Autologous Fat Transfer for Total Breast Reconstruction

From Trials to Triumphs



W.B.W. van der Venne

stellingen behorende bij het proefschrift

AUTOLOGOUS FAT TRANSFER FOR TOTAL BREAST RECONSTRUCTION
From Trials to Triumphs

Wessel Benjamin William van der Venne

1. Reconstruction should be tailored to individual preferences, lifestyle and psychosocial context to optimise satisfaction and thereby Quality-of-Life. (this thesis)
2. AFT is a safe breast reconstruction technique that does not increase the long-term risk of oncologic events or negatively affect overall survival. (this thesis)
3. EVE does not significantly increase graft retention and augmentation percentage, and additional evidence is needed to establish the clinical relevance and appropriate application of EVE in AFT-breast reconstruction. (this thesis)
4. Standardised e-learning can meaningfully support clinical decision-making and facilitate broader implementation of AFT. (this thesis)
5. Studies on intratissular expension techniques, exploring alternative methods to reduce treatment burden, without affecting graft retention, have been initiated.
6. Er is niks standaard in de plastische chirurgie. (drs. Marleen Meesters)
7. Het is de taak van de oncologisch chirurg om radicaal te zijn, en van de plastisch chirurg om dit te herstellen. (Prof. dr. dr. Andrzej Piatkowski)
8. Laat het eerst maar eens mooi granuleren. (dr. Tom van Mulken, dr. Mark Smeulders)
9. There's nowt so queer as folk.
10. Jij sterft nog eens voor schoonheid. (Mascha van Es)

Autologous Fat Transfer for Total Breast Reconstruction:
From Trials to Triumphs

Wessel Benjamin William van der Venne

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Autologous Fat Transfer for Total Breast Reconstruction

From Trials to Triumphs

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I

Introduction

HISTORY OF RECONSTRUCTIVE SURGERY

Reconstructive surgery is the surgical process of restoring form and function of a body part affected by trauma, disease or congenital defects.[1,2] From 1838 on, these surgeries were additionally named 'plastic', referring to the Greek *Plastikós,* which means mouldable.[3] The earliest allusions to plastic and reconstructive surgery are again found in Greek sources, exemplified by Achilles' care for Patroclus' wounds in Homer's Iliad. The first non-mythical reconstructive surgery is described as early as 600 B.C. when Shushruta originated the forehead flap for nasal reconstruction.[4] However, the first complete book on reconstructive surgery was not written until 1597, when the *Curtorum Chirurgia per Insitionem* was published by Gaspare Tagliacozzi. His work describes the 'Italian method' of using a pedicled flap from the arm to reconstruct the nose, and contains systematic approaches and even anatomic illustrations.[5] However, despite his efforts, reconstructive surgery would only become more successful centuries later, when anaesthesia, antibiotics and antiseptic measures made it feasible.

History of Reconstructive surgery of the breast

The female breast is not exempt from congenital anomalies, disease or traumatic injury, and can consequently require reconstructive procedures. In 1895, Vincenz Czerny performed the first systematic approach of a reconstruction of the breast. Czerny performed a mastectomy for a benign tumour, and reconstructed the breast by transplanting a large lumbar lipoma to the defect. [6] Since then, breast reconstructions have continuously undergone refinements and innovations. A major development was the introduction of alloplastic breast reconstructions. Alloplastic, commonly Referred to as Implant-Based Reconstructions, were already on the scene in the 1800s, but only gained popularity after Cronin and Gerow successfully placed the first silicone implant for primary breast augmentation.[7]This development resulted in the division of breast reconstruction into autologous breast reconstruction (ABR) and Implant-Based Reconstruction (IBR).

Voyages, Virtues and Vices

Implant-based reconstruction

Following the introduction of the first silicone implant by Cronin and Gerow, prosthetics were soon applied not only for augmentation but also for post-mastectomy reconstruction.[8] Alongside Cronin, Dingman and

Rees were among the early pioneers in this field. Since the 1960s, IBR has evolved considerably. A major limitation, insufficient soft-tissue coverage after mastectomy, was addressed by Radovan, who introduced the tissue expander, an inflatable device gradually filled with saline to create a pocket for the definitive implant.[9] This two-stage approach became the gold standard from the 1980s onward.[10] Subsequent refinements, including the use of acellular dermal matrices, pre- or subpectoral placement, and variations in implant surface texture, have further shaped the technique, though no consensus on an optimal approach has been reached.[11] However, the aesthetic outcome is often less natural, and complications such as capsular contracture, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), and systemic responses described as Breast Implant Illness or the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) have been reported.[12,13] Moreover, implants are less compatible with postoperative radiotherapy, which may further compromise aesthetic and reconstructive outcomes.[14]

Autologous breast reconstruction using flaps

Several decades after Tagliacozzi, Italy once again produced a pioneer in reconstructive surgery: Iginio Tansini of Pavia. He introduced the pedicled latissimus dorsi flap for post-mastectomy reconstruction. Although described in 1896, it was not until the 1970s that his technique became standard practice. The term flap derives from the Dutch flappe, referring to tissue that hangs freely while remaining attached on one side.[15] The principle of the pedicled flap is to transfer tissue while maintaining its vascular pedicle. In 1979, Holström reported the first free Transverse Rectus Abdominis Muscle (TRAM) flap, paving the way for Koshima and Soeda, who introduced the Deep Inferior Epigastric Perforator (DIEP) flap, sparing the rectus abdominis muscle. [16,17] Robert Allen later standardised the DIEP flap in 1992, making it a mainstay of autologous reconstruction.[18] Autologous reconstruction offers several advantages: it is biocompatible, repurposes excess adipose tissue, and produces a softer, warmer, and more natural breast. Sensory recovery and long-term satisfaction are superior to implant-based reconstruction, while fewer secondary procedures are required. [19-21] However, free-flap reconstruction is demanding, often lasting up to eight hours depending on flap type and surgeon experience, and leaves long donor-site scars with prolonged recovery. [22] Complications such as infection, seroma, pulmonary embolism, or total flap loss can occur. [23-25] Moreover, sufficient donor tissue is essential, limiting options for women with small body habitus.

Autologous reconstruction using fat transfer

Since the pioneering work of Czerny, fat grafting to the breast has remained a topic of both interest and controversy. In the 1950s, it was mainly used to correct small contour defects of the face and breast, with highly variable outcomes.[26] The mechanisms underlying graft survival were, and still are, not fully understood, and fat necrosis often led to oil cyst formation, rendering the technique unreliable at the time. In the 1980s, Illouz, Fournier, and Klein introduced minimally invasive, atraumatic harvesting methods, improving safety. Later, Bircoll and Novak reported the first breast augmentation using fat grafting, marking the advent of lipofilling.[26] However, the American Society of Plastic and Reconstructive Surgeons (ASPRS) raised oncologic concerns that oil cysts might obscure early cancer detection, and their cautionary statement effectively halted its clinical use. [27] A decade later, Coleman revitalized the technique by standardizing atraumatic harvesting, centrifugation, and microdroplet injection, which improved graft survival and reproducibility. [26,27] Building on this work, Khouri and Piatkowski proved AFT's efficacy as a stand-alone breast reconstruction, combined with external vacuum expansion of the recipient site to enhance vascularisation and graft take. [28,29] In recent years, technical refinements have continued. The use of closed liposuction systems now allows for atraumatic fat harvesting and reinjection without the need for centrifugation, minimising manipulation and contamination of the graft. This approach, together with pre-expansion techniques such as EVE® or BRAVA®, represents the next evolution in fat grafting, aiming to simplify the procedure, shorten operative time, and improve graft viability.[30] AFT-reconstructed breast hold the same advantages as other autologous techniques, such as the soft and warm feel and natural ptosis. Furthermore, the technique is minimally invasive with shorter operative time, while leaving no lengthy scars. Lastly, it offers women with small habitus, who have no sufficient donor site for flap reconstruction, another autologous option. However, AFT can still be burdensome, as several sessions of AFT are required to reconstruct a total breast due to limited graft survival.[28,29]

Autologous Fat Transfer: Status Quo

The multicentre randomised controlled BREAST-I trial proved AFT to be a safe and effective stand-alone breast reconstruction technique. It showed to be superior to IBR in patient satisfaction, but also sensibility, donor site satisfaction and cost effectiveness.[29,31,32] These findings led to the inclusion of AFT in the Dutch basic health insurance in January 2023. [33] Although implant-based and free-flap reconstructions remain the most

frequently performed techniques, the results of the BREAST-I trial have positioned AFT as an emerging alternative within reconstructive breast surgery. Consequently, its popularity has increased, and many women across the Netherlands now request this method of reconstruction. Since 2023, 350 women in the Netherlands have opted for a breast reconstruction via AFT. Several measures have been undertaken to support clinical implementation. Rijkx et al. addressed key radiological considerations in oncologic follow-up, clarifying what radiologists need to recognise after fat transfer.[34] Additionally, perioperative use of antibiotics in AFT-breast reconstruction has been researched, and prolonged use of antibiotics has been found ineffective.[35] Nevertheless, AFT is still in its nascent phase, compared to reconstructive techniques that have been well established for decades. Several aspects of AFT have not been thoroughly researched due to its novelty. Broader generalisability must be established, followed by further technical refinement and structured training for plastic surgeons. Moreover, while national acceptance has grown, the oncological safety of AFT continues to be debated internationally, and ongoing efforts are required to support its clinical implementation.

AIM OF THIS THESIS

The aim of this thesis is to gain a more comprehensive understanding of AFT as a total breast reconstruction technique and, where possible, to refine it further. Following the results of the BREAST-I trial, several questions have arisen. In this thesis, subsequent research aims to address five of these questions. Firstly, though AFTs safety and efficacy has been proven in a randomised controlled trial, it should be assessed in a larger cohort.

Research question 1: ***'Does AFT as a total breast reconstruction improve the Quality of Life, and is it a safe technique?'***

When considered in the context of breast reconstruction, safety pertains not only to procedure-related complications but also to oncological safety.

Research question 2: ***'Does AFT as total breast reconstruction (negatively) affect the risk of breast cancer recurrence, distant metastases or overall survival?'***

We know from the BREAST-I trial AFT proved superior to IBR in QoL and cost-effectiveness, but how does AFT compare to other autologous techniques, such as the well-established DIEP-flap?

Research question 3: ***'How does an AFT-reconstructed breast compare with a DIEP flap breast, from a patient's perspective?'***

After establishing safety and efficacy, AFT can be gradually implemented into the Dutch Healthcare system. To facilitate this implementation on a national level, our team have developed an e-learning module designed to introduce AFT. This e-learning aims to educate plastic surgeons in this new technique, and alleviate their demanding schedules.

Research question 4: ***'Is an E-learning module an effective way to educate experienced plastic surgeons in a new breast reconstruction technique?'***

As with any emerging surgical technique, AFT remains subject to refinement. Several aspects of this reconstructive approach are not yet fully understood and continue to be explored. The perioperative use of External Vacuum Expansion (EVE) by the EVE bra® (Lipocosm) can be experienced as burdensome for patients. They often describe pain, skin irritation and pruritus. The primary purpose of this device is to enhance graft survival and augmentation percentage, hereby achieving greater breast volume; however, its efficacy in reconstructive contexts has not been thoroughly assessed.

Research question 5: ***'Is the External Vacuum Expansion in total breast reconstruction using AFT effective to achieve greater breast volumes?'***

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II

Evaluation of the BREAST-II Trial for Total Breast Reconstruction Solely Using Autologous Fat Transfer: 1-Year Follow-Up

A multicentre nonrandomised clinical trial

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ABSTRACT

Background:

Autologous Fat Transfer (AFT) has emerged as a promising technique for total breast reconstruction post-mastectomy, particularly in patients unsuitable for other reconstruction methods. Evaluating its efficacy, safety, and impact on quality of life is essential.

Objective:

To assess the efficacy and safety outcomes of AFT as total breast reconstruction in women post-mastectomy, based on 12-month follow-up data from the BREAST-II trial.

Methods:

This multicentre, nonrandomised clinical trial included women aged ≥18 years with a history of or planned mastectomy across eight Dutch hospitals. Participants underwent multiple AFT sessions combined with external expansion using the EVE-bra device, with a maximum of five sessions over 12 months. Primary outcome was quality of life measured by BREAST-Q and BODY-Q questionnaires. Secondary outcomes included safety (serious adverse events [SAEs]), operating time, hospital stay, and number of sessions.

Results:

A total of 229 women were included. At 12 months post-AFT, significant improvements were observed in psychosocial well-being (+5.72 ±16.79), sexual well-being (+8.05 ±19.61), physical well-being of the chest (+5.97 ±20.44), and chest satisfaction (+17.22 ±27.27) (all $p<0.001$). BODY-Q scores showed significant increases in satisfaction with abdomen, back, body, hips/outer thighs, inner thighs, and scars (all $p<0.001$). Among 805 AFT sessions, 52 (S)AEs occurred (6.46% complication rate). Hospital stays were less than one day per session.

Conclusions:

AFT is an effective and safe total breast reconstruction technique post-mastectomy, significantly improving quality of life with low complication rates. These findings support AFT as a valuable addition to breast reconstruction options.

INTRODUCTION

Breast cancer is the most prevalent malignancy among women worldwide.[1] Fortunately, due to effective treatment and early detection, breast cancer survival rates have increased. [2] This permits further research into Quality of Life (QoL) after mastectomy and breast reconstruction. Breast reconstruction following mastectomy is roughly divided in autologous breast reconstruction (ABR, mostly via free flaps such as the DIEP-flap)[3] and implant based reconstruction (IBR). Post-mastectomy breast reconstruction is known to improve QoL. [4,5] When comparing the two, ABR has a more positive effect on QoL than IBR. [6,7] However not all women are eligible for ABR using free-flaps, as it requires a substantial excess of tissue in one donor area. Women (With a small body habitus) were in need of a reconstruction technique that was not dependent on implants or one substantial donor area. In search of a new autologous technique to accommodate more women, autologous fat transfer (AFT) was introduced. A technique described as early 1987, and adapted and standardised by Coleman.[8-10] This minimally invasive technique utilises multiple donor sites with modest surplus of adipose tissue. In several sessions, the breast is reconstructed by harvesting adipose tissue via liposuction and injecting this into several subdermal planes on the thorax.[11] Khouri then added the use of pre- and postoperative external expansion of the thoracic skin, and further developed the technique.[11,12]

AFT as a total breast reconstruction was investigated in the BREAST trial, a randomised controlled trial comparing AFT to IBR.[13] Inclusions of the BREAST trial ended on October 1st 2019. Though this trial and literature showed promising preliminary results [12], all participants needed to finish their reconstruction process and reach the end point of 12 months post-reconstruction before definitive results could be analysed and published. Awaiting these results and the verdict of the Dutch Health Ministry, AFT gained attention and more women requested this reconstruction. At this point, the technique was still experimental and could only be performed in a trial setting by experienced and well-trained plastic surgeons. This study, the BREAST-II trial was set up to accommodate these women in their wishes and further investigate the efficacy and safety of AFT in a larger cohort without randomisation, and compare postoperative QoL to preoperative QoL. Following the results of the BREAST trial, hypotheses are that AFT is a safe and effective autologous breast reconstruction technique. This article reports the one-year follow-up of the BREAST-II.

METHODS

Study design

This interim analysis of the BREAST-II trial reports the 12-month follow-up results. The BREAST-II trial is a multicentre nonrandomised clinical trial, as participants were actively recruited and included, and given an (at that moment in time) experimental treatment. The study adheres to the TREND guidelines.[14] Ethical approval was obtained by the Medical Ethics Committee of Maastricht University Medical Centre (METC20-005). Informed consent was obtained from all included patients. Inclusion of patients occurred from December 9, 2020, to March 16, 2022.

The trial included eight hospitals across The Netherlands, for an overview, see appendix 1. Three new centres were added to the centres that participated in the BREAST trial.

Participants

To be eligible for this trial, women had to be at least 18 years of age, a mastectomy in their medical history or a planned (preventative) mastectomy in near future. Participants wished for AFT as a total breast reconstruction, they had to be able to wear the external expansion device EVE-bra device [15]. Exclusion criteria included , but were not limited to, a Body Mass Index (BMI) over 30 kg/m^2, a breast size larger than cup C (unless the patient preferred a reduction mammoplasty contra laterally towards a cup C). A complete overview of inclusion and exclusion criteria can be found in appendix 2. Patients could be referred to participating centres through general surgeons, other plastic surgeons or general practitioners. Participants were included if they were eligible and interested after several reconstruction interviews with participating plastic surgeons.

Intervention

All patients received a total breast reconstruction via AFT, accompanied by EVE-bra usage. Patients started four weeks preoperatively with the EVE-bra device to gradually increase hours. Eventually the device was worn for a minimum of 10 hours per day, with a minimum total of 200 hours preoperatively. The last 48 hours preoperatively, the device was worn continuously up until the surgery. The preoperative setting included intermittent negative pressure, alternating between -20 and -60 mmHg. Postoperatively, no pressure was applied to the breast for five days. After five days, the EVE-bra was used again for 10 hours per day, with a

continuous negative pressure of -20 mmHg, for a period of two weeks. A minimum wait of ten weeks between mastectomy and AFT-reconstruction was upheld to ensure safe use of the EVE-bra. For the harvesting of fat cells and re-injection, basic principles of Coleman were used. [16] First, incisions of two to three millimetres are made in the donor area, specified in table 1. Then a saline solution and lidocaine with adrenaline is infiltrated into the fat grafting area. After this, fat is harvested, either manually or with the help of power-assisted liposuction. The fat is then filtered or decanted with the preferred method of the performing surgeon. In this trial most surgeons used gravity assisted separation. After fat-preparation, the fat graft is infiltrated into the breast in micro-droplets and aliquots in different planes and depths. Postoperative check-ups were in the outpatient clinic at two and six weeks postoperatively. A minimum of ten weeks between consecutive AFT-sessions was mandatory. The number of sessions was determined by the desired volume and shape of the breast and fat graft survival per operation, with a maximum of five sessions in this trial. The reconstructions were performed by plastic surgeons from the participating centres.

Table 1. Preferred donor sites

Donor sites
Abdomen
Lumbar region
Flanks
Lateral thigh area
Medial thigh area, either proximally or distally

Outcomes

The primary outcome was the effect of AFT on breast and body-related QoL 12 months postoperatively. The validated Dutch questionnaires BREAST-Q and BODY-Q version 2.0 were used to measure QoL. The included domains: psychosocial wellbeing, sexual wellbeing, satisfaction with breast area, physical wellbeing of the chest area, satisfaction with abdomen, satisfaction with back, satisfaction with body, satisfaction with hips and outer thighs, satisfaction with inner thighs and satisfaction with scars. These domains covered the satisfaction related to the reconstructed breast(s) as well as donor sites. Included patients received the questionnaire upon inclusion, 12 and 24 months after the last AFT.

The secondary outcome was the safety of AFT, according to the number of non-oncological adverse events (AEs) and serious adverse events (SAEs) during the treatment. AEs and SAEs were reported by the surgeons according to a pre-specified list. Only AEs related to the treatment, or which had impact on the reconstruction were included. Known, frequently occurring and transient AEs related to anaesthesia, or the external vacuum expander (EVE) were not included. Another outcome was efficacy, according to the number of required AFT-sessions, the operating time (OT) and the treatment time. The treatment time was defined as the time between two weeks before the first AFT session (i.e. start of EVE-bra usage) and the six-week follow-up of the last AFT-session.

Data collection

Data were collected in the system of Castor, Castor EDC (Ciwit B.V., also known as "Castor", Amsterdam, The Netherlands; versions 2020.1, released 12 Feb 2020, to 2025.2.0.0, released 01 Jul 2025) is an electronic data capture platform designed for clinical and research data management. It supports secure, web-based case report form creation and complies with international standards and regulations, including FDA 21 CFR Part 11, GDPR (EU), ICH GCP, HIPAA (US), ISO 27001, and ISO 9001. Data were collected pre- and post-surgery, during clinical check-ups and during the entirety of the trial. Data consisted of BREAST-Q and BODY-Q scores, baseline characteristics, surgical information per session and oncological and non-oncological (S)AEs.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 27 (IBM Corp). The difference in QoL preoperatively and 12 months postoperatively was expressed as the mean difference and 95% confidence interval and tested for differences using the paired 2-tailed t-test. A 2-tailed p-value < 0.05 was considered significant. We used stochastic regression imputation with fully conditional specification to impute incomplete records. Imputations for continuous variables were drawn using predictive mean matching; logistic regression was used for categorical variables. We imputed outcome variables and patient characteristics (e.g. age, BMI, bra- and cup size pre-mastectomy and prior breast reconstructions).

RESULTS

From December 9, 2020, to March 16, 2022, a total of 229 patients were included in eight hospitals (Appendix 1). Due to drop-out, 196 patients were analysed for the primary outcomes. The patient flow diagram is presented in Figure 1.

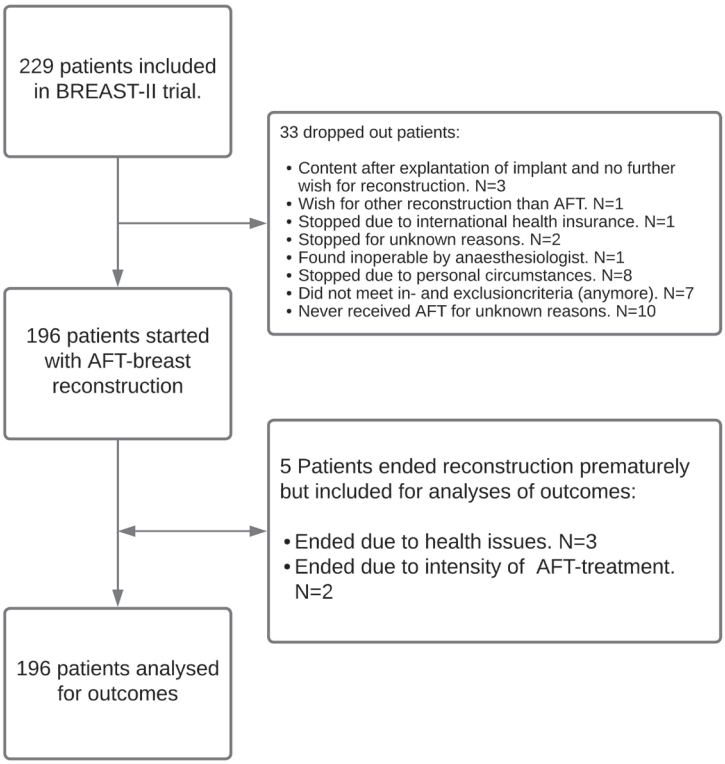

Figure 1.

Baseline characteristics

Baseline characteristics can be found in table 2. The majority of participants had received a prior breast reconstruction, four of which had an autologous reconstruction beforehand which included DIEP-flap, Latissimus Dorsi (LD) flap [17] and septocutaneous gluteal artery perforator (ScGAP) makeover flap.[18]The flaps were either on the contralateral breast or did not achieve aspired result due to total flap-loss. After prior reconstruction (either failed flap, TE/IBR with clinical complaints) the flap was removed, TE/IBR explanted. After this, a minimum of 10 weeks recovery was upheld so that the external expander could be used before total breast reconstruction using AFT. In total, 162 women (82.65%) had

(a history of) breast cancer (bilateral and/or unilateral) and 34 women (17.35%) who did not have breast cancer. These 34 women all received bilateral mastectomies and bilateral reconstructions. Tumour characteristics of the breast cancer can be seen in table 3, which is divided in right and left breast. Results of AFT breast reconstructions of two participants can be seen in figure 2 and 3.

Table 2. Baseline patient characteristics.

	Baseline characteristics	N(% of total N=196)
Age, mean (SD) in years	49.8 (±10.51)	
BMI, mean (SD) in kg/m^2	24.6 (±2.57)	
Bra size, mean (SD) in cm	79.8 (±5.56)	
Cup size	AA	3 (1.53)
	A	16 (8.16)
	B	74 (37.76)
	C	64 (32.65)
	D	20 (10.20)
	E	9 (4.59)
	F	2 (1.02)
	G	1 (0.51)
	Not reported	7 (3.57)
	Total	196
Genetic Mutation	BRCA-1	26 (13.27)
	BRCA-2	19 (9.69)
	BRCA-1 and BRCA-2	1 (0.51)
	CHECK2	1 (0.51)
	No	107 (54.59)
	Not reported	44 (22.45)
(History of) Breast cancer	Yes, Unilateral (and unilateral reconstruction)	112 (57.14)
	Yes, Unilateral (with contralateral preventative mastectomy, bilateral reconstruction	28 (14.29)
	Yes, Bilateral (and bilateral reconstruction)	12 (6.12)
	Yes, Bilateral (and unilateral reconstruction)	10 (5.10)
	No breast cancer, bilateral preventative mastectomy	34 (17.35)

Table 2. Baseline patient characteristics. (*continued*)

	Baseline characteristics	N(% of t otal N=196)
Reconstruction laterality	Bilateral	74 (37.8)
	Right side	63 (32.1)
	Left side	59 (30.1)
Prior reconstruction	Yes	119 (60.71)
	TE/IBR	88 (44.90)
	Autologous	4 (2.04)
	Type not reported	27 (13.78)
	No	60 (30.61)
	Not reported	17 (8.67)

Abbreviations: BMI: Body Mass Index, BRCA2: BReast CAncer gene 2 mutation, BRCA1: BReast CAncer gene 1 mutation, CHECK2: Checkpoint Kinase 2 genetic mutation. TE: Tissue Expander, IBR: Implant Based Reconstruction

Table 3. Tumour characteristics

TNM-stage		Right breast, N (%) N = 88	Left breast, N (%) N = 80
T	In situ	23 (26)	20 (25)
	0	6 (7)	4 (5)
	1	33 (38)	32 (40)
	2	18 (20)	16 (20)
	3	5 (6)	4 (5)
	4	0 (0.0)	0 (0.0)
	Not reported	3 (3)	4 (5)
N	0	80 (91)	62 (78)
	1	7 (8)	15 (19)
	2	1 (1)	0 (0.0)
	3	0 (0.0)	1 (1)
	Not reported	0 (0.0)	2 (3)
M	0	88 (100)	80 (100)
	1	0 (0.0)	0 (0.0)
Bloom-Richardson Grade			
Grade 1 (well differentiated)		21 (24)	18 (23)

Table 3. Tumour characteristics (continued)

TNM-stage	Right breast, N (%) N = 88	Left breast, N (%) N = 80
Grade 2 (moderately differentiated)	39 (44)	38 (48)
Grade 3 (poorly differentiated)	25 (28)	16 (20)
Not reported or not performed	3 (3)	8 (10)

Primary outcome: Quality of Life measured by BREAST-Q and BODY-Q

At the time of analysis, 193 patients (98.47%) had officially completed their treatment. Three patients (1.53%) had not completed their reconstruction. However, their last AFT-session was more than one year ago and it was unclear if they wished to continue. Therefore, it was decided to mark the treatment as completed and include these patients in the analyses. Five patients ended their reconstruction prematurely due to the intensity of the treatment, their scores are still included in the analyses.

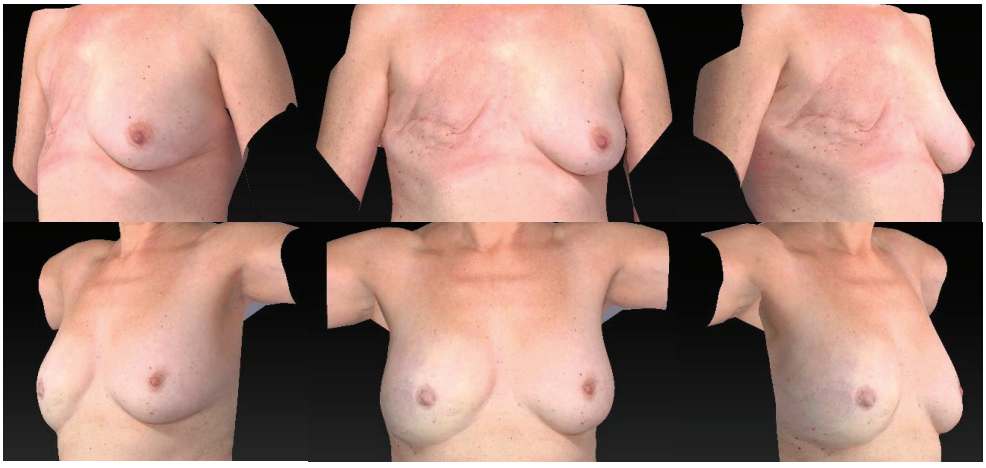

Figure 2. Top row: Patient 1 after modified radical mastectomy of right breast. Bottom row: Final result of patient 1 after AFT-reconstruction, nipple reconstruction, Nipple Areolar Complex (NAC) medical tattoo, without correction of healthy contralateral breast.



Figure 3. Top row: Patient 2 after risk reducing bilateral skin and nipple-sparing mastectomy. Bottom row: Final result of patient 2 after AFT-reconstruction

Psychosocial well-being showed a mean increase of 5.72 points (±16.79), while sexual well-being improved by 8.05 points (±19.61). Physical well-being of the chest area rose by an average of 5.97 points (±20.44), and satisfaction with the chest demonstrated a remarkable gain of 17.22 points (±27.27). The BODY-Q results echoed this positive trend. Satisfaction with the abdomen improved by 12.68 points (±27.63), the back by 11.40 points (±23.67), and overall body satisfaction increased by 7.98 points (±16.54). Satisfaction with the hips and outer thighs rose by 12.01 points (±26.74), the inner thighs by 8.87 points (±27.66), and satisfaction with scars improved by 8.46 points (±25.26). All of these improvements were statistically significant, with p-values <0.001 A detailed overview of the scores can be found in Table 4.

SECONDARY OUTCOMES

Safety

Across the total of 805 AFT-sessions 52 (S)AEs were reported. This results in a complication risk of 6.46%, including 47 AEs (5.84% of total of 805). Most common AEs were reported in the breast; benign palpable lesions i.e. fat necrosis (N=18, 2.24%), seroma (N=12, 1.61%), infection (N=6, 0.75%) and hematoma (N=3, 0.37%). Permanent varicose veins were reported once (0.12%) following incorrect settings of the EVE-bra device. Donor site AEs included hematoma (N=2, 0.25%) and seroma (N=2, 0.25%). Five SAEs (0.62%) were reported; pneumothorax (N=3,

0.37%), an abscess in the axillary region that required surgical drainage (N=1, 0.12%) and seroma in the breast (N=1, 0.12%). There were 5 oncological SAEs. For an overview of the (S)AEs, see appendix 3.

Efficacy

On average 4.11 (±1.09) AFT-sessions were necessary for a total breast reconstruction. Per session, a mean of 237.36 (±59.13) CC fat was re-injected in the breast. For bilateral reconstruction mean OT was 101.74 (±19.71) minutes and 75.76 (±17.73) minutes for unilateral reconstruction. Mean hospital stay per AFT-session was 0.11 (±0.57) days. Seventeen (8.67%) patients required symmetrising reduction mammoplasty of the contralateral breast. Reverse Abdominoplasty and Fat Transfer (RAFT) was performed in 7 (3.57%) patients, 23 (11.73%) women had their nipple-areolar complex (NAC) reconstructed, and 28 (14.29%) women opted for 3-dimensional NAC-tattoo.

Table 4. BREAST-Q and BODY-Q scores upon inclusion and at 12 months follow up.

BREAST-Q and BODY-Q-Domain	Score, mean (SD±)		Mean difference (SD±)	95% CI*	P-value
	Inclusion	**12 months follow up**			
Psychosocial wellbeing	58.39 (±15.37)	64.11 (±16.76)	5.72 (±16.79)	3.35-8.08	<0.001
Sexual wellbeing	45.45 (±16.78)	53.49 (±19.71)	8.05 (±19.61)	5.28-10.81	<0.001
Physical wellbeing chest area	67.06 (±22.00)	73.04 (±21.75)	5.97 (+20.40)	3.10-8.84	<0.001
Satisfaction with breast area	45.57 (±18.41)	62.79 (±23.89)	17.22 (±27.27)	13.37-21.06	<0.001
Satisfaction with abdomen	45.72 (±25.96)	58.40 (±27.15)	12.68 (±27.63)	8.79-16.57	<0.001
Satisfaction with back	69.64 (±26.33)	81.05 (±21.30)	11.40 (±23.67)	8.07-17.74	<0.001
Satisfaction with body	51.56 (±16.90)	59.54 (±18.70)	7.98 (±16.54)	5.65-10.31	<0.001
Satisfaction with hips and outer thighs	52.93 (±24.28)	64.93 (±25.32)	12.01 (±26.74)	8.24-15.77	<0.001
Satisfaction with inner thighs	49.83 (±27.30)	58.70 (±28.46)	8.87 (±27.66)	4.97-12.76	<0.001
Satisfaction with scars	71.47 (±20.41)	79.93 (±20.19)	8.46 (±25.26)	4.69-12.02	<0.001

Abbreviations: 95%-CI: 95%-confidence interval, SD: Standard Deviation

DISCUSSION

This multicentre nonrandomised clinical trial study assesses QoL, efficacy and safety of AFT as a total breast reconstruction post-mastectomy. This interim analysis focuses on the results of the 12 month follow up.

Results indicate that breast reconstruction via AFT significantly increases QoL, which is also reported in the original BREAST trial. [19] Compared to BREAST-I, the BREAST-II trial offers novel insights, demonstrating that AFT not only benefits the recipient site but also significantly enhances donor site satisfaction, surpassing BREAST-I outcomes and highlighting improvements linked to the surgeons' learning curve.[19–21]

Increase in satisfaction with breasts, psychosocial well-being and sexual well-being is also reported after IBR and other ABR. [4,5,22,23] At our 12-month follow-up moment, all domains of the BODY-Q showed significant increase in scores compared to preoperative scores. Literature shows that breast reconstruction contributes to recovery and improvement of the total body image after a mastectomy, regardless of reconstruction technique. [24] Furthermore, literature reports lower scores in domains Satisfaction with Breast, Psychosocial well-being, Physical well-being of the chest and Sexual well-being in women post-mastectomy without any reconstruction, compared to women who opted for reconstruction.[5]

AFT proves superior to IBR in several domains. AFT-breasts have superior sensibility[25], and satisfaction with the breast. [6] These superior outcomes may be attributed to the natural feel and behaviour of an AFT-breast, which often women prefer to the feel of an implant.[26] Women often prefer autologous breasts for several reasons; not only do autologous breasts mature in a natural way, they undergo ptosis and follow weight fluctuations in terms of size, contrary to IBR-breasts. [7,27] Scores for psychosocial well-being and sexual well-being are comparable to IBR .[6] When comparing AFT to other ABR, AFT BREAST-Q -scores are comparable to the postoperative scores of patients with other ABR in a Dutch cross-sectional study. [6]

Assessing donor site satisfaction and morbidity is crucial in evaluating QoL. Donor site satisfaction and morbidity are really only applicable in autologous reconstructions. In AFT, the liposuction can correct body contour, which can lead to increased donor site satisfaction. Conversely, liposuction can leave irregularities in body contour, which can negatively affect QoL. Our results show a significant increase in donor site and scar satisfaction, compared to pre-operatively. Donor site morbidity and satisfaction after ABR and AFT are scarcely reported in literature. [28,29] Miseré et al. compared donor site satisfaction in ABR compared to IBR. Their BODY-Q scores are comparable to our findings.[6] In the original BREAST

trial, AFT scored lower than implants in satisfaction with inner thighs, and for the back comparable to implants. [19] Contrary to our findings, literature reports lesser outcomes for AFT in satisfaction with hips and outer thighs, inner thighs, abdomen and back, and more contour irregularities in the donor sites.[20] Our results show superior satisfaction, which may be attributed to the improved surgical technique, and more experienced surgeons. Scar satisfaction in our trial is comparable to IBR and superior to other ABR.[6] Superior scar satisfaction may be due to AFT's minimally invasive nature, leaving no lengthy scars on the donor site[20]

The total treatment time for AFT is long compared to other reconstructions, with a mean of 461.68 days total treatment time. On average, a mean of 4.11 AFT-sessions was required to reconstruct a breast. Symmetrising reduction mammoplasty can be performed in the last AFT-session, eliminating the need for an additional surgery and anaesthesia for this final corrective procedure. Ahmed et al. report requiring 1.96 sessions on average. However, they used reversed expansion, with an already developed skin envelope which in theory allows for a larger graft and possibly therefore requiring less sessions. In addition to this, they injected fat into the pectoralis muscle, which might increase graft take and thereby decrease required sessions.[30] However, in this trial the pectoral muscle was not injected, because participants from the previous BREAST trial noted animation from the pectoral graft when moving their arms, which negatively affected their satisfaction. Other autologous reconstructions require an average of 1.9–2.04 surgeries to achieve sufficient volume and desired breast shape [31,32], with the majority of reoperations occurring within 6 months.[32] However, compared to other ABR, the mean hospital stay and operative time for AFT are shorter. Patients undergoing free-flap-ABR have a hospital stay of 3.8–10.1 days. [33,34] The majority of patients with AFT-reconstruction do not require postoperative over-night hospital admittance, with a mean hospital stay of 0.11 days, literature also reports no admittance postoperatively.[35] Free flap surgery takes an average of 358.9 minutes to 10.1 hours [33,34], while the average operative time in our trial for AFT is 101.74 minutes for bilateral reconstructions and 75.76 minutes for unilateral reconstructions. For AFT, literature reports operating times varying from 60 to 144 minutes, depending on surgeon experience and case difficulty.[30,36] While the AFT-hospital stay and OT are lower compared to other reconstructions, it is worth noting that the full reconstruction trajectory takes over one year, and patients can find the process burdensome. Ideally, the plastic surgeon assesses

the patient's compliance in their reconstruction interview and discuss whether the patient is willing and able to engage in this reconstruction.

The advantage of AFT compared to other ABR is the smaller complication risk. [11,19,36,37] The risk of a non-serious, non-oncological complication was 5.84% per AFT session, the risk of a serious, non-oncological complication was 0.62% per AFT session and the risk of an oncological complication 0.62% per session. Literature shows comparative results. [19,35] Preliminary results of the BREAST-I trial showed no increased risk for loco-regional breast cancer recurrence after AFT, compared to IBR. [38] Literature reviews also show no increased recurrence after AFT.[39] Most frequently reported AEs related to AFT were fat necrosis, seroma and local infection and the most frequently reported SAEs were pneumothorax and local infection. Pneumothorax only occurred in a new AFT-centre during their first AFT-sessions. Aforementioned complications are related to breast augmentation and reconstruction, and are not solely related to AFT-reconstruction, though reported more often in other reconstructions. [11,19,24,36 40-43].

Key strengths

Strengths of this study include its multicentre design, which increases generalizability and allows for larger study population to enhance statistical power, larger than prior cohorts.[36] Furthermore the prospective design allows investigation into the causal relationship between autologous fat transfer and outcomes. The design minimises recall bias since data are collected prospectively. This is an advantage compared to previous retrospective studies.[44,45] All participants received the same breast reconstruction, the homogeneous intervention makes it more straightforward to attribute the results to AFT. Lastly, the use of Patient Reported Outcome Measures (PROMs) is a key strength, as It is the gold standard for evaluating efficacy and patient's experience. [46]

Limitations

This study has limitations. All but three patients had completed their reconstruction or their 12-month follow-up at the time of analyses.

A possible selection bias arises from participants' strong preference for the treatment that was only available within the study. In addition, treatment burden (i.e. EVE-bra usage, longevity of treatment) caused a high dropout beforehand, leaving only the most motivated participants. Though this is comparable to the normal clinical setting, where women

actively choose for a certain reconstruction type as well. The fact that the treatment was exclusive to the study setting might have led to overrepresentation of patients who are more inclined to seek or accept innovative therapies, potentially affecting the generalizability of the findings. Furthermore, there was no active control group.

In the protocol, it was decided to not include known, frequently occurring and transient, complications related to the EVE-bra as they do not affect the reconstruction process. However, these complications do make the process of AFT burdensome for patients. Patients need to be informed about possible transient side effects of the EVE-bra such as pain, skin irritation, blisters and pruritus.

These positive results confirm the findings of the original, though smaller, BREAST trial. [19] Fortunately, AFT has been accepted into the basic health insurance in the Netherlands as total breast reconstruction since 2023. [47] With more positive findings regarding AFT, it is more likely more patients will opt for this reconstruction technique and start their reconstruction trajectory more confidently. Furthermore, it means implementation into the Dutch Healthcare system can proceed, and should be enhanced, to offer this reconstruction to as many women as possible. It also stresses the need to educate and train plastic surgeons in this effective and safe technique to make it more available throughout the Netherlands.

Future studies should report oncological safety, monitoring the long-term effects, efficacy in more heterogeneous population, e.g. irradiated patients.

CONCLUSION

This large nonrandomised clinical trial reports the 12-month follow-up of AFT as total breast reconstruction. It shows that Autologous Fat Transfer, a minimally invasive, autologous reconstruction technique, enhances Quality of Life with significant increase in all measured domains of the BREAST-Q and BODY-Q. Furthermore, this study confirms its safety, with low complication risk and short hospital stays. This evidence strengthens the findings of the BREAST trial and confirms AFT as an effective and safe total breast reconstruction technique.

SUPPLEMENTAL DIGITAL CONTENT:

Appendix 1.

Overview of participating (university) hospitals.

Appendix 2.

Overview of inclusion criteria of BREAST-II trial.

Overview of exclusion criteria of BREAST-II trial.

Appendix 3.

List of pre-specified non-oncological (Serious) Adverse Events.

Additional contributions:

We express our gratitude to the patients depicted for their consent to publish this information. We sincerely thank all participants of the BREAST trial; the Breast Cancer Association Netherlands; the investigators, patient advisors, participating hospitals, referring physicians, and all institutions involved in this study; as well as the Dutch Health Institute and the Health Insurance Alliance Netherlands for their valuable contributions.

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APPENDIX 1.

Participating hospitals

1. Alexander Monro Hospital, Bilthoven, The Netherlands (NL)
2. Viecuri Medical Centre, Venlo, The Netherlands (NL)
3. Amphia Hospital Breda , Breda, The Netherlands (NL)
4. Leeuwarden Medical Centre, Leeuwarden, The Netherlands (NL)
5. Rijnstate Hospital Arnhem, Arnhem, The Netherlands (NL)
6. Hospital Group Twente, Almelo, The Netherlands (NL)

APPENDIX 2.

Inclusion Criteria:

Female gender
Age of 18 years and older
History or in candidate for a mastectomy procedure in the near future
Patients undergoing preventive mastectomy
Wanting to participate in this study
Patient is able to wear the external expansion device

Exclusion Criteria:

Active smoker or a history of smoking 4 weeks prior to surgery
Current substance abuse
History of lidocaine allergy
History of silicone allergy
4 weeks or less after chemotherapy
History of radiation therapy in the breast region
Oncological treatment includes radiotherapy on the thorax after mastectomy
Kidney disease
Steroid dependent asthma (daily or weekly) or other diseases
Immune-suppressed or compromised disease
Uncontrolled diabetes
BMI>30
Large breast size (i.e. larger than cup C), unless the patient prefers reduction of the contralateral side towards Cup C
Extra-capsular silicone leaking from the encapsulated implant from a previous breast reconstruction
The treating plastic surgeon has strong doubts on the patient's treatment compliance

APPENDIX 3.

Non-oncological Adverse Events:

	Number of reports
Benign palpable lesions i.e. fat necrosis breast	18
Infection breast	6
Seroma breast	12
Hematoma breast	3
Wound healing problems breast	2
Permanent varicose veins breast	1
Infection donor site	1
Hematoma donor site	2
Seroma donor site	2
Total	47

Non-oncological Serious Adverse Events:

	Number of reports
Pneumothorax	3
Axillary abscess	1
Seroma	1
Total	5



III

Preliminary data on the oncological safety of Autologous Fat Transfer (AFT) for total breast reconstruction from the BREAST trial.

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ABSTRACT

Background

Total breast reconstruction via autologous fat transfer (AFT) improves the quality of life compared to implant-based reconstruction (IBR). Hypotheses are that AFT may affect oncologic outcomes. As predetermined in the study protocol, we present the loco-regional recurrence data from the BREAST trial.

Methods

This prospective cohort study is based on participants from the BREAST trial, comparing AFT to IBR after mastectomy. Patients were randomized 1:1 to AFT or IBR. Oncological follow-up, including clinical exams and imaging, was conducted annually for five years post-reconstruction in the intervention group. Data on demographics, tumour characteristics, and treatment details of the first tumour were collected from medical records and national pathology databases. Primary outcome for analysis was loco-regional breast cancer recurrence (LRR).

Results

In total, 77 patients were included in the AFT arm and 86 in the control arm. Time from breast cancer diagnosis to first AFT exposure was considered control time to minimize immortal time bias. Eight patients in the AFT group and 5 in the control group experienced loco-regional recurrence. This was not significantly different (hazard ratio 1.74 (95% CI: 0.56 – 5.44, p = 0.341) in comparison to control. After adjustment for confounders, the difference remained non-significant.

Conclusion

Per study protocol, loco-regional recurrence in the BREAST trial was analysed: no significant difference was observed between AFT-reconstruction and IBR-reconstruction. This study was underpowered for oncological endpoints, the population was too heterogeneous, and not all participants received recommended oncological care.

INTRODUCTION

Breast reconstruction following mastectomy plays a critical role in enhancing patients' health-related quality of life. [1-3] Post-mastectomy breast reconstruction options include implant-based reconstruction and autologous tissue reconstruction. The Deep Inferior Epigastric Perforator (DIEP) flap is the most common autologous breast reconstruction, which utilizes abdominal tissue to reconstruct the breast(s).[4] While the DIEP flap or other free flap procedures provide a natural aesthetic outcome, its success depends on the availability of sufficient donor tissue.

Autologous fat transfer (AFT) has emerged as a promising additional technique for autologous breast reconstruction.[5] Findings from the BREAST trial demonstrated that AFT is a minimally invasive, effective, and safe option, with superior quality of life outcomes compared to implant-based reconstructions. [6] During AFT, fat is harvested from donor sites (e.g. lumbar region, abdomen, and inner and outer thighs) and reinjected into the recipient site to reconstruct the amputated breast in several sessions. [7]

Despite the widespread use of reconstruction techniques, literature reports up to 40% of breast cancer patients are estimated to experience breast cancer recurrence after breast reconstruction. [8] More recently, Loco-Regional Recurrence rates (LRR) after breast reconstruction are estimated to be lower, around 4.7%.[9] Oncological safety after breast reconstruction is an ongoing debate, especially in total breast reconstruction with AFT. This is due to the presence of adipose-derived stem cells (ADSCs) in the transplanted fat. ADSCs are cells known to improve vascularization [10], which mitigates fat necrosis and volume loss in the reconstructed breast. However, ADSCs share histological similarities with bone marrow mesenchymal stromal cells (BM-MSCs).[11] Some have hypothesized that they potentially stimulate tumour growth and contribute to local cancer recurrence. [12-15]

Previous studies suggest that AFT can be safely used in breast reconstruction following breast cancer surgery, though AFT is mostly not used as total breast reconstruction. [16-22] Although the BREAST trial was not powered to detect differences in oncologic outcomes, we report the incidence of the loco-regional recurrence rates in this prospective study per study protocol of the Dutch randomized controlled BREAST trial.

METHODS

Study population

Participants from the BREAST trial were included in this analysis. [23] The BREAST trial was a multi-centre randomized clinical trial with an active control. The aim was to assess the effect of total breast reconstruction with autologous fat transfer in comparison to breast implants on patient-reported quality of life. All patients were eligible for both the intervention and control treatment. Patients were allocated in a 1:1 ratio to either AFT (intervention) or tissue expander followed by breast implants (control). All participants were randomised from November 2, 2015, to September 30, 2019. After enrolment by the local investigators, patients were assigned to a treatment group by the coordinating investigators using the ALEA randomization system (ALEA Clinical) to address allocation concealment. The randomization process was stratified by medical centre. All participants were female patients above the age of 18. The patients all underwent therapeutic or risk reducing mastectomy, though the population was heterogeneous regarding their oncologic status in terms of indication, timing, and other oncologic treatment. This means a patient may have had either a risk reducing mastectomy or a therapeutic mastectomy for recurrent breast cancer; where the therapeutic mastectomy may have been performed years before inclusion to the BREAST trial. In the oncological safety analysis, Risk Reducing Mastectomies (RRM) were excluded due to their distinct risk profile compared to women with (a history of) breast cancer. RRM are performed in individuals without active cancer, typically as risk-reducing measure in women with genetic predispositions, and are associated with different oncological outcomes and surveillance protocols. Finally, patients were included in the BREAST trial and this study regardless of whether they completed their oncological treatment as recommended (e.g. a patient who refused post mastectomy radiation therapy or chemotherapy, or who had positive margins which were not adequately treated). Exclusion criteria for the BREAST trial consisted of the presence of metastatic breast cancer disease before inclusion to the BREAST trial, and patients with a history of radiation therapy in the breast region. After breast reconstruction completion, patients were followed for 5-year after their final reconstruction surgery for oncological follow-up.

Study design

An analysis of loco-regional recurrence in the BREAST trail was performed, comparing the AFT and IBR reconstruction groups.

Interventions

All procedures were performed under general anaesthesia, and perioperative single shot antibiotic prophylaxis was administered before surgical incisions according to the BREAST trial study protocol. [23] Patients were randomized for AFT or IBR.

Intervention group

Patients allocated to the intervention group received AFT with the use of a pre-expansion and post-expansion device (EveBra Nonsurgical Natural Breast Enlargement; Lipocosm) as a total breast reconstruction method. In general, four AFT sessions are necessary to reconstruct a total breast[6] Patients could receive mastectomy and AFT sequentially in the same operation, or implant removal and AFT sequentially in the same operation. Between every AFT procedure, there is a minimum timeframe of 10 weeks. AFT was performed per the BREAST trial protocol by the standardised method according to the Coleman technique. [6,23,24] After breast reconstruction completion, patients allocated to the intervention group were instructed to be examined in the outpatient clinic yearly with annual diagnostic mammography of the reconstructed breast (in contrast to the control group which received clinical examination only).

Control group

The control treatment consisted of patients who received an implant-based breast reconstruction. No AFT was performed on top of the implants. Patients in the control group were followed up as per the current national guideline with annual physical examination at the outpatient clinic, without annual imaging of the reconstructed breast. [25]

Data collection

Data were collected via medical records and PALGA. [26] Medical records connected with the municipal administration were checked for deaths during the follow up. Data were collected for patient demographics, tumour characteristics, surgical treatment information, and non-surgical treatment information. For an overview of all the collected data points, see table 1.

Table 1. Overview of collected data of the BREAST trial

Patient demographics	• Date of first breast cancer diagnosis • Age at first breast cancer diagnosis • Genetic mutations (BRCA1,BRCA2, CHEK2)
Tumour characteristics (of the first breast cancer diagnosis)	• TNM-stage • Histological type of breast cancer • Radicality • ER-status, PR-status, and human epidermal growth factor receptor 2 (HER2) amplification status • Grading of tumor status (Bloom-Richardson or DCIS/LCIS grading) • Lymphovascular invasion (yes/no)
Surgical treatment information	• Mastectomy indication (therapeutic/preventive) • Sentinel node procedure • Axillary lymph node dissection
Non-surgical treatment information	• (neo-adjuvant) chemotherapy • Hormonal therapy • Radiation therapy

End points/outcomes

The primary endpoint was loco-regional breast cancer recurrence (LRR). Local recurrence was defined as histologically confirmed breast cancer in the chest wall, ipsilateral skin, or reconstructed breast (fat) tissue. Regional recurrence was defined as a recurrence in the following lymph nodes: supra- and/or infraclavicular, ipsi- and/or contralateral axillary, and intra- and/or interpectoral. [27] It should be noted that the study was not powered to detect differences in oncologic outcomes and heterogeneity of the population limits interpretation of the results.

Statistical analysis

Baseline characteristics were described stratified by reconstruction type as mean and standard deviation (SD) or as count and percentage. Time to event data was evaluated in relation to the date of the first breast cancer diagnosis. To prevent immortal time bias (i.e. bias due to excluding events after diagnosis but before exposure to AFT), we used Cox proportional hazards regression with time-varying covariates. This means that all participants start follow-up time considered as not exposed to AFT. Patients who received AFT were considered exposed from the date of the first AFT session. Events occurring before their first AFT sessions were not counted in the AFT period, but in their control period. As sensitivity analysis, we used conventional Cox proportional hazards regression analysis comparing the randomized groups. In this analysis, all events

in the AFT group were counted as recurrence, even if it occurred before the first procedure/ session. To prevent any remaining confounding, all analyses were first performed without adjustment, and then with adjustment for the presence of the following potential confounders present at baseline: Tumour and Nodal state according to the TNM staging system, the presence of lymphovascular invasion, the presence of a DCIS component, and the corresponding Bloom-Richardson grading. The correction for confounders was performed using the characteristics of the first breast cancer diagnosis if applicable.

Results are expressed as hazard ratio (HR) with 95% confidence interval (CI) and were based on the per protocol set as this concerns a safety analysis (i.e. patients who did not receive AFT were not counted in the AFT group).

Ethical approval

This oncological safety overview is part of the secondary outcomes from the BREAST trial. The BREAST trial has been approved by the Medical Ethical Committee of Maastricht University Medical Centre/Maastricht University (NCT02339779; METC142059). This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

Baseline characteristics

For the oncological follow-up, we included 163 patients of the 187 patients who had been randomized. Ninety-three patients allocated to the AFT group, and 94 patients to the control group. There were 2 dropouts in the control group, 1 loss to follow-up in the AFT group and 7 participants originally randomized in the AFT group but declined to receive the AFT treatment and therefore placed in the control group (2 patients opted for DIEP-flap, 2 patients declined any breast reconstruction, 3 patients received IBR). For these analyses, only participants who received at least one AFT session were considered intervention group, and any other reconstruction type (e.g. IBR, DIEP flap) were considered control group. After these exclusions, the per protocol groups for analyses are 77 patients for the AFT group and 86 patients for the control group. Figure 1 shows the flowchart.

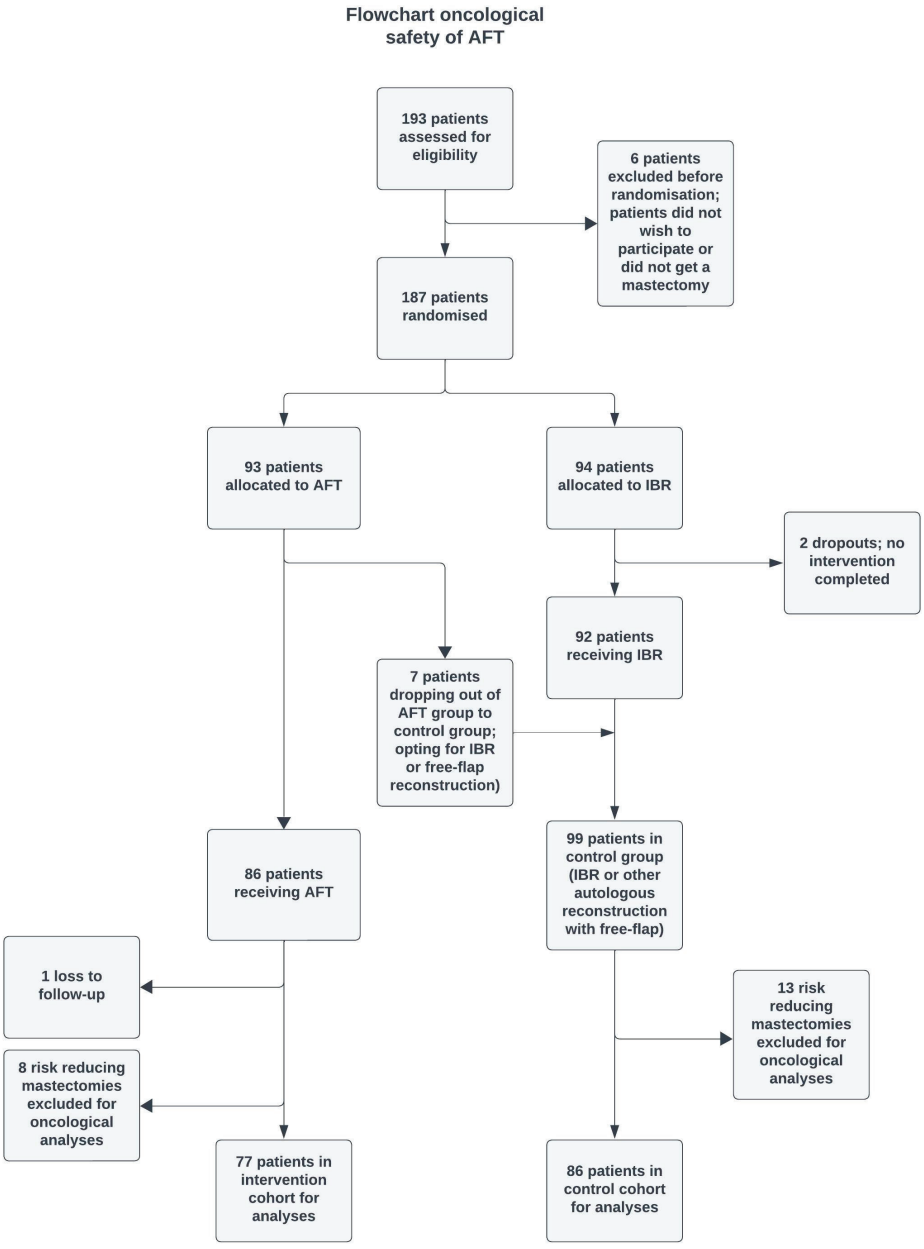

Figure 1. Flowchart depicting allocation of participants

Out of the 163 patients in this cohort, the majority (N=71 (44%)) were aged 50 years or older. The mean time between breast cancer diagnosis and reconstruction was 26.84 months. The most common type of tumour

was invasive breast cancer (N=123, 75%). Based on the Bloom-Richardson scale, most tumours were grade 2 (N=48, 29%). Most patients in the cohort exhibited ER+/HER2- status (N=96, 59%). Most patients achieved free resection margins (N= 146, 90%). Five out of 163 patients were diagnosed with triple-negative breast cancer (3.07%). Fifteen patients (9.20%) carried a genetic mutation associated with increased breast cancer risk, while 31 (19%) had a positive family history of breast cancer. For a detailed overview of all patients, tumour, and treatment characteristics per group, please see Table 2.

Table 2. Baseline characteristics of patients, including tumour- and treatment characteristics per group.

Total	AFT		Control		Total	
	N	%	N	%	N	%
	77		86		163	
Age						
< 35 years	5	6.49	6	6.98	11	6.75
35-39 years	7	9.09	7	8.14	14	8.59
40-44 years	13	17	14	16	27	17
45-49 years	20	26	20	23	40	25
≥ 50 years	32	42	39	45	71	44
Time from diagnosis – first reconstruction						
Months (SD)	26.80 (38)		26.88 (62)		26.84 (52)	
Tumour size						
Tis	14	18	19	29	33	20
T1	2	2.60	1	1.16	3	1.84
T1a	3	3.90	7	8.14	10	6.13
T1b	9	12	5	5.81	14	8.59
T1c	20	26	19	29	39	24
T2	19	25	22	26	41	25
T3	3	3.90	3	3.49	6	3.68
Not reported	7	9.09	9	10	16	9.81
Lymph node status						
N0	57	74	64	74	121	74

Table 2. Baseline characteristics of patients, including tumour- and treatment characteristics per group. (*continued*)

Total	AFT		Control		Total	
N1	14	18	16	19	30	18
Not reported	6	7.79	6	6.98	12	7.36
Bloom & Richardson Grade						
Grade 1	21	27	15	17	36	22
Grade 2	21	27	37	43	48	29
Grade 3	14	18	9	10	15	9.20
Not applicable	16	21	13	15	29	18
Not reported	5	6.50	12	14	17	10
Lymphovascular invasion						
Yes	13	17	8	9.30	21	13
No	44	57	52	60	96	59
Not reported	14	18	26	30	40	25
Margins						
Negative	72	94	74	86	146	90
Positive	2	2.60	7	8.14	9	5.52
Not reported	3	3.90	5	5.81	8	4.90
ER+/HER2-						
Yes	44	57	52	60	96	59
No	14	18	12	14	26	16
Not applicable	16	21	12	14	28	17
Not reported	3	3.90	10	12	12	6.52
HER2+						
Yes	12	16	10	12	24	15
No	47	61	54	33	101	62
Not applicable	16	21	12	14	28	17
Not reported	2	2.60	10	12	12	7.36
Triple negative tumour						
Yes	3	3.90	2	2.33	5	3.07
No	56	73	62	72	118	72
Not applicable	16	21	12	14	28	17
Not reported	2	2.60	10	12	14	8.59
Genetic Mutation						
No	53	69	62	72	115	71

Table 2. Baseline characteristics of patients, including tumour- and treatment characteristics per group. (*continued*)

Total	AFT		Control		Total	
BRCA1	2	2.60	4	4.65	6	3.68
BRCA2	4	5.19	2	2.33	6	3.68
CHEK2	1	1.29	2	2.33	3	1.84
Other	0	-	1		1	0.61
Positive family history	16	21	15	17	31	19
Not reported	1	1.29	0	-	1	0.61

Abbreviations: DCIS; Ductal carcinoma in situ, LCIS; Lobular carcinoma in situ, IDC; ILC; invasive lobular cancer, SSM; skin sparing mastectomy, NSSM; nipple and skin sparing mastectomy. Genetic mutations include BRCA1, BRCA2 and CHEK2. Margins; negative is defined as 'no ink on tumour'.

Loco-regional recurrence rates

In total, 13 patients developed a loco-regional recurrence (LRR). Eight patients of the AFT group (10%) and 5 patients of the control group (5.81%) experienced a loco-regional recurrence after inclusion to the BREAST trial. In table 3 the proportions of regional versus local recurrence per group are described. Two patients in the AFT group experienced their event before their first AFT session. There were no significant differences between the AFT and control group in terms of local or regional recurrences. All recurrences were found after therapeutic mastectomies.

Table 3. Recurrences found in the BREAST trial follow up. (HR; Hazard Ratio, CI; Confidence Interval)

	AFT	*Control*	*HR**	*95% CI*	*p-value*
No. of patients	*77*	*86*			
Loco-regional recurrence (LRR)	*8 (10%)*	*5 (5.81%)*	*1.74*	*(0.56-5.44)*	*0.341*
Local recurrence (LR)	*5 (2.48%)*	*3 (5.19%)*	*2.41*	*(0.53-10.89)*	*0.254*
Regional recurrence (RR)	*4 (5.19)*	*3 (3.49)*	*1.33*	*(0.29-6.03)*	*0.709*

* HR adjusted for confounding

Univariable analysis shows no significant difference in loco-regional recurrence in the AFT group compared to control:

The HR was 1.74 (95% CI: 0.56 – 5.44, p = 0.341). For local recurrence (separate from regional recurrence) also no significant difference was observed (HR 2.41 (95% CI: 0.53 to 10.89, p = 0.254). The HR for a re-

gional recurrence in the AFT group compared to control was 1.33 (95% CI: 0.29 – 6.03, p = 0.709). After adjusting for confounders, all differences remained not-significant. Due to the very limited number of events, multivariable models showed convergence issues and hence, univariable results are presented here.

Timing of LRR

In the AFT group, the mean interval from breast cancer diagnosis to LRR was 6 years and 3 months. The interval from the first breast reconstruction surgery date to LRR was 4 years and 6 months. In the control group, the mean interval from breast cancer diagnosis to LRR was 6 years and 3 months. The interval from the first breast reconstruction date to LRR was 4 years. A schematic overview of the timing of the recurrences can be seen in figure 2.

Tumour characteristics of the loco-regional cancer recurrences

The patients in the AFT group with a pathological proven LRR had a mean age of 44 years, 4 patients had a T1 tumour (one grade 3, two grade 1 and 1 was not reported), 1 patient had Tis (with no clear resection margins) and 1 woman had a T2 tumour, with isolated tumour cells in the lymph node. One patient had a positive family history for breast cancer and 1 patient had a proven BRCA2 genetic mutation.

Patients in the control group with a pathological proven LRR had a mean age of 47 years.

For the LRR in the control group, a mean interval from breast cancer diagnosis to LRR was 6 years and 1 month. The interval from the moment of the first breast reconstruction date to LRR was 4 years. Three Patients had pT1 breast cancer (2 grade 1 and 1 not reported), 1 pTis, 2 pT2G1 tumours, and the T stage was not reported in 1 patient. From the patients with LRR in the control group, there was no genetic or familiar history of breast cancer. For an overview of the initial breast cancer characteristics of the patients with LRR, we kindly refer you to supplement 1.

DISCUSSION

The results of the BREAST trial show no significant difference in loco-regional recurrence within the 5-year oncological follow up. No new tumours were found after preventative mastectomies, all reported

recurrences were after therapeutic mastectomies. The AFT-group has a total of eight (10%) loco-regional recurrences after being exposed to AFT, compared to five (5.81%) in the control group resulting in an HR of 1.74 (95% CI of 0.56-5.44, p=0.341) and a very broad CI which indicates that there is no significant effect. To assess the oncological safety of AFT, it is paramount to discuss the oncological safety of other reconstruction techniques. Various studies have reported controversial oncological safety results in free-flap breast reconstructions. [28,29] A large meta-analysis reported local recurrences of 2.9% and 5.6% for autologous and implant-based reconstructions, respectively. [9] These lower recurrence rates in literature in comparison to our findings may be a result of including regional recurrences and excluding irradiated patients in the BREAST trial. These results nevertheless affirm in line with earlier studies the hypothesis that AFT is at least as safe as other autologous reconstructions and implant-based reconstruction (IBR). [16-19]

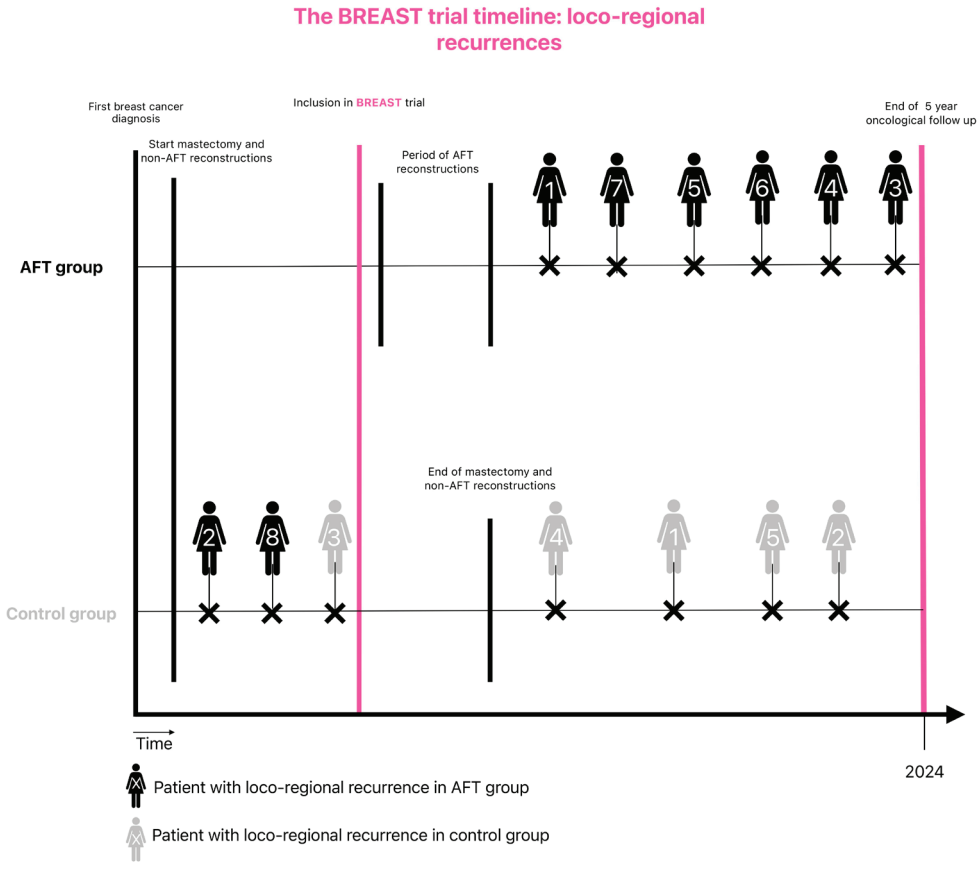

Figure 2: This figure depicts the timeline of the BREAST trial participants in their respective groups with loco-regional recurrences.

There is almost no difference in the groups in mean time for the interval between first date of diagnoses and the time to recurrence, and the first reconstruction date and time to recurrence. In the AFT group, the mean time between first reconstruction (first time being exposed to AFT) and LRR was 4 years and 6 months, compared to a mean time of 4 years in the control group. In both the control group and the intervention (AFT) group the mean time between first breast cancer diagnosis and LRR was 6 years and 3 months. The risk of breast cancer recurrence is at its highest in the first 5 years post-treatment. [30] These results could indicate that AFT does not affect those first crucial 5 years, as the mean time to recurrence is longer than those 5 years.

Baseline characteristics of patients with LRR in the AFT group cause discussion. In the AFT group 2 patients did not have clean resection margins after their mastectomy, which would normally be an indication for irradiation of the thoracic wall or even re-operation, as it is associated with higher risk of local recurrence. [31,32] However, these patients did not receive post-mastectomy radiation therapy or a re-operation. Furthermore, both in the AFT and the control group there were patients with pN positive tumours. These patients again did not receive any post-mastectomy radiotherapy.

It is worth noting that some of these mentioned AFT patients were probably never desirable candidates for AFT and did not receive all indicated treatment for their tumours. This can cause a serious selection bias in this oncologic safety analysis, as these patients do not fully represent the population that AFT should be available for. In future cohorts or RCTs assessing the oncologic safety of breast reconstruction including AFT, patients should only be eligible for inclusion if they have completed their oncologic treatment as recommended per (inter)national guidelines and local tumour boards. In clinical practice out of research context, plastic surgeons offering AFT or any other breast reconstruction to patients who have not fully completed oncologic treatment as recommended or indicated, should consult the surgical oncologist regarding the breast cancer recurrence chance, to weigh this against the patient's wish for breast reconstruction.

The BREAST trial is (to our knowledge) the first and only prospective multi-centre RCT with an active control, giving valuable insights in the oncological safety of AFT compared to IBR. [23] However, this study has some limitations.

The population was heterogeneous in presence and stage of breast cancer, timing of the mastectomy and completion of their oncologic treatment.

First, all indications for mastectomy were allowed (i.e. therapeutic mastectomy as a first treatment of cancer, mastectomy for positive margins after breast conserving surgery, and salvage mastectomy after recurrence of previously treated breast cancer). This means the baseline prognosis of included patients varies widely. Furthermore, some patients underwent mastectomy shortly after inclusion in the breast trial (as a primary treatment and planned reconstruction), whereas others had undergone mastectomy years before inclusion in the breast trial. Completion of oncologic treatment according to guidelines was not a requirement – patients who refused chemotherapy or radiation therapy for any reason were accepted in the BREAST trial. Especially in a small population like this, heterogeneity may seriously impact these oncologic outcomes, and the small numbers make it extremely difficult to correct for them. This means that results should be interpreted with caution, and more research is needed to specifically address the oncologic outcomes of total breast reconstruction with AFT. This requires larger cohorts, which can be stratified to oncologic status, with full information on tumour characteristics including subtype, and oncologic treatment. An exclusion criterion worth mentioning was irradiation of the chest area. To gain more generalizability, more research is required on AFT as reconstruction in irradiated patients.

An additional consideration of this study is the different follow-up protocols between the two groups, which may have introduced bias. For AFT patients, annual mammographic screening of both reconstructed and non-reconstructed breast sides was recommended for at least five years post-reconstruction. The control group followed Dutch guidelines that involve physical examination of the reconstructed breast and mammographic screening only for the healthy contralateral breast. In practice, this could mean that a non-palpable recurrence could have been found in the AFT group, but not in the control group. The control group would only receive imaging upon indication which includes a palpable mass in the reconstructed breast.[32] This difference may have introduced a lead-time bias in the AFT group due to more intensive imaging, and a potential length-time bias in the control group complicating direct outcome comparisons. In terms of timing there is also the matter of follow up. At inclusion, some participants had a new breast cancer diagnosis, where others had their diagnosis several years ago. Although sensitivity

analyses were performed, this could have led to a time-dependent bias. Future studies are needed to evaluate an optimal, standardized follow-up strategy for AFT patients to avoid unnecessary biopsies while ensuring early detection of potential recurrences. Lastly, in this report we only focus on the LRR, as the information on distant metastases were not yet available. We recognise this limitation. Reports on distant metastases are needed in future.

These findings provide preliminary reassurance regarding the oncological safety in total breast reconstruction with AFT. Conducting larger-scale studies (with stratification for baseline risk of recurrence) with extended follow-up will be essential to build robust evidence based data on the oncological safety of AFT for total breast reconstruction and to develop well-supported guidelines that enhance patient care.

CONCLUSION

This study reporting the oncological follow-up of an RCT comparing AFT to IBR found no evidence that a total breast reconstruction with AFT increases the loco regional recurrence (LRR) risk compared to IBR after therapeutic mastectomies.

ETHICAL APPROVAL

This oncological safety overview is part of the secondary outcomes from the BREAST trial. The BREAST trial has been approved by the Medical Ethical Committee of Maastricht University Medical Centre/Maastricht University (NCT02339779; METC142059). This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

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IV

Establishing Oncological Safety of Autologous Fat Transfer for Total Breast Reconstruction: Results from the Multicentre BREAST-I and BREAST-II Trials

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ABSTRACT

Background:

Autologous fat transfer (AFT) has gained popularity as a minimally invasive alternative for autologous breast reconstruction post-mastectomy. It offers aesthetic advantages and improvements in quality-of-life, though concerns persist regarding its oncological safety due to the presence of adipose-derived stem cells (ADSCs).

Methods:

This pooled follow-up analysis combined data from the multicentre randomised controlled BREAST-I trial and the nonrandomised clinical BREAST-II trial, including women who underwent total breast reconstruction with AFT between 2015 and 2025. The AFT-cohort was compared with a nationwide control group of breast cancer patients derived from the Netherlands Cancer Registry (IKNL), matched by inverse probability weighting. The primary outcome was overall survival (OS). Local and regional recurrences and distant metastases were not included in statistical analyses due to known underreporting in the national registry, but were descriptively assessed within the study cohort.

Results:

A total of 242 AFT-patients and 19936 controls were included. The mean follow-up time was 8.0 years for AFT and 6.9 years for controls. Ten-year crude OS was 97.6% (95% CI 95.5–99.7%) for AFT and 75.7% (95% CI 74.7–76.8%) for controls. After adjustment for confounders and immortal time bias, AFT was not associated with increased mortality (HR 0.34; 95% CI 0.14–0.88; p = 0.025). Residual confounding and differences in follow-up intensity between cohorts constitute key study limitations

Conclusions:

In this pooled multicentre cohort with long-term follow-up, AFT for total breast reconstruction after mastectomy did not negatively affect mortality compared with national registry controls. These results support the oncological safety of AFT as a reconstructive technique. Future research should include larger cohorts and assess disease-free survival.

INTRODUCTION

Breast reconstruction after mastectomy significantly improves patients' health-related quality of life.[1] Reconstruction options include implant-based methods and autologous tissue techniques, with the Deep Inferior Epigastric Perforator (DIEP) flap being the most commonly used autologous procedure, utilising excess abdominal tissue.[2] Autologous fat transfer (AFT) has emerged as a promising, minimally invasive adjunct for breast reconstruction. In several sessions, adipose tissue is harvested from donor sites such as the abdomen and thighs, then reinjected to the mastectomy area to reconstruct the breast.[3] The Dutch BREAST-I trial demonstrated that AFT is a safe and effective option, with superior quality-of-life outcomes compared to implant-based reconstruction (IBR).[4,5] Following these results, AFT has been approved as standardised health care in the Netherlands, hereby offering women who are unable or unwilling to undergo IBR or free-flap reconstruction an alternative. [6]

Despite these advances, concerns regarding the oncological safety of AFT remain, particularly due to the presence of Adipose-Derived Stem Cells (ADSCs) in transplanted fat. ADSCs enhance vascularization, reducing fat necrosis, but their similarity to bone marrow mesenchymal stromal cells has raised concerns about potential tumour stimulation and the risk of local or distant recurrence and metastases.[7-10] Hereby questioning its effect on overall survival.

Nevertheless, literature reports evidence suggesting AFT's oncological safety.[11-13] In addition to this, the randomised controlled BREAST-I trial reported no difference in loco-regional recurrence (LRR) rates compared to IBR, though it was not powered for oncological endpoints.[14] To further assess oncological safety and increase generalisability, a combined follow-up of patients from both the BREAST-I and BREAST-II trial is now being conducted. This larger cohort allows for a more robust assessment of oncological safety, benchmarked against the national Dutch cancer registry dataset (IKNL), which includes all breast cancer patients diagnosed in the Netherlands in the same timeframe.[15] Hypotheses are that AFT does not increase the risk of loco-regional or distant recurrence, and does not adversely affect overall survival.

METHODS

This pooled and weighted cohort study is a combined follow-up analysis of two previous clinical trials: the randomised controlled BREAST-I trial and the non-randomised clinical BREAST-II trial. Reporting followed STROBE guidelines.[16] Both studies were multicentre in design and investigated the outcomes of AFT as total breast reconstruction. The current study focuses on long-term oncological outcomes in patients who underwent post-mastectomy AFT and compares them with a national control cohort derived from the Dutch cancer registry (IKNL).[15] Anonymised data from the IKNL-registry were obtained under data request number 24-00340. The registry contains nationwide data on cancer incidence, treatment, and outcomes in the Netherlands.

Study population

Patients included in this follow-up analysis were women who received a total breast reconstruction with AFT within the BREAST-I or BREAST-II trial between 2015 and 2025. Full inclusion and exclusion criteria are described in the BREAST-I trial protocol.[5] For the current analysis, patients who had undergone Risk Reducing Mastectomy were excluded due to their distinct oncological risk profiles. The control group consisted of all women diagnosed with breast cancer in the Netherlands between 2015 and 2022, registered in the Netherlands Cancer Registry (IKNL). Participants were excluded from the control cohort based on the following BREAST trial exclusion criteria: active smokers or history of smoking three months prior to surgery, history of radiation therapy in the breast region, oncologic treatment includes radiotherapy after mastectomy, Body Mass Index (BMI) >30. As a result of these exclusion criteria, tumours with a TNM stage higher than T3 are not represented in both cohorts. Other BREAST trial exclusion were not applied to the IKNL-cohort, as these were not reported in the registry, these included: current substance abuse, history of lidocaine or silicone allergy, less than four weeks of chemotherapy prior to inclusion, kidney disease, steroid-dependent asthma or other diseases, immune-suppressed or compromised disease, uncontrolled diabetes, extra-capsular silicone leaking from the encapsulated implant from a previous breast reconstruction, large breast size (i.e. larger than C cup), unless the patients prefers reduction mammoplasty of the contralateral side to a C cup.

Interventions

The study cohort received a total breast reconstruction using solely AFT. In this minimally invasive technique, adipose tissue is harvested from a preselected donor site such as abdomen, outer thighs, and lumbar region, and injected in microdroplets and aliquots in several planes of the thoracic skin of the breast region to reconstruct the breast mound in several sessions, accompanied by perioperative external vacuum expansion of the thoracic skin. On average, patients undergo four fat-grafting sessions, with a mean reinjected adipose tissue volume of 218 mL per session. [4]The technique is described in detail by Piatkowski et al.[4] Post-mastectomy reconstructions of the control cohort are not specified, as this was not reported in the control dataset; patients may have received no reconstruction, implant-based or free-flap reconstruction.

Follow-up

Patients in the BREAST-I trial underwent annual clinical follow-up including imaging, as per protocol.[5] In the BREAST-II trial, patients received annual mammography, or if mammography was declined by patients, Magnetic Resonance Imaging (MRI) at 1, 3, and 5 years post-reconstruction; additional imaging was performed only upon clinical indication. In the IKNL control group, clinical check-ups and follow-up imaging was performed upon indication only, typically following detection of symptoms (e.g. palpable lesions). This is per the national guideline.[17]

Outcomes

The primary outcome for this follow-up study was to assess overall survival in women with AFT as total breast reconstruction, in comparison with a control cohort. Local and regional recurrences, as well as distant metastases, were not included as endpoints in the analyses because these outcomes are known to be underreported in the national cancer registry.[18] However, these outcomes were collected for the study cohort and discussed descriptively and in comparison with existing literature.

Data collection

Trial participants' data on oncological follow-up were prospectively collected, and registered in Castor EDC (Ciwit B.V., Amsterdam, The Netherlands) is a secure, web-based electronic data capture platform for clinical and research data management. It enables the creation of customizable case report forms and complies with major international standards and regulations, including FDA 21 CFR Part 11, GDPR, ICH-GCP, HIPAA, ISO 27001, and ISO 9001.[19]

Ethical considerations

Both BREAST trials (BREAST-I; NCT02339779 and BREAST-II; NCT04261829) were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines. The protocols were reviewed and approved by the appropriate institutional ethics committees, and written informed consent was obtained from all participants prior to enrolment. As per the predefined trial protocols, oncological safety outcomes are reported in this publication. Both trials were registered in public trial databases under the registration numbers listed above. For the IKNL-data, individual informed consent was not required, as the data were completely anonymised.

Statistical analysis

Baseline characteristics are summarized as mean and standard deviation (SD) or as count and percentage. Missing data were imputed using stochastic regression imputation with fully conditional specification. Predictive mean matching was used to draw imputations for incomplete continuous variables.

We used Kaplan-Meier curves stratified by group to present crude survival probabilities over time. To account for baseline differences between the AFT and control groups, we used propensity score weighting. The propensity score was developed using patient and tumour characteristics, and calendar time. We used weighted multivariable Cox proportional hazards regression with a time-varying covariate for AFT (i.e. to account for immortal time bias) to estimate the association between having had AFT and time-to-event outcomes. Patients were considered 'control' until their first exposure (i.e. first grafting session) to AFT. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). The proportional hazards assumption was tested as the association between scaled Schoenfeld residuals and time.

RESULTS

In total, we included 242 participants who had received at least one AFT procedure, and 19936 controls. For the inclusion process, please see figure 1. The mean age was 50.6 ± 10.2 years in the AFT cohort and 60.5 ± 14.6 years in the control cohort. After propensity score weighting, this difference remained statistically significant ($p < 0.001$). BMI was higher

in the AFT group both before and after weighting ($p < 0.001$). In addition, the AFT cohort had a higher proportion of Tis compared with the control group ($p=0.01$). For an overview of patient and tumour characteristics before and after propensity score weighting, please see table 1, with covariate balance assessed using standardised mean differences (SMD) and corresponding p-values. Figure 2 shows the corresponding Love plot illustrating covariate balance before and after propensity score weighting. Table 2 includes clinically relevant tumour characteristics, such as ER+/Her2- . For an overview of oncological events in the study cohort, see table 3.

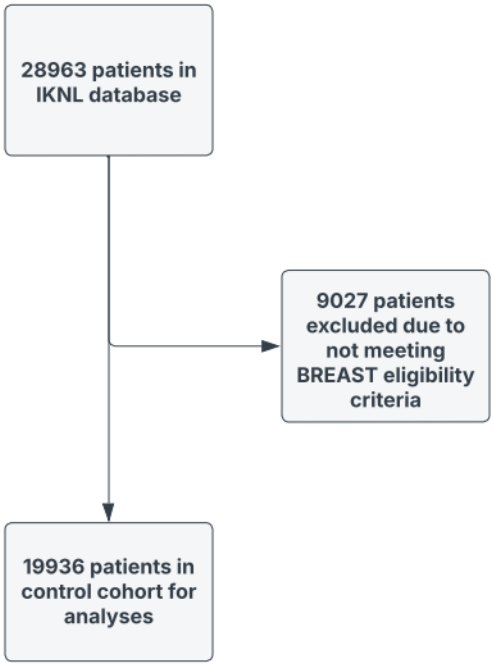

Figure 1a IKNL flowchart

OVERALL SURVIVAL

The median follow-up time from the time of cancer diagnosis was 8.0 years for the AFT group, and 6.9 years for the control group. The crude 10-year survival probabilities were 97.6% (95% CI: 95.5 – 99.7%) for the AFT group and 75.7% (95% CI: 74.7 – 76.8%) for the control group. Figure 3 shows the Kaplan-Meier curves for both groups, with a number-at-risk table below.

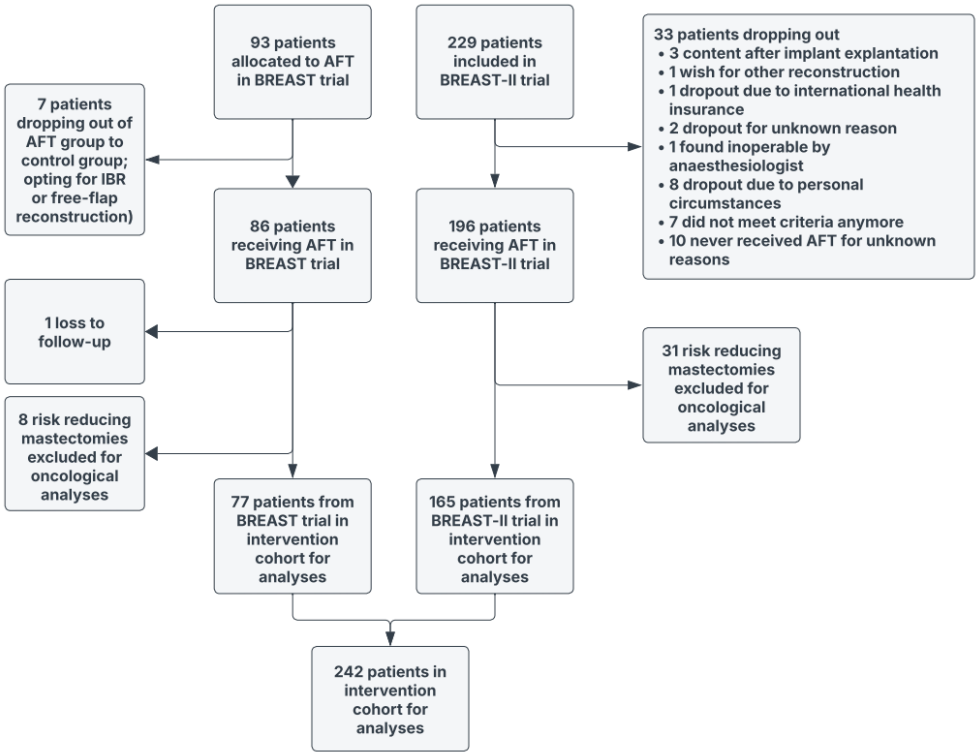

Figure 1b BREAST flowchart

Left side depicts the BREAST trials' patient selection, right side shows the IKNL data's exclusion process.

Table 1. Baseline Characteristics Before and After Propensity Score Weighting

	Unweighted				Weighted			
Total	AFT	Control (IKNL)			AFT	Control (IKNL)		
	Mean ± SD or %	Mean ± SD or %	SMD	p-value	Mean ± SD or %	Mean ± SD or %	SMD	p-value
BMI (kg/m²)	24.4 ± 2.6	23.2 ± 4.6	0.25	<0.001	24.1 ± 2.4	23.2 ± 4.6	0.19	<0.001
Tumour size (cm²)	2.4 ± 7.0	3.6 ± 5.1	−0.23	0.008	3.2 ± 2.7	3.6 ± 5.1	−0.08	0.238
Age (year)	50.6 ± 10.0	60.5 ± 14.6	−0.68	<0.001	53.0 ± 10.2	60.5 ± 14.6	−0.51	<0.001
Year mastectomy	2015 ± 6	2018 ± 2.2	−1.14	<0.001	2018 ± 2	2018 ± 2	0.03	0.686
Tumour stage								
Tis	24.8	21.6	0.08	0.152	33.5	21.6	0.29	0.011
T1	43.0	46.5	−0.07		40.0	46.6	−0.13	
T2	26.9	28.6	−0.04		21.7	28.6	−0.15	
T3	5.4	3.3	0.12		4.9	3.3	0.09	
Lymph node status								
N0	83.1	90.3	−0.24	<0.001	90.9	90.3	0.02	0.806
N1	15.7	8.2	0.27		8.2	8.2	0.00	
N2	0.4	1.0	−0.06		0.6	1.0	−0.04	
N3	0.8	0.6	0.03		0.2	0.6	−0.05	
Bloom & Richardson Grade								
Grade 1	26.0	16.6	0.25	<0.001	20.5	16.6	0.11	0.628
Grade 2	45.5	49.9	−0.08		47.1	49.9	−0.05	
Grade 3	28.5	34.0	−0.12		32.4	34.0	−0.04	
ER+	67.4	67.1	0.01	0.941	60.2	67.1	−0.15	0.069
PR+	58.3	54.5	0.08	0.233	54.1	54.5	−0.01	0.943
HER2+	25.6	19.1	−0.16	0.013	18.4	19.3	−0.02	0.783

Abbreviations: AFT; Autologous Fat Transfer group, SD; Standard Deviation; SMD; Standardised Mean Difference, Tis: In Situ Tumour, ER+: Estrogen Receptor positive, HER2+: Human Epidermal growth factor Receptor 2 negative

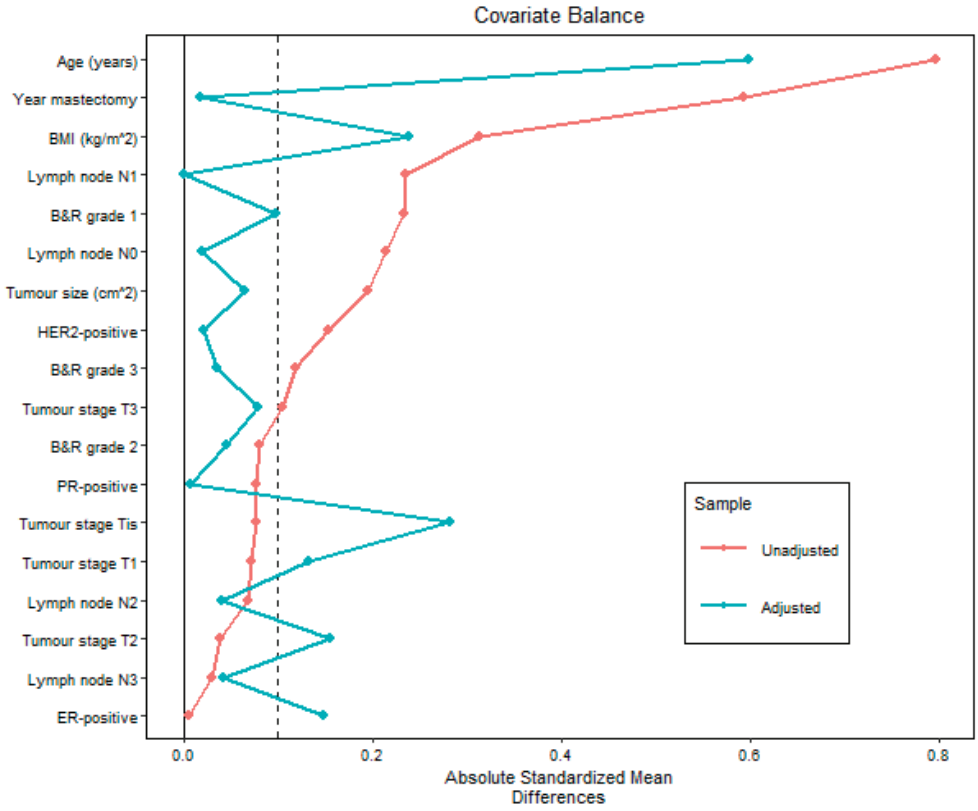

Figure 2. Covariate balance before and after propensity score weighting.

Standardized mean differences (SMDs) for baseline covariates are shown before and after weighting.

Table 2. Clinically relevant tumour characteristics of participants

Total	AFT		Control (IKNL)	
	N	%	N	%
	242		19936	
ER+/HER2-				
Yes	133	55	11924	59.8
No	109	45	8012	40.2
HER2+				
Yes	64	26.4	4757	23.9
No	178	73.6	15179	76.1
Triple negative tumour				
Yes	43	17.8	3171	15.9
No	199	82.2	16765	84.1

Table 2. Clinically relevant tumour characteristics of participants (*continued*)

Total	AFT		Control (IKNL)	
Genetic Mutation				
None	217	65.3	Not collected	-
BRCA1	10	4.1	Not collected	-
BRCA2	11	4.5	Not collected	-
Other	4	1.7	Not collected	-
Positive family history	16	6.6	Not collected	-

Abbreviations: Tis: In Situ Tumour, ER+/-: Estrogen Receptor positive or negative, HER2-: Human Epidermal growth factor Receptor 2 negative, BRCA: BReast CAncer gene 1 or 2.

Table 3. AFT-cohort follow-up

	AFT-cohort (n =242)	Control cohort (n=19936)
Follow-up since first breast cancer diagnosis Median and 1st and 3rd quartile in years	8.0 (5.0 – 12.0)	6.2 (4.0 – 8.0)
Follow-up since exposure to AFT Mean in years ± SD, range	3.4 (3.0 – 5.6)	NA
Recurrences, loco-regional or not specified N (%)	10 (4.13%)	NA
New other tumours, not specified N (%)	1 (0.41%)	NA
Metastasis N (%)	16 (6.61%)	NA
Deaths (all cause) N (%)	8 (3.31%)	3106 (15.1%)

Percentages are based on Kaplan-Meier estimates with a total of 2152 person-years follow-up time. Abbreviations: SD: standard deviation, AFT: autologous fat transfer.

The crude HR for survival for the AFT group compared to the control group was 0.10 (95% CI: 0.04 – 0.25, p < 0.001), indicating better survival in the AFT group. The propensity score weighted and confounder adjusted model accounting for immortal-time bias yielded an HR of 0.34 (95% CI: 0.14 – 0.88, p = 0.025).

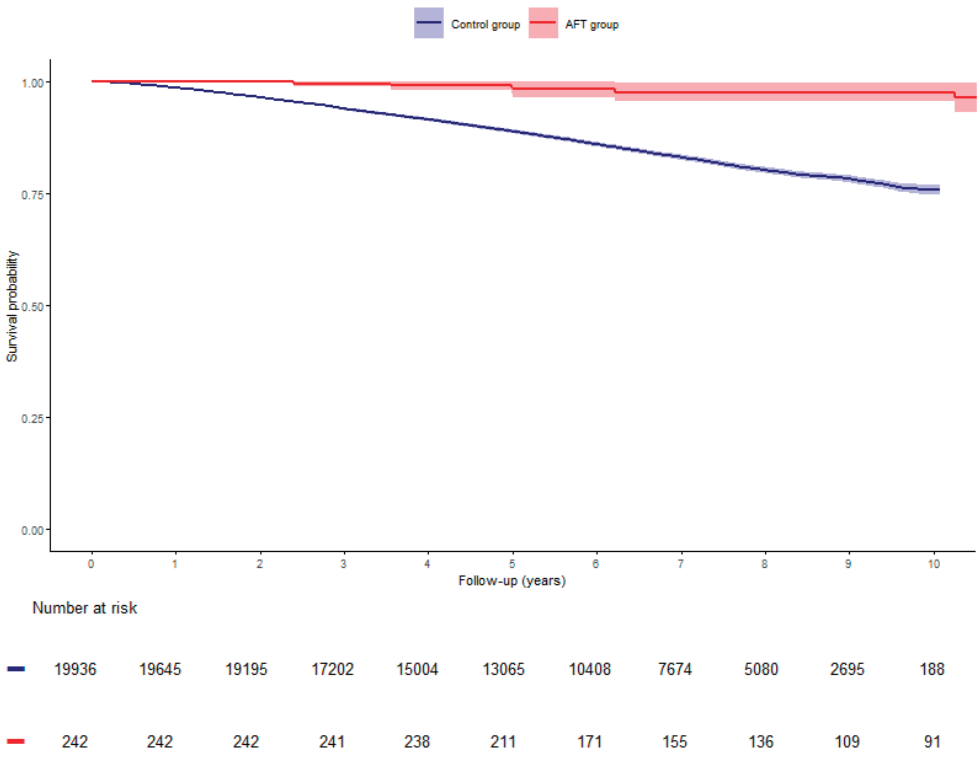

Figure 3. Kaplan-Meier curves of the probability of surviving over 10 years of follow-up.

Shaded areas indicate the 95% confidence intervals around the survival estimates, with number at risk table below the graph.

DISCUSSION

In this multicentre study with prospectively collected data, we found no evidence of a higher risk of mortality after receiving AFT as breast reconstruction technique. These findings contribute to resolving ongoing concerns regarding the potential tumour-promoting effects of AFT.

Regarding OS, the available literature echo our results, indicating that post-oncologic AFT does not adversely affect OS.[7,20]

Krastev et al. reported no increase in oncologic events after AFT: OS was unchanged, and HRs for LRR and distant disease were below one, but not statistically significant, hereby supporting safety, but not necessarily indicating a protective effect.[7] However, their study focussed on AFT after

breast-conserving therapy, not AFT as total breast reconstruction following mastectomy. Laas et al. observed adjusted HRs < 1 for disease-free and OS among younger women (18–45) after mastectomy who underwent fat grafting, compared with other reconstruction or no reconstruction.[20] Our intervention cohort is, on average, ten years younger than the control cohort. Although the control group would theoretically have a higher risk of death due to age-related factors, breast cancer in younger women is often characterised by more aggressive tumour behaviour, which in turn may adversely impact OS in a younger population.[21–23] Statistically, age was also included as confounder in the multivariable analysis. Another recognised prognostic factor in breast cancer is BMI. [24] Although BMI differed statistically between groups, mean BMI values in both cohorts remained below the threshold for overweight, making it unlikely that BMI meaningfully contributed to differences in oncological outcomes.

To summarise, literature, like our results, does not report negatively affected OS following AFT. However, our study is unique in that it assesses AFT for total breast reconstruction post-mastectomy. Additionally, aforementioned studies would suggest a favourable association of AFT on OS in a selected, younger, subgroup. However, given the observational design and potential residual confounding, they should not be interpreted as evidence of a causal protective effect of AFT for total breast reconstruction on OS.

Though we did not compare LRR and metastases to a control cohort, we feel it important to address them in our discussion. Multiple studies have showed no increase in LRR in AFT-patients, compared to control cohorts. The Randomised Controlled BREAST trial reports no significant difference in LRR rates in AFT-patients, compared to IBR-patients.[14] Consistent with our observations, Cohen et al. found that patients who underwent fat grafting were, on average, younger than the comparison cohort. They also found no increased risk of LRR.[25] Several (matched) case control studies with substantial study populations show no increased risk for LRR, both in partial and total breast reconstruction with AFT. [26–30] These studies also have adequate oncologic follow-up period, ranging from 4.6 years by Petit et al. to 7.6 years by Rigotti et al. Myckatyn et al. report in their multicentre case cohort study of 1197 patients a regional recurrence rate of 11%, and 34% for local recurrences, which is higher than both the results of the BREAST trial, and our current findings.[14] While participants in the study of Myckatyn et al. have a mean age of 47 years old (comparable to our AFT cohort), the authors did not include women

with in situ carcinomas. Including in situ tumours is paramount, as their recurrences can also occur after mastectomy, and have high mortality rates. [31] More literature favouring AFT's safety include those of Krastev et al., Goncalves et al., and La Torto et al. All find no increased risk for LRR in their systematic reviews of 8791, 8541, and 14.078 participants, respectively.[7,12,13] In contrast, Chung et al. conducted a retrospective study of 339 women, and found an increased risk for recurrences with a HR of 2.52 (95% BI 1,005–6,317; p=0,0488).[32]

For metastases, literature also confirms AFT's safety in studies with substantial study populations.[29,33] Petit et al.'s matched case control study with 644 participants shows, in addition to LRR, no increased risk for distant metastases following post-oncologic AFT.[27]

To summarize, the concern that is raised by pre-clinical (rodent) studies, in which ADSCs can promote breast-cancer cell proliferation, invasion, and metastatic behaviour in in-vitro and rodent models, is not being confirmed by results of clinical trials and research.[9]

Strengths and limitations

This study benefits from the pooling of prospectively collected data from two multicentre clinical trials, providing a large and representative cohort. A key strength is the use of nearly identical in- and exclusion criteria and matching timeframes for both the intervention cohort and the control cohort. This enhances comparability and reduces confounding due to differences in case mix or treatment era. Consequently, the cohorts are comparable with respect to TNM staging, suggesting broadly similar prognostic profile. Long-term follow-up, weighted analyses, and the inclusion of a large nationwide control group further strengthen the validity and generalisability of the findings.

Despite these strengths, unmeasured confounding cannot be excluded. Factors such as comorbidities and genetic predispositions may not have been equally collected in the registry cohort. Not all BREAST trial exclusion criteria could be applied to the control cohort, comorbidities such as kidney disease, uncontrolled diabetes and steroid dependent diseases are not present in the AFT-cohort, but could not be excluded from the control cohort. These comorbidities could negatively affect overall survival in the older control cohort. The potentially healthier AFT cohort may be subject to healthy-user bias, which could limit the reproducibility of the results and their generalisability to the wider breast cancer care setting.

Additionally, follow-up intensity differed between groups. The intervention cohort received annual structured physical examinations and imaging, following the study protocols, whereas patients in the control cohort were followed up only upon clinical indication. This may have led to underdetection of recurrences in the control group. Adding to this, the registry is known to underreport recurrences and metastases. For this reason, these outcomes were not analysed, which may limit comparison with studies assessing disease-free survival. Another discrepancy is initial breast cancer diagnosis in the intervention cohort. Some participants may have had their first diagnosis years before their AFT reconstruction. The control cohort all had their initial diagnosis between 2013 and 2022, this means that participants in the intervention cohort might have received cancer treatment which would now be obsolete. Another limitation is that the AFT-cohort included a higher proportion of carcinoma in situ (Tis) compared with controls. Carcinoma in situ (e.g., ductal carcinoma in situ) is a non-invasive entity with an overall favourable prognosis and low breast cancer–specific mortality; however, it remains associated with a measurable risk of (ipsilateral) local recurrence, including progression to invasive recurrence.[31,34] To mitigate potential confounding due to these baseline differences, tumour stage (including Tis) was incorporated in the propensity score model and covariate balance was assessed using standardized mean differences before and after weighting. Nevertheless, residual confounding related to disease severity and unmeasured factors cannot be fully excluded in this observational setting. Lastly, although BREAST-I was randomised, BREAST-II was observational, and the use of registry data precludes full control for unmeasured confounding despite methodological adjustment.

Clinical implications and future recommendations

These results strengthen earlier reported literature, and can improve the widespread use of AFT as total breast reconstruction. Future research should continue to monitor AFTs safety in a large cohort with substantial follow-up period, and include disease-free survival. For this reason, the authors have initiated a national registry for follow-up of all AFT-participants in the Netherlands. Lastly, the efficacy and oncological safety of AFT should be assessed in trials in women with irradiated chest walls after more aggressive lesions.

CONCLUSION

This pooled, propensity score matched cohort of AFT-patients compared to a nationwide control registry shows that AFT used for total breast reconstruction does not increase mortality in long-term follow-up. Consistency with prior trials and systematic reviews strengthens confidence in its oncologic safety, despite the observational elements and potential differences in follow-up intensity. Future research should continue with large cohorts and assess disease-free survival.

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V

Eight Women With Autologous Fat Transfer and Deep Inferior Epigastric Perforator Flap Breast Reconstruction: Which Do They Prefer, and Why?

A cross-sectional, mixed methods study

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ABSTRACT

Background

Autologous fat transplantation (AFT) is emerging as an alternative autologous reconstruction post-mastectomy. This study compares patient-reported outcomes of AFT and Deep Inferior Epigastric Perforator (DIEP) flap in women who experienced both procedures

Methods

In this mixed-methods, cross-sectional study, eight women meeting inclusion criteria completed BREAST-Q and BODY-Q surveys, of whom six subsequently participated in semi-structured interviews. Quantitative data compared satisfaction, physical well-being, and sensation. Qualitative thematic analysis explored patient experiences. Additional clinical data were collected retrospectively.

Results

DIEP reconstruction showed superior scores across domains, with a statistically significant advantage in physical well-being ($p=0.029$, Cohen's $d=0.80$). Satisfaction and sensation differences were small to moderate, with qualitative data revealing more nuanced experiences. Participants described DIEP as a one-time, more invasive procedure with longer recovery and visible scarring, whereas AFT was perceived as gradual, less traumatic, and with minimal scarring, albeit requiring multiple sessions and showing variable volume retention. Sensory recovery was limited in both. Decision-making was influenced by treatment availability and patient values, in which social support played a critical role.

Conclusions

In this exploratory study in women who experienced both DIEP and AFT-breast reconstruction, AFT appeared to yield satisfaction similar to DIEP reconstruction, but further research is required to validate these observations.

INTRODUCTION

Breast reconstruction following mastectomy plays a crucial role in restoring body image and improving quality of life (QoL) for breast cancer patients.[1] Among the various reconstruction techniques, the Deep Inferior Epigastric Perforator (DIEP) flap has become the gold standard for autologous breast reconstruction (ABR) due to its natural aesthetic outcomes and biocompatibility.[2] The DIEP flap procedure involves en bloc microsurgical transplantation of vascularized skin and subcutaneous tissue to recreate the breast. This is an extensive surgery with hospital admittance, risk of abdominal wound healing problems, pulmonary embolism and flap loss. [3–5]

Autologous Fat Transfer (AFT) is an emerging technique for total breast reconstruction. Contrary to the DIEP, AFT is a minimally invasive technique in which adipose tissue is harvested from various donor sites and injected into the thoracic area to reconstruct the breast.[6]

Clinical trials have demonstrated that AFT is a safe and effective option for total breast reconstruction, with low complication rates and considerable patient satisfaction.[7,8] Compared to implant-based reconstruction, AFT has proven superior in terms of patient preference, largely due to its fully autologous nature. Nevertheless, given its relative novelty, AFT has not yet been systematically compared to other well-established autologous reconstruction techniques, such as the DIEP flap. A better understanding of patient preferences and perceived differences between DIEP and AFT reconstructions could provide valuable insights for surgical planning, informed consent discussions, and the promotion of patient-centred care.

In the Netherlands, a small group of women had undergone both DIEP flap and AFT as breast reconstruction, with AFT being performed after flap loss, offering a unique opportunity to assess their experiences and preferences regarding these two techniques.

In this exploratory study, we aim to investigate patient-reported satisfaction in women who underwent both DIEP flap reconstruction and total breast reconstruction using AFT. Our goal is to understand how these techniques compare within this population with complex reconstructive history, and to gain insight into satisfaction after a challenging and prolonged reconstructive process involving multiple techniques. We

hypothesise that patient-reported experiences and satisfaction will vary between AFT and DIEP reconstruction, and that qualitative analyses will provide context to potential quantitative differences.

METHODS

Ethical Considerations

The institutional review board determined that the study was exempt from the requirements of the Medical Research Involving Human Subjects Act (WMO), and ethical approval was granted under reference number METC2025-0002. All participants provided written informed consent for participation and the use of their data for research purposes.

Study Design

This study employed a cross-sectional, mixed methods design to investigate satisfaction among women who had undergone DIEP flap breast reconstruction and AFT reconstruction. A sequential explanatory mixed methods approach was used, consisting of a quantitative survey phase followed by a qualitative interview phase.

Participants

Participants were recruited from two centres in the Netherlands: Maastricht University Medical Centre (MUMC+) and Amphia Hospital Breda. Inclusion criteria were adult women who had undergone both a DIEP flap and an AFT reconstruction of the (contralateral) breast. Eligible women were approached to participate by their plastic surgeon and were included after written Informed Consent was provided.

Outcomes

The primary outcome of this study was patient-reported satisfaction with each breast, evaluated separately for the DIEP flap and AFT-reconstructed sides. Secondary outcomes included patient-reported physical well-being and sensation, as well as perceptions of social support, and factors influencing the decision-making process.

Data Collection

Quantitative Phase

After providing written informed consent, participants completed various modules of the validated BREAST-Q 2.0 questionnaire. The BREAST-Q

assess health-related quality of life (QoL) through multiple domains, including satisfaction with breast appearance, psychosocial well-being, and physical sensations. The domains Physical well-being of the chest area, Satisfaction with the breast, Breast sensation and Breast symptoms were assessed for the DIEP and AFT breasts separately. Psychosocial well-being, sexual well-being, Breast sensation; QoL impact were assessed not per breast but per participant. Data were collected between January and May 2025, reconstructive history and relevant medical history were collected retrospectively.

Qualitative Phase

Following the survey, audio recorded, 20-minute semi-structured interviews were conducted through teleconsultation from January to May 2025. Interviews were conducted by first author (MD, doctor-researcher) and second author (BSc, research assistant). Interviewers had no prior relationship with participants. Interviews explored reasons for (dis) satisfaction, the importance placed on sensory outcomes and natural appearance, and participants' perceptions of the information and support received during the decision-making process. Results were transcribed using the audio-recordings and field notes.

Data Analysis

Quantitative Analysis

Quantitative data were analysed using IBM SPSS Statistics version 29.00. Descriptive statistics were used to summarize participant characteristics. Paired t-tests were conducted to compare BREAST-Q scores between the DIEP and AFT sides. Given the small sample size, statistical analyses were considered exploratory. Accordingly, p-values were interpreted with caution, and greater emphasis was placed on effect sizes (Cohen's d) to evaluate the magnitude and potential clinical relevance of observed differences.

RESULTS

Participant Characteristics

From the database of two plastic surgeons, ten women were eligible. Eight women provided informed consent and were included and completed the quantitative surveys. The flowchart is depicted in figure 1, baseline characteristics can be found in table 1. Additionally, six women

completed semi-structured interviews. The reconstructive history of these six participants can be found in table 2. The DIEP flaps were performed as described by Allen.[2] The AFT-reconstruction was performed as per the BREAST trial protocol.[7,9,10] On average, participants required 3.63 (±1.2) sessions of AFT for a total breast reconstruction. All participants had a partner during the reconstructions and the conduct of this study. Three women had IBR in their medical history. One woman has a unilateral DIEP breast, and a contralateral AFT breast after stacked Lateral Thigh Perforator (LTP) flap loss of that side. Overall mean time since DIEP reconstruction was 65 months, mean time since completion of AFT reconstruction was 23 months. One participant required one more session of AFT during the conduct of this study. Figures 2-4 show results of completed reconstructions of participants.

Table 1. Participant demographics. Abbreviations: BMI: Body Mass Index, BRCA1: Breast Cancer gene 1

Table 1. Participant demographics	
Age, mean (SD), y	52.9 (±8.4)
BMI, mean (SD)	27.8 (±2.6)
Cup size	
B	1
C	4
D	1
E	2
Mastectomy	
Bilateral	6
Unilateral	2
Mastectomy indication	
Breast cancer	6
Risk reducing	2
Tumour stage	
In situ	1
IA	1
IIA	2
IIB	1
IIIA	1
Genetic predisposition	

Table 1. Participant demographics. Abbreviations: BMI: Body Mass Index, BRCA1: Breast Cancer gene 1 (*continued*)

Table 1. Participant demographics	
BRCA1 mutation	2
None	4
Not reported	2
Reason for flap loss	
Vascular complications	5
Infection	1
Trauma	1
Unknown	1

Table 2. Reconstructive history per participant of the six interviewed participants

Participant	Year mastectomy	Mastectomy indication	Reconstructive history	Year DIEP flap reconstruction	Indication for AFT	Final status	Last AFT session
1	2017	Bilateral; fibroadenoma and phyllodes tumour	Immediate TE/IBR-reconstruction. Implant-removal followed by bilateral DIEP flap.	2020	Intra-flap thromboses, total flap loss of left breast. Then IBR, complicated by implant infection and capsular contracture, implant-removal and capsulectomy, later AFT	Right breast: DIEP flap Left breast: AFT	2024
2	2022	Bilateral; breast cancer left breast, BRCA mutation	Delayed bilateral DIEP reconstruction	2023	Arterial bleeding of left DIEP anastomosis resulting in total flap loss, later AFT	Right breast: DIEP flap Left breast: AFT	2024
3	2009, 2019	Mastectomy right side, Mastectomy left side later, both breast cancer	Right side IBR. Left side immediate bipedicled DIEP.	2019	Capsular contracture in right breast, implant-removal and capsulectomy, later AFT	Right breast; AFT Left breast: DIEP flap	2024
4	2017	Bilateral; right side breast cancer, left side RRM	Immediate bilateral TE reconstruction. TEs removed due to complaints. Bilateral DIEP flap reconstruction followed by total flap loss of left breast. Later tertiary LTP-flap reconstruction left breast.	2018	Tertiary LTP-flap reconstruction of left breast. Total flap loss after four re-anastomoses, later AFT.	Right breast: DIEP flap Left breast: AFT	2022

Table 2. Reconstructive history per participant of the six interviewed participants (*continued*)

Participant	Year mastectomy	Mastectomy indication	Reconstructive history	Year DIEP flap reconstruction	Indication for AFT	Final status	Last AFT session
5	2018, 2019	Mastectomy left side, later mastectomy right side. Both breast cancer	Immediate DIEP reconstruction of left breast. Later immediate stacked LTP-flap reconstruction for right breast.	2018	Total flap loss of stacked LTP-flaps on right side due to trauma. Later AFT	Right breast; AFT Left breast: DIEP flap	2023
6	2019	Bilateral; RRM for BRCA mutation	Immediate bilateral DIEP reconstruction.	2019	Venous congestion of left DIEP and fat necrosis, resulting in total flap loss. Later AFT	Right breast: DIEP flap Left breast: AFT	2022

Abbreviations: RRM; Risk Reducing Mastectomy, DIEP: Deep Inferior Epigastric Perforator flap, LTP-flap: Lateral Thigh Perforator flap, TE; Tissue Expander, IBR; Implant Based Reconstruction, BRCA; BReast Cancer gene, AFT; Autologous Fat Transfer

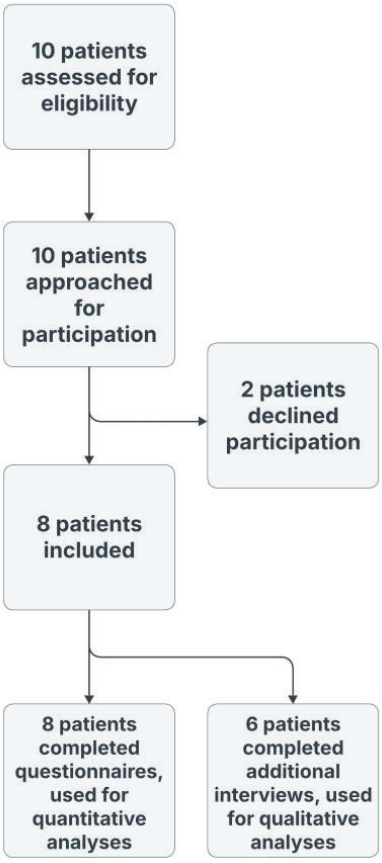

Figure 1. Flowchart depicting inclusion process

Quantitative results

Table 3 depicts the BREAST-Q scores for the DIEP and AFT breast individually, and the results of their paired T-test. Though the DIEP shows higher scores for all domains, only Physical well-being showed a statistically higher score for the DIEP compared to AFT, with p=0.029 and Cohen's d of 0.798.

Qualitative results

Thematic analysis of interviews of women who underwent AFT-reconstruction after DIEP flap-loss revealed seven central themes: satisfaction, sensation, physical wellbeing, decision-making, and divergence in DIEP and AFT procedures. In the discussion we will address these central themes and combine these with the quantitative data.

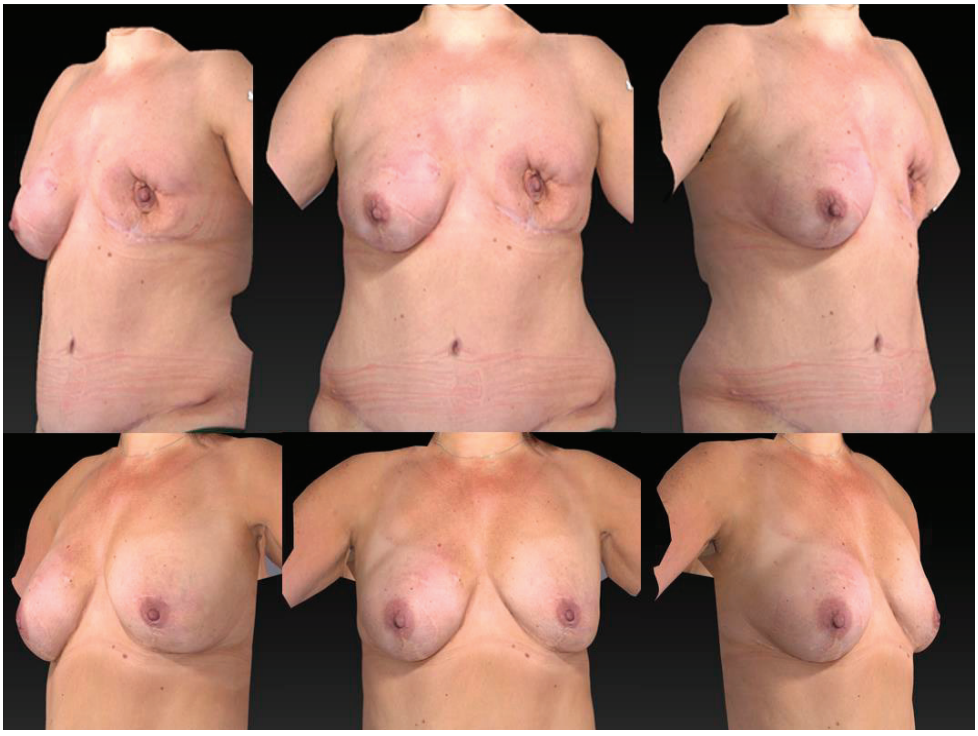

Figure 2.
Top row: Participant after bilateral nipple- and skin-sparing mastectomy, bilateral DIEP flap, flap-loss of left breast. Bottom row: Final result after AFT-reconstruction of left breast.

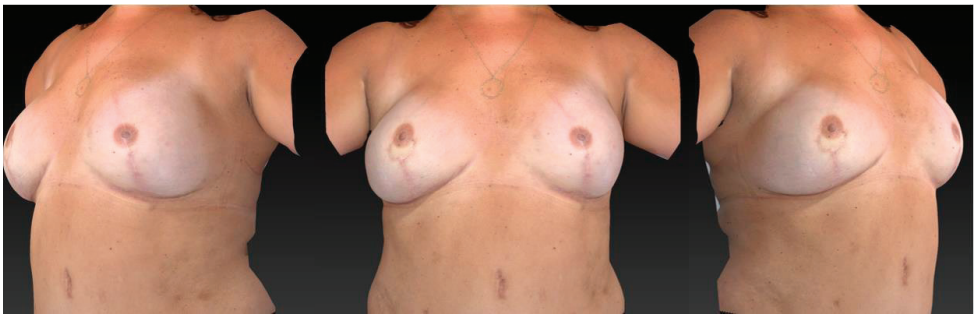

Figure 3.
Final result results after bilateral mastectomy, bilateral DIEP flap, flap-loss of left side, AFT-reconstruction of left side. This participant opted for nipple areola complex reconstruction combined with 3-dimensional tattoo.

Satisfaction with breast

The effect size for satisfaction in these eight participants, measured by Cohen's d (0.49, 95% CI [-0.32 to 1.26]), indicates a small to moderate advantage of the DIEP reconstruction over AFT, with a mean difference of 5.00 (Table 3).

Table 3. Paired T-test results of BREAST-Q domains for DIEP and AFT breast

Domain	DIEP breast mean ± SD	AFT breast mean ± SD	Mean difference	SD	P	Cohen's d	CI
Satisfaction with breast	65.7 ±17.6	60.8 ± 16.4	5.0	10.2	0.122	0.489	-4.462-14.462
breast Sensation	49.6 ± 34.1	48.9 ± 33.7	0.7	4.2	0.668	0.170	-3.163-4.591
Physical wellbeing of the chest	84.1 ± 14.7	70.1 ± 14.7	14.0	17.5	0.029	0.798	-0.665-28.665
Symptoms in the breast	81.1 ± 14.2	73.8 ± 15.3	6.6	13.8	0.073	0.477	-6.164-19.307

Abbreviations: SD: Standard Deviation, CI: 95% Confidence Interval

In the qualitative interviews in six patients satisfaction was described based on volume, symmetry, firmness and overall appearance. Three participants preferred their DIEP breast over their AFT breast, two preferred AFT over DIEP. The DIEP flap breast was frequently referred to be more voluminous and more natural. Literature also reports high satisfaction scores for the DIEP, even up to 92% satisfaction rate. [11,12] Women noted that the mastectomy scar of the AFT-breast had become noticeably less apparent after fat grafting: *'I prefer the AFT breast, it has little to no visible scars anymore, and has stayed firm, but natural.'* For AFT, literature reports higher satisfaction rates than our findings. [7,8] A paramount notion is that DIEP was at the time the first choice for the participants, and almost only after flap-loss, AFT was performed as a salvation. This might explain AFTs inferior scores to the DIEP. Furthermore, one participant had not completed her AFT reconstruction, with the final session taking place during the conduct of this study. As she had not yet achieved her end result, her lower satisfaction scores might influence the mean score in this small sample size. However, this does not take away her experiences of the AFT-reconstruction trajectory, and her preference in treatment overall.

Two participants described their breasts as two different shapes, which they attributed to having had two different reconstruction methods. Two

participants stated they were happy with the result but still make you use of small external prosthetic over the AFT breast, especially in certain clothes; "*Eventually, I settled for a small external implant for my bikini.*"

Overall, participants had moderate satisfaction scores for both reconstruction methods. Satisfaction with reconstruction was highly individual and was strongly influenced by expectations, lifestyle, and perceptions of completeness. These findings highlight that satisfaction is not purely a surgical outcome, but a personal and evolving perception shaped by expectations and available information. Satisfaction, in this sense, is less a fixed endpoint and more a reflection of how well the chosen method aligns with a woman's individual recovery goals.

Sensation

Quantitative data from the BREAST-Q indicates a small difference favouring the DIEP reconstruction over AFT, with a mean difference of 0.71 (Table 3).

Sensory experience was important to all women in varying degrees. Though the quantitative data favoured DIEP, qualitatively AFT showed more sensory stimuli. These moderate differences suggest that while some sensory recovery or residual feeling may occur, sensation is often incomplete and varies greatly across individuals. Two participants expressed having tingling pain or hypersensitivity in cold weather in the DIEP breast. Four participants indicated that the AFT breasts had slightly ''more'' sensation. One participant shared, "*In the AFT side, I feel something when touched. In the DIEP, it's just... nothing.*" Studies have shown that DIEP flaps have a great loss in tactile and temperature sensation, especially in DIEPs without nerve coaptation. [13,14] Our findings are supported by research indicating that AFT may offer sensibility recovery, superior to for example IBR. [15] The inferior quantitative scores for AFT in this study may again be attributed to the fact that the DIEP breasts have had more recovery time, and AFT has not yet achieved final sensory recovery. The sensation (or lack thereof) affected self-perception; "*Sensation matters, because otherwise it feels cold and dead, like it's not your own.*" Still, five participants had accepted the sensory changes: "*I've made peace with it. It's not what it was, but it's mine*" and "*It's not painful, just different.*" A limitation of this study is that sensation is only reported by participants, and not objectified by standardised testing, making it less reliable to compare with existing literature.

The variance in importance and experience of sensory recovery in each patient underlines that sensory expectations should be explicitly addressed in preoperative counselling.

Physical well-being and symptoms

Physical well-being of the chest was higher in the DIEP group compared to the AFT breast, with a statistically significant difference ($p = 0.029$) and a corresponding effect size of Cohen's $d = 0.798$ (95% CI: −0.27 to 1.583). In the Breast-Q domain 'Symptoms', DIEP showed less symptoms than AFT; this difference was not statistically significant ($p= 0.073$), with an effect size of Cohen's $d= 0.477$ (95% CI: −0.326 to 1.247).

In the interviews, participants interpreted physical well-being as general, not specifically for the chest. Quantitative data showed superior scores in Physical well-being of the chest in DIEP breasts compared to AFT breasts. Quantitatively, there were more symptoms in AFT breasts, though this did not necessarily appear so in the qualitative analysis. The physical toll of breast reconstruction was frequently emphasized, particularly following the DIEP flap procedure. Participants described the recovery as greatly strenuous, longer than expected, and physically demanding. Participants experienced postoperative abdominal pain, fatigue, oedema in the breast, and restricted movement in the chest area due to pain or swelling after DIEP reconstruction. Flap reconstructions are proven to have good long-term outcomes and less long-term complications as well as improve quality of life, especially compared to IBR.[16,17] However, remaining symptoms postoperatively in DIEP breasts indicate a need for better post-surgical rehabilitation support.

AFT was generally perceived as less physically burdensome. AFT also proved superior to IBR in terms of physical well-being.[7] Two participants reported having benign palpable lesions (i.e. oil cysts, a typical symptom following fat necrosis) in their AFT breast, these were not painful. Three participants noted numbness of the AFT-donor site (only in outer thighs), even months after completion of the AFT-reconstruction. Donor site complaints are known for both reconstructions.[18,19]

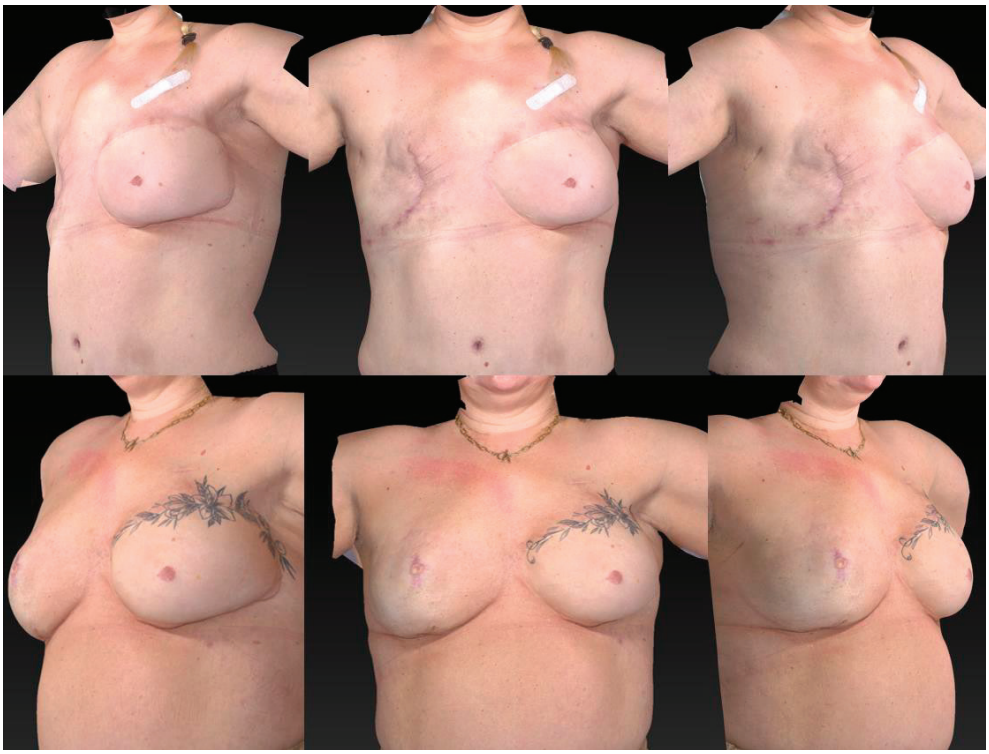

Figure 1. Top row: Participant after bilateral mastectomy, DIEP flap on left side, failed LTP-flap on right side.
Bottom row: Final result after AFT on the right side, and bilateral NAC-reconstruction. This participant opted for tattoo coverage of the mastectomy scar on the DIEP breast.

Decision-making

Decision-making was influenced by medical advice, available options at the time, personal values, and body type. Four participants expressed a primary preference for autologous reconstruction. Participants either had an aversion to IBR, three described complicated IBR reconstructions in their medical history*: "I didn't want implants. I wanted something that was mine"* , or were advised by their oncologic physician: *"My oncologist advised against implants for follow-up reasons."* Five participants stated that AFT was not yet an established total breast reconstruction and therefore not available at the time of their first reconstruction. They would have considered it had it been available. Participants reported that they felt they did not have a real choice in their first reconstruction interview. After communicating their autologous reconstruction wish, their plastic surgeon at the time only gave the DIEP as an option: '*My surgeon said it*

was a DIEP or an implant, so the choice, if you can even call it that, was made rather quickly.'

This variability in counselling highlights broader disparities in access and information, particularly concerning newer or less standardized techniques such as AFT. Disparities in counselling are no novelty, and are known to negatively affect women post-reconstruction.[20,21] Social support emerged as a crucial factor in the decision-making process. Participants who felt emotionally supported by partners, friends, or healthcare providers reported better psychosocial adjustment. Participants valued support from their partner over that of their medical team or support groups, which slightly contradicts current literature.[22]: "*Without my partner's support, I wouldn't have gotten through it*."

Our findings underscore crucial ethical and practical considerations in patient autonomy and equitable access to information. A true shared decision making process, and well-established patient-physician relationship positively impacts outcomes in breast cancer survivors.[23] Post-mastectomy care should focus on improving shared decision making by ensuring all patients receive balanced, comprehensive information on all reconstruction options, including newer techniques like AFT. Standardized decision aids and clinician training in unbiased counselling can help reduce disparities and support truly informed, patient-centred choices.

Divergence in DIEP and AFT procedure

Participants described the DIEP as being a 'one-and-done surgery', compared to AFT's several sessions. However, participants described DIEP as a heavier procedure, more invasive, longer recovery time, with visible scarring, especially on the abdomen. Regarding the DIEP breast, participants underestimated the recovery. One participant stated: "*If I had known how hard the recovery was, I might've chosen differently."*

The AFT reconstruction was described as gradual, and less traumatic to the body, leaving virtually no additional scars on the donor sites, contrary to the DIEP scar on the abdomen. However, participants expressed volume retention during sessions as disappointing. Import decisive factors for the AFT method were treatment time and perioperative factors, such as the external vacuum expander. One participant noted: *"I would do AFT again, but without the external expander."* Participants stressed the burden of the external expander, which indicates that further research on the AFT trajectory, particularly its efficacy without external vacuum

expanders, is needed. Importance of expectation management regarding longevity of the treatment was also stressed: *"AFT was long, but I knew what I was signing up for."*

The contrast between the physical demands of DIEP reconstruction and the repetitive nature of AFT highlights a tension in reconstructive care: a single, intensive procedure and multiple, less invasive procedures. This contrast reflects true patient preference: some favoured the one-time invasiveness of DIEP, others the longer AFT process. These findings echo existing literature emphasizing the importance of individualized treatment that considers patient values and preferences in reconstructive surgery.[24]

Strengths and Limitations

This study has several strengths, including the unique within-subject comparison since all participants underwent both DIEP flap and AFT. Additionally, the mixed-method approach, combining quantitative validated questionnaires with qualitative interviews, allowed for a comprehensive understanding of both objective outcomes and subjective patient experiences. The clinical relevance is high, reflecting real-world reconstructive challenges. This study has some important limitations, in addition to the small sample size. In most cases, AFT was performed following a failed or complicated DIEP reconstruction, which inevitably introduces bias in patient perceptions. Furthermore, several participants underwent their initial DIEP reconstruction before AFT was widely available as a total breast reconstruction option. Some women indicated that, had AFT been an established alternative at the time, they might have chosen it as their primary reconstruction. These discrepancies influence interpretation and highlights how evolving availability of reconstructive options and provided information can affect patient preferences and satisfaction. Nevertheless, the unique perspective of women who have experienced both techniques offers valuable qualitative insight into reconstructive decision-making and outcome perception.

The clinical implications of this study highlight the importance of effective expectation management; women should be thoroughly informed about the potential outcomes of all available autologous reconstructions. Reconstruction should be tailored to individual preferences, lifestyle, and psychosocial context to optimize satisfaction and QoL. Furthermore, offering psychosocial support and promoting shared decision-making

throughout the reconstruction process are essential to address patients' concerns.

CONCLUSIONS

In this small exploratory mixed-methods study in women who experienced both DIEP and AFT-breast reconstruction, AFT appeared to provide satisfaction comparable to DIEP reconstruction. Given the very limited sample size and cross-sectional design, these findings should be interpreted with caution. Further research is needed to confirm whether AFT can offer outcomes comparable to DIEP in broader patient populations.

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VI

Development and pilot evaluation of an e-learning module for Autologous Fat Transfer (AFT) in total breast reconstruction in the Dutch Healthcare System: Insights from 9 Plastic Surgeons

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ABSTRACT

Introduction

Autologous Fat Transfer (AFT) for total breast reconstruction is a novel, minimally invasive technique recently introduced into the Dutch healthcare system. Although plastic surgeons are experienced with AFT for aesthetic and partial reconstructive procedures, its application for total breast reconstruction presents unique challenges, necessitating standardized training

Methods

A multidisciplinary team developed an e-learning module on The Huddle platform, guided by adult learning theory, context-specific instruction, visual learning aids, and key insights from a clinical research program (BREAST trial). The module included text, videos, illustrations, and case-based learning. Nine Dutch plastic surgeons with varying experience levels pilot-tested the module. Semi-structured interviews assessed clarity, relevance, and usability.

Results

Feedback was predominantly positive. Participants appreciated the structured format, permanent accessibility, and visual materials that supported procedural understanding. Several surgeons reported intended changes to their surgical approach, such as modifications in fat harvesting. Suggested improvements included patient selection criteria, radiological aspects, and information on common complications. The absence of narrated videos was perceived as a limitation.

Discussion

The pilot demonstrated that a flexible, visually rich e-learning format can support knowledge acquisition in a novel surgical technique. Interdisciplinary collaboration and iterative feedback were key strengths. Limitations include the small sample size and the purely qualitative design, which restrict generalizability.

Conclusion

We developed and pilot-tested an e-learning module for AFT in total breast reconstruction. The module was well received and considered clinically relevant, and could hereby fill an (inter)national gap in standardised training. Future research should evaluate learning outcomes quantitatively, compare efficacy to traditional training, and assess long-term impact on surgical practice.

INTRODUCTION

The term Autologous Fat Transfer (AFT) is used to describe the act of transplanting the patient's own fat tissue to another region in the body for the purpose of correcting volume or contour deformities. It is a minimally invasive surgical technique in which the adipose tissue is aspirated from a donor site (liposuction) and relocated to a (contour)defect of the body (lipofilling), either as (defect) reconstruction or aesthetic breast augmentation. [1] [2] Although plastic surgeons are widely trained in the technique of liposuction for the removal of fat, re-injection (often referred to as lipofilling) is a procedure which has some challenges and must be adapted to the clinical goal. The most important applications of AFT in plastic and reconstructive surgery are the face, the breast and in scar tissue.

AFT has until recently only been known to correct small breast deformities. Recently, however, it has been introduced as an option for total breast reconstruction following mastectomy. The Dutch BREAST trial showed that AFT as total breast reconstruction improves quality of life compared to implant-based reconstruction, leading to its inclusion in the Dutch national health insurance. AFT can now be offered as standard breast reconstruction, but only when adhering to the same strict criteria as the BREAST trial protocol. [3,4] As the number of centres offering this treatment expands, the Dutch Association for Plastic Surgery has emphasized the need for proper training. [5]

Due to its novelty, however, AFT as total breast reconstruction is not yet standardised in residency. Absence of standardized training in Plastic Surgery is no new phenomenon, and extends beyond the Dutch context, with literature describing substantial differences across continents, between countries, and even regionally.[6,7]

Traditional training methods, such as in-house courses with presentations, videos, and supervised practice, are effective but time-consuming and therefore costly. With demanding schedules, surgeons often lack the time to travel, whether nationally or internationally, for additional training.

E-learning offers a promising solution. Well-designed e-modules can provide continuous access to high-quality educational content, allowing surgeons to learn at their own pace and revisit complex material as

needed. Moreover, literature has shown that e-learning can effectively support surgical training, enhancing both knowledge and skills acquisition.[8,9]

Our hypothesis is that an AFT e-learning is a valuable addition to the regular training, and might be effective without in-house training. To assess this, an application for Promising Healthcare Practices was granted to develop a dedicated e-learning module for AFT, using a multidisciplinary team.[10] This pilot study focuses on module design and usability.

METHODS

The institutional ethical review board of the Maastricht university hospital confirmed that the Law on Medical Research Involving Human Subjects (WMO) did not apply during the development and pilot testing of the e-learning, ethical approval was hereby appointed under METC 2024-0482. As such, formal written informed consent was not required, and verbal consent was considered sufficient. All plastic surgeons provided verbal consent.

Steps taken for development and implementation of innovation

Developing an effective e-learning module requires a structured, evidence-based approach, guided by models such as ADDIE [11] and multimedia learning principles. [12] After a needs analysis to define objectives and assess the target group, design principles need to be determined. These design principles are the basis for content and technical development. Content development focuses on high-quality visuals and text that support learning while minimizing cognitive overload. The technical phase ensures the module is accessible, multimedia-supported, and allows progress tracking. A pilot test, evaluation through learner feedback, leads to continuous improvement.

Target group and needs analysis

The target group of the module consists of designated plastic surgeons in the Netherlands. This group includes recently board certified plastic surgeons, those at intermediate career stages and those with years of experience. Some of them may have experience with AFT for total breast reconstruction when their residency training centre was involved in the BREAST trial or was part of the appointed AFT-centres. Most have used

AFT in cosmetic procedures or to correct contour deformities. However, the majority have never performed total breast reconstruction with AFT. The module should therefore not directly focus on the technique of AFT, but rather put emphasis on it in the context of total breast reconstruction. The e-learning should elaborate on the trajectory of AFT breast reconstruction in its entirety, including secondary corrections such as scar release, and patient counselling. This approach enables the creation of flexible, scalable training modules, allowing surgeons to master procedures like AFT breast reconstruction at their own pace and according to their learning needs.

Design principles

The aim of the module is to provide comprehensive and accessible information about the procedures, ensuring that plastic surgeons gain a complete understanding of the relevant protocols. To reach this aim, we designed the e-learning module based on four design principles. The design principles were defined based on literature on adult learning [13], instructional strategies for skill acquisition [14], the role of visual information in e-learning [15], and the key knowledge to be conveyed from the BREAST trials. [5,16]

1. Alignment with Adult Learning Theory
   The module should take into account the adult learning principles, recognizing that the target audience consists of experienced, motivated plastic surgeons who are already familiar with the fundamentals of AFT. [17] Adult learners need to understand the relevance of what they are learning, build on their prior experiences, and value autonomy in their learning process. Adults prefer education that offers practical, applicable outcomes, sometimes embracing theoretical insights but often dismissing abstract knowledge if perceived as irrelevant. In the context of online learning environments, this means that the adult learner must be able to use the available technology and have the skills to search for and identify reliable information. [18] Based on these principles, the focus is placed on presenting new information specifically related to applying AFT for total breast reconstruction, rather than revisiting foundational knowledge or general AFT techniques. Based on the content of the module, the plastic surgeons should be able to assess their own proficiency in performing AFT in the context of total breast reconstruction and determine whether they need to assist under supervision or operate under the guidance of a more experienced surgeon.

2. Guidance specific to context
   Literature on skill acquisition emphasizes that providing overly detailed instructions on how to perform a task can be counterproductive. Instead, it is more effective to explain what needs to be achieved [19], except when necessary to ensure clarity. [20] This is particularly important for experts, as excessive procedural guidance can disrupt automatization and hinder performance. Focusing on the desired outcomes supports more flexible, adaptive skill execution. This principle is supported by studies on expertise development and cognitive load theory, which show that too much guidance can cause the "reinvestment" of conscious control over automated skills, leading to performance breakdowns. [14,21]
3. Use of supportive visual materials
   Supportive visual materials are necessary for effective e-learning design, particularly for complex skill acquisition. Combining visuals with verbal information reduces cognitive load and enhances understanding. Visuals help learners form accurate mental models, direct attention to key aspects of tasks [15] and improve knowledge retention when closely aligned with learning objectives. [22] Videos featuring an expert plastic surgeon performing the procedures are particularly helpful, as they not only demonstrate how to execute the techniques but also activate the observer's mirror neuron system, enhancing learning through observation. [23]
4. Emphasis on essential knowledge from BREAST Trials
   The module should highlight critical insights gained from previous breast trials to prevent users from repeating mistakes made during the development of the AFT procedure in the context of total breast reconstruction. The BREAST trials demonstrated that AFT is a safe and effective procedure for total breast reconstruction when the adapted Coleman technique is used and appropriate patient selection is applied. [5,24] Therefore in the Dutch healthcare system, AFT can only be performed using these exact techniques. Critical insights include the liposuction with caution, preparing the skin of the thorax for lipofilling, management of the volume of injected fat, and aligning surgical outcomes with patient expectations.[16] Integrating this evidence ensures that learners are trained in evidence-based decision-making to optimize patient care.

Content and technical development

The e- module was created in an online platform called The Huddle. [25] In this online environment, a variety of media formats such as text, video

and images can be added to a module, which suited the needs of our design team. The huddle is available on mobile devices. Participants can track their process in this environment, pause the e-learning and can continue when they wish to. The content of the module is permanently accessible. The module is structured according to the sequential stages of the full AFT procedure for total breast reconstruction (see Table 1 for an overview). We highlighted the importance of patient counselling, because the success of the reconstruction is highly dependent on patients' understanding of the total reconstruction process and their compliance in wearing the external expansion device. The use of the external expansion device also required elucidation, as most plastic surgeons are not familiar with this procedure. This device is placed on the thoracic skin pre- and postoperatively to prepare the thorax for lipofilling and to act as a splint after the operation.

The perioperative chapters contain a step-by-step guidance of what needs to be achieved by surgery. This included how the patient should be positioned in the operating theatre, how the breast should be prepared for lipofilling, and which operative techniques should be used. [4,5] Following the explanations of the operative procedures, secondary corrections to optimize breast contour are explained. The final (postoperative) chapters of the module include recovery. As explained in the design principles, it was important to put extra emphasis on the most valuable lessons learned from the BREAST trials. The key lessons have been integrated into various components of the module. To further emphasize them, they are also highlighted in the sections 'Frequently Asked Questions' and 'Take-Home Messages'.

The text was supported by several photographs, illustrations and videos. The photographs and videos were taken during either surgery or during clinical check-ups. The photographs were anonymized and patients consented to their use. A medical illustrator designed several illustrations that depicted parts of the process in similar design style. Figure 1 depicts an example of an illustration. Figure 2 provides an example of a module overview. Videos were used to show the procedures during surgery. Videos from a camera that was placed on the head (at eye-level) of an expert plastic surgeon showcased a surgeon point-of-view. Videos from a camera on tripod at the foot of the operating table showcased the procedures from the point of view of an observer. Videos were recorded and exported in high-definition (HD) resolution (1920 × 1080 pixels), and were edited in the apple application iMovie. The use of video foot-

ages from various perspectives was intended to make it easier for plastic surgeons to understand the procedures and apply them independently. Video length was on average up to three minutes, with one longer video containing step-by-step approach for the RAFT technique.

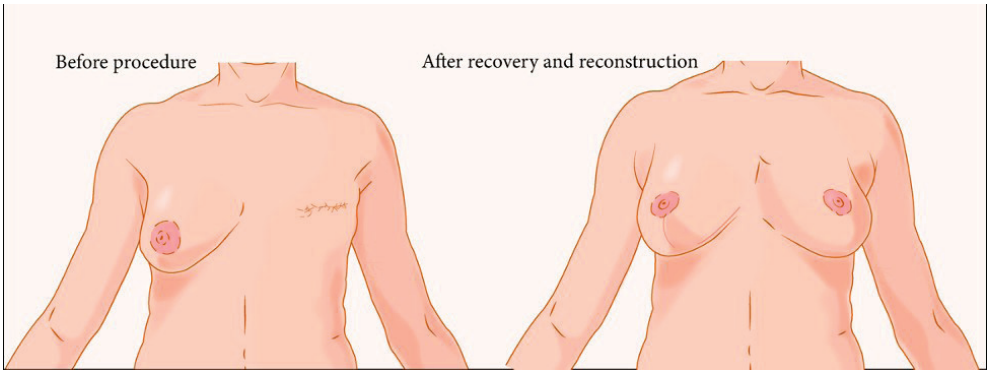

Figure 1. Left side, after amputation of left breast. Right side, after AFT-reconstruction of left breast, nipple reconstruction and reduction mammoplasty of right breast. Illustration: © Ava Krueger



Figure 2. This figure provides an example of one of the modules, the use of the External Vacuum Expander (EVE-bra®) on the chest, as preparation before the surgery. Illustration: © Ava Krueger

Table 1. Content of the module

E-module content	Elaboration
General introduction	General introduction on AFT, (learning) goals of the module and BREAST team contact information
Preoperative Counselling of the patient	How to select patients, how to counsel them for AFT, what to discuss in the outpatient clinic.
Expansion device	Usage of the External Expansion device: Why, how and when to use this.
Perioperative Planning Positioning of the patient Massaging the breast Donor site infiltration Liposuction of the donor site Preparing the breast for lipofilling Lipofilling the breast Decantation of fat and rebuilding the grafting system	In this chapter, the total operative procedure is outlined. This contains a very detailed exposition of the preparing the patient for the surgery, followed by the technique in its entirety. Why, how and when to use the techniques is explained. This chapter contains additional videos.
Perioperative tips and tricks Rigottomy (scar release) Reverse Abdominoplasty and Fat Transfer (RAFT, secondary correction technique)	This section depicts secondary corrective techniques, again with why, how and when to use these. This chapter contains additional videos.
Postoperative Antiseptic ointment Recovery Expansion	This chapter depicts patient care once the surgical aspect is completed.
Frequently Asked Questions	Frequently Asked Questions were noted during AFT-masterclasses by the BREAST team, and answered in this chapter.
Take home messages	A brief summary with relevant take home messages concludes the module.

RESULTS

Evaluation of innovation

To evaluate whether the intended aim of the module was achieved, we incorporated a pilot-testing with nine plastic surgeons. All surgeons were experienced in the application of AFT but varied in experience with the context of total breast reconstruction. Three of them had participated in the BREAST trials and were experienced (expert group), three had some experience (novice group) and three were about to start (aspiring group). The surgeons were affiliated with nine different Dutch hospitals, both academic and non-academic. For an overview of the plastic surgeons' experience level, see table 3. After they had completed the module, they were interviewed about their experiences. Interviews were conducted in a remote setting with questions regarding strengths and weaknesses, user-friendliness, timespan, whether they would recommend the module to colleagues and whether they would alter anything in their own practice after completion of the module. Examples of the interview questions can be found in table 2. The surgeons who participated in the BREAST trials were also asked whether they felt any information was missing or redundant.

On average, completion of the module took around 90 minutes, varying between 30 minutes and three hours. After nine interviews, thematic saturation was reached. All interviewed surgeons were positive about the module. They appreciated the thoroughness and the accessibility of the e-learning. They liked the well thought-out structure and permanent accessibility of the information. The videos and illustrations were seen as helpful components of the module. The surgeons with more experience experienced the module as a familiar repetition and as a refresher course. Overall, all surgeons would recommend the module to other plastic surgeons and felt well prepared to perform AFT in the context of total breast reconstruction after completing the module. Among the surgeons who were about to start with total breast reconstruction (i.e. the aspiring group), there was a degree of nuance between those who had previously observed a total breast reconstruction and those who had not. For the former, the module content was largely familiar and recognizable. The latter tended to rely more on their own established working methods, based on their experience with other applications of AFT. For example, they would prefer not to use small syringes as recommended to inject the fat in micro droplets (i.e. very small portions of fat, to improve cell-survival). They would also not use a closed liposuction system, as they were

familiar with their own liposuction system. All in all, all surgeons highlighted also the value of in-person training and observations, besides following the module.

The tips that were given for possible improvement of the module differed per degree of experience among the surgeons. The surgeons with some and with extensive experience recommended to add information on common side effects. A common side effect is that a small piece of fatty tissue may not survive. This fatty tissue feels as a breast lump but is usually not cancer. It is important that patients are informed in advance, so that they do not worry. They must report to the outpatient clinic for further examination. The surgeons also pointed out the importance that radiologists can accurately identify and differentiate between fat and tumour tissue and that radiologist thus need to be informed about the new application and this common side effect. In addition, some surgeons asked in the interviews for experiences with postoperative antibiotics. This was not addressed in module, but literature showed that postoperative antibiotics has no effect. [26]

The surgeons with some experience also advised to present patient cases with varying initial conditions. In clinical practice, women can present themselves not only with amputated breasts, but often already with an implant, or even another autologous reconstruction. These different conditions require different approaches. Interviewees would prefer that these differences be discussed. The surgeons who are about to start with total breast reconstruction gave other suggestions to further improve the module. They were interested in further information about legislation and logistics, but also about inclusions and exclusions criteria among patients. AFT has been included in the basic health care service since 2023, but only under strict criteria for patient selection, as described in the BREAST trial[5]. The surgeons would like to have this more elaborated. They would also have preferred to receive verbal just-in-time information while watching the videos. Videos were presented silent, because after filming, the sound was of bad quality. Consequently, participants now felt more as a passive observer rather than an active participant.

Responses to the question regarding changes in surgical approach after completing the module varied across surgeons. The most experienced surgeons explained that they would start to perform liposuction in the inframammary fold of the breast to increase a better shape of the breast. The module also prompted surgeons with some and with extensive ex-

perience to apply scar tissue release following fat grafting, instead of before. Furthermore, based on the pictures and photos in the module, the surgeons with some experience and starting surgeons learned to place the EVE-bra device (which patients wear two weeks before and after surgery) lower on the thorax, to no longer close injection sites, because these typically heal spontaneously and do not require suturing, and to also use inner and outer thighs as donor site (besides back and abdomen).

Table 2. First questions of semi-structured interview

	Questions
1.	Could you describe your overall experience with the e-learning program?
2.	What elements of the e-learning program did you find particularly positive or valuable?
3.	Are there any aspects of the e-learning program that you would like to see improved or changed? If so, which ones and why?
4.	How much time did you spend to complete the e-learning?

Table 3. Baseline characteristics of participating plastic surgeons

Group	**Experience as certified plastic surgeon** (mean in years, SD))	**Experience with aesthetic lipofilling** (-, +, ++)	**Experience with AFT as total breast reconstruction** (mean in years, extracurricular activities)
Aspiring	17 ± 9.63	++	No autonomous experience yet
Novice	15 ± 4.64	+	1-2 years, have attended masterclasses
Expert	17 ± 2.49	++	10 years, expert level, received and have given masterclasses

DISCUSSION

In this study, we developed and pilot-tested an e-learning module to support plastic surgeons in performing AFT for total breast reconstruction. Nine Dutch plastic surgeons with varying levels of experience (with AFT) evaluated the module. Interviews showed not all participants would adhere to the techniques described in the e-learning, but rather to their own techniques, especially when they have used aesthetic lipofilling in their career. Nevertheless, several surgeons indicated that the module prompted changes in their intended surgical practice. For example, one surgeon noted she would perform the rigottomy after the re-injection of fat, while another stated she would place the external vacuum expander lower than she had done previously. Overall, participants valued

the structured content, visual materials, and permanent accessibility of the platform. Suggestions for improvement of the module included the addition of information on side effects, patient selection, and radiological findings. These subjects have since been included.

The findings suggest that the e-learning module was considered relevant for clinical practice. This aligns with previous research showing that e-learning can be an effective adjunct in surgical training. [8,9] Studies in surgical education have demonstrated that video-based online learning tools can improve procedural understanding and confidence, particularly when combined with traditional training. [27,28]Our results echo these observations, as surgeons highlighted the added value of the visual materials and its permanent accessibility. At the same time, the absence of audio or narrated videos was perceived as a limitation, which is consistent with literature emphasizing enhanced learning in e-learnings with audio, compared to silent videos. [29]

Strengths and limitations

The development of the module was strengthened by a multidisciplinary design team, which allowed integration of clinical and scientific expertise, and educational principles. Including surgeons with diverse experience levels provided valuable insights into different learning needs and helped tailor the module to a broad target group. The thoroughness, visual materials and permanent accessibility were also recognized as a particular strength, supporting engagement and knowledge retention.

Several limitations should be addressed. First, the pilot sample was small and drawn exclusively from only Dutch plastic surgeons, possibly limiting generalizability. Second, evaluation was qualitative and based on self-report, without objective measures of knowledge gain or performance. Third, no control group was included, which prevents conclusions on the efficacy of the module compared to traditional training. Finally, all participants were volunteers, possibly introducing selection bias.

Future recommendations

Now that the module has been pilot tested and finessed, future studies should include quantitative assessment, such as pre- and post-module testing, validated questionnaires, or clinical performance data. Larger-scale evaluations are needed to validate the efficacy of the module. Comparative studies with in-person or hybrid training could determine whether e-learning is equally effective or more cost-efficient. Long-term

follow-up is also necessary to examine whether the module translates into sustained changes in surgical practice and possibly therefore, patient outcomes. For now, the principles and operative techniques are described adequately to train residents, but not yet to implement this technique in global healthcare. To achieve this, adaptations to local regulatory and healthcare contexts should be carefully addressed.

CONCLUSION

We developed and pilot-tested the feasibility of an e-learning module for AFT in total breast reconstruction. The module was positively evaluated and considered valuable for surgical training, although further refinement and rigorous evaluation are required. Despite limitations related to sample size and study design, this work represents an important step towards standardized training in this novel reconstructive technique.

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VII

External Vacuum Expansion in Autologous Fat Transfer as Total Breast Reconstruction: is it worth it?

The interim analysis of the multicentre randomised controlled EVE trial

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ABSTRACT

Background:

Autologous fat transfer (AFT) is an emerging option for total breast reconstruction. To improve graft survival, perioperative external vacuum expansion (EVE) is used to optimise recipient-site environment. However, the efficacy of EVE, and its treatment burden on women needs consideration. This interim analysis of a multicentre randomised controlled trial (RCT) evaluates the effect of EVE on volumetric outcomes and safety.

Methods:

Women undergoing total breast reconstruction with AFT were randomised 2:1 to perioperative EVE or no EVE. All participants underwent three AFT sessions followed by Magnetic Resonance Imaging (MRI)-based volumetric assessment at six months. Primary outcomes were percentage augmentation and graft retention. Secondary outcomes included (serious) adverse events (SAEs). Quality-of-life (QoL) outcomes were not analysed in this interim analysis, as reconstruction was ongoing.

Results:

Fifty-three participants were included (EVE n=32; control n=21). Mean augmentation was 190.7% with EVE versus 176.4% without (adjusted difference 14.6%; 95% CI -80.0 to 109.1; p=0.757). Graft retention was 39.3% and 34.9%, respectively (difference 4.5%; 95% CI -6.4 to 15.4; p=0.405). Both outcomes showed no statistically significant between-group differences. The EVE group experienced more AEs (22 AEs, 5 SAEs) compared with the control group (3 AEs, 2 SAEs), predominantly skin-related complications.

Conclusions:

Perioperative EVE use did not yield significant improvements in augmentation or graft retention, while it was associated with higher treatment burden and more (S)AEs. Final analyses of our ongoing RCT, incorporating patient-reported QoL outcomes need to be awaited. Based on this interim analysis, the clinical benefit of EVE in reconstructive settings remains uncertain and warrants additional research.

INTRODUCTION

In breast cancer survivors, post-mastectomy breast reconstruction is a key factor in improving health-related Quality of Life (QoL).[1,2] There are numerous ways to reconstruct the breast. Women can opt for either an implant-based reconstruction (IBR) or an autologous reconstruction (ABR). In ABR, the patient's own tissue is transplanted to recreate the breast, via either pedicled or free flap. A new option in ABR is autologous fat transfer (AFT).[3,4] AFT is a minimally invasive technique that utilises autologous adipose tissue to recreate the breast. In several sessions, adipose tissue is harvested from donor sites with moderate surplus of fat via liposuction. The fat is injected in the breast in several subdermal layers. The reconstruction can be accompanied by pre- and postoperative external vacuum expansion. [3,5]

Despite its advantages, total breast reconstruction using AFT entails several challenges. In high-volume fat grafting, elevated interstitial pressure may impede oxygen diffusion, thereby compromising adipocyte viability and graft retention.[6] Optimisation of graft survival necessitates a well-vascularised recipient site to promote neovascularisation. It has been accepted that adipose tissue should be injected in microdroplets and aliquots, to ensure intimate contact with the recipient bed and maintain oxygen diffusion.[7] Additionally, the recipient site must possess sufficient mechanical compliance (i.e. interstitial space and skin elasticity) thereby avoiding elevated interstitial pressure which may impede graft viability.[8,9] Early postoperative immobilization is critical to facilitate capillary ingrowth and successful graft integration.[10-12] To address the latter two challenges, patients in reconstructive settings receive external vacuum expansion (EVE) perioperatively. Most commonly, the EVE-bra® device is used, which is a a semi-rigid, transparent plastic dome placed on the thorax to apply controlled external negative pressure to the breast. [3,5 13]

The use of this device comes with physical and psychological burden. Women report erythema, pruritus, blistering of the skin, and pain.[14-16] Psychologically, patients report feelings of shame and hesitation to leave their home while wearing the device.[13] This may interfere with their activities of daily living, as protocol requires EVE-bra usage daily for several weeks perioperative. These burdens may also negatively affect patients' compliance. In contrast, literature reports successful total breast reconstruction with AFT, without external vacuum expansion (EVE).[17] There-

fore, we designed this study to assess the effect of EVE on autologous fat retention, augmentation percentage and complication rate.

METHODS

The present study constitutes an interim analysis of the EVE-trial, a multicentre, prospective randomised controlled trial (RCT), which takes place in four academic and non-academic hospitals in The Netherlands. These hospitals can be found in appendix 1. Inclusion criteria include adult women, with a stable Body Mass Index (BMI) of 18-35 and have undergone mastectomy (risk reducing or therapeutic) at least three months prior to inclusion. Additionally, they have to be able to tolerate the EVE-bra device during a 20-minute test. Exclusion criteria include history of radiation therapy of the involved breast, active chemotherapy, wound healing problems or seroma post-mastectomy, and active smokers. A full overview of in- and exclusion criteria can be found in appendix 2. This interim analysis includes only the first half of the expected study population. Investigating surgeons all have experience with total breast reconstruction with AFT.

Randomisation

After providing written informed consent, participants were allocated with a 2:1 probability to the EVE or control groups, as we anticipated higher dropout rates in the EVE cohort. Treatment assignment randomised using random permuted blocks of varying size stratified by centre, in Castor (Ciwit B.V., also known as "Castor", Amsterdam, The Netherlands; versions 2020.1, released 12 Feb 2020, to 2025.2.0.0, released 01 Jul 2025), an electronic data capture platform designed for clinical and research data management. It supports secure, web-based case report form creation and complies with international standards and regulations, including FDA 21 CFR Part 11, GDPR (EU), ICH GCP, HIPAA (US), ISO 27001, and ISO 9001.[18]

Interventions

BREAST-Q and BODY-Q questionnaires were completed upon inclusion. After a minimum wait of three months post-mastectomy, participants received baseline Magnetic Resonance Imaging (MRI), three-dimensional photographs using VECTRA, and two-dimensional photographs of the thorax. After establishing baseline volumetric measurements, reconstruction could commence. Surgically, all participants were treated

equally, AFT was performed as described by Piatkowski et al.[3] A minimum interval of ten weeks was maintained between each AFT-session.

In the EVE trial, all participants underwent three AFT-sessions, followed by a mandatory minimum six-month interval, based on reports indicating that graft survival stabilizes after this period. [19] After these six months, breast-MRI, two- and three-dimensional imaging were repeated. This interim analysis includes only the first half of the expected study population, all of whom completed their initial three sessions. Originally, volumetric assessments would be performed after one fat grafting session. However, it was noted that after one session, augmentation was too slight to be appropriately measured, therefore it was decided to perform volumetric assessments after three sessions, with knowledge from the BREAST trial that most participants required three to four sessions.[3] After the end of the trial, participants were offered the option to receive additional sessions if desired.

EVE group

Participants allocated to the intervention group received AFT, accompanied by EVE and PexyBra application. The PexyBra is a skin-tape- and adhesive-based external support applied to immobilize and protect the graft during the early postoperative phase. Fourteen days prior to an AFT-session, the participants started wearing the EVE-bra® (by Lipocosm, LLC). The EVE-bra is illustrated in figure 1. The device was worn for a minimum of ten hours per day, with negative pressure alternating between -20 mmHg and -60 mmHg. The last 48 hours prior to surgery, participants wore the EVE-bra continuously, until the surgeon would remove it preoperatively. In total, a minimum of 180-200 hours of expansion preoperatively was required. Two- and three-dimensional photographs were taken preoperatively on the day of an AFT-session. Five days postoperatively, EVE-bra use was restarted, now with a continuous negative pressure of -20 mmHg, for eight to ten hours per day, for four weeks. This postoperative schedule is per the Khouri-BRAVA-protocol. The EVE-bra device acts as a protective dome, immobilising the graft. Additionally, the negative pressure is proven to enhance neovascularisation and wound healing. Maintaining the new skin envelope and ensuring vascularisation is especially of importance in a secondary setting. The post-mastectomy defect can be severely scarred and therefore very tight with little vascularity.[21] After the second and third session, a period of two weeks EVE use was upheld. Four weeks postoperatively, the PexyBra was applied to immobilise and protect the graft, at six weeks the PexyBra was changed and at nine weeks it was removed completely.

During every check-up in the outpatient clinic (two, four, six and nine weeks postoperatively), 3D VECTRA imaging and 2D photographs were taken. During the perioperative intervals in the study, participants also reported their physical state according to pre-specified lists (including pain, pruritus, bruising) in diaries.

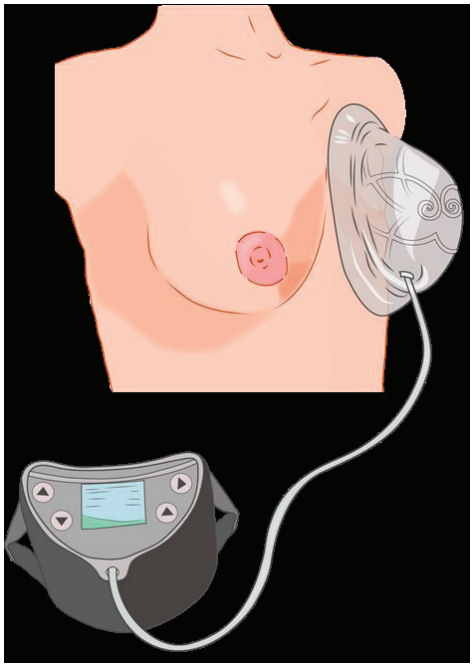


Figure 1. EVE-bra device, image copyright Ava Krueger ©

Control group

Participants allocated to the control group received equal surgical intervention. However, this group did not use the EVE-bra device, and did not receive PexyBra. Clinical check-ups in this group took place at two and six weeks postoperative, including 3D VECTRA imaging and 2D photographs.

Follow up

Follow up for both groups was performed at six, 12 and 24 months after the third surgery. This follow-up consisted of questionnaires, and 2D- and 3D-photographs. Their reconstruction process may have been continued after these three sessions, if adequate volume had not been reached. This means that in practice, participants could still be actively in their reconstruction process during the follow-up.

Outcomes

Primary outcome

The primary outcome of this study was the difference in percentage augmentation after three sessions of AFT, as measured by breast-MRI, comparing the EVE group to the control group. Radiologists calculated volumes on T2 weighted sequences, and used the protocol of Killaars et al. for volumetric assessment.[22] Change in breast volume (i.e. percent augmentation) was calculated as ΔV (%) = (Final breast volume - Baseline breast volume) / Baseline breast volume × 100%. Additionally, graft retention was calculated as the proportion of retained grafted volume relative to the total injected fat.

Secondary outcomes

Secondary outcomes include safety, which was evaluated through the prospective collection of Adverse Events (AEs). Additionally, patient satisfaction was assessed using the BREAST-Q and BODY-Q questionnaires in both groups, however, this interim analysis will focus on volume retention and safety.

Ethical considerations

This randomised controlled trial is conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Review Committee (METC) under reference number METC20-099. The trial is registered in the Clinical Trials Registry with the identifier NCT05003635.

Statistical analysis

Baseline characteristics will be presented on the patient-level and summarised as mean and standard deviation (SD) or as count and percentage. For between-group differences in change in volume and graft retention, we used multilevel linear regression analysis to account for bilateral procedures. We did not perform null hypothesis testing on perioperative characteristics.

For this interim analysis, O'Brien–Fleming stopping bounds were applied to control the one-sided Type I error, with significance thresholds of p=0.0072 at interim and p=0.0226 at final analysis, as determined using SAS SEQDESIGN (v14.1). Secondary outcomes were analysed two-sided with a significance level of 0.05, and 95% two-sided confidence intervals were reported.

RESULTS

Participant allocation is depicted in figure 2. For this interim analysis, 53 participants were included between August 2021 and April 2024. The EVE group consisted of 32 participants, compared to 21 in the control group. A summary of their baseline characteristics can be found in table 1, oncologic characteristics are reported in Appendix 3. For clinical results, we refer to figures 3 and 4.

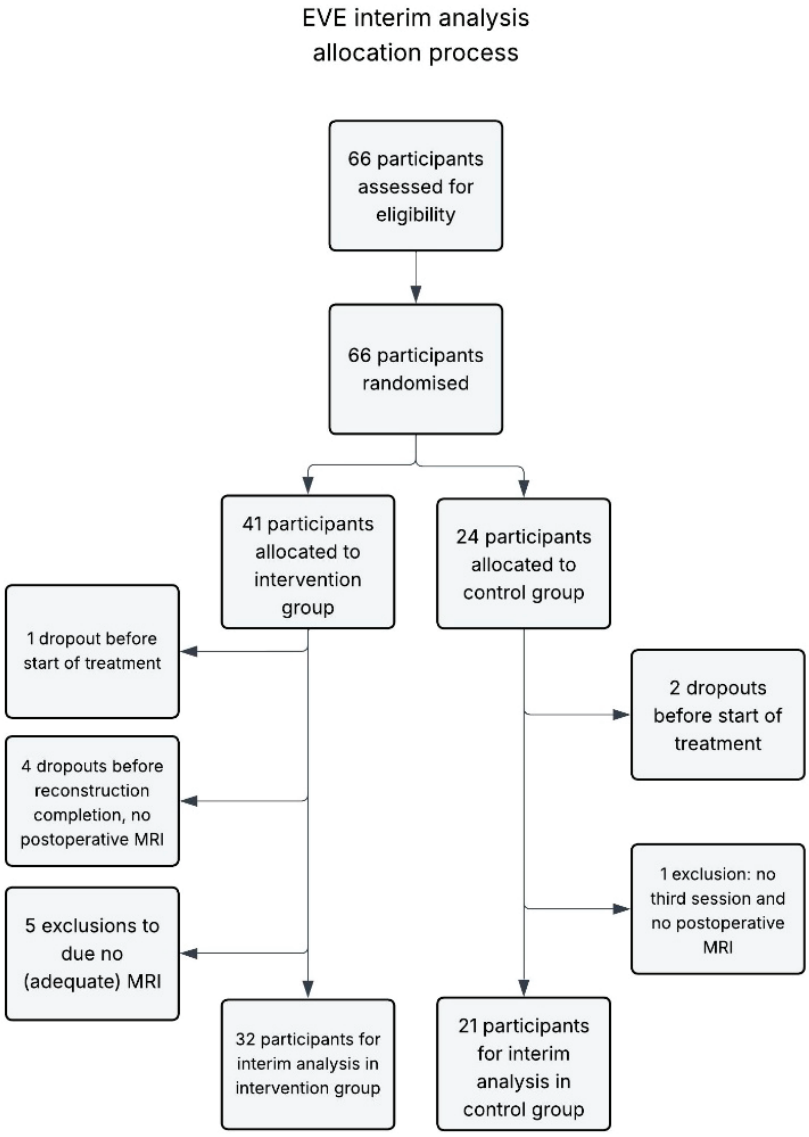


Figure 2. Allocation of participants

Table 1. Baseline characteristics

Characteristic or indication	Participants, N	
	EVE (N=32)	**control (N=21)**
Indication		
(History of) Breast cancer	**24 (75)**	**15 (71)**
Risk Reducing Mastectomies	**8 (25)**	**6 (29)**
Prior reconstruction		
(TE/IBR)	17 (53)	15 (71.4)
DIEP	0 (0)	1 (4.8)
Characteristic		
Age (mean ± SD)	52 ± 8.36	49 ± 10.83
BMI (mean ± SD)	23.8 ± 2.24	23.6± 2.93
Pre-mastectomy cup size		
AA	1 (3.1)	0 (0)
A	6 (19)	3 (14)
B	11 (34)	9 (43)
C	7 (22)	6 (29)
D	2 (6.3)	1 (4.8)
E	1 (3.1)	1 (4.8)
F	1 (3.1)	0 (0)
Not reported	3 (9.4)	1 (4.8)
Bilateral reconstruction	9 (28)	8 (38)

Abbreviations: TE: Tissue Expander, IBR: Implant Based Reconstruction, BMI: Body Mass Index, SD: Standard Deviation



Figure 3. Participant in the EVE group, a woman with nipple and skin sparing mastectomy: Top row before AFT. Bottom row six months after three sessions of AFT



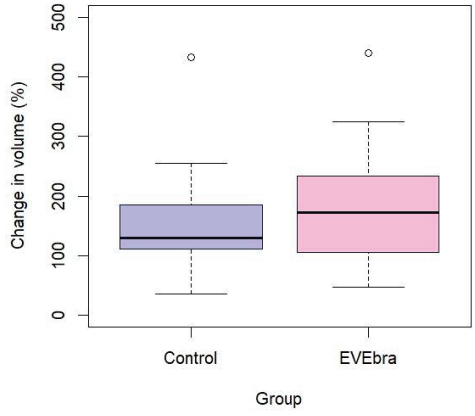
Figure 4. Participant in the NO-EVE group, a woman with skin sparing mastectomy: Top row before AFT. Bottom row six months after three sessions of AFT

Volumetric assessments

Perioperative data demonstrated comparable total fat grafting volumes between the EVE and control groups (758 ± 187.6 cc vs. 737 ± 177.9 cc, respectively). The mean augmentation was 190.7% in the EVE group versus 176.4% in the control group. The (multilevel-adjusted) mean difference was 14.6% (95% CI: -80.0; 109.1, p = 0.757). The volumetric analysis demonstrated a mean graft retention of 39.3% in the EVE group compared to 34.9% in the control group. The mean difference in graft retention was 4.5% (95% CI: -6.4; 15.4, p = 0.405). The differences between groups in augmentation and graft retention were both not statistically significant. Boxplots of the distributions of change in volume (augmentation) and of graft retention stratified by group are presented in Figures 5 and 6.

Perioperative results

In the EVE cohort, progressive preoperative expansion hours decreased across sessions, indicating a shortening preparation time before subsequent autologous fat transfer procedures. During the trial, participating plastic surgeons experienced increased difficulty injecting adipose tissue in the EVE group, attributing this to oedema-related breast firmness, compared with the non-EVE group. During the trial, plastic surgeons attempted to address this firmness by applying circular pressure intraoperatively to reduce edema prior to fat re-injection. For further perioperative results, see table 2.



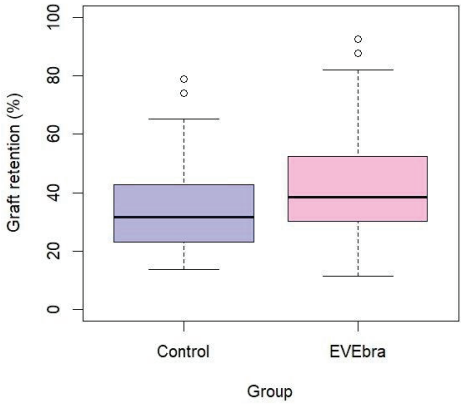


Figure 5. Distribution of augmentation in groups, figure 6. Distribution of volume retention in groups

Table 2. Perioperative characteristics

	EVE (n = 32)	Non-EVE (n = 21)
Pre-expansion time (hours per session)	**Mean ± SD (median, range)**	
Prior to AFT1	217.3 ± 56.7 (212; 115–436)	N/A
Prior to AFT2	205.7 ± 70.2 (212; 11–387)	N/A
Prior to AFT3	172.5 ± 90.6 (206.5; 0–372)	N/A
Injected volume (cc)		
AFT1	247 ± 87.2 (250; 100–420)	228 ± 99.5 (225; 110–400)
AFT2	255 ± 71.4 (250; 120–400)	257 ± 79.7 (250; 120–400)
AFT3	248 ± 70.2 (252; 140–450)	254 ± 59.4 (250; 144–395)
Total injected volume (cc)	758 ± 187.6 (790; 383–1150)	737 ± 177.9 (717; 374–1100)

Abbreviations: AFT1; First fat grafting session, AFT2: Second fat grafting session, AFT3: Third fat grafting session

Adverse events:

EVE

During the conduct of this study, there were five Serious Adverse Events over 96 surgeries in the EVE group; one participant died after completion of her reconstruction due to metastatic breast cancer. One participant experienced supraventricular tachycardia during her preoperative EVE usage, after which she did not continue the study and was lost to follow-up. Two participants had seromas, which drained, one of which was treated with triamcinolone acetonide. One hematoma was found, which required surgical drainage and oral antibiotics. Two participants were diagnosed with benign palpable lesions. Lastly, one participant received oral antibiotics for a soft-tissue infection of the reconstructed breast.

All participants experienced erythema of the skin during EVE use. Furthermore, 22 Adverse Events were reported. Four (12.5%) participants had bullae at the application site of EVE. Pain, tenderness/bruising and pruritus of the breast in relation to perioperative EVE usage were reported in mandatory participant diaries. Pain was reported by 14 participants (43.8%, 9.38% reported severe pain), tenderness or bruising by 17 (53.1%, 6.25% reported severe bruising), and pruritus by 13 (40.6%, 12.5% reported severe pruritus).

Seven (21.9%) participants discontinued PexyBra use due to erythema, another six (18.6%) experienced bullae at the application site. Figure 7 shows a participant just before an AFT-session with perioperative EVE use, with erythema of the skin and skin lesions.

A total overview of the (S)AEs can be found in Appendix 4.



Figure 7. Erythema and skin lesions during perioperative EVE use

Control

Two SAEs were reported in the Non-EVE group over 63 surgeries during the conduct of this study, up until the interim analysis. These SAEs consisted of two seromas in the breast, which both required surgical drainage, and one required triamcinolone acetonide. There were three AEs; postoperative oedema in the calves, one participant with two fibrotic lesions in the donor site (abdomen) and one indentation of the reconstructed breast after mammography.

DISCUSSION

This interim analysis of the multicentre randomised controlled EVE study evaluates the efficacy of perioperative external vacuum expansion during autologous fat transfer for total breast reconstruction. Graft retention at six months postoperative differed 4.5% between groups, favouring EVE. For augmentation percentage, mean adjusted difference was 14.6%, again

favouring EVE. Both of these findings were not statistically significant. Furthermore, more AEs were reported in the intervention cohort.

Current literature regarding EVE mainly focuses on breast augmentation, rather than post-mastectomy reconstruction. Literature reports superior augmentation percentage with EVE usage; Khouri et al. report up to 160% augmentation of the breast after EVE and fat grafting in a cohort of 81 participants.[4] The study of Del Vecchio et al. yields a mean augmentation percentage of 106%. However, these studies cover results of small sample sizes, and only in pure augmentation settings. It is a paramount notion that in reconstruction settings, the recipient site has entirely different condition, with even less interstitial space, no parenchymal space, an excess of fibrotic tissue, and less subcutaneous tissue. Our study yields higher results in augmentation percentage, despite aforementioned factors present in post-mastectomy tissue. A possible explanation could be that participants received three AFT-sessions within the trial. In terms of retention rate, Qin et al. drew similar conclusions with their meta-analysis of 1152 patients, that EVE increases retention rate, but with higher complication rate.[23] Homsy et al. report in a small cohort successful total breast reconstructions with AFT, without EVE-use. They report higher retention rates, but their MRIs were obtained only after full completion of the reconstruction, during routine post-reconstruction follow-up. In contrast, our MRIs were performed after the third session, at a stage when reconstruction was not necessarily complete and additional sessions could still be required to achieve the desired volume.

Secondary outcomes included safety of the EVE procedure. Once again, few studies report EVE in oncologic breast reconstruction settings. Though we report one death after metastatic breast cancer, fat grafting has been deemed oncologically safe by literature.[24-26]

Howes et al. have assessed safety and QoL in their prospective cohort of 26 women who experienced EVE, with 7 dropouts due to intensity or consequences of EVE. Dermatitis was reported in almost 58% of the participants, ranging from irritation to hemorrhagic bullae. This is similar to the 53% skin adverse reactions in our study-group. The study of Uda et al. seems to adhere to similar protocols as our study, with several fat grafting sessions and perioperative EVE use in reconstruction settings. Dermatitis was reported in 78.6% of their small cohort of 14 patients, even with structural use of topical steroids on the breast.[27]Their high rates may be attributed to including irradiated patients, who they have

found to be more prone to dermatitis.[27] In women using EVE for augmentation purposes, fewer skin problems are described.[28] This may be because there is less shear force on the still present breast, whereas in reconstructions, negative pressure is applied on a flat hemi-thorax with less subcutaneous tissue. Additionally, many of the skin-related problems in our study are related to the PexyBra.

It is plausible that negative pressure could also induce more seromas, as seromas are normally prevented by applying pressure garments. However, seromas were reported twice in both the EVE and control cohort, suggesting no clear evidence for this effect in our findings, although the small sample size limits firm conclusions. Consistent with the Meta analysis of Qin et al., we report more benign palpable lesions (i.e. fat necrosis) with EVE use.[23]

Strengths and limitations

This trial has several methodological strengths in addition to the strengths of a randomised controlled design. The inclusion of both academic and regional centres increases generalisability of the findings, while adherence to a strict, standardised protocol ensures procedural consistency across all sites. Objective volumetric assessment using MRI, according to the protocol of Killaars et al. provides high measurement accuracy and minimises observer bias.[22] Furthermore, although blinding of participants and surgeons was not feasible, detection bias was limited by blinding radiologists involved in volume analyses.

This interim analysis also has limitations. With only half of the calculated sample size currently enrolled, statistical power is insufficient for definitive conclusions or subgroup analyses, such as the relationship between baseline breast volume and graft integration. However, the analysis is performed as per the trial protocol, due to slow enrolment. In addition, the six month follow-up period reflects early graft stabilisation and does not capture long-term outcomes such as patient-reported satisfaction. Recently, Ørholt et al. reported that weight fluctuations influence graft retention.[29] Weight fluctuations were an exclusion criterion, so substantial weight change was not observed, but small changes were not taken into consideration in the analyses. Furthermore, selection bias may have influenced the study population, as recruitment was partially driven by treatment preference. During the first two years of the trial, AFT for breast reconstruction was available only within trial setting, which may have led to the inclusion of participants who were more open to experi-

mental therapies. Following the admission of AFT in the national health insurance system in 2023, a substantial proportion of eligible women expressed willingness to participate only if allocation to the control group, without EVE, could be guaranteed. Since this was not possible, these eligible women could not be included, slowing the recruitment. This shift in patient motivation and treatment preference over time may limit the generalisability of the findings to the broader population of women undergoing breast reconstruction with AFT in clinical settings. Lastly, the drop-out rate in this smaller cohort of the interim analysis may influence the interpretation of the findings.

Clinical implications

Many participants described a considerable treatment burden associated with EVE use, including pain, pruritus, blister formation, tenderness, and ecchymosis, as well as a notable psychological burden. These adverse effects are generally tolerated in the expectation of achieving the desired breast volume more rapidly and potentially reducing the number of required fat-grafting procedures. In our study, however, augmentation percentage and graft retention did not differ significantly between the EVE and control groups, indicating that EVE did not yield clinically meaningful improvements in postoperative breast volume. Importantly, increased volume does not necessarily translate into improved QoL. In addition to the physical and psychological burden, EVE use is associated with increased healthcare costs and environmental impact. The treatment requires prolonged device use, repeated follow-up, and substantial patient time investment, all of which may contribute to higher direct and indirect costs. Moreover, the need for multiple clinical visits may increase travel-related costs and emissions. Furthermore, it generates considerable plastic waste due to disposable components such as rigid expansion domes, adding to its environmental footprint. In the context of growing awareness of sustainable and value-based healthcare, these factors should be taken into account when evaluating the overall benefit of EVE. This raises a central question: to what extent are patients willing to accept the physical and psychological burden of EVE for an average 14.6% increase in initial postoperative volume or a 4.5% increase in graft survival, compared to no EVE? The final analysis of this trial, which incorporates patient-reported QoL outcomes, will be essential to determining whether the benefits of EVE justify its associated burden in routine clinical practice.

Future recommendations

Future research should focus on efficacy of EVE in irradiated patients, as these were not included in our trial. Furthermore, the long-term follow-up of this trial could report on weight fluctuations in regards to graft retention, and a larger study population allows for analyses on the relationship between baseline breast volume and graft integration. Many participants did not complete their reconstruction in three sessions, so additional operations should be assessed as well. The preoperative EVE wear-time schedule also warrants further investigation. Although all participants adhered to the prescribed 48-hour continuous use, surgeons occasionally reported pronounced tissue firmness attributable to oedema, which increased the technical difficulty of fat grafting. These observations suggest that modifying the duration of preoperative EVE application may mitigate tissue rigidity, facilitate more efficient fat deposition, and potentially enhance graft survival.

CONCLUSIONS

The interim analysis of this multicentre RCT shows that EVE does not yield statistically significant improvements in augmentation percentage or graft retention following autologous fat transfer for total breast reconstruction. Although numerical differences favoured EVE, they were small and accompanied by more adverse events and higher patient-reported burden. At this stage, the clinical value of EVE remains uncertain. Completion of the full study cohort and inclusion of long-term, patient-reported quality-of-life outcomes will be essential to determine whether EVE offers a meaningful advantage in reconstructive practice.

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APPENDIX 1.

Participating hospitals

1. Maastricht University Medical Centre+, Maastricht, The Netherlands (NL)
2. Amsterdam University Medical Centre, VUMC location, Amsterdam, The Netherlands (NL)
3. Alexander Monro Hospital Bilthoven, The Netherlands (NL)
4. Hospital Group Twente, Almelo, The Netherlands (NL)

APPENDIX 2.

Inclusion Criteria:

Female gender
Age between 23-69 years old
BMI 18-35 – stable weight, no fluctuations
Have undergone a total mastectomy at least 3 months prior the study, whether therapeutic or prophylactic, whether unilateral or bilateral, with no resection of the pectoralis muscle
Agrees to have reconstruction at the time of study involving only autologous fat grafting (AFT)
Assessed by surgeon to have enough donor fat
Passes a 20-minutes tolerance test with EVEBRA Device. (Patient will be fitted, instructed on the use, and given the EVEBRA Device to try in the office for 20 minutes. She passes if she tolerates its use, feels comfortable wearing it, and is able to comply with the required wear of the device.)

Exclusion Criteria:

Untreated breast cancer
History of radiation therapy on the involved breast, even if it was part of a previous breast conservation procedure
Completed chemotherapy course less than 2 months prior (acceptable to still be on aromatase inhibitors)
Except for the biopsy leading to the diagnosis of cancer, had surgery to breast prior to the mastectomy (e.g., multiple biopsies, implant augmentation, mastopexy, fat grating)
Had mastectomy wound healing complications, e.g., seroma, wound breakdown, infection
Mastectomy defect/scar has significant skin excess and deep folds adherent to the chest wall
Has a pacemaker or aneurysm clips
Pregnancy or breastfeeding
Had a cardiac stent placed within the last 2 months
Claustrophobic, as reported by patient
Known current substance abuse, as reported by patient
BMI>30
History of silicone and/or lidocaine and/or Gadolinium allergy, as reported by patient
Bleeding diathesis, whether primary or iatrogenic, as reported by patient
Cigarette smoker and/or Smokeless cigarette smokers, as reported by patient
Medical conditions that preclude breast reconstruction including uncontrolled hypertension or diabetes, renal failure, steroid dependent asthma, and on immuno- suppressant medications, as reported by patient

APPENDIX 3.

Characteristic or indication	Participants, N (%)	
	EVE (N=32)	**control (N=21)**
Indication		
Tumour morphology in case of malignancy		
Ductal Carcinoma In Situ	5 (16)	9 (43)
Ductal Carcinoma	7 (22)	3 (14)
Ductal and Lobular carcinoma	1 (3.1)	0 (0)
Adenocarcinoma	2 (6.3)	0 (0)
Invasive carcinoma, no special type	1 (3.1)	2 (9.5)
Tubular carcinoma	0 (0)	2 (9.5)
Not reported	8 (25)	0 (0)
Tumour staging		
In situ	5 (16)	7 (33)
I	6 (19)	6 (29)
II	3 (9.4)	1 (4.8)
III	2 (6.3)	0 (0)
IIII	1 (3.1)	0 (0)
Not reported	6 (19)	1 (4.8)
Genetic disposition		
BRCA1	5 (16)	2 (9.5)
BRCA2	2 (6.3)	5 (24)

APPENDIX 4.

EVE group:

Adverse Events:

	Number of reports
Benign palpable lesions i.e. fat necrosis	2
Infection breast during EVE usage requiring oral antibiotics	1
Bullae during EVE usage	4
Bullae during PexyBra usage	6
Erythema/dermatitis during PexyBra usage	7
Allergic reaction to antibiotics	1
Oedema arms	1
Total	22

Serious Adverse Events:

	Number of reports
Death after metastatic breast cancer	1
Supraventricular tachycardia during EVE usage	1
Seroma requiring drainage and triamcinolone acetonide	1
Seroma requiring drainage	1
Hematoma breast requiring drainage and oral antibiotics	1
Total	5

Non-EVE group:

Adverse Events:

	Number of reports
Fibrotic lesions donor site (abdomen)	1
Indentation in reconstructed breast after mammography	1
Postoperative oedema in the calves	1
Total	3

Serious Adverse Events:

	Number of reports
Seroma requiring drainage and triamcinolone acetonide	1
Seroma requiring drainage	1
Total	2



VIII General Discussion

SCOPE OF THE GENERAL DISCUSSION

The purpose of this thesis was to expand the evidence for autologous fat transfer (AFT) as a total breast reconstruction technique. Although the BREAST-I trial demonstrated favourable outcomes compared with implant-based reconstruction, questions remained regarding effectiveness in a larger cohort, treatment burden, complication patterns, oncological safety, comparison with other autologous techniques, and the requirements for structured implementation.

This general discussion follows the sequence of these topics. First, the efficacy of AFT is reviewed, evaluated by patient-reported outcomes. Second, procedure-related safety of this relatively new reconstruction technique is considered. Third, long-term oncological safety is evaluated using combined follow-up of the BREAST trials. AFT is then discussed in relation to another autologous option, the Deep Inferior Epigastric Perforator (DIEP) flap, focusing on how patient preference and counselling affect reconstruction choices. The need for structured implementation is addressed through the development and pilot-test of an e-learning module. Finally, the interim results of the External Vacuum Expansion (EVE) trial are used to assess whether this adjunct offers sufficient clinical benefit to justify its added treatment burden

ON EFFICACY OF AUTOLOGOUS FAT TRANSFER

The aim of a breast reconstruction is to restore or enhance femininity, and mitigate possible post-mastectomy sequelae, while ensuring oncological safety. In other words; enhancing Quality of Life (QoL) safely. A successful breast reconstruction is not only characterised by its aesthetic outcome and volume, but also by sensibility, symmetry, donor site satisfaction, which all affect the ultimate composite outcome: patient satisfaction. Consequently, the evaluation of reconstructive outcomes has shifted from surgeon-reported aesthetic assessment toward multidimensional, patient-reported measures, which more accurately capture the overall impact of reconstruction on health-related QoL.

The results of the multicentre randomised controlled BREAST-I trial resulted in national acceptance of AFT, both by clinicians and patients.[1,2] The BREAST-I trial answered many, but not all questions, and therefore the BREAST-II trial was initiated. **Chapter II** addresses efficacy and safety

of AFT. The results of this large multicentre nonrandomised clinical trial echo the findings of its predecessor: AFT as total breast reconstruction improves QoL. In this nonrandomised clinical trial of 196 participants, a statistically significant improvement across all measured domains of BREAST-Q and BODY-Q were observed after AFT-breast reconstruction, compared with pre-AFT. The BREAST-Q assessed domains including satisfaction with breast, sexual well-being, and physical well-being of the chest. BODY-Q focussed on donor-site satisfaction and morbidity. Improvements in health-related QoL were observed across both BREAST studies, showing that AFT has meaningful effects beyond aesthetic outcomes. The larger BREAST-II cohort further strengthens these conclusions and highlights the importance of Patient Reported Outcome Measures (PROMs) in evaluating the multidimensional aspects of reconstruction.

Comparison of both trials illustrates how AFT outcomes have improved over time, not only because of broader clinical experience but also through concrete methodological refinements. Donor-site satisfaction increased in BREAST-II, particularly in inner thigh harvests, likely reflecting both evolving surgical expertise and optimisation of liposuction techniques. In the BREAST-I trial, participants reported inner thigh contour irregularities, which were not reported in BREAST-II. Similarly, recognising graft animation during arm movement in BREAST-I-participants led to the discontinuation of intrapectoral grafting, demonstrating how clinical experience drives improved practice. Together, these insights highlight the dynamic nature of AFT's development and the importance of continuous technical evaluation.

Effectiveness is also closely related to operative time and the number of sessions required to achieve the desired outcome. On average, participants underwent four sessions to complete their breast reconstruction, with contralateral reduction mammoplasty or mastopexy often performed during the final fat-grafting procedure. Unilateral and bilateral AFT-procedures typically take 76 and 102 minutes, respectively, which is notably shorter than the duration of free-flap breast reconstruction.[3] Finally, patients are generally treated on an outpatient basis and are rarely admitted for more than one day. Short postoperative hospital stays have been shown to reduce complications and lessen the burden on the healthcare system.[4] Despite these advantages, the treatment burden associated with AFT remains substantial. Reconstruction typically requires multiple operative sessions over an extended period, and adjunct

EVE can cause (psychological) discomfort, skin irritation and practical inconvenience. These factors underscore the importance of quality of preoperative counselling. Thorough preoperative counselling, grounded in the available evidence and plastic surgeon experience, is essential to help women anticipate the length, intensity and potential side-effects of the reconstruction process. In addition to scientific evidence, incorporating clinical experience can also be valuable. Surgeons have observed that women often face a particularly challenging period after the second grafting session. By this stage, approximately six to nine months into the reconstruction, they may still see only limited volume gain, which can negatively affect their motivation. Addressing this phenomenon during preoperative counselling may help prepare women for this phase, thereby reducing its mental strain.

The BREAST-II trial, while informative, also carries methodological limitations. The absence of an active control group may have introduced selection bias by attracting highly motivated participants; however, this mirrors standard clinical decision-making, where women similarly select the reconstruction that suits their preferences and motivation. This parallel supports the generalisability of the trial's findings, though it also highlights the need for future comparative studies. Remaining uncertainties particularly regarding the efficacy of AFT in irradiated chest walls, a patient group with few reconstructive options, warrants further research. In addition, the substantial treatment burden compels us to critically assess the true value of burdensome components such as EVE, addressed later in this discussion.

The findings of the BREAST-II trial prove AFT to be an effective option for total breast reconstruction, improving QoL in a large cohort.

ON SAFETY OF AUTOLOGOUS FAT TRANSFER

AFT is associated with a relatively low complication rate, especially compared with other autologous reconstruction techniques.[2,5–7] In 805 AFT-sessions, there was a low complication rate of 6.46%. Major complications were few, and included pneumothorax. Most complications were transient and benign, yet their mental impact can be greater than their clinical severity. Reported complications included benign palpable lesions in the breast, seroma in the breast, infection, and breast and donor site hematoma. Palpable changes in a reconstructed breast, usually repre-

senting fat necrosis (i.e. oil cysts), can understandably cause concern in women with a history of breast cancer. This once again highlights the importance of elaborate preoperative counselling and accessible and responsive postoperative evaluation when patients notice a palpable lesion. Interpretation of complications showed a frequent trend: the learning curve plastic surgeons go through in a new technique.[8] Pneumothorax was reported in three participants, in a new centre with less experience with AFT as total breast reconstruction. The pneumothoraxes were reported only during the initial phase of the trial and did not recur once the surgeons gained experience, particularly in handling the bent cannulas used for adipose-tissue reinjection, which had been responsible for the complication

With increasing experience, clinicians have not only become better surgically, but also at recognising typical post-AFT findings and distinguishing them from suspicious lesions. The imaging recommendations described by Rijkx et al. provide helpful guidance on when and how to assess the AFT-reconstructed breast, supporting both timely reassurance and appropriate clinical action.[9] Centres with more experience also report fewer procedure-related issues, illustrating the learning curve associated with AFT.[8] This pattern indicates that safety will continue to improve as clinical expertise expands.

ON ONCOLOGICAL SAFETY OF AUTOLOGOUS FAT TRANSFER

Questions about the oncological safety of AFT are common, both among patients and clinicians. Internationally, AFT has been subject to ongoing debate for its possible effect on breast cancer recurrence, metastases and survival. Most available studies, including those with substantial cohort sizes, show no negative impact on these outcomes.[10–13] Yet, concerns persisted within the plastic and breast surgery community, making a thorough evaluation of long-term oncological safety essential.

BREAST-I: early evaluation with methodological challenges

Chapter III describes the oncological follow-up of the BREAST-I trial. Assessing oncological endpoints in this study was challenging, as the trial was not originally designed for this purpose. Participants differed substantially in oncological baseline: some had a recent primary tumour, others were years past diagnosis, and a small number entered the trial

with a (loco)regional recurrence (LRR), rather than a primary tumour. Additionally, some women declined the recommended oncologic treatment. For instance, a number of participants had involved resection margins after mastectomy or positive lymph nodes, which would normally warrant additional therapy. These differences required statistical adjustment; for example, immortal time bias was accounted for in the analysis. For the oncologic analyses we excluded participants with Risk Reducing Mastectomies (RRM), as their prognosis differs from that of participants with diagnosed breast cancer. Thirteen LRR were reported, eight in the AFT-group, and five in the control cohort. Two of the eight LRR in the AFT-group occurred before exposure to AFT. So despite these limitations, BREAST-I showed no increased risk of LRR after AFT-breast reconstruction compared with implant-based reconstruction (IBR).[14] However, definitive data on distant metastases and overall survival were not available yet, therefore results were preliminary and could not provide definitive conclusions.

BREAST-II and combined follow-up: a more robust assessment

A more robust oncological evaluation became possible through the BREAST-II trial and the combined analysis of both BREAST cohorts, seen in **Chapter IV**. Together, these studies provide substantially greater follow-up and statistical power than BREAST-I alone, allowing a more confident assessment of oncological safety. In this study, we compared oncologic follow-up of 242 BREAST participants to a national control cohort of 19.936 participants, with a median follow-up of 8 and 6 years, respectively. We once again excluded participants with RRM. It should be noted, however, that the baseline oncologic imbalances present in BREAST-I, as well as the fact that not all women accepted recommended care, remain part of the pooled dataset. Nevertheless, the increased sample size and methodological strength of the combined analysis mitigate the influence of these limitations, reducing their potential impact on the overall conclusions. Although the national registry data used for comparison had limitations, particularly regarding the underreporting of recurrence and metastatic disease, the overall pattern across our analyses and existing literature is consistent: AFT does not appear to increase the risk of recurrence or metastasis. Most published studies focus on AFT after lumpectomy, making our post-mastectomy-based findings a meaningful addition to the field. Overall survival could be assessed reliably. AFT did not negatively affect survival; if anything, the trend suggested a small protective effect, as also reported elsewhere.[10,15] Nevertheless, because

observational studies cannot establish causality, the observed association should not be interpreted as evidence of a true protective effect. The ten-year survival probability for the control-cohort was 97.6%, compared to 75.7% in the control cohort, with an adjusted Hazard Ratio of 0.34 (95% CI: 0.14-0.88, p=0.025). While the AFT cohort was younger, younger age does not automatically confer better prognosis, as young women are often diagnosed with more aggressive lesions.[16] The available evidence supports the conclusion that AFT is oncologically safe. It is important that these results reach not only plastic surgeons, but also (oncologic) breast surgeons and patients who may still have doubts about the safety of AFT. Long-term surveillance remains important as AFT becomes more widely implemented in the Dutch healthcare system. To support this, our research group has initiated a national AFT-registry, facilitating structured follow-up of oncological events after reconstruction, providing more adequate data on disease-free survival.

Chapters III and IV *strengthen existing evidence and support the conclusion that AFT is a safe breast reconstruction technique that does not increase the long-term risk of oncologic events or negatively affect overall survival.*

ON PATIENT EXPERIENCES WITH AUTOLOGOUS TECHNIQUES

Chapter V describes an exploratory mixed-methods analysis of eight women who underwent both Deep Inferior Epigastric Perforator (DIEP) flap reconstruction and AFT. This unique clinical situation offers valuable qualitative insights, but the small sample size and uncontrolled bias preclude any firm conclusions regarding comparative outcomes. The main source of bias was that most participants had sustained unilateral total flap loss and subsequently underwent AFT for breast reconstruction. This resulted in a DIEP-breast on one side, and an AFT-reconstructed breast contralaterally. While the total flap loss of the original preferred reconstruction causes bias, their experiences remain of interest. Quantitative data showed superior scores for DIEP breasts in regards to satisfaction, sensation and symptoms of the breast. Thematic analyses of qualitative data did not necessarily reflect a real preference in DIEP. Instead, the findings primarily underline the importance of thorough counselling and truly tailor-made breast reconstruction, as women weigh surgical burden, donor-site morbidity, aesthetic goals, (i.e. personal preferences) differently. For example, some participants preferred completing their

reconstruction in a single operation with a DIEP and did not mind the abdominal scar. In contrast, others highlighted the minimally invasive nature of the AFT procedure, leaving virtually no new scars and were accepting of the need for multiple sessions. The study also highlights that reconstructive options are not uniformly available across centres. A number of participants reported that had AFT been available, they would have chosen this option over the DIEP. Improving the dissemination and implementation of new techniques, in this case AFT, is therefore essential to ensure that women are aware of the full range of reconstructive options. Additionally, if the reconstruction is not (yet) available at their local treating centre, patients should be made aware of the technique, and be counselled for a possible referral to centres where these options are available. In future, the comparison between DIEP and AFT-reconstructed breasts should be assessed in more unbiased patients, in larger cohorts.

Patient experiences highlight the need for thorough counselling and uniform availability of reconstructive option. To further compare DIEP and AFT we need larger, less biased cohorts.

ON TRAINING AND IMPLEMENTATION OF AFT IN THE DUTCH HEALTHCARE SYSTEM

The Dutch Society for Plastic Surgery (NVPC) has delineated essential criteria governing the national implementation of AFT, one of which is addressed in ***Chapter VI***: the need for structured, uniform, evidence-based training. We emphasised how patient counselling and individualised treatment planning strongly influence outcomes, and how variation in counselling and treatment across centres affects access to care. The development and pilot evaluation of an e-learning module builds on these themes by offering an accessible tool to spread uniform knowledge and reduce variability in surgical practice. Designed according to adult learning theory and cognitive load principles, and informed by key insights from the BREAST trials, the e-learning provides a standardised educational foundation to support surgeons in applying AFT safely and consistently.[8,17] The e-learning contains all aspects of an AFT-reconstruction, from patient selection and counselling, to perioperative management, and images and videos elaborating on surgical techniques. The study assessed design and feasibility, showing how well-designed digital training can influence perioperative decision-making and may facilitate

national implementation of AFT. Nine plastic surgeons with varying clinical experience pilot-tested the module, and completed semi-structured interviews. The surgeons were divided in an expert group (experience with AFT since BREAST-I trial), and a novice and aspiring group. The e-learning was generally well-perceived, all surgeons would recommend it to fellow surgeons. Surgeons from all groups reported planned changes in their approach after completing the e-learning, both in counselling and surgically. Surgeons described the e-learning as a valuable adjunct to hands-on trainings. Integrating such e-learning with supervised clinical exposure will be crucial to ensure uniform quality as more centres begin offering this minimally invasive reconstructive option. Because decision-making in reconstructive surgery often begins during the oncologic process, adapting the e-learning for surgical oncologists and specialised nurses could raise awareness and support broader implementation of AFT.

*The results discussed in **Chapter VI** suggest that standardised e-learning can meaningfully support clinical decision-making and facilitate broader implementation of AFT.*

ON EFFICACY OF EXTERNAL VACUUM EXPANSION

While ensuring broad and consistent implementation of AFT is crucial, continuous assessment and refinement of the technique itself remains essential. In this context, ***Chapter VII*** reports the interim analysis of the multicentre randomised External Vacuum Expansion (EVE) trial. In this trial, participants were randomised in a 2:1 ratio to the intervention or control cohort. In the intervention group participants received AFT accompanied by perioperative EVE, in the control cohort participants did not receive EVE. Volumetric assessments were performed by breast-MRIs pre-operatively, and six months after the third fat-grafting session, with independent radiologists adhering to the protocol of Killaars et al.[18] The results offer an important clinical signal, indicating that perioperative EVE did not lead to statistically significant improvements in graft retention or augmentation percentage after three AFT-sessions, when compared with AFT without EVE. A 4.5% difference in volume retention and a 14.6% difference in augmentation were found in favour of EVE, neither statistically significant. At the same time, EVE was associated with a substantially higher treatment burden, including (skin-related) adverse effects.

These early results suggest that the modest volumetric gains achieved with EVE may not outweigh the burdens. In addition to discomfort, pruritus, pain, and blistering of the skin, participants noted difficulty with sleeping and leaving their homes during EVE use. There seemed to be a practical burden as well, participants reported trouble with keeping negative vacuum pressure, as the domes of the device did not always fit onto the thorax adequately. Ultimately, EVEs true clinical value can only be determined once patient-reported QoL outcomes are incorporated, as (increased) postoperative volume does not necessarily reflect patient satisfaction. As the final trial outcomes become available, they will be critical to determining whether EVE can play a meaningful role in standardised AFT-breast reconstruction. Importantly, the interim data also highlight where technical refinement may still be beneficial: Surgeons reported increased difficulty with injecting adipose tissue when the breast was excessively firm due to oedema. This oedema resulted from continuous EVE administered 48 hours preoperatively, as per the trial protocol. Optimising wear-time schedule and understanding how donor and recipient tissue characteristics influence graft behaviour should be evaluated in future. Additionally, future research could evaluate the efficacy of EVE in selected subgroups, such as irradiated patients. Moreover, the potential role of internal expansion techniques, as an alternative to external approaches, warrants further investigation.[19] These insights collectively emphasise that AFT requires not only effective implementation strategies, but also rigorous evaluation of adjunct treatments to establish whether these offer real, clinically meaningful benefits for patients.

EVE does not significantly increase graft retention and augmentation percentage, and additional evidence is needed to establish the clinical relevance and appropriate application of EVE in AFT- breast reconstruction.

Collectively, the findings of this thesis demonstrate that AFT is an effective, safe, and patient-centred reconstructive option, while also highlighting where further optimisation is required. Continued evaluation of the technique and standardised training are essential to ensure consistent and safe use of AFT. Future clinical research will further support its optimisation, and broad, structured implementation will be essential to ensure that all women who desire and are suitable for AFT have access to this reconstructive option.

IMPACT PARAGRAPH

The work presented in this thesis has several implications that extend beyond the immediate clinical findings of the individual chapters.

First, it provides evidence supporting the efficacy, safety, and patient-centred value of autologous fat transfer (AFT) as a reconstructive option, thereby strengthening its position within the (inter)national breast reconstruction portfolio. By integrating long-term oncological analyses, patient-reported outcomes, and technical evaluations, this thesis contributes to a more comprehensive and nuanced understanding of AFT that can inform future guidelines, reimbursement policy, and shared decision-making.

Second, the thesis highlights structural factors that influence access to AFT, including variability in counselling, surgical expertise, and training. The development and evaluation of a national e-learning programme provide a practical and feasible approach to standardising knowledge and improving the consistency of care across centres. This work therefore supports the broader implementation of AFT within the Dutch healthcare system, expanding beyond plastic surgery. Ideally, awareness and knowledge would reach surgical oncologists, nurse specialists, and possibly even general practitioners.

Third, the thesis proves that ongoing innovation and objective evaluation of adjunct measures are necessary to ensure that new techniques yield meaningful clinical results. A potential consequence of these findings could be the discontinuation of external vacuum expansion, should it be determined that it offers no significant benefit. The findings also introduce gaps in evidence regarding AFT, such as safety and efficacy in irradiated patients, comparison in patient-satisfaction between different autologous reconstructions, long-term disease-free survival data, and recipient-site characteristics that may influence graft retention.

Based on the results of the BREAST trials and findings of this thesis efforts to set up a new study focusing on AFT in irradiated patients have been made. Additionally, studies on intratissular expansion techniques, exploring alternative methods to reduce treatment burden, without affecting graft retention, have been initiated. Finally, to further enhance the quality of prospective, long-term oncological follow-up data, a national AFT registry has been established. These ongoing efforts aim

to optimise the effectiveness of AFT and contribute to the ongoing refinement of reconstructive treatment options for breast cancer patients.

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IX

Summary

Breast reconstruction aims to enhance quality of life (QoL) by mitigating post-mastectomy sequelae, restoring form and femininity, while maintaining oncological safety. Over the past decades, reconstructive breast surgery has seen substantial innovation in both implant-based and autologous techniques. Autologous fat transfer (AFT) has emerged as a minimally invasive alternative, offering a natural aesthetic result without the donor-site morbidity associated with free-flap reconstruction. Following the results of the multicentre randomised controlled BREAST-I trial, AFT was recognised as a safe and effective total breast reconstruction technique and was included in the Dutch basic health insurance in 2023. As AFT was increasingly implemented in clinical practice, new questions emerged regarding its broader effectiveness, oncological safety, patient experiences, training requirements, treatment burden and technical optimisation. This thesis aims to address these questions and to contribute to the responsible and evidence-based integration of AFT into reconstructive breast surgery.

The effectiveness of AFT was further evaluated in the BREAST-II trial, a substantial multicentre nonrandomised clinical trial, described in ***Chapter II***. Consistent with earlier findings, AFT as total breast reconstruction resulted in significant improvements in health-related QoL. Patient-reported outcome measures demonstrated statistically and clinically meaningful improvements across all domains of the BREAST-Q and BODY-Q, including satisfaction with breast, sexual well-being, physical well-being of the chest, and donor site satisfaction. These results underline the importance of multidimensional, patient-centred evaluation of reconstructive outcomes. Comparison between BREAST-I and BREAST-II revealed that outcomes improved over time, reflecting growing surgical experience and technical refinement, such as optimisation of harvesting techniques and adaptation of re-injection strategies. Although AFT offers advantages including short operative times, outpatient treatment, and reduced hospital stay, the overall treatment burden remains considerable due to the need for multiple sessions and use of External Vacuum Expansion (EVE). These findings highlight the importance of thorough preoperative counselling to set realistic patient expectations regarding the reconstructive process.

Safety analyses showed that AFT is associated with a low complication rate. Across more than 800 AFT procedures, most complications were minor and transient. Benign palpable lesions (i.e. fat necrosis, oil cysts) were the most frequently reported adverse finding. Although clinically

harmless, these lesions may cause considerable psychological distress due to fear of breast cancer recurrence and should therefore be explicitly addressed during preoperative counselling. Serious complications were rare and primarily observed during the early learning phase in centres with limited experience, emphasising the role of surgical expertise and training.

Chapters III and IV report oncological safety, which was evaluated through long-term follow-up of the BREAST trials. Early analyses from BREAST-I, despite methodological limitations, showed no increased risk of (loco)regional recurrence after AFT compared with implant-based reconstruction. More robust conclusions were enabled by pooled analyses of BREAST-I and BREAST-II combined with comparison to a large national control cohort. These analyses demonstrated that AFT does not negatively affect overall survival. Disease-free survival was not directly assessed in these analyses; however, comparison with existing literature likewise revealed no evidence of a negative effect of AFT on disease-free outcomes. Although observational data cannot establish causality, the findings suggest an association between AFT and improved survival, a pattern that has also been reported in previous studies. To facilitate continued monitoring as AFT becomes more widely implemented, a national AFT registry has been initiated to enable structured long-term follow-up.

Chapter V presents an exploratory mixed-methods study of eight women who have experienced both Deep Inferior Epigastric Perforator (DIEP) flap and AFT as total breast reconstruction. In this cohort, AFT was performed only after total flap loss. Although the small and inherently biased cohort precludes definitive comparative conclusions, the qualitative and quantitative findings underscore the importance of personalised counselling and shared decision-making. Women described different considerations when choosing between reconstructive options, carefully weighing surgical burden, donor-site morbidity, aesthetic goals, and recovery time. These insights highlight the need for uniform availability of reconstructive options and improved dissemination of information to ensure that patients can make informed choices, including referral to specialised centres when appropriate.

After establishing the efficacy and safety of AFT, the next step is to facilitate its structured clinical implementation. Nationwide implementation depends not only on clinical evidence, but also on uniform and accessible training. To support this process, an evidence-based e-learning module

was developed and pilot-tested among plastic surgeons with varying levels of experience, presented in ***Chapter VI***. The module was well received and influenced both counselling strategies and surgical decision-making. Surgeons considered e-learning a valuable adjunct to hands-on training, supporting uniformity and quality of care. Broader dissemination of such educational tools, potentially extending to oncologic surgeons and specialised nurses, may further enhance awareness and integration of AFT into clinical practice.

Finally, this thesis explored the role of External Vacuum Expansion (EVE) as a routine adjunct to AFT, as described in ***Chapter VII***. EVE aims to enhance graft survival, thereby facilitating more efficient achievement of the desired breast volume. Interim analyses from a multicentre randomised controlled trial, where participants were allocated to either AFT with EVE, or without EVE, did not demonstrate a statistically significant improvement in graft retention or breast volume with EVE. Additionally, EVE usage was associated with an increased treatment burden. Although these preliminary findings do not allow for definitive conclusions, they raise the question of whether the routine use of EVE is justified for all patients. These results underscore the importance of critically evaluating adjunctive practices by assessing potential volumetric benefits against treatment burden. Final trial results with QoL-analyses will determine clinical efficacy of EVE. Further research is warranted to determine whether specific patient subgroups may benefit from expansion techniques and to explore alternative strategies for optimising graft survival.

In conclusion, this thesis demonstrates that autologous fat transfer is a safe and effective option for total breast reconstruction, providing clinically meaningful improvements in QoL without compromising oncological safety. Beyond establishing efficacy and safety, the findings emphasise the importance of structured implementation, realistic patient counselling, and standardised training to ensure high-quality and uniform access to AFT. Together, these insights support the responsible integration of AFT into reconstructive breast surgery, while identifying areas where continued evaluation and refinement remain warranted. As AFT becomes increasingly embedded in clinical practice, ongoing research and coordinated implementation will be essential to maximise its clinical value for women undergoing breast reconstruction.

NEDERLANDSE SAMENVATTING

Borstreconstructie heeft als doel de kwaliteit van leven na een borstamputatie te verbeteren, door het herstellen van de vorm van de borst en het verminderen van lichamelijke en psychische gevolgen van de operatie, zonder de oncologische veiligheid in gevaar te brengen. In de afgelopen decennia zijn er veel ontwikkelingen geweest binnen de reconstructieve borstchirurgie, zowel met implantaten als met lichaamseigen weefsel.

Autologe vettransplantatie (AFT) is een relatief nieuwe, minimaal invasieve vorm van borstreconstructie. Hierbij wordt lichaamseigen vet gebruikt om een borst te reconstrueren. Deze methode kan een natuurlijk resultaat geven, zonder de grotere littekens en langere hersteltijd die inherent zijn aan vrije lapreconstructies. Na de positieve resultaten van de multicentrische, gerandomiseerde BREAST-I studie werd AFT erkend als een veilige en effectieve methode voor een volledige borstreconstructie. Sinds 2023 wordt deze behandeling vergoed vanuit het basispakket van de Nederlandse zorgverzekeraars. Naarmate AFT vaker werd toegepast in de praktijk, ontwikkelden nieuwe vraagstukken. Deze vragen betroffen de effectiviteit bij grotere groepen patiënten, de veiligheid op lange termijn, ervaringen van patiënten, de duur en intensiteit van de behandeling, de benodigde training van plastisch chirurgen en mogelijke technische verbeteringen. Dit proefschrift heeft als doel deze vragen te beantwoorden en bij te dragen aan een zorgvuldige en goed onderbouwde invoering van AFT binnen de reconstructieve chirurgie.

De effectiviteit van AFT werd verder onderzocht in de BREAST-II studie, een grote multicentrische klinische studie, beschreven in ***hoofdstuk II***. Net als in eerdere onderzoeken leidde AFT tot duidelijke verbeteringen in de kwaliteit van leven. Patiënten rapporteerden verbetering rondom het welzijn van hun borst, evenals lichamelijk en seksueel welzijn. Ook de tevredenheid over de plekken waar het vetweefsel werd weggenomen nam toe. Deze resultaten laten zien dat het belangrijk is om het succes van borstreconstructies te beoordelen vanuit verschillende perspectieven van de patiënt.

Vergelijking tussen de BREAST-I en BREAST-II studies liet zien dat de resultaten in de loop van de tijd zijn verbeterd. Dit hangt samen met toenemende ervaring van chirurgen en aanpassingen in de techniek, zoals betere manieren om vet te oogsten en opnieuw in de borst te plaatsen. Hoewel AFT voordelen heeft, zoals een korte operatieduur, behandeling

in dagopname en een kort ziekenhuisverblijf, blijft de totale impact voor patiënten groot. Er zijn meerdere operaties nodig en wordt gebruikgemaakt van externe vacuüm expansie van de huid van de borstkas. Dit onderstreept het belang van goede en eerlijke voorlichting voor aanvang van de reconstructie, zodat patiënten weten wat zij kunnen verwachten.

Uit analyses rondom veiligheid bleek dat er weinig complicaties optreden tijdens een borstreconstructie met AFT. In meer dan 800 AFT-behandelingen waren de meeste complicaties mild en tijdelijk. Het meest voorkomend waren goedaardige, voelbare verhardingen in de borst, veroorzaakt door vetnecrose of oliecysten. Hoewel deze veranderingen onschuldig zijn, kunnen zij veel angst veroorzaken bij vrouwen die eerder borstkanker hebben gehad. Het is daarom belangrijk om deze mogelijke bijwerkingen expliciet te bespreken tijdens de voorbereiding op de operatie. Ernstige complicaties kwamen zelden voor en vooral in de beginfase bij centra met weinig ervaring, wat het belang van training en ervaring benadrukt.

De oncologische veiligheid van AFT werd onderzocht in ***hoofdstukken III en IV*** aan de hand van langdurige oncologische opvolging van de BREAST-studies. Ondanks enkele methodologische limitaties liet de BREAST-I studie geen verhoogd risico zien op een lokaal of regionaal recidief van borstkanker na AFT, vergeleken met protheseconstructie. Door data van BREAST-I en BREAST-II samen te analyseren en te vergelijken met een grote nationale controlegroep, konden sterkere conclusies worden getrokken. AFT had geen nadelig effect op de overleving. Het effect op ziektevrije overleving werd niet direct onderzocht, maar uit vergelijking met bestaande literatuur bleek geen verhoogd risico op het terugkeren van lokale of regionale borstkanker, of op het ontwikkelen van een metastase op afstand. Hoewel met observationeel onderzoek geen oorzakelijk verband kan worden aangetoond, wijzen de resultaten op een verband tussen AFT en een betere overleving. Om de (oncologische) veiligheid ook in de toekomst goed te kunnen volgen, is een landelijke AFT-registratie opgezet.

Hoofdstuk V beschrijft een exploratieve studie naar ervaringen van acht vrouwen die zowel een DIEP lapreconstructie als AFT hebben ondergaan. In deze groep werd AFT toegepast nadat een vrije lapreconstructie éénzijdig was gefaald. Door het kleine aantal deelnemers en de zeer specifieke situatie kunnen hier geen harde conclusies uit worden getrokken. De resultaten laten echter wel zien hoe verschillend vrouwen omgaan

met keuzes rondom borstreconstructie. Zij wegen factoren zoals de zwaarte van de operatie, (nieuwe) littekens, het uiterlijk van de borst en de hersteltijd op een persoonlijke manier af. Dit benadrukt het belang van persoonlijke begeleiding en goede informatie over alle beschikbare opties, inclusief verwijzing naar gespecialiseerde centra indien nodig.

Na het vaststellen van effectiviteit en veiligheid is een goede implementatie van AFT in het Nederlandse zorgsysteem essentieel. Landelijke toepassing vraagt niet alleen om wetenschappelijk bewijs, maar ook om toegankelijke en uniforme scholing voor alle betrokken partijen bij postoncologische reconstructieve chirurgie. In ***hoofdstuk VI*** wordt een online leerprogramma beschreven dat is ontwikkeld om plastisch chirurgen te ondersteunen bij het veilig toepassen van AFT. Deze e-learning werd positief ontvangen en had invloed op zowel de manier van voorlichting aan patiënten als de operatieve aanpak. Deelnemers zagen het programma als een waardevolle aanvulling op praktische training. Verbreding van dit soort scholing, ook richting oncologisch chirurgen en gespecialiseerde verpleegkundigen, kan bijdragen aan betere samenwerking en bredere toepassing van AFT.

In ***hoofdstuk VII*** werd het gebruik van externe vacuüm expansie (EVE) als bijbehorende voorbereiding op AFT onderzocht. Het doel van EVE is om het teruggeplaatste vet meer overlevingskans te bieden en daarmee sneller het gewenste borstvolume te bereiken. Tussentijdse resultaten van een multicentrische gerandomiseerde studie lieten echter geen duidelijk voordeel zien van EVE op het behouden van volume en percentage van augmentatie van de borst. Het gebruik van EVE bleek echter wel erg belastend voor patiënten. Hoewel deze voorlopige resultaten nog geen definitieve conclusies toelaten, roepen zij de vraag op of routinematig gebruik van EVE voor alle patiënten wenselijk is. De definitieve resultaten, inclusief analyses met betrekking op kwaliteit van leven, zullen meer duidelijkheid geven. Toekomstig onderzoek moet uitwijzen of bepaalde patiëntgroepen wel baat hebben bij deze techniek of dat andere methoden effectiever zijn.

Samenvattend laat dit proefschrift zien dat autologe vettransplantatie een veilige en effectieve manier is voor een volledige borstreconstructie. De behandeling leidt tot duidelijke verbeteringen in kwaliteit van leven, zonder dat de oncologische veiligheid in het gedrang komt. Naast medische effectiviteit is aandacht nodig voor realistische voorlichting aan patiënten en uniforme scholing van zorgverleners. Door meerdere

aspecten van AFT zorgvuldig te blijven evalueren en gestructureerd toe te passen in de praktijk, kan deze reconstructieve techniek optimaal worden ingezet voor vrouwen die een borstreconstructie overwegen.



A

Appendices
Acknowledgements – Dankwoord

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CONFERENCES & SYMPOSIA

Wetenschapsmiddag MUMC+:

Evaluation of the BREAST-II Trial for Breast Reconstruction Using Autologous Fat Transfer: 1-Year Follow-Up (*Winner in category Patient-Centered Care)*

Preliminary data on the oncological safety of autologous fat transfer (AFT) for total breast reconstruction from the BREAST trial (*Poster)*

NVPC:

Evaluation of the BREAST-II Trial for Breast Reconstruction Using Autologous Fat Transfer: 1-Year Follow-Up (*Oral presentation)*

Oncological Safety of Autologous Fat Transfer for Total Breast Reconstruction: Results from the Multicentre (Non)Randomised BREAST Trials (*Top 3 abstracts*)

Londen Breast meeting:

Preliminary data on the oncological safety of autologous fat transfer (AFT) for total breast reconstruction from the BREAST trial (*poster*)

Oncological Safety of Autologous Fat Transfer for Total Breast Reconstruction: Results from the Multicentre (Non)Randomised BREAST Trials (*Oral presentation*)

ABOUT THE AUTHOR



Wessel van der Venne was born on 15 February 2000 in Heerlen, the Netherlands. He completed his pre-university education (Gymnasium) at Grotius College in Heerlen in 2018 and subsequently moved to Maastricht to study Medicine at Maastricht University, graduating in 2024. During his final clinical rotations in Plastic and Reconstructive Surgery at Maastricht University Medical Centre, Zuyderland Medical Centre and VieCuri Medical Centre in Venlo, he developed a strong interest in reconstructive surgery.

In September 2024, he began working as a doctor-researcher within the Department of Plastic, Reconstructive and Hand Surgery under the supervision of Prof. dr. Andrzej Piatkowski, Prof. dr. René van der Hulst, and dr. Esther Heuts. This resulted in the present thesis entitled *Autologous Fat Transfer for Total Breast Reconstruction: from Trials to Triumphs*. He currently works as a resident not in training (ANIOS) in Plastic, Reconstructive and Hand Surgery at Zuyderland Medical Centre.

Since early childhood, horses have been a constant in his life and spent much of his younger years at the stables. Initially, he aspired to become a veterinarian, inspired by his close connection to animals. His dedication to equestrian sport led him to become both regional and national champion. Although his medical studies temporarily limited the time he could devote to competitions, he continues to compete, with his horse remaining an essential part of his life.

Outside the hospital, he enjoys spending time with friends, dining out, and has a particular appreciation for fine bags and shoes. His long-term ambition is to ultimately become a plastic surgeon, and a Grand Prix dressage rider.