Clinical results and patient-reported outcomes in breast reconstructive surgery

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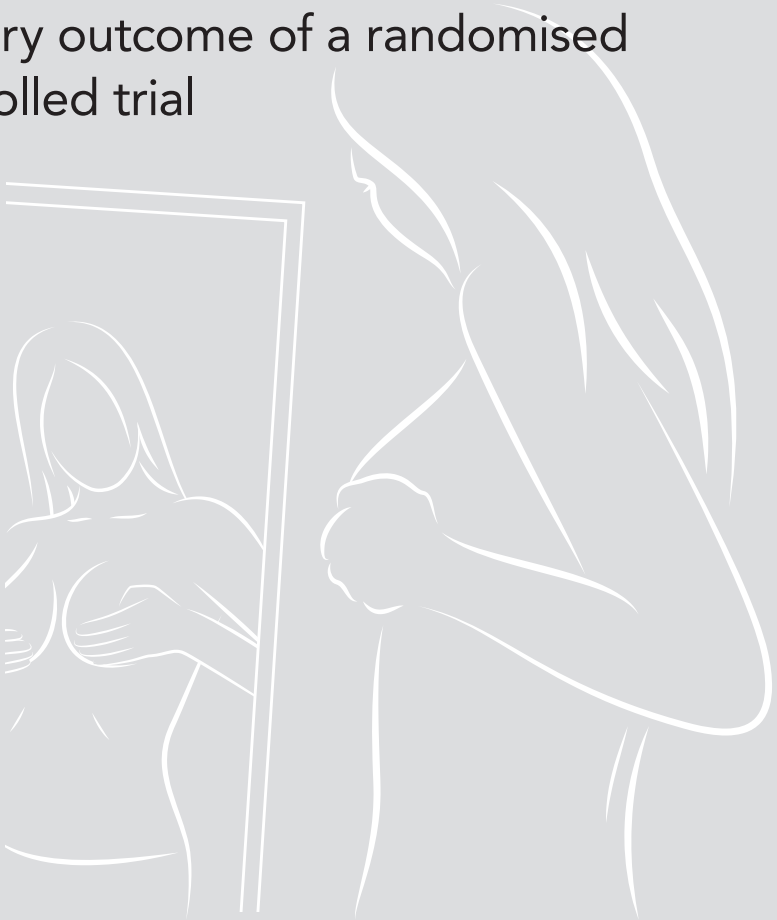
CHAPTER 6

Quality of life and patient satisfaction after one-stage implant-based breast reconstruction with an acellular dermal matrix versus two-stage reconstruction (BRIOS)

Primary outcome of a randomised controlled trial



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ABSTRACT

Introduction There is increasing interest in the use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR). Suggested advantages are that ADMs facilitate one-stage IBBR and improve aesthetic outcomes. We compared immediate one-stage ADM-assisted IBBR with two-stage IBBR (current standard of care). Our previously reported secondary endpoint showed that one-stage ADM-assisted IBBR was associated with significantly more adverse outcomes. Here, we present the primary endpoint results aiming to assess whether one-stage IBBR with ADM provides higher patient-reported quality of life (QOL) compared with two-stage IBBR.

Methods This multicentre, open-label, randomised controlled trial (BRIOS study) was done in eight hospitals in the Netherlands. We recruited women aged older than 18 years with breast carcinoma or a genetic predisposition who intended to undergo skin-sparing mastectomy and immediate IBBR. Participants were randomly assigned to undergo one-stage IBBR with ADM (Strattice, LifeCell, Branchburg, NJ, USA) or two-stage IBBR. Randomisation was stratified by centre and indication for surgery (oncological or prophylactic) in blocks of ten participants. The primary endpoint was patient-reported QOL, as measured with the BREAST-Q (ie, health-related QOL scales and satisfaction scales), in the modified intention-to-treat population. The study follow-up is complete. This study is registered with the Netherlands Trial Register, number NTR5446.

Results Between April 14, 2013, and May 29, 2015, we enrolled 142 women, of whom 69 were randomly assigned to receive one-stage ADM-assisted IBBR and 73 to receive two-stage IBBR. After exclusions, the modified intention-to-treat population comprised 60 patients in the one-stage group and 61 patients in the two-stage group. Of these, 48 women (mean follow-up 17.0 months [SD 7.8]) in the one-stage group and 44 women (17.2 months [SD 6.7]) in the two-stage group completed the BREAST-Q at least 1 year after implant placement. We found no significant differences in postoperative patient-reported QOL domains, including physical wellbeing (one-stage mean 78.0 [SD 14.1] vs two-stage 79.3 [12.2], p = 0.60), psychosocial wellbeing (72.6 [17.3] vs 72.8 [19.6], p = 0.95), and sexual wellbeing (58.0 [17.0] vs 57.1 [19.5], p = 0.82), or in the patient-reported satisfaction domains: satisfaction with breasts (63.4 [15.8] vs 60.3 [15.4], p = 0.35) and satisfaction with outcome (72.8 [19.1] vs 67.8 [16.3], p = 0.19).

Conclusion Taken together with our previously published findings, one-stage IBBR with ADM does not yield superior results in terms of patient-reported QOL compared with two-stage IBBR. Risks for adverse outcomes were significantly higher in the one-stage ADM group. Use of ADM for one-stage IBBM should be considered on a case-by-case basis.

RESEARCH IN CONTEXT

Evidence before this study

Implant-based breast reconstruction (IBBR) is the most common reconstruction method after a mastectomy. The use of an acellular dermal matrix (ADM) facilitates one-stage IBBR and improves aesthetic results through better definition of the inframammary fold, improved lower pole projection, increased coverage of the implant, and reduced risk of capsular contraction. By improving aesthetic results and reducing treatment burden, ADMs are thought to improve health-related quality of life (HRQOL). We searched PubMed for publications using the following search string: acellular dermis [Mesh] OR acellular dermis [tiab] OR acellular dermal matri* [tiab] OR acellular tissue matri* [tiab] OR collagen matri* [tiab] OR ADM [tiab] OR Strattice [tiab] OR Alloderm [tiab] OR Veritas [tiab] OR Egis [tiab] OR Artia [tiab] AND (mammaplasty[Mesh] OR mammaplast* [tiab] OR breast [tiab] AND reconstruct* [tiab] OR mammoplast* [tiab] OR mamma [tiab] AND reconstruct* [tiab] AND quality of life [tiab] OR patient-reported outcomes[tiab] OR patient reported outcome measures [Mesh] OR PROM OR patient satisfaction [tiab]. Data about the potential benefits of ADMs in IBBR are scarce and inconclusive. Moreover, most evidence is from retrospective cohort studies without a control group. Different questionnaires are used to measure HRQOL, which prevents direct comparison of findings across studies. We found two studies reporting on the use of the BREAST-Q to assess HRQOL after ADM-assisted one-stage IBBR. Only the crude BREAST-Q scores were reported and these were not converted with the recommended QScore Scoring Software to calculate validated BREAST-Q scores; therefore, comparison with other results is not possible.

Added value of this study

To our knowledge, the BRIOS study is the first randomised trial assessing HRQOL and aesthetic satisfaction after one-stage IBBR with ADM compared with conventional two-stage IBBR. Our study provides valuable insights regarding patient-reported HRQOL and aesthetic satisfaction after IBBR.

Implications of all the available evidence

In the BRIOS study, one-stage IBBR with ADM was associated with significantly more surgical complications, reoperations, and removal of implants. HRQOL and aesthetic satisfaction did not differ between the two groups, even after adjustment for removal of implant. We did not confirm the hypothesised benefits associated with the use of ADM. Future studies should determine for which patients the additional use of ADM in IBBR could be of benefit for their HRQOL and aesthetic satisfaction.

INTRODUCTION

Over a decade of experience has been acquired with the use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR) worldwide. However, the debate on the potential benefit of their use is still ongoing. Initially, the use of ADMs was suggested because it might facilitate one-stage IBBR. ADMs are used to augment the subpectoral pocket, allowing for direct placement of an implant of larger volume.
Improvement of aesthetic results is an important additional advantage, due to better definition of the inframammary fold, improved lower pole projection, and more coverage of the implant. It was later suggested that ADMs might also reduce the risk of capsular contracture.[1-3]
So far, data on these potential benefits have been inconclusive[2, 4] Most studies on this topic are of low quality with a high risk of selection bias.[1] Reported outcomes on the safety of ADM-assisted IBBR vary widely, with complication rates ranging from 4% to 50%.[1, 5] Furthermore, data on patient satisfaction after ADM-assisted breast reconstruction are scarce. Diverse patient-reported outcome measures (PROMs) are being used to assess patient satisfaction after breast reconstruction, ranging from self-designed surveys to validated questionnaires.[1] With a general shift in health care towards patient-centeredness, patient-reported outcomes (PROs) have gained importance as a way to assess health outcomes from the patients' perspective.[6] The BREAST-Q, which was introduced in 2009, was developed to assess health-related quality of life (QOL) and patient satisfaction after breast surgery. It has been widely used to evaluate PROs after breast reconstruction and can detect small clinically meaningful differences between individual patients and groups.[7, 8]

The Breast Reconstruction in One Stage (BRIOS) study was started in 2012 to compare QOL after ADM-assisted IBBR with QOL after conventional two-stage expander or implant breast reconstruction. The BRIOS study was an open-label, phase 4, multicentre, randomised, controlled trial done in the Netherlands. We hypothesised that patient-reported QOL and aesthetic satisfaction (measured by the BREAST-Q) would be increased after ADM-assisted IBBR because of improved aesthetic outcomes and reduced treatment burden on patients. We also hypothesised that safety outcomes would be similar for the two procedures. In May, 2015, the Dutch Health Care Inspectorate requested that we do a preliminary safety analysis because of concerns about safety of ADM use in IBBR.[9] ADM-

assisted IBBR was associated with significantly more adverse outcomes, which was a secondary outcome of the BRIOS study. These early safety outcomes were reported previously.[9, 10] Here, we report patient-reported QOL (ie, health-related QOL and satisfaction), which was the primary endpoint of the BRIOS study, and physician-reported aesthetic outcome (a secondary outcome).

METHODS

Study design and patients

The BRIOS study was a multicentre, randomised controlled trial. We aimed to compare QOL outcomes of one-stage IBBR combined with ADM (Strattice, LifeCell, Branchburg, NJ, USA) with that of conventional two-stage tissue expander or implant breast construction (two-stage IBBR). For this study, QOL as measured with BREAST-Q consisted of relevant scales from the health-related QOL domain (ie, physical, psychosocial, and sexual wellbeing) and satisfaction domain (ie, satisfaction with breasts and with outcome). Eight hospitals in the Netherlands participated (Erasmus Medical Center, Groningen Medical Center, Maastricht University Medical Center, VU University Medical Center, Meander Medical Center, Orbis Medical Center, Haga Hospital and Alexander Monro Breast Cancer Hospital), which were selected on the basis of having surgical experience with two-stage IBBR. Patients were eligible to participate if they had confirmed breast cancer or a genetic predisposition (ie, a BRCA1 or BRCA2 gene mutation), were aged 18 years or older, and intended to undergo a skin-sparing mastectomy followed by immediate IBBR. The protocol was approved by the institutional review board at each study centre. All patients provided written informed consent. This study is registered with the Netherlands Trial Register, number NTR5446. The BRIOS study was performed in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice, and the CONSORT statement.[11] The full study design, methodology, inclusion and exclusion criteria, and surgical techniques were previously described.[9] The protocol can be found in the online article.

Randomisation and masking

Patients were randomly assigned (1:1) to the two types of breast reconstruction. The coordinating researcher (REGD) used an online randomisation system (ALEA; version 2.2) to generate the randomisation schedule,

which was stratified by study centre and type of indication for surgery (oncological or prophylactic) in blocks of ten patients to achieve roughly balanced groups. The study was open label. Surgeons and patients were informed about the allocated treatment at least 3 days before surgery.

Procedures

All patients underwent skin-sparing mastectomy, followed by either an immediate one-stage IBBR, in which a de nite implant was placed in combination with a Strattice ADM, or a two-stage IBBR, which involved immediate total submuscular placement of a tissue expander that was later exchanged for a definite implant.[9]

Patients were invited by email or regular mail to complete BREAST-Q and EuroQol 5 dimensions (EQ-5D) questionnaires before the initial surgery and 1 year after placement of the definite implant. The BREAST-Q is a validated questionnaire to evaluate patient-reported health-related QOL and satisfaction after breast reconstruction.[7]

The BREAST-Q reconstruction module contains 14 independent scales representing health- related QOL and satisfaction domains. Domains pertaining to health-related QOL are psychosocial wellbeing (Q4), sexual wellbeing (Q5), and physical wellbeing: chest and upper body (Q6). Satisfaction domains are satisfaction with breasts (BQ1), visibility of the implant (Q2a), and feeling of rippling (Q2b), satisfaction with outcome (Q3), satisfaction with nipples (Q10), and satisfaction with care regarding information (Q11), surgeon (Q12), the medical team (Q13), and office staff (Q14). After we implemented the protocol, direct measurement of postoperative pain was not feasible so we decided, for logistical reasons, to measure pain using the BREAST-Q physical wellbeing scale only. Specifically, we used question O of the BREAST-Q physical wellbeing scale, assessing 'Aching feeling in your breast area?' on a five-point scale: 1 (none of the time), 2 (a little of the time), 3 (some of the time), 4 (most of the time), and 5 (all of the time). Additionally, we recorded demographic data.

We assessed physician-reported aesthetic outcome from photographs using the Aesthetic Items Scale,[12] which is a standardized method that was first described by Visser and colleagues[13] and Brinkman and colleagues.[14] Five standardized photographs (frontal, oblique and lateral) were taken before and at 1 year after placement of the breast implant. The photos were evaluated independently by five plastic surgeons, each with at least 10 years of clinical experience. All photographs were compiled into a Power-

Point slideshow presentation. They were shown in random order without giving any additional information (e.g., on pre- or postoperative status, reconstruction method used, or whether secondary revisions had been done). To minimize bias, blank slides were shown between photographs and the random order of the photographs was different for each observer. The surgeons rated the aesthetic outcome on five items with a five-point Likert-scale[12] and were also asked to give an overall rating on a scale from 0 (lowest) to 10 (highest) for both breasts and for each breast separately. 20 random photographs were shown twice to determine intraobserver agreement.[9]

Additional procedures in patients with a two-stage reconstruction were needed during their second surgery (ie, secondary revision surgeries), including scarification of the capsule, capsulotomy or capsulectomy, lipofilling, symmetrisation reduction mammoplasty or augmentation, or a combination. All additional surgeries besides the initial surgery according to the protocol were noted.
The procedures were divided into improvement of redundant tissue (dog-ear correction and scar revision), layer thickness (lipofilling), position of the implant (lowering of the inframammary fold, new implant, contralateral symmetrisation reduction mammoplasty or augmentation), contralateral preventive mastectomy, or a combination.

Outcomes

The primary outcome was patient-reported QOL at 1 year after placement of the definite implant, measured with the five most relevant BREAST-Q scales: psychosocial, sexual, and physical wellbeing (chest and upper body) and satisfaction with breasts and outcome, in the modified intention-to-treat population.[8] Secondary outcomes were incidence of perioperative and postoperative complications (safety), physician-reported aesthetic outcomes (assessed by a panel of independent plastic surgeons, based on standardised photographs taken 1 year after surgery), pain (assessed via the BREAST-Q physical wellbeing scale), general QOL (EQ-5D), and burden on patients in terms of number of procedures and time invested. The EQ-5D and burden on patients are used to assess the cost-effectiveness of both methods and these data will be published separately. All outcomes were prespecified. Here, we report the primary outcome and physician-reported aesthetic outcomes. Safety outcomes have been published previously.[9, 10]

Statistical analysis

We calculated the sample size on the basis of the expected satisfaction with breast score via BREAST-Q in the two-stage IBBR group. We expected a mean score of 60 points (SD 20) in the two-stage IBBR group and considered a difference of 10 points between groups to be clinically relevant.[15]
We estimated that 65 women in each group would provide 80% power to detect at least a 10-point difference with Student's t-test ($\alpha = 0.05$). To account for a dropout rate of 8%, we aimed to enrol 70 women per group. We used descriptive statistics for demographic data and clinical outcomes. For all BREAST-Q scales, we assessed differences between groups using Student's t-tests for continuous variables, χ^2 tests for categorical variables, and linear regression analyses. All analyses were corrected for the stratification variables (indication of surgery and centre of treatment).

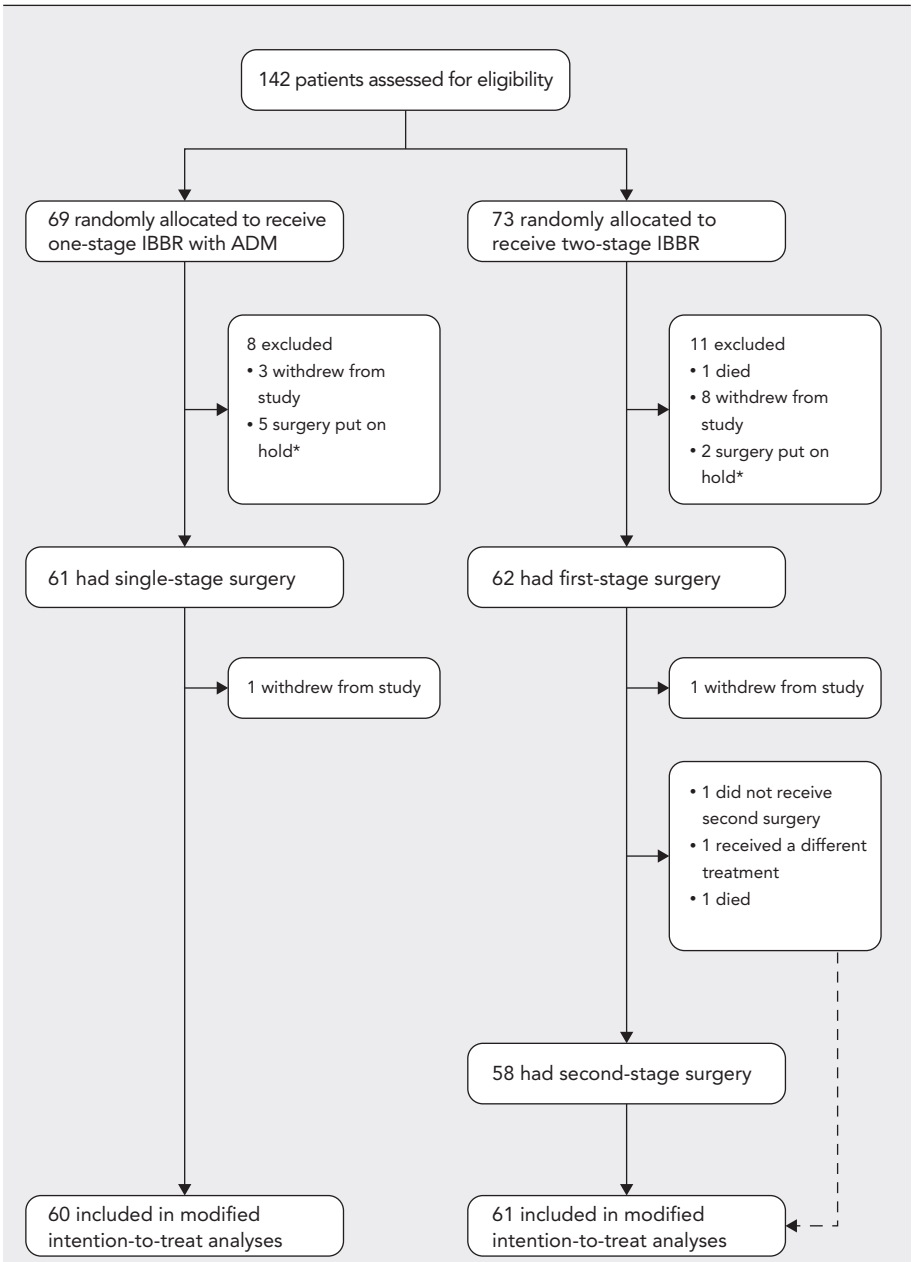
We estimated that a group size of 65 women in each group would provide 80% power to detect at least a 10-point difference with Student's t-test ($\alpha = 0.05$). Anticipating a dropout rate of 8%, we therefore aimed to enrol 70 women per group.[16, 17] We did an additional post-hoc exploratory analysis to correct for implant removal, due to the unexpected, high difference in implant removal rate between the groups. We used Fisher's exact test to analyse differences in postoperative pain.
For physician-reported aesthetic outcomes, we used the mean scores from the five surgeons to analyse differences between the groups using linear regression analysis in which the influence of the preoperative scores, implant removal, and secondary revision surgery were also assessed. We determined interobserver and intraobserver agreement among the five surgeons via intraclass correlation coefficients (ICCs). An ICC above 0.7 showed good reliability. We calculated (post-hoc) the Pearson correlation coefficient to explore correlations between patient-reported satisfaction with breasts and overall physician-reported aesthetic outcome. We used SPSS (version 22) and STATA (version 14.1) for statistical analyses.
This study is registered with the Netherlands Trial Register, number NTR5446.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and final responsibility to submit for the decision to submit for publication.

RESULTS

We recruited participants between April 14, 2013, and May 29, 2015. 142 eligible patients were randomly allocated to receive one-stage IBBR with ADM (69 [49%] patients) or to receive two-stage IBBR (73 [51%] patients; Figure).
In May, 2015, the Dutch Health Care Inspectorate requested a preliminary safety analysis due to concerns about the safety of ADM.[9] The local ethics committee suspended surgery in patients who had not yet been operated on. As a result, seven (5%) patients did not have surgery. Before surgery, 11 (8%) patients withdrew consent for further study participation and one patient (1%) died from severe progression of breast carcinoma, including metastases.
One-stage IBBR was done in 61 (43%) of 142 patients and two-stage IBBR in 62 (44%) patients. In both groups, one patient withdrew from the study after surgery. In the two-stage IBBR group, one patient received another treatment and one patient died from metastatic breast cancer after receiving the first surgery and one patient did not receive surgery (Figure). In total, 60 (42%) patients 40 (92 procedures) in the one-stage group and 61 (43%) patients (91 procedures) in the two-stage group were included in modified intention-to-treat analyses. Only one patient received two-stage IBBR instead of the allocated one-stage IBBR. This patient withdrew from study follow-up after the second surgery. This patient did not participate in regular follow-up at 1 year, but clinical data were available for this patient and they were analysed in the one-stage group according to intention-to-treat analyses. The mean follow-up after placement of the definite implant at time of completing the BREAST-Q was 17.0 months (SD 7.8) in the one-stage group and 17.2 months (SD 6.7) in the two-stage group.
Baseline demographic characteristics after randomisation were similar in both groups (Table 1). The mean age was 43.5 years (SD 11.6) in the one-stage group and 47.4 years (12.2) in the two-stage group. Treatment was prophylactic in 21 (35%) of 60 patients in the one-stage group and 23 (38%) of 61 patients in the two-stage group. 32 (53%) patients in the one-stage group and 30 (49%) patients in the two-stage group had bilateral reconstruction. Skin-sparing mastectomies were more common than nipple-sparing mastectomies were and, in 45 (25%) of 183 procedures, an incision was made at the inframammary fold. Adjuvant chemotherapy was given to 15 (25%) of 60 patients in the one-stage group and 18 (30%) of 61 patients in the two-stage group. Six (10%) patients in the one-stage group and nine (15%) in the two-stage group had adjuvant radiotherapy.



IBBR = implant-based breast reconstruction. ADM = acellular dermal matrix. * The ethics committee put surgery on hold for these patients.

Figure Trial profile

	One-stage ADM-assisted IBBR group (n = 60; 92 procedures)	Two-stage IBBR group (n = 61; 91 procedures)
Mean age, years (SD)	43.5 (11.6)	47.4 (12.2)
Prophylactic mastectomy	21 (35%)	23 (38%)
Therapeutic mastectomy	39 (65%)	38 (62%)
Unilateral reconstruction		
Right	15 (25%)	12 (20%)
Left	13 (22%)	19 (31%)
Bilateral reconstruction	32 (53%)	30 (49%)
Axillary lymph node dissection		
Right	2 (2%)	1 (1%)
Left	4 (4%)	2 (2%)
Nipple-sparing mastectomy		
Right	18 (20%)	14 (15%)
Left	17 (18%)	19 (21%)
Skin-sparing mastectomy		
Right	29 (32%)	28 (31%)
Left	28 (30%)	30 (33%)
Incision		
Inframammary fold		
Right	11 (12%)	10 (11%)
Left	10 (11%)	14 (15%)
No vertical component		
Right	28 (30%)	29 (32%)
Left	28 (30%)	28 (31%)
Vertical or diagonal		
Right	7 (8%)	2 (2%)
Left	7 (8%)	6 (7%)
Wise pattern		
Right	1 (1%)	1 (1%)
Left	0	1 (1%)
Mean mastectomy weight, g (SD)		
Right	384.3 (151.1)	376.8 (149.8)
Left	362.5 (132.5)	357.0 (128.4)
Mean implant volume, mL (SD)		
Right	384.7 (105.3)	426.9 (127.2)
Left	394.6 (95.5)	406.4 (115.1)
Adjuvant chemotherapy	15 (25%)	18 (30%)
Adjuvant radiotherapy*		
Right	3 (5%) 3 (5%)	
Left	3 (5%) 6 (10%)	
Number of participants followed up	48 (79%)	44 (72%)
Mean duration of follow-up at time of BREAST-Q, months (SD)	17.0 (7.8)	17.2 (6.7)

Data are n (%) or number of procedures (%) unless otherwise stated. For the primary outcome of the study, all breasts are taken into account for the evaluation of radiotherapy. ADM = acellular dermal matrices. IBBR = implant-based breast reconstruction. * For one patient, only the left side was included in the study, but the right breast was irradiated.

Table 1 Patient characteristics

	One-stage ADM-assisted IBBR group (n = 60)	Two-stage IBBR group (n = 61)
Removal		
Any	17 (29%)	4 (7%)
Tissue expander	..	3 (5%)
Implant	6 (10%)	1 (2%)
ADM	1 (2%)	..
ADM and implant	10 (17%)	..
Secondary reconstruction method after implant removal		
No reconstruction	2 (3%)	0
New expander	..	1 (2%)
New implant	0	1 (2%)
Expander or implant	9 (15%)	0
Combined autologous and implant reconstruction	1 (2%)	0
Autologous reconstruction	4 (7%)	2 (3%)

Data are n (%). ADM = acellular dermal matrix. IBBR = implant-based breast reconstruction.

Table 2 Removal of implants and reoperations (per-protocol population)

	One-stage ADM-assisted IBBR group (n = 60)	Two-stage IBBR group (n = 61)
BREAST-Q		
Questionnaires completed	48 (80%)	44 (72%)
Uncomplicated course	39 (65%)	40 (66%)
Implant removal with new reconstruction	7 (12%)	4 (7%)
Implant removal without reconstruction	2 (3%)	0
Physician-reported aesthetic outcome		
Photographs available	54 (90%)	52 (85%)
Uncomplicated course	41 (68%)	50 (82%)
Implant removal with new reconstruction	10 (17%)	2 (3%)
Implant removal without reconstruction	3 (5%)	..

Data are n (%). ADM = acellular dermal matrix. IBBR = implant-based breast reconstruction.

Table 3 Postoperative BREAST-Q and physician-reported aesthetic outcome (modified intention-to-treat population)

Surgical complications and reoperations have been reported previously.[9] Implant removal was more common in the one-stage group (17 [29%] of 59 patients, 24 procedures) than it was in the two-stage group (four [7%] of 62 patients, four procedures; Table 2). Most patients in the one-stage group who had their implants removed subsequently underwent two-stage expander or implant reconstruction. In the two-stage group, patients who had their tissue expander removed underwent secondary reconstruction with a new expander, implant or autologous flap (Table 2). During the exchange of the tissue expander to the definite implant, the following additional procedures were performed: scarification of the capsule (one [2%] of 61 patients), capsulotomy or capsulectomy (10 [16%]), lipofilling (five [8%]), contralateral symmetrisation reduction mammoplasty or augmentation (nine [15%]), or a combination (four [7%]). In the patient who was randomly assigned to the one-stage group but underwent two-stage reconstruction, scarification of the capsule and a capsulotomy was done. 12 (20%) of 60 patients in the one-stage group and 16 (26%) of 61 patients in the two-stage group had additional secondary revision surgeries. Improvement of redundant tissue was performed in one (1%) of 60 patients in the one-stage group compared with three (5%) of 61 patients in the two-stage group, improvement of layer thickness in four (7%) patients in the one-stage group versus one (2%) patient in the two-stage group, and improvement of the implant in two (3%) patients in the one-stage compared with seven (12%) in the two-stage group. A combination was performed in four (7%) patients in both groups. A contralateral preventive mastectomy was performed in one (2%) patient in each group.

The preoperative BREAST-Q were completed by 32 (53%) of 60 patients in the one-stage IBBR and 31 (51%) of 61 patients in the two-stage IBBR; post-operative BREAST-Q were completed by 48 (80%) of 60 patients in the one-stage group and 44 (72%) of 61 patients in the two-stage group (Table 3). The mean preoperative score for satisfaction with breasts was 75.8 (SD 17.5) in the one-stage group and 70.9 (19.5) in the two-stage group; the postoperative scores were 63.4 (15.8) in the one-stage group and 60.3 (15.4) in the two-stage group (Table 4). There were no statistically significant differences between the groups for any of the other five BREAST-Q scales (Table 4, Table 5). When only the patients with an uncomplicated course were analysed, similar results were seen: satisfaction with breasts was 64.4 (SD 15.9) in the one-stage group versus 62.7 (12.8) in the two-stage group. A secondary post-hoc exploratory analysis, in which we adjusted for implant removal, did not show statistically significant differences in BREAST-Q

	Preoperative		Postoperative		
	One-stage ADM-assisted	Two-stage IBBR	One-stage ADM-assisted	Two-stage IBBR	p-value*
Available questionnaires, n	32 (53%) of 60	31 (51%) of 61	48 (80%) of 60	44 (72%) of 61	
Satisfaction with breasts					
Data available, n (%) of N	32 (53%) of 60	31 (51%) of 61	48	43	
Mean (SD)	75.8 (17.5)	70.9 (19.5)	63.4 (15.8)	60.3 (15.4)	0.35
Visibility of rippling					
Data available, n (%) of N	..	..	44	40	
Mean (SD)	..	..	3.2 (1.0)	2.9 (0.9)	0.14
Sensation of rippling					
Data available, n (%) of N	..	..	43	40	
Mean (SD)	..	..	3.1 (1.0)	2.8 (0.9)	0.26
Satisfaction with outcome					
Data available, n (%) of N	..	..	48	43	
Mean (SD)	..	..	72.8 (19.1)	67.8 (16.3)	0.19
Psychosocial wellbeing					
Data available, n (%) of N	32 (53%) of 60	31 (51%) of 61	48	44	
Mean (SD)	68.2 (11.8)	68.4 (19.5)	72.6 (17.3)	72.8 (19.6)	0.95
Sexual wellbeing					
Data available, n (%) of N	32 (53%) of 60	28 (46%) of 61	47	39	
Mean (SD)	63.5 (14.4)	63.5 (23.8)	58.0 (17.0)	57.1 (19.5)	0.82

Table 4 Preoperative and postoperative BREAST-Q scales

	Preoperative		Postoperative		
	One-stage ADM-assisted	Two-stage IBBR	One-stage ADM-assisted	Two-stage IBBR	p-value*
Physical wellbeing: chest and upper body**					
Data available, n (%) of N	32 (53%) of 60	31 (51%) of 61	48	44	
Mean (SD)	78.4 (15.7)	84.3 (11.2)	78.0 (14.1)	79.3 (12.2)	0.60
Median (IQR)	..	..	77.0 (91.0 – 68.8)	81.0 (85.0 – 71.8)	
Satisfaction with nipples					
Data available, n	..	..	17	13	
Mean (SD)	..	..	73.3 (17.2)	76.7 (20.7)	0.63
Satisfaction with care: information					
Data available, n (%) of N	..	..	48	44	
Mean (SD)	..	..	65.1 (15.5)	69.5 (19.9)	0.24
Satisfaction with care: surgeon**					
Data available, n (%) of N	..	..	48	44	
Mean (SD)	..	..	84.1 (18.6)	84.6 (21.7)	0.63
Median (IQR)	..	..	91.0 (31 – 100)	100.0 (25 – 100)	
Satisfaction with care: medical team**					
Data available, n (%) of N	..	..	48	44	
Mean (SD)	..	..	86.7 (22.0)	82.8 (24.1)	0.47
Median (IQR)	..	..	100 (0 – 100)	100 (0 – 100)	
Satisfaction with care: office staff					
Data available, n (%) of N	..	..	48	44	
Mean (SD)	..	..	86.4 (18.8)	84.7 (21.0)	0.69

ADM = acellular dermal matrix. IBBR = implant-based breast reconstruction. * Difference between the postoperative BREAST-Q of the one-stage and two-stage IBBR. ** Nonnormal distribution, thus median is also reported.

	Difference*	p-value	Adjusted analyses**	p-value
Satisfaction with breasts (n = 91)	1.4 (-5.1 to 8.0)	0.665	2.8 (-3.5 to 9.2)	0.378
Satisfaction with outcome (n = 91)	4.3 (-3.6 to 12.2)	0.283	5.4 (-2.5 to 13.3)	0.179
Psychosocial wellbeing (n = 92)	-1.9 (-9.8 to 5.9)	0.622	-0.6 (-8.3 to 7.2)	0.887
Sexual wellbeing (n = 86)	-0.3 (-8.9 to 8.2)	0.937	0.6 (-8.1 to 9.2)	0.899
Physical wellbeing (n = 92)	-3.0 (-8.6 to 2.6)	0.291	-2.8 (-8.5 to 2.9)	0.329

Data are the difference (95% CI) between the two groups. ADM = acellular dermal matrices. IBBR = implant-based breast reconstruction. * Analyses adjusted for stratification factors (indication and centre). ** Secondary analyses regarding possible factor influencing patient-reported outcomes (off-protocol analyses); adjusted for indication, centre, and implant removal.

Table 5 Regression analyses of differences between one-stage ADM-assisted IBBR and two-stage IBBR

	Preoperative		Postoperative		
	One-stage ADM-assisted IBBR (n = 56)	Two-stage IBBR (n = 54)	One-stage ADM-assisted IBBR (n = 54)	Two-stage IBBR (n = 52)	p-value*
Shape (1-5)	4.5 (0.5)	4.5 (0.7)	3.5 (0.9)	3.2 (0.7)	0.075
Volume (1-5)	4.5 (0.5)	4.4 (0.7)	3.9 (0.9)	4.0 (0.6)	0.867
Symmetry (1-5)	4.3 (0.7)	4.3 (0.8)	3.4 (1.0)	3.1 (0.8)	0.087
Scars (1-5)	4.9 (0.4)	4.8 (0.5)	3.3 (0.8)	3.4 (0.7)	0.362
NAC (1-5)**	4.9 (0.2)	4.9 (0.3)	3.8 (0.9)	3.7 (0.8)	0.721
Total score (1-10)	8.2 (0.8)	8.2 (1.2)	6.3 (1.5)	6.2 (1.0)	0.569
Only side of reconstruction included in the study (1-10)***	8.4 (0.4)	8.3 (0.8)	6.2 (1.6)	6.2 (0.9)	0.909

Data are mean (SD). ADM = acellular dermal matrix. IBBR=implant-based breast reconstruction. NAC = nipple areolar complex. * Difference between postoperative aesthetic score of one-stage and two-stage IBBR. ** Not applicable if a skin-sparing mastectomy without a nipple reconstruction was done or if patients had a history of skin-sparing mastectomy. Data were only available from 56 participants for preoperative one-stage IBBR, from 52 for preoperative two-stage IBBR, from 37 for postoperative one-stage IBBR, and from 39 for postoperative two-stage IBBR. *** Only left or right side if unilateral reconstruction was done.

Table 6 Preoperative and postoperative aesthetic scores based on photographs per group

outcomes between the two groups (Table 5). Postoperative pain did not differ between the groups, with a mean score of 1.58 (SD 0.87) in the one-stage group and 1.41 (0.66) in the two-stage group (p = 0.875).
Photographs were available for 54 (90%) of 60 patients in the one-stage group and 52 (85%) of 61 patients in the two-stage group (Table 3). The mean preoperative score for physician-reported aesthetic outcome was 8.4 (SD 0.4) in the one-stage group and 8.3 (0.8) in the two-stage group. The postoperative scores were lower than the preoperative scores in both groups, with a mean score of 6.2 (1.6) in the one-stage group and 6.2 (0.9) in the two-stage group (Table 6). There were no statistically signiffiant differences between the two groups based on the physician-reported Aesthetic Item Scale, or when we adjusted for preoperative panel score (difference -0.0 [95% CI -0.5 to 0.5]; p = 0.998), implant removal (0.3 [-0.2 to 0.8]; p = 0.217), and secondary revision surgeries (0.0 [-0.5 to 0.5]; p = 0.859). When only the patients without reoperations were taken into account, similar results were seen with regard to the aesthetic score (one-stage group 6.5 [SD 1.3] versus two-stage group 6.2 [1.0]).
The intraobserver agreement was good in all observers with ICCs of at least 0.843 (95% CI 0.461-1.000). The interobserver agreement for physician-reported aesthetic outcomes was moderate, with ICCs ranging from 0.516 (0.355-0.640) to 0.758 (0.704-0.804) (Table S1).

We did a post-hoc exploratory analysis to assess the correlation between patient-reported outcomes of the BREAST-Q and physician-reported aesthetic scores at 12 months after surgery. This correlation was low, with a Pearson correlation of r = 0.343 (p = 0.002) between the satisfaction with breasts and the mean overall physician-reported aesthetic score. Correlations between other scales and physician-reported aesthetic outcomes ranged from 0.113 to 0.448.

DISCUSSION

The first reports after the introduction of ADM in the field of breast reconstruction in 2005 were overwhelmingly promising,[18, 19] suggesting that the use of ADM is cost-effective, because it makes one-stage IBBR feasible and leads to improved aesthetic results by creating a more natural-looking breast.[1, 3] However, evidence of these potential benefits remained inconclusive. We did the multicentre, randomised, controlled BRIOS study to

investigate these possible benefits of ADM-assisted one stage IBBR relative to the conventional two-stage IBBR. We found that patient-reported QOL, as measured by the BREAST-Q at least one year after placement of the definite breast implant, did not differ between the two groups, even after we adjusted for implant removal. Assessment of the aesthetic outcome by experienced plastic surgeons did not reveal significant differences between both groups. Therefore, we were not able to confirm the presumed advantages of one-stage IBBR with ADM over two-stage IBBR.

Because breast reconstruction primarily aims to restore physical appearance and wellbeing, its value can only really be judged by the patient. The BREAST-Q was developed in the context of the worldwide momentum to adopt PROs. The BREAST-Q is a comprehensive tool to evaluate QOL by assessing both health-related QOL and satisfaction, which is now used in clinical care in many centres and is used in studies to evaluate outcomes for breast surgery. Patient-reported satisfaction with breasts after breast reconstruction with implants varies between 55 and 70.[20, 21] Our findings are within this range (63.4 in the one-stage group vs. 60.3 in the two-stage group). We found higher rates of surgical complications, reoperations, and implant removal in the one-stage group than in the two-stage group. A complicated course can negatively affect the patient's experience, QOL, and satisfaction. After additional secondary exploratory analyses to adjust the 12-month BREAST-Q scores for implant removal, BREAST-Q scores between groups were still not significantly different. For patients with an uncomplicated course (ie, breast reconstruction without implant removal), the values were similar to those of the entire group, including patients with a complicated course (one-stage 64.4, two-stage 62.7). Overall, postoperative BREAST-Q scores were lower than preoperative scores. Only psychosocial wellbeing scores were increased postoperatively, indicating improved emotional health and self-esteem after breast reconstruction.

Two studies[22, 23] have reported on the use of the BREAST-Q to assess ADM-assisted IBBR, showing a high level of patient satisfaction. The authors did not use the recommended QScore Scoring Software to calculate validated BREAST-Q scores, which prevents comparison with our results. The Mastectomy Reconstruction Outcomes Consortium (MROC) study[24, 25] is a large prospective, observational cohort study of all patients undergoing first-time breast reconstruction assessing PROs using several questionnaires, including the BREAST-Q. Since large numbers of patients were in-

cluded, the results may improve our understanding of which factors are most important for patient satisfaction after breast reconstruction. However, results after solely one-stage IBBR with ADM are not yet available from the MROC study. Srinivasa and colleagues[21] reported on the MROC study comparing one-stage IBBR (n = 99, 6.9%) and two-stage IBBR (n = 1329, 93%), and found that use of ADM was significantly more common in the one-stage group (one-stage 93% vs. two-stage 52%; $p < 0.001$). BREAST-Q scores were similar between groups (one-stage 68.3 vs two-stage 63.8). Their mean BREAST-Q scores are similar to mean scores reported in our trial. We chose to also assess patient-reported experience measures (ie, BREAST-Q satisfaction with information, satisfaction with care, and satisfaction with surgeon). Despite increased prevalence of complications after use of ADM, there were no differences between the groups, indicating that patients were equally satisfied with preoperative communication and information about potential risks and benefits.[21]

Supporters of the use of ADMs in IBBR are enthusiastic about the technique because it could allow for more natural aesthetic outcomes than could two-stage submuscular reconstructions. In our study, the aesthetic outcomes were assessed by a panel of five experienced plastic surgeons. We could not establish improved cosmesis after ADM-assisted reconstruction. For patients who underwent successful one-stage reconstruction with ADM without reoperations, the postoperative physician-reported aesthetic score averaged 6.5, compared with 6.2 in the two-stage group. When adjusting for reoperations or implant removal, this difference in aesthetic scores between the groups was not statistically significant. Possible differences in cosmesis between the two IBBR techniques were smaller than our detection limit (with the present sample size, a difference ≥ 0.8 in aesthetic score could be detected). The overall mean postoperative aesthetic scores were considerably lower than preoperative scores (6.2 vs 8.2). One explanation might be that the reconstructed breast often does not match the natural breast. Further research on the effect of the two IBBR techniques on factors such as shape or symmetry is needed.

Generally, it is assumed that cosmesis is an important factor in the satisfaction and QOL of the patient. However, consistent with previous studies, the correlation between patient-reported satisfaction with breasts and physician-reported aesthetic score was low ($r = 0.343$), suggesting that patient satisfaction cannot be explained by the aesthetic outcome observed by plastic surgeons.[12, 26, 27]

Although we could not verify the advantages of one-stage IBBR with ADM, we should be cautious not to draw definite conclusions. This study is limited by a lower than anticipated response and inclusion rate, in which 48 (80%) patients in the one-stage group and 44 (72%) patients in the two-stage group completed the BREAST-Q, instead of the anticipated 65 patients per group. With this number of respondents, the difference in BREAST-Q score must be greater than 9.5 to be able to detect a statistically significant difference. Hence, a smaller difference in patient satisfaction between the two groups might still be present, but whether such potentially smaller differences are clinically relevant remains uncertain. To date, there are no widely accepted clinically relevant differences, known as minimal important differences. Pusic and colleagues[24] reported distribution-based minimal important differences for the BREAST-Q scales, with a difference of 4.0 points within groups for the satisfaction with breast and sexual wellbeing domains and 3.6 points for the psychosocial wellbeing domains. Based on these differences, patients in the one-stage IBBR with ADM group report clinically relevant, but non-signifficant, increased satisfaction with outcome (mean 72.8 [SD 19.1]) compared with the two-stage group (67.8 [16.3]), but decreased satisfaction with information (one-stage 65.1 [15.5] vs two-stage 69.5 [19.9]). The interpretation and clinical meaning of PROs are still unknown. Future studies should focus on the interpretation of these relevant outcomes.
Although we started the BRIOS study at a time when there were high expectations regarding the potential benefits of ADMs, the results should be interpreted on the basis of what we know today. ADM-assisted breast reconstruction is a delicate procedure, requiring strict patient selection and a well trained and experienced surgical team.[28-30]

One-stage breast reconstruction is inherently less forgiving than two-stage breast reconstruction is, since implant volume cannot be adapted and more strain is placed on the mastectomy skin flap and the wound. Two-stage IBBR reconstruction is often more successful because the one-stage technique requires an experienced team that recognise tacit risk factors, which cannot be quantified yet. It remains unclear whether the use of an ADM in one-stage breast reconstruction is an additional complicating factor because no randomised studies have compared one-stage IBBR with and without ADM. Moreover, we do not know which type of ADM is preferable. Although most ADMs in North America are derived from humans, these are not approved in Europe. In the BRIOS study, we

used Strattice, which is a porcine-derived ADM. It is unclear whether differences in performance exist between ADMs derived from animals and humans.

In summary, the multicentre randomised BRIOS trial showed that one-stage IBBR with ADM was not associated with higher health-related QOL or patient satisfaction compared with the conventional two-stage expander or implant-based IBBR. Furthermore, both patient-reported and physician-reported aesthetic outcomes were similar between the groups. With a higher risk of complications, the added value of ADM in IBBR has yet to be proven, and its use should be considered on a case-by-case basis.

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Pearson correlation	Physician-reported total score	p-value
BREAST-Q 1 total score	0.325	0.002
a. how you look in the mirror clothed?	0.262	0.01
b. The shape of your reconstructed breast(s) when you are wearing a bra?	0.280	0.01
c. How normal you feel in your clothes?	0.200	0.06
d. The size of your reconstructed breast(s)?	0.323	0.002
e. Being able to wear clothing that is more fitted?	0.179	0.10
f. How your breasts are lined up in relation to each other?	0.311	0.003
g. How comfortably your bras fit?	0.191	0.08
h. The softness of your reconstructed breast(s)?	0.167	0.12
i. How equal in size your breasts are to each other?	0.337	0.001
j. How natural your reconstructed breast(s) looks	0.328	0.002
k. How naturally your reconstructed breast(s) sits/hangs?	0.326	0.002
l. How your reconstructed breast(s) feels to touch?	0.113	0.30
m. How much of your reconstructed breast(s) feels like a natural part of your body?	0.182	0.09
n. How closely matched (similar) your breasts are to each other?	0.448	< 0.001
o. How your reconstructed breast(s) look now compared to before you had any breast surgery?	0.358	0.001
p. How you look in the mirror unclothed?	0.383	< 0.001

Table S1 Correlations between BREAST-Q scales and physician-reported aesthetic outcomes