BREAST RECONSTRUCTIVE SURGERY

Improving outcomes and patient satisfaction

Yara Lynn Blok

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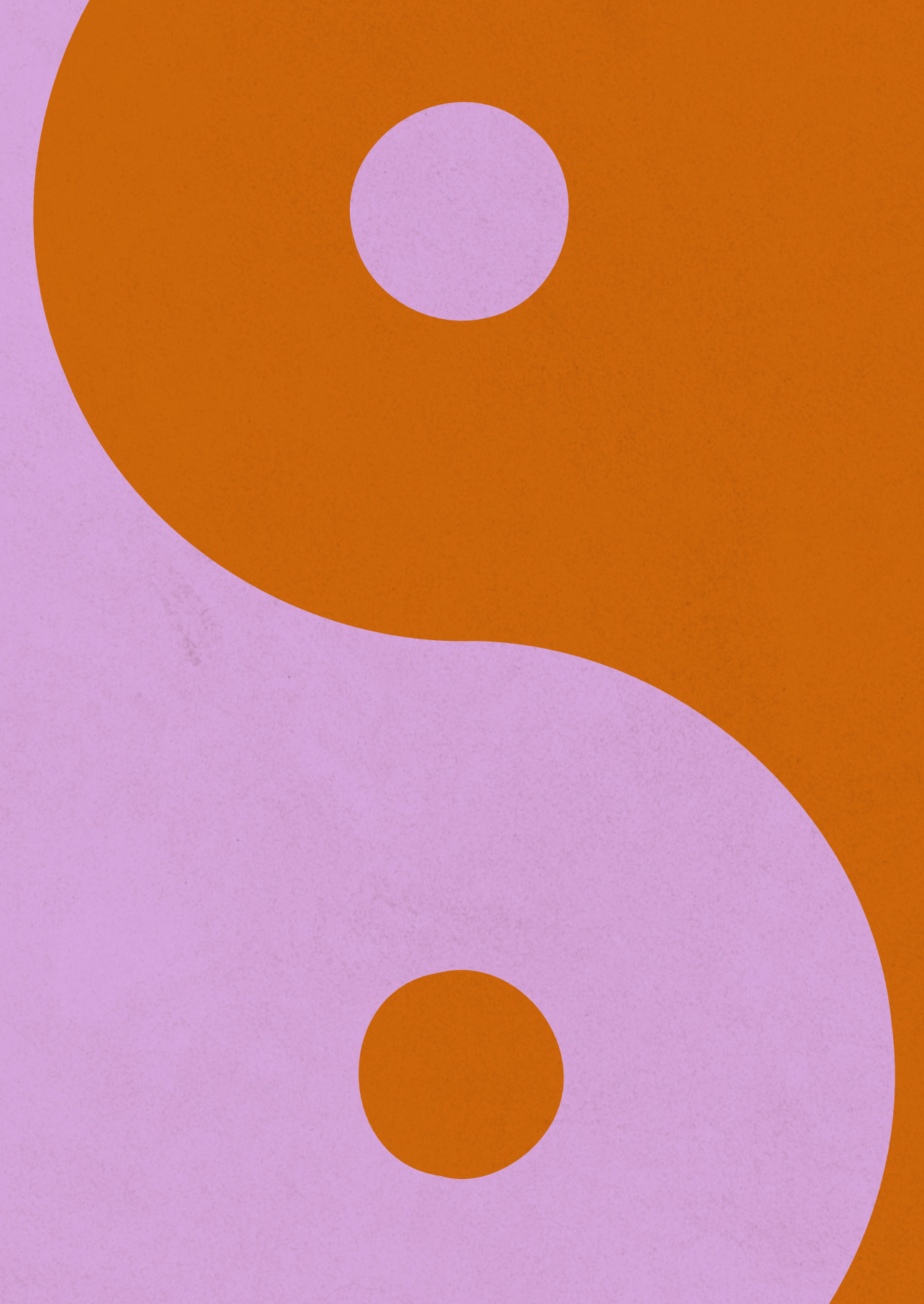
TABLE OF CONTENTS



1

General Introduction and Thesis Outline

Breast Cancer

Breast cancer is, with a ten-year prevalence of 120.000, the most common type of cancer among women in the Netherlands.[1] Approximately 1 in 8 women will develop breast cancer at some point in their life. On average, 87% of the women with breast cancer survive at least 5 years and over 77% survives at least 10 years.[2] Because of improvements in early diagnosis and more efficient therapies, breast cancer becomes more a chronic condition than a life-threatening illness.[3] The treatment for breast cancer is very personalized and depends on tumor subtype, tumor stage, genomic tests, the presence of known mutations in inherited breast cancer genes and patient characteristics. For treating early-stage and locally advanced breast cancer, the general recommendation is breast surgery to remove the tumor, and (neo-) adjuvant treatment depending on the tumor characteristics, such as radiotherapy, chemotherapy, immunotherapy and/or hormonal therapy.[4,5]

Breast Cancer Surgery

Cosmetic results after breast cancer surgery have become increasingly important, partly because of the current favorable life expectancy after breast cancer treatment. While breast cancer surgery has developed over the years, the goals have remained the same: complete removal of the tumor obtaining negative margins, with the least degree of breast deformity. In breast-conserving surgery, the tumor is removed with a safe cancer-free margin and most of the healthy breast tissue is preserved. An oncoplastic procedure may be necessary to obtain an aesthetically pleasant result. Breast-conserving surgery is mostly followed by adjuvant radiotherapy. The alternative is a mastectomy, in which all breast tissue is removed. The breast mound can be restored with an autologous or implant-based breast reconstruction, or a combination of these two procedures.[6] In some cases, adjuvant radiotherapy is necessary following mastectomy to eliminate microscopic disease.

Oncoplastic Breast Surgery

Oncoplastic breast surgery (OPS), which involves plastic surgery techniques to reconstruct the breast after breast-conserving surgery, has gained popularity over the last decades. It optimizes oncological safety and cosmetic outcomes at the same time, combining wide resection margins with the best principles of plastic reconstructive surgery.[6] Therefore, compared to conventional breast-conserving surgery, OPS may be associated with fewer conversions to mastectomy and lower re-excision rates.[7] There are two different approaches for OPS, based on the location of the tumor, the volume of the excised tissue and the size and ptosis of the patient's breast.[8] The volume replacement technique fills up the defect after excision of the tumor with tissue adjacent to the breast. The volume displacement technique uses the remaining tissue of the breast to reconstruct the defect. Volume replacement techniques are islanded or pedicled chest wall

fasciocutaneous perforator flaps, such as the thoracodorsal artery perforator (TDAP) flap and the anterior- or lateral intercostal artery perforator (AICAP or LICAP) flap. These techniques are indicated in patients with small breasts without ptosis. The most used volume displacement technique is the Wise pattern mammoplasty with a variation in nipple areola complex pedicles. For this technique, a larger breast with some degree of ptosis is required.[9-11]

Mastectomy

Despite the rise in the use of breast-conserving surgery, mastectomy remains indicated in a substantial part of patients with breast cancer. In 2020 in the Netherlands, 1372 patients with ductal carcinoma in situ (DCIS) underwent surgery, 67% underwent breast-conserving surgery and 31% a mastectomy. For invasive breast cancer, 10.574 patients underwent breast surgery of whom 65.2% underwent breast-conserving surgery and 34.5% received a mastectomy.[12] In addition, the rates of contralateral and bilateral risk reducing mastectomy procedures have increased substantially.[13, 14] Therefore, studies focusing on improving outcomes of mastectomy remain important.

Over the past decades, less invasive oncological breast surgery has become increasingly popular. Halsted's radical mastectomy, which completely removed the pectoralis major muscle (PM), was replaced by the simple mastectomy, in which the PM was spared and only the pectoral fascia (PF) was removed, with better biomechanical outcomes and fewer postoperative pain.[15-17] The development of skin and nipple-sparing mastectomies and the rise of breast-conserving surgery as an oncologically safe alternative to mastectomy, are the result of a greater focus on long-term outcomes.[17] The majority of those changes are the result of the awareness that more extensive surgery does not always lead to better oncological outcomes and may even harm long-term aesthetic outcomes and quality of life (QoL).

In addition to the realization that more extensive surgery does not always lead to better outcomes, the following question arises: 'is it still necessary to remove the PF during a mastectomy?' Presently, it is common practice to routinely remove the PF during a (skin-sparing) mastectomy to guarantee tumor-free margins. However, the need for this is debatable. The PF is part of the muscular anatomy, instead of the breast glandular tissue. Therefore, other than in extremely rare cases of tumor growth into the PF, the oncological benefit of PF resection seems questionable.[18] In fact, PF preservation may enhance breast reconstructive outcomes and postoperative results. It might reduce seroma formation due to its function in lymph drainage. Furthermore, postoperative bleeding and pain may be decreased by avoiding surgical injury to the PM. In addition, the PF, which is a strong fibro-elastic layer, might improve breast implant coverage.[19, 20] Although the potential advantages of PF preservation seem evident, literature on this topic

is scarce and opinions and surgical techniques differ between surgeons, medical centers and countries.

Implant-Based Reconstruction

Implant-based reconstruction is the most common technique for reconstructing the breast following a mastectomy.[21] It can be performed in two stages or in one stage (direct-to-implant (DTI)). Generally, the reconstruction is performed in two stages. First, a tissue expander (TE) is placed subpectorally at the time of mastectomy, which is replaced by a definitive implant during a second surgery. The alternative is a DTI approach, where the definitive implant is placed immediately, and no second procedure is indicated. However, with DTI reconstructions, it is more challenging to obtain symmetry and complication rates (including infection, skin necrosis, and implant exposure) may be higher, compared to two-stage procedures.[22] Although implant-based reconstruction generally leads to a less natural result compared with an autologous reconstruction, the advantages of implant-based breast reconstructions are the simplicity, safety, and cost-effectiveness without potential donor-site morbidity. Furthermore, the operative time is shorter, the overall recovery is quicker and there is a shorter length of hospital stay.[23, 24]

Among all possible complications, such as surgical site infections (SSI), skin flap necrosis, nipple necrosis, seroma, and hematoma,[25] implant loss is the most serious complication, which is observed after 1.8%-16.9% of all implant-based breast reconstructions. It significantly affects the patient's life in both a physical and emotional manner. Re-operations related to implant loss may cause an important decrease in patient satisfaction and a substantial increase in hospital expenses. It might also postpone the start of additional adjuvant therapy.[26-31]

Several risk factors for implant loss have been identified in the literature over time, such as advanced age, obesity, smoking status, and DTI reconstruction.[27] However, a risk assessment model to improve patient information and decision-making regarding the most appropriate type of mastectomy and reconstruction has not been developed yet and would be of great value for better preoperative counseling.

Aim and Thesis Outline

This thesis aimed to improve patient satisfaction and the postoperative outcomes after reconstructive surgery following breast cancer. **Part I** of the thesis addresses oncoplastic breast surgery and aimed to analyze whether patients are satisfied after oncoplastic breast surgery and whether there are differences between the two techniques in postoperative outcomes and patient satisfaction. Studies in **part II** investigated the evolution of mastectomy techniques and focus on pectoral fascia preservation. This part aimed to provide an answer to the following questions: is pectoral fascia preservation oncologically safe, does it improve

postoperative outcomes and do surgeons actually use this technique in the Dutch practice? **Part III** contains studies concerning implant-based breast reconstruction and aimed to create a validated risk prediction model for implant loss.

Part I – Oncoplastic breast surgery
In **chapter 2**, oncoplastic breast surgery and the postoperative outcomes are discussed. The study focuses on complications, patient satisfaction and cosmetic outcomes. Furthermore, the outcomes of the two different techniques, volume replacement and volume displacement, were analyzed and compared.

Part II – Pectoral fascia preservation in immediate breast reconstruction
Pectoral fascia removal during a mastectomy is still common practice in the Netherlands. **Chapter 3** provides an overview of literature concerning pectoral fascia preservation during a mastectomy, with the main outcomes oncological safety, complication rates, implant loss and cosmetic outcomes. In addition to this topic, **chapter 4** reports on a nation-wide survey on the opinions of Dutch plastic surgeons and breast surgeons regarding pectoral fascia preservation.

Part III – Implant loss in implant-based breast reconstruction
Implant loss is the most feared complication following implant-based reconstructions. Therefore, significant risk factors for implant loss following implant-based reconstructions were identified in **chapter 5** and a multi-center risk model for implant loss was created. The study in **chapter 6** aimed to validate the risk model for implant loss, which was developed in the previous chapter using data from the Dutch Breast Implant Registry (DBIR). The study in **chapter 7** aimed to create a validated risk prediction model for implant loss with DBIR data which would be very useful in decision-making and preoperative counseling for women who consider implant-based reconstruction.

Finally, in **chapter 8,** the main findings and conclusion of this thesis are discussed and suggestions for future research are provided.

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PART

Oncoplastic breast surgery

2

An analysis of complication rates and the influence on patient satisfaction and cosmetic outcomes following oncoplastic breast surgery

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ABSTRACT

Introduction: This study aimed to evaluate complication rates, patient satisfaction and cosmetic outcomes after oncoplastic breast-conserving surgery. Furthermore, outcome differences between volume displacement and volume replacement techniques and the effect of postoperative complications on outcomes were evaluated.
Methods: This was a prospective single-center study addressing patients who underwent oncoplastic breast-conserving surgery from 2017 to 2020. The BREAST-Q was used to measure patient satisfaction and cosmetic outcomes were assessed by patient self-evaluation and panel evaluation based on medical photographs.
Results: A total of 75 patients were included. The overall complication rate was 18.7%, of which 4% required invasive interventions. Median BREAST-Q scores ranged from 56 to 100 and cosmetic outcomes were scored good to excellent in 60-86%. No differences in complications were observed between volume replacement and volume displacement techniques. Following volume displacement techniques, patients reported higher BREAST-Q scores for the domain 'physical well-being of the chest' and lower cosmetic outcomes scores for 'mammary symmetry'. Patients with complications scored significantly lower on several domains of the BREAST-Q and in various cosmetic outcome categories.
Conclusion: In this cohort, an overall complication rate of 18.7% was observed. Patients were generally satisfied and most cosmetic outcomes were good to excellent. Volume displacement or replacement techniques were performed for different indications and generally showed comparable results. Expected differences in physical discomfort and symmetry between both techniques were observed. In addition, the occurrence of complications resulted in lower patient satisfaction and cosmetic outcomes. These findings emphasize the importance of thorough preoperative counselling.

INTRODUCTION

While breast cancer surgery has evolved over the years, the goals have remained the same: complete removal of the tumor acquiring negative margins, with the least degree of breast deformity. The cosmetic results after breast cancer surgery have become increasingly important, partly because of the current favorable life expectancy after breast cancer treatment.[1] Therefore, oncoplastic breast-conserving surgery (OPS) has rapidly gained popularity over the last decade. It optimizes oncological safety and cosmetic outcomes, combining the best principles of surgical oncology with the possibility of larger resection margins with plastic reconstructive surgery.[2] As a result, OPS might be associated with less conversions to mastectomy and lower re-excision rates compared to breast-conserving surgery alone.[3] In addition, breast-conserving surgery plus radiotherapy might even result in an improved survival compared to mastectomy in early breast cancer.[4] By combining OPS with neoadjuvant chemotherapy, leading to preoperative tumor reduction, more patients are eligible for this technique. This implies that OPS can be a cosmetically acceptable alternative to breast-conserving surgery or mastectomy without compromising local oncological safety, even in tumors that are relatively large compared to the breast size.[5, 6]

OPS can be categorized in two different approaches, based on tumor location and excised volume, in combination with the volume and ptosis of the patient's breast.[7] Volume replacement is a technique using tissue adjacent to the breast, to fill up the gap that is left behind after tumor removal. Volume displacement is a technique that uses the remaining breast tissue to fill up the defect.[8] Volume replacement techniques are required in patients with small and non-ptotic breasts. Most suitable techniques are islanded or pedicled chest wall fasciocutaneous perforator flaps like the lateral or anterior intercostal artery perforator flap (LICAP or AICAP)[9] or the thoracodorsal artery perforator (TDAP) flap.[10] For volume displacement, only possible in patients with some degree of ptosis, the Wise pattern mammoplasty using different nipple areola complex pedicles is the most common approach.[11]

The objectives of this study were to assess complication rates, patient satisfaction and cosmetic outcomes after OPS, investigate the influence of complications on patient satisfaction and cosmetic outcomes, and compare these results between volume replacement and volume displacement techniques.

METHODS

Study design

This study was designed as a prospective single center study, including all patients who underwent OPS (volume replacement or volume displacement) for breast cancer between January 2017 and December 2020 at the Alrijne Hospital in the Netherlands.

Ethical considerations

The study protocol was approved by the local institutional ethical review board (N21.053) and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[12, 13]

Surgical technique

All patients were operated by four plastic surgeons. For volume displacement, the Wise or Grisotti technique was used.[11, 14] For volume replacement, the TDAP flap or bilobed swing flap was used.[10, 15]

Complications and definitions

All complications were collected in a prospective manner. Postoperative complications (seroma, hematoma, surgical site infection (SSI), wound dehiscence and necrosis) were graded according to Clavien-Dindo classification (CD).[16] In this study, for grade 1 complications, the normal postoperative course was not deviated and no interventions were necessary. Grade 2 complications required pharmacological treatment with antibiotics. Grade 3 complications required surgical drainage. Clinically relevant postoperative complications were defined as complications with a CD score of 2 or more.

BREAST-Q

Patient reported quality of life and satisfaction was measured with the BREAST-Q breast conserving therapy (BCT) module, which was sent online to all participating patients (Castor EDC). The BREAST-Q is a validated, disease-specific patient reported outcome measure and patient reported experience measure to assess patient satisfaction and health-related quality of life.[17] Responses from each scale were summed and transformed into Q-scores ranging from 0 to 100, with higher numbers representing greater satisfaction or quality of life.

Patient reported cosmetic outcomes

Patients received an online questionnaire for self-assessment of cosmetic outcomes. Participants were asked to provide a score, from 1-4 (1: poor, 2: fair, 3:

good, 4: excellent), for each of the following four categories: mammary symmetry, scarring, areola-nipple symmetry and global judgment. The score and cosmetic categories were derived from previous research.[18] In case the patient underwent a contralateral symmetrization, patients were asked to fill in these questions according to the situation before the symmetrizing surgery. Patients in whom the nipple was excised, the nipple areolar symmetry was not scored.

Panel reported cosmetic outcomes

In accordance with the standard postoperative protocol after breast reconstruction, five-point view medical photographs were made at a minimum of three months after the surgery and uploaded in the patient files. In case these photographs were not present in the patient files, patients were invited for an appointment with the medical photographer. Based on these photographs, cosmetic outcomes were evaluated by a panel consisting of two independent plastic surgeons and two laymen. The members of the panel scored cosmetic outcomes independently and were blinded for any clinical information. All members of the panel were invited to evaluate the breasts in the previously mentioned four categories with a score from 1-4. Patients who underwent a contralateral symmetrization without available photographs before this procedure, were excluded from the analysis. The nipple areolar symmetry was not scored if the nipple was excised during OPS.

Statistical analysis

Continuous variables are presented as median values with interquartile ranges (IQRs) and frequency percentages were calculated for categorical variables. Differences in baseline characteristics between groups were tested with Mann-Whitney U tests, chi-square tests or Fisher's exact tests. Comparisons between volume displacement and volume replacement techniques were performed using the chi-square test for postoperative complications and Mann-Whitney U test for BREAST-Q and cosmetic outcomes. The same tests were performed for comparisons between patients with and without complications. Patients with missing data on (domains of) the BREAST-Q or cosmetic outcomes were excluded from this specific part of the analysis. The level of inter-observer agreement between the two laymen and the two specialists was derived from Cohen's kappa values and defined as follows: 0-0.20 slight agreement, 0.21-0.40 fair agreement, 0,41-0.60 moderate agreement, 0.61-0.80 substantial agreement and 0.81-1 excellent agreement. A two-sided P-value of <0.05 was considered statistically significant. IBM SPSS statistics (version 26) was used for standard statistical analysis.

RESULTS

Patient selection

Between January 2017 and December 2020, a total of 75 patients underwent OPS. Five patients were lost to follow-up and the remaining 70 patients were invited to participate in the BREAST-Q, self-assessment of cosmetic outcomes and panel evaluation of cosmetic outcomes. The BREAST-Q was completed by 52 patients (response rate 74.3%), self-assessment of cosmetic outcomes by 50 patients (response rate 71.4%) and panel evaluation was performed in 40 patients (57.1%).

Study population

The total study population consisted of 75 women with a median age of 61 years (IQR: 52-67 years) and a median BMI of 27 kg/m^2 (IQR: 24.0-30.1 kg/m^2). Volume displacement techniques were used in 74.7% of the patients, involving the Wise pattern (n=54, 96.4%) and the Grisotti technique (n=2, 3.6%). Volume replacement techniques were used in 25.3% of patients, involving the TDAP-flap (n=18, 94.7%) and a bilobed swing (n=1, 5.3%). Follow-up time varied from one to four years.

Baseline characteristics were compared between patients who underwent OPS with volume replacement versus volume displacement. A significant difference (P<0.001) between the groups was found in the tumor location, with 17 out of 19 tumors (90%) located in the cranio-lateral quadrant in the volume replacement group while the tumors were more equally distributed in the volume displacement group. Furthermore, 20 patients (35.7%) in the volume displacement group versus only one patient (5.3%) in the volume replacement group underwent a contralateral symmetrization (P<0.01). In all patients, tumor- and surgical characteristics are depicted in Table 1.

Postoperative complications

Overall, an 18.7% clinically relevant complication rate was found, of which 14.7% had a CD score of 2, and 4% had a CD score of 3. Hematoma and wound dehiscence were reported in one patient (1.3%). Necrosis occurred in two patients (2.7%). An SSI was found in ten patients (13.3%) and led to a CD score of 3 in three patients (4%). No other complications led to a CD score of 3. The presence of seroma never resulted in a CD score of 2 or more.

There was no significant difference in complications between the volume replacement and volume displacement groups. Re-excision rates after OPS were similar in both groups: 5.4% in the volume displacement group and 5.3% in the volume replacement group.

Table 1. Preoperative and surgical characteristics of the total group, volume displacement and volume replacement

Preoperative characteristics	Total (n=75)	Volume displacement (n=56)	Volume replacement (n=19)	*P*-value
Age, years	61.0 (52.0-67.0)	59.5 (52.0-67.0)	62.0 (51.5-68.0)	0.985
BMI, kg/m²	27.0 (24.0-30.1)	27.1 (24.1-30.1)	26.1 (23.8-30.3)	0.950
Cup size				0.339
A,B,C	32 (42.7)	23 (41.1)	9 (47.4)	
D,E,H,F	33 (44.0)	27 (48.2)	6 (31.6)	
Missing	10 (13.3)	6 (10.7)	4 (21.1)	
ASA score				0.492
1	6 (8.0)	5 (8.9)	1 (5.3)	
2	62 (82.7)	47 (83.9)	15 (78.9)	
3	7 (9.3)	4 (7.1)	3 (15.8)	
Comorbidity	57 (76.0)	41 (73.2)	16 (84)	0.535
Current smoker	6 (8.0)	3 (5.4)	3 (15.8)	0.166
Tumor focality				1.000
Unifocal	62 (82.7)	46 (82.1)	16 (84.2)	
Multifocal	13 (17.3)	10 (17.9)	3 (15.8)	
Tumor size combined, mm	25 (20.5-35.0)	24.5 (19.5-34.0)	25.0 (23.0-33.5)	0.609
Location tumor 1				*<0.001*
Cranial	5 (6.7)	5 (9)	0 (0)	
Craniomedial	8 (11)	8 (15)	0 (0)	
Craniolateral	29 (39)	12 (22)	17 (90)	
Caudal	4 (5)	4 (7)	0 (0)	
Caudolateral	9 (12)	8 (15)	1 (5)	
Caudomedial	11 (15)	11 (20)	0 (0)	
Retro-areolar	1 (1)	1 (20)	0 (0)	
Medial	7 (10)	6 (11)	1 (5)	
Location tumor 2				0.118
Craniomedial	2 (15.4)	2 (20)	0 (0)	
Craniolateral	4 (30.8)	1 (10)	3 (100)	
Caudal	1 (7.7)	1 (10)	0 (0)	
Caudolateral	1 (7.7)	1 (10)	0 (0)	

Table 1. Continued

Preoperative characteristics	**Total (n=75)**	**Volume displacement (n=56)**	**Volume replacement (n=19)**	***P*-value**
Caudomedial	1 (7.7)	1 (10)	0 (0)	
Medial	4 (30.8)	4 (40)	0 (0)	
Neoadjuvant chemotherapy	18 (24.0)	12 (21.4)	6 (31.6)	0.370
Neoadjuvant hormone therapy	3 (4.0)	3 (5.4)	0 (0.0)	0.567
Contralateral symmetrization	21 (28.0)	20 (35.7)	1 (5.3)	*0.011*
Surgical characteristics	**Total (n=75)**	**Volume displacement (n=56)**	**Volume replacement (n=19)**	***P*-value**
Operative time, min	108 (90-129)	105 (89-126)	117 (103-136)	0.061
Weight resected specimen, gram	84 (46-102)	80 (45-94)	98 (46-135)	0.469
Reduction weight, gram	-	147 (45-305)	-	
Sentinel node	67 (89.3)	51 (91)	16 (84)	0.360
Adjuvant radiotherapy	70 (93.3)	52 (95)	18 (95)	1.000
Adjuvant chemotherapy	20 (26.7)	17 (30)	3 (16)	0.249
Adjuvant hormone therapy	40 (53.3)	30 (54)	10 (53)	1.000

Data are n (%) or median (IQR). Significant P-values are denoted in italic. ASA indicates American Association of Anesthesiologists; BMI, body mass index; DCIS, ductal carcinoma in situ.

BREAST-Q questionnaire

Fifty-two patients completed the BREAST-Q questionnaire. Of these patients, only 34 (65.4%) filled out the domain 'sexual well-being'. The domains 'satisfaction with breasts', 'satisfaction with information about the surgery' and 'satisfaction with plastic surgeon' were filled out by 51 patients (98.1%). Al other domains were fully completed. The median time from surgery until completion of the BREAST-Q was 28 months (IQR: 16-39 months).

The BREAST-Q scale scores were compared between OPS with volume replacement and volume displacement. Women who underwent volume displacement techniques reported significantly higher scores for 'physical well-

being of the chest', than patients who underwent volume replacement techniques (median 63 vs 38, P=0.003). Scores in all other domains were comparable. All the results for the BREAST-Q questionnaires are shown in Table 2. BREAST-Q scores of patients with and without complications were compared. Patients without complications had significantly higher scores in the domain 'satisfaction with the breast' and 'satisfaction with information about the surgery', compared to patients with complications (median 65 (IQR: 56-78) vs 56 (IQR: 43-53), P=0.007 and median 71 (IQR: 64-100) vs 55 (IQR: 46-78), P=0.026, respectively). In the other domains, no significant differences were seen.

Table 2. Q scores BREAST-Q BCT domains for total cohort and stratified for volume replacement and volume displacement.

Domain	Total	Volume replacement	Volume displacement	P-value
Psychosocial well-being	63 (51-71)	64 (49-73)	56 (53-66)	0.453
Sexual well-being	56 (46-66)	58 (45-68)	56 (50-66)	0.838
Satisfaction with breasts	65 (55-74)	63 (55-70)	65 (54-83)	0.410
Physical well-being: chest	56 (38-66)	63 (45-71)	38 (20-53)	*0.003*
Satisfaction with information surgery	71 (59-91)	76 (64-96)	64 (49-76)	0.074
Satisfaction with plastic surgeon	100 (82-100)	100 (86-100)	87 (75-100)	0.173

Data are depicted in median and IQR. Significant P-values are denoted in italic.

Patient self-assessment of cosmetic outcomes

Fifty patients completed the self-assessment questionnaires for cosmetic outcomes. The individual global aesthetic judgment scores are presented in Table 3. A poor score was reported by two patients (4%), fair by five patients (10%), good by 18 patients (36%) and an excellent score by 25 patients (50%). This resulted in a median global aesthetic judgment score of 3.5. Scarring and areola-nipple symmetry scored 3.0, and breast symmetry scored 2.5.

No significant difference was found between patients who underwent OPS with volume replacement versus volume displacement techniques (Table 4). Self-assessment scores in patients with and without complications were compared, showing a significantly higher score for symmetry in patients without complications (median 3.0 (IQR: 2.0-4.0) vs 1.0 (IQR: 1.0-2.0), P=0.001). In the other categories, no significant differences were observed.

Panel evaluation of cosmetic outcomes

In 40 patients medical photographs could be obtained that were amenable for panel evaluation, with a median postoperative time of 16 months (IQR: 8-43).

Medical photographs were taken within the first postoperative year in 13 out of 30 patients (43%) and in three out of ten patients (30%) in the displacement and replacement group, respectively (P=0.456). Global aesthetic judgment scores distributed in the categories poor, fair, good and excellent are summarized in Table 3. The median scores by the specialists and laymen for global aesthetic judgment, symmetry of the breast, scarring, and areola-nipple symmetry are presented in Table 4.

Table 3. Individual global aesthetic judgment scores, categorized as poor, fair, good and excellent, by patients and panel.

	Patient (n=50)	**Plastic surgeon 1 (n=40)**	**Plastic surgeon 2 (n=40)**	**Laymen 1 (n=40)**	**Laymen 2 (n=40)**
Poor	2 (4.0)	3 (7.5)	2 (5.0)	5 (12.5)	10 (25.0)
Fair	5 (10.0)	6 (15.0)	7 (17.5)	11 (27.5)	5 (12.5)
Good	18 (36.0)	21 (52.5)	19 (47.5)	17 (42.5)	14 (35.0)
Excellent	25 (50.0)	10 (25.0)	12 (30.0)	7 (17.5)	11 (27.5)

Data are n (%).

Table 4. Cosmetic outcomes for patients, plastic surgeons and laymen in the four categories.

	Total	**Volume replacement**	**Volume displacement**	***P*-value**
Patient	N=50	N=12	N=38	
Global aesthetic judgment	3.50 (3.00-4.00)	3.00 (3.00-4.00)	4.00 (3.00-4.00)	0.500
Symmetry	2.50 (1.00-4.00)	3.00 (2.00-4.00)	2.00 (1.00-3.00)	0.246
Scar	3.00 (3.00-4.00)	3.00 (2.00-4.00)	4.00 (3.00-4.00)	0.120
Areola-nipple symmetry*	3.00 (2.50-4.00)	4.00 (2.50-4.00)	3.00 (2.00-4.00)	0.379
Specialist	N=40	N=10	N=30	
Global aesthetic judgment	3.00 (2.50-3.50)	3.00 (2.50-3.50)	3.00 (2.50-3.50)	1.000
Symmetry	2.50 (2.00-3.00)	3.00 (2.50-3.50)	2.50 (2.00-3.00)	*0.020*
Scar	3.00 (3.00-3.50)	3.00 (3.00-4.00)	3.00 (3.00-3.50)	0.939
Areola-nipple symmetry**	3.00 (2.50-3.50)	3.50 (3.00-4.00)	3.00 (2.50-3.50)	0.053
Laymen	N=40	N=10	N=30	
Global aesthetic judgment	2.75 (2.00-3.50)	2.75 (2.00-3.50)	2.75 (2.00-3.50)	0.866
Symmetry	2.50 (1.00-3.00)	3.00 (2.50-3.50)	1.75 (1.00-3.00)	*0.031*
Scar	3.00 (2.00-3.50)	2.25 (1.50-3.00)	3.00 (2.00-3.50)	0.221
Areola-nipple symmetry**	2.75 (2.00-3.50)	3.00 (2.50-3.50)	2.50 (2.00-3.50)	0.241

Numbers are median (IQR). For areola-nipple symmetry, numbers are lower than mentioned in the 'total' column because of exclusion criteria. *47 patients, 12 volume replacement, 35 volume displacement. ** 36 patients, 10 volume replacement and 26 volume displacement. Significant P-values are depicted in italic.

The inter-observer agreement between laymen was fair to moderate, with a significant kappa value of 0.288, 0.478 and 0.372 for global aesthetic judgment, symmetry of the breast and scarring respectively. The agreement between specialists was also fair to moderate, with a kappa of 0.497, 0.236 and 0.357 for global aesthetic judgment, symmetry of the breast and scarring respectively. No significant agreement for areola-nipple symmetry was observed.

Subgroup analysis between patients who underwent OPS with volume replacement versus volume displacement is presented in Table 4, showing a significantly higher symmetry score in the volume replacement group, according to the specialist and the laymen (median 3.0 vs 2.5 (P=0.020) and median 3.0 vs 1.75 (P=0.031) respectively). Cosmetic outcomes scored by the panel in patients with and without complications were compared. The laymen provided a significantly higher score for global aesthetic judgment in patients without complications (median 3 (IQR: 2.0-3.5) vs 2 (IQR: 1.0-3.0), P=0.046). The specialists provided a significantly higher score for symmetry in patients without complications (median 2.5 (IQR: 2.0-3.0) vs 2.5 (IQR: 1.5-2.0), P=0.002). In the other categories, no significant differences were observed.

DISCUSSION

In this study, postoperative complication rates, patient-reported outcomes and cosmetic outcomes were evaluated after OPS with volume displacement or volume replacement techniques, as well as the influence of the occurrence of complications on these outcomes. An overall clinically relevant complication rate of 18.7% was found in this study. Overall, patients were satisfied after their surgery. Cosmetic outcomes were scored as good to excellent by both patients and the panel in 60-86%. These results emphasize that OPS should be considered in eligible patients planned for oncological breast surgery.

The occurrence of complications following breast surgery has a major impact on the patient's life[19, 20] and oncological treatment, as it might delay the start of adjuvant chemo or radiotherapy.[21, 22] The current literature shows several studies about complication rates after OPS. However, these studies used various or no complication scoring systems and studies about the influence of complications on patient satisfaction are limited. Mattingly et al reported a total complication rate of 33.9% of which in 20.3% an intervention was required,[23] in contrast to the substantially lower percentage of 4%, found in this current study. The study of Kronowitz et al reported a complication rate of 24% after immediate reconstructions, however, the severity of complications was not specified.[24]

Patient satisfaction is considered an important outcome measure following OPS, which was evaluated with the BREAST-Q BCT module in this study. In all domains, scores were above average. The lowest scores were found in the domains 'sexual well-being' and 'physical well-being of the chest', both with a median score of 56, with 'sexual well-being' having a lower response rate (65.4%). This is similar to the findings in the study by Rose et al,[25] where they compare BREAST-Q outcomes after OPS and breast-conserving surgery. Overall, patients were satisfied with their breasts and with psychosocial well-being, with a median score of respectively 65 and 63 in these domains. However, other studies on this topic showed better outcomes as compared to this present study.[26, 27] Yet, there are notable differences compared to our study: patients were either younger, various types of reconstructions were included or small breasts (cup B or smaller) were excluded.

When evaluating global aesthetic judgment, patients were satisfied with a score from fair to excellent in 96%, which was 75-95% by panel evaluation. This was in line with a study by Clough et al,[28] in which a panel used a similar grading system to evaluate cosmetic outcomes of 101 breast cancer patients who underwent OPS with volume displacement, at two and five years follow-up 88% and 82% scored fair to excellent.

The baseline comparison between volume replacement and volume displacement, showed significant differences in the location of the tumor and in contralateral symmetrizations. This was expected as the volume replacement technique is most often used in patients with smaller breasts and laterally located tumors, where adjacent tissue is used to fill the defect, leading to little asymmetry without the need for contralateral symmetrizations. No differences in complications were found between the groups. After volume replacement a lower score in the BREAST-Q domain 'physical well-being of the chest' (median score 38 vs 63) was reported, which is probably due to the more extensive surgery and the donor site morbidity, compared to the displacement group. As expected, subgroup analysis showed a significant higher score of mammary symmetry in the volume replacement group (median 2.8 vs 2.2, P=0.048).

Outcomes of patients with and without clinically relevant complications were compared. BREAST-Q results showed that patients with complications were less satisfied with the breast and with the information about the surgery. The need for adequate preoperative information was emphasized in previous research in which patients after failed breast reconstructions were interviewed.[29] As for cosmetic outcomes, patients with complications had lower mammary symmetry scores, reported by the patients and specialists, and lower global aesthetic judgment scores, reported by the laymen. Presented results imply that complications have a negative impact on patient satisfaction and on the cosmetic outcomes after

OPS. This is in line with recent research, including 1871 breast cancer patients after various procedures in which the EQ-5D questionnaire was used to value the effect of surgical complications. This study showed that complications resulted in poorer health-related quality of life.[30] Furthermore, complications leading to inferior cosmetic outcomes were expected, as they may lead to skin retractions contributing to asymmetry or a lower global aesthetic judgment, even though the expected influence on scarring was not found.

There are several limitations of this study. First of all, the data were obtained in one study center, and may not be generalizable to the oncoplastic reconstructive population at large. Second, patients completed the BREAST-Q at variable time points after surgery, which could lead to recall bias, especially for the patient reported experience measures. Furthermore, no preoperative BREAST-Q was available for comparison. Third, patient reported cosmetic outcomes and the cosmetic panel evaluation were assessed at different time points and no explanation of the given score was obtained. Fourth, general quality of life, next to breast related quality of life, was not assessed in this study. Finally, the small sample size and limited number of available postoperative photographs (57.1%) resulted in the inability to accurately assess for confounding, such as patient characteristics, surgical characteristics and adjuvant therapies. Future studies, preferably with a larger sample size and multicenter design, should implement both BREAST-Q and medical photographs in a standard protocol, involving more frequent and fixed time points.

In conclusion, postoperative complications were observed in 18.7% of patients after OPS, which required (surgical) intervention in only in 4%. No differences in complication rates were observed between techniques. Furthermore, 60-86% of cosmetic outcomes were scored good to excellent, in which patients given the highest scored followed by the plastic surgeons and laymen. Volume displacement or replacement was performed for different indications and generally showed comparable results. Expected differences in physical discomfort and symmetry between both techniques were observed. The occurrence of complications resulted in lower BREAST-Q scores and cosmetic outcome scores. Ultimately, these insights could be used to thoroughly counsel patients by using information from patient, specialist and laymen experience.

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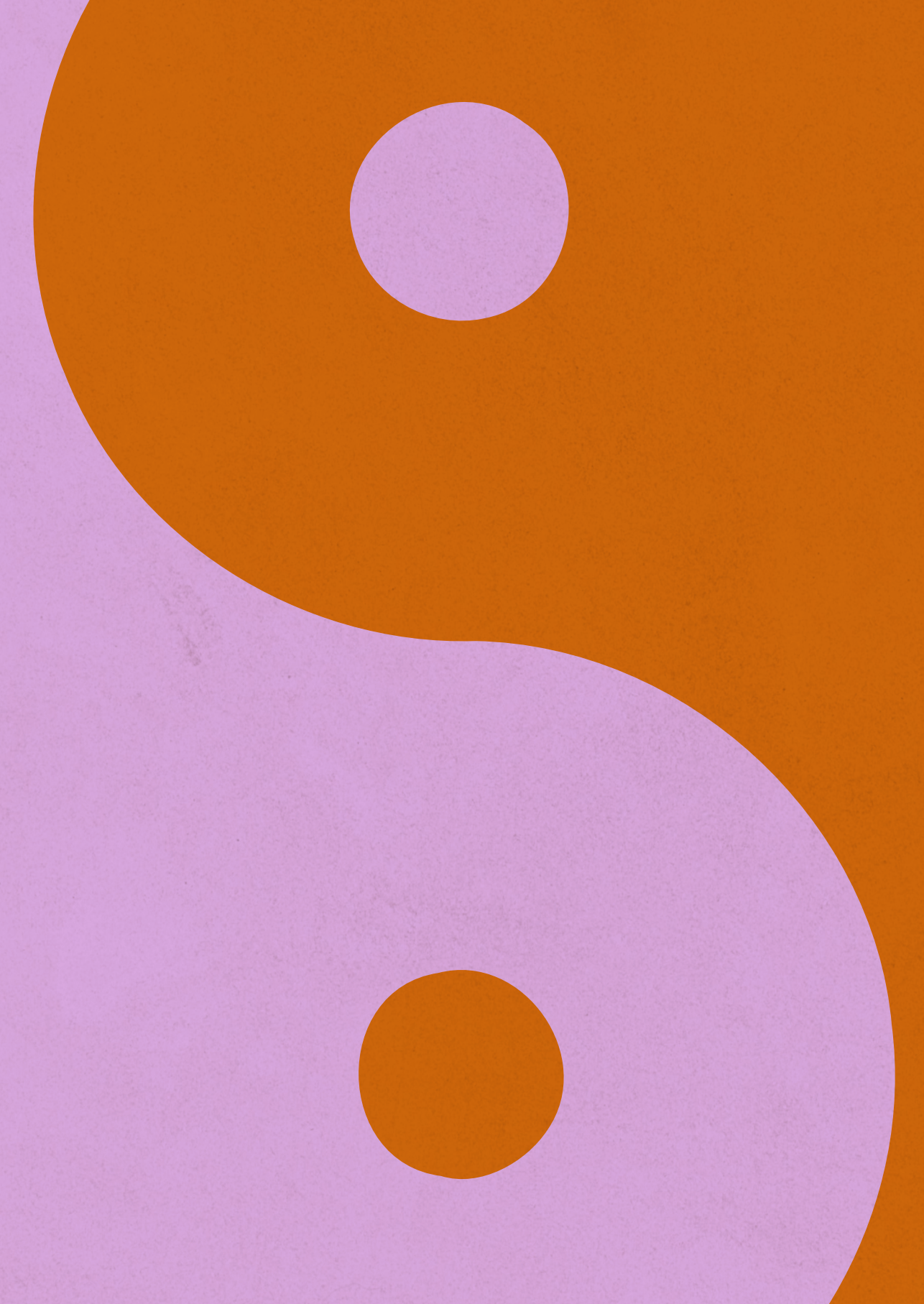
PART

Pectoral fascia preservation in immediate breast reconstruction



3

Pectoral fascia preservation in oncological mastectomy to reduce complications and improve reconstructions: a systematic review

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ABSTRACT

Introduction: Excision of the pectoral fascia (PF) is routinely performed in oncological mastectomies. Preservation of the PF may however decrease postoperative complication rates for bleeding, infections and seroma. It may also improve reconstructive outcomes by better prosthesis coverage, thereby reducing implant extrusion rates and improving cosmetic outcomes.
Methods: A systematic review according to the PRISMA principles was performed. Studies describing PF preservation were searched in three databases. All studies including more than ten patients were included. The main outcomes were oncological safety (local recurrence, regional and distant metastases, mortality rates), complication rates (bleeding, infections, seroma), loss of the prosthesis after reconstructive surgery, and cosmetic outcomes following reconstruction.
Results: Five studies were included. Three reported on two different randomized controlled trials (n=73, and n = 244), two studies were retrospective case series (n=203, and n=256). PF preservation did not affect oncological outcomes in terms of local recurrences, regional and distant metastases, nor mortality rates. One study described a significantly lower incidence of seroma in the PF preservation group. No differences were found for bleeding complications and infections. No objective data were provided for reconstructive complications nor cosmetic outcomes.
Conclusions: The literature on PF preservation is scarce. Based on the current evidence, PF preservation seems oncologically safe while potentially reducing postoperative complication rates. It is expected that reconstructive outcomes will benefit from PF preservation, but these studies lack evidence on this topic. Future studies should provide insight into all aspects of PF preservation.

INTRODUCTION

Over the past decades, there has been a tendency toward less extensive oncological breast surgery. Mastectomy procedures changed from Halsted's radical mastectomy, including removal of the pectoralis major muscle (PM) toward the simple mastectomy, in which the PM was preserved and only the pectoral fascia (PF) was resected. This resulted in less postoperative pain and better biomechanical outcomes.[1-3] Increased focus on long-term outcomes subsequently led to the introduction of skin and nipple sparing mastectomies, as well as the emergence of breast-conserving surgery as an oncological equivalent alternative for mastectomy in many cases. Furthermore, the axillary lymph node dissection has been largely replaced by the sentinel node procedure.[3-5] Most of these changes are driven by the realization that more extensive surgery does not necessarily result in better oncological outcomes, and may worsen long-term cosmetic results and quality of life (QoL).

Removal of the PF is still widely performed in the Modified Radical Mastectomy (MRM) and simple mastectomy. However; the necessity of this procedure is questionable. The PF is part of the muscular anatomy instead of the breast glandular tissue, and therefore, it seems theoretically of no oncological benefit to excise the PF except in those cases of tumor invasion in the PF. There is a strict adherence of the PF to the underlying PM. No separating epimysium is present between the PF and the PM, in contrary to the deep fascia in many other body parts (limbs, thoracolumbar fascia, rectal sheet and neck fasciae).[6] The PF and PM should therefore be viewed as one myofascial unit in which the PF has a role in proprioception, due to its many nerve endings. Therefore, excision of the PF is both from a functional and surgical technical point of view not the most obvious choice. [7, 8]

It is hypothesized that preservation of the PF has several advantages. It may reduce postoperative bleeding complications by preventing injury to the PM itself. Studies showed that 50% of postoperative bleeding requiring reoperation following mastectomy originated from the PM.[9] Furthermore, PF preservation may decrease postoperative seroma formation due to its function in lymph drainage.[10] From a reconstructive point of view, the strong fibro-elastic layer, although thin (mean thickness 151 µm ± 37), can be a valuable aid in implant coverage.[8] The previously described subfascial breast reconstructions that have been applied emphasize the strength of the PF as an extra layer covering the breast implant.[11, 12]. PF preservation may therefore reduce the rates of postoperative implant extrusion. Previous studies even described the use of the PF in the mediocaudal lower pole to improve projection making direct-to-implant reconstruction possible

instead of 2-stage breast reconstruction.[7, 13] PF preservation may thereby expand reconstructive possibilities and improve cosmetic outcomes

A systematic review of the literature was initiated to evaluate the current evidence for PF preservation. The main outcome measures were oncological safety, postoperative complications such as bleeding and seroma, reconstructive complications and cosmetic outcomes.

METHODS

Search Strategy

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (www.prisma-statement.org). A comprehensive search was performed in the bibliographic databases PubMed, Embase.com and Wiley/Cochrane Library in collaboration with a medical librarian. Databases were searched from inception up to March 26, 2018. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Mastectomy," "Breast amputation," "Breast ablation," "Fasciectomy," "Fascia," and "Pectoral." The search was performed without date, language or publication status restriction. Duplicate articles were excluded. Cross-reference check was also performed on screened full-text articles.

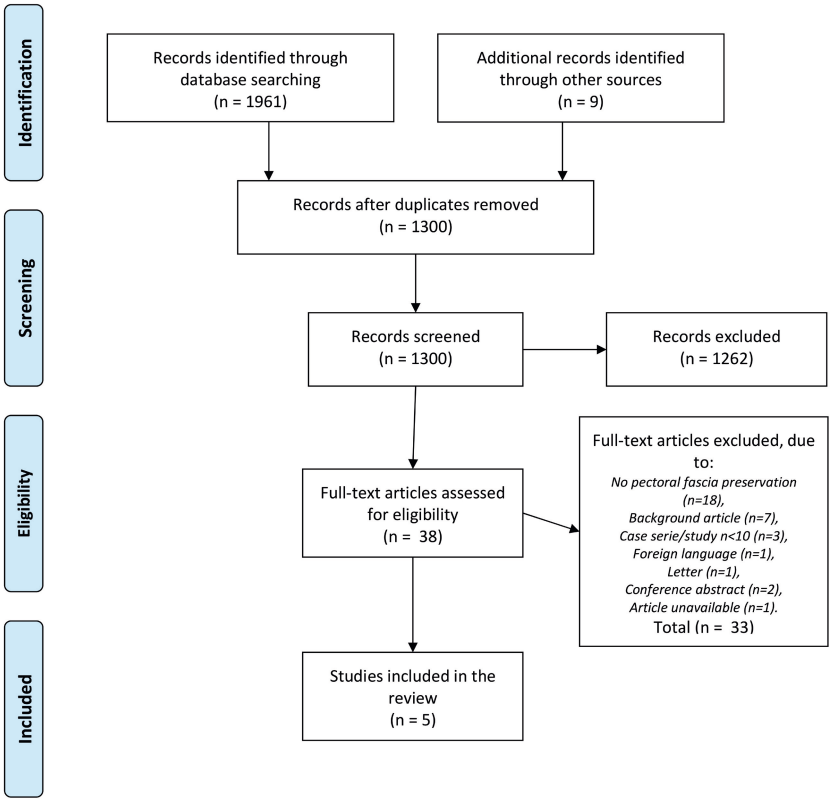
Study Selection

Two researchers used the blinded mode on rayyan.org, the systematic review web app, to identify all prospective and retrospective studies on PF preservation, regardless of whether or not a control group was made. Only studies written in English were included. Studies that did not describe preservation of the PF in relation to complications or oncological outcomes were excluded. Case reports, case series with less than 10 patients, letters and reviews were excluded as well. All articles for which no consensus on exclusion or inclusion was reached initially were discussed. When no agreement was reached, the final decision was made in consultation with the third (senior) author. Details for the flow diagram of studies in this review are presented in Figure 1.

Outcomes

Oncological outcomes of interest were local recurrences, regional recurrences, distant metastasis and mortality. Local recurrence was defined as the recurrence of malignant cells in the scar, in the skin surrounding the scar or on the chest wall after complete initial tumor removal. Regional recurrences, or regional metastases, were defined as metastases located in the ipsilateral axillary lymph nodes, internal mammary nodes or infraclavicular nodes. Distant metastases were all tumor

Figure 1. Flow Chart according to the PRISMA principles describing the selection process of this Systematic Review of the literature towards pectoral fascia preservation in oncological mastectomy.



depositions located further away or not included in those defined as local or regional.

Complications of interest were post-operative bleeding, especially those cases requiring reoperation, seroma formation, infectious complications for which antibiotics were started or adjacent surgeries were required, and implant extrusion. Seroma formation was defined as any clinically detected collection of fluid anywhere along the skin incisions leading to discomfort.

The cosmetic appearance of the breast after reconstruction as assessed by the surgeon was evaluated as well.

RESULTS

Study and patient characteristics

A total of 1961 articles were identified. Nine possibly relevant articles were identified by cross-reference check. After removal of duplicates 1300 articles remained, and 38 were found to be possibly relevant after screening titles and abstracts. These 38 manuscripts were assessed for eligibility, of which five articles were included. (Figure 1; Table 1)

Three articles reported outcomes of two Randomized Controlled Trials (RCT's).[10, 14, 15] Two of those concerned the RCT reported by Dalberg *et al*, with different lengths of follow up.[14, 15] In this study n=244 female patients were randomized to either mastectomy with PF preservation (n=123) or PF removal (n=121). Patients were with invasive breast cancer (n=227 / 91.9%) or DCIS (n=20 / 8.9%) aged 75 or younger and requiring a mastectomy were included. Exclusion criteria were inflammatory breast cancer or a tumor located close to the PF clinically or on mammogram.

Table 1. Study and patient characteristics of the five included studies.

Study Reference	Study Type	Country	No. patients	Age Mean (SD)	No. mastectomies	Invasive carcinoma N (%)
Dalberg, 2004	RCT	Sweden	247	58.1 (-)	247	227 (91.9%)
Dalberg, 2010	RCT	Sweden	244	58.2 (-)	244	224 (91.8%)
Abdelhamid, 2017	RCT	Egypt	73	56.7 (-)	73	73 (100%)
Sandelin, 2004	Retro-spective	Sweden	203	- (-) *Median (range) 48 (23-70)*	203	203 (100%)
Salgarello, 2011	Retro-spective	Italy	220	47.5 (-) *(range) (25-72)*	256	234 (91.4%)

PF: pectoral fascia. SD: Standard deviation.
* 40% had no indication for total axillary lymph node dissection after sentinel node procedure. Therefore the 140 (60%) that underwent total axillary lymph node dissection are expected to be the number of patients with positive lymph nodes.

This 'close relationship to the PF' was not further specified. Median follow up was 11 years (10-14 years). This study was a cross trial in which randomization for PF preservation versus PF removal also was randomized between short (1 day) or long (multiple days) axillary drainage. For the oncological outcomes, presented in both publications, the most recent publication was used.[15] The first publication was used for data on complications, because those were not reported in the most recent article.[14]

The other RCT was reported by Abdelhamid *et al*, in which a total of 73 women with Grade 1 or 2 breast cancer were randomized into mastectomy with PF preservation or PF removal. The total follow up was median 41 months (34-48 months). No data were provided for regional recurrences, distant metastasis, nor mortality rates.[10]

Two of the included articles were retrospective case series.[13, 16] Sandelin *et al* described a total of 203 patients who received a mastectomy with PF preservation for ductal carcinoma (n=113, 56%), lobular carcinoma (n=21, 10%) or invasive (ductal or lobular) in combination with DCIS (n=69, 34%). No patients with inflammatory carcinoma were included. All underwent a standard or skin-sparing mastectomy

Positive lymph nodes N (%)	**Inflammatory carcinoma included**	**Carcinoma invading or close to PF included**	**Minimal tumor to fascia distance (mm)**	**Follow up (years)** **Median (range)**	**Comments**
116 (51.1%)	No	No	-	>5 (-)	Cross trial 2x2 in which also was randomized for drain duration.
115 (51.3%)	No	No	-	11 (10-14)	Long-term outcomes of same group as RCT Dalberg 2004
41 (56.2%)	No	No	5	- (2.8-4.0) *Mean 3.4*	
61 (30.0%)	No	No	-	> 5 (-)	
140 (60%)*	No	-	-	2.4 (0.3-5)	

followed by reconstruction, either with Tissue Expander (TE), permanent implants or transverse rectus abdominis muscle (TRAM) flap autologous reconstruction. The follow up time was at least five years.[16]
Salgarello *et al* reported the results of 220 patients receiving 256 mastectomies with PF preservation. All patients received an immediate one-stage reconstruction with a definitive prosthesis by using the PF to cover the prosthesis in the lower pole. Tumor types were either invasive breast cancer (n=234, 91.5%) or DCIS (n=22 (8.5%). The length of the follow-up was relatively short with a mean of 29 months (range 3 months – 5 years).[13]

Oncological outcomes
In the RCT of Dalberg *et al,* chest wall recurrences occurred in 18 patients (14.6%) in the PF preservation group, compared to 10 patients (8.3%) in the PF removal group, which was not statistically significant (p=0.12). No significant difference (p=0.82) in regional recurrences was observed, with seven (5.7%) regional recurrences in the PF preservation group versus eight (6.6%) in the PF removal group. No difference (p=0.61) in the occurrence of distant metastasis was observed with 39 (31.7%) in the PF preservation group versus 35 (28.9%) of n=121 patients in in the PF removal group, and mortality rates were similar as well (43.1% *versus* 38.8% respectively, p=0,47, Table 2).[15]

There were no local recurrences in both groups in the RCT by Abdelhamid *et al*.[10]
In the retrospective study of Sandelin *et al*, locoregional recurrences were reported in 13 of 203 patients (6.4%), of which nine (4.4%) were chest wall recurrences, and 4 (2.0%) were regional recurrences. Distant metastases were reported in six patients (3%). Thirty-one patients (15.4%) died due to advanced breast cancer.[16]

Table 2. Oncological outcomes in the five included studies.

Study Reference	**Local recurrence**			**Regional recurrence**		
	PF preservation	PF removal	P-value	PF preservation	PF removal	P-value
Dalberg, 2004	n=16 (12.8%)	n=8 (6.6%)	P=0.09	n= 8 (6.4%)	n= 8 (6.6%)	p=0.99
Dalberg, 2010	n=18 (14.6%)	n=10 (8.3%)	P=0.12	n= 7 (5.7%)	n= 8 (6.6%)	P=0.82
Abdelhamid, 2017	n=0 (0.0%)	n=0 (0.0%)	P=1.0	-	-	-
Sandelin, 2004	n=9 (4.4%)	-	-	n=5 (2.5%)	-	
Salgarello, 2011	N=2 (1.1%)	-	-	-	-	-

PF: pectoral fascia.

Salgarello *et al* reported two chest wall recurrences (1.1%). No data on regional recurrences, distant metastasis, nor mortality rates were provided.[13]

Complications

Postoperative bleeding

Information on bleeding complications was provided in two publications.[13, 16] In the study of Sandelin *et al*, only the bleeding complications that required reoperation were reported, being 2 of n=188 patients (1.1%) who underwent implant reconstruction, and 3 of n=13 patients (23.1%) who underwent TRAM flap reconstruction, in which the location of the bleeding was not further specified.[16] Salgarello *et al* reported the presence of postoperative hematoma in six of 256 (2.7%) mastectomies, of whom four (1.8%) required reoperation (Table 3).[13]

Seroma

Occurrence of seroma was compared between the two mastectomy groups in the trial by Dalberg *et al*, in which seroma was defined as any clinically detected collection of fluid requiring aspiration in the axilla or anywhere along the skin incisions. Data on the occurrence of seroma were collected in 198 of the total of 244 patients in this trial. Of those in the PF preservation group 31 out of 100 patients (31%) developed seroma, versus 39 out of 98 patients (39.8%) in the PF removal group. This difference was not statistically significant (p=0.20).[14] Abdelhamid *et al* reported a significant reduction of the incidence of seroma in the PF preservation group (5.6% vs 24.3%, p=0.025).[10] In the study by Salgarello *et al* three seromas were reported (1.3%).[13] However, the definition of seroma was not provided in both studies. The report by Sandelin *et al* did not report on occurrence of seroma.[16]

Metastasis			**Mortality**		
PF preservation	PF removal	P-value	PF preservation	PF removal	P-value
n=30 (24.0%)	N=28 (23.0%)	P=0.73	n=35 (28.0%)	n=28 (23.0%)	p=0.37
n= 39 (31.7%)	n= 35 (28.9%)	P=0.61	n=53 (43.1%)	n=47 (38.8%)	P=0.47
-	-	-	-	-	-
-	-	-	N=31 (15.4%)	-	-
-	-	-	-	-	-

Table 3. Occurrence of complications in four studies reporting on complications.

Study Reference	Seroma			Postoperative bleeding		
	PF preservation	PF removal	P-value	PF preservation	PF removal	P-value
Dalberg, 2004	n= 31* (31.0%)	n= 39* (39.8%)	p=0.20	-	-	-
Abdelhamid, 2017	n=2 (5.6%)	n=9 (24.3%)	P=0.025	-	-	-
Sandelin, 2004	-	-	-	N=2 (1.1%)**	-	-
Salgarello, 2011	n=3 (1.3%)	-	-	n=6 (2.7%)	-	-

PF: pectoral fascia.
*measured in the part of the total study sample also enrolled in the drainage trial. In the drainage trial patients were randomized between axillary drainage <24 hours regardless of drain production (n=99) or drainage until drain production <40cc/24u (n=99).
**measured in the n=188 with implant reconstruction. The n=13 with TRAM reconstruction were left out of this table since it is impossible to know if complications are due to the mastectomy or TRAM reconstruction based on the current information provided.

Infectious complications

Infectious complications were reported in two of the five included articles.[13, 16] In the report by Sandelin *et al*, five patients (2.7%) developed an infection, resulting in three cases (1.6%) of implant removal.[16] Salgarello reported thirteen wound infections (6.4%). In two cases (0.9%) reoperation with implant removal was required.[13]

Reconstructive outcomes

Reconstructive outcomes were described in the retrospective case series by Salgarello *et al.*[13] These outcomes were not standardized, but based on the operator and other surgeons' perception of the cosmetic result. The reconstructive outcomes of all immediate reconstructions with a definitive prosthesis were found to be very good or good in 78.6%, acceptable in 14.0% and poor in 7.3% of all cases. In 12 cases (5.4%) additional surgery was necessary to improve cosmetic results. Abdelhamid *et al* mentioned an improved aspect of the skin flaps after fascia preservation, but these statements were not based on any objective data.[13]

DISCUSSION

This systematic review was performed to provide a comprehensive overview of the current literature concerning preservation of the fascia over the PM. Relevant outcomes were assessed, including oncological outcomes, complications and

Infection			**Skin slough/necrosis**		
PF preservation	PF removal	P-value	PF preservation	PF removal	P-value
-	-	-	-	-	-
-	-	-	-	-	-
N=5 (2.7%)**	-	-	-	-	-
Implant loss n=3 (1.6%)					
n=13 (6.4%)	-	-	n=17 (8%)	-	-
Implant loss n=2 (0.9%)					

reconstructive results. The systematic (PRISMA) method that was used for this systematic review leads to a complete overview of the current literature concerning PF preservation. Unfortunately, the number of studies on PF preservation is low. Moreover, the current studies are heterogenic and patient groups included are relatively small.

The RCT by Dalberg *et al* reported no significant difference in local recurrences. It should be mentioned that the differences reported might have become significant if more patients were included. On the other hand, there were no cases of local recurrence in both groups in the RCT by Abdelhamid *et al*, and local recurrence rates were low in both retrospective case series being 4.5% at 5-year FU and 1.1% at 29 months (3 months – 5 year).[10, 13, 16]

Obviously, tumor invasion into the PF increases the risk of developing local recurrence when preserving the PF, and a risk factor for tumor invasion into the PF is proximity of the tumor to the PF.[17-20] Unfortunately, no definite data are available for the minimal safe distance from the tumor to PF. Dalberg *et al* described that PF removal was performed when the tumor was infiltrating the PF or located close to the PF, but no definition of 'close' was provided. The actual distance from the tumor to the PF may be a key factor in determining whether or not to remove the PF. Several studies have shown that PF invasion can occur when tumors are located within 5 millimeters of the PF, and is less likely to occur with more than five millimeters distance.[19, 20] The study of Abdelhamid *et al* supports this view of tumor to PF distance as an important factor. In all cases, the tumor to PF distance was at least five millimeters, and no locoregional recurrences occurred in both study arms (p=1.0).[10] In support of this is also the fact that the PF is preserved in

almost all lumpectomies without resulting in inferior oncological outcomes, except for when the tumor is located too close to the PF.[21]

Based on the current literature, it can be stated that with proper patient selection -in terms of minimal (more than 5 mm) tumor distance to the PF- the effect of PF preservation on locoregional recurrence is not clinically relevant and routine removal of the PF does not seem evident.[20, 22] It is recommended to remove the PF at the tumor site when the tumor is located within 5 mm of the PF, in order to obtain clear margins. Direct macroscopic invasion of the PF warrants not just removal of the PF but also removal of a portion of the underlying muscle. Furthermore, post-mastectomy radiation therapy should be considered in these cases.

The ten year incidence of regional metastasis after mastectomy has previously been reported to be 3.8%.[23] The observed 5.7% in the PF preservation group and 6.6% in the PF removal group in the study by Dalberg *et al* are somewhat higher. However, multiple factors influence these recurrence rates, including tumor stage at the time of the operation, tumor biology and adjuvant therapy. More importantly, no significant difference was observed between the two treatment arms. Sandelin *et al* reported a low incidence of 2.0% regional recurrences. Based on these data, there are no indications that preservation of the PF leads to higher rates of regional recurrence, distant metastasis, or mortality.[15] These oncological outcomes seem reasonable, because multiple studies showed that breast cancer is a systemic disease from the start without any influence of the *status localis* on the systemic outcomes of distant metastasis and mortality.[21, 24, 25]

The amount of bleeding complications requiring reoperation were 1.1% and 1.8%.[13, 16] These data are in concordance or lower when compared with the previously described 1.0%-3.9% in simple mastectomy with direct reconstruction.[9, 26, 27] It seems reasonable that preservation of the PF decreases the incidence of postoperative bleeding complications requiring reoperation, because 50% of postoperative bleeding complications requiring reoperation have been found to originate from the PM (caused by dissection on the surface of the well vascularized muscular tissue).[9]

Seroma is a burdensome problem for patients and caregivers, often leading to multiple additional hospital visits. The incidence of seroma differs widely in the literature, and studies report ranges from 3 to 85%.[28] These wide ranges are probably caused by the various definitions that are given to the complication 'seroma', for example in terms of drainage days or seroma requiring a reoperation. Salgarello *et al* reported an incidence of 1.2% in their study, but these rates could be an underestimation being a retrospective analysis without a primary focus on seroma rates.[13] The results from the RCT's are more suitable to answer the question if PF preservation lowers the incidence of seroma. In Dalberg's RCT the

incidence of seroma was slightly lower in the PF preservation arm (31% vs 39.8%), but these differences were not statistically significant. In the RCT by Abdelhamid *et al* a significant lower incidence of seroma formation was observed in the PF preservation group of 5.6% vs 24.3%. Unfortunately, no definition of seroma was provided in this study.[10]

Better coverage of the prostheses by PF preservation may theoretically lower the infection rates as well as the rates of implant extrusion.[7, 13] There is a 3.8% incidence of infectious complications in breast surgery in general (including mastectomy and lumpectomy).[29] Higher rates of infections have been reported for mastectomies, ranging from 5.3-8.9%,[30-32] and of 6.0% of all patients undergoing a mastectomy with TE placement.[33] In the studies by Sandelin *et al* and Salgarello *et al*, the occurrence of infections after mastectomy with PF preservation was 2.7% and 6.4%, respectively. The rates of implant extrusion of 1.6% and 0.9% in studies by Sandelin and Salgarello respectively are lower than the least (1.9%) reported in the literature.[34] However, based on these two studies no definite conclusions can be drawn on these topics.

By removing the fascia, the oncologic surgeon may also compromise the underlying muscle to a certain extent. This may cause a risk for implant extrusion, but may also result in localized and irregular bulging of the muscle as expansion occurs. Unfortunately, there are very little data about assessing the esthetic results with and without the fascia being preserved.
The cosmetic outcomes reported were based on the subjective surgeons' and their colleagues opinions. These data do not seem to be sufficient to answer the question if PF preservation leads to better reconstructive outcomes.[13] Abdelhamid only described an improvement of skin flap appearance after PF preservation, but did not provide any information on how this was tested.[10] Future studies should focus on the objective assessment of the effect of PF preservation on reconstructive outcomes.

Additional advantages of PF preservation reported were decreased intraoperative blood loss, decreased operative time, decreased drain output and decreased time to drain removal.[10] However, these are results from only one study, and the techniques and drainage protocols may differ from other centers.
A frequently heard argument to promote PF resection is that it facilitates pathological examination of the dorsal margins. However, in our experience, the PF is rarely identified microscopically and it is not likely that a preserved fascia will lead to more false positive margins.[14, 16]

CONCLUSION

Although breast cancer surgery is increasingly focusing on less extensive procedures, the need for standard removal of the PF during mastectomy has not frequently been questioned nor studied. The studies described are heterogenic with relatively small patient groups. Based on the current literature, PF preservation seems to be an oncologically safe procedure, especially when the tumor is located at a safe distance from the PF.

Preservation of the PF might decrease the postoperative seroma formation. It may also decrease bleeding complications, infection rates, and the rates of implant extrusion while improving cosmetic outcomes. However, the current literature lacks evidence on these topics. More studies are required to systematically assess all relevant outcomes.

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4

Preservation of the pectoral fascia in mastectomy with immediate reconstruction, a nationwide survey

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ABSTRACT

Background: Pectoral fascia removal during mastectomy still seems to be the standard procedure. However, preservation of the pectoral fascia might improve postoperative and cosmetic outcomes, without compromising oncological safety. Here, we report on a national survey among Dutch plastic surgeons and oncological breast surgeons to evaluate their techniques and opinions regarding the pectoral fascia.
Materials and methods: A survey based study was performed in the Netherlands, in which both plastic surgeons and oncological breast surgeons were included, each receiving a different version of the survey. The surveys were distributed to 460 and 150 e-mail addresses, respectively.
Results: A total of 68 responses were included from more than half of all Dutch medical centers. The results of this study indicate that circa one in five plastic surgeons and breast surgeons routinely preserve the pectoral fascia during mastectomies, and even more surgeons preserve the pectoral fascia in specific cases. The surgical techniques and opinions regarding pectoral fascia preservation widely differ between surgeons.
Conclusion: Preservation of the pectoral fascia does occur in a substantial part of the Dutch medical centers, and techniques and opinions are contradictory. Future studies on this topic should clarify the effect of pectoral fascia preservation on oncological safety, complication rates, postoperative pain, cosmetic outcomes and patient satisfaction.

INTRODUCTION

Although breast-conserving surgery has gained popularity over the past decades, mastectomy remains indicated in a substantial part of breast cancer patients. In 2019, a mastectomy was performed in 31.4% of patients with invasive breast cancer and in 25.9% of patients with ductal carcinoma in situ in the Netherlands.[1] Furthermore, there is a notable rise in contralateral and bilateral prophylactic mastectomies.[2, 3] Thus, studies toward improving outcomes of mastectomies remain relevant.

During a skin sparing mastectomy, removal of the pectoral fascia (PF) is widely performed. However, its necessity to do so is questionable. Historically, the PF was excised to ensure that no remnant breast tissue was left behind. However, the PF is part of the muscular anatomy instead of the breast glandular tissue. Therefore, the oncological benefit of PF excision is unlikely, except in rare cases of tumor invasion into the PF.[4] In fact, PF preservation may improve postoperative and breast reconstructive outcomes. It prevents surgical damage to the pectoralis major muscle (PM), thereby possibly enhancing breast implant coverage, and decreasing seroma formation, postoperative bleeding and pain.[5] It has been hypothesized that PF preservation may reduce re-operation rates and improve cosmetic outcomes.[6]

Although the potential benefits of PF preservation seem evident, the literature on this subject is scarce. Previous studies described heterogeneous outcomes based on small samples.[4] For this reason, there is currently insufficient evidence to support implementation of PF preservation as the standard approach in the national guidelines. Here we report on a national survey in which attitudes on PF preservation among Dutch breast surgeons and plastic surgeons were studied.

METHODS

A survey based study was performed, in which both plastic surgeons and oncological breast surgeons were included, each receiving a different version of the survey. The surveys were distributed through the Dutch Society of Plastic Surgery (NVPC) and the Dutch Society of Surgical Oncology (NVCO). In the Netherlands it is required for all plastic surgeons and breast surgeons (i.e. all oncological surgeons specialized in oncological breast surgery) to be a member of the NVPC or NVCO. Because no patients were involved, no permission of a medical ethics committee or informed consent was required.

The survey for the plastic surgeons was sent twice to 460 e-mail addresses by the NVPC with a three-week time interval. The survey for the breast surgeons

was sent to 150 e-mail addresses by the NVCO and in a newsletter of the clinical research center of the Leiden University Medical Center two months later. As the breast surgeon response rate (RR) was low, the survey was resent directly to nonresponding breast surgeons.
The RR calculation was based on the total amount of e-mail addresses of plastic surgeons registered by the NVPC and of breast surgeons registered by the NVCO to whom the surveys were sent to, which were 460 and 150 e-mail addresses, respectively.

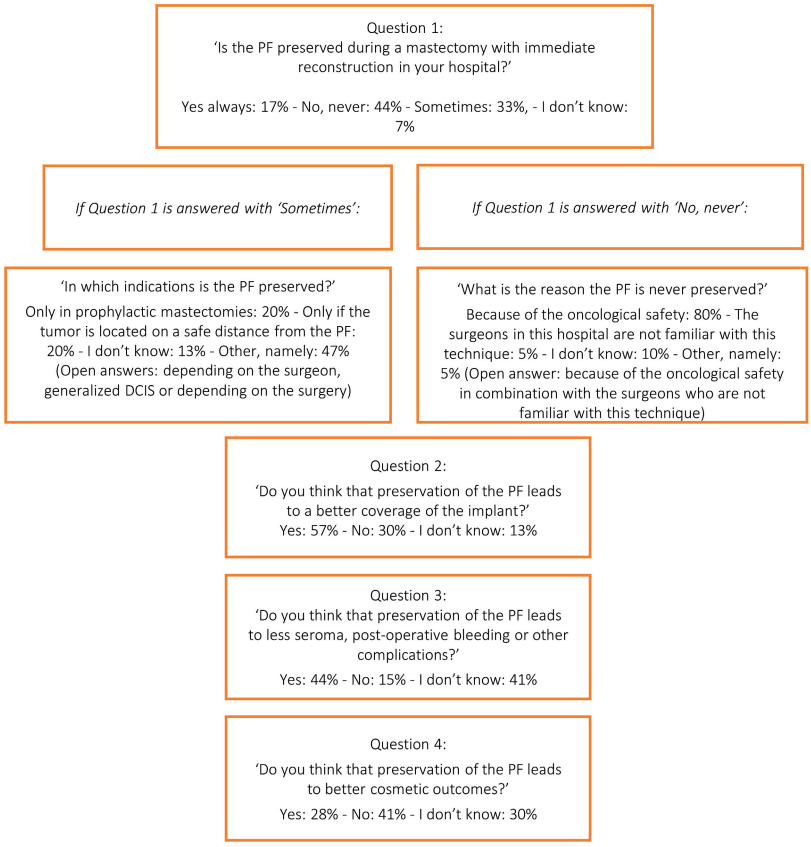
RESULTS

A total of 68 responses were included, consisting of 46 plastic surgeons (RR 10%) and 22 breast surgeons (RR 15%) from 41 different medical centers. These represent more than half of all Dutch medical centers (59%), and included both academic and peripheral medical centers, one oncological center and one specialized breast cancer center.

Plastic surgeons
Of all plastic surgeons, 17% indicated that the PF was preserved at all times during a mastectomy with an immediate reconstruction; 44% answered that the PF was never preserved; 33% answered that the PF was preserved in some cases; and 7% did not know whether the PF was preserved or excised.
According to the plastic surgeons who responded that the PF was never preserved, oncological safety was the main reason (80%).
Of all plastic surgery respondents, 57% believed that PF preservation may improve implant coverage, 44% that it may reduce complication rates, and 28% that it may improve cosmetic outcomes.

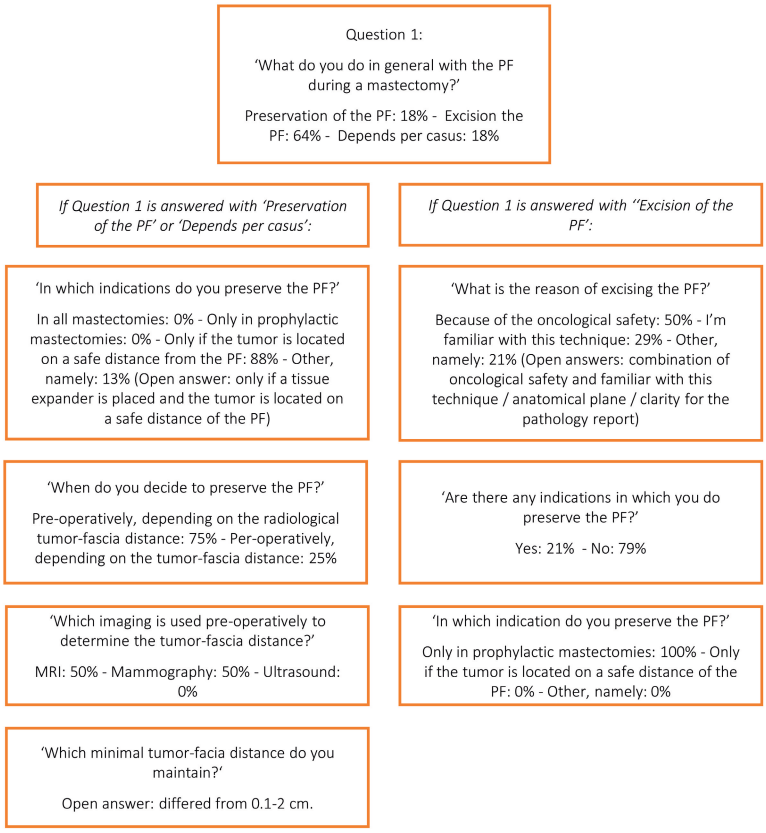
Breast surgeons
Of all breast surgeons, 18% responded that the PF was preserved at all times; 64% responded that the PF was routinely excised; and 18% responded that the PF was preserved only in those cases when the tumor is located at a safe distance from the fascia, which varied between 1 mm and 2 cm. This distance is set intraoperatively in 25% and preoperatively in 75% by using mammography (50%) or MRI (50%).
According to the breast surgeons who responded that the PF was excised, oncological safety was the main reason (50%), followed by not being familiar with this technique (29%). In this group, 21% does exceptionally preserve the PF in prophylactic mastectomies.
Questions and responses of the plastic surgeons and breast surgeons are shown in Figure 1 and Figure 2, respectively.

Figure 1: Survey overview on the practice of and attitudes towards PF preservation, and answers as provided by 46 included plastic surgeons.



PF indicates pectoral fascia

Figure 2: Survey overview on the practice of and attitudes towards PF preservation, and answers as provided by 22 included breast surgeons.



PF indicates pectoral fascia

DISCUSSION

This study provides an overview on the current practice and opinions among Dutch plastic surgeons and breast surgeons toward handling of the PF during mastectomy. The results indicate that circa one in five plastic surgeons and breast surgeons routinely preserve the PF during mastectomies. Including those who responded that the PF is preserved on an occasional basis, half of the plastic surgeons and more than one-third of the breast surgeons do not stick to the standard dogmatic PF removal.

The survey of the plastic surgeons shows that opinions differ on whether PF preservation may improve postoperative outcomes. Of all plastic surgical

respondents, 57% believes that PF preservation may improve implant coverage, 44% believes that it may reduce postoperative complications and 28% thinks that it may improve cosmetic outcomes.

Literature shows that the PF could be a valuable aid for implant coverage, since it is a thin but strong fibroelastic layer.[7] The PF is even used as a layer to cover the breast implant in a subfascial way, emphasizing its strength.[8, 9] Furthermore, it could be hypothesized that preservation of the PF reduces postoperative complications, as 50% of postoperative hemorrhage requiring surgery originates from the PM.[10] Moreover, seroma is mainly caused by muscle damage. One study on PF preservation indeed found a decrease in postoperative seroma formation.[5]

The main reason why the PF was never preserved according to the respondents of both surveys was because of oncological safety, although there is no proof of this statement in the current literature.[6] Thereby, according to the breast surgeons, circa one in five responded that the PF was preserved only in those cases when the tumor is located on a safe distance from the fascia, which varied between 1 mm and 2 cm. This implies that there is no consensus regarding the definition of this 'safe distance'.

If the oncological safety would be compromised by PF preservation, this should result in an increased rate of chest-wall recurrences, caused by invasion in the PF. However, previous studies show that chest-wall recurrences are rare, with an incidence of 0.97-1.68%.[11, 12]
A previous trial comparing PF preservation with PF removal found no significant differences in oncological outcomes (local recurrence, regional recurrence or distant metastasis).[13] However, several studies have shown that PF invasion can occur when tumors are located within 5 millimeters of the PF, and is unlikely to occur with more than five millimeters distance.[4, 14] This suggests that a tumor-fascia distance of more than 5 mm could be interpreted as safe.[6]

Another important reason why the PF was never preserved according to the breast surgeons was because they are not familiar with this technique. However, although the PF and the PM muscle should be considered together as one myofascial unit, excision of the PF is not the most understandable choice from a surgical technical point of view.[6, 7] Moreover, at least one third of the Dutch breast surgeons already uses this PF preserving technique.
The strength of this study is that the surveys were sent to all plastic surgeons and breast surgeons with respondents operating in the majority of Dutch medical centers, which implies that this study provides a valuable overview of handling of the PF during mastectomies in the Dutch practice.

However, RRs were low. Although the surveys were compact and sent multiple times, the RR remained 10-15%, compared to substantial higher rates of 53% in other doctor surveys.[15] This could be explained by the fact that not all plastic surgeons are specialized in breast surgery, so plastic surgeons with less interest in this topic were probably less likely to participate. Also, there could be some selection bias, as breast surgeons and plastic surgeons with a special interest in this subject were more tending to respond.

This study reported a preliminary overview of the Dutch practice and opinions regarding preservation of the PF. Yet, the results are interesting and important to draw more attention to this topic. The planned follow-up study should focus on increasing response rates by contacting the surgery and plastic surgery departments in all Dutch hospitals directly for the distribution of the surveys and additional questions should be added.

In conclusion, preservation of the PF does occur in a substantial part of the Dutch medical centers, and techniques widely differ between medical centers. Future studies on this topic should clarify the effect of PF preservation on oncological safety, complication rates, postoperative pain, cosmetic outcomes and patient satisfaction.

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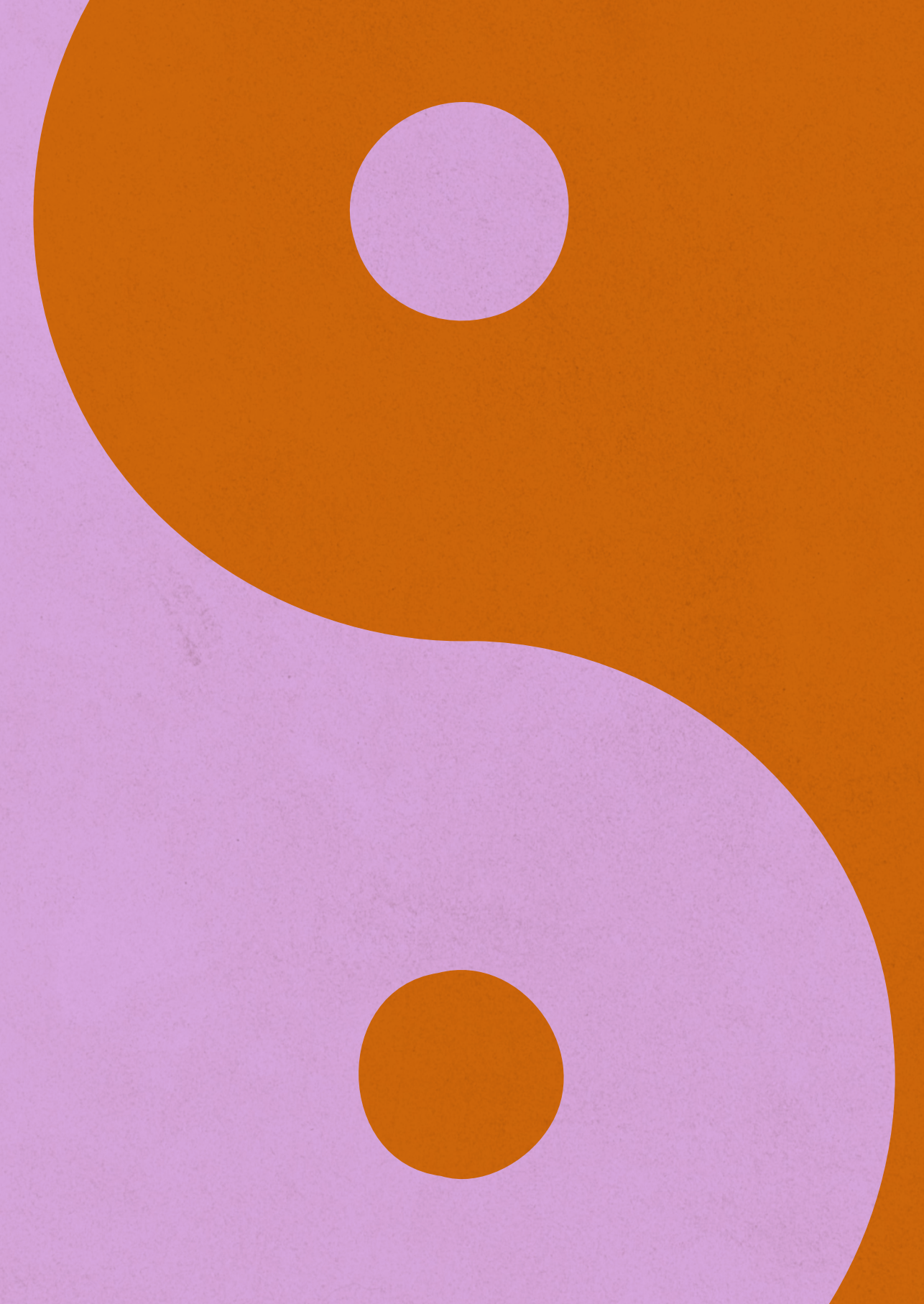
PART

Implant loss risk in implant-based breast reconstruction



5

Implant loss and associated risk factors following implant-based breast reconstructions

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ABSTRACT

Background: Implant loss is the most severe complication of implant-based breast reconstructions. This study aimed to evaluate the incidence of implant loss and other complications, identify associated risk factors, and create a risk model for implant loss.

Methods: This was a retrospective cohort study of all patients who underwent a mastectomy, followed by either a two-stage or a direct-to-implant breast reconstruction. Patient variables, operative characteristics, and postoperative complications were obtained from the patient records. A multivariate mixed-effects logistic regression model was used to create a risk model for implant loss.

Results: A total of 297 implant-based breast reconstructions were evaluated. Overall, the incidence of implant loss was 11.8%. Six risk factors were significantly associated with implant loss: obesity, a bra cup size larger than C, active smoking status, a nipple-preserving procedure, a direct-to-implant reconstruction, and a lower surgeon's volume. A risk model for implant loss was created, showing a predicted risk of 8.4%–13% in the presence of one risk factor, 21.9%–32.5% in the presence of two, 47.5%–59.3% in the presence of three, and over 78.2% in the presence of four risk factors.

Conclusions: The incidence of implant loss in this study was 11.8%. Six associated significant risk factors were identified. Our risk model for implant loss revealed that the predicted risk increased over 78.2% when four risk factors were present. This risk model can be used to better inform patients and decrease the risk of implant loss by optimizing surgery using personalized therapy.

INTRODUCTION

Implant-based breast reconstruction remains the most popular method to reconstruct the breast after a mastectomy,[1] partly due to the notable increase in prophylactic bilateral mastectomies.[2, 3] Generally, implant-based breast reconstruction is performed in two stages. First, a tissue expander (TE) is placed in the breast, which is replaced by a definitive implant during a second surgery. Alternatively, a single-stage surgery can be performed using a direct-to-implant (DTI) approach. Implant-based breast reconstruction is considered a simple, safe, and cost-effective technique without donor-site morbidity. Other advantages of implant-based breast reconstruction compared with autologous breast reconstructions are a shorter operative time, quicker overall recovery, and a shorter length of hospital stay.[4]
Among other complications, such as surgical site infections (SSI), skin flap/nipple necrosis, hematoma, and seroma,[5] implant loss is the most severe and is reported in 1.8%–16.9% of all implant-based breast reconstructions.[6-9] This wide range is presumably based on the variations in inclusion criteria, implant loss definitions, and follow-up time. Reoperations associated with implant loss result in a substantial increase in hospital costs and a significant decrease in patient satisfaction.[10]

A growing body of literature has emerged over the years, and several risk factors for implant loss have been described, such as an older age, obesity, an active smoking status, and DTI reconstruction.[10] However, a risk assessment model to improve patient information and decision-making for the optimum type of mastectomy and reconstruction has not been created. The objectives of this study were to evaluate the incidence of implant loss and other complications following implant-based breast reconstructions, identify the risk factors associated with implant loss, and create a practical risk model. Ultimately, the study findings could be used to help patients make informed decisions and decrease the risk of implant extrusion through personalized therapy.

METHODS

Study design

All patients who underwent a mastectomy—followed by immediate breast reconstruction, either a two-stage or a DTI breast reconstruction—between January 2016 and December 2019 in Alrijne Hospital and Leiden University Medical Centre were retrospectively included in this study. The patient variables were extracted from the patient records, including age, body mass index (BMI), bra size, medical comorbidities, the American Society of Anesthesiologists score, smoking status, tumor characteristics, previous breast radiotherapy, and (neo-) adjuvant therapy. Additional surgical characteristics were collected, including

mastectomy type (skin-sparing or nipple-sparing), duration of surgery, surgeon/plastic surgeon, type and size of the implant (TE/definitive prosthesis), initial TE saline fill volume, implant placement technique (submuscular/subglandular), and type of axillary surgery (sentinel node and/or axillary lymph node dissection). This study was conducted in accordance with the Declaration of Helsinki[11] and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12] The local institutional review boards approved the study protocol.

Surgical technique

In this study, the mastectomy technique used was either nipple-sparing or skin-sparing. Antibiotics were administered perioperatively (cefazolin) and (in most cases) postoperatively during hospital stay (Augmentin or flucloxacilline). The implants used were mostly smooth and round (manufactured by Eurosilicone and Mentor). No acellular dermal matrix or mesh was used. The implant placement was pre- or subpectoral. In most of the breasts, drains were used.

Clinical course

The data on complications were collected retrospectively. Postoperative complications (seroma, hematoma, SSI, wound dehiscence, nipple/skin flap necrosis, and implant loss) were graded according to the Clavien-Dindo classification [13]. In grade 1 complications, the normal postoperative course did not deviate, and no interventions were necessary. Grade 2 complications required pharmacological treatment, grade 3 required a radiological or surgical intervention with or without general anesthesia, while grade 4 consisted of life-threatening complications requiring ICU admittance. Seroma was defined as a palpable, unexpected swelling along the operated area without signs of infection (erythema or fever). Hematoma was defined as postoperative hemorrhage or an area of blue/yellow color of the skin and subcutaneous fat. SSI was characterized by erythema, potentially combined with a palpable, unexpected fluctuating swelling along the operated area with or without fever. Wound dehiscence was defined as the widening of the surgical wound. Nipple or skin necrosis was defined as the darkening of the nipple or skin. Implant loss was defined as the need for a second surgery to expand the TE or prosthesis because of the visibility of the implant through the skin, implant infection, or any other reason. Salvage procedures were also scored as implant loss. Other data collected were the timing of drain removal, the reported timing of complication occurrence, and the timing and volume of the first TE saline filling.

Statistical analyses

IBM SPSS statistics (version 26) was used for standard statistical analysis. Differences in baseline characteristics between the groups were tested with the

Mann-Whitney U test, chi-square tests, or Fisher's exact test (in the case of small cell counts). Univariate logistic regression, using individual breasts as the unit of analysis, was performed to determine the association between patient or surgical risk factors and implant loss, providing odds ratios (ORs) with 95% confidence intervals (CIs) and p-values. Cases with missing data on risk factors were excluded from the analysis. Multivariate mixed-effects logistic regression was used to adjust for confounders and correct for clustered data of patients who underwent bilateral mastectomies and therefore contributed two breasts to the analysis. All pre- and perioperative variables were considered potential confounders (obesity, age, bra size, comorbidities, smoking status, tumor type, year of operation, nipple-sparing procedure, sentinel node dissection, type of reconstruction, neoadjuvant chemotherapy, bilateral operation, and radiotherapy). In addition, the patients were divided into subgroups (TE and DTI) before repeating the analysis. Significant univariate risk factors were inserted into a multivariate logistic regression model, and backward stepwise selection was performed to develop a practical risk model. Risk factors with p-values less than 0.05 were retained in the risk model. A maximum of four risk factors were included, based on the number of implant loss events. The multicollinearity of the individual risk factors was tested before introducing them to the logistic regression model. Surgeon's volume was not included in the risk model, as this factor cannot be generalized to other practices. The predicted and observed risk of implant loss was computed for each risk factor (accumulating from zero to four). Continuous data are presented as median (range) and categorical variables as frequency and percentages.

RESULTS

Study population

A total of 297 implant-based breast reconstructions were performed among 225 patients during the study period. Follow-up time varied from 1–4 years. The patients had a median age of 50 years (range: 22–72 years) and a median BMI of 24.3 (range: 16.5–44.1). In 27.6% of the patients, the bra cup size was larger than C, and in 6.2%, the American Society of Anesthesiologists score was three or more. Of the patients, 14.7% were active smokers. The median operative time was 137 minutes (range: 36–300 minutes).

In 50.8% of the implant-based breast reconstructions, the underlying cause was invasive carcinoma, while in 18.5%, the underlying cause was ductal carcinoma in situ. In 29.0% of the reconstructions, a prophylactic mastectomy was performed. The median weight of the resected specimen was 397 grams (range: 39–1300 grams). In 40.1%, a nipple-preserving mastectomy was performed. In 79.8%, a TE was placed, and in 20.2%, a DTI reconstruction was performed. Most implants (94.6%) were placed in the subpectoral pocket, and postoperative radiotherapy was administered in 19.9% of the breast reconstructions.

Postoperative outcomes

The most frequently reported complication was SSI, which occurred in 53 (17.7%) implant-based breast reconstructions, with 16 (5.4%) requiring surgical intervention (CD ≥ 3). SSI was reported at median postoperative day 18. Seroma was reported in 50 (16.8%) implant-based breast reconstructions and was reported in the electronic patient files at median postoperative day 13. One case of seroma (0.3%) resulted in a CD score of ≥ 3. Skin or nipple necrosis was described in 32 (10.8%) implant-based breast reconstructions, which appeared on median postoperative day 11 and led to a CD score of ≥ 3 in 21 cases (7.1%). Implant loss occurred after 35 (11.8%) implant-based breast reconstructions, with a yearly variation in incidence of 5.5%–18.3%. The implant was surgically removed on median postoperative day 36. In 10 of the 35 breasts (28.6%), the extruded implant was replaced within the same surgical procedure. The underlying complications in these 10 breasts were SSI, necrosis, or wound dehiscence. Additional postoperative data are summarized in Table 1.

Table 1. Summary of clinical course
The data are numbers and percentages of total breast reconstructions (n = 297); postoperative day is presented as median and range. CD: Clavien-Dindo; SSI: surgical site infection

Postoperative outcomes	Number	Postoperative day	CD ≥ 3
Seroma	50 (16.8)	13 (7–33)	1 (0.3)
SSI	53 (17.7)	18 (3–220)	16 (5.4)
Dehiscence	15 (5.1)	29 (8–137)	7 (2.4)
Necrosis	32 (10.8)	11 (0–29)	21 (7.1)
Implant leakage	7 (2.4)	192 (54–474)	7 (2.4)
Hematoma	36 (12.1)	11 (0–61)	5 (1.6)
Implant loss	35 (11.8)	36 (9–362)	35 (11.8)
Drainage days		3 (0–16)	

Baseline characteristics were compared between all implant-based breast reconstructions with and without implant loss (35 vs 262 breasts, respectively). A significantly higher BMI was reported in implant-based breast reconstructions with implant loss compared with those without implant loss (median 27.3 vs 24.1, $p = 0.007$). Furthermore, a bra cup size larger than C (48.6% vs 27.1%, $p = 0.012$) and active smoking (34.3% vs 13.4%, $p = 0.002$) were more frequently reported in the group with implant loss. Operative time was prolonged (median 170 vs 135 minutes, $p < 0.001$), mastectomy specimen weights were higher (median 571 vs 385 grams, $p = 0.003$), the nipple was more frequently preserved (62.8% vs 37.0%, $p = 0.002$), the TE size was larger (median 500 vs 400, $p = 0.005$), and a higher perioperative TE filling was applied (median 200 vs 150, $p = 0.008$) in the implant loss group compared with the group without implant loss. All preoperative and

surgical characteristics for individual implant-based breast reconstructions with and without implant loss are summarized in Table 2.

Table 2. Preoperative and surgical characteristics
Baseline characteristics of the overall group and stratified for implant loss. Data are n (%) or median (range).

Preoperative characteristics	**Total (n = 297)**	**No implant loss (n = 262)**	**Implant loss (n = 35)**	**p-value***
Age, years	48 (22–72)	48 (22–72)	50 (25–66)	0.863
BMI, L^2/m	24.3 (16.5–44.1)	24.1 (16.5–39.9)	27.3 (17.6–44.1)	*0.007*
Cup size				*0.012*
A, B ,C	166 (55.9)	152 (58)	14 (40)	
D, E, F, H	88 (29.6)	71 (27.1)	17 (48.6)	
Missing	43 (14.5)	39 (14.9)	4 (11.4)	
ASA score				0.143
1–2	278 (93.6)	243 (92.7)	35 (100.0)	
3–4	19 (6.4)	19 (7.3)	0 (0.0)	
Comorbidity	93 (31.3)	80 (30.5)	13 (37.1)	0.428
Current smoker	47 (15.8)	35 (13.4)	12 (34.3)	*0.002*
Missing	7 (2.4)	7 (2.7)	0 (0.0)	
Indication surgery				0.581
Preventive	86 (29.0)	74 (28.2)	12 (34.3)	
Invasive carcinoma	151 (50.8)	136 (51.9)	8 (22.9)	
DCIS	55 (18.5)	47 (17.9)	15 (42.9)	
Other	5 (1.7)	5 (1.9)	0 (0.0)	
Neoadjuvant chemotherapy	87 (29.3)	78 (29.8)	9 (25.7)	0.594
Missing	11 (3.7)	10 (3.8)	1 (2.9)	
Surgical characteristics	**Total (n = 297)**	**No Implant loss (n = 262)**	**Implant loss (n = 35)**	**p-value***
Operative time	137 (36–300)	135 (36–300)	170 (47–263)	*< 0.001*
Weight resected specimen	397 (39–1300)	385 (39–1245)	571 (166–1300)	*0.003*
Mastectomy type				*0.002*
Nipple-sparing	119 (40.1)	97 (37.0)	22 (62.8)	
Skin-sparing	175 (58.9)	163 (62.2)	12 (34.3)	
Missing	3 (1.0)	2 (0.8)	1 (2.9)	
Sentinel node	183 (61.6)	163 (62.2)	20 (57.1)	0.662

Table 2. Continued

Preoperative characteristics	Total (n = 297)	No implant loss (n = 262)	Implant loss (n = 35)	p-value*
Missing	3 (1.0)	2 (0.8)	1 (2.9)	
Axillary dissection	12 (4.0)	10 (3.8)	2 (5.7)	0.637
Missing	4 (1.3)	3 (1.1)	1 (2.9)	
Type of reconstruction				*0.002*
Prosthesis	60 (20.2)	46 (17.6)	14 (40.0)	
Tissue expander	237 (79.8)	216 (82.4)	21 (60.0)	
Prosthesis size	413 (175–750)	375 (175–750)	495 (240–680)	0.143
Tissue expander size	400 (200–800)	400 (200–800)	500 (300–800)	*0.005*
Perioperative filling	150 (40–400)	150 (40–400)	200 (100–400)	*0.008*
First filling day	27 (11–193)			
Location				1.000
Prepectoral	4 (1.3)	4 (1.5)	0 (0)	
Subpectoral	281 (94.6)	249 (95.0)	32 (91.4)	
Missing	12 (4.0)	9 (3.4)	3 (8.6)	
Radiotherapy				0.747
No	227 (76.4)	200 (76.3)	27 (77.1)	
Yes (postoperative)	59 (19.9)	53 (20.2)	6 (17.1)	
Preceding	11 (3.7)	9 (3.4)	2 (5.7)	
Hormonal therapy	118 (39.7)	106 (40.5)	12 (34.3)	0.483
Bilateral	145 (48.8)	124 (47.3)	21 (60.0)	0.159

Significant p-values are denoted in italic. ASA: American Association of Anesthesiologists; BMI: Body mass index; DCIS: Ductal carcinoma in situ.

Among the implant-based breast reconstructions with implant loss, the following additional complications were significantly more observed compared with those without implant loss: SSI (54.3% vs 13%, $p < 0.001$), wound dehiscence (22.9% vs 2.7%, $p < 0.001$), necrosis in general (62.9% vs 3.8%, $p < 0.001$), and necrosis of the nipple (40% vs 2.7%, $p < 0.001$). A comparison of all postoperative outcomes between these two groups is presented in Table 3.

Table 3. Postoperative outcomes of implant-based breast reconstructions with and without implant loss
Data are n (%) or median (range). Significant p-values are denoted in italics. SSI indicates surgical site infection.

Postoperative outcomes	No implant loss (n = 262)	Implant loss (n = 35)	p-value*
Seroma	46 (17.6)	4 (11.4)	0.363
SSI	34 (13.0)	19 (54.3)	*< 0.001*
Dehiscence	7 (2.7)	8 (22.9)	*< 0.001*
Necrosis (general)	10 (3.8)	22 (62.9)	*< 0.001*
Nipple necrosis	7 (2.7)	14 (40)	*< 0.001*
Hematoma	32 (12.2)	4 (11.4)	1.000
Drainage days	3 (0–16)	3 (0–8)	0.891

Individual risk factors

After adjusting for confounders, six factors were significantly associated with implant loss. These risk factors included obesity (defined as BMI > 30) (adjusted OR: 3.226, p = 0.020), a bra cup size larger than C (adjusted OR: 3.132, p = 0.015), active smoking status (adjusted OR: 3.935, p = 0.009), a nipple-preserving procedure (adjusted OR: 4.182, p = 0.004), DTI reconstruction (adjusted OR: 2.609, p = 0.032), and a lower surgeon's volume (adjusted OR: 3.070, p = 0.019 and adjusted OR: 4.086, p = 0.010 between a volume of > 50 and 25–50 or < 25, respectively). Subgroup analysis stratified for TE or DTI did not result in significant risk factors after adjusting for confounders. All factors and their correlation with implant loss before and after adjusting for confounders are summarized in Table 4.

Risk model

After multivariate stepwise backward regression analysis, the following risk factors remained significant and were included in the risk model: obesity, nipple-sparing procedure, active smoking status, and a DTI approach. The risk of implant loss was predicted by the number of risk factors present and is depicted in Table 5.

Table 4. Risk factors associated with implant loss
Univariate and multivariate mixed-effects analysis of risk factors associated with implant loss, resulting in unadjusted and adjusted ORs, confidence intervals, and corresponding p-values (significant values are denoted in italics). Event rate describes the rate of implant loss in breast reconstructions with and without the evaluated risk factor. BMI: Body mass index; OR: Odds ratio; TE: Tissue expander.
* Oncological surgeon's volume (number of mastectomies performed within the study period)

Risk factors	Group	Event rate (%)	Unadjusted OR	p-value	Adjusted OR	p-value
Obesity	BMI < 30	9.6	1		1	
	BMI > 30	23.4	2.877 (1.299–6.376)	*0.009*	3.226 (1.208–8.617)	*0.020*
Breast size	≤ C cup	8.4	1		1	
	> C cup	19.3	2.600 (1.214–5.566)	*0.014*	3.132 (1.249–7.858)	*0.015*
Active smoking	No	9.5	1		1	
	Yes	25.5	3.280 (1.498–7.181)	*0.003*	3.935 (1.414–10.950)	*0.009*
Nipple-preserving procedure	No	6.9	1		1	
	Yes	18.5	3.081 (1.460–6.502)	*0.003*	4.182 (1.596–10.964)	*0.004*
Reconstruction type	TE	8.9	1		1	
	Prosthesis	23.3	3.130 (1.483–6.610)	*0.003*	2.609 (1.089–6.252)	*0.032*
Duration of surgery	< 140 min	7.5	1		1	
	> 140 min	17.4	2.320 (1.021–5.271)	*0.044*	1.476 (0.616–3.539)	0.381
Mastectomy specimen weight	< 400 gram	6.4	1		1	
	> 400 gram	14.6	2.526 (1.055–6.047)	*0.037*	1.640 (0.420–6.690)	0.488
Surgeon's volume*	> 50	6.1	1		1	
	25–50	16.7	2.881 (1.124–7.388)	*0.028*	3.070 (1.201–7.848)	*0.019*
	< 25	18.9	3.550 (1.237–10.189)	*0.019*	4.086 (1.397–11.953)	*0.010*

Table 5. Risk model
Accumulating number of risk factors and corresponding predicted implant loss rates. Additionally, the observed implant loss rates are summarized.

Risk factors	Predicted risk	Observed risk
0	< 3.6%	2%
1	8.4%–13.0%	10.5%
2	21.9%–32.5%	23.0%
3	47.5%–59.3%	60.0%
4	> 78.2%	—

DISCUSSION

The risk of implant loss following an implant-based breast reconstruction in this study was 11.8%, with a yearly variation of 5.5%–18.3%. A growing body of literature has estimated several risk factors for implant loss, most of which are consistent with our findings. Six individual risk factors were associated with implant loss: obesity, a bra cup size larger than C, an active smoking status, a nipple-preserving procedure, a DTI approach, and a lower surgeon's volume.
Obesity is well known as a risk factor for complications following implant-based reconstructions. According to a theory proposed by Hirsch et al.[14] this might be caused by a proportionally larger breast with larger mastectomy flaps, accompanied by a decreased blood supply, more postoperative dead space, and prolonged duration of surgery, which increase the potential for complications. Our result is consistent with this theory, as obesity and a bra cup size larger than C were both significant risk factors for implant loss. A breast cup size larger than C has also been reported by Francis et al. as a risk factor for implant loss.[15] Smoking is known to have an adverse effect on outcomes following implant-based breast reconstructions,[16, 17] which is in line with our findings. This is probably due to the negative effect of nicotine as a vasoconstrictor that reduces nutritional blood flow to the skin.[18] Furthermore, previous studies have shown that complication rates after using a DTI approach are higher than after performing a two-stage procedure.[10] Our results confirm a significant relationship between the DTI approach and implant loss. This relationship also appears in the yearly variation of implant loss in this study. The highest incidence of implant loss (18.3%) was in the first year, in which in 53.7% of the procedures, a DTI approach was used. This high rate resulted in a shift toward two-stage reconstructions in the following years.

Nipple-preserving surgery appeared to be the most significant risk factor for implant loss in this study. A review of the literature showed that this is the first time that nipple preservation proved to have a negative effect on surgical outcomes, specifically on implant loss. The most common complication that led to a surgical

intervention was nipple necrosis (65.6%). Nipple necrosis occurred significantly more often in the implant loss group compared with the group without implant loss, supporting that a nipple-preserving procedure is a significant risk factor.
A risk model for implant loss was created based on four of the risk factors found in this study (obesity, active smoking, a nipple-preserving procedure, and a DTI approach). This risk model showed the direct relationship between the number of risk factors present and the predicted risk of implant loss. The predicted risk in the presence of one risk factor was 8.4%–13.0%, which increased to 21.9%–32.5% in the presence of two risk factors. In the case of three risk factors, the predicted risk was 47.5%–59.3%, which increased to more than 78.2% in the presence of four risk factors. For example, the calculated predicted risk of implant loss was 21.9%–32.5% in a patient with obesity and active smoking status. Based on our risk model, a nipple-preserving mastectomy or a DTI approach is not recommended in this patient because of the increased risk of implant loss of 47.5% to over 78.2% if both procedures were to be performed. Our recommendation would be to not exceed these two risk factors if they are already present in a patient; rather, to choose a safer skin-sparing mastectomy technique with a two-stage reconstruction. These findings would help patients to make informed decisions and could be used to decrease the risk of implant extrusion through personalized therapy.

A total of nine oncological surgeons were included in this study, and their contribution to the number of surgical procedures varied widely. A significantly higher risk of implant loss was observed when the surgeon had performed fewer than 50 procedures in four years. It is hypothesized that this may be caused by the quality of the mastectomy flaps, which may be affected by the expertise of the surgeon. However, information on the quality of the skin flaps is absent in this study.

Radiotherapy is commonly described in the literature as a risk factor for implant loss.[8, 14] However, the risk of radiotherapy on implant loss was not observed in this study. A reason for this might be the retrospective design of the study, thereby lacking accurate data on the amount and timing of radiotherapy. Therefore, the correlation between the exact timing of radiotherapy and implant loss could not be examined.

Furthermore, diabetes mellitus and hypertension were found to be predictors for implant loss, but due to the small number of patients (<10% of the total), they could not be interpreted as significant risk factors even though hypertension is a risk factor supported by the literature.[16]

This study has several limitations. The first limitation is that the data were obtained from only two medical centers with overlapping plastic surgeons and may therefore not be generalizable to the reconstructive population at large. The

second limitation is the retrospective approach. Because of the retrospective approach, some data, such as the details and timing of radiotherapy, some comorbidities, and information about the decision-making process were lacking. Ultimately, the present results should be tested in a larger cohort to confirm the validity of this risk model.

It is hypothesized that preservation of the pectoral fascia may influence the rates of implant loss as well. Removal of the pectoral fascia is routinely performed during oncological mastectomies and was performed preceding all implant-based breast reconstructions included in this study. Therefore, this hypothesis could not be tested in this study. A previous systematic review on this topic showed that preservation of the pectoral fascia may improve breast reconstructive outcomes by enhancing prosthesis coverage, thereby reducing implant extrusion rates and improving cosmetic outcomes. It may also decrease seroma formation, postoperative bleeding, and postoperative pain.[19] The incidence of implant extrusion in mastectomies with pectoral fascia preservation varies in the literature, from 0.9% to 1.6%,[20, 21] which is substantially lower than the incidence of implant loss in our study. However, current evidence on this topic is limited. For this reason, the effect of pectoral fascia preservation on complications, including implant loss, postoperative pain, and reconstructive outcomes, will be investigated by our study group.

CONCLUSION

Implant loss after implant-based breast reconstructions occurred in 11.8% of the study population. The following risk factors were significantly associated with implant loss: obesity, a bra cup size larger than C, active smoking, a nipple-preserving procedure, a DTI approach, and a lower oncological surgeon's volume. A risk model was created based on the following risk factors: obesity, active smoking, a nipple-preserving procedure, and a DTI approach. This model showed that the predicted risk increased up to over 78.2% when the number of present risk factors accumulated. This risk model could be used to better inform patients and decrease the risk of implant extrusion by optimizing the surgical strategy in a personalized fashion.

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6

Nation-wide validation of a multicenter risk model for implant loss following implant-based breast reconstruction

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ABSTRACT

Introduction: Implant loss following breast reconstruction is a devastating complication which should be prevented as much as possible. This study aimed to validate a previously developed multicenter risk model for implant loss after implant-based breast reconstructions, using national data from the Dutch Breast Implant Registry.

Methods: The validation cohort consisted of patients who underwent a mastectomy followed by either a direct-to-implant or two-stage breast reconstruction between September 2017 and January 2021 registered in the Dutch Breast Implant Registry. Reconstructions with an autologous adjunctive and patients with missing data on the risk factors extracted from the multicenter risk model (obesity, smoking, nipple preserving procedure, direct-to-implant reconstruction) were excluded. The primary outcome was implant loss. The predicted probability of implant loss was calculated using beta regression coefficients extracted from the multicenter risk model and compared to the observed probability.

Results: The validation cohort consisted of 3769 reconstructions and implant loss occurred after 307 reconstructions (8.1%). Although the observed implant loss rate increased when the risk factors accumulated, the predicted and observed probabilities of implant loss did not match. Of the four risk factors in the multicenter risk model, only obesity and smoking were significantly associated to implant loss.

Conclusion: The multicenter risk model could not be validated using nationwide data of the Dutch Breast Implant Registry and is therefore not accurate in Dutch practice. In the future, the risk model should be improved by including other factors to provide a validated tool for the preoperative risk assessment of implant loss.

INTRODUCTION

Implant loss is the most severe complication following implant-based breast reconstruction. It has a major impact on the patient's life, both physically and emotionally.[1] Re-operations associated with implant loss may result in a significant decrease in patient satisfaction and in a substantial increase in hospital costs. In addition, it could lead to a delay in further adjuvant treatment.[2-6]

According to the literature, the occurrence of implant loss varies from 1.8% to 16.9%. Several risk factors for implant loss have been described over the years, including radiotherapy, obesity, smoking, higher age and direct-to-implant (DTI) reconstruction.[3, 7, 8] Recently, a risk model to improve patient information and decision making for the type of mastectomy and reconstruction was developed by our study group. However, this model was derived from retrospective data obtained in two medical centers, so the findings may not be generalizable to the reconstructive population at large.[9]

Therefore, a nationwide population-based cohort with data from the Dutch Breast Implant Registry (DBIR) was used to validate our multicenter risk model for implant loss after implant-based breast reconstructions for mastectomy.[10, 11] The aims were to improve patient information on the risk of implant loss and its risk factors, and to improve decision making for the type of mastectomy and reconstruction.

METHODS

Study design

For this nationwide population-based validation study, data were extracted from the Dutch Breast Implant Registry (DBIR), which is a national, prospective, opt-out registry, with mandatory registration of all breast implant surgery performed in The Netherlands.[12] All breast implants (tissue expanders (TE) and permanent implants) used for reconstructive or cosmetic purposes in the Netherlands are registered in the DBIR. The DBIR started in 2015 and all Dutch hospitals performing breast implant reconstructions participate in this registry.[12] The multicenter risk model was extracted from our recently published study.[9] The study protocol was approved by the scientific committee of the DBIR. No informed consent or ethical approval was required. The study was conducted in accordance with the Declaration of Helsinki and reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[13, 14]

Validation cohort

Patients who underwent a mastectomy for any reason followed by either a two-stage or a DTI breast reconstruction between September 2017 and January

2021 were identified from the DBIR. Patients in whom an autologous adjunctive reconstruction was used and patients with missing data on the variables of the multicenter risk model were excluded.

Multicenter risk model

Data from the multicenter risk model for implant loss were extracted and used in this study for validation of the results. Details on methods, results and conclusions were published previously.[9] In short, 297 breasts in 225 patients were evaluated after implant-based breast reconstruction. The occurrence of implant loss was 11.8%. A risk model was created that identified the following risk factors for implant loss: obesity (defined as body mass index (BMI) >30 kg/m^2), active smoking status, nipple sparing procedure and a DTI approach. The corresponding beta regression coefficients and odds ratios were extracted and are depicted in Table 1. The predicted implant loss risk ranged from 3.6% to 78.2% in patients with zero to four risk factors.[9]

Table 1. Data from multicenter risk model
The four risk factors in the multicenter risk model and corresponding beta regression coefficients.

Risk factors	Beta regression	OR	*P*-value
Obesity	1.381	1	
		2.877 (1.299-6.376)	*0.009*
Active smoking	1.172	13.280 (1.498-7.181)	*0.003*
Nipple preserving	1.110	13.081 (1.460-6.502)	*0.003*
Reconstruction type	0.902	13.130 (1.483-6.610)	*0.003*
Constant	-3.286		

ORs and *P*-values are presented. OR indicates odds ratio, significant *P*-values are noted in italic.

Outcome measures and definitions

The primary outcome was implant loss due to a wound healing related complication. The following outcomes available in the DBIR were considered as implant loss: (1) explantation of TE or permanent implant because of flap problems, infection, skin necrosis, hematoma, seroma or when no reason was provided; (2) planned replacement of TE with permanent implant combined with flap problems, infection and skin necrosis; (3) unplanned replacement of TE with permanent implant because of flap problems, infection, skin necrosis, hematoma or seroma; (4) replacement of TE or permanent implant with TE because of flap problems, infection, skin necrosis, hematoma, seroma or when no reason was provided; (5) replacement of TE or permanent implant with autologous tissue combined with flap problems, infection or skin necrosis; (6) replacement of permanent implant

with permanent implant because of flap problems, infection, skin necrosis, hematoma or seroma. The following indications for explantation or revision were not considered as implant loss due to a wound healing related complication: dissatisfaction with size, asymmetry, breast pain, autoimmune syndrome induced by adjuvants (ASIA), suspected anaplastic large cell lymphoma (ALCL), newly diagnosed breast cancer, device malposition, scarring, capsular contracture or device rupture. The following incision sites available in the DBIR were considered as nipple preserving procedures: mastectomy scar (nipple sparing), inframammary, periareolar and axillary incisions. Mastectomy scar (general) was interpreted as not nipple sparing.

Statistical analysis

Categorical variables were depicted as frequencies with percentages and continuous variables are presented as mean with standard deviations (SD) or median with interquartile range (IQR) based on the distribution. Differences in baseline characteristics between groups were tested with unpaired T test, Mann-Whitney U test or chi-square tests. To assess the validity of the local risk model, the beta regression coefficients listed in Table 1 were used to calculate the predicted probability of implant loss in the validation cohort. For each predicted probability group the observed probability, with corresponding SD, was calculated. This was visualized in a calibration plot, with predicted probability on the y-axis and observed probability on the x-axis. Finally, univariate logistic regression was performed to determine the association between risk factors and implant loss in the current cohort, providing odds ratios (OR) with 95% confidence intervals (CI) and *P*-values. IBM SPSS statistics (version 26) was used for statistical analysis, and a *P*-value <0.05 was considered statistically significant.

RESULTS

Validation study population

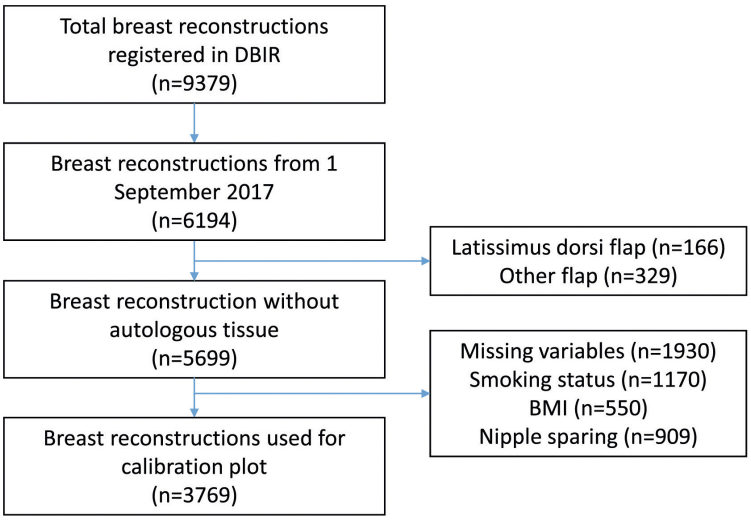
A total of 9373 implant-based breast reconstructions were registered in the DBIR between inception and January 2021; 6194 reconstructions were registered during the study period. After exclusion of patients in whom autologous adjunctive procedures were used, 5699 reconstructions remained. To validate the previously described risk model, 1930 patients were excluded because data of one or more risk factors was missing, resulting in a total of 3769 reconstructions. The mean age in this cohort of 3769 reconstructions was 48.8 ± 11.3 years with a mean BMI of 24.7 ± 4.2 kg/m^2. Patient selection and distribution are visualized in a flowchart in Figure 1. The baseline characteristics of the validation study population were compared to the baseline characteristics of the previous multicenter risk model population (Table 2).

Table 2. Baseline comparison between cohorts

Baseline characteristics	Validation cohort (n=3769)	Multicenter cohort (n=297)	*P*-value*
Age, years	48.8 ± 11.3	47.5 ± 11.3	0.068
BMI, L^2/m	24.7 ± 4.2	25.3 ± 4.8	*0.033*
Obesity	401 (10.6)	47 (15.8)	*0.006*
ASA score			*<0.001*
I	1919 (51.3)	75 (25.3)	
II	1652 (44.2)	203 (68.4)	
III	169 (4.5)	18 (6.1)	
IV	0 (0)	1 (0.3)	
Missing	29	0	
Current smoker	486 (12.9)	47 (16.2)	0.108
Missing	0	7	
Indication			*<0.001*
Breast cancer	3064 (81.3)	211 (71.0)	
Prophylactic	705 (18.7)	86 (29.0)	
Type reconstruction			0.453
Permanent implant	832 (22.1)	60 (20.2)	
Tissue expander	2937 (77.9)	237 (79.8)	
Nipple preserving	1126 (29.9)	119 (40.5)	*<0.001*
Missing	0	3	
Volume permanent implant	388 (295-480)	413 (305-515)	*0.007*
Volume tissue expander			*<0.001*
<100	848 (30.2)	68 (28.8)	
100-200	1677 (59.7)	114 (48.3)	
>200	285 (10.1)	54 (22.9)	
Missing	127	1	

Baseline characteristics of the validation cohort compared to the baseline characteristics of the previous multicenter cohort.

Figure 1. Flow-chart of in- and excluded patients



Risk model validation

The validation cohort consisted of 3769 reconstructions and implant loss occurred after 307 reconstructions (8.1%). Patient and surgery characteristics stratified for implant loss are summarized in Table 3. There were active smokers in 486 (12.9%) reconstructions and obese patients (BMI>30) in 401 (10.6%) reconstructions. A nipple sparing procedure was performed in 1126 (29.9%) reconstructions and a definite implant was directly placed in 832 (22.1%) reconstructions. This resulted in no risk factors for 1764 reconstructions, one risk factor for 1480 reconstructions, two risk factors for 485 reconstructions, three risk factors for 39 reconstructions and four risk factors for one reconstruction. The observed implant loss rates for each number of risk factors are presented in Table 4. The predicted probabilities for each risk factor combination were extracted and compared to the observed probabilities of the validation cohort. This comparison was visualized in a calibration plot (Figure 2). A substantial agreement in probabilities was observed from 0.0 to 0.13, as the reference line lies within the CI of four out of five data points. However, the rest of the predicted and observed probabilities did not match, indicating a poor agreement.

Association between risk factors and implant loss in current cohort

The associations between risk factors and implant loss were determined in the current cohort using univariable logistic regression. Obesity and active smoking status were significantly associated with implant loss (OR: 1.499 (1.072-2.094), P=0.019 and OR: 1.772 (1.315-2.387), P<0.001 respectively). A nipple preserving procedure and DTI reconstruction were not significantly related to implant loss (OR: 1.005 (0.799-1.295), P=0.971 and OR: 0.984 (0.742-1.305), P=0.984 respectively). These results are summarized in Table 5.

Table 3. Validation cohort
Baseline characteristics of the validation cohort and stratified for implant loss.

Baseline characteristics	No implant loss (n=3462)	Implant loss (n=307)	*P*-value*
Age, years	48.7 ± 11.4	50.3 ± 10.3	*0.007*
BMI, L^2/m	24.6 ± 4.2	25.6 ± 4.7	*<0.001*
Obesity	356 (10.3)	45 (11.2)	*0.017*
ASA score			0.112
I	1775 (51.7)	144 (47.4)	
II	1512 (44.0)	140 (46.1)	
III	149 (4.3)	20 (6.6)	
Missing	26	3	
Current smoker	425 (12.3)	61 (19.9)	*<0.001*
Indication			0.081
Breast cancer	2803 (81.0)	261 (85.0)	
Prophylactic	659 (19.0)	46 (15.0)	
Neoadjuvant radiotherapy	155 (4.5)	24 (7.8)	*0.009*
Missing	19	0	
Preoperative antibiotics	3341 (96.8)	297 (97.1)	0.794
Missing	10	1	
Antiseptic rinse	3169 (91.9)	273 (88.9)	0.070
Missing	14	0	
Kellerfunnel	329 (9.6)	33 (10.7)	0.495
Missing	17	0	
Nippleguards	1001 (29.0)	85 (27.7)	0.617
Missing	15	0	
Type reconstruction			0.912
Permanent implant	765 (22.1)	67 (21.8)	
Tissue expander	2697 (77.9)	240 (78.2)	
Nipple preserving	1034 (29.9)	92 (30.0)	0.971
PM cover	3134 (91.1)	264 (86.3)	*0.001*
Missing	21	1	
Mastopexy	69 (2.0)	9 (2.9)	0.271
Missing	20	1	
Drains	3304 (95.5)	293 (95.4)	0.949

Table 3. Continued

Baseline characteristics	No implant loss (n=3462)	Implant loss (n=307)	*P*-value*
Missing	3	0	
Volume permanent implant	375 (290-475)	420 (340-535)	0.344
Volume tissue expander			0.167
<100	777 (30.2)	71 (30.2)	
100-200	1545 (60.0)	132 (56.2)	
>200	253 (9.8)	32 (13.6)	
Missing	122	5	
Adjuvant radiotherapy	182 (6.7)	22 (8.5)	0.267
Missing	746	49	
Postoperative antibiotics	2015 (58.5)	176 (57.7)	0.776
Missing	20	2	

Data are n (%), mean ± SD or median (IQR). Significant *P*-values are denoted in italic. ASA indicates American Association of Anesthesiologists; BMI, body mass index, PM; pectoralis major

Table 4. Validation of risk model
Accumulating number of risk factors and corresponding observed implant loss rates.

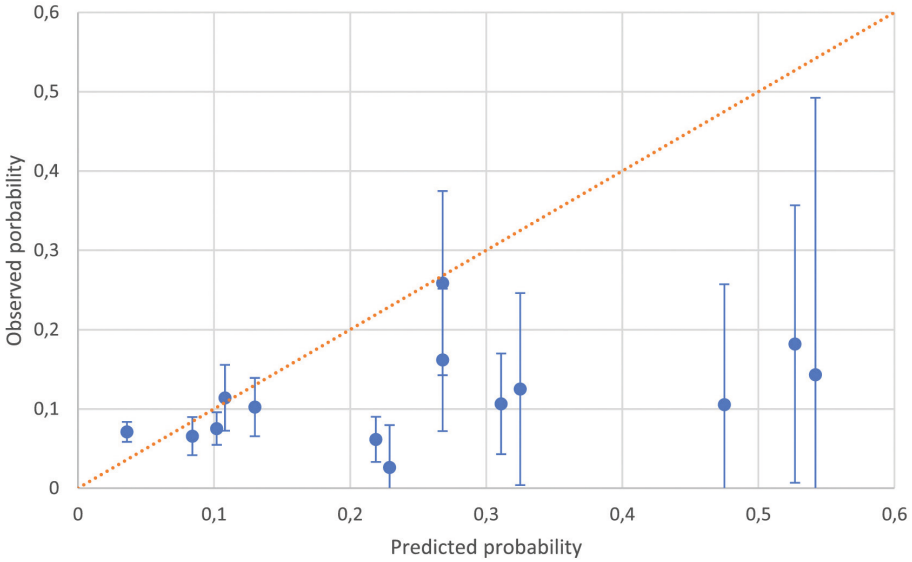
Risk factors	Reconstructions	Implant loss
0	1491	114 (7.1)
1	1413	128 (8.3)
2	508	58 (10.2)
3	49	7 (12.5)
4	1	0 (0.0)

Table 5. Risk factors in current cohort
Association between risk factors and implant loss in current cohort using univariable logistic regression.

Risk factors	Group	Event rate (%)	OR	*P*-value
Obesity	BMI <30	7.8	1	
	BMI >30	11.2	1.499 (1.072-2.094)	*0.018*
Active smoking	No	7.5	1	
	Yes	12.6	1.772 (1.315-2.387)	*<0.001*
Nipple preserving	No	8.1	1	
	Yes	8.2	1.005 (0.799-1.295)	0.971
Reconstruction type	TE	8.2	1	
	Prosthesis	8.1	0.984 (0.742-1.305)	0.984

Event rate describes the rate of implant loss in breast reconstructions with and without the risk factor. BMI indicates body mass index; OR, odds ratio; TE, tissue expander. Significant *P*-value noted in italic.

Figure 2. Calibration plot
Ratio between the predicted probability on implant loss based on the previous risk model and the observed probability in the current cohort.



DISCUSSION

This study aimed to validate a multicenter risk model for implant loss after implant-based breast reconstructions, using the DBIR database. Although the observed implant loss rate increased when the risk factors accumulated, the calibration plot showed that the predicted probability of implant loss based on the previous risk model and the observed probability in the current nationwide cohort do not match. This implies that the previous created risk model is not generalizable to the reconstructive population at large.

It is crucial that any developed model is generalizable and predicts well in 'comparable but different' patients outside the development set.[15] In the current validation cohort, an implant loss rate of 8.1% was found after implant-based breast reconstruction, which is slightly lower than the 11.8% implant loss rate found in the original cohort. The previous risk model consists of four risk factors: obesity, active smoking status, a nipple sparing procedure and a DTI approach. BMI, smoking status and a DTI approach could directly be extracted from the DBIR data. However, a nipple sparing procedure was not an exact variable in the DBIR database and could only be derived from the incision type. Furthermore, substantial differences in baseline characteristics were observed between the validation cohort and previous multicenter cohort. Next to ASA score, indication

for surgery, permanent implant volume and tissue expander volume, the rate of nipple sparing reconstructions was significantly lower in the validation cohort compared to the multicenter cohort (29.9% vs 40.5% respectively). Furthermore, the incidence of obesity was significantly lower in the validation cohort (10.6% vs 15.8%). The other risk factors were not significantly different between the two cohorts.
A nipple sparing procedure and a DTI approach were not significantly associated to implant loss in the current validation cohort. Since these factors represented half of the risk model, it is understandable that the risk model was not accurate in the current validation cohort. It could be hypothesized that the risk of implant loss increases in a nipple sparing procedure, as wound problems or necrosis seem to be most common in the nipple area. However, to date, a nipple sparing procedure has not been described as a risk factor for implant loss, thereby confirming the results of this validation cohort. In addition, a DTI approach is a frequently described risk factor for implant loss,[3] but this was not observed in the current validation cohort. However, the literature is contradictory on this topic, and critical patient selection, for instance by judgment of mastectomy flap tissue quality, is an important component.[16-18]

Although the current study contained a large sample size with data of a nationwide population, this database study has certain limitations. First of all, the accuracy of all DBIR data could not be confirmed due to its anonymized nature and privacy regulations. Another limitation is the restriction to the data collected in the database. One of the risk factors in the multicenter risk model was a nipple sparing procedure, which was not a direct variable in the DBIR database. However, this factor could be indirectly derived from the variable 'incision site'. The same applied to the definition of implant loss, which was created based on the available data in the DBIR database. However, the accuracy of these definitions could not be confirmed due to privacy regulations within the anonymized data. Finally, the registration of explantations might be an underestimation of the clinical practice due to under registration.

In conclusion, the observed incidence of implant loss in the validation cohort was 8.1% and does increase if the number of risk factors accumulates. However, the predicted probability of implant loss based on the multicenter risk model did not match the observed probability in the current nationwide cohort, indicating that the multicenter risk model is not accurate in Dutch practice. In the future, attempts will be made to improve the risk model and provide a validated tool for the risk assessment of implant loss. This could lead to improved pre-operative information for patients and the ultimate goal to decrease the risk of implant loss by optimizing the surgical strategy in a personalized fashion.

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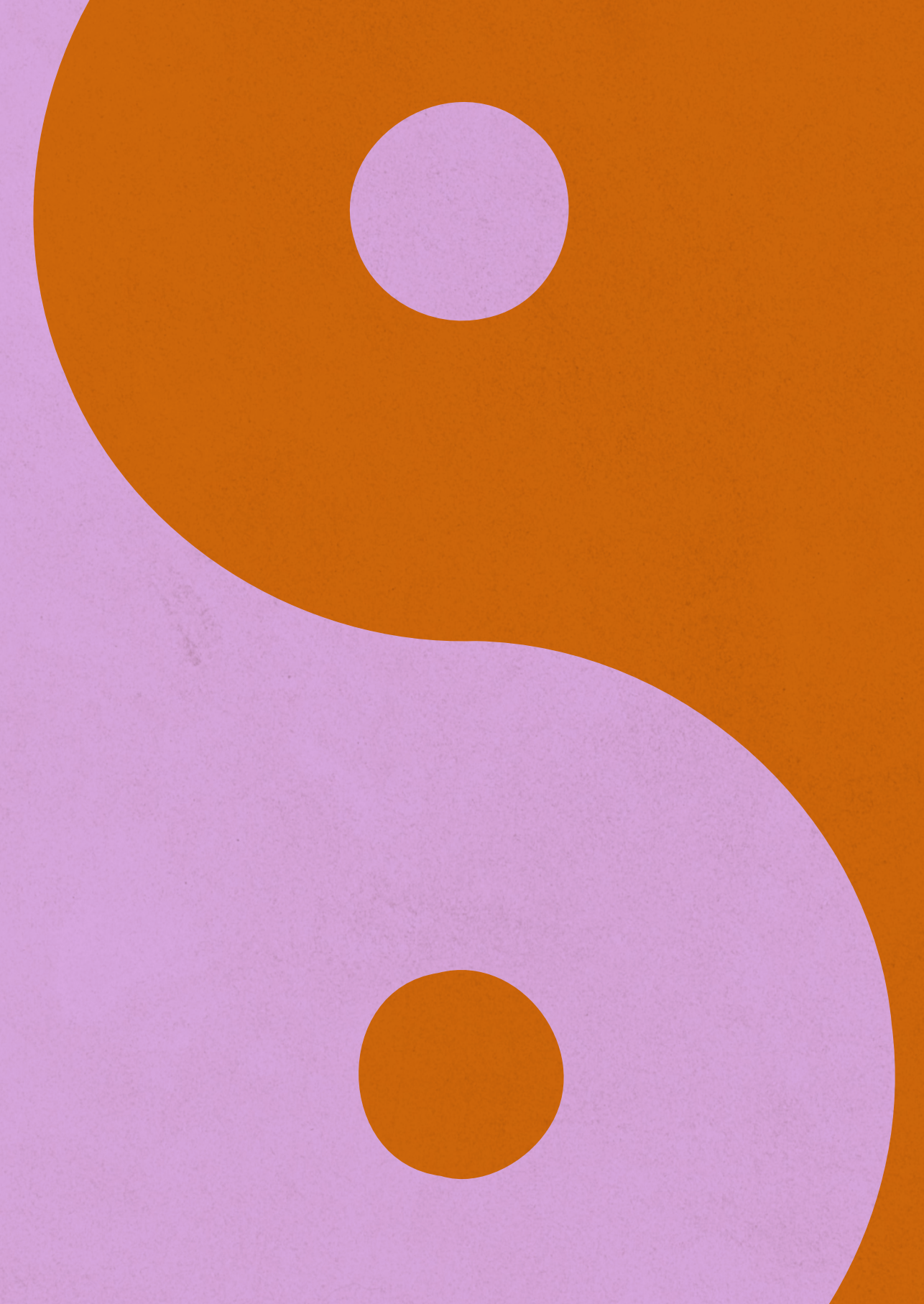

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Risk prediction of implant loss following implant-based breast reconstruction: a population-based study using Dutch Breast Implant Registry (DBIR) data

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ABSTRACT

Introduction: Implant loss following implant-based breast reconstruction (IBBR) is a serious complication, resulting in re-operations, patient suffering, and a significant decrease in quality of life. This study aimed to create a validated risk prediction model for implant loss after IBBR using perioperative risk factors.
Methods: Patients who had undergone either a two-stage or a direct-to-implant postmastectomy IBBR were identified from the Dutch Breast Implant Registry. The cohort was divided in a training cohort (80%) and a validation cohort (20%). A multivariate logistic regression model was used to create a risk prediction model for implant loss in the training cohort, which was subsequently internally validated in the validation cohort. Implant loss was defined as explantation or replacement of the implant due to postoperative wound healing-related complications within 6 months after placement.
Results: A total of 5260 IBBRs were divided into a training cohort and validation cohort. Significant risk factors included in the risk prediction model were: BMI, active smoking status, previous radiotherapy and prepectoral placement. The model was able to predict an increasing probability of implant loss from 4.5% without any risk factors to 38.0% if four risk factors were present. Furthermore, the calibration plot showed good agreement.
Conclusion: Nationwide population-based data were extracted from the Dutch Breast Implant Registry and used to create a risk assessment model for implant loss after implant-based breast reconstruction. The model was accurately internally validated, making it applicable to general practice and a valuable aid in preoperative counseling of women who consider implant-based breast reconstruction.

INTRODUCTION

Most breast reconstruction techniques after mastectomy involve the use of breast implants.(1) The most serious complication following implant-based breast reconstruction (IBBR) is implant loss, resulting in re-operations, patient suffering, a significant decrease in quality of life, and a possible delay in adjuvant treatment. According to the literature, the incidence of implant loss varies from 1.8 to 16.9% with multiple risk factors described.(2-7)

We previously tried to create a risk prediction model using multicenter retrospective data, consisting of the following risk factors: obesity, smoking, nipple sparing surgery and a direct-to-implant approach.(8) However, the subsequent study showed that this prediction model could not be externally validated, so the necessity remained to create a validated tool to predict the risk of implant loss in the preoperative phase. Knowing an accurate estimate of the risk of implant loss for a specific patient is valuable during the preoperative workup and could guide the treating physician in planning the type of mastectomy and reconstruction and in counseling women who consider IBBR.

Therefore, nationwide population-based data were used in the present study to identify risk factors for implant loss following direct-to-implant (DTI) or two-stage IBBR. Furthermore, these risk factors were used to create and subsequently validate a risk prediction model for implant loss.

METHODS

Study design

This population-based cohort study used data from the Dutch Breast Implant Registry (DBIR). In the Netherlands, all breast implants used for reconstructive or cosmetic purposes are registered in the DBIR. The registry started in 2015 and all Dutch hospitals participate.(9) This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was performed in accordance with the Declaration of Helsinki. (10, 11) The study protocol was approved by the scientific committee of the DBIR. Ethical approval or informed consent was not required according to Dutch legislation.

Patient selection

All patients who had undergone either an immediate two-stage or immediate DTI implant-based postmastectomy breast reconstruction between September 2017 and September 2020 were identified from the DBIR. This timeframe was selected because all relevant patient characteristics were only included in the registry from

September 2017 and a minimum follow-up of 6 months was determined. Patients in whom an autologous adjunctive procedure was used were excluded.

Variables for risk factor analysis

The following patient characteristics were used in univariable and multivariable analyses: age in years (continuous), body mass index (BMI, continuous), American Association of Anesthesiologists (ASA) grade (1-2 and 3-4) and active smoking (yes or no). Furthermore, surgery characteristics involved: indication for surgery (breast cancer or prophylactic surgery), previous radiotherapy (yes or no), preoperative antibiotics (yes or no), antiseptic rinse (yes or no, if yes: using an antiseptic (betadine) solution, an antibiotic solution or a combination of an antiseptic and antibiotic solution), nipple guards (yes or no), nipple preserving procedure which was derived from incision site (yes or no, if yes: mastectomy scar - nipple sparing, inframammary, periareolar and axillary incisions, if no: mastectomy scar - general), type of reconstruction (TE or permanent implant), prepectoral placement (yes or no, if no: partial or complete cover with pectoralis major muscle), concurrent mastopexy (yes or no), postoperative drains (yes or no), volume of permanent implant (continuous), maximum volume of TE (continuous), intraoperative volume TE in cubic centimeters (<100, 100-200 or >200), postoperative antibiotics (yes or no) and adjuvant radiotherapy (yes or no).

Outcome measures and definitions

The outcome of interest was implant loss, which was defined as explantation of the implant due to postoperative wound healing-related complications within 6 months after placement. The following available variables in the DBIR were considered implant loss: (1) explantation of the implant (TE or permanent implant) or replacement of the implant (TE or permanent implant) with TE due to flap problems, infection, skin necrosis, hematoma, seroma or if no reason was provided. (2) Replacement of implant (TE or permanent implant) with permanent implant because of flap problems, infection, skin necrosis, hematoma or seroma. (3) Replacement of implant (TE or permanent implant) with autologous tissue combined with flap problems, infection or skin necrosis.

Other indications for revision or explantation (dissatisfaction with size, asymmetry, breast pain, breast implant associated illness (BII), suspected or confirmed anaplastic large cell lymphoma (ALCL), newly diagnosed breast cancer, device malposition, scarring, capsular contracture or device rupture) were not included in the definition.

Statistical analysis

Statistical analysis was performed using SPSS (version 26 IBM Corp, Armonk, NY). A two-sided *P*-value of <0.05 was considered statistically significant. For continuous

data, median and interquartile ranges (IQR) were given, other data are reported using frequencies and percentages.

The dataset was randomly divided into a training cohort and a validation cohort, involving 80 and 20 percent of the data, respectively. The training cohort was used to identify risk factors and create a risk prediction model for implant loss. Univariable logistic regression analysis were performed to determine the association between potential risk factors and implant loss, providing odds ratios (OR) with 95% confidence intervals (CIs) and *P* values. Individual breasts were used as the unit of analysis and cases with missing data on risk factors were excluded from the analyses. Multivariable logistic regression analysis was used to adjust for all possible confounding variables. Finally, univariate risk factors with a *P* value below 0.157, based on the Akaike information criterion,(12) were inserted in a multivariable logistic regression model. Backward stepwise selection was performed to create the risk prediction model. Risk factors with a *P* value of <0.05 retained in the model.

The risk prediction model was tested in the validation cohort. First, predicted probabilities of implant loss for each subject were calculated using β regression coefficients. Second, the subjects were divided into ten groups by using ten percentiles of the predicted probabilities. For each group, the observed probability of implant loss was calculated with corresponding 95% confidence interval. Finally, the probabilities were visualized in a calibration plot with predicted probability on x-axis and observed probability on y-axis. IBM SPSS statistics (version 26) was used for standard statistical analysis.

Additional analyses

Additional analyses were performed to investigate whether risk prediction models were more accurate for TE and permanent implants separately. Therefore, subgroups were created, stratified for TE and DTI, after which the analyses were repeated.

Probability range for each number of risk factors

In order to simplify the use of the risk model, the continuous variable (BMI) was dichotomized in BMI <30 and ≥30 kg/m^2, excluding percentiles 0-2.5 and 97.5-100, resulting in a total of four dichotomous variables. The predicted probability range for each number of risk factors (zero to four) was computed using β regression coefficients. Furthermore, the observed implant loss rate was extracted from the training and validation cohort for each number of risk factors and visualized in a table.

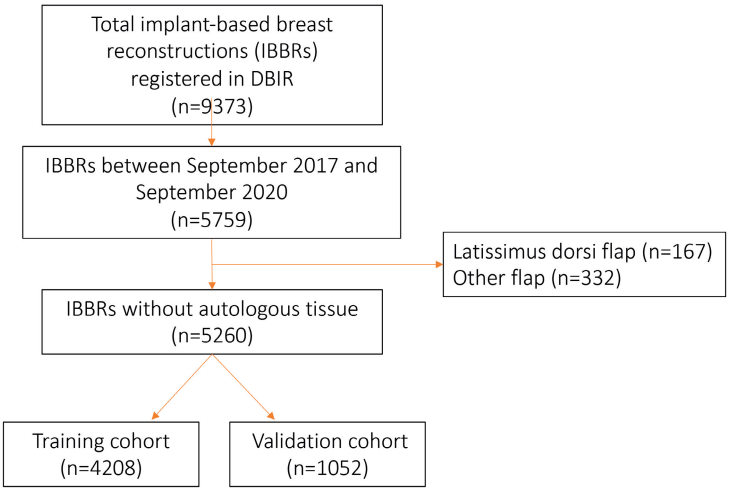
RESULTS

Study population

A total of 9373 IBBRs were registered in the DBIR between inception and January 2021, of which 6194 were registered during the study period. After exclusion of patients in whom autologous adjunctive procedures were used (latissimus dorsi flap or other flap), 5260 IBBRs. Implant loss within 6 months occurred after 354 reconstructions (6.7%) and the median time to surgical removal of the implant was 42 days (IQR: 21 to 83 days).

The total group of 5260 IBBRs was divided into a training cohort consisting of 4208 reconstructions (80%) and a validation cohort consisting of 1052 reconstructions (20%), with an implant loss rate of 7.0% and 5.6%, (P=0.104) respectively. Patient selection and distribution is visualized in a flow-chart in Figure 1. Baseline characteristics were compared between all IBBRs with and without implant loss in the training and validation cohort. The implant loss group within the training cohort showed a significantly higher BMI, a higher ASA classification, more active smokers, less often use of preoperative antibiotics, more often prepectoral implant placement and a higher volume of the permanent implant or TE. The implant loss group within the validation cohort showed a significantly higher rate of nipple preserving procedures. Further baseline comparisons are presented in Table 1.

Figure 1. Flowchart of patient selection and distribution of the training cohort and validation cohort



Individual risk factors

After adjusting for confounders, four individual risk factors were significantly associated to implant loss. These risk factors included BMI (adjusted OR: 1.050 per 1 kg/m increment, CI: 1.023-1.077), active smoking status (adjusted OR: 2.081, CI: 1.513-2.862), previous radiotherapy (adjusted OR: 1.811, CI: 1.064-3.081), prepectoral placement (adjusted OR: 1.911, CI: 1.346-2.713) and volume of the permanent implant (adjusted OR: 1.306, CI: 1.109-1.539, calculated per 100 cubic centimeters increase of volume). All factors and their correlation with implant loss before and after adjusting for confounders are summarized in Table 2.

Risk prediction model

After multivariable backward stepwise logistic regression analysis, the following four significant risk factors retained in the risk prediction model: BMI, active smoking status, previous radiotherapy and prepectoral placement. Within the training cohort, 974 out of 4208 reconstructions (23.1%) were excluded because of missing data on one or more risk factors. As volume of the permanent implant was not applicable to the total study population (about two third were TEs), it was only included in the subgroup analysis. The included factors and corresponding ORs, 95% CIs, β regression coefficients and *P* values are summarized in Table 3. An accurate risk prediction could be calculated for each individual patient using the following formulas. Log odds = -3.8715 + (BMI*0.0439) + (active smoking status*0.7823) + (previous radiotherapy*0.5213) + (prepectoral placement*0.5566). BMI is filled in as a continuous variable, active smoking status = 1, previous radiotherapy = 1 and prepectoral placement = 1. The predicted probability = ($e^{\log odds}$)/(1+$e^{\log odds}$)*100%. For example, the predicted probability of implant loss in a patient with a BMI of 25 kg/m2, active smoking status, no previous radiotherapy and no prepectoral placement is 12.01%, as calculated with the formula as: -3.8715 + (25*0.0439) + (1*0.7823) + (0*0.5213) + (0*0.5566) = -1.9917 (log odds). ($e^{-1.9917}$)/(1+$e^{-1.9917}$) *100% = 12.01%.

In addition, to facilitate an easy risk calculation, BMI was dichotomized to calculate the predicted probabilities of implant loss for each number of risk factors. BMI ranged from 18.6 to 30 and 30 to 34.6 (excluding percentiles 0-2.5 and 97.5-100). The predicted probabilities were compared to the observed implant loss rates in the training and validation cohort (Table 4).

Risk prediction model validation

The model was applied to the validation cohort, 273 out of 1052 reconstructions (26.0%) were excluded because of missing data on one or more risk factors. The predicted probabilities of ten percentiles were compared to the corresponding observed probabilities. Each tenth contained 74 to 83 subjects and the ratio between the observed and predicted probability ranged from 0.215 to 1.050, with

Table 1. Baseline characteristics of the training and validation cohort

	Training cohort (n=4208)			Validation cohort (n=1052)		
Baseline characteristics	**No implant loss (n=3913)**	**Implant loss (n=295)**	***P*-value**	**No implant loss (n=993)**	**Implant loss (n=59)**	***P*-value**
Age, years	47.9 ± 11.4	48.8± 11.2	0.079	48.7 ± 11.7	49.8 ± 11.9	0.455
BMI, L^2/m	24.7 ± 4.2	25.7 ± 4.8	*<0.001*	24.7 ± 4.1	25.7 ± 4.2	0.085
ASA score			*0.004*			0.926
I	2186 (56.4)	135 (46.4)		545 (55.4)	33 (56.9)	
II	1546 (39.9)	138 (47.4)		394 (40.1)	23 (39.7)	
III	143 (3.7)	18 (6.2)		44 (4.5)	2 (3.4)	
IV	1 (0.0)	0 (0.0)		0 (0.0)	0 (0)	
Missing	37	4		10	1	
Current smoker	383 (12.3)	55 (22.5)	*<0.001*	88 (11.4)	8 (18.2)	0.178
Missing	791	51		224	15	
Indication			0.476			
Breast cancer	3170 (81.0)	234 (79.3)		798 (80.4)	49 (83.1)	0.613
Prophylactic	743 (19.0)	61 (20.7)		195 (19.6)	10 (16.9)	
Bilateral	1590 (40.6)	119 (40.3)	0.921	374 (37.7)	27 (45.8)	0.213
Previous radiotherapy	170 (4.9)	18 (6.8)	0.185	36 (4.1)	3 (5.7)	0.485
Missing	471	30		123	6	
Preoperative antibiotics	3793 (97.6)	281 (93.1)	*0.039*	957 (97.3)	56 (96.6)	0.673
Missing	25	1		9	1	
Antiseptic rinse	3067 (78.4)	224 (75.9)	0.538	755 (76.0)	47 (79.7)	0.606
Missing	34	2		13	0	
Nipple guards	960 (24.5)	57 (19.3)	0.095	260 (26.2)	19 (32.2)	0.438
Missing	43	2		12	0	
Type of reconstruction			0.327			0.388

Permanent implant	1375 (35.1)	112 (38.0)		358 (36.1)	18 (30.5)	
Tissue expander	2538 (64.9)	183 (62.0)		635 (63.9)	41 (69.5)	
Nipple preserving	1030 (31.0)	80 (33.1)	0.510	262 (31.4)	21 (45.7)	*0.044*
Missing	593	53		159	13	
Prepectoral placement	309 (9.2)	42 (16.2)	*<0.001*	75 (8.9)	8 (16.0)	0.125
Missing	539	35		147	9	
Concurrent mastopexy	112 (3.3)	9 (3.5)	0.894	24 (2.8)	4 (7.8)	0.069
Missing	112	9		24	4	
Drains	3727 (95.2)	282 (95.6)	0.760	951 (95.8)	56 (94.9)	0.712
Missing	7	0		6	0	
Volume permanent implant*	375 (290-475)	418 (353-495)	*0.002*	385 (295-495)	430 (350-510)	0.147
Maximum volume TE**	450 (350-550)	450 (400-575)	*0.033*	450 (355-550)	525 (350-550)	0.291
Intraoperative volume TE**			*0.011*			*0.022*
<100	659 (27.8)	45 (24.7)		175 (29.2)	15 (35.7)	
100-200	1448 (61.0)	103 (56.6)		366 (61.0)	18 (42.9)	
>200	267 (11.2)	34 (18.7)		59 (9.8)	9 (21.4)	
Missing	148	17		32	2	
Adjuvant radiotherapy	196 (7.2)	18 (8.6)	0.457	57 (8.4)	2 (4.7)	0.381
Missing	1199	86		317	16	
Postoperative antibiotics	2090 (60.5)	158 (60.3)	0.961	535 (61.6)	30 (56.6)	0.472
Missing	456	33		124	6	

Baseline comparisons of the training cohort and validation cohort, stratified for implant loss.
Data are n (%), mean ± SD or median (IQR). Statistically significant *P*-values are denoted in italic.
ASA indicates American Association of Anesthesiologists; BMI, body mass index; TE, tissue expander.
*Data of permanent implants within training cohort (n=1606) and validation cohort (n=418).
**Data of TEs within training cohort (n=2969) and validation cohort (n=706).

Table 2. Risk factors associated with implant loss within the training cohort

Risk factors	Group	Event rate (%)	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
BMI*	-	-	1 1.050 (1.023-1.077)	<*0.001*	1 1.050 (1.023-1.077)	<*0.001*
Current smoker	No Yes	189 (6.5) 55 (12.6)	1 2.081 (1.513-2.862)	<*0.001*	1 2.081 (1.513-2.862)	<*0.001*
Previous radiotherapy	No Yes	247 (7.0) 18 (9.6)	1 1.403 (0.848-2.319)	0.187	1 1.811 (1.064-3.081)	*0.029*
Prepectoral placement	No Yes	218 (6.6) 42 (12.0)	1 1.911 (1.346-2.713)	<*0.001*	1 1.911 (1.346-2.713)	<*0.001*
Volume permanent implant**	-	-	1 1.306 (1.109-1.539)	*0.001*	1 1.306 (1.109-1.539)	*0.001*

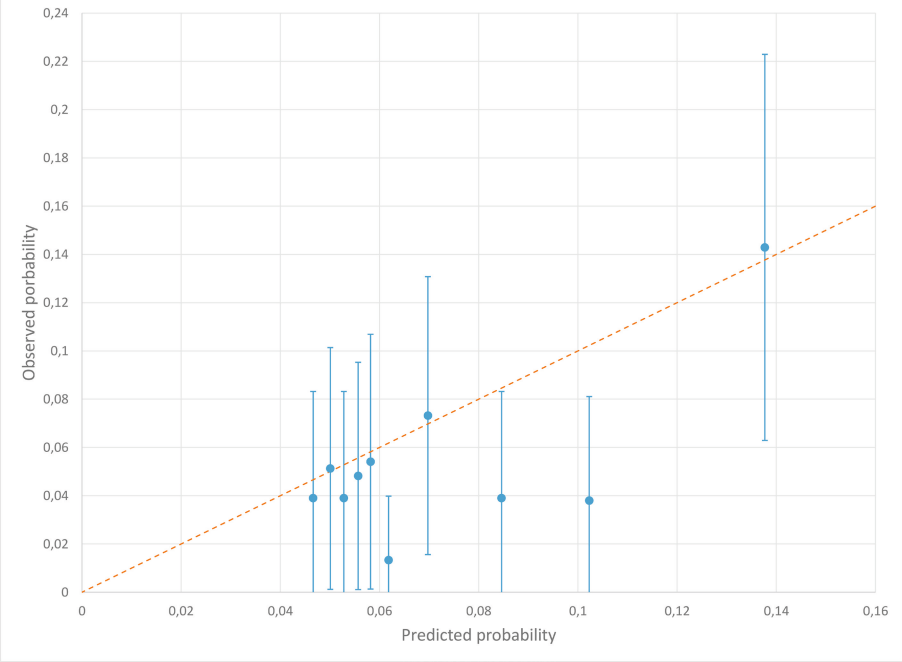
Univariate and multivariate analysis of risk factors associated with implant loss within the training cohort, resulting in unadjusted and adjusted ORs, confidence intervals and corresponding *P*-values (significant values are denoted in italic).
Event rate describes the rate of implant loss in reconstructions with and without the corresponding risk factor. BMI indicates body mass index; CI, confidence interval; OR, odds ratio; TE, tissue expander.
*OR was calculated per 1 kg/m increment **Data of permanent implants within training cohort (n=968). OR was calculated per 100cc increase of volume.

Table 3. Risk model for implant loss

Risk factors	OR (95% CI)	β coefficient	P-value
BMI*	1.045 (1.015-1.075)	0.0439	*0.003*
Current smoker	2.186 (1.584-3.019)	0.7823	*<0.001*
Previous radiotherapy	1.684 (1.007-2.816)	0.5213	*0.047*
Prepectoral placement	1.745 (1.205-2.526)	0.5566	*0.003*
Constant		-3.8715	

Risk model including four risk factors associated with implant loss within the training cohort. Corresponding ORs (95% CIs), beta regression coefficients and *P*-values (significant values are denoted in italic) are depicted. BMI indicates body mass index; CI, confidence interval; OR, odds ratio.
*Continuous variable, OR calculated per 1 kg/m increment.

Figure 2. Validation of the risk prediction model using a calibration plot



Comparison between predicted probabilities (x-axis) and the observed probabilities (y-axis, with corresponding 95% CIs) of implant loss in the validation cohort (blue line). The orange line indicates perfect agreement.

Table 4. Predicted probabilities and observed implant loss rates for each amount of risk factors

		Training cohort			Validation cohort		
Number of risk factors	**Predicted probability***	**Reconstructions**	**Implant loss**	**Observed probability**	**Reconstructions**	**Implant loss**	**Observed probability**
0	4.5% - 7.2%	2142	125	5.8%	523	23	4.4%
1	7.2% - 14.5%	926	79	8.5 %	225	13	5.8%
2	11.6% - 22.8%	158	32	20.3%	30	6	20.0%
3	18.6% - 33.3%	8	2	25.0%	1	0	0.0%
4	33.3% - 38.0%	0	0	-	0	0	-

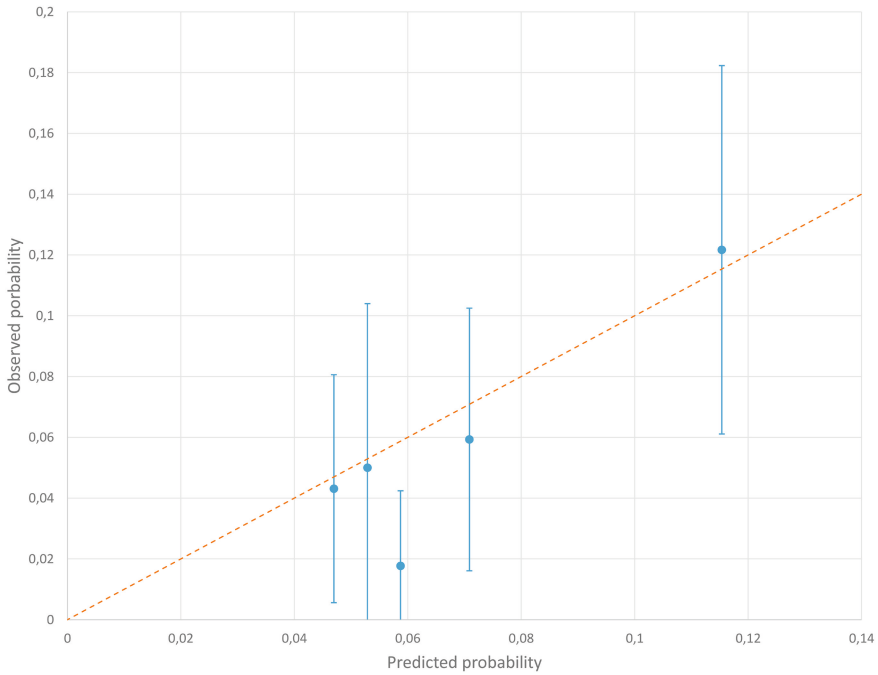
* BMI (continuous variable) was dichotomized in BMI <30 (no risk factor) and ≥30 kg/m^2 (risk factor)

a mean ratio of 0.753 across all tenths. The tenths, with CIs for observed probability, are visualized in a calibration plot (Figure 2). As the reference line lies within the CIs of seven of the tenths, a good agreement can be concluded.

Additional analyses

A subgroup of TE and DTI reconstructions was separately analyzed. A risk prediction model for implant loss after TE reconstructions was created in the training cohort. This model included the following risk factors: BMI (β: 0.046, OR: 1.047, CI: 1.012-1.082), active smoking status (β: 0.453, OR: 1.573, CI: 1.035-2.389) and prepectoral placement (β: 0.763, OR: 2.145, CI: 1.337-3.440). The model was applied to the validation cohort and divided into quintiles because of a low sample size. Each quintile contained 113 to 120 subjects. The ratio between the observed and predicted probability ranged from 0.301 to 1.055, with a mean ratio of 0.811. This comparison is visualized in Figure 3. The reference line lies within the CIs of four out of five quintiles.

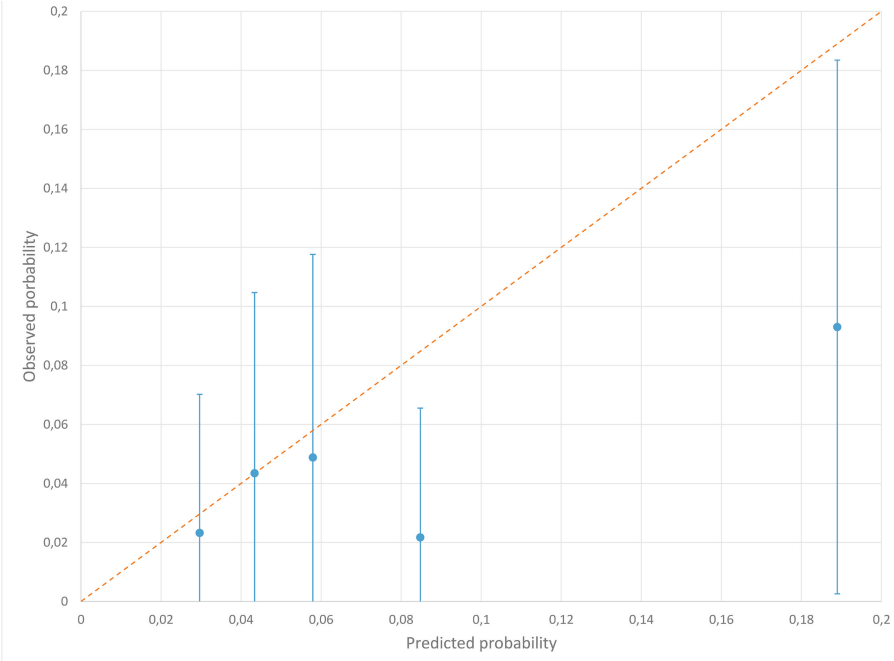
Figure 3. Validation of the TE risk prediction model using a calibration plot



Subsequently, a risk prediction model was created for DTI reconstructions in the training cohort. This model included the following risk factors: prophylactic mastectomy (β: 0.867, OR: 2.380, CI: 1.378-4.109), active smoking status (β: 1.495,

OR: 4.458, CI: 2.563-7.754), previous radiotherapy (β: 0.989, OR: 2.689, CI: 1.039-6.959) and increase in implant volume per 100 cubic centimeters (β: 0.290, OR: 1.336, CI: 1.117-1.599). The model was applied to the validation cohort and divided into quintiles, containing 41 to 46 subjects. The ratio between the observed and predicted probability ranged from 0.256 to 1.003, with a mean ratio of 0.676. The calibration plot is shown in Figure 4. The reference line lies within the CIs of three out of five quintiles.

Figure 4. Validation of the DTI risk prediction model using a calibration plot



DISCUSSION

In this study an internally validated risk prediction model for implant loss following DTI or two-stage implant-based breast reconstruction was created using nationwide population-based data of the DBIR database. Four risk factors were included in the model (BMI, active smoking status, previous radiotherapy and prepectoral placement). The calibration plot showed good agreement, indicating the model may be extrapolated to the Dutch reconstructive population at large. Alternative risk prediction models were created, in which a subgroup of TEs and DTI reconstructions was analyzed separately. Results showed that in the TE model (including: BMI, active smoking status and prepectoral placement) the mean ratio between the observed and predicted probability was slightly better compared

to the original model and good agreement was observed in the calibration plot. Consequently, the risk prediction model for TE reconstructions can be used for this subgroup of patients.

The results of the DTI model showed a decreased mean ratio between the observed and predicted probability compared with the original and TE model. Therefore, based on the data used in this study, it is suggested that this DTI model is not superior to the original risk prediction model and could not be accurately validated.

According to the literature, the incidence of implant loss varies between 1.8 and 16.9%.(2-7) With 6.7%, the incidence of implant loss in this study lies well within this range. Even though the accuracy of DBIR data is annually published, with a completeness of 93% or more for most variables,(9) an underestimation of the actual implant loss rate due to possible underreporting of explantations could still be present. The incidence is also depending on the definition of implant loss and not all studies have used the same definition. In the current study, implant loss was defined as the necessity of explantation or replacement (with the same or other implant or autologous tissue) due to postoperative complications related to wound healing problems. If the definition would be expanded to implant loss due to any reason (i.e. device rupture, capsular contracture, pain, malposition of the prosthesis), the incidence is expected to increase.

The four risk factors included in the prediction model were BMI, active smoking status, previous radiotherapy and prepectoral placement. Previous studies have determined patient characteristics and comorbidities affecting the risk of complications after implant-based reconstructions: smoking and obesity are well-known risk factors. In literature, reported cutoff points for obesity are a BMI ≥ 25 or 30 kg/m^2.(13-18) However, it is more accurate to address BMI as a continuous variable, as some information will be lost when converting continuous to binary data. Previous radiotherapy has been described as risk factors for complications as well,(4) unlike prepectoral implant placement. Two previous meta-analysis have shown that either a prepectoral or subpectoral implant position is not associated with the occurrence of complications.(19, 20) This illustrates that most of the risk factors from the risk prediction model in the current study all have been previously described as risk factors for complications or implant loss after implant-based reconstruction.

Furthermore, in this study, neither DTI or two-stage reconstructions were significant risk factors. Previous studies comparing DTI with two-stage reconstructions showed contradictory outcomes in complication rates.(21-24) A large study of Singh et al. reported similar results after one-stage and two-stage reconstructions

as measured by the frequency of return visits for treatment of complications and additional procedures.(25)

The Dutch national guideline recommends preferably not to perform immediate implant-based breast reconstruction (DTI) in patients with more than two of the following preoperative risk factors: smoking, BMI ≥30 kg/m^2, bilateral surgery, age >55 years and larger breasts.(26) This recommendation is, among others, partially based on a large study which performed a risk analysis in 14.585 patients who underwent an immediate breast reconstruction.(3) In this study the overall implant loss rate was very low (0.8%) compared to 6.7% in current study, which can be attributed to the short follow-up time of 30 days as our median time to surgical removal of the implant was 42 days (IQR: 21 to 83 days).

As mentioned in the results, a precise risk prediction of implant loss could be calculated for each individual patient, using the given formula. To facilitate an easier risk calculation, BMI was dichotomized to calculate the predicted probabilities of implant loss for each number of risk factors. During the preoperative consultation, the treating physician can clearly outline the estimated risk of implant loss by using these prediction tools, enabling the patient to make a well-informed decision. Other alternatives, such as an autologous reconstruction, a delayed reconstruction, or no reconstruction at all, should be taken into consideration for individuals with an unacceptable high anticipated risk.

This nationwide population-based study has several limitations. First of all, the data from the database are all anonymized due to privacy regulations. For this reason, the relatively high percentage excluded reconstructions, because of missing data on one or multiple risk factors could not be decreased. Furthermore, in this cohort, no subjects with four risk factors present were included, therefore, for this number of risk factors, the observed probability could not be calculated. Next, there was a restriction to the data collected from the DBIR database. Since implant loss was not an existing variable, the outcome was composed of multiple variables. Also nipple sparing was not a direct variable and had to be derived from the 'incision site'. Finally, the DBIR is filled in directly after surgery, therefore the accuracy of adjuvant radiotherapy cannot be guaranteed as the indication for adjuvant therapy may change after postoperative pathology reports or multidisciplinary tumor board meetings.

In conclusion, these nationwide population-based DBIR data were applied to create an easy to use risk prediction model for implant loss after immediate implant-based breast reconstruction. Four risk factors were included: BMI, active smoking status, previous radiotherapy and prepectoral placement. The model reported the predicted risk for implant loss for each number of risk factors,

increasing from 4.5% to 38%, enabling the surgeon to establish a cut-off at their own discretion. However, in patients with a significant number of risk factors, it may be wise to avoid prepectoral placement to not further increase the risk of implant loss. The model was accurately internally validated, making it easy to implement in current surgical practice and a valuable aid in preoperative counseling in breast cancer patients.

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Discussion and conclusion

8

General discussion and future directions

DISCUSSION

The overall aim of this thesis was to analyze postoperative outcomes and patient satisfaction after reconstructive surgery following breast cancer. Different aspects of reconstructive breast surgery were assessed, focusing on oncoplastic breast-conserving surgery (part I), a less extensive mastectomy technique with pectoral fascia preservation (part II) and the risk of implant loss after implant-based breast reconstruction (part III).

Oncoplastic breast-conserving surgery

Oncoplastic breast-conserving surgery (OPS) has gained popularity in the past decades and has shown to be a reliable and effective way to reconstruct the breast after breast-conserving surgery.[1] Studies have shown similar rates of disease-free survival and local recurrence rates, compared to breast-conserving surgery alone, and association with increased patient satisfaction and favorable cosmetic outcomes.[2] This thesis provided additional evidence that patients in general are pleased with the outcomes after OPS. Chapter 2 showed that patients were overall satisfied after OPS, as measured with the BREAST-Q, with 86% of patients rating their cosmetic outcomes as good to excellent. However, patients who underwent volume replacement techniques reported significantly lower scores for the BREAST-Q domain "well-being of the chest", which may be the result of more extensive surgery that is required for this technique. Further comparison of volume replacement with volume displacement techniques revealed similar complication rates, in contrast to the study of Clough et al, in which more complex reshaping techniques lead to higher complication rates.[3]

This thesis also highlighted the association between complications and patient satisfaction. In patients who underwent OPS, the occurrence of complications resulted in decreased BREAST-Q scores and cosmetic outcome scores. Patients with complications were less satisfied with their breast(s) and with the information provided concerning the surgery. This association was also reported in a systematic review from 2016, which found that patients with complications experienced a significantly worse quality of life and other psychosocial outcomes, with long term effects, compared to patients without complications.[4] The importance of adequate preoperative information provision was also appointed in previous literature. One study interviewed patients after a failed breast reconstruction. The necessity for adequate preoperative information concerning the psychological impact was brought up most frequently. After a failed breast reconstruction, explicit recognition of the patients' suffering and emotional wellbeing by the plastic surgeon is a crucial component of recovery for all patients.[5]

As patients are overall very satisfied with their results after OPS, all eligible patients should be counseled for an oncoplastic reconstruction, even though more extensive surgery could lead to more complications. In accordance with the literature, chapter 2 of this thesis highlighted how surgical complications are negatively associated with patient satisfaction and other patient-reported outcomes in patients after OPS. The importance of providing the patient with extensive information concerning all possible outcomes was emphasized, especially regarding the influence of related complications. Future research should focus on better preoperative counseling strategies and how additional information following the consultation per individual could be optimized.

Pectoral fascia preservation

The surgical technique of mastectomy has undergone significant changes in time and has become less and less extensive. Today, the majority of patients can undergo nipple or skin sparing mastectomies, offering patients enhanced cosmetic results without compromising the oncological safety.[6] Although removal of the pectoralis major (PM) muscle has long been outdated, routine excision of the pectoral fascia (PF) is still part of the current technique.

Chapter 3 of this thesis consists of a systematic review concerning preservation of the PF in oncological mastectomies.[7] Based on the five studies in the review, PF preservation appears to be an oncologically safe procedure, it might reduce postoperative seroma, infection rates, implant extrusion, and bleeding complications, while improving cosmetic outcomes. Unfortunately, the evidence in the available literature is weak since the included studies [8-12] have heterogeneous patient populations with relatively small patient groups, lacking high quality data to support these statements.

Since the systematic review, a few new studies have been published investigating this topic. Mohamed et al. conducted a randomized controlled trial (RCT) with a total number of 101 patients and found a significantly lower cumulative seroma volume in patients who had PF preservation, compared to patients with PF excision. No significant differences in oncological outcomes were found between the groups.[13] Furthermore, in one other study the PF is advocated as the preferred coverage of an implant over an acellular dermal matrix (ADM) in pre-pectoral reconstruction.[14] Another recent review, which summarized common dissection planes for mastectomies, reported it is unusual to detect breast ducts or glandular tissue beyond the dorsal fascia of the breast, so removing the fascia is not routinely performed and depends on the tumor location and degree of muscle invasion. Furthermore, the authors of this review point out PF preservation might decrease surgical complications, but that there is a lack of consensus about the need of removal, unless it is necessary to achieve clear margins.[15]

Another recently published study protocol is the PROFAS study, a double blinded, prospective, randomized controlled pilot study, including patients who are opting for bilateral prophylactic mastectomies in the Academic Breast Cancer Centre Rotterdam, with a within-subject design.[16] The PF will be preserved in one breast, and in the other breast, the PF will be removed. The focus of the study is to assess the impact of PF removal versus preservation on seroma formation and drain policy, and it is hypothesized that PF preservation will decrease seroma, drain volume and postoperative complications. The study started in 2021 but due to the COVID-19 pandemic, prophylactic mastectomies were postponed, and inclusion is still in progress.

The influence of PF preservation on seroma formation has already been studied in two RCT's included in the previous mentioned systematic review in chapter 3. The incidence of seroma was reduced (31% vs 39.8%) in the PF preservation group in the study of Dalberg et al., but these differences were not statistically significant.[9] In the study of Abdelhamid et al., the PF preservation group showed a significantly lower rate of seroma formation—5.6% vs. 24.3%.[8] Unfortunately, this study did not define seroma, so the outcomes of the PROFAS study will hopefully provide more evidence for this specific outcome.

An advantage of the PROFAS study is the small sample size (21 patients) because of the within-subject design, which eliminates all confounders (apart from the performing surgeon and left/right dominance). Unfortunately, the results will be unable to address the oncological safety of PF preservation, because the population only consist of women opting for bilateral prophylactic mastectomies. Except for the studies included in the systematic review, in which no significant differences in oncological outcomes (local recurrence, regional recurrence, or distant metastasis) were found and the study of Mohamed et al,[13] no other recent, large studies have been published on the oncological safety of PF preservation. Because of this, our study group developed the 'PRESERVED' study protocol, a multicentre RCT of patients undergoing a mastectomy with either PF removal or PF preservation, followed by a direct two-stage reconstruction. A total of 354 patients were required, with 177 patients in each group. Unfortunately, after multiple attempts, we were not able to receive sufficient funding to perform this trial.

The nation-wide survey included in this thesis shows that oncological safety is the primary reason for surgeons and plastic surgeons in the Netherlands to remove the PF, even though there is no evidence for this statement in the present literature.[17] One in five breast surgeons reported that the PF was only preserved in cases when the tumor was placed at a safe distance from the fascia, which varied between 1 mm and 2 cm. This suggests that there is no agreement on what constitutes a "safe distance" in this situation. Previous studies showed that

PF invasion may occur when tumors are situated within five millimeters of the PF, but is unlikely to happen with a distance of more than five millimeters.[18, 19] The survey's findings also revealed that breast surgeons' lack of expertise with this method is an important barrier to preserve the PF, even though this seems a more logical anatomical plane, as the PF and the PM muscle should be seen as a single myofascial unit.[7, 20]

Therefore, in line with the development of less invasive mastectomy techniques, the next logical step would be to preserve the PF. However, current evidence is not strong enough to implement this as new golden standard technique. Despite the studies included in this thesis, not enough recent literature assessing the outcomes of PF preservation has been published. Future studies, preferably a large randomized controlled trial, reporting on all outcomes, including oncological safety, remain necessary. Meanwhile, if the PROFAS study will show favorable results of PF preservation, it could already be considered in patients undergoing prophylactic mastectomies, since this is without additional oncological risks.

Implant-based reconstructions

Women planned for a mastectomy should be counseled for the different options of breast reconstruction. Compared to autologous reconstruction, implant-based reconstruction (IBR) remains the most prevalent method to reconstruct the breast. Although the complication and reoperation rates are lower, the failure rate (reconstructive failure due to implant loss) for IBR is higher.[21] It would be of great value if the implant loss rate could be decreased, as it leads to higher rates of re-operations and hospital costs, it might delay adjuvant therapy and leads to a significant decrease in patient satisfaction.[22-26] Multiple risk factors have been described for implant loss, such as obesity, smoking, advanced age, radiotherapy, bilateral procedures, sentinel node biopsy and direct-to-implant (DTI) reconstructions.[23, 27-29] All studies reported slightly different risk factors, probably due to different cohorts and different definitions of implant loss with different follow-up times.

In this thesis, the risk of implant loss was investigated in three chapters. In chapter 5, six risk factors were significantly associated with implant loss; obesity, smoking, a nipple-sparing mastectomy, a DTI approach, and a lower oncological surgeon's volume. Based on four of these risk factors, obesity, smoking, a nipple-sparing mastectomy and a DTI reconstruction, a risk-model was created. The study in chapter 6 aimed to validate this risk-model with a large database from the Dutch Breast Implant Registry (DBIR). Unfortunately this was not successful and the need for a validated risk-model remained. Consequently, in chapter 7, a successfully validated prediction-model was created with data from the DBIR, based on four risk factors; BMI, smoking, prior radiotherapy, and prepectoral placement. Risk

factors were treated as dichotomous variables, and the predicted probability of implant loss ranged from 4.5% in the absence of any risk factors to 38% in the case of four risk factors. Since the model was subsequently internally validated, the model could be expanded to the Dutch reconstructive population at large.

Several studies in literature already assessed the risk on implant loss. One study created an evidence-based intervention bundle with a multidisciplinary team. After implementing this protocol, the implant loss rate in 3 months decreased from 14% to 0%. Among other things, a patient selection was introduced where no more than one risk factor was allowed (BMI>30 kg/m2, smoker, diabetes, radiotherapy, neoadjuvant chemotherapy) and only implants <500 cc were placed.[24] The Dutch national guideline also recommends patient selection, suggesting not to perform immediate implant-based breast reconstruction in patients with more than two risk factors (smoking, BMI≥30 kg/m2, age >55 years, larger breast, bilateral surgery). Moreover, the guideline recommends preferably not to perform immediate implant reconstruction if there is a high chance of postoperative radiotherapy.[30] This guideline was partly based on the study of Fischer et al, where risk factors for implant loss were identified and odds ratios were used to assign weighted risk scores in three categories, low, intermediate and high risk.[23] Although this is the largest study assessing outcomes in IBR associated with implant loss, they only covered 'early' implant loss within the first 30 postoperative days, with a very low overall implant loss rate of 0.8%. This was a much lower rate compared to the study in chapter 7, reporting on 5260 implant-based breast reconstructions included from the DBIR, with an implant loss rate of 6.7%. Moreover, the study in chapter 7 reported a median time to surgical removal of the implant of 42 days (IQR: 21 to 83 days). Based on these results, a substantial part of patients who will suffer from implant loss will be missed with a 30 day follow-up. Some literature even suggest that follow-up should be at least one year for infectious complications, which can lead to implant loss.[31]

Following the results of this thesis, we can conclude that in different cohorts, different risk factors for implant loss were identified. If we compare the study in chapter 5, including data of two medical centers in the Netherlands, with the risk factors derived from the DBIR database in chapter 7, just two risk factors are consistent, which were smoking and obesity. One risk factor, a lower volume of the oncological surgeon, could not be derived from the DBIR database, but could be linked to another important factor. The quality and vascularization of the mastectomy skin flaps are the most important aspects in a successful IBR and could be influenced by the experience of the surgeon. Additionally, until experience is gained establishing skin perfusion, for inexperienced surgeons a two-stage reconstruction is a safer option compared to a DTI reconstruction.[21]

Finally, for the Dutch reconstructive population at large, the best representable cohort to determine implant loss after IBR consists of DBIR data, implicating the paper described in chapter 7 is of great value and could be used for preoperative counseling in the Dutch practice. Moreover, this paper provides a validated prediction model, where the predicted risk of implant loss can easily be calculated for each patient. As an addition to the Dutch national guideline, in which it is advised not to perform immediate IBR in patients with more than two risk factors, this predicted risk can give more detailed information for the treating physician and the patient in a personalized fashion. The treating physician and patient should together define what is an acceptable risk for them, while keeping alternative options in mind. In patients with an unacceptably high predicted risk, alternative options should be considered, such as an autologous reconstruction, a delayed reconstruction or no reconstruction at all. With a delayed reconstruction, the risk factors BMI and smoking and subsequently the predicted risk can be reduced by lifestyle interventions. In patients with more than one risk factor, prepectoral placement should be avoided. Moreover, if implant loss does occur, previous literature emphasizes the importance of clinical and psychological support,[32] and every (plastic) surgeon should strive for full postoperative support of patients who suffered a failed reconstruction.

Strengths and limitations

This thesis has several strengths and limitations. One of the strengths is that this thesis covers a wide spectrum of reconstructive breast surgery, including implant-based reconstructions after mastectomy and oncoplastic surgery in breast-conserving treatments. In addition to the chapters that evaluated reconstructive surgery, the surgical technique of mastectomy was also addressed in this thesis, making it relevant to both plastic and breast surgeons. Finally, an internally validated risk model based on national data was created that could be used in daily clinical practice.

In addition, several limitations can be addressed in this thesis. Some of the papers in this thesis were based on data obtained in one or two centers, which hampered the generalizability to the reconstructive population at large. Furthermore, most studies used a retrospective approach, which inevitably resulted in some missing data of interest, weakening the analysis and conclusions.

Conclusion

This research showed that patients are overall satisfied after OPS and gave positive scores for cosmetic outcomes. In addition, a significant negative effect on these outcomes was observed if a complication occurred. Patients were less satisfied with the breast and with the information provided concerning the surgery,

emphasizing the importance of comprehensive preoperative counseling with extra attention concerning the impact of complications.
Furthermore, a less extensive mastectomy technique was assessed with PF preservation, with promising outcomes. Preserving the PF leads to a more logical anatomical dissection plane in mastectomies and it might have several advantages. Furthermore, it appears to be an oncologically safe procedure based on the most recent research, particularly if the tumor is situated at a safe distance from the PF. Still, future studies are necessary reporting on all outcomes to implement this technique in general practices. In patients opting for prophylactic mastectomies, PF preservation could already be considered as soon as the PROFAS study will show the advantages of PF preservation.
The last part focused on implant loss after IBR, and a validated risk prediction model on implant loss was developed. This prediction model, based on the risk factors BMI, active smoking status, previous radiotherapy and prepectoral placement, will be of great value for preoperative patient counseling and for a better patient selection to reduce implant loss rates.

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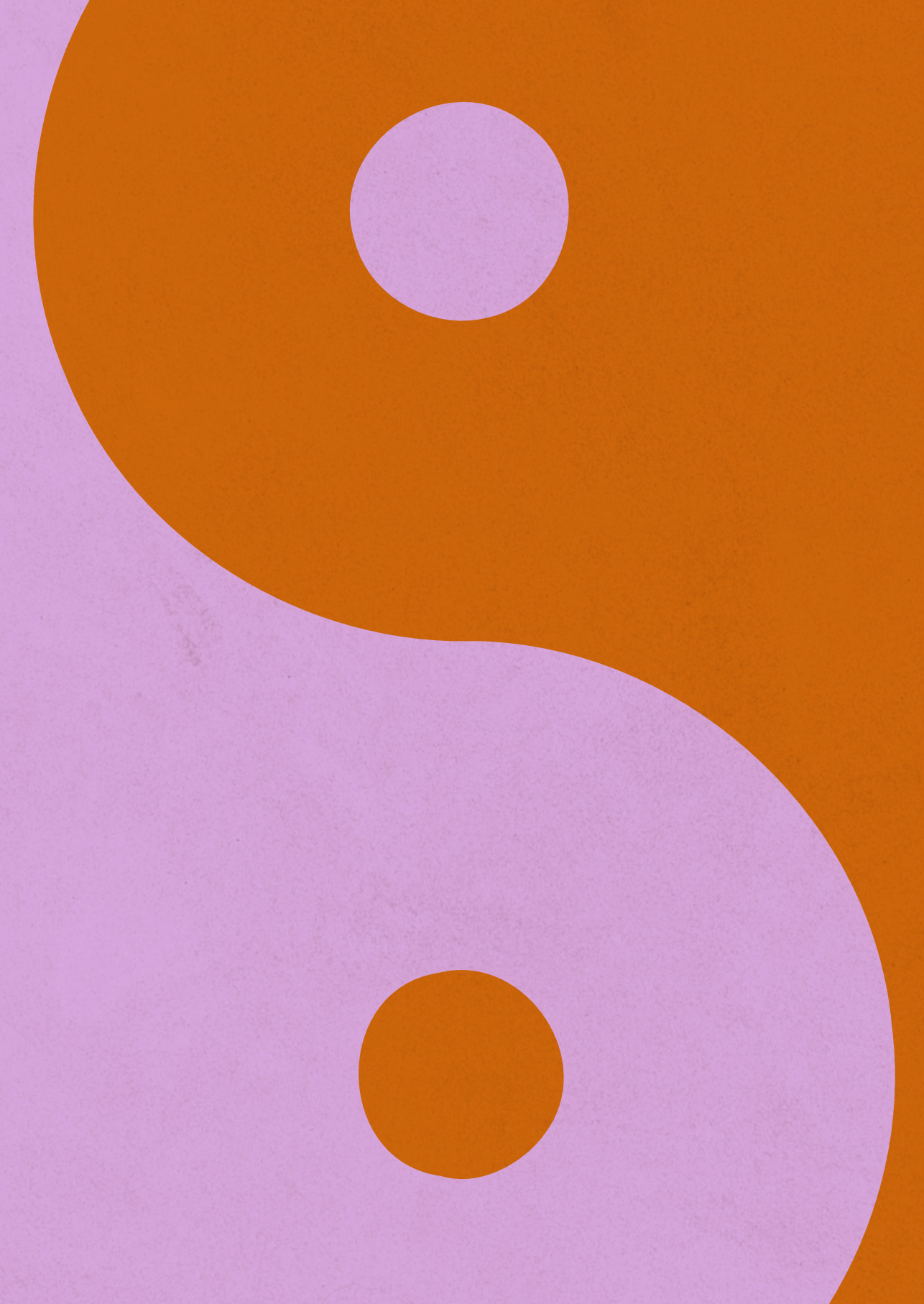

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English summary
Nederlandse samenvatting

ENGLISH SUMMARY

In this thesis, various aspects of reconstructive surgery following breast cancer were investigated. Postoperative outcomes and patient satisfaction after oncoplastic breast-conserving surgery were analyzed. The effects of pectoral fascia preservation during a mastectomy were reviewed and discussed. Furthermore, risk factors for implant loss after implant-based breast reconstruction were studied. A validated risk prediction model for implant loss was developed to improve decision-making and pre-operative counseling.

PART I – Oncoplastic breast-conserving surgery

Cosmetic results after breast cancer treatment have become increasingly important, partly due to improved life expectancy. Oncoplastic breast-conserving surgery (OPS) involves plastic surgery techniques to reconstruct the breast after breast-conserving surgery and aims to improve cosmetic results and oncological safety by obtaining wide resection margins. In the prospective single-center study in **chapter 2,** complication rates, patient satisfaction and cosmetic outcomes after OPS were evaluated, and differences between volume displacement and volume replacement techniques were analyzed. To measure patient satisfaction, the BREAST-Q was used. Cosmetic outcomes were measured by patient self-evaluation and by evaluation of a panel consisting of two independent plastic surgeons and two laymen, based on medical photographs. An overall complication rate of 18.7% was found, with (surgical) intervention needed in 4%. No differences in complication rates were observed between the two techniques and only the expected differences were noted in physical discomfort and symmetry. Patients were generally satisfied, and cosmetic outcomes were scored good to excellent in 60-86%. Additionally, complications had a negative impact on patient satisfaction and cosmetic results. These results highlight the value of extensive preoperative counseling.

PART II – Pectoral fascia preservation in immediate breast reconstruction

The pectoral fascia (PF) is a strong fibro-elastic layer and part of the muscular anatomy, rather than the breast glandular tissue. However, removal of the PF during a mastectomy is still part of the standard procedure. It is hypothesized that preservation of the PF might improve postoperative outcomes, such as reducing seroma formation due to its function in lymph drainage, postoperative bleeding and pain by avoiding injury to the pectoralis major muscle, and enhancing implant reconstructions due to additional coverage, without compromising oncological safety. The systematic review in **chapter 3** provides a structured overview of the literature regarding mastectomy with PF preservation. The main

outcomes assessed were oncological safety, complication rates, implant loss after reconstructive surgery and cosmetic outcomes following reconstruction. Five studies were included. PF preservation did not affect oncological outcomes in terms of local recurrences, regional and distant metastases, or mortality rates. One study reported a significantly lower incidence of seroma with PF preservation. No significant differences were found for infection or bleeding complications, and no objective data were provided for cosmetic outcomes or reconstructive complications. Overall, the literature on PF preservation is scarce. Based on the current evidence, PF preservation seems to be an oncologically safe procedure that potentially reduces complications. Future research is necessary to systematically assess all relevant outcomes.

In the study described in **chapter 4**, we report on a national survey examining attitudes toward PF preservation among Dutch breast surgeons and plastic surgeons. More than half of the Dutch medical centers contributed to a total of 68 responses. The results show that the PF is routinely preserved by one in five breast surgeons and plastic surgeons, and even more surgeons preserve the PF in specific cases. However, opinions and surgical techniques regarding the PF vary widely between the surgeons. These results indicate this subject remains controversial and that the impact of PF preservation on oncological safety, complication rates, postoperative pain, patient satisfaction, and cosmetic outcomes needs to be clarified in future studies on this topic.

PART III – Implant loss risk in implant-based breast reconstruction

Following a mastectomy, implant-based breast reconstruction (IBR) remains the most common form of breast reconstruction. **Chapter 5** reports a retrospective cohort study that included all patients who underwent a mastectomy followed by either a direct-to-implant (DTI) or two-stage breast reconstruction. Implant loss is the most devastating complication of IBR and had an overall incidence of 11.8% in this cohort. Obesity, a bra cup size greater than C, smoking, a nipple-preserving treatment, a DTI reconstruction, and a smaller surgeon's volume, were all risk factors significantly associated with implant loss. In this study, a risk model for implant loss was created based on four of these risk factors (obesity, smoking, nipple-preserving procedure, DTI reconstruction) and showed a predicted risk of 8.4-13% in patients with one risk factor, 21.9-32.5% in the presence of two risk factors, 47.5-59.3% in patients with three risk factors and over 78.2% in the presence of four risk factors.

The study in **chapter 6** aimed to validate the multicenter risk model for implant loss developed in the previous chapter. The validation cohort in this study consisted of 3769 patients who underwent a mastectomy followed by either a two-stage or DTI

reconstructions, registered in the Dutch Breast Implant Registry (DBIR) between 2017 and 2021. Implant loss occurred in 8.1%. Even though the observed implant loss rate increased with the number of risk factors, the observed probability and the predicted probability of implant loss did not match. Only obesity and smoking were significantly related to implant loss among the four risk factors in the risk model (obesity, smoking, nipple-preserving procedure, and DTI reconstruction). In conclusion, the multicenter risk model could not be validated with nationwide data from the DBIR.

Knowing the predicted risk of implant loss during the preoperative workup remains valuable. This can guide the treating physician in planning the mastectomy and type of reconstruction, which will improve counseling women who are considering implant-based breast reconstruction. Therefore, the study in **chapter 7** aimed to create a validated risk prediction model for implant loss after breast reconstruction using perioperative risk factors. Patients who had undergone either a two-stage or DTI breast reconstruction were identified from the DBIR. The cohort was divided into a training (80%) and a validation cohort (20%). A risk prediction model for implant loss was created in the training cohort with multivariate logistic regression, which was subsequently validated in the validation cohort. Risk factors included smoking, BMI, pre-pectoral placement and previous radiotherapy. The model predicted an increasing probability of implant loss from 4.5% without any risk factors to 38% with four risk factors present. Due to the model's successful validation, it may be used in general practice and is a useful tool for preoperative counseling in women who are considering implant-based breast reconstruction.

NEDERLANDSE SAMENVATTING

In dit proefschrift hebben we gekeken naar verschillende aspecten van de reconstructieve mammachirurgie. De postoperatieve uitkomsten en patiënttevredenheid na oncoplastische borstsparende chirurgie werden onderzocht, de uitkomsten na het behouden van de fascia pectoralis tijdens een borstamputatie en de risicofactoren voor implantaatverlies na implantaatreconstructies. Tevens hebben we een gevalideerd risicomodel voor implantaatverlies ontwikkeld wat kan worden ingezet voor een betere preoperatieve planning en om patiënten beter te kunnen informeren.

DEEL I – Oncoplastische borstsparende chirurgie

Het cosmetisch resultaat van de borst na borstkankerchirurgie is, mede door de huidige gunstige levensverwachting na de behandeling van borstkanker, steeds belangrijker geworden. Oncoplastische borstsparende chirurgie is een methode waarbij plastische chirurgische technieken worden gebruikt om de borst te reconstrueren na een borstsparende operatie, met als doel om een beter cosmetisch resultaat te verkrijgen, terwijl de oncologische veiligheid gewaarborgd blijft, of zelfs wordt verbeterd door de mogelijkheid om de tumor met ruimere resectiemarges te omsnijden.
In het prospectieve 'single-center' onderzoek in **hoofdstuk 2** werden complicaties, patiënttevredenheid en cosmetische uitkomsten na oncoplastische borstsparende chirurgie geëvalueerd en werden uitkomstverschillen tussen volume verplaatsing en volume vervangende technieken geanalyseerd. Om de patiënttevredenheid te meten, werd de BREAST-Q vragenlijst gebruikt. Cosmetische resultaten werden gemeten op basis van zelfevaluatie van patiënten en op basis van medische foto's die werden beoordeeld door een panel, bestaande uit twee onafhankelijke plastisch chirurgen en twee leken. Er werd in 18.7% van de patiënten een complicatie gevonden, waarbij in 4% (chirurgische) interventie nodig was. Er werden geen verschillen in complicaties gevonden tussen de twee technieken en alleen de te verwachten verschillen werden gezien in fysiek ongemak en symmetrie. Patiënten waren over het algemeen tevreden en cosmetische resultaten werden in 60-86% goed tot uitstekend beoordeeld. Verder zagen we dat complicaties een negatieve invloed hebben op de patiënttevredenheid en de cosmetische resultaten. Dit benadrukt hoe belangrijk het is om patiënten vooraf goed in te lichten.

DEEL II – Behoud van de fascia pectoralis bij directe reconstructies

De fascia pectoralis is een sterke fibro-elastische laag die onderdeel is van de pectoralis major spier. Hoewel deze structuur dus niet tot het borstklierweefsel behoort, is het verwijderen van deze fascia nog steeds onderdeel van de

standaardprocedure bij een borstamputatie. Het behouden van deze structuur zou zelfs de postoperatieve resultaten kunnen verbeteren, zoals minder seroomvorming door de lymfedrainage functie, minder postoperatieve bloedingen en pijn door minder schade aan de pectoralis major spier en verbeterde implantaatreconstructies door een betere bedekking, zonder dat dit de oncologische veiligheid in gevaar zou brengen. **Hoofdstuk 3** bevat een '*systematic review*' waarin een gestructureerd overzicht van de literatuur wordt gegeven over het behouden van de fascia pectoralis tijdens een borstamputatie. De belangrijkste uitkomsten waren oncologische veiligheid, complicaties, implantaat verlies na reconstructieve chirurgie en cosmetische uitkomsten na reconstructies. Er werden vijf studies geïncludeerd. Het behouden van de fascia pectoralis had geen invloed op de oncologische uitkomsten waarbij werd gekeken naar lokale recidieven, regionale en afstand metastasen en sterftecijfers. Eén studie rapporteerde een significant lagere incidentie van seroom in de groep waar de fascia pectoralis werd behouden. Er werden geen verschillen gevonden voor infectie- of bloedingscomplicaties en er waren geen objectieve resultaten van cosmetische uitkomsten of reconstructieve complicaties. Concluderend is de literatuur over het behoud van fascia pectoralis schaars. Gebaseerd op wat er nu bekend is, lijkt het behoud van de fascia de kans op complicaties te verminderen en oncologisch veilig te zijn. Verder onderzoek is nodig om alle relevante uitkomsten systematisch te beoordelen.

In **hoofdstuk 4** wordt een enquête studie beschreven naar de mening van Nederlandse oncologisch mammachirurgen en plastisch chirurgen ten aanzien van het behouden van de fascia pectoralis. Er reageerden in totaal 68 respondenten uit meer dan de helft van de Nederlandse medische centra. De resultaten laten zien dat de fascia pectoralis routinematig wordt gespaard door één op de vijf chirurgen en door nog een groter deel van de respondenten werd aangegeven dat de fascia pectoralis alleen in specifieke gevallen werd behouden. Verder laten de resultaten zien dat de opvattingen en chirurgische technieken met betrekking tot de fascia pectoralis sterk uiteenlopen. Dit toont aan dat de meningen over dit onderwerp verdeeld zijn en dat de impact van het behoud van fascia pectoralis op oncologische veiligheid, complicaties, postoperatieve pijn, patiënttevredenheid en cosmetische resultaten verder moet worden onderzocht in toekomstige studies.

DEEL III – Risico op implantaatverlies na implantaatreconstructies

Na een borstamputatie blijft een borstreconstructie met implantaten de meest voorkomende vorm om een borst te reconstrueren. In **hoofdstuk 5** wordt een retrospectieve cohortstudie beschreven waarin alle patiënten werden geïncludeerd die een borstamputatie ondergingen, gevolgd door een reconstructie met een directe prothese of een twee-fase reconstructie. Na een implantaatreconstructie

is implantaatverlies de ernstigste complicatie, wat voorkwam in 11.8% in dit cohort. De risicofactoren voor implantaatverlies waren obesitas, een cupmaat groter dan C, roken, een tepelsparende behandeling, reconstructie met een directe prothese en een kleiner jaarlijks volume van operaties door de chirurg. In deze studie werd een risicomodel gemaakt voor implantaatverlies gebaseerd op vier van deze risicofactoren (obesitas, roken, tepelsparende behandeling, reconstructie met directe prothese). Het model toonde een voorspeld risico op implantaatverlies van 8.4-13% in patiënten met één risicofactor, 21.9-32.5% bij patiënten met twee risicofactoren, 47.5-59.3% wanneer er drie risicofactoren waren en meer dan 78.2% bij patiënten met vier risicofactoren.

Het doel van de studie in **hoofdstuk 6** was het valideren van het multicenter risicomodel voor implantaatverlies uit het vorige hoofdstuk. Het validatiecohort in deze studie bestond uit 3769 patiënten die een borstamputatie ondergingen gevolgd door een borstreconstructie in twee fasen of met een directe prothese, geregistreerd in de Nederlandse Borstimplantaten Registratie (DBIR) tussen 2017 en 2021. Verlies van het implantaat trad op in 8.1%. Hoewel het geobserveerde percentage van implantaatverlies toenam naarmate er meer risicofactoren aanwezig waren, kwam de geobserveerde kans niet overeen met de voorspelde kans op implantaatverlies. Van de vier risicofactoren (obesitas, roken, tepelsparende procedure en een reconstructie met een directe prothese) waren alleen obesitas en roken significant gerelateerd aan implantaatverlies. Het multicenter risicomodel kon dus niet gevalideerd worden met landelijke DBIR data.

Het blijft waardevol om het voorspelde risico op implantaatverlies tijdens het preoperatieve consult te bespreken met de patiënt. Het kan de behandelend arts helpen bij het plannen van de borstamputatie en het type reconstructie, om zo de begeleiding van vrouwen die deze ingreep overwegen te verbeteren. Het doel van de studie in **hoofdstuk 7** was daarom om een gevalideerd predictiemodel te maken voor het risico op implantaatverlies na borstreconstructies met behulp van risicofactoren. Patiënten die een borstreconstructie in twee fasen of met een directe prothese hebben ondergaan, werden geïncludeerd vanuit de DBIR database. Het cohort was verdeeld in een trainingscohort (80%) en een validatiecohort (20%). In het trainingscohort werd een predictiemodel voor implantaatverlies gemaakt met multivariate logistische regressie, dat vervolgens werd gevalideerd in het validatiecohort. De risicofactoren in het predictiemodel waren roken, BMI, pre-pectorale plaatsing en eerdere radiotherapie. Het model voorspelde een toenemende kans op implantaatverlies van 4.5% bij patiënten zonder risicofactoren tot 38% bij patiënten met vier risicofactoren. Doordat het predictiemodel succesvol intern gevalideerd is, kan het worden gebruikt in de algemene praktijk en als hulpmiddel worden gebruikt tijdens de preoperatieve counseling van vrouwen die een borstreconstructie met implantaten overwegen.

APPENDIX

List op publications
Dankwoord
Curriculum Vitae

LIST OF PUBLICATIONS

Becherer BE, van Bommel ACM, Hommes JE, Hoornweg MJ, Keuter XHA, Young-Afat DA, Liem PLT, Mureau MAM, Rakhorst HA; DBIR collaborators. Dutch Breast Implant Registry (DBIR) Annual Report 2018: Version 2019.01. Leiden (NL): Dutch Institute for Clinical Auditing; 2019 Nov.

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Vrolijk JJ, Becherer BE, van Bommel ACM, Hommes JE, Hoornweg MJ, Keuter XHA, Young-Afat DA, Liem PLT, Verkooijen HM, Mureau MAM, Rakhorst HA; DBIR collaborators. Dutch Breast Implant Registry (DBIR) Annual Report 2020: Version 2021.01. Leiden (NL): Dutch Institute for Clinical Auditing; 2021 Oct.

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Melse PE, Moes I, Becherer BE, de Boer M, van Bommel ACM, Hommes JE, Hoornweg MJ, Keuter XHA, Liem PLT, Verkooijen HM, Vrolijk JJ, Young-Afat DA, Mureau MAM, Rakhorst HA; DBIR collaborators. Dutch Breast Implant Registry (DBIR) Annual Report 2022: Version 2023.01. Leiden (NL): Dutch Institute for Clinical Auditing; 2024 Feb.

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ABOUT THE AUTHOR

Yara Lynn Blok was born on the 1st of January, 1993, and grew up in Muiderberg, the Netherlands. She attended secondary school at Willem de Zwijger college in Bussum and already knew at young age she wanted to become a plastic surgeon. After completing the Gymnasium in 2010, she went for voluntary work to Nepal to teach English at a primary school in Pokhara. In 2011, she started studying medicine at the Vrije Universiteit Amsterdam and moved to the city. After graduating medical school in 2018, she obtained clinical experience as a resident not in training at the department of cardiothoracic surgery in Amsterdam (VUMC) and at the department of surgery in Beverwijk (RKZ). After this, she worked at the department of plastic surgery in Leiden (Alrijne hospital and Leiden University Medical Center) and in Rotterdam (Erasmus Medical Center), where she was admitted for the plastic surgery residency. In September 2023, Yara started her plastic surgery residency in Hoorn (DLZ). Besides her clinical work, she started with medical research in 2018 in the field of breast reconstructive surgery, which eventually progressed into a PhD traject at Leiden University Medical Center. Next to her career, she likes bike racing, running, snowboarding, traveling and all kinds of creative projects. She lives in the north of Amsterdam with her husband Victor and loves to spend time with her family, friends and cats.