Original article

Predictors of complications after direct-to-implant breast reconstruction with an acellular dermal matrix from a multicentre randomized clinical trial

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Background: In the multicentre randomized trial BRIOS (Breast Reconstruction In One Stage), direct-to-implant (DTI) breast reconstruction with an acellular dermal matrix (ADM) was associated with a markedly higher postoperative complication rate compared with two-stage tissue expander/implant breast reconstruction. This study aimed to identify factors that contribute to the occurrence of complications after DTI ADM-assisted breast reconstruction.

Methods: Data were obtained from the BRIOS study, including all patients treated with DTI ADM-assisted breast reconstruction. Logistic regression analyses were performed to identify factors predictive of postoperative complications.

Results: Fifty-nine patients (91 breasts) were included, of whom 27 (35 breasts) developed a surgical complication. Reoperations were performed in 29 breasts (32 per cent), with prosthesis removal in 22 (24 per cent). In multivariable analyses, mastectomy weight was associated with complications (odds ratio (OR) 1·94, 95 per cent c.i. 1·33 to 2·83), reoperations (OR 1·70, 1·12 to 2·59) and removal of the implant (OR 1·55, 1·11 to 2·17). Younger patients (OR 1·07, 1·01 to 1·13) and those who received adjuvant chemotherapy (OR 4·83, 1·15 to 20·24) more frequently required reoperation. In univariable analyses, adjuvant radiotherapy showed a trend towards more complications (OR 7·23, 0·75 to 69·95) and removal of the implant (OR 5·12, 0·76 to 34·44), without reaching statistical significance.

Conclusion: Breast size appeared to be the most significant predictor of complications in DTI ADM-assisted breast reconstruction. The technique should preferably be performed in patients with small to moderate sized breasts. Registration number: NTR5446 (http://www.trialregister.nl).

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Introduction

The use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR) has increased rapidly over the past two decades[1,2]. The dermal matrix is mainly used to provide inferolateral implant coverage, which allows a larger implant to be inserted and decreases pectoralis major retraction. This is thought to reduce postoperative pain and to enhance aesthetic outcome. In the longer term, reduced capsular contracture rates have been reported after IBBR in combination with an ADM[2–4]. ADMs may be used in both direct-to-implant (DTI) IBBR and a two-stage expander/implant-based reconstruction. Although several articles have reported on the outcomes of ADM-assisted IBBR, evidence for

the suggested advantages is still limited[1]. Moreover, evidence for the safety of ADM use in IBBR is also sparse, with contradictory results. Complication rates in published studies[1,5–8] vary widely from 4·0 to 50·0 per cent. Reported complications include haematoma, seroma, infection, skin necrosis, flap or nipple ischaemia, and exposure of the ADM or implant[5–7]. Several factors have been reported to increase the risk of complications, including age, smoking, BMI exceeding 30 kg/m^2, periareolar incision, mastectomy weight over 600 g, and implant size larger than 600 ml[5,7,9].

To optimize patient selection and treatment, it is important to discern which factors affect the outcomes of ADM-assisted IBBR, thereby reducing complication and rates of implant removal. The BRIOS study was an open-label phase IV multicentre RCT that compared DTI breast reconstruction combined with ADM and a conventional two-stage expander/implant breast reconstruction (without ADM)[10]. The early postoperative complication rate was significantly higher in the DTI ADM-assisted group than the two-stage group (38·5 *versus* 14·1 per cent; odds ratio (OR) 3·81; $P < 0·001$). A high rate of wound healing problems was observed, leading to implant loss in 26·6 per cent of breasts[10]. The aim of the present study was to identify factors that contributed to the occurrence of adverse outcomes in DTI ADM-assisted breast reconstruction.

Methods

In the BRIOS trial, DTI ADM-assisted breast reconstruction using Strattice Tissue Reconstructive Matrix™ (LifeCell, Branchburg, New Jersey, USA) was compared with conventional two-stage tissue expander/implant IBBR. The primary endpoint was health-related quality of life assessed with the BREAST-Q at 1 year after placement of the definitive implant. Secondary outcomes were the incidence of perioperative and postoperative complications, aesthetic outcome, pain, and burden on the patients in terms of number of procedures and time invested. The protocol was approved by the institutional review board at each study centre. All patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice. The full study design and methodology have been described previously[10]. The study was preregistered in the Netherlands Trial Register (NTR5446). Owing to worries about safety, just after the final patient had been enrolled in the BRIOS study, but before seven women had undergone surgery, the Dutch Health Care Inspectorate requested a preliminary safety analysis. The early safety outcomes have been reported previously[10]. The aim of the present study was to identify factors contributing to the occurrence of adverse outcomes in DTI ADM-assisted breast reconstruction. Therefore, no preregistered analysis plan was available.

Patient selection and data collection

Patients included in the BRIOS study who underwent DTI breast reconstruction with the additional use of an ADM were included in the present study. Patient demographics and possible risk factors for adverse events were extracted from the study database and medical charts, including data on surgical techniques and the postoperative course. All adverse events and their subsequent course and management were reviewed in detail. Cultures after implant removal were reported if available. The final complication and reoperation rate per patient was scored. For example, if a necrosectomy was performed that eventually led to removal of the implant, this was scored as implant loss.

Outcome measures

Adverse events were grouped into three categories: occurrence of any surgical complication; reoperation after a surgical complication; and removal of the implant and/or ADM after a surgical complication. Complications were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), in which grade 1 and 2 correspond to mild or moderate adverse events, and grade 3 to severe adverse events requiring serious interventions[11]. There were no grade 4 or 5 events. The time frame for registration of postoperative complications was the entire study follow-up, 1 year after placement of the definitive implant.

Patient-related factors included in the analyses were: age, BMI, diabetes mellitus, history of smoking (yes or no), neoadjuvant chemotherapy and adjuvant chemotherapy, radiotherapy, hormone therapy and targeted therapy. Surgery-related factors were: type of incision, skin-sparing or nipple-sparing mastectomy, axillary surgery including sentinel node biopsy or axillary lymph node dissection, mastectomy weight, size of the prosthesis, and the relationship between mastectomy weight and weight of the prosthesis. Nipple-sparing mastectomies were performed via an incision in the inframammary fold (IMF). Other incision types were both nipple- and skin-sparing mastectomies and comprised only a horizontal component, incisions with a vertical or diagonal component including the nipple–areola complex, or a boomerang and a wise pattern incision (inverted-T incision). To identify a learning curve effect, patients were divided into three consecutive groups

Table 1 Patient demographics and clinical data

	No. of patients* (*n* = 59)
Age (years)†	43·5(11·7)
Body mass index (kg/m^2)†	23·4(2·9)
Treatment	
Unilateral	27 (46)
Bilateral	32 (54)
Indication for surgery	
Prophylactic	21 (36)
Therapeutic	38 (64)
Smoker	12 (20)
Diabetes mellitus	2 (3)
Previous breast surgery‡	*n* = 91
None	85 (93)
Excision cyst	1 (1)
Lumpectomy, benign	1 (1)
Lumpectomy, malignant	4 (4)
Chemotherapy	
Preoperative	7 (12)
Postoperative	15 (25)
Radiotherapy (adjuvant)	6 (10)
Hormone therapy	19 (32)
Targeted therapy	3 (5)
Follow-up after surgery (months)†	24·7(7·1)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.); ‡number of breasts.

Table 2 Surgical characteristics

	No. of breasts* (*n* = 91)
Type of axillary surgery	
None	50 (55)
Sentinel lymph node biopsy	35 (38)
Axillary lymph node dissection	6 (7)
Nipple-sparing mastectomy	35 (38)
IMF incision	21 (23)
Incision without vertical component	7 (8)
Vertical/diagonal	6 (7)
Wise pattern	1 (1)
Skin-sparing mastectomy	56 (62)
Incision without vertical component	49 (54)
Vertical/diagonal	7 (8)
Mastectomy weight (g) (*n* = 87)	365 (260–453)
Implant weight (*n* = 90)	370 (335–445)
Mastectomy weight – implant weight (g) (*n* = 87)	−19 (−100 to 32)

*With percentages in parentheses unless indicated otherwise; †values are median (i.q.r.).

of 30–31 reconstructions based on the date of surgery (early, middle and late).

Statistical analysis

Univariable and multivariable logistic generalized estimating equation (GEE) analyses were performed to determine the predictive value of patient- and surgery-related factors for the occurrence of a surgical complication, reoperation and implant removal. Because data were analysed per breast, GEEs were used to adjust for the dependency of the observations within one patient. Factors with univariable $P < 0{\cdot}200$ were selected for multivariable GEE analyses. A backward selection procedure was used to obtain the final models for the three outcomes, in which only variables with $P < 0{\cdot}100$ were selected. In addition, possible associations between date of surgery and adverse outcomes were assessed by means of logistic GEE analyses. Two-sided $P < 0{\cdot}050$ was considered statistically significant. SPSS® version 22 (IBM, Armonk, New York) was used for the analyses.

Table 3 Adverse outcomes

	No. of breasts (*n* = 91)
Complications	
No surgical complication	56 (62)
Haematoma	3 (3)
Red breast syndrome	5 (5)
Wound infection	7 (8)
Skin necrosis	11 (12)
Wound dehiscence with exposure of	8 (9)
ADM	5 (5)
ADM + implant	2 (2)
Unknown	1 (1)
Incomplete resection*	1 (1)
Reoperation for surgical complications	
No reoperation for surgical reasons	62 (68)
Haematoma evacuation	3 (3)
Botulinum toxin injection	1 (1)
Necrosectomy	1 (1)
Removal of implant	24 (27)
ADM	2 (2)
Implant only	10 (11)
ADM + implant	12 (13)

Values in parentheses are percentages. ADM, acellular dermal matrix. *Complication regardless of the reconstruction method.

Results

In total, 59 women (91 breasts) who underwent DTI ADM-assisted breast reconstruction were included. Demographic data are shown in *Table 1*. The patients had a mean(s.d.) age of 43·5(11·7) (range 25–71) years and a BMI of 23·4(2·9) (range 18·3–31·8) kg/m^2. There were 21 prophylactic and 38 therapeutic mastectomies. Adjuvant radiotherapy was administered in six breasts (7 per cent). One incomplete resection was noted (unrelated to the reconstruction), for which a second procedure was performed. Mean clinical follow-up was 24·7(7·1) (range 11–37) months.

Table 4 Univariable logistic regression analyses of factors influencing outcomes

	Any complication (n = 35 reconstructions)		Any reoperation (n = 29 reconstructions)		Any removal of ADM and/or implant (n = 24 reconstructions)	
Factor	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Age (years)	1·0 (0·96, 1·05)	0·773	1·03 (0·99, 1·09)	0·145	1·04 (0·99, 1·01)	0·151
BMI (kg/m^2)	1·08 (0·91, 1·28)	0·371	1·00 (0·84, 1·19)	0·999	1·06 (0·89, 1·28)	0·501
Smoking	0·89 (0·30, 2·65)	0·832	0·64 (0·19, 2·23)	0·488	0·68 (0·16, 2·84)	0·593
Diabetes mellitus	2·26 (0·12, 38·64)	0·573	3·06 (0·18, 52·48)	0·441	3·63 (0·21, 62·96)	0·376
Previous breast surgery	1·06 (0·78, 1·42)	0·711	–*		–*	
Chemotherapy						
Preoperative	0·70 (0·20, 2·36)	0·560	0·67 (0·16, 2·81)	0·585	0·86 (0·21, 3·55)	0·839
Postoperative	2·03 (0·63, 6·56)	0·235	2·27 (0·69, 7·47)	0·177	1·65 (0·47, 5·91)	0·435
Adjuvant radiotherapy	7·23 (0·75, 69·95)	0·087	3·61 (0·55, 23·77)	0·181	5·12 (0·76, 34·44)	0·093
Hormone therapy	1·46 (0·54, 3·99)	0·457	0·84 (0·27, 2·62)	0·769	0·88 (0·26, 2·98)	0·834
Targeted therapy	–†		–†		–†	
Incision technique						0·152
IMF	1·00 (reference)		1·00 (reference)		1·00 (reference)	
Other‡	1·40 (0·49, 3·99)	0·527	3·56 (0·79, 15·95)	0·097	8·75 (0·45, 170·96)	
Nipple-sparing mastectomy						
Yes	1·00 (reference)		1·00 (reference)		1·00 (reference)	
No	0·56 (0·20, 1·55)	0·266	0·63 (0·22, 1·84)	0·400	0·55 (0·17, 1·80)	0·332
Mastectomy weight (g)§	1·94 (1·33, 2·82)	< 0·001	1·54 (1·09, 2·20)	0·015	1·55 (1·11, 2·17)	0·010
Mastectomy weight – implant weight (g)§	1·33 (0·92, 1·92)	0·126	1·18 (0·82, 1·71)	0·336	1·18 (0·80, 1·73)	0·397

Values in parentheses are 95 per cent confidence intervals. Ninety-one breasts were included in the analyses. *None of the patients who had undergone breast surgery previously were reoperated. †All patients who underwent targeted therapy had complications, reoperations and implant removal. ‡All incisions other than an incision in the inframammary fold (IMF). §Odds ratio calculated for a 100-g weight difference. ADM, acellular dermal matrix.

Table 5 Multivariable logistic regression analyses of factors influencing outcomes

	Any complication (n = 35 reconstructions)		Any reoperation (n = 29 reconstructions)		Any removal of ADM and/or implant (n = 24 reconstructions)	
	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Age (years)	–		1·07 (1·01, 1·13)	0·026	–	
Postoperative chemotherapy	–		4·83 (1·15, 20·24)	0·031	–	
Mastectomy weight (g)*	1·94 (1·33, 2·83)	< 0·001	1·70 (1·12, 2·59)	0·014	1·55 (1·11, 2·17)	0·010

Values in parentheses are 95 per cent confidence intervals. Ninety-one breasts were included in the analyses. *Odds ratio calculated for a 100-g weight difference. ADM, acellular dermal matrix.

Surgical characteristics

The incision for the mastectomy was made at the IMF only in 21 breasts (23 per cent), and a nipple-sparing mastectomy was performed in 35 (38 per cent). The median mastectomy weight was 365 (i.q.r. 260–453) g. On average, implanted prostheses were comparable to the volume of mastectomy weight resected, with a median weight of inserted prosthesis of 370 (335–445) g, and a median difference of –19 (–100 to 32) g (*Table 2*).

Complications, reoperations and implant removals

Only complications that occurred during the first year after placement of the definite implant were included in the analyses. Complications mainly occurred in the first month after surgery, a median of 13·5 (range 1–350) days (mean(s.d.) 33·4(70·8) days) after surgery. Surgical complications developed in 27 (46 per cent) of the 59 women (35 breasts, 38 per cent). Complications are listed in *Table 3*. Reoperation was necessary in 22 patients (37 per cent) (29 breasts, 32 per cent) for haematoma evacuation (3), necrosectomy (1), botulinum toxin injection for breast animation deformity (1), and removal of the ADM (2), the implant (10) or both (12). One case of incomplete resection was reported.

Univariable and multivariable analyses

The results of univariable and multivariable logistic GEE analyses are shown in *Tables 4* and *5* respectively.

Because all three patients (3 breasts) who received targeted trastuzumab therapy had complications and subsequent implant removal, and none of the six patients who had undergone previous breast surgery had a reoperation, these two variables were not included in the GEE analyses.

In the final multivariable model, a greater mastectomy weight was associated with a higher complication rate (OR 1·94, 95 per cent c.i. 1·33 to 2·83; $P < 0·001$), more reoperations (OR 1·70 1·12 to 2·59; $P = 0·014$) and more implant removals (OR 1·55, 1·11 to 2·17; $P = 0·010$). Younger patients were at higher risk of reoperation owing to complications (OR 1·07, 1·01 to 1·13; $P = 0·026$). Furthermore, adjuvant chemotherapy resulted in more reoperations (OR 4·83, 1·15 to 20·24; $P = 0·031$).

Association with learning curve

The first 30 breast reconstructions were performed between 18 April 2013 and 6 January 2014, the following 31 between 23 January 2014 and 25 July 2014, and the final 30 reconstructions between 1 September 2014 and 24 June 2015. Although severe adverse events (CTCAE grade 3) were common at the beginning of the study, there were no statistically significant differences between patients who underwent surgery in the early phase and those operated later in the study (*Table S1*, supporting information).

Association with bacterial cultures

Removal of the implant was necessary in 17 patients (24 breasts) with severe complications (CTCAE grade 3). Samples from 15 patients (19 breasts) were submitted for microbiological culture. Most cultures were sterile (11) or showed only commensal skin flora (4). Abnormal bacterial cultures were found in four patients (4 breasts). No associations between outcomes and culture results could be established, owing to the variety of bacterial cultures found (data not shown).

Discussion

In the BRIOS randomized trial, conventional two-stage reconstruction was compared with DTI breast reconstruction with the additional use of an ADM[10]. A high rate of complications was found in the DTI ADM-assisted group, which was at the high end of complication rates reported in the literature[1,5–7]. To assess risk factors for adverse outcomes, clinical outcomes of the 59 patients (91 breast reconstructions) who underwent DTI ADM-assisted breast reconstruction were reviewed in detail here. Breast size, as represented by mastectomy weight, was the most significant risk factor associated with complications, reoperations and removal of implants. Large breast size has previously been identified as a risk factor for complicated DTI immediate breast reconstruction. An increased risk of complications was reported for a mastectomy weight greater than 600 g[5]. In the present cohort, increasing breast size was associated with complications, although mastectomy weight was below 600 g in 87 of 91 breasts. Inserting a larger prosthesis than the original breast size did not result in severe adverse events, indicating that the higher complication rate was associated primarily with the initial breast size and not with placement of a larger prosthesis. Hunsicker and colleagues[7] reported a significant risk of complications when implants of 600 ml or larger were used. This cannot be verified from the present data, as implant sizes were smaller in this study. The Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons[12] recommend the use of an ADM in patients with small to moderate sized breasts, defined by Dundas and colleagues[13] as no more than a C-cup. The present results validate these guidelines with regard to DTI reconstruction using an ADM.

Several factors related to surgical technique have been suggested to affect outcomes, including incision type and mastectomy skin flap thickness[14]. Here, skin flap quality and thickness were not measured, as no methods were available for objective measurement of these variables. Therefore, their effect on the outcomes cannot be assessed. The location of the incisions could affect wound healing[15,16]. Previous studies[16–18] showed a higher complication rate after periareolar or wise pattern incisions compared with an inframammary or lateral/inferolateral incision. A trend towards more complications was also noted in the present study when the incision was other than in the IMF.

The experience of the surgeon with DTI ADM-assisted breast reconstruction has been mentioned as an important factor for a successful outcome[19]. Colwell and colleagues[19] described learning as an improved ability of surgeons to accurately determine the viability of the mastectomy skin envelope. They carried out a retrospective review of patients who underwent IBBR, with the experimental group receiving ADM-assisted DTI breast reconstruction (331 reconstructions) and the control group two-stage IBBR without ADM (148). The final choice of type of surgery was based on intraoperative evaluation of the perfusion of the mastectomy skin flaps. In the BRIOS study, treatment allocation was, however, by randomization. Although surgeons could decide to deviate from the protocol if they thought this necessary for safety reasons, only one patient received the two-stage treatment

instead of the allocated one-stage reconstruction. Because of the randomized study design, patient selection was not adapted over the course of the study. Therefore, a learning effect pertaining to patient selection is not applicable. Although all surgeons in the BRIOS study were experienced in performing breast reconstructions, learning may have occurred in terms of surgical technique and postoperative care. The complication rate in three consecutive periods was therefore assessed, but no significant association between time interval and complication rates was observed.

Infection-induced hypoxia can compromise skin flap survival. The risk of infection is up to ten times higher in patients with cancer undergoing IBBR than in those having cosmetic augmentation[20]. Wound infection developed in seven breasts in the present cohort, leading to removal of the implant and/or ADM in five instances. Adjuvant radiotherapy is a known risk factor for adverse outcomes after breast reconstruction[21,22]. Adjuvant chemotherapy is also likely to have a negative effect on wound healing[23]. In the present cohort, only the association between adjuvant chemotherapy and reoperation reached statistical significance. The lack of significant association between radiotherapy and adverse events was likely due to the small number of patients in the cohort who received radiotherapy. The impact of smoking on complications is well established, but was difficult to assess in the present study. Smoking was analysed as a binary variable, with smokers including all patients with a history of smoking. The patients were strongly advised to quit smoking at least 2 weeks before surgery, although this was not verified with a nicotine test.

All complications ultimately leading to implant removal in the present cohort were related to wound-healing problems. Impairment of the blood supply to the mastectomy skin flap is likely the direct cause of such problems. The hypothesis that wound-healing problems are a result of poor skin flap perfusion, and consequently mastectomy skin flap necrosis, finds broad consensus in the field of breast reconstructive surgery[14,22]. However, this hypothesis is hard to confirm, because objective measures of intraoperative skin flap quality or perfusion are still not available. Some progress has been made using fluorescence angiography[24–26]. However, fluorescence angiography is not yet recommended as standard care, as at present it is not cost-effective for use in all patients[27]. To date, the trained eye of an experienced surgeon is the only available benchmark. A strong dependency of outcomes on surgeon experience, especially with regard to patient selection, could explain why some expert centres report low complication rates but others report a high rate[1,5–7]. Future studies should focus on determining an objective, reliable method for assessment of skin flap quality during surgery.

One hypothesis is that the increased risk of wound complications in a one-stage reconstruction may be inherent to the use of an ADM, as opposed to synthetic materials. However, ADMs are regularly used in many types of surgery, without any convincing evidence that they cause an adverse tissue response[28,29]. Furthermore, using an ADM in a two-stage reconstruction is not associated with an increased complication rate, implying that the high complication rate observed here is primarily associated with the surgical technique (direct placement of the definitive implant) and not the ADM[30,31]. A prospective study comparing DTI breast reconstruction with and without the use of ADM is lacking.

The strength of the BRIOS study is its prospective randomized design. This ensures a comprehensive data set and prevents selection bias. A weakness of the study is that the number of patients was rather small. Furthermore, owing the randomized set-up, patients might not have received the reconstruction that would have been the surgeons' first choice outside a study. The high complication and implant removal rate in the DTI group implies that stricter patient selection is warranted for DTI ADM-assisted breast reconstruction. As mastectomy weight was a significant predictor of adverse outcomes in DTI ADM-assisted breast reconstruction, these reconstructions should preferably be performed only in patients with small to moderate sized breasts.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.