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Patient reported outcome and quality of life after delayed breast reconstruction - An RCT comparing different reconstructive methods in radiated and non-radiated patients

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Running Title: Patient reported outcome after delayed breast reconstruction

Conflict of interest

The authors have no conflict of interest.

MicroAbstract

This study compares different techniques in radiated and non-radiated patients, respectively, as regards health-related quality of life. The radiated patients were randomized to latissimus dorsi flap or DIEP flap and non-radiated patients to thoracodorsal flap or expander/implant. There was a clear improvement in quality of life in all groups; although, no distinct differences could be seen for different methods.

Abstract

Background: Health-related quality of life (HRQoL) is one of the core outcomes for breast reconstruction. The aim of this study was to evaluate whether the method of delayed breast reconstruction affects long-term HRQoL.

Methods: Participants were divided into two arms dependent on previous radiotherapy, and subsequently randomized between two methods of breast reconstruction: a latissimus dorsi flap or a deep inferior epigastric artery perforator flap in the radiated arm and a thoracodorsal flap and implant or an expander in the non-radiated arm. Validated instruments were used: BREAST-Q to evaluate breast specific HRQoL and satisfaction, RAND-36 and EQ-5D to evaluate generic HRQoL, and BDI-21 to measure symptoms of depression and anxiety.

Results: During the recruitment period (2009-2015), 233 patients were randomized. After opt-outs and exclusions, the remaining 107 participants comprise the study sample. Postoperative HrQoL was measured on average seven to eight years post-operatively. Response rates varied between 60 and 82 per cent. The BREAST-Q scores were higher after the reconstruction than before for the great majority of domains in both arms; albeit statistically significant only between the two methods for physical well-being chest in the radiated arm. Most participants in both arms had minimal or mild depression both before and after the operation.

Conclusion: No distinct differences in long-term HrQoL could be seen for different methods There was a clear improvement in HrQoL compared to pre-reconstruction in all groups, but the effect of specific reconstructive methods on scores could not be reliably demonstrated.

ClinicalTrials.Gov identifier NCT03963427

Key words: breast reconstruction, quality of life, patient reported outcome, PROM, DIEP, latissimus dorsi flap, expander, implant, thoracodorsal flap, randomized controlled trial

Clinical Practice Points

There are few studies providing high-quality evidence supporting the use of different techniques for breast reconstruction. In this study, the patients' health related quality of life was increased in all groups. The BREAST-Q scores were higher after the reconstruction than before for the great majority domains in both arms; albeit statistically significant only between the two methods for physical well-being chest in the radiated arm. Most participants in both arms had minimal or mild depression both before and after the operation. The study highlights the difficulty of conducting randomized controlled trials in preference sensitive procedures, such as breast reconstruction. Selection, inclusion, and attrition biases complicate the interpretation of the results.

Introduction

A breast reconstruction is performed to improve the patient's quality of life and satisfaction with her breasts. Quality of life, women's cosmetic satisfaction, normality, self-esteem, emotional well-being, and physical well-being are part of the core outcome set for breast reconstruction[1]. Nonetheless, there is no consensus regarding how these outcomes should be evaluated. There are few studies providing high-quality evidence supporting the use of different techniques for breast reconstruction and it is well-known that it is challenging to conduct randomized clinical trials

(RCTs) in breast reconstruction, mainly due to patients' and surgeons' preferences leading to recruitment difficulties [2]. Consequently, there are few RCTs comparing quality of life in different breast reconstruction techniques [3-5].

Quality of life can be defined in different ways and can allude to health, quality of life, and health-related quality of life (HrQoL) and there is no golden standard to measure it [6]. In practice, HrQoL is measured using generic patient reported outcome measures (PROMs), which can be used in any patient independent of health condition, and disease- or condition-specific PROMs, which measure symptoms of relevance in a certain disease. Generic instruments can be used to compare patients with different conditions to each other but might be too general to capture some of the problems particular patient groups have and therefore a combination of the two are often used [7]. Several of the most widely used generic instruments have been used previously to evaluate breast reconstruction: the Medical Outcomes Study 36-Item Short Form (SF-36) Health survey/RAND 36-Item Short Form Health Survey [8, 9], Health Utilities Index (HUI) [10], EuroQol Instrument (EQ-5D) [11], and Patient-Reported Outcomes Measurement Information System (PROMIS) [12]. Moreover, symptom specific instruments have been used previously, such as the Beck Depression Inventory (BDI) and Hospital Anxiety Depression Scale (HADS) [13]. There are three validated and reliability tested breast reconstruction specific PROMs [14]: BREAST-Q, BRECON-31, and EORTC QLQ-BRECON-23, of which BREAST-Q is the most widely used [15]. They all contain items on aspects of the core outcomes [1]: cosmetic satisfaction, normality, self-esteem, emotional well-being, and physical well-being related to the breast/s.

The aim of this study was to evaluate whether the method of delayed breast reconstruction affects long-term HRQoL in recurrence free women treated for breast cancer with unilateral mastectomy. Participants were divided into two arms dependent on previous radiotherapy, and subsequently randomized between two methods of breast reconstruction: a latissimus dorsi flap (LD) or a deep inferior epigastric artery perforator

(DIEP) flap in the radiated arm and a thoracodorsal flap and implant (TD) or expander (EXP) in the non-radiated arm. Validated instruments were used: BREAST-Q to evaluate breast specific HRQoL and satisfaction, RAND-36 and EQ-5D to evaluate generic HRQoL and BDI-21 to measure symptoms of depression and anxiety.

Patients and methods

Study design, protocol, and ethics

This study is a clinical randomized prospective trial with two arms: non-radiated and radiated patients. The Go Breast Prospective study protocol has been published on ClinicalTrials.Gov (identifier NCT03963427). The Regional Ethical Committee of Gothenburg reviewed and approved the study (043-08). Procedures followed were in accordance with the Helsinki Declaration of 1964, as revised, and the Good Clinical Practice (GCP) guidelines. Participants gave their written informed consent to participate in the study and to publication of the results.

Participants and randomization

Participants, recruitment, and sample size have been described previously [16]. In brief, all women aged > 18 years with a unilateral mastectomy defect referred to our department for delayed breast reconstruction were assessed for inclusion. Women who smoked, had a BMI>30, or were unable to give informed consent were excluded. Radiated women who previously had had abdominal liposuction or surgery that make a DIEP flap inappropriate and/or were over the age of 60 years were also excluded, as well as non-radiated women with extensive scaring on the thorax. When

the study was designed, the department was reluctant to reconstruct patients over the age of 60 and comorbidities with DIEP flaps and therefore they were excluded from randomization. This is no longer departmental practice. If a patient had a recurrence during the follow-up time of the study, she was excluded. In the non-radiated arm, patients were randomized to either a one-stage lateral thoracodorsal flap with a permanent implant (TD) [17] (a perforator based flap similar to the anterior lateral intercostal artery perforator flap (LICAP) [18], but without intramuscular dissection of the perforator) or a two-staged expander reconstruction (EXP) [19]. In the radiated arm, patients were randomized either to a latissimus dorsi-flap (LD) combined with a permanent implant [20] or to a deep inferior epigastric artery perforator flap (DIEP) [21]. Contralateral procedures for symmetry were performed at the time of the breast reconstruction, if indicated. Information on demographics, patient characteristics, comorbidities, breast cancer stage, breast cancer treatment, and early complications have been published previously [16].

Patient reported outcomes

Patient reported outcomes were measured pre- and post-operatively. The participants were sent an envelope including the questionnaires and a stamped return envelope. The participants received two reminders, after two and five weeks, and a maximum of five attempts to reach non-responders by phone were made 3-9 months later. The instruments used are described below.

BREAST-Q reconstruction measures different aspects of satisfaction with breast reconstruction, with care and health-related quality of life specific to the breast/s. The following domains were analysed: Satisfaction with breast/s (16 items), Satisfaction with outcome (7 items), Psychosocial well-being chest (10 items), Sexual well-being (6 items), Physical well-being chest (16 items), and Satisfaction with information (15 items). Each item is rated on a Likert scale and for each domain a raw scale summed scores is calculated and converted to a standardized score

between 0 and 100, based on a conversion table created with transformed Rasch logits. A higher score indicates a higher level of patient satisfaction. Normative data have been described for two American populations including a total of 1500 women [22, 23] and one Australian population including 500 women [24] (Electronic supplement 1). There are no anchor-based minimal important differences (MIDs) published for BREAST-Q [25], but distribution-based MIDs, indicating the lowest change value beyond the measurement error [26, 27], is 4 for Satisfaction with Breasts, 4 for Psychosocial Well-being, 3 for Physical Well-being, and 4 for Sexual Well-being [28]. BREAST-Q has been validated [29, 30] and translated to Swedish. It has been extensively used in previous studies on breast reconstruction [15]. Use of BREAST-Q, authored by Drs. Klassen, Pusic and Cano, was made under license from Memorial Sloan Kettering Cancer Center, New York, USA.

Beck's Depression Inventory (BDI-2) comprises 21 items on the patient's symptoms of depression during the last week. Each item is rated on a 4 point-scale (0-3), where 0 indicates minimal symptoms and 3 maximum symptoms, and a total score is calculated. A total score of 0-13 indicates minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression [31, 32]. BDI-21 has previously been used to evaluated breast reconstruction [8]. BDI-21 was purchased from Pearson Clinical.

RAND 36-Item Short Form Health Survey [33], a public domain form of the Medical Outcome Study Short Form 36- Item Health Survey (MOS SF-36) [34], is a generic health-related quality of life questionnaire. RAND 36 was developed as part of the Medical Outcomes Study (MOS)[35]. It comprises eight subdomains: physical functioning (10 items), role limitations caused by physical health problems (4 items), role limitations caused by emotional problems (3 items), social functioning (2 items), emotional well-being (5 items), energy/fatigue (4 items), pain (2 items), and general health perceptions (5 items). The patients score their health during the last four weeks on Likert scales. Items are transformed into a percentage of the highest possible score with each item utilizing 100 as the most positive result. Individual constituent items are

	DIEP (n=14)			**LD** (n=12)			d DIEP vs. d LD (⍰)
Satisfaction with breast	38 (19)	73 (14)	26 (20)	46 (10)	57 (16)	4 (15)	0.29
Psychosocial well-being	55 (16)	86 (25)	20 (18)	46 (9)	70 (18)	19 (14)	0.76
Physical well-being chest	79 (8)	79 (11)	6.5 (11)	73 (9)	65 (19)	0 (16)	0.22
Sexual well-being	37 (13)	72 (14)	18 (11)	40 (15)	49 (24)	4 (18)	0042
Satisfaction with outcome		86 (15)			61(25)		0.82

Table 2. BREAST-Q scores in the two study arms

GDelta – difference between pre- and postoperative values

DIEP Deep inferior epigastric artery perforator flap

EXP Expander

IQR Intraquartile range

LD Latissimus dorsi flap

TD Thoracodorsal flap

BDI 21	**NON-RADIATED ARM**				**RADIATED ARM**			
N (%)	**EXP**		**TD**		**DIEP**		**LD**	
	Pre (n=37)	Post (n=37)	Pre (n=29)	Post (n=29)	Pre (n=10)	Post (n=10)	Pre (n=9)	Post (n=9)
Minimal	31 (84%)	37 (100%)	25 (86%)	26 (87%)	9 (90%)	9 (90%)	6 (67%)	7 (78%)
Mild	5 (14%)	0	3 (10%)	2 (7%)	0	0	2 (22%)	0
Moderate	1 (3%)	0	1 (3%)	0	0	0	1 (11%)	2 (22%)
Severe	0	0	0	1 (3%)	1 (10%)	1 (10%)	0	0

Table 3. BDI 21 scores in the two study arms.

BDI-21 Beck's depression index

DIEP Deep inferior epigastric artery perforator flap

EXP Expander

LD Latissimus dorsi flap

TD Thoracodorsal flap

RAND-36 Dimension	Preoperative Median (IQR)	Postoperative Median (IQR)	□	Preoperative Median (IQR)	Postoperative Median (IQR)	□	Difference between groups (Mann Whitney U-test)
	NON-RADIATED ARM						
	EXP n=45			**TD** n=34			d EXP vs. d TD (□)
Physical functioning	90 (5)	92.5 (10)	0 (10)	95(5)	95 (7.5)	0 (5)	0.56
Role physical	100 (13)	100 (13)	0 (13)	100 (13)	100 (25)	0 (13)	0.25
Bodily pain	74 (14)	74 (15)	0 (16)	75 (20)	74 (20)	0 (13)	0.99
General	60 (2.5)	57 (3)	-5 (8.8)	57 (6)	60 (2.5)	0 (5)	0.099

Health	61 (8.2)	55 (7.7)	-5.1 (11)	60 (9.3)	57 (7.6)	-3.3 (12)	
Vitality	55 (5)	55 (5)	0 (7.5)	55 (7.5)	50 (6.3)	0 (7.5)	0.78
Social functioning	100 (13)	100 (13)	0 (6.2)	100 (6.3)	100 (13)	0 (6.3)	0.05
Role emotional	100 (12)	100 (12)	0 (17)	100 (17)	100 (17)	0 (0)	0.12
Mental health	64 (4)	68 (4)	8 (6)	66 (2)	64 (4)	0 (4)	0.0017
	RADIATED ARM						
	DIEP n=14			**LD** n=12			DIEP vs LD (?)
Physical functioning	95 (6.2)	95 (13)	0 (6.2)	90 (7.5)	80 (18)	-10 (7.5)	0.22
Role physical	100 (13)	100 (0)	0 (0)	75 (38)	100 (50)	0 (13)	0.17
Bodily pain	74 (12)	73 (22)	0 (15)	64 (6)	51 (23)	-10 (41)	0.17

General Health	60 (3.2)	56 (8.2)	-5 (7.5)	62 (5)	59 (6.5)	0 (13)	0.15
Vitality	50 (6.2)	50 (5)	-5 (10)	60 (7.5)	55 (5)	0 (7.5)	0.91
Social functioning	100 (16)	100 (6.2)	0 (13)	88 (17)	75 (28)	-13 (16)	0.12
Role emotional	100 (17)	100 (0)	0 (8.2)	67 (50)	67 (34)	17 (51)	0.85
Mental health	48 (5)	64 (4)	4 (8)	68 (8)	66 (6)	4 (6)	0.94

Table 4. RAND-36 scores in the two study arms

GDelta – difference between pre- and postoperative values

DIEP Deep inferior epigastric artery perforator flap

EXP Expander

IQR Intraquartile range

LD Latissimus dorsi flap

TD Thoracodorsal flap

EQ 5 D	NON-RADIATED ARM	RADIATED ARM

	EXP		**TD**		**Difference between EXP and TD**	**DIEP**		**LD**		**Difference between DIEP and LD**
Dimensions	Pre (n=47)	Post (n=47)	Pre (n=31)	Post (n=31)	Chi ^{2}	Pre (n=14)	Post (n=14)	Pre (n=12)	Post (n=12)	Chi ^{2}
Mobility n (%)										
Any problem	6	3	1	0		0	0	0	1	
No problem	41 (87%)	44 (94%)	30 (96%)	31 (100%)	0.91	14 (100%)	14 (100%)	12 (100%)	11 (92%)	0.71
Self-care n (%)										

Any problem	1	1	0	1		0	0 (0%)	0	1	
No problem	46 (98%)	46 (93%)	31 (100%)	30 (97%)	0.92	14 (100%)	14 (100%)	12 (100%)	11 (92%)	0.71
Usual activities n (%)										
Any problem	5	3	1	2		1	1	3	1	
No problem	42 (89%)	44 (94%)	31 (97%)	30 (94%)	0.81	13 (93%)	13 (93%)	9 (75%)	11 (92%)	0.54
Pain/discomfort n (%)										
Any problem	14	17	11	13		8	6	8	9	
No problem	33 (70%)	30 (64%)	20 (65%)	18 (58%)	0.98	6 (43%)	8 (67%)	4 (33%)	3 (25%)	0.58
Anxiety/depression n (%)										
Any problem	21	8	8	9		4	2	6	3	

No problem	26 (55%)	39 (83%)	23 (74%)	22 (71%)	0.25	10 (71%)	12 (86%)	6 (43%)	9 (75%)	1

VAS (Median (IQR))	Pre (n=42)	Post (n=42)	G	Pre (n=29)	Post (n=29)	G	EXP vs. TD (G) (Mann Whitney U)	Pre (n=14)	Post (n=14)	G	Pre (n=11)	Post (n=11)	G	DIEP vs. LD (G) (Mann Whitney U)
	80 (7.5)	85 (8)	0 (10.5)	90 (5)	90 (6)	3 (7.25)	0.85	77.5 (7)	90 (9.5)	10 (5)	75 (9)	80 (13.2)	0 (11.2)	039

Table 5. EQ-5D scores in the two study arms

GDelta – difference between pre- and postoperative values

DIEP Deep inferior epigastric artery perforator flap

EQ-5D EuroQol 5 dimensions

EXP Expander

IQR Intraquartile range

LD Latissimus dorsi flap

TD Thoracodorsal flap

VAS Visual analogue scale

Fig. 1