Patient-reported health-related quality of life outcomes following mastectomy for breast cancer, with immediate, delayed or no breast reconstruction: Four-year follow-up from a prospective cohort study

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ABSTRACT

Background: Breast reconstruction (BR) improves women's health-related quality of life (HRQOL) following mastectomy for breast cancer, yet factors contributing to improved HRQOL remain unclear. This study aimed to explore the overall impact of mastectomy with or without BR on participants' perceptions of HRQOL over time in a cohort of women with high-risk breast cancer; to examine differences in mean HRQOL scores between immediate BR, delayed BR and no BR groups; to assess the influence of patient characteristics potentially associated with HRQOL scores; and to determine the feasibility of long-term collection of patient-reported outcome measures in clinical settings.
Methods: A prospective, longitudinal study of 100 women with high-risk breast cancer who underwent mastectomy with or without breast reconstruction and were likely to require post-mastectomy radiotherapy. Four validated patient-reported questionnaires, comprising 21 outcome measures relating to HRQOL, administered at baseline and up to 4 years post-mastectomy. Demographic, clinical and surgical data extracted from patient medical records.
Results: Consistently significant declines in perceptions of future health and arm symptoms, consistently significant improvements in treatment side effects, breast symptoms and fatigue, as well as significant improvements, compared to baseline, in social functioning and financial difficulties at 48 months. No significant differences in mean HRQOL scores between women given a choice of reconstructive options.
Conclusion: Similar trajectories of HRQOL scores were found in women with high-risk breast cancer who were offered a choice of BR. Informed choice may be an independent contributing factor in long-term maintenance of most HRQOL indicators at their pre-mastectomy levels.

1. Introduction

Breast reconstruction (BR) has been reported to reduce the negative physical and emotional experiences associated with having mastectomy [1–3], and also to improve body image and quality of life more broadly [4–6]. Previous research on this same cohort of women showed they had similar trajectories of body image scores regardless of whether they chose to have BR immediately, later or not at all [7]. In the past, women with high-risk breast cancer requiring post-mastectomy radiotherapy (PMRT) were not offered immediate BR. We made a unit policy to offer women all options of reconstruction at the timing of their choice. At that time immediate autologous reconstruction was not recommended by plastic surgeons so an immediate expander implant was the common IBR option, with the possibility of second stage autologous or implant reconstruction. The focus of this article is women's perceptions of how their chosen BR option affected their health-related quality of life (HRQOL) [8], as assessed by patient-reported outcome measures (PROMs) [9].

Both terms acknowledge and respect the centrality of patients' perceptions to the assessment of their health. Much of the literature has focused on comparisons of different BR options [10–13]; and many studies have focused on different BR outcomes such as satisfaction [14,15], decisional regret [16,17], body image [7,18,19] or aesthetic concerns [20,21]. It is unsurprising that systematic reviews have failed to demonstrate any clear conclusions due to the diversity of measures used, the variables considered and range of study designs [6,22].

This article reports findings from a prospective four-year study using PROMs to assess patient views on 21 HRQOL indicators in women with high-risk breast cancer who all required mastectomy and were likely to require PMRT. This article has four aims: first, to explore the overall impact of mastectomy with or without BR on women's perceptions of HRQOL over time (pre-mastectomy baseline to 4 years); second, to examine differences in mean HRQOL scores between Immediate BR (IBR), Delayed BR (DBR) and No BR (NBR) groups; third, to assess the potential influence of a range of patient characteristics that may be associated with HRQOL scores after breast cancer surgery; and fourth, to determine the feasibility and utility of long-term collection of PROMs in clinical settings.

2. Methods

This paper reports on a selection of HRQOL patient-reported outcomes from women recruited to the 'Quality of Life of Immediate and Delayed breast reconstruction in women undergoing mastectomy and adjuvant radiotherapy for breast cancer' (QOLID) study (ethics approval 30/04/2013 from St Vincent's Hospital Sydney HREC 13/059). Trial registration: ACTRN12614000045617. Signed written consent was obtained from all study participants.

2.1. Study design

This study used a prospective, longitudinal quantitative methodology comprising the administration of validated patient-reported outcome measures relating to HRQOL. Demographic, clinical and surgical data were extracted from patient medical records.

2.2. Selection criteria

Women of any age with newly diagnosed high-risk primary invasive breast cancer, defined as cancer at high risk of local or systemic recurrence, such as cancer requiring mastectomy and likely to require PMRT, were potentially eligible for this study. PMRT is recommended when the tumour is larger than 5 cm, has spread to four or more lymph nodes, has positive margins or involves the chest wall or skin. It is also considered for women with 1–3 involved nodes and tumours between 2 and 5 cms, especially if multifocal. Women were ineligible if they were not clinically suitable for breast reconstruction (immediate or delayed) or, based on pre-operative assessment, unlikely to require PMRT.

2.3. Settings, patient recruitment and timeline

The initial study site was in Sydney, Australia. It was subsequently expanded to include a second site in Hamilton, NZ to increase recruitment, patient diversity and the number of surgeons. The Sydney site comprised three breast/oncoplastic surgeons (July 2013 to May 2016) and the New Zealand site had four breast/oncoplastic surgeons (November 2014 to May 2016).

Consenting participants had one or more pre-operative consultations with their surgeon to discuss cancer management and their preferred options regarding the type and timing of BR: IBR; DBR or none NBR. All participants were asked to complete a set of questionnaires at baseline (pre-operatively) and at seven time points post-operatively (3, 6, 12 and 18 months and 2, 3 and 4 years). This paper reports on HRQOL assessments at baseline, 12 months and 2, 3 and 4 years. Twenty-one HRQOL susbscales were selected from four validated questionnaires (see Fig. 1).

2.4. Data collection

Study participants had the option of completing the PROMs either electronically, via Survey Monkey, or in hard copy. Patients were asked to complete the PROMs at baseline and at 12, 24, 36 and 48 months post-mastectomy. Questionnaires were sent to individual patients a week or two prior to each post-mastectomy time point.

2.5. Data analysis

HRQOL data at baseline, 1, 2, 3 and 4 years were extracted for analysis. All participants who completed baseline and at least one follow-up set of questionnaires were included in the analysis. Items were scored into scales following standard scoring algorithms for each PROM. At any particular time-point, women who were missing 50% or more of the items on any particular scale were excluded from the analysis for that scale.

Longitudinal data analysis (mixed-models with random effects) was used to compare means at baseline and at each of the four follow-up time points for each of the 21 HRQOL measures, as well as to compare the mean scores of variables of interest between the three BR groups (IBR, DBR, NBR) and patient characteristics (age, body mass index (BMI) and marital, employment and health insurance status). Data analysis was performed using IBM SPSS v25 (Armonk, NY: IBM Corp), and RStudio (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). A two-sided p value of <0.05 was considered significant.

3. Results

3.1. Characteristics of the study population

One hundred women completed baseline questionnaires, 77 from Australia and 23 from NZ; 61 women (61%) chose IBR, 23 (23%) chose NBR and 16 (16%) chose DBR. Women were aged between 35 and 79, with a median age of 52. Seven patients (7%) were aged over 70 at time of recruitment. The majority were pre-menopausal. Baseline patient characteristics are presented in Table 1 and tumour characteristics are presented in Table 2. Table 1 showed differences in private health insurance membership between Australian (87%) and New Zealand (9%) women, and women who selected NBR tended to be to be older than those who chose DBR and IBR ($\chi_1^2 = 51.6, p < 0.001$). The type and number of BR procedures are outlined in Tables 3a-3c.

All patients in this study were at the higher-risk end of the disease

1. **EORTC Quality of Life Questionnaire Cancer (QLQ–C30)** (version 3.0) [23] is a 30-item questionnaire composed of both multi-item scales and single-item measures. Eight of these scales were identified prior to analysis as of primary interest for this article. These included the five functioning scales (physical, role, social, emotional and cognitive) and a global health status/HRQOL score; these scales range in score from 0 to 100, with higher scores indicating better outcomes. The remaining three scales were pain, fatigue and financial distress, also with a 0-100 range, but with higher scores indicating worse outcomes.

2. **EORTC Quality of Life Questionnaire Breast Cancer (QLQ-BR23)** [24] is a 23-item breast cancer-specific questionnaire about the common side effects of therapy, body image and sexuality related to breast cancer. It yields eight summary scales: five multi-item scales (systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning), and three single item scales (sexual enjoyment, hair loss and future perspective). This article reports on all scales except body image which was covered in a previous paper [8]. Each scale ranges from 0-100, with higher scores indicating worse outcomes for all scales except sexual functioning and sexual enjoyment, for which higher scores reflect better outcomes.

3. **BREAST-Q (Reconstruction & Mastectomy) Modules** are validated breast surgery-specific instruments, with a range of modules for different types of breast surgery [25]. Each module has six domains assessing patient satisfaction with their breast, overall surgical outcome, psychosocial, physical, and sexual well-being and satisfaction with care. It yields 9-12 summary scales (depending on surgery type). Three of these scales were of primary interest in this study, with scores ranging from 0-100: Physical Well-being: Chest and Upper Body and Physical Well-being: Abdomen (higher scores representing worse outcomes); and Satisfaction with Outcome (higher scores representing better outcomes). The remaining scales were previously examined in the body image paper [7].

4. **The Brief Pain Inventory (BPI)** comprises 14 items, one on pain location, six measuring pain severity and seven measuring pain interference in daily activities, all rated on 0–10 scales where higher scores indicate greater severity and interference [26]. For comparison, these were converted to 0-100 in Table 1.

Fig. 1. Patient-reported outcome measures (PROMs) [23–27].

spectrum and were expected to require PMRT (a study inclusion criterion). However, on post-operative histopathological review, eight women were found to not require PMRT (one from Australia and seven from NZ) and one each from NZ and Australia declined the recommended PMRT. These ten women were excluded from the analysis.

Table 3b provides information on IBR women who had Stage 2 procedures undertaken within 48 months of mastectomy and insertion of an expander. It shows 73% of 41 Australian patients (n = 30) opted for a permanent implant. The remaining 11 patients (27%) chose autologous reconstruction, with 6 bilateral TRAM procedures and five unilateral DIEPs. Of the three Stage 2 NZ patients, 1 had exchange of expander to permanent implant, 1 had a ruptured expander removed with no replacement, and the third did not have Stage 2 surgery.

3.2. Impact of mastectomy on HRQOL over time (Aim 1)

A summary of mean changes in the 21 HRQOL domains from baseline to 4 years is presented in Table 4.

In the cohort overall, persistent significant changes were observed on four subscales. BR23 Future Perspectives and QLQ-BR23 Arm symptoms saw large, consistent and significant deteriorations from baseline scores at each subsequent time point.

Conversely, QLQ-BR23 side effects from systemic therapy and QLQ-C30 Social functioning both improved significantly at each timepoint. Three other scales reached significant improvements from Baseline, two by 36 months (QLQ-BR23 Breast symptoms and QLQ-C30 Fatigue) and QLQ-C30 Financial difficulties by 48 months.

3.3. Differences in mean HRQOL scores between IBR, DBR and NBR groups (Aim 2)

The timing of BR, including the option of declining BR, did not have a significant impact on any of the 21 HRQOL measures. After adjusting for baseline scores, there were no meaningful differences in changes in mean scores over time between the three groups. These results are graphed in Appendix A.

3.4. Impact of patient characteristics on HRQOL (Aim 3)

There were no meaningful differences over time in the mean scores

Table 1
Patient sociodemographic characteristics at baseline.

Sociodemographics	Australian Site				New Zealand Site				Combined
	IBR n = 51 (%)	DBR n = 12 (%)	NBR n = 14 (%)	Total n = 77 (%)	IBR n = 10 (%)	DBR n = 4 (%)	NBR n = 9 (%)	Total n = 23 (%)	Total n = 100 (%)
Age									
Mean (Median)	50 (48)	53 (50)	60 (61)	52 (49)	50.9 (49)	52 (50)	58 (55)	54.3 (53)	52.0 (49)
Range	35–75	40–74	43–79	35–79	37–72	45–63	44–79	37–79	35–79
Menopausal status n (%)									
Pre	28 (36)	7 (9)	8 (10)	43 (56)	9 (39)	2 (9)	3 (13)	14 (61)	57 (57)
Peri	4 (5)	1 (1)	0 (0)	5 (6)	0 (0)	0 (0)	1 (4)	1 (4)	7 (7)
Post	15 (19)	4 (5)	6 (8)	25 (32)	1 (4)	1 (4)	5 (22)	7 (30)	32 (32)
Unsure	5 (6)	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (5)
Body mass index n (%)									
Mean (Median)	24.4 (24)	25.2 (24)	26.8 (26)	25.5 (24)	28 (27)	24.2 (21.4)	28.8 (29.2)	27.7 (28.4)	25.9 (25.3)
Range	16–37	21–35	20–37	16–37	19–38	19–35	22–34	19–38	16–38
Missing	2 (3.9)	1 (8.3)	2 (14.2)	5 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	5 (5)
Health insurance n (%)									
Private	45 (86.5)	11 (91.7)	11 (78.6)	67 (85.9)	0 (0)	2 (50)	0 (0)	2 (8.3)	69 (69)
None	6 (11.8)	1 (8.3)	3 (21.4)	10 (13.0)	10 (100)	2 (50)	9 (100)	21 (91.3)	31 (31)
Living situation n (%)									
Living alone	4 (7.7)	1 (8.3)	3 (21.4)	8 (10.3)	1 (9.1)	0 (0)	3 (33.3)	4 (16.7)	12 (12)
Living with family	47 (92.2)	10 (83.3)	11 (78.6)	68 (88.3)	9 (90)	4 (100)	5 (55.6)	18 (78.2)	86 (86)
Living with others	0 (0)	1 (8.3)	0 (0)	1 (1.3)	0 (0)	0 (0)	1 (11.1)	1 (4.2)	2 (2)
Marital Status n (%)									
Single	2 (3.8)	2 (16.7)	1 (7.1)	5 (6.4)	1 (9.1)	2 (50)	4 (44.4)	7 (29.2)	12 (12)
Married/De facto	44 (84.6)	7 (58.3)	10 (71.4)	61 (78.2)	9 (90)	2 (50)	4 (44.4)	15 (65.2)	76 (76)
Divorced/ Separated	5 (9.8)	1 (8.3)	1 (7.1)	7 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (7)
Widowed	0 (0)	2 (16.7)	2 (14.3)	4 (5.1)	0 (0)	0 (0)	1 (11.1)	1 (4.2)	5 (5)
Employment n (%)									
Employed	44 (86.3)	9 (75.0)	7 (50.0)	60 (77.9)	8 (80)	2 (50)	6 (66.7)	16 (70.8)	76 (76)
Home duties	4 (7.7)	2 (16.7)	2 (14.3)	8 (10.3)	0 (0)	2 (50)	1 (11.1)	3 (12.5)	11 (11)
Training/education	1 (1.9)	0 (0)	0 (0)	1 (1.3)	1 (9.1)	0 (0)	0 (0)	1 (4.2)	2 (2)
Retired	2 (3.8)	1 (8.3)	5 (35.7)	8 (10.3)	1 (9.1)	0 (0)	2 (18.2)	3 (12.5)	11 (11)

of 21 HRQOL measures when comparing the different groups of patient characteristics: age — 49 years and younger versus 50 years and older; body mass index (BMI) — underweight/normal ($<$25.00 kg/m^2) versus overweight/obese ($>$25.00 kg/m^2); marital status — married or in a de facto relationship versus other; employment status — employed versus other (students, home duties or retired); or health insurance status — private health insurance versus no private health insurance. Graphs for all HRQOL scales by patient characteristics are provided in Appendix B.

4. Feasibility and utility of long-term collection of PROMs in clinical settings (Aim 4)

Questionnaire completion rates over time are provided in Fig. 2. Nineteen women with completed baseline questionnaires were lost to study follow up within the first 12 months; of these 19 women, eight did not require PMRT. The attrition rate slowed considerably in subsequent years. Thirty percent of participants completed all four rounds of follow-up questionnaires, and a further 40% completed either two or three rounds. Of the 30 participants who did not satisfy the inclusion criteria, 8 did not wish to continue, 8 did not require PMRT and became ineligible for the study, 2 declined PMRT, 3 were non-compliant, 6 developed distant metastases and 3 died. Four years on from mastectomy, 2 of the 61 women who chose IBR had not undergone the second stage (patient choice), while 8 of the 16 who chose DBR had not had reconstruction (6 due to cancer progression or death; 2 patient choice).

4.1. Discussion

This study demonstrated no key differences in mean HRQOL scores between women declining breast reconstruction and those opting for IBR or DBR. A 2016 systematic review [28] showed that individual women have many different reasons for their BR choices. Yet much of the previous research has focused on physical constructs such as BR type, timing or level of complications in the authors' assessments of

which form of BR is "best." [10–13] Our findings highlight the importance of informed choice as an independent moderator of an individual's HRQOL. This allows women to "own" their decision and to potentially accept any physical or psychosocial consequences resulting from their choice. This hypothesis assumes that if the woman's choice is based on their own informed preferences and values, they will be more accepting of the outcomes.

The importance of informed decision-making is supported by a 2018 systematic review of decisional regret (12 studies, 5672 participants) that reported all studies had identified a relationship between higher levels of decisional regret and an insufficient amount, inadequate quality, or unclear nature of information provided to women prior to undergoing mastectomy [16]. These findings are echoed by the 2021 Breast Cancer Network Australia report on breast reconstruction, based on a national survey of 3350 women sharing their experiences of breast reconstruction [29]. One of the report's seven key recommendations was the need for comprehensive breast reconstruction information prior to mastectomy "to ensure women are empowered to make the most appropriate decision for them" [29]. Our earlier work on increasing the BR rate in Australia by offering more women a choice of BR [30] and on PROMs related to body image [7] also support this proposition.

Results showed that all women followed a similar recovery path as measured by 21 validated quality of life questions and that the timing and type of reconstruction did not matter, a finding that differed from previous studies (**Aim 1**). The persistent significant and negative responses to the Future Perspectives question "Were you worried about your health in the future?" suggests a more permanent fear of recurrence in these women, which supports previous research. Cancer Australia recognises uncertainty about the future and fear of cancer recurrence as common concerns [31], while a systematic review of fear of cancer recurrence found it remained stable over the survivorship trajectory [32]. The continuing deterioration in arm symptoms may reflect the frequency of lymphoedema, and potentially shoulder stiffness, in this high-risk group of women: 74.1% of Australian women and 63.6% of NZ

Table 2
Tumour characteristics and treatments at baseline.

	Australian site (n = 78 women, 85 breasts & axillae)				New Zealand site (n = 22 women, 23 breasts & axillae)				Combined sites
	IBR (n = 52)	DBR (n = 12)	NBR (n = 14)	Total (n = 78)	IBR (n = 10)	DBR (n = 3)	NBR (n = 9)	Total (n = 22)	n = 100 women; 108 breasts; 108 axillae
Affected breasts (# women)									
Bilateral synchronous	4 (5.1)	0 (0.0)	3 (3.8)	7 (9.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (4.5)	8 (8.0)
Unilateral	48 (61.5)	12 (15.4)	11 (14.1)	71 (91.0)	9 (41.0)	3 (13.6)	9 (41.0)	21 (95.5)	92 (92.0)
Invasive tumour type (# breasts)									
Ductal	39 (45.9)	6 (7.1)	11 (12.9)	56 (65.9)	5 (21.7)	2 (8.7)	7 (30.4)	14 (60.9)	70 (64.8)
Lobular	14 (16.5)	6 (7.1)	5 (5.9)	25 (29.4)	4 (17.4)	0 (0.0)	2 (8.7)	6 (26.1)	31 (28.7)
Mixed	1 (1.2)	0 (0.0)	1 (1.2)	2 (2.4)	2 (8.7)	1 (4.3)	0 (0.0)	3 (13.0)	5 (4.6)
Other	2 (2.4)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)
Invasive tumour Grade (# breasts)									
1	5 (5.9)	0 (0.0)	0 (0.0)	5 (5.9)	2 (8.7)	0 (0.0)	1 (4.3)	3 (13.0)	8 (7.4)
2	29 (34.1)	6 (7.1)	11 (12.9)	46 (54.1)	7 (30.4)	1 (4.3)	6 (26.1)	14 (60.9)	60 (55.6)
3	19 (22.4)	6 (7.1)	6 (7.1)	31 (36.5)	2 (8.7)	2 (8.7)	1 (4.3)	5 (21.7)	36 (33.4)
Unknown	3 (3.5)	0 (0.0)	0 (0.0)	3 (3.5)	0 (0.0)	0 (0.0)	1 (4.3)	1 (4.3)	4 (3.7)
Invasive tumour size (# breasts)									
≤20 mm	12 (14.1)	1 (1.2)	2 (2.4)	15 (17.6)	4 (17.4)	2 (8.7)	1[c] (4.3)	7 (30.4)	22 (20.4)
21 mm–50 mm	23 (27.1)	7 (8.2)	8 (9.4)	38 (44.7)	5 (21.7)	1 (4.3)	5 (21.7)	11 (47.8)	49 (45.4)
>50 mm	21 (24.7)	4 (4.7)	7 (8.2)	32 (37.6)	2 (8.7)	0 (0.0)	3 (13.0)	5 (21.7)	37 (34.3)
Number of tumours (# breasts)									
One	28 (32.9)	5 (5.9)	12 (14.1)	45 (52.9)	7 (30.4)	1 (4.3)	6 (26.1)	14 (60.9)	59 (54.6)
More than one	28 (32.9)	7 (8.2)	5 (5.9)	40 (47.1)	4 (17.4)	2 (8.7)	3 (13.0)	9 (39.1)	49 (45.4)
Types of axillary surgery (# axillas)									
SLNB	19 (22.4)	4 (4.7)	7 (8.2)	30 (35.3)	4 (17.4)	0 (0.0)	4 (17.4)	8 (34.8)	38 (35.2)
Level 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.3)	1 (0.9)
Level 2	17 (20.0)	6 (7.1)	1 (1.2)	24 (28.2)	6 (26.1)	1 (4.3)	3 (13.0)	10 (43.5)	34 (31.5)
Level 3	20 (23.5)	2 (2.4)	9 (10.6)	31 (36.5)	1 (4.3)	2 (8.7)	2 (8.7)	4 (17.4)	35 (32.4)
Axillary nodes positive (# axillas)									
Median	2	1.5	1.5	2	0	1	0	1	1.25
Range	0–25	0–31	0–20	0–31	0–4	0–7	0–12	0–12	0–31
Adjuvant chemotherapy (# women)									
Yes	23 (29.5)	9 (11.5)	11 (14.1)	43 (55.1)	6 (27.3)	1 (4.5)	6 (27.3)	13 (59.1)	56 (56.0)
No	29 (37.2)	3 (3.8)	3 (3.8)	35 (44.9)	4 (18.2)	2 (9.1)	3 (13.6)	9 (40.1)	44 (44.0)
Neoadjuvant chemotherapy (# women)									
Yes	25 (32.1)	1 (1.3)	4 (5.1)	30 (38.5)	5 (22.7)	0 (0.0)	4 (18.2)	9 (40.1)	39 (39.1)
No	27 (34.6)	11 (14.1)	10 (12.8)	48 (61.5)	5 (22.7)	3 (13.6)	5 (22.7)	13 (59.1)	61 (61.0)
Lymphovascular Invasion (# breasts)									
Yes	24 (28.2)	5 (5.9)	8 (9.4)	37 (43.5)	1 (4.3)	1 (4.3)	3 (13.0)	5 (21.7)	42 (38.9)
No	27 (31.8)	7 (8.2)	8 (9.4)	42 (49.4)	10 (43.5)	2 (8.7)	4 (17.4)	16 (69.6)	58 (53.7)
Unknown	5 (5.9)	0 (0.0)	1 (1.2)	6 (7.1)	0 (0.0)	0 (0.0)	2 (8.7)	2 (8.7)	8 (7.4)
Oestrogen Receptors (# breasts)									
Positive	49 (57.6)	10 (11.8)	14 (16.5)	73 (85.9)	11 (47.8)	2 (8.7)	8 (34.8)	21 (91.3)	94 (87.0)
Negative	7 (8.2)	2 (2.4)	3 (3.5)	12 (14.1)	0 (0.0)	1 (4.3)	1 (4.3)	2 (8.7)	14 (13.0)
Progesterone Receptors (# breasts)									
Positive	44 (51.8)	9 (10.6)	13 (15.3)	66 (77.6)	6 (26.1)	1 (4.3)	5 (21.7)	12 (52.2)	78 (72.2)
Negative	12 (14.1)	3 (3.5)	4 (4.7)	19 (22.4)	5 (21.7)	2 (8.7)	4 (17.4)	11 (47.8)	30 (27.8)
HER2 Receptors (# breasts)									
Positive	9 (10.6)	4 (4.7)	3 (3.5)	16 (18.8)	4 (17.4)	2 (8.7)	3 (13.0)	9 (39.1)	25 (23.1)
Negative	47 (55.3)	8 (9.4)	13 (15.3)	68 (80.0)	7 (30.4)	1 (4.3)	6 (26.1)	14 (60.9)	82 (75.9)
Unknown	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Triple Negative Tumour (# breasts)									
Yes	5 (5.9)	0 (0.0)	2 (2.4)	7 (8.2)	0 (0.0)	0 (0.0)	1 (4.3)	1 (4.3)	8 (7.4)
No	51 (60.0)	12 (14.1)	15 (17.6)	78 (91.8)	11 (47.8)	3 (13.0)	8 (34.8)	22 (95.7)	100 (92.6)

ALND = axillary lymph node dissection; HER2 human epidermal growth factor receptor 2; IBR immediate breast reconstruction.
DBR delayed breast reconstruction; NBR no breast reconstruction; SLNB = sentinel lymph node biopsy.

Table 3a
Type of immediate breast reconstruction surgery (stage 1 of 2 and direct to implant, direct to autologous).

Type of IBR n (%)	Aust (n = 51)	NZ (n = 10)	Total (n = 61)
Expander	45 (86.5)	3 (30)	48 (78.7)
Direct to Implant[a]	6 (13.5)	2 (20)	8 (13.1)
DIEP	0 (0)	4[b] (40)	4 (6.6)
TRAM	0 (0)	1[c] (10)	1 (1.6)

DIEP = deep inferior epigastric perforator; TRAM = transverse rectus abdominis muscle.
[a] 4 had contralateral prophylactic mastectomy (also direct to implant).
[b] 2 women did not require PMRT.
[c] Woman recommended but declined PMRT.

women in this study required Level 2 or 3 axillary lymph node dissection (Table 2). A systematic review of 19 studies including over 3000 patients concluded that the incidence of lymphoedema in patients undergoing both ALND and regional lymph node radiation was 33.4% [33]. This supports previous research which noted a significant association between arm function and the clinical variables oedema (p = 0.006) and radiation therapy (p = 0.017) [34]. That study concluded that arm disability influences quality of life of patients after mastectomy [34], an adverse effect of breast cancer treatment that cannot be improved by BR.

As expected, physical symptoms including side effects from systemic therapy, breast symptoms and fatigue, significantly improved with time since mastectomy. Social functioning improved significantly at all time points, indicating breast cancer treatment only had short term impacts

Table 3b

Type of immediate breast reconstruction surgery (stage 2 of 2).

Type of IBR n (%)	Aust (n = 45)	NZ (n = 3)	Total (n = 48)
Permanent implant[a]	30 (73)	1 (33.3)	31 (64.6)
DIEP unilateral	6 (14.6)	0 (0)	6 (12.5)
DIEP bilateral	0 (0)	0 (0)	0 (0)
TRAM unilateral	0 (0)	0 (0)	0 (0)
TRAM bilateral	5 (12.2)	0 (0)	5 (10.4)
Removal of expander/implant	3[b] (7.3)	1[b] (33.3)	4 (8.3)
No Stage 2	1[c] (2.4)	1[c] (33.3)	2 (4.2)

DIEP = deep inferior epigastric perforator; TRAM = transverse rectus abdominis muscle.

[a] 7 had contralateral surgery: 1 prophylactic mastectomy with expander; 4 reduction mammoplasty; 1 augmentation; and 1 mastopexy.

[b] Removal of expander/implant with no replacement (2 infected; 1 ruptured; 1 patient choice).

[c] No Stage 2 procedure undertaken within 48 months (patient choice).

Table 3c

Type of delayed breast reconstruction surgery.

Type of DBR n (%)	Aust (n = 12)	NZ (n = 4)	Total (n = 16)
DIEP unilateral	2 (16.7)	0 (0)	2 (12.5)
DIEP bilateral	2 (16.7)	0 (0)	2 (12.5)
TRAM unilateral	1 (8.3)	0 (0)	1 (6.3)
TRAM bilateral	3 (25.0)	0 (0)	3 (18.8)
None	4[a] (33.3)	4[b] (100)	8 (50.0)

DIEP = deep inferior epigastric perforator; TRAM = transverse rectus abdominis muscle.

[a] Two had progressive breast cancer, one died from breast cancer and one had lung cancer.

[b] Two were not interested, one had metastatic breast cancer and one died from breast cancer.

(less than 12 months) on interference with family life or social activities. The authors were unable to find any previous research that reported QLQ-C30 mean social functioning scores as a separate measure for comparison.

Financial difficulties were assessed by a single question: Has your physical condition or medical treatment caused you financial difficulties? Mean scores showed a lessening in financial difficulties at all post-baseline time points, although it was not until 48-months post-mastectomy that the difference from baseline scores became statistically significant. This is not surprising considering the high out-of-pocket costs for the majority of this cohort, who were treated in Australian private hospitals. Over 50% of respondents to a national survey estimated they were more than $5000 out-of-pocket, with 10% indicating they would be more than $15,000 out-of-pocket [29]. Delays in returning to paid work and costs associated with on-going investigations, such as specialist fees, imaging costs, time off work and travel costs will also contribute to financial difficulties.

Of interest is the finding that changes in QLQ-C30 Global health/QoL mean scores did not reach significance at any timepoint. They were fairly stable, with non-significant improvements at 12 and 24 months, no meaningful change at 36 months and then a non-significant worsening at 48 months (p = 0.59). The QLQ-C30 is the only breast cancer surgery questionnaire to directly ask patients to assess their HRQOL via two questions: *How would you rate your overall health during the past week?* and *How would you rate your overall quality of life during the past week?* Scores range from very poor to excellent on a 7 point Likert scale, providing a Global Health/QoL mean score. Most QoL questionnaire items measure a range of factors that are considered to contribute to, and act as proxies for, HRQOL. For example, national data from the UK National Mastectomy and Breast Reconstruction Audit 'demonstrated the effectiveness of breast reconstruction in improving quality of life following mastectomy' [3], yet based this finding on the BREAST-Q modules, which infer QoL from measures of Psychosocial, Sexual and

Physical Well-being. Hence our finding of overall stable HRQOL during a four year period may relate to the limited direct assessment of a multi-faceted and complex dimension, not necessarily fully captured by proxy measures.

This study also found no significant between-group differences in HRQOL (**Aim 2**). This finding supports a prospective longitudinal survey study of 67 women with mastectomy in which psychosocial function scores were recorded over three timepoints: pre-mastectomy; one-year post-mastectomy; and long-term post-mastectomy (mean 6.3 years) [14]. In addition, psychosocial functioning was compared between the 39 women who underwent mastectomy only and the 28 women who had DBR within the study period. At long-term follow-up, women with DBR had significantly higher levels of total distress (p = 0.01), obsessiveness (p = 0.03) and cancer-related distress (p = 0.02) compared to those with mastectomy alone. However, there were no differences in HRQOL between the two groups at any time point. Metcalfe et al. concluded that QoL improved in all women in this cohort over time, regardless of BR [14].

It is well-established that PMRT may have a negative impact on the cosmetic outcome following breast reconstruction. However, this does not necessarily correlate with a negative impact on patient-reported quality of life. Beesley et al. found that women value other attributes of BR above satisfaction with aesthetic outcomes: "patients' subjective evaluation of reconstruction after cancer treatment extends well beyond cosmesis, and experience of cancer influences what they consider important" [35]. Previous studies by our group in Sydney support this view. A retrospective audit study of 136 patients reported women were accepting of the potential damage to the skin and muscles of the breast that may follow PMRT, and also of the increased risk of capsular contracture of the expander or implant used in the reconstruction [36]. Similarly, a separate retrospective cohort study of 47 different women with high-risk breast cancer undergoing BR followed by PMRT, found women were largely satisfied with less than perfect cosmetic outcomes and concluded that "when an informed choice is made, high levels of satisfaction can be achieved" [30].

Perceptions of HRQOL are highly subjective. The current authors previously examined body image outcomes in this same cohort of women and suggested that choice of BR may be a contributing factor to the lack of differences in body image outcomes between the three surgical groups [7]. When women were fully informed of the potential benefits, harms and costs of a particular BR option, and were free to make their choice, then the timing and type of BR they chose did not lead to significant between-group differences in body image measures.

While our interpretation of the findings from our previous research and this current HRQOL paper is necessarily subjective due to the observational nature of these studies, it is challenging to come up with other possible explanations. Even differences in patient characteristics that may be thought to play a role in HRQOL outcomes (**Aim 3**) – such as age, BMI, marriage, education or employment status – did not produce any meaningful between-group differences.

The final aim of this research (**Aim 4**) was to determine the feasibility and utility of long-term collection of PROMs in clinical settings. Overall, this project successfully recruited 100 women across two sites, to take part in a longitudinal study over five years, involving completion of a set of questionnaires at baseline and seven subsequent time points. Seventy percent of women completed our a priori criterion for inclusion in analysis of completing baseline and a minimum of one other annual questionnaire. While research on acceptable compliance rates is ongoing [37], we believe that a compliance rate of 70% is reasonable, particularly over a five-year period and with multiple questionnaires. At 48 months post-mastectomy, there were significant differences identified in seven of the 21 scales, with all seven demonstrating consistent trends in the same direction (either better or worse). Hence, we believe that 48 months is an appropriate period to document long-term HRQOL changes in these measures.

Table 4
Mean change from baseline in 21 HRQOL subscales over 48 months.

Scale (question numbers)	T0 mean (Baseline) n = 100	Baseline to T1 (1 year) n = 81		P value	Baseline to T2 (2 years) n = 80		P value	Baseline to T3 (3 years) n = 72		P value	Baseline to T4 (4 years) N = 70		P value
QLQ-BR23 Future perspective (13)[a]	38.65	15.43	Worse	0.001*	17.45	Worse	0.001*	19.82	Worse	0.001*	20.26	Worse	0.001*
QLQ-BR23 Sexual function (14, 15)[b]	18.72	3.78	Better	0.13	0.11	Same	0.96	0.81	Same	0.76	−2.46	Worse	0.43
QLQ-BR23 Sexual enjoyment (16)[b]	55.33	−6.95	Worse	0.15	1.39	Better	0.77	−7.35	Worse	0.16	−4.67	Worse	0.46
QLQ-BR23 Side effects (1–4, 6–8)[a]	21.67	−5.17	Better	0.01*	−6.19	Better	0.001*	−6.57	Better	0.001*	−8.26	Better	0.001*
QLQ-BR23 Breast symptoms (20–23)[a]	14.74	−0.15	Same	0.94	−3.54	Better	0.06	−5	Better	0.01*	−5.8	Better	0.01*
QLQ-BR23 Arm symptoms (17–19)[a]	9.58	8.96	Worse	0.001*	7.4	Worse	0.001*	5.51	Worse	0.01*	6.55	Worse	0.01*
QLQ-BR23 Upset by hair loss (5)[a]	42.99	−2.65	Better	0.78	−17.13	Better	0.06	−15.86	Better	0.09	−6.57	Better	0.53
QLQ-C30 Global health/ HRQOL (29,30) [b]	72.19	1.67	Better	0.51	3.76	Better	0.14	0.4	Same	0.88	−1.61	Worse	0.59
QLQ-C30 Physical functioning (1–5)[b]	94.43	−3.2	Worse	0.01*	−1.89	Worse	0.14	−3.6	Worse	0.01*	−1.85	Worse	0.22
QLQ-C30 Role functioning (6,7)[b]	84.9	3.99	Better	0.15	5.13	Better	0.06	3.8	Better	0.19	5.43	Better	0.1
QLQ-C30 Emotional functioning (21–24)[b]	71.83	6.91	Better	0.001*	4.4	Better	0.06	5.3	Better	0.06	5.1	Better	0.23
QLQ-C30 Cognitive functioning (20,25)[b]	79.39	−0.27	Same	0.91	−3.27	Worse	0.17	−0.02	Same	0.99	2.34	Better	0.41
QLQ-C30 Social functioning (26,27)[b]	73.45	11.02	Better	0.001*	10.56	Better	0.001*	9.88	Better	0.001*	14.74	Better	0.001*
QLQ-C30 Fatigue (10,12,18)[a]	28.16	−2.12	Better	0.37	−3.96	Better	0.09	−5.88	Better	0.02*	−6.08	Better	0.03*
QLQ-C30 Financial difficulties (28)[a]	34.55	−2.72	Better	0.46	−5.07	Better	0.17	−6.24	Better	0.11	−10.66	Better	0.02*
QLQ-C30 Pain (9,19)[a]	12.04	2.75	Worse	0.26	2.51	Worse	0.3	1.45	Worse	0.57	−2.46	Better	0.4
BREAST-Q Physical Well-being[a,c]	79.24	−6.74	Better	0.001*	−4.72	Better	0.01*	−3.62	Better	0.05	−3.84	Better	0.08
BREAST-Q Satisfaction with Abdomen[a,c]	77.89	−6.02	Better	0.5	−5.71	Better	0.41	−1.58	Better	0.81	3.78	Worse	0.63
BREAST-Q Satisfaction with outcome[b,c]	N/A	70.63	Better	N/A	−1.61	Worse	0.52	0.04	Same	0.99	−1.41	Worse	0.64
BPI Severity (2–5)[a]	13.5	1.0	Worse	0.63	2.0	Worse	0.31	1.2	Worse	0.57	−1.2	Better	0.61
BPI Interference (8a-8g)[a]	13.4	−0.4	Same	0.88	−0.8	Same	0.76	−1.1	Better	0.68	−2.9	Better	0.36

All scales ranged from 0–100. Mean changes of <1.0 were classified as Same. * = statistically significant.
Significantly better than Baseline at all timepoints.
Significantly worse than Baseline at all timepoints.
[a] Higher score = worse outcome.
[b] Higher score = better outcome.
[c] Question number varies.

4.2. Limitations and strengths

As an observational, non-randomised study there are potential confounders which may bias the results. Multiple models were created on each of the 21 scales (overall, by BR group and by patient characteristics), so tests of significance should be interpreted with caution. In addition, the sample size per group was relatively small, particularly for those who chose to delay BR (n = 16), as reflected in the wide confidence intervals for some HRQOL measures.

Furthermore, not all women completed their Baseline questionnaires prior to mastectomy. Of the 77 women in the Australian cohort, 20 (26%) completed their baseline PROMs after their initial surgery [7] (13 because the surgeons recruited them on the day of surgery after earlier consultations where study recruitment was overlooked; six because they were given the surveys pre-op but did not complete them until after their surgery; and one because she completed IBR questionnaires pre-operatively, but subsequently chose to delay her BR (and so completed her DBR questionnaires post-operatively). This delay to baseline questionnaire completion reflects the complexity and logistical challenges of collecting pre-operative data, particularly for women with high-risk breast cancer, in a setting where time from first consultation to

surgery may be within one week. These women were asked to complete their baseline surveys "with a pre-op mind". Subsequent analysis removing these 20 women from the dataset resulted in no meaningful changes to the overall results.

Although 30% of participants were not followed up for the full 48 months and there is the potential for selection bias to be introduced into the study, we compared the mean scores between those who completed every questionnaire and those who were lost to follow-up. Given there were no significant differences in the scores, we have some confidence that selection bias is minimised during the study.

Another limitation is our inability to account for the negative HRQOL effects of adjuvant breast cancer treatments such as chemotherapy, endocrine therapy and targeted therapy. Table 2 shows that 93.6% of Australian women and 99.2% of NZ women in this study had chemotherapy. As only five women in the study did not receive chemotherapy, meaningful sub-analysis was not possible. Similarly, of the 108 breast cancers, 94 breasts (87%) were oestrogen receptor positive, 8 breasts (7.4%) were triple negative, and 25 breasts (23.1%) were HER2 positive, making sub-analyses difficult and any conclusions obtained from subgroup analysis unreliable.

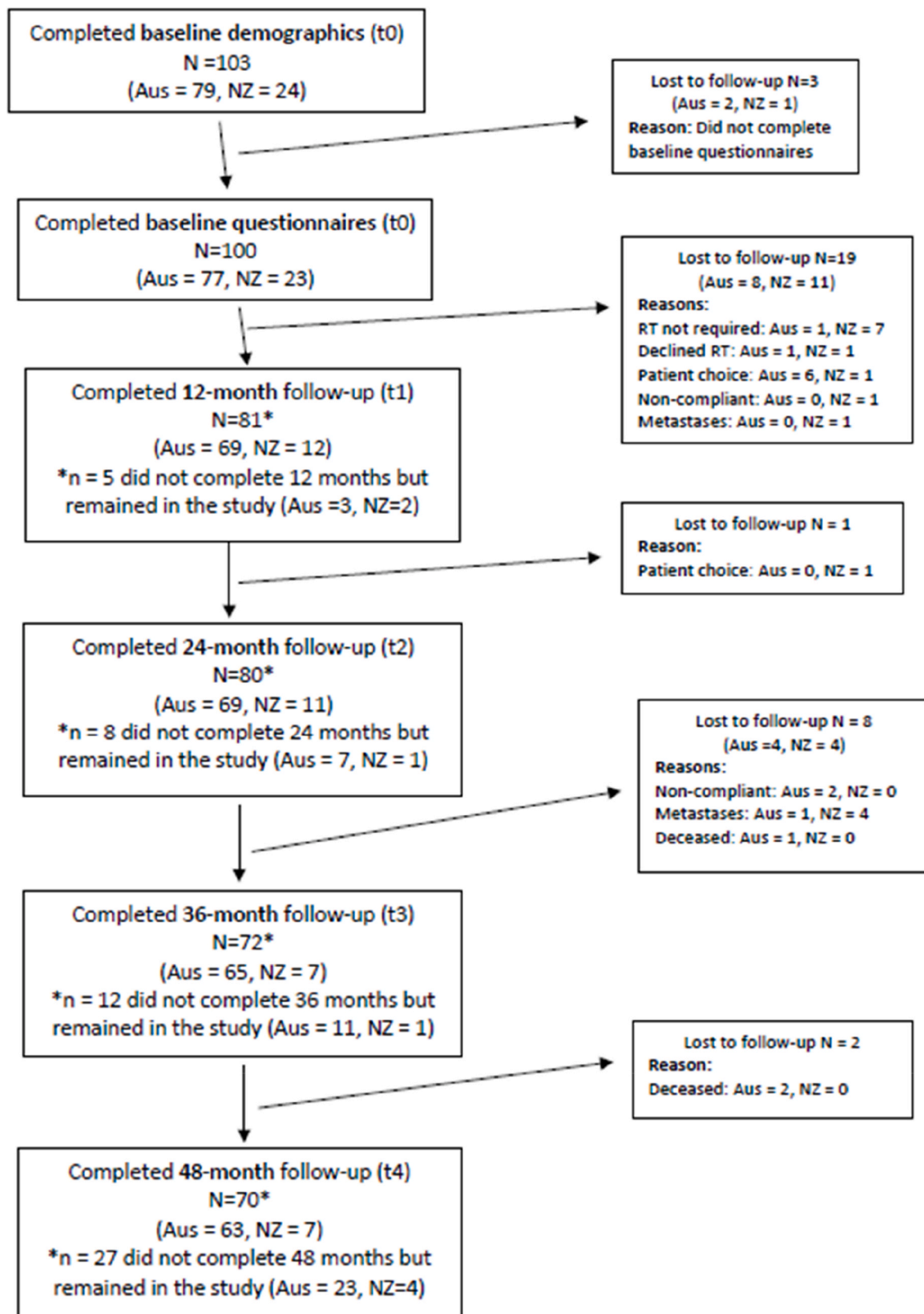HRQOL may also be adversely impacted by the severity of breast

Fig. 2. Questionnaire Completion Rates
Aus = Australia; NZ = New Zealand; t = time (t0 = baseline; t1-4 = annual follow-ups).

cancer and associated fear of cancer recurrence. We were unable to control for these factors in our analysis. However, all patients in this study were at the higher-risk end of the disease spectrum to warrant consideration of PMRT, so that individual variations in breast cancer characteristics may be less relevant in this cohort than in the total breast cancer population.

For the 90 women who did require PMRT, immediate autologous reconstruction was generally not offered. At the time of the study, breast plastic and reconstructive surgeons were generally averse to performing immediate autologous reconstruction that would then be subjected to radiotherapy, due to the increased likelihood of skin, tissue and blood vessel damage, potentially resulting in inferior aesthetic outcomes and a greater risk of serious adverse patient outcomes. The Australian women who required PMRT were offered a choice of either no reconstruction, immediate one-stage implant-based BR (direct-to-implant) or two-stage BR, with an immediate expander, followed by either delayed implant or autologous reconstruction. It is not clear how many of these women would have opted for immediate autologous BR if this was offered. In New Zealand, two women requiring PMRT underwent immediate DIEP (one resulting in immediate flap failure).

Strengths of this research include its prospective nature, long-term follow-up, multi-site recruitment and acceptable questionnaire completion rates. Another important strength is PROMs were administered in two clinics where the need for PMRT did not preclude women, who had been informed of the potential risks of poorer outcomes, opting for immediate implant-based BR. Hence the study controlled for the potentially major impact of PMRT on HRQOL, as all women who continued to the 12-month questionnaires did receive PMRT. In women who have undergone implant-based BR (the majority of this cohort), the addition of chest wall PMRT dramatically increases the rate of capsular contracture from 32 to 73% [38]. Capsular contracture has a significant effect on breast asymmetry [39], which in turn is a major contributor to poor satisfaction with breast surgical outcomes [40]. PMRT also adversely affects autologous BR, with adverse tissue fibrosis and volume effects [17]. While capsular contracture may be associated with tightness and pain [39], PMRT and mastectomy are also independently capable of causing chronic pain and tightness [41]. Failure of previous studies to control for PMRT may account for differences in HRQOL mean scores.

5. Conclusion

Our study design allowed us to track changes in women's mean HRQOL scores from four validated questionnaires. It showed consistent declines in future perspectives, driven mainly by fear of cancer recurrence, and arm symptoms, a consequence of extensive breast and/or axillary surgery. While these long-term concerns are not directly related to breast reconstruction, they do present opportunities for future research on how best to address these highly impactful consequences of breast cancer diagnosis and treatment.

This study demonstrated no important differences in mean HRQOL scores between women declining breast reconstruction and those opting for IBR or DBR. The fact that 56% of women considered likely to require PMRT opted to have immediate implant-based BR, despite their awareness of the possible long-term side effects, illustrates the role of individual choice. Immediate reconstruction was obviously important to these women, and gave them the option of having either implant-based or autologous-based definitive reconstruction. This supports the hypothesis that being given an informed choice of the type and timing of BR allows women to "own" their decision and better accept whatever limitations may result from their choice.

5.1. Clinical implications

This study has demonstrated very similar trajectories of HRQOL scores in women who were offered a choice of BR options. Empowering women through shared decision-making and informed choice may be an important contributing factor in restoring most HRQOL indicators to pre-mastectomy levels, regardless of their BR choices. Surgeons should explain the potential benefits and harms of all BR options to all women requiring mastectomy, prior to surgery, along with the potential impact of adjuvant therapies such as PMRT on reconstructive outcomes. More than one pre-operative consultation may be needed to ensure that the patient has all the information required to make an informed choice. Furthermore, surgeons should assist patients to access their preferred BR option, through referral to other surgeons either within their surgical team or to external clinics.

While trials of interventions to address fear of cancer recurrence have become a mainstream focus in psycho-oncology research, more attention to the benefits of pre- and post-surgical physiotherapy to improve arm symptoms would be welcome.

Ethics approval

This paper reports on a selection of HRQOL patient-reported outcomes from women recruited to the 'Quality of Life of Immediate and Delayed breast reconstruction in women undergoing mastectomy and adjuvant radiotherapy for breast cancer' (QOLID) study (ethics approval 30/04/2013 from St Vincent's Hospital Sydney HREC 13/059). Trial registration: ACTRN12614000045617.

Author contributions

The study was conceived by April Wong, Andrew Spillane, Kathy Dempsey, Meagan Brennan, Kylie Snook, Ian Campbell and Frances Boyle. AS, KS and IC also recruited patients for the study. Health-related quality of life expertise was provided by Meagan Brennan, Frances Boyle and Madeleine King. Erin Mathieu performed the statistical analysis. Julia Hoffman, Jenni Scarlet and Heather Flay were responsible for data collection. The first draft of the manuscript was written by Kathy Dempsey and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

Signed written consent was obtained from all study participants.

Consent to publish

No individual or identifiable patient data is included in this manuscript. All patients received a detailed Participant Information Sheet, prior to signing the consent form, explaining only aggregate data would be published.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.breast.2023.08.001.

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