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Patient Reported Outcomes (PROs) after immediate latissimus dorsi breast reconstruction and adjuvant treatments, and their predictors at two and three-year follow-up

This is an Original Article.

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ABSTRACT

Aims: To estimate the impact at two and three years post-surgery of implant-assisted latissimus dorsi (LDI) and autologous LD (ALD) flap breast reconstructions (BRRs) on patient-reported outcomes (PROs), and secondarily, to determine whether baseline characteristics predict PROs.

Methods: Multi-centre prospective cohort study. The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30) and breast cancer module (QLQ-BR23); Functional Assessment of Cancer Therapy-Breast and Hospital Anxiety and Depression Scale PROs, were completed pre-operatively and at 2- and 3-years after BRR. The effects of LDI and ALD, adjusted for baseline clinico-demographic characteristics, were estimated with multiple linear regressions. Effect-sizes over 0.5 were considered clinically important.

Results: 206 patients (93 LDI and 113 ALD) were recruited (2007-2013); 66% were node negative; 34% received radiotherapy (RT). Women with adverse clinico-pathology were more likely to have received RT and undergo ALD. Each surgical group showed clinically important impacts at two and three-years, including improvements in emotional scales, but worse physical functioning, social well-being, body image and anxiety. RT adversely affected social function at two years (P=0.002). Women undergoing ALD BRR had significantly improved sexual functioning (P=0.003) at 3-years relative to those who had LDI BRR, even after adjusting for case-mix (P=0.0067). Younger women experienced worse arm symptoms (P=0.005) and physical well-being (P=0.006) than older women at 3-years.

Conclusion: Clinically important changes occurred in physical functioning, breast symptoms, body image and psychological distress. These results will guide selection of key PRO domains and sample size calculations of future studies.

INTRODUCTION

Improvements in early detection and systemic treatments of breast cancer have resulted in 500,000 long-term survivors in the United Kingdom[1]. Currently, 53% of women are recommended for mastectomy with an increasing annual trend[2]. In 2009, 15,479 breast cancer patients undergoing mastectomy were audited in the UK National Mastectomy and Breast Reconstruction (NMBR) audit[2], where 4796 (31%) underwent breast reconstruction.

The loss of a breast adversely affects a range of patient-reported outcomes (PROs), which may be considered multidimensional aspects of a woman's health-related quality of life (HRQL)[3-5]. The pedicle latissimus dorsi (LD) or "back flap" procedure involves transferring muscle, fat and skin to the chest wall and is commonly used[2, 5]. The autologous tissue LD (ALD) procedure involves an extended donor/back site dissection of tissues potentially avoiding an implant[5]. The implant-assisted LD reconstruction (LDI) minimises the extent of donor site dissection using an implant to achieve the desired volume[5]. Current evidence does not support the superiority of either type of LD procedure in terms of PROs[2, 3, 6]. Clinicians may favour immediate autologous procedures when post-mastectomy radiotherapy (PMRT) is predicted pre-operatively. This is based on studies suggesting superior cosmetic outcomes, although there is poor evidence comparing this approach to delayed procedures[2, 3, 5-8].

The NMBR audit, that assessed PROs from 3- to 18-months using the BREAST-Q breast reconstruction questionnaire[9]. The most commonly reported adverse effects on PROs were physical and functional difficulties with the shoulder girdle and abdomen (34% reported difficulties most or all of the time); dissatisfaction with the reconstructed breast (40%) and donor site (15-30%); general pain and psychosocial difficulties ranging from 15-40%[10]. In the

current study, the European Organisation for the Research and Treatment of Cancer (EORTC) core PRO questionnaire (QLQ-C30) was used[11] supplemented by the breast-specific module (QLQ-BR23)[12] and the Functional Assessment of Cancer Therapy-Breast Cancer scale (FACT-B)[13]. While these questionnaires address wide-ranging issues relevant to women with breast cancer, they do not cover issues specific to breast reconstruction. Therefore, an EORTC breast reconstruction module was recently developed[14].

A systematic review of PROs after breast reconstruction showed no clinical trials and only a few prospective longitudinal cohort studies (4 out of a total of 11) that reported PROs up to 24-months after reconstruction[3]. None of the prospective cohort studies evaluated the effects of PMRT on PROs[3], although PMRT may confer a survival benefit when combined with systemic adjuvant therapies[15, 16]. Increasingly, there is a reliance on methodologically robust cohort studies for evidence on the comparative effectiveness of different types of reconstructions, where randomized trials are challenging[17, 18]. There is no consensus in the literature regarding the impact and duration of breast reconstruction effects on PROs[3]. Despite the known clinical efficacy of both types of LD breast reconstructions, there is a paucity of information on the effect-sizes of core PRO domains in all studies[3, 8].

This paper reports on an ongoing multi-centre cohort study. We have previously reported PROs 12 months post-operatively[8]. The aims of the current paper are to evaluate: effect-sizes for change from baseline (pre-operative) at 2- and 3-years post-operatively on all PRO domains of two common types of breast reconstructions; which baseline factors are predictive of PRO domain scores at 2- and 3-years; which PRO domains are most sensitive to demonstrating changes over time; and what differences exist between LDI and ALD groups in PRO scores at 2-

or 3-years after adjusting for clinico-demographic case-mix. This study aims to generate hypotheses and provide estimates of domain effect-sizes to guide subscale selection within PROs and sample-size calculation for future studies[19].

METHODS

Study design, quality control and risk of bias:

This study was developed as a protocol-driven prospective design[18]. Several clinical risk factors potentially biased the comparison of PROs in ALD versus LDI reconstructions, as higher risk breast cancer patients were more likely to have poorer PROs at diagnosis consequent to more aggressive treatments[4, 8]. It is this clinically higher risk group that was more likely to be recommended for immediate ALD rather than LDI reconstructions[8, 15]. These clinical risk factors were assessed and compared between ALD and LDI groups at baseline, and adjusted for in regression analyses of PROs. All missing data (PROs and clinical) was accounted for (Figure 1).

Study sample:

This paper describes the extended follow up (January 2007 to May 2013) of a multi-centre prospective longitudinal cohort study ethically approved (National Research Ethics Committee Wiltshire: 05/Q2008/14) and conducted in six UK centres (Bristol, Cambridge, Glasgow, Hull, Swindon and York). Eligibility criteria have been previously described[8]. These included women with early breast cancers (Stages I-II) in one or both breasts, and excluded women with previously diagnosed breast cancers, confirmed metastatic disease and recommended for delayed breast reconstructions[8].

Detailed study processes have been described relating to: clinical diagnosis; local multidisciplinary team decision-making regarding PMRT recommendations; dual localisation sentinel lymph node biopsy and magnetic resonance imaging according to clinical guidelines[8, 15]. Women who consented then self-reported questionnaires prior to mastectomy and breast reconstruction (baseline) at their pre-operative assessment clinic, and were subsequently posted their 2- and 3-year post-reconstruction questionnaires using a self-addressed envelope. Two postal reminders prompted patients to return their questionnaires. Recurrent (local or distant) disease did not exclude questionnaire administration, except in the case of cerebral metastases.

Primary endpoints:

Four PRO questionnaires were used to evaluate the levels of change (expressed as the mean change from baseline at 2- and 3-years post-operatively divided by the standard deviation of change, i.e. 'effect-size') on patient-reported symptom and functioning over time after immediate ALD or LDI reconstructions treated with PMRT or no PMRT. The EORTC core quality of life questionnaire, QLQ-C30, was used to assess core PRO domains of quality of life (functioning and symptoms)[11], alongside the breast cancer module, QLQ-BR23, to evaluate breast and arm symptoms, sexual functioning and body image[12]. The Hospital Anxiety and Depression Scale (HADS), distinguishing anxiety and depression, was also used[20]. FACT-B was used to assess physical, social, emotional and functional well-being[13]. Items within each subscale of each PRO were summed and transformed to a range of 0 to 100[12, 13]. For body image, functioning and well-being scales, higher scores were indicative of better outcomes; positive change indicated improvement and negative change indicated worsening. In contrast, for symptom scales (breast, arms, pain and fatigue), anxiety and depression, higher scores

were indicative of worse outcomes; positive change indicated worsening and negative change reflected improvement[12, 13]. Selection of these PROs was based on previously reported PRO studies; with no validated breast reconstruction-specific questionnaires at the time this study was designed[8, 19, 21]. In the Michigan Breast Reconstruction Outcomes Study (MBROS), these PROs showed significant differences in mean scores after types of immediate and delayed breast reconstruction[19, 21].

Secondary endpoints:

Patient's compliance rates for completion of PROs were documented (Figure 1). Adverse clinical events were graded using the Dindo-Clavien classification[22]. Early surgical complications were recorded up to and including 3-months after breast reconstruction, compared to late complications occurring between 4-months to 3-years. Loco-regional recurrence and distant metastatic disease were assessed using established criteria[23].

Clinical and demographic characteristics:

Clinical Report Forms (CRFs) were used to record all clinical details as described including socio-demographic factors[8] (Table 1). Additional surgeries (complications or cosmetic procedures) were documented over 3-years. Annual clinical follow-up occurred on or close to the anniversary date of breast reconstruction.

Statistical analysis:

As this was primarily a hypothesis-generating study, the sample size was based on obtaining sufficient numbers of women in the main treatment groups of interest to provide reasonably reliable estimates of effect-size for all domains/subscales within the selected PROs. The

purpose of these preliminary effect-size estimates was to guide PRO domain selection and sample size calculation for future studies[24, 25]. At the time of analyses for this paper, the total sample was sufficiently powered to evaluate relatively small effect-sizes (0.3) for intra-group changes from baseline to 2-years (87% power) and 3-years (76%) in the pooled surgical groups, and moderate effect-size changes (0.5) within each reconstruction group (ALD, LDI separately) (>95% power at 2 years, >75% at 3 years). It was somewhat underpowered to detect moderate effect-size differences between ALD and LDI groups at 2-years (68% power) and more so at 3-years (54%). Cognizant of the large number of p-values generated, a cut off of $p<0.01$ was used to indicate statistical significance. All analyses were performed using the R-program version 2.15.1 (The R Foundation for Statistical Computing, Bell Laboratories, Lucent Technologies, USA). No imputation of missing values was made and each result was based on all patients for whom relevant data were recorded.

Baseline clinical and socio-demographic data were compared between the two surgical groups. Categorical variables, summarised as proportions, were compared using the Chi square test or Fisher's exact test. Continuous data, summarised using the mean and standard deviation or the median and range where distributions were non-normal, were compared using the Student's t-test or the non-parametric rank sum test.

Mean domain score changes from baseline (pre-operative) to 2- or 3-years were calculated within the whole sample (Table 2) and within each surgical group (Figure 2). Effect-sizes were measured by Cohen's d[26]. The clinical significance of effect sizes for the QLQ-C30 and FACT-G data were interpreted using evidence-based guidelines[24-27]. As similar guidance is lacking for the other PROs, general guidance was used whereby an effect-size less than about 0.3 was

considered 'small' but clinically relevant[26, 27], and effect-sizes exceeding about 0.5 were referred to as 'moderate' and considered 'unequivocally clinically important', and finally effect-sizes of larger than 0.8 were called 'large'[24-27].

Longitudinal analysis of PROs at 2- and 3-years was done by fitting a separate generalized estimating equations model for each PRO domain, including the corresponding baseline PRO value as a covariate to improve precision of estimates of other predictors (Figure 3). Each model included the following baseline variables as potential predictors: type of reconstruction, PMRT, chemotherapy (adjuvant or neo-adjuvant), age at operation (50 years and over, or under 50 years), early (up to 3-months) and late complications (4-months to 3-years) for each PRO domain. The contribution of each baseline parameter to predicting each PRO domain was measured by the p-value of the corresponding regression coefficient. Since P-values do not indicate the direction of an effect, each was converted to a Z-score[27] (e.g. p-value of 0.05 converts to a Z score of ±1.96).

A second multiple linear regression model (supplementary data not shown) was used to generate case-adjusted estimates of differences between LDI and ALD groups in PRO changes at 2- and 3- years. In these models, the main predictor of interest was type of surgery. Covariates included were: baseline PRO value (to improve precision, as above); and each variable in Table 1 (body mass index, chemotherapy, tumour size, margin positivity, lymph node positivity, PMRT and late complications) that differed between surgical groups at baseline ($p<0.10$ to be inclusive of all potential confounders). Type of axillary surgery was omitted as it was considered a surrogate for lymph node positivity. Given the large number of covariates, the Holm-Bonferroni allowance was used to adjust for multiple testing.

RESULTS

Study sample characteristics:

Two hundred and forty patients were prospectively screened at multidisciplinary meetings, with recruitment of 206 (86%) women undergoing immediate LD BRRs. These comprised 93 (45%) LDI procedures and 113 (55%) ALD reconstructions (Figure 1). The proportions of women undergoing ALD reconstructions were often in keeping with the clinician's perception of the likelihood for PMRT[6]. The extent to which this decision-making materialised into administering PMRT was not recorded in this study. Compared with women who had LDI procedures, those who had ALD reconstructions had significantly higher body mass indices, larger tumors, greater likelihood of lymph node positivity and treatment with neo-adjuvant or adjuvant chemotherapy as well as PMRT (Table 1). Thirty percent of women had undergone a recent therapeutic wide local excision, which subsequently required completion mastectomy based on microscopic margin positivity. The significantly greater margin positivity rate of 25% for invasive disease in the LDI group, compared with 7% in the ALD group, is largely inexplicable and would necessitate consideration of PMRT[15]. Details regarding particular contributors to margin positivity were not determined. There were no other significant differences in pathological characteristics between the surgical groups (data not shown)[8]. There were 16 patients with bilateral breast cancers, but only one was included due to missing data. As previously reported, women undergoing ALD reconstructions more frequently received axillary lymph node dissections while those who had LDI surgeries had lesser axillary procedures[8]. Previously reported clinico-pathology and socio-demographic characteristics were similar between the surgical groups (data not shown)[8]. One of the 78 women who had LDI reconstructions developed a local recurrence and five of the 104 women undergoing ALD procedures developed distant metastases.

PRO questionnaire completion and missing data rates (Figure 1):

Of 206 recruits, 182 (88%) women completed baseline questionnaires as a study prerequisite: 157/182 (86%) completed at 1-year (data published elsewhere)[8]; 157/182 (86%) at 2-years and 122/182 (67%) at 3-years. Reasons for missing data included patient non-compliance and administrative issues. Patient's compliance rates for questionnaire completion were consistently high: 91% at baseline, 92% at 2-years and 87% at 3-years. Logistical and administrative issues were: questionnaires not sent out and missing clinical data from CRFs.

Surgical complications (Table 1):

As previously reported[8], early complications of the breast and/or donor site comprised: hematoma, infection, skin necrosis, fat necrosis, and wound dehiscence. Implant-related complications and others were also recorded. Additional donor site complications comprised persistent seromas (arbitrarily defined as 5 or more outpatient aspirations) and back pain. There were no differences between surgical groups regarding early complications.

Long-term complications included: capsular contracture and implant complications, breast lymphoedema, restricted movement of shoulder girdle, back symptoms, lymphoedema of the arm, and cosmetic issues. Although long-term complications between surgical groups did not differ, there was a trend to more grade 2 and 3 complications[22] after ALD reconstructions.

Long-term effects on PROs after immediate breast reconstruction (Table 2):

Table 2, presents the mean baseline levels of PROs and mean domain score change from baseline at 2- and 3-years post-breast reconstruction within both ALD and LDI groups. These results demonstrated statistically significant and clinically important gains in a number of

psychosocial functioning scales (EORTC QLQ-C30: emotional and social functioning, and FACT-B: emotional and functional well-being scales), and reductions in depression (HADS), with overall improvements in quality of life (total FACT-B) at 3-years[24-27]. However, long-term deteriorations, also statistically significant and clinically important, occurred in physical function (QLQ-C30), body image (QLQ-BR23) and social wellbeing (FACT-B) at both time points. In contrast to the emotional gains noted above, the HADS anxiety scale detected persistent anxiety at 2- and 3-years, respectively[24-27].

PRO effect-size and direction of effects for types of LD breast reconstruction at 2 and 3 years (Figure 2 and Supplemental material):

The mean changes in levels of PROs from baseline to 2- and 3-years in each surgical group (Figure 2) are shown with the effect-size threshold of 0.5 (+/-) standard deviations indicating unequivocal clinical significance[27]. This univariate analysis provides important clinical insights into women's experiences in the two reconstruction groups, and the PRO effect-sizes facilitate interpretation of their magnitude and direction. There were no statistically significant differences in change in PRO levels between the two types of breast reconstruction.

For each breast reconstruction type, there were clinically unequivocal changes in PROs from baseline levels at 2-years (Figure 2A), with the ALD group experiencing notable improvements in breast symptoms, but worsened physical function and arm symptoms. In contrast, the LDI group experienced improved levels of depression and functional well-being.

At 2-years, despite both reconstruction groups experiencing clinically unequivocal improvements in emotional function and well-being, women also experienced heightened

anxiety and reductions in body image and social well-being (all with clinically significant effect-sizes). Notable reductions apparent in social well-being at 2-years, persisted at 3-years. Social well-being includes issues such as feeling close to partner and friends, and getting support from family and friends that arguably may relate to body image problems. By 3-years (Figure 2B), both groups experienced notable improvements in breast symptoms, and while there were large (effect size of about 0.8) improvements in emotional function and well-being, both groups were also experiencing clinically unequivocal (effect size of about 0.5) levels of anxiety, likely related to fear of cancer recurrence[24-27]. Levels of anxiety were greater in the ALD group, consistent with worse prognostic factors compared to the LDI group, with continued worsening anxiety from 2- to 3-years in both groups.

Importantly, reductions in body image persisted at 3-years only in the LDI group, who also experienced considerable reductions from baseline in sexual function at 3-years. Women undergoing ALD procedures experienced improved overall quality of life at 3-years through increased total FACT-B scores (small effect-size) and functional wellbeing (moderate effect-size), despite worse physical function (small effect-size) and increased arm symptoms (moderate effect-size) at this time[24-27]. This descriptive data provide information about the responsiveness of PRO subscales /domains in evaluating these surgical procedures.

Multivariate analyses of baseline predictors on long-term PROs (Figure 3):

Some clinical and demographic characteristics were independent predictors of PROs in multiple regression analyses with 2- and 3-year results alongside those reported at 1-year[8]. Women receiving PMRT showed deteriorations in the QLQ-C30 social functioning domain (Z score: -3.113, p=0.002) at 2-years, resolving at 3-years. There were no significant effects of

chemotherapy at 2-years, but worse EORTC QLQ-BR23 arm symptoms at 3-years (Z score: 2.860, p=0.005). Younger women reported significantly worse FACT-B physical well-being (Z score: -2.820, p=0.006). The types of LD breast reconstruction surgery did not independently predict any of the PROs at 2-years, and only one at 3-years, where an immediate ALD breast reconstruction was associated with significantly improved sexual functioning (Z score: 3.075, p=0.003) relative to LDI procedures.

Trends to significance for Z scores ($0.01<p\leq0.05$) were seen (data not shown) where: PMRT was associated with increased EORTC QLQ-BR23 arm symptoms after (2-years); chemotherapy was associated with worse EORTC QLQ-C30 physical functioning (2-years), FACT-B breast cancer subscale (2- and 3-years) and total FACT-B score (3-years); younger women experienced poorer EORTC QLQ-C30 role functioning (2-years) and total FACT-B score (3-years). Somewhat paradoxically, early surgical complications were associated with reduced depression (2-years), whilst late complications were associated with improvements in FACT-B social and emotional well-being (2-years), potentially reflecting increased clinical interactions[28]. There were no significant differences between the reconstruction types in PRO changes at 2- and 3-years, respectively in a second regression model adjusted for case-mix (data not shown), with the exception of an interesting finding of improved sexual functioning after ALD procedures (Z score 2.792, P=0.0067).

DISCUSSION

This study expands on the PRO 12-month follow-up data[8] (Figure 3), and evaluates changes in a wide range of PRO domains at 2- and 3-years in terms of effect-sizes, for each type of breast

reconstruction. The EORTC and FACT questionnaires proved complimentary, and should not be regarded as substitutable[29]. These results are novel, with no previous publications or the NMBR audit specifically describing effect-sizes for relevant PRO domains over this time period[3, 8, 19, 21]. Our analyses were sufficiently powered to demonstrate that regardless of whether immediate breast reconstruction was autologous or implant-assisted, it produced significant long-term gains in psychosocial functioning and reductions in depression relative to pre-operative (baseline) PRO domain scores (Figure 2). Despite this, however, notable deteriorations in physical function, body image and social well-being persisted at 2- and 3-years post-reconstruction. However, this study had insufficient power to detect differences between surgery types, with some tantalising differential patterns warranting further investigation in larger samples. This study has therefore generated hypotheses about the specific PRO domains that differ over time, and provides good effect-size estimates on which to base sample size calculations and selected PRO outcomes for a well-powered study.

This study affirms the effects of known clinical characteristics on long term PROs in women undergoing immediate reconstructions. Regression analyses showed three independent adverse predictors on PRO subscales: PMRT, chemotherapy and young age (Figure 3). PMRT, a likely surrogate for biologically aggressive breast cancers, was associated with significantly impaired social functioning at 2-years. Likewise, chemotherapy and young age may be surrogates for more aggressive disease adversely affecting arm symptoms and physical wellbeing, at 3-years. Autologous immediate breast reconstruction (ALD) significantly improved sexual functioning at 3-years independent of other clinical and demographic variables, with no other long-term PRO effects by type of surgery. In keeping with CONSORT-PRO reporting standards, establishing the effect-sizes and independent significance of core

PRO domains from disease-specific and surgery-specific questionnaires is crucial in the future selection of primary outcomes measures in all study designs[30].

A Cochrane systematic review showed inadequate reporting of psychosocial functioning after immediate breast reconstructions[31, 32]. The time-points and level at which psychosocial outcomes stabilise are unknown. In the NMBR audit, only the proportion of women (20-40%) with psychosocial issues at 18-months after immediate reconstructions was reported with no results on effect-sizes[10]. This study doubles the follow-up time of the NMBR audit to 3-years. There were distinct differences between QLQ-C30's social functioning and FACT-B's social well-being in this study[29]. The former, which assesses impacts on social activities and family life, showed a significant improvement at 2-years after all reconstructions (Table 2 and Figure 2), with no effects by 3-years. By comparison, FACT-B's social well-being, which evaluates impaired social support and relationships, deteriorated significantly after ALD and LDI at 2- and 3-years, respectively. Consistent with our study, the Michigan breast Reconstruction Outcomes Study (MBROS) cohort reported a significant (p=0.0099) decline in social well-being (FACT-B) at 2-years after immediate breast reconstruction[19]. However, the MBROS cohort omitted patients' clinical characteristics and adjuvant treatments making contextual comparisons with this study difficult[19]. In our previous publication[8], the adverse effects of chemotherapy (p=0.001) and early complications (p=0.001) on social well-being at 1-year notably dissipated at 2- and 3-years (Figure 3).

This study showed significantly worse sexual function (EORTC QLQ-BR23) after LDI procedures, at 3-years. Other studies have not detected differences in sexual functioning either by type of breast reconstruction or by extent of breast surgery[4, 19]. While the MBROS cohort did not

evaluate sexual functioning or validated body image items[19], it used a study-specific questionnaire that showed significantly improved body image at 2-years after autologous procedures compared to implant-based reconstructions[19]. Restoration of a women's body image after mastectomy by immediate reconstruction was less than expected in both the MBROS cohort[19], including another large (n=2000) cohort study on sexuality[4], and in our data. Surprisingly, mastectomy with breast reconstruction negatively impacted on a somewhat greater proportion (45%) of women's sex lives compared to 41% after mastectomy alone[4]. Although the EORTC QLQ-BR23 body image subscale showed dramatic intra-group reductions at 2-years in this study, only sexual function (EORTC QLQ-BR23) remained a significant independent factor (regressions) affecting quality of life over time compared to body image at 3-years (Figure 3). The significant improvements ($p<0.0001$) in general mental health and the role emotional subscale (Short Form (SF)-36) at 2-years in the MBROS cohort[19], is similar to the dramatic increases in emotional functioning and well-being in this study at 2- and 3-years. However, we also observed clinically significant heightened anxiety from baseline to 2- and 3-years with moderate effect-sizes, more so after ALD procedures, potentially reflecting concerns about cancer recurrence.

Consistent with Roland et al[4], and King et al[33], our 1-year results show younger women fare worse that older women across a spectrum of PRO domains; in our study these were social functioning ($p=0.02$), body image ($p=0.02$) and anxiety ($p=0.01$)[8]. The current analyses demonstrate the value of longer-term follow-up by showing that these problems had resolved by 2- and 3-years (Figure 3). However, physical wellbeing (FACT-B) had become significantly impaired at 3-years ($p=0.006$). The observation that significantly worse arm symptoms (EORTC QLQ-BR23) were associated with PMRT at 2-years and chemotherapy at 3-years is likely a

reflection of more aggressive disease meriting extensive treatments, rather than direct causation by the latter (Figure 3). The somewhat paradoxical observation at 2-years of associations of early surgical complications with reduced depression, and late complications with improvements in FACT-B social and emotional well-being, may be explained by potentially increased clinical interactions enhancing patient doctor communications and hence PROs[28].

Specific strengths of this study are the pre-surgery baseline assessment of PROs and a good coverage of clinical and demographic variables[18]. Uniquely, it integrates surgical complications and long-term effects of adjuvant treatments, particularly PMRT. Despite a prospective design, there remain methodological limitations of missing data. Cohort studies would benefit from similar operational funding and research infrastructure within clinical trials. The majority of cohort studies in breast reconstruction report 12-month data only[3], where this study informs longer-term outcomes, and value-adds by extending our knowledge of the evolution and resolution of PROs. Some biases may remain un-adjusted for through unmeasured characteristics, but we assessed all known potential predictors (Table 1 and Figure 3). Our sample size was underpowered for intergroup comparisons by different types of breast reconstruction. Despite it's limited sample size, this paper provides preliminary indications of the PRO domains that may differ by each reconstruction group, and preliminary estimates that can be used to determine sample sizes for future studies designed to test the hypotheses generated by the results in this paper. Furthermore, the suite of PROs used may not be responsive to all breast reconstruction surgery-specific effects on PROs.

As this study commenced prior to phase 4 validation of the BREAST-Q, it remains for future studies to evaluate the psychosocial and sexual well-being domains of the BREAST-Q on these

specific reconstructions[9]. Currently, there are no other known studies evaluating the long-term effect-sizes of the BREAST-Q domains on which to base any meaningful comparisons with the findings described. The recently developed and phase 3 validated EORTC breast reconstruction (BRR) validated questionnaire has the advantages of being used alongside the EORTC QLQ-C30 and QLQ-BR23 in breast cancer patients[14] and could provide future confirmation of these findings. This study underlines the importance of identifying core PRO subscales /domains such as those from the EORTC QLQ-C30, FACT-B and HADS to be used alongside the future EORTC BRR surgery questionnaire[14]. Definitive studies investigating the differential effects of types of breast reconstruction can use our findings to frame 'a priori' hypotheses about the size and direction of expected effects, and determine sample sizes required to detect them with confidence[30].

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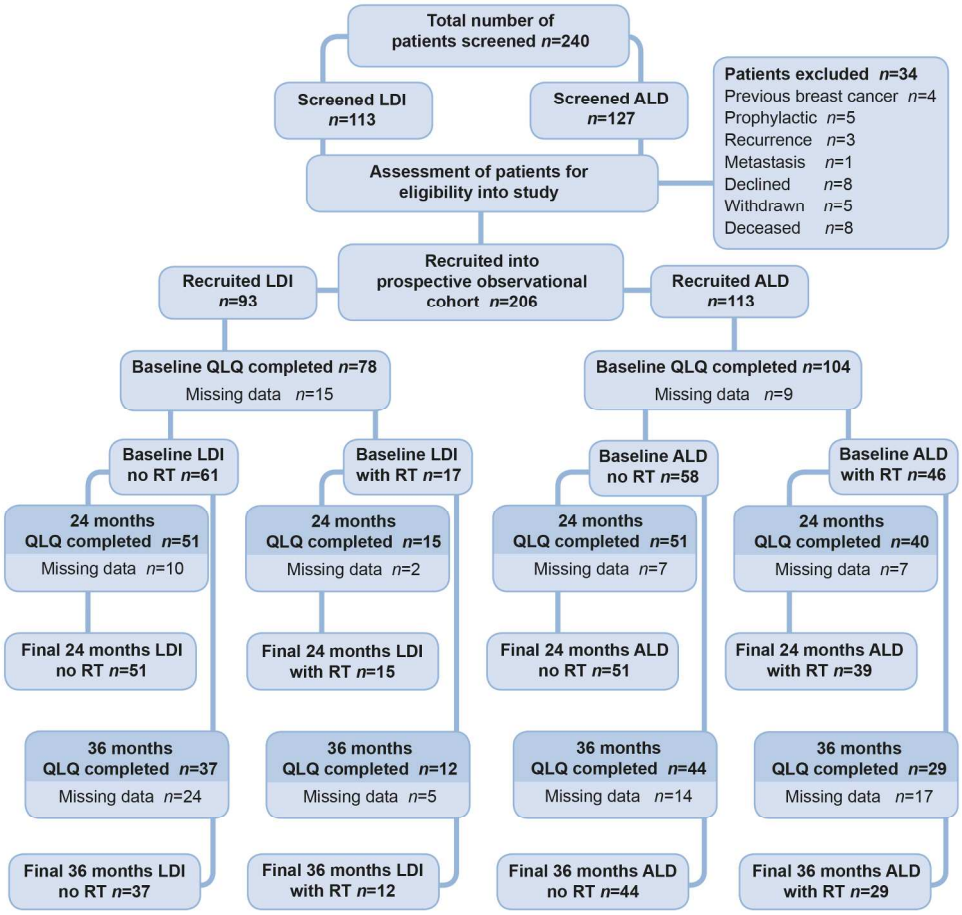

Figure 1: Progress of participants through the study in keeping with the STROBE checklist. Missing data signifies patient compliance (QLQ not returned) and administrative logistics (QLQ not sent out and missing data entry).

Abbreviations:
LDI, implant-assisted latissimus dorsi breast reconstruction; ALD, autologous latissimus dorsi breast reconstruction; QLQ, quality of life questionnaires; baseline, questionnaires prior to mastectomy and immediate breast reconstruction (BRR); 24 months, 24 months after BRR; 36 months, 36 months after BRR; RT, post-mastectomy radiotherapy.

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Table 1: Comparison of baseline clinical, demographical and pathological characteristics in women having immediate implant-assisted (LDI) or autologous latissimus dorsi (ALD) breast reconstruction

Baseline patient characteristics		LDI (n = 78)	ALD (n = 104)	$P^{\ddagger}$
Age (years)**		50 (22-70)	50.5 (25-68)	0.425¶
Body mass index (kg/m^2)*		25.1 (4.3)	27.4 (4.9)	<0.001¶
Neoadjuvant chemotherapy	No	76 (97)	91 (88)	0.026§
	Yes	2 (3)	13 (13)	
Presenting diagnosis	Screen-detected	38 (49)	42 (40)	0.293§
	Symptomatic	40 (51)	62 (60)	
Type of axillary surgery	None	5 (6)	6 (6)	0.021π
	Previous axillary surgery	3 (4)	4 (4)	
	SLNB	20 (26)	24 (23)	
	Axillary lymph node sample	14 (18)	18 (17)	
	Axillary clearance	36 (46)	52 (50)	
Tumour size (mm)*		16.6 (15.7)	23.7 (20.4)	0.016¶
Multi-focal /-centric	No	35/73 (48)	50/103 (49)	1.000§
	Yes	38/73 (52)	53/103 (51)	
Lymphovascular invasion	No	52/72 (72)	63/100 (63)	0.447§
	Yes	20/72 (28)	37/100 (37)	
Margin positivity (<1mm)	Invasive	18/73 (25)	7/103 (7)	<0.001π
	DCIS	13/56 (23)	11/61 (18)	0.488π
Lymph node positivity	No	59 (76)	62 (60)	0.027§
	Yes	19 (24)	42 (40)	
Adjuvant chemotherapy	No	49 (63)	46 (44)	0.030§
	Yes	29 (37)	58 (56)	
Adjuvant radiotherapy	No	62 (79)	58 (56)	<0.001§
	Yes	16 (21)	46 (44)	
Early Complications (0-3 months)	No	29/76 (38)	47/97 (48)	0.217§
	Yes (Grd. 1)	21/76 (28)	19/97 (20)	
	Yes (Grd. 2 to 3)***	26/76 (34)	31/97 (32)	
Late Complications (4-36 months)	No	19/76 (25)	38/99 (38)	0.074§
	Yes (Grd. 1)	46/76 (61)	28/99 (28)	
	Yes (Grd. 2 to 3)***	11/76 (15)	33/99 (33)	

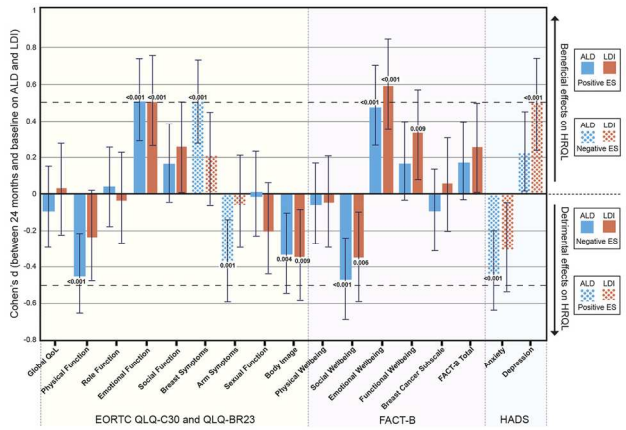
Values in parentheses are percentages unless indicated otherwise; **values are median (range) and *values are mean (SD). ***Dindo-Clavien classification of surgical complications[22]. ****Margin positivity at mastectomy. Abbreviations: LDI, implant-assisted latissimus dorsi breast reconstruction; ALD, autologous latissimus dorsi breast reconstruction; SLNB, sentinel lymph node biopsy; DCIS, ductal carcinoma in situ; Grd., Grade of surgical complications by Dindo-Clavien[22].

‡Statistical tests: ¶Student's *t*-test; §Fisher's exact test and πChi square test.

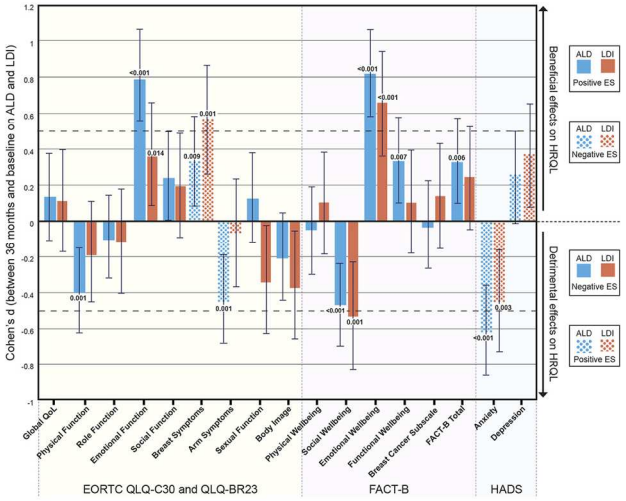
Table 2: Pre-operative (baseline) and post-operative (2 years and 3 years) Health Related Quality of Life (HRQL) domain scores, and change at 2 and 3-years, in all patients with immediate types of LD breast reconstructions (ALD and LDI)

HRQL subscale	Baseline Median n=175 (167- 182)	2 years Median n=154 (143-155)	HRQL change over 2 years Median n=123 (135 -155)		3 years Median n=148 (114-124)	HRQL change over 3 years Median n=117 (107-124)	
	Mean score	Mean score	Mean change (SD)	p-value	Mean score	Mean change (SD)	p-value
EORTC QLQ-C30 and QLQ-BR23							
Global QoL	75.7	75.4	-0.61 (20.9)	0.720	77.6	2.45 (20.3)	0.191
Physical Function	94.8	89.7	**-5.30** (15.1)	**<0.001**	90.3	**-4.90**(15.7)	**<0.001**
Role Function	87.5	88.6	0.55 (29.1)	0.816	87.1	-2.89(28.4)	0.264
Emotional Function	67.1	80.4	**11.97** (23.3)	**<0.001**	82.1	**14.27**(24.4)	**<0.001**
Social Function	83.4	89.5	**5.07** (24.5)	**0.013**	90.1	5.70 (25.3)	0.016
Pain	12.6	15.3	3.75 (22.7)	0.044	16.1	4.68 (24.3)	0.036
Fatigue	21.8	21.5	0.11 (24.9)	0.957	20.5	0.51 (25.9)	0.831
Breast Symptoms	15.4	8.6	**-6.78** (18.2)	**<0.001**	8.3	**-7.36(**18.1)	**<0.001**
Arm Symptoms	8.0	12.3	3.56 (16.9)	0.012	13.1	**4.95** (18.0)	**0.004**
Sexual Function	69.5	66.6	-2.47 (29.8)	0.338	66.5	-1.40(28.6)	0.613
Body Image scale	82.8	74.0	**-8.91** (26.9)	**<0.001**	76.9	**-7.30**(26.4)	**0.004**
FACT-B							
Physical Wellbeing	24.7	24.6	-0.24 (5.2)	0.566	24.9	0.02 (5.3)	0.967
Social Wellbeing	24.6	22.8	**-2.00** (4.8)	**<0.001**	22.5	**-2.38** (4.9)	**<0.001**
Emotional Wellbeing	16.1	19.3	**3.12** (6.0)	**<0.001**	19.5	**3.63** (4.8)	**<0.001**
Functional Wellbeing	20.5	22.1	**1.62** (6.7)	**0.003**	22.1	1.46 (6.4)	0.016
Breast Cancer Subscale	26.0	26.3	-0.15 (6.6)	0.780	26.9	0.29 (5.9)	0.604
FACT-B Total	107.6	114.3	5.80 (30.0)	0.017	115.5	**7.93** (26.8)	**0.001**
HADS							
Anxiety	10.7	11.9	**1.08** (3.0)	**<0.001**	12.2	**1.51** (2.8)	**<0.001**
Depression	9.1	8.6	**-0.59** (1.7)	**<0.001**	8.5	**-0.55** (1.8)	**0.001**

Abbreviations: ALD, autologous latissimus dorsi; LDI, implant-assisted latissimus dorsi; HRQL, Health-Related Quality of Life; *n*, median number of respondents and (range); EORTC QLQ, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires; HADS, Hospital Anxiety and Depression Scale; FACT-B, Functional Assessment of Cancer Therapy-Breast. S.D., Standard Deviation. *P* <0.01 (Bold) indicates a statistically significant mean score change from baseline at 2- and 3-years with positive or negative (-) directions of change[24-26]. Mean score changes considered as clinically relevant comprised large scale changes of -3 to 3; 2 represented medium and 1 represented small[24,25, 27]. Data for effect Sizes are not shown here for the overall group, but for each type of breast reconstruction (Figure 2 and supplemental material)[26].



A: Effect-sizes in HRQL domain scores at 24 months after ALD and LDI breast reconstructions versus pre-operative scores



B: Effect-sizes in HRQL domain scores at 36 months after ALD and LDI breast reconstructions versus pre-operative scores

Figure 2: Bar diagrams illustrating effect-sizes (ES) in EORTC QLQ-C30 and QLQ-BR23, FACT-B and HADS change scores at 24 months (A) and 36 months (B) versus pre-operative (baseline) scores after ALD (Blue) and LDI (Red) immediate breast reconstructions. Effect-sizes with 95% Confidence intervals. ES values from 0 to 1.0/1.2 represent beneficial effects on HRQL with solid bars indicating positive values for functioning scales, compared to stippled bars indicating negative values for symptomatic scales and depression. Pain and fatigue scales are not shown (data in appendices 1 and 2). ES values from 0 to -0.8/-1.0 represent detrimental effects on HRQL with solid bars indicating negative values for functioning scales, compared to stippled bars indicating positive values for symptomatic scales and anxiety.
P <0.01 (Bold) indicates a significant ES from baseline with directions of effects. Effects-sizes measured by Cohen's D statistic defined as the difference between two means divided by the pooled standard deviation where <0.2 indicates a 'trivial' ES, 0.2-0.5 indicates a 'small' ES, 0.5-0.8 indicates a 'medium' ES and >0.8 indicates a 'large' ES. The dotted lines at 0.5 ES indicate unequivocal clinical significance[24-27].

Abbreviations: HRQL, Health-Related Quality of Life; ALD, Autologous Latissimus Dorsi; LDI, Implant-assisted Latissimus Dorsi; EORTC QLQ, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires; HADS, Hospital Anxiety and Depression Scale; FACT-B, Functional Assessment of Cancer Therapy-Breast.

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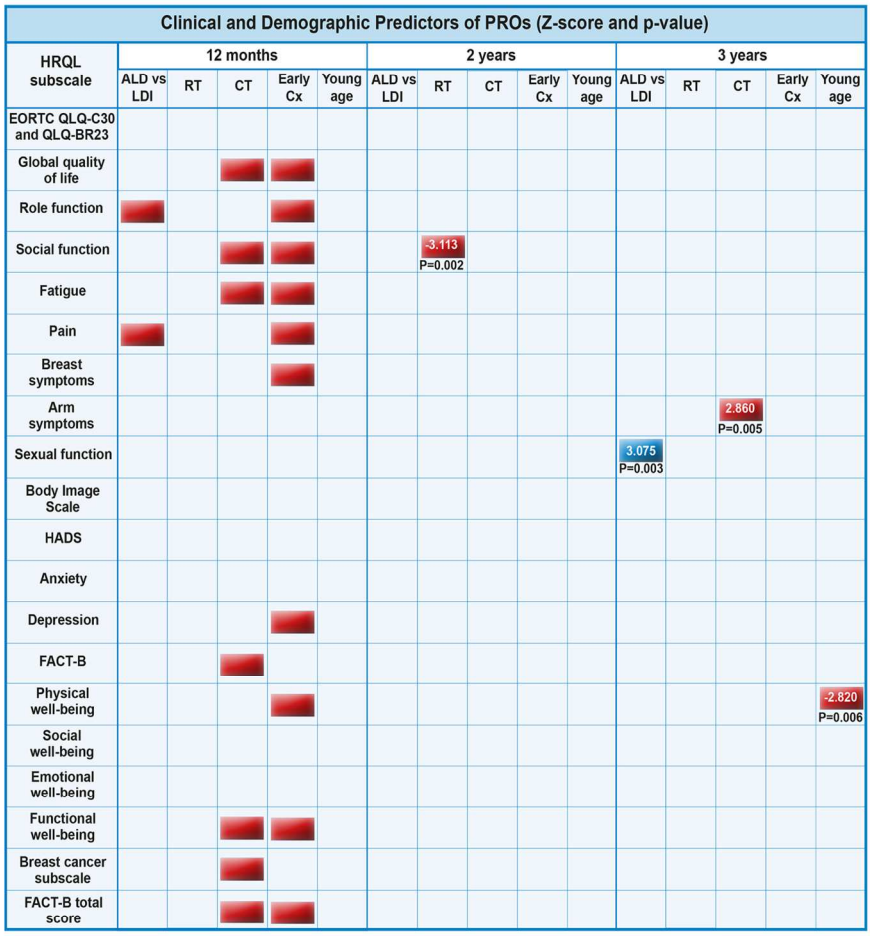
Figure 3: Results of generalized estimating equation models investigating clinical and demographic predictors of Patient Reported Outcomes (PROs) after breast reconstruction surgery at 2- and 3-years



PRO, Patient Reported Outcome; ALD, autologous latissimus dorsi breast reconstruction; LDI, implant-assisted latissimus dorsi breast reconstruction; RT, radiotherapy; CT, chemotherapy; Cx, complications; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; HADS, Hospital Anxiety and Depression Scale; FACT-B, Functional Assessment of Cancer Therapy - Breast Cancer scale. Summary findings from one-year data as published[8] are shown by comparison with 2 and 3-year results.

Multi-level linear regression models for 2 and 3-year data were fitted for each PRO subscale and regressed on the predictors as shown, including baseline PRO subscale values. Variables not represented were not significant at 2- and 3-years, respectively (Body Mass Index, type of axillary surgery, tumour size, margin positivity, lymph node positivity and late complications). P<0.01 indicates that the predictor was significantly associated with worse levels of the PRO subscale as indicated by RED boxes which detail the Z-score and the P-value. The BLUE box indicates a significantly improved PRO subscale with the Z-score and P-value as shown.

189x260mm (300 x 300 DPI)

Appendix 1: Pre-operative (baseline) and post-operative (2- and 3-years) Health Related Quality of Life (HRQL) domain scores and change at 2- and 3-years in patients with immediate ALD breast reconstructions

HRQL Subscale	Baseline		2 years		HRQL Change over 2 years						3 years		HRQL Change over 3 years					
	n	Mean Score	*n*	Mean Score	*n*	Mean change	S.D.	Effect-size	*p*-value	95% CI	*n*	Mean Score	*n*	Mean change	S.D	Effect-size	*p*-value	95% CI
EORTC QLQ-C30 and QLQ-BR23																		
Global QoL	99	76.5	88	75.8	84	-1.49	22.0	-0.068	0.537	-0.286 0.150	74	78.2	70	2.26	17.5	0.129	0.283	-0.110 0.368
Physical Function	101	95.0	88	88.6	85	-6.98	16.0	**-0.436**	**<0.001**	-0.635 -0.219	74	89.4	72	-6.48	16.2	**-0.399**	**0.001**	-0.635 -0.163
Role Function	101	85.8	88	88.4	85	1.18	31.8	0.037	0.734	-0.180 0.254	74	86.9	72	-2.55	26.3	-0.097	0.415	-0.333 0.139
Emotional Function	98	67.4	88	81.5	83	12.05	23.5	**0.513**	**<0.001**	0.293 0.733	74	84.0	69	17.31	21.8	**0.794**	**<0.001**	0.533 1.053
Social Function	97	82.8	88	88.8	82	4.47	26.5	0.169	0.130	-0.052 0.390	74	89.9	68	6.13	25.1	0.244	0.048	0.002 0.486
Pain	101	15.0	88	15.9	85	2.94	24.7	0.119	0.275	-0.098 0.336	74	18.0	72	5.09	25.0	0.204	0.088	-0.032 0.440
Fatigue	101	22.1	88	22.2	85	1.37	25.7	0.053	0.624	-0.164 0.270	74	21.5	72	2.24	24.6	0.091	0.443	-0.145 0.327
Breast Symptoms	96	17.2	88	7.1	81	-9.57	18.9	**-0.506**	**<0.001**	-0.728 -0.284	73	9.7	66	-6.57	19.9	**-0.330**	**0.009**	-0.576 0.084
Arm Symptoms	96	8.0	88	14.6	81	5.83	16.0	**0.365**	**0.001**	0.143 0.587	73	14.8	66	7.49	16.8	**0.446**	**0.001**	0.200 0.692
Sexual Function	93	70.4	79	69.0	73	0.00	31.5	0.000	1.000	-0.234 0.234	66	73.0	62	3.76	29.6	0.127	0.321	-0.127 0.381
Body Image scale	97	83.8	88	76.3	81	-8.02	24.5	**-0.328**	**0.004**	-0.550 -0.106	73	79.2	67	-4.73	23.0	-0.206	0.097	-0.450 0.038
FACT-B																		
Physical Wellbeing	99	24.5	88	24.5	83	-0.29	5.7	-0.052	0.639	-0.272 0.168	74	24.7	70	-0.28	5.8	-0.048	0.691	-0.287 0.191
Social Wellbeing	100	24.8	88	22.8	84	-2.35	5.0	**-0.467**	**<0.001**	-0.685 -0.249	74	22.5	71	-2.48	5.3	**-0.468**	**<0.001**	-0.706 -0.230
Emotional Wellbeing	98	16.3	88	19.7	83	3.26	6.7	**0.486**	**<0.001**	0.266 0.706	74	19.7	69	4.11	5.0	**0.821**	**<0.001**	0.581 1.061
Functional Wellbeing	98	20.4	88	21.8	83	1.24	6.9	0.179	0.106	-0.041 0.399	74	22.3	69	1.99	5.9	**0.334**	**0.007**	0.094 0.574
Breast Cancer Subscale	98	25.8	88	25.8	82	-0.56	6.0	-0.093	0.404	-0.314 0.128	73	26.4	69	-0.15	5.1	-0.030	0.804	-0.270 0.210
FACT-B Total	104	106.1	89	113.4	89	6.37	35.6	0.179	0.095	-0.033 0.391	74	115.2	74	8.89	26.9	**0.330**	**0.006**	0.098 0.562
HADS																		
Anxiety	99	10.7	88	12.2	83	1.24	3.0	**0.421**	**<0.001**	0.201 0.641	71	12.3	68	1.76	2.9	**0.614**	**<0.001**	0.372 0.856
Depression	100	8.9	87	8.7	83	-0.39	1.7	-0.228	0.041	-0.448 -0.008	73	8.6	70	-0.46	1.7	-0.262	0.031	-0.501 0.023

Complete data set for Figures 2A and B. Abbreviations: ALD, autologous latissimus dorsi breast reconstruction; HRQL, Health-Related Quality of Life; N, number; EORTC QLQ, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires; QoL, quality of life; FACT-B, Functional Assessment of Cancer Therapy-Breast; HADS, Hospital Anxiety and Depression Scale. S.D., Standard Deviation. *P* <0.01 (Bold) indicates a significant mean difference in scores from baseline with positive or negative (-) directions of effects. CI indicates 95% confidence intervals. Effect-sizes (ES) measured by Cohen's *d* statistic defined as the difference between two means divided by the pooled standard deviation where <0.2 indicates a 'trivial' ES, 0.2-0.5 indicates a 'small' ES, 0.5-0.8 indicates a 'medium' ES and larger than 0.8 indicates a 'large' ES[24-27].

Appendix 2: Pre-operative (baseline) and post-operative (2- and 3-years) Health Related Quality of Life (HRQL) domain scores and change at 2- and 3-years in patients with immediate LDI breast reconstructions

HRQL Subscale	Baseline		2 years		HRQL Change over 2 years							3 years		HRQL Change over 3 years						
	n	Mean Score	*n*	Mean Score	*n*	Mean Change	S.D.	Effect-size	p-value	95% CI		*n*	Mean Score	*n*	Mean Change	S.D	Effect-size	*p*-value	95% CI	
EORTC QLQ-C30 and QLQ-BR23																				
Global QoL	77	74.6	67	74.9	66	0.51	19.4	0.026	0.834	-0.220	0.272	50	76.8	49	2.72	24.0	0.114	0.430	-0.172	0.400
Physical Function	77	94.5	67	91.1	66	-3.13	13.8	-0.228	0.069	-0.474	0.018	50	91.6	49	-2.59	14.6	-0.177	0.223	-0.463	0.109
Role Function	77	89.6	67	88.8	66	-0.25	25.4	-0.010	0.936	-0.256	0.236	50	87.3	49	-3.40	31.4	-0.108	0.451	-0.394	0.178
Emotional Function	77	66.8	67	79.0	66	11.87	23.2	**0.511**	**<0.001**	0.265	0.757	50	79.3	49	9.98	27.2	0.366	0.014	0.080	0.652
Social Function	77	84.2	67	90.3	66	5.81	22.0	0.264	0.036	0.018	0.510	50	90.3	49	5.10	25.7	0.198	0.172	-0.088	0.484
Pain	77	9.5	67	14.4	66	4.80	20.0	0.240	0.056	-0.006	0.486	50	13.3	49	4.08	23.5	0.174	0.229	-0.112	0.460
Fatigue	77	21.4	67	20.6	66	-1.52	24.0	-0.063	0.610	-0.309	0.183	50	19.1	49	-2.04	27.8	-0.073	0.610	-0.359	0.213
Breast Symptoms	74	13.1	67	10.6	64	-3.26	16.6	-0.196	0.123	-0.446	0.054	48	6.1	45	-8.52	15.3	**-0.556**	**0.001**	-0.854	-0.258
Arm Symptoms	74	8.0	67	9.3	64	0.69	17.8	0.039	0.756	-0.211	0.289	48	10.6	45	1.23	19.1	0.065	0.667	-0.233	0.363
Sexual Function	74	68.2	64	63.5	62	-5.38	27.6	-0.195	0.130	-0.449	0.059	48	57.6	45	-8.52	25.8	-0.330	0.032	-0.628	-0.032
Body Image Scale	74	81.4	67	70.9	64	-10.03	29.8	**-0.336**	**0.009**	-0.586	-0.086	50	73.5	46	-11.05	30.5	-0.362	0.018	-0.658	-0.066
FACT-B																				
Physical WB	77	24.9	66	24.7	66	-0.18	4.5	-0.040	0.745	-0.286	0.206	50	25.2	49	0.45	4.6	0.097	0.499	-0.189	0.383
Social WB	77	24.2	66	22.8	66	-1.56	4.5	**-0.348**	**0.006**	-0.593	-0.103	50	22.5	49	-2.23	4.3	**-0.520**	**0.001**	-0.806	-0.234
Emotional WB	77	16.0	66	18.7	66	2.93	4.9	**0.595**	**<0.001**	0.349	0.841	50	19.3	49	2.95	4.5	**0.659**	**<0.001**	0.373	0.945
Functional WB	77	20.7	67	22.4	67	2.09	6.4	**0.327**	**0.009**	0.083	0.571	50	21.7	49	0.73	7.2	0.101	0.482	-0.185	0.387
Breast Cancer Subscale	74	26.3	66	27.0	63	0.37	7.3	0.051	0.690	-0.201	0.303	49	27.7	45	0.97	7.0	0.138	0.359	-0.160	0.436
FACT-B Total	78	109.6	66	115.5	66	5.03	20.3	0.248	0.049	0.002	0.494	50	115.8	50	6.51	26.9	0.242	0.093	-0.041	0.525
HADS																				
Anxiety	77	10.6	66	11.5	65	0.88	3.0	0.292	0.022	0.044	0.540	50	12.0	49	1.16	2.6	**0.441**	**0.003**	0.155	0.727
Depression	76	9.3	66	8.4	64	-0.84	1.7	**-0.490**	**<0.001**	-0.740	-0.240	50	8.5	48	-0.69	1.9	-0.363	0.015	-0.652	-0.074

Complete data set for Figures 2A and B. Abbreviations: LDI, implant-assisted latissiumus dorsi breast reconstruction; HRQL, Health-Related Quality of Life; N, number; EORTC QLQ, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires; QoL, quality of life; FACT-B, Functional Assessment of Cancer Therapy-Breast; HADS, Hospital Anxiety and Depression Scale. S.D., Standard Deviation. *P* <0.01 (Bold) indicates a significant mean difference in scores from baseline with positive or negative (-) directions of effects. CI indicates 95% confidence intervals. Effect-sizes (ES) measured by Cohen's *d* statistic defined as the difference between two means divided by the pooled standard deviation where <0.2 indicates a 'trivial' ES, 0.2-0.5 indicates a 'small' ES, 0.5-0.8 indicates a 'medium' ES and >0.8 indicates a 'large' ES[24-27].