Cooper's ligament with interrupted 0 nonabsorbable suture. The cranial edge of the material was sutured to the posterior layer of the rectus sheath, just below the costal margin. Horizontal mattress sutures of 0 nonabsorbable suture was used to fix the reinforcement material to the medial and lateral cuff of the posterior layer of the rectus sheath. A running 1 nonabsorbable suture was used to close the anterior layer of the rectus sheath primarily above the umbilicus. Below the umbilicus, the anterior layer of the rectus sheath was pulled as medially as possible. Two suction drains were placed and the abdominal was closed with progressive tension sutures.

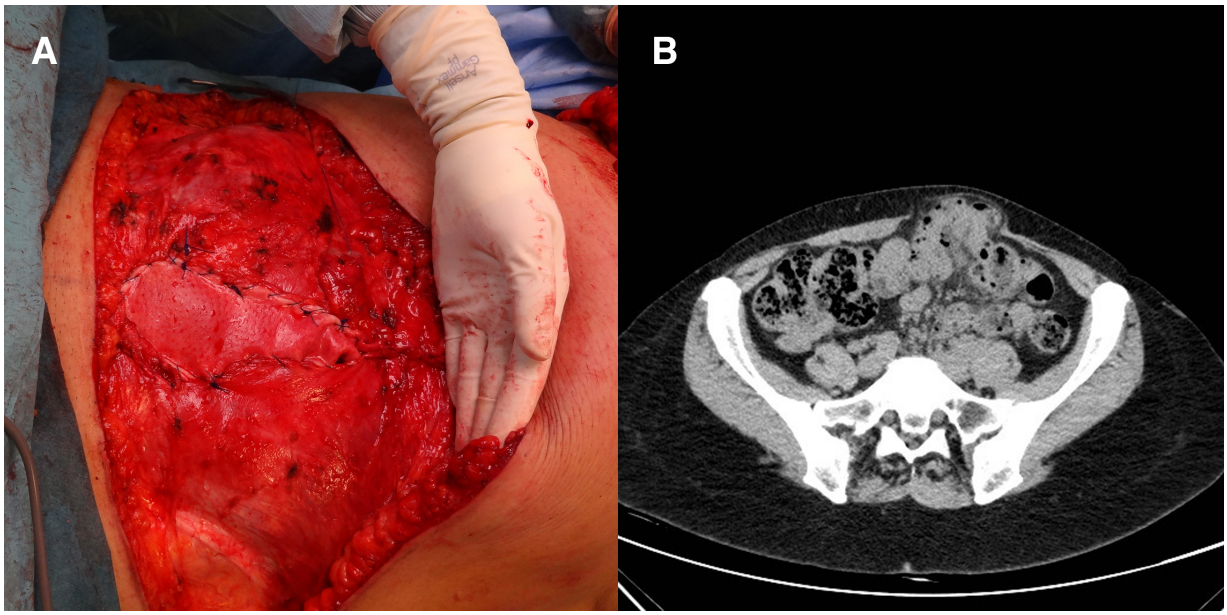

Figure 1. A. Reinforcement of the abdominal donor-site with ADM (Strattice™) B. CT scan illustrating donor-site hernia after reinforcement with ADM.

Outcomes

Primary endpoint was bulge or hernia at the abdominal donor-site diagnosed by computerized tomography (CT) scan at 24-month follow-up. Patient and investigator assessment of bulging or hernia was also reported. Bulge was defined as a visible protrusion of the abdominal wall, without a defect in the abdominal fascia. Hernia as a protrusion of the abdominal wall with a defect in the abdominal fascia. Patient assessment was obtained in a study specific questionnaire concerning the entire abdominal wall

and not specified in donor-side (mesh side) and contralateral side (no-mesh side) (Q: Have you noticed abdominal bulge or signs of hernia? Y/N).

Investigator assessment was performed with inspection and palpation of the abdominal wall under Valsalva's maneuver at clinical follow-up visits. An abdominal CT scan was performed under Valsalva's maneuver 12 and 24 months postoperatively. One radiologist, blinded to the randomization reviewed all CT scans.

The secondary outcomes were abdominal muscle strength, complications and pain as described. Abdominal muscle strength was measured with fixated hand-held dynamometer before surgery and at 12 and 24 months follow up. All measurements were performed by investigator in the same standardized way using The PowerTrack II™ (JTech Medical Industries, Salt Lake City, USA) (see Supplementary material 1.1, page 121, which illustrates the setup for measuring abdominal muscle strength using the fixed hand-held dynamometer). The patient was placed in a supine position with legs straight and the arms along the body. The dynamometer was placed in a tripod, adjustable with belts, and placed below the xiphoid process. After instruction the patient performed a trial run to familiarize with the dynamometer. The patient was strongly encouraged to perform maximal effort at each trial in a standardized manner. A resting period at 30 seconds was allowed between each test and the test was repeated until peak was clearly reached and the maximum score was chosen. Immediately after the last test the patient was asked to assess pain during the exercise on a Visual Analogue Scale (VAS) instrument.

Donor-site complications were pooled in major and minor complications. Major complications included hematoma requiring surgical intervention, infection requiring surgery, and skin necrosis requiring revision. Minor complications included cellulitis/wound infection requiring treatment with antibiotics and seroma requiring intervention. All complications were identified through review of patient records at 4-month follow-up visit.

Information regarding preoperative abdominal pain or discomfort were obtained from the patient by investigator at the preoperative clinical examination (Q: Do you feel pain or discomfort located to the abdomen? Y/N). The patients fulfilled a study specific questionnaire at follow-up visits consisting of the following four questions: Have you, within the last month, had a feeling of tightness located to the abdomen? (Y/N). Have you, within the last month, had a cutting /stabbing / shooting sensation located to the abdomen? (Y/N). Furthermore, patients completed the Dolotest® (EvidenceProfile ApS, Denmark) regarding abdominal pain at each follow-up visit. Dolotest® is a validated instrument measuring pain intensity and health related quality of life (QoL) in pain patients in average over the past week (13). The instrument consists of eight domains each evaluated on a VAS scale with 0 representing no problems and 100 representing worst possible problems (to what extent do you experience pain; problems with light physical activity; problems with more strenuous physical activity; problems doing your job; reduced energy and strength; low spirit; reduced social life; and problems sleeping) (see Supplementary material 1.2, page 122, which illustrates Dolotest®). Patients were instructed according to the developers' recommendation. A

total score was calculated by summating the eight scores (range 0-800) with higher scores representing worse pain related QoL.

Sample size

Sample size calculation was based on bulging as endpoint. The minimum relevant difference the study was aiming for was a 6 % absolute reduction in bulging frequency between the synthetic mesh and the ADM group. Bulging frequency was estimated by following studies to 7% (14) and 10% (7) for reinforcement with synthetic mesh and 0% (12) for reinforcement with ADM. It was planned to include 20 patients in each treatment arm but inclusion was terminated 16th November 2016 to be able to achieve two years of follow-up within the duration of the project.

Randomization

Patients were randomized using a permuted block design with blocks of 4 and 6 according to the SNOSE principles (15) and a researcher without involvement in the study prepared the allocation sequence. Investigator enrolled patients and an instructed nurse performed the randomization peroperatively.

Blinding

The plastic surgeon wrote a standard text for the patient record without revealing what material was used for reinforcement of the abdominal donor-site. The randomization was revealed if complication occurred, that could be related to the use of reinforcement material and after two years of follow-up. The investigator did not participate during the breast reconstruction procedure and thus the patient, care providers, radiologist, and investigator were blinded for the intervention.

Statistical analysis

Descriptive statistics were used for patients' demographics with stating mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test. Binary outcomes were analysed using generalized linear model with log link function and repeated observations were taken into account. Continuous outcomes were analysed using mixed model for repeated measurements by including patient id as random effect. Due to the small sample size, the Kenward Roger approximation method was used to calculate the degrees of freedom. Follow-up time and the group (ADM or synthetic mesh) variables were used as fixed effects in the model, and the interaction of them. Risk or risk ratios for the dichotomous outcome and mean or mean difference for the continuous outcome were presented with 95% confidence interval and p values. Dolotest® score were scaled up to eight questions for the two patients who answered only seven questions by multiplying their mean score by eight. Two sensitivity analysis were performed. One without the patient who had very high value at four months follow up and influencing the model result and another sensitivity analysis without the two patients who answered only seven questions. Abdominal strength

measurements were adjusted for VAS score. Significance level was set to 0.05. Statistical analyses were performed using STATA® software IC16 (Stata Corporation, College Station, TX).

Ethical considerations and registrations

This study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent. The Ethics Committee of the Central Region of Denmark (1-10-72-10-13) and The Danish Data Protection Agency (1-16-02-7-13) approved this study and it was submitted in ClinicalTrials.gov (NCT02076724). Study data were collected and managed using REDCap electronic data capture tools hosted at Department of Clinical Medicine, Aarhus University. This study followed Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Results

A total of 29 patients were included in the study. After randomization 14 patients were assigned to reinforcement of the abdominal donor-site with ADM and 15 patients to reinforcement with synthetic mesh. No patients were lost to follow-up (Figure 2).

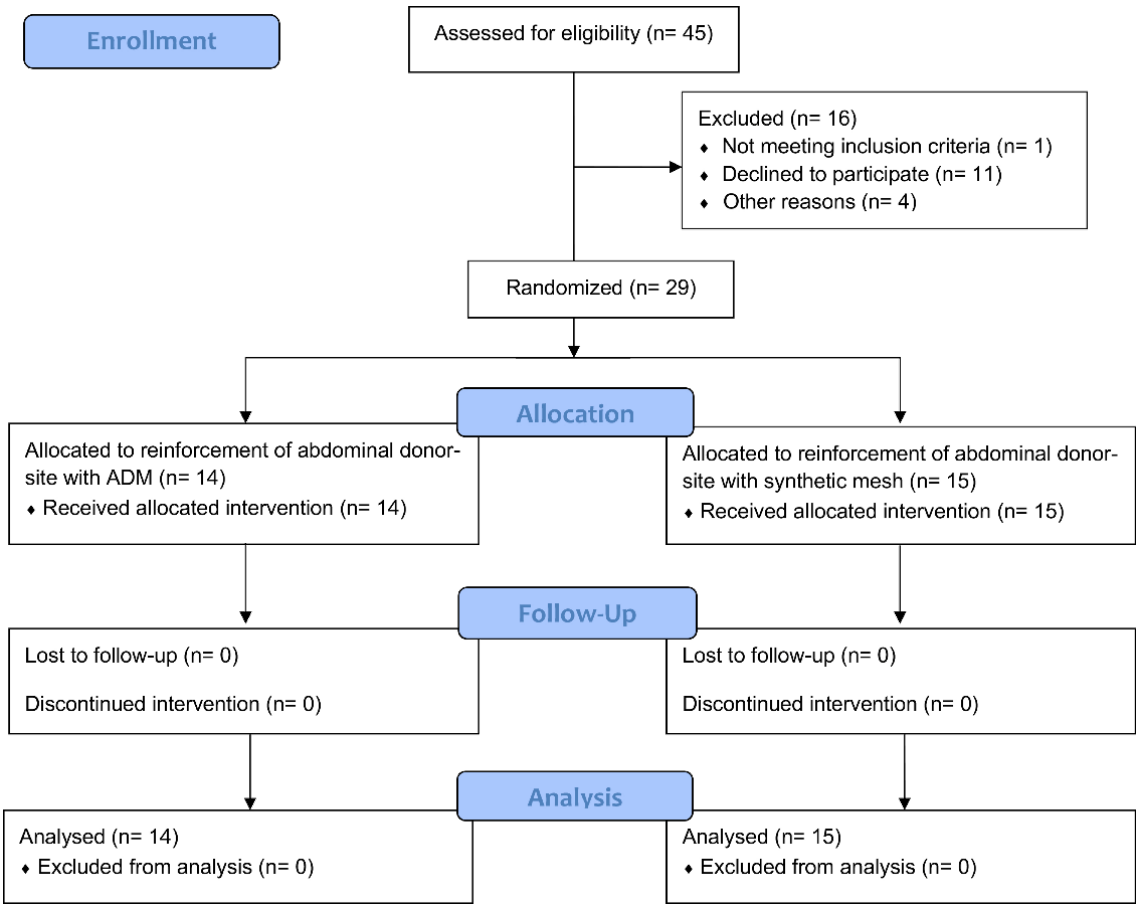

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram.

The two treatment groups did not differ significantly regarding demographics and clinical characteristics as summarized in Table 1.

Table 1. Demographics and clinical characteristics.

	ADM **Patients n= 14**	**Synthetic mesh** **Patients n= 15**
Age, years, mean (SD)	51.9 (8.7)	51.6 (9.9)
BMI, kg/m^2, mean (SD)	26.2 (2.9)	26.4 (3)
Comorbidity ^	5	6
Timing of breast reconstruction Immediate Delayed	 1 13	 0 15
Anti-estrogen treatment	7	10
Pain in abdominal wall prior to surgery	2	0
Former abdominal surgery	7	10
Hospitalization, days, mean (SD)	10 (4)	9.2 (2.8)
Sick leave, days, mean (SD)*	66.6 (32.3)	53.7 (34.3)

BMI indicates body mass index.

^ Missing value for 1 patient in the synthetic mesh group.

** Missing value for 4 patients in the ADM group and 5 patients in the synthetic mesh group.*

The patients observed an increasing tendency of abdominal wall weakness from four to 24 months follow-up where more than 50% in both treatment arms experienced abdominal bulge or hernia (Table 2). Investigator observed no bulging at the donor-side at four months follow-up, but a higher risk in the ADM group (51.7%) compared to the synthetic mesh group (20%) at 24 months follow-up, although this was not significant (RR 2.9, p=0.068). CT scan confirmed bulging at the donor-side in 35.7% of patients in the ADM group, but only in 6.7% of the synthetic mesh group (RR 5.4, p=0.109). The investigator also observed a 21-28% risk of bulging at the contralateral side (no-mesh side) in both groups. This phenomenon was already present at four-month follow-up and did not change through the study period. The investigator observed hernia at the donor-side in two patients (14%) in the ADM group at 12 months follow-up and this finding was confirmed by CT scan at 12- and 24-months follow-up (Figure 1 B). Only one patient in the synthetic mesh group was found to have a hernia at the mesh side at 24 months follow-up, but this was not confirmed by CT.

Table 2. Abdominal bulge or hernia

	ADM n= 14 (n) risk (95% CI)			**Synthetic mesh n= 15 (n) risk (95% CI)**			**RR (95% CI)^**	**P**
	4 months	12 months	24 months	4 months	12 months	24 months		
Patient assessed bulging/hernia	(2) 15.4% (4.2% - 56.3%)	(6) 46.2% (25.4% – 83.9%)	(9) 64.3% (43.2% – 95.6%)	(4) 36.4% (16.4% – 80.6%)	(5) 33.3% (16.1% – 69.1%)	(8) 53.3% (32.9% – 86.3%)	1.2 (0.6 – 2.3)	NS
Investigator observed bulge at donor-side	0	(5) 35.7% (17.5% – 73%)	(8) 57.1% (36% – 90.7%)	0	(4) 26.7% (11.4% – 62.6%)	(3) 20% (7.1% – 56%)	2.9 (0.9 – 8.8)	NS
Investigator observed bulge at contralateral side	(3) 21.4% (7.7% – 59.5%)	(1) 7.1% (1% – 48.9%)	(4) 28.6% (12.3% – 66.4%)	(3) 21.4% (7.7% – 59.5%)	(4) 26.7% (11.4% – 62.6%)	(4) 26.7% (11.4% – 62.6%)	1.1 (0.3 – 3.6)	NS
Investigator observed hernia at mesh side	0	(2) 14.3% (3.9% – 52.7%)	0	0	0	(1) 6.7% (1% – 45.8%)		
CT verified bulge at mesh side	N/a	(5) 35.7% (17.5% – 73%)	(5) 35.7% (17.5% – 73%)	N/a	(2) 13.3% (3.6% – 49.6%)	(1) 6.7% (1% – 45.8%)	5.4 (0.7 – 41.8)	NS
CT verified hernia at mesh side	N/a	(2) 14.3% (3.8% – 54.1%)	(2) 14.3% (3.8% – 54.1%)	N/a	0	0		

N/a, not available, NS not significant.

^ Comparison between groups at 24 months (synthetic mesh group as reference)

There was no significant difference in the mean dynamometer test score between the groups at any time point (p=0.69) and no significant difference between baseline score and 24-month score within any of the two treatment groups (ADM difference -12.2, 95% CI -25.8 - 1.4, p= 0.077; synthetic mesh difference -4.5, 95% CI -18.6 - 9.7, p= 0.519). The ADM group had a higher preoperative mean abdominal muscle strength (53.3 N, 95% CI 39.2 - 67.5) compared to the synthetic mesh group (47.3 N, 95% CI 33 - 61.7), but a lower test score at 24 months follow-up (ADM: 40.9 N, 95% CI 27.1 - 54.7; synthetic mesh 42.8 N, 95% CI (29.5 - 56.1) (Figure 3). Adjusting for VAS score did not change the conclusions.

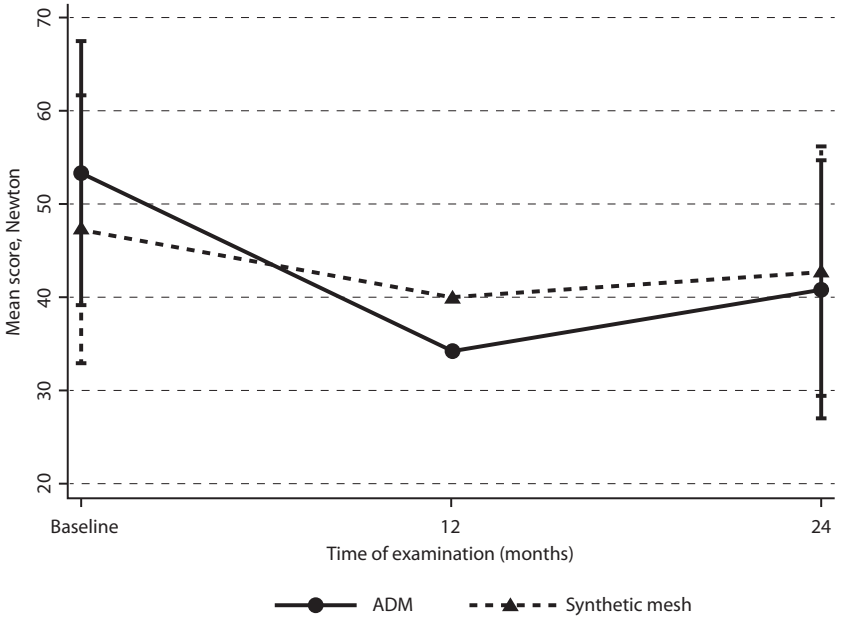

Figure 3. Abdominal muscle strength adjusted for VAS score.

There was no significant difference between groups regarding postoperative complications at the abdominal donor-site. Major complications, resulting in surgery, were distributed as follows: One patient in the ADM group had an infection, two patients in the synthetic mesh group experienced necrosis. No patients in the synthetic mesh group suffered from minor complications, whereas two patients in the ADM group had seroma and cellulitis, respectively.

Feeling of abdominal tightness decreased from four to 24-months follow-up. In the ADM group from 77% (CI 57%-104%) to 43% (CI 23% - 79%), and in the synthetic mesh group from 75% (CI 54%-105%) to 60% (CI 39% - 91%), respectively. At 24-month follow-up there was not statistically significant difference between groups (RR 0.7, p= 0.376). Feeling of cutting/stabbing/shooting sensations also decreased from four to 24-months follow-up. At four-month follow-up 67% (CI 44%-100%) of the patients in the ADM reinforcement group reported cutting/stabbing/shooting sensations which decreased to 43% (CI 23% - 79%) at 24-month follow-up. Similarly, in the synthetic mesh group 82% (CI 62%-109%) of the patients reported cutting/stabbing/shooting sensations at four-month follow-up compared to 53% (CI 33% - 86%) at 24-month follow-up. The difference between groups at 24-month follow-up was not statistical significance (RR 0.8, p= 0.583).

There was no significant difference in pain related QoL between the treatment groups at any of the time points (p=0.65) (Figure 4).

The synthetic mesh group demonstrated a significant decrease in pain related QoL over time (increasing Dolotest® score) as baseline Dolotest® score was 59 points less (95% CI: -117 - 2, p= 0.044) than 24-month follow-up score. In the ADM group a difference at 38 points less at baseline (95% CI -96 - 20, p= 0.197) was observed. The two sensitivity-analysis did not change the conclusions.

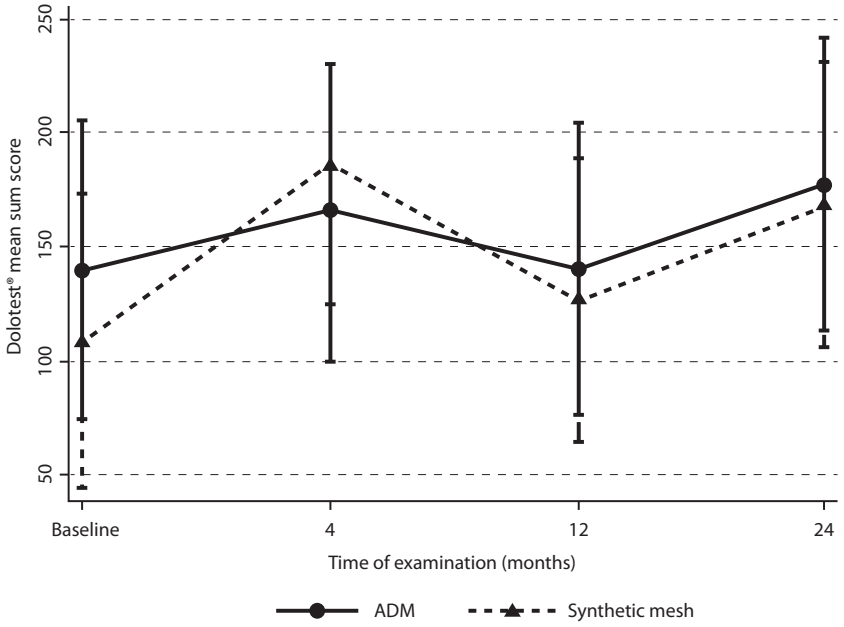

Figure 4: Pain related quality of life. Dolotest® score range 0-800. Higher scores representing worse pain related QoL.

Discussion

The purpose of the present study was to evaluate abdominal weakness in its broadest sense, applying patient- as well as investigator assessment and in addition CT of the abdominal wall. The investigator and CT did not always align in the diagnosis of bulging and herniation and one could argue, that the opinion of the patients is of most importance. Twenty-four months after BR more than 50% of patients observed abdominal bulging. The patients did not distinguish whether the bulge was located at the donor-side or the contralateral side. At the contralateral side an equally high frequency of bulging (21-28%) was observed in the two treatment groups, leading to the conclusion, that the reinforcement material might in some have been tightened too much perioperatively, resulting in paradox bulging of the contralateral side of the abdominal wall. This phenomenon has, to our knowledge, not been described by others. Both investigator and CT scan observed a higher frequency of bulging at the donor side at 24-months follow-up in the ADM group compared to the synthetic mesh group although this tendency was not significant (investigator p=0.068; CT scan p=0.109). CT diagnosed hernia was only observed in the ADM group (14%). One other study has used the same ADM product and found no development of bulge or hernia within a 10-20 months period after surgery. The diagnose of bulge or hernia was in this study based upon clinical finding in a standing position without Valsalva's maneuver. No CT scan was performed to verify the clinical finding

(12). The rate of CT verified bulging and hernia in the synthetic mesh group of this study after 24-months follow-up (bulging 6.7%; hernia 0%) is in accordance with previously published data from our institution after reinforcement with synthetic mesh (bulging 10%; hernia 0%) (7) and comparable with hernia and bulge risk found by others after reinforcement with synthetic mesh (16, 17).

Multiple factors play a role in the risk of development of hernia or abdominal weakness after TRAM flap surgery including obesity (18), prior lower abdominal surgery with midline incision (19) and chemotherapy (20). None of the patients in this study had a BMI>30 kg/m^2, received adjuvant chemotherapy or had undergone abdominal surgery with midline incision. Recently Huber et al. investigated the association between anti-estrogen treatment and development of bulge or hernia. They found increased odds ratio for development of hernia (OR 1.5, 95% CI 0.698-3.311) for patients treated with anti-estrogen therapy compared with patients not treated with anti-estrogen medication (16). The present study could not verify this. Patients not receiving anti-estrogen treatment had a 42% higher risk of developing bulge or hernia at the abdominal donor-site than the patients treated with anti-estrogen medicine at 24-months follow up (RR 1.42; 95% CI 0.43 - 4.67, p= 0.57).

Other biological materials have been studied in an attempt to find a substitute for synthetic mesh. In 1998 a study was published using dermal autograft for reinforcement of the pedicled TRAM flap donor-site where a bulging rate at 8.6% and hernia rate at 4.2% was demonstrated (21). Later Glasberg et al. used human acellular dermal matrix (Alloderm) for reinforcement and found a bulging rate at 16.7% with insertion under appropriate tension and no explantation of the biological mesh despite exposure (22). In 2009 Boehmler et al. demonstrated a bulging rate at 20% with reinforcement with Alloderm inlay graft and primary closure but also concluded that synthetic mesh as an inlay graft had a lower bulging rate (5%) and that Polypropylene mesh was preferable over human ADM when mesh was needed (14). In a meta-analysis from 2011 Adetayo et al. found a bulging rate at 28.1% and hernia rate at 27.6% after reconstruction of the abdominal wall with Alloderm (11). Others have used porcine ADM in a cross-linked variety for reinforcement of the abdominal donor-site after TRAM flap BR. Reinforcement with this material resulted in 50% incidence of local wound complications and more than 25% developed hernia. The authors hypothesized that the complications were due to limited tissue integration and chronic inflammation, a foreign body reaction in the subacute period that might be attributed to the preparation of these cross-linked collagen products (23). It has previously been shown that non-crosslinked porcine ADM became infiltrated with host cells and vessels rather than being encapsulated by scar tissue, as occurred with cross-linked porcine ADM (24).

Abdominal wall function has been assessed by using different objective measurements including the ability to perform sit-ups (25) and by isometric dynamometer (26, 27). In this study hand-held dynamometer fixed with a tripod was used to measure concentric activity (muscle contracting whilst simultaneously shortening). This method has previously been found reliable for the assessment of back extensor muscle strength (28). Analysis were adjusted for VAS score as it was expected, that patients would perform worse if the exercise induced pain. The present study did not demonstrate any statistically

significant difference in mean concentric abdominal muscle strength between the treatment groups at any timepoint. Furthermore, no statistically significant difference between 24-month follow-up and baseline mean test score in any of the treatment groups was found. It was expected to see a decrease in abdominal muscle strength after transposition of one of the rectus muscles, and the result in this study is in accordance with Dulin et al. who found a decreased abdominal strength, but not significant, after one year in the pedicled TRAM flap group (27). In contrast, Kind et al. demonstrated a significant impairment of isometric trunk flexion for the pedicled TRAM flap group at one-year follow-up (26). It was expected to see that the patient with time regains strength of the abdominal muscles or use adjacent muscles to compensate. This phenomenon has also been demonstrated by others (26).

The hypothesis that reinforcement using synthetic mesh leads to discomfort or pain due to the rigid properties of the material could not be verified. Even though patients in the ADM group experienced less abdominal tightness and less cutting /stabbing /shooting sensations this was not statistically significant (p= 0.376 and p= 0.583, respectively). Atisha et al. reported that 45% - 50% of patients reconstructed with the pedicled TRAM flap reported tightness in the abdomen with a mean follow-up time at 7.7 years after BR (29). Compared to this, the result of this study does not stand out. In the present study no effect of reinforcement material on pain related QoL measured by Dolotest ® was demonstrated. But it was noted that the synthetic mesh group had a significantly higher score (decreasing pain related QoL) at 24-months follow-up compared to baseline. This should be taken with some precautions as this group had a lower baseline score compared to the ADM group.

The randomized and blinded study design is a strength for this study. Furthermore, only three experienced surgeons and one investigator was involved. Any detectable bulge or hernia was registered by the independent investigator (MEB) and in addition, objective evaluation of the endpoints (CT scan, dynamometer) was applied. This study is limited by small sample size and consequently large confidence intervals. Due to a decreased number of patients referred to BR with the pedicled TRAM flap it was not possible to include the planned number of participants in the study. A study specific questionnaire was used to assess pain as a Danish version of a validated questionnaire to assess postoperative outcome e.g. Breast-Q was not available.

Many plastic surgeons would aim for using the deep inferior epigastric perforator (DIEP) flap for autologous BR when possible, but the TRAM flap may be a valid alternative in selected patients and is still an important part of the plastic surgeon's armamentarium like other rectus abdominis muscle-based flaps for reconstruction of perineal, pelvic, thoracic and head and neck defects.

Therefore, further randomized studies are necessary to identify techniques or materials to decrease the donor-side morbidity after reconstruction using rectus abdominis muscle-based flaps. In the present study hernia and bulge at the donor-side were diagnosed at 12-month follow-up and remained unchanged until 24-month follow-up leading to the conclusion, that for studies aiming to describe hernia and bulging frequency, 12 months follow-up time may be the minimum.

Conclusion

The present study did not demonstrate any statistically significant differences between treatment groups regarding risk of bulging or hernia, postoperative abdominal muscle strength, complications, pain or pain related QoL within two years of follow-up. Thereby the hypothesis that reinforcement with ADM is superior to reinforcement with synthetic mesh cannot be confirmed. Further research into methods for decreasing donor-side morbidity related to the TRAM flap or other rectus abdominis muscle-based flaps is needed. Finally, bulging and herniation seems to develop within the first postoperative year and for future studies aiming to investigate this endpoint 12 months is suggested to be the minimum time of follow-up.

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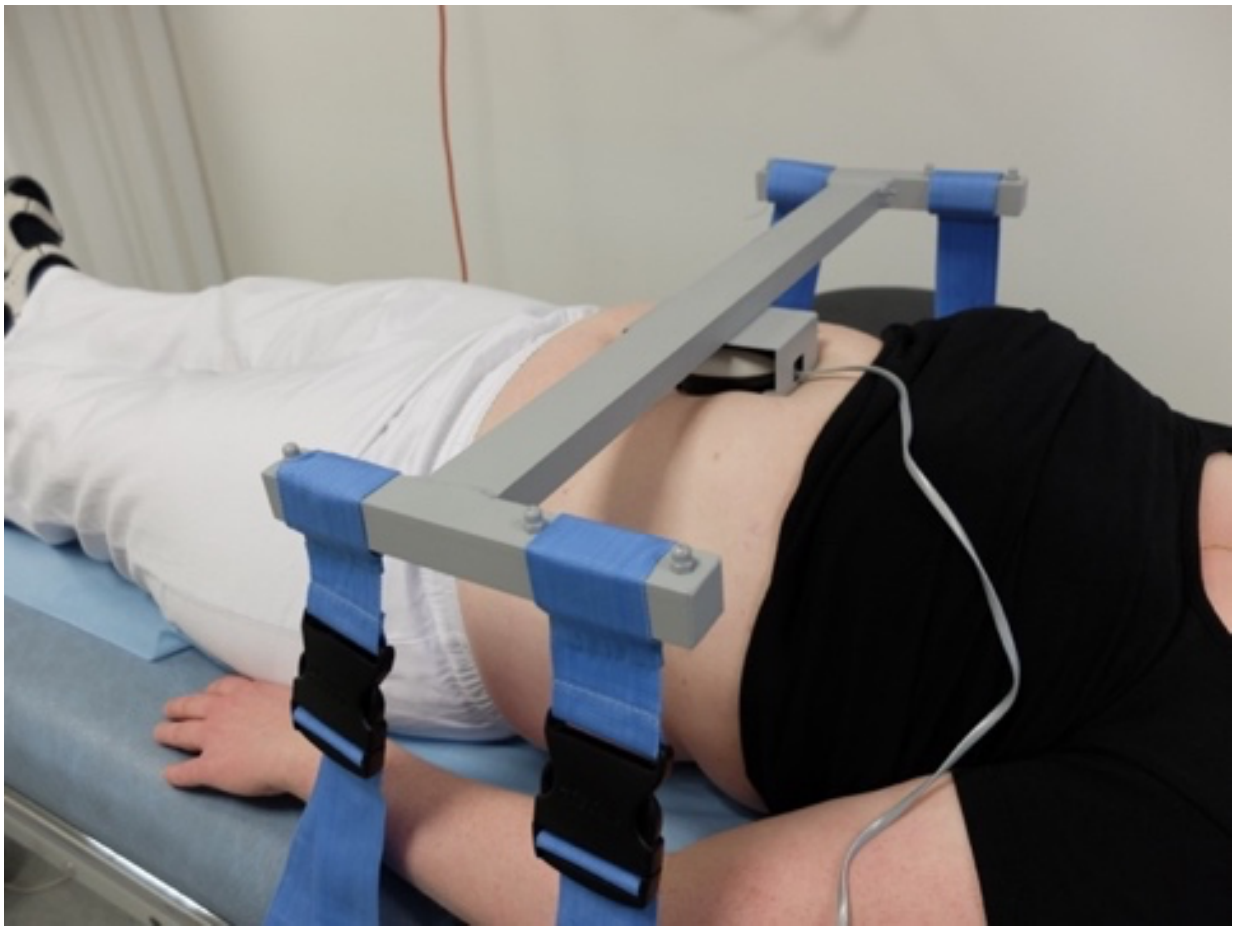
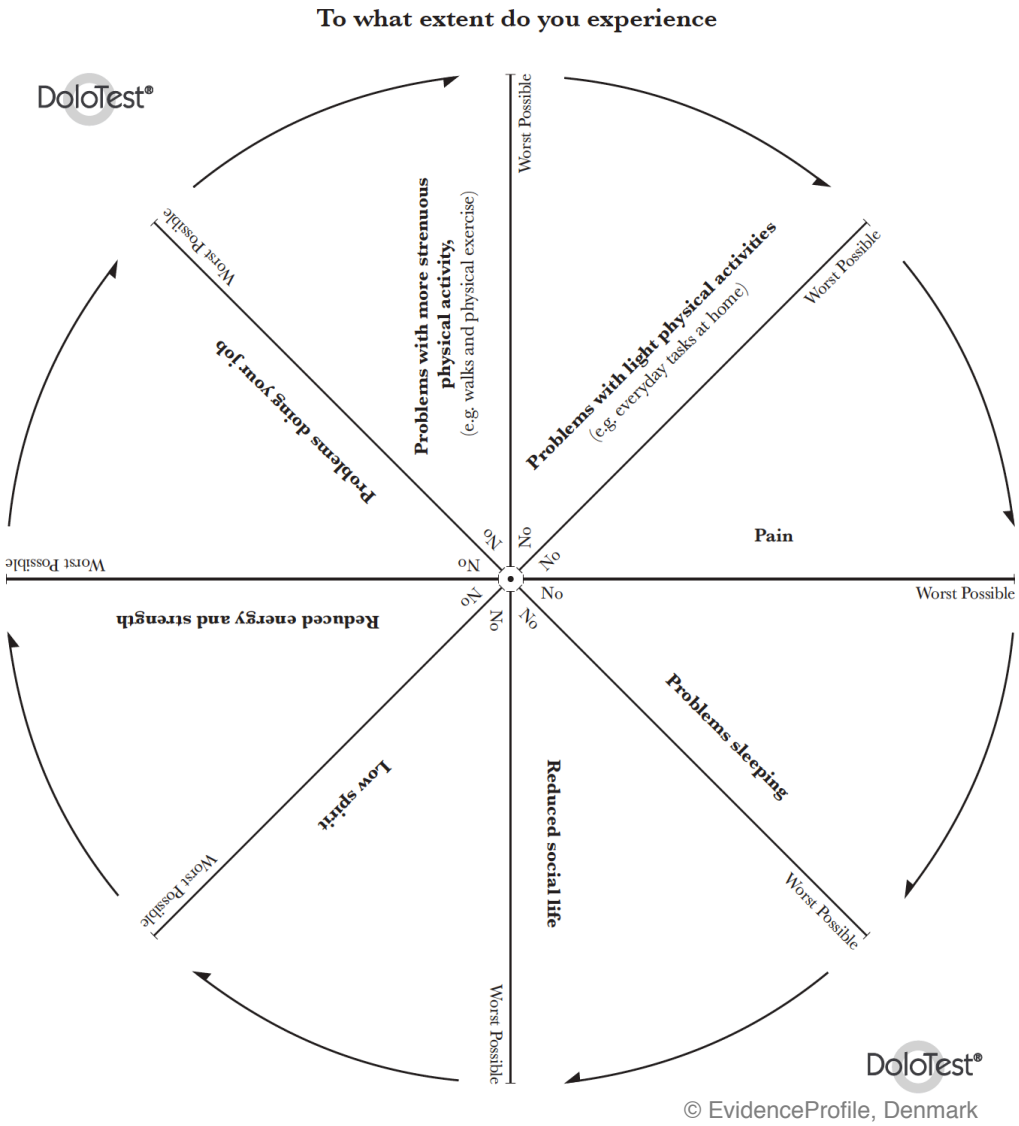
Supplementary material manuscript III

Supplementary material 1.1



Setup for abdominal muscle strength measurement using fixated hand-held dynamometer.

Supplementary material 1.2



Dolotest® instrument.

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Mette Eline Brunbjerg

This declaration concerns the following article/manuscript:

Title:	Reinforcement of the abdominal wall with acellular dermal matrix or synthetic mesh after breast reconstruction with the pedicled transverse rectus abdominis musculocutaneous flap. A prospective double-blind randomized study.
Authors:	Mette Eline Brunbjerg, Thomas Bo Jensen, Peer Christiansen, Jens Overgaard, Tine Engberg Damsgaard

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Journal of Plastic Surgery and Hand Surgery

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study protocol was designed by the PhD student and main supervisor in collaboration. The detailed description of the study, setup of research facilities and organization of the study programme was primarily done by the PhD student.	
The acquisition, analysis, or interpretation of data:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has collected all data and interpreted all analyzes. Data analysis was carried out in collaboration with a statistician.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student has prepared the first draft of the manuscript. This was discussed with the co-authors and adjusted accordingly.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
Submission of the manuscript was performed by the PhD student.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
7/8 2020	Mette Eline Brunbjerg	Mette Eline Brunbjerg
7/8 2020	Tine Engberg Damsgaard	Tine Engberg Damsgaard

Date: 8/8 - 2020

Mette Eline Brunbjerg

Signature of the PhD student