# Quality of Life Outcomes Associated With Optimization of Treatment by Omitting Radiotherapy in Early Breast Cancer

Lesley Stafford,[1,2] Michelle Sinclair,[3] Phyllis Butow,[4] Janemary Hughes,[5] Allan Park,[5] Leslie Gilham,[6] Allison Rose,[5,7] G. Bruce Mann[3,5,6]

## Abstract

**Following on from PROSPECT[ANZ:1002], we compared women with early breast cancer (EBC) who omitted RT (n = 125) with women who received RT(n = 175) on quality of life (QoL) outcomes. Omission of RT was consistently associated with superior QoL and was highly acceptable to patients. If recurrence is low in select women with EBC who omit RT, QoL may influence treatment planning.**

**Purpose:** Improved prognosis of early breast cancer (EBC) has created opportunities for treatment optimization but reducing morbidity should not inadvertently compromise quality of life (QoL). PROSPECT[1] used pre-operative MRI and pathology findings to identify women suitable for radiotherapy (RT) omission following breast conserving surgery. We retrospectively explored the association between de-escalation by omission of RT and QoL in women with EBC. **Materials and methods:** Three groups were recruited: PROSPECT participants who omitted RT following preoperative MRI (A); participants who received RT following preoperative MRI (B); and women who received usual care - No MRI, received RT (C). Measures included the EORTC QLQ-C30 and BR23, BCTOS, DASS-21 and a measure of decision regret. Between group differences were assessed using ANOVA or nonparametric equivalents. Semi-structured interviews were analyzed with qualitative description (n = 44). **Results:** Data from 400 women were analyzed (125A, 102B, 173C). Group A had fewer symptoms and better body image (breast symptoms: A-B $P = .003$, A-C $P = <.001$; arm symptoms: A-B $P = .004$, A-C $P = .011$; body image: A-C $P = .041$) and fewer differences between the treated and untreated breasts (cosmetic: A-B $P < .001$, A-C $P < .001$; functional: A-C $P = .011$; breast specific pain: A-B $P < .001$, A-C $P < .001$). Two qualitative themes were found: *Treatment with the biggest impact on QoL*, and *Specific impact of RT on QoL*. **Conclusions:** Omission of RT was associated with better QoL and functional and cosmetic outcomes. It was highly acceptable to patients. Clinicians should consider the potential for preserved QoL associated with treatment optimization via omission of RT in treatment planning for patients with EBC.

*Clinical Breast Cancer,* Vol. 24, No. 5, 447–456 

**Keywords:** Treatment de-escalation, Health-related quality of life, Psychosocial oncology, Patient reported outcomes, Radiation therapy

*Abbreviations:* EBC, Early breast cancer; RT, Radiation therapy; MRI, Magnetic Resonance Imaging; PRIME, Post-operative Radiotherapy In Minimum-risk Elderly; PROSPECT, Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial; EUROPA, Exclusive endocrine Therapy Or Radiation theraPy for Women Aged ≥70 years early stage breast cancer; EXPERT, EXamining PErsonalised Radiation Therapy for low-risk early breast cancer; DEBRA, De-Escalation of Breast Radiation trial; LUMINA, A Prospective Cohort Study Evaluating Risk of Local Recurrence Following Breast Conserving Surgery and Endocrine Therapy in Low Risk Luminal A Breast Cancer; PRIMETIME, Post-operative avoidance of radiotherapy: biomarker selection of women categorised to be in a very low risk group by IHC4+C; HRQoL, Health related quality of Life; QoL, Quality of life; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; BR23, European Organization for Research and Treatment of Cancer Breast Cancer-Specific Module; BCTOS, Breast Cancer Treatment Outcomes Scale; DASS-21, Depression Anxiety Stress Scale Short Form-21; ASTRO, American Society for Radiation Oncology; KQ4, key question 4.

[1]Familial Cancer Centre, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[2]Melbourne School of Psychological Sciences, University of Melbourne, Victoria, Australia
[3]Department of Surgery, University of Melbourne, Victoria, Australia
[4]School of Psychology, University of Sydney, Sydney, New South Wales, Australia
[5]The Breast Service, The Royal Melbourne and Royal Women's Hospitals, Parkville, Victoria, Australia
[6]Breast Cancer Trials, Newcastle, New South Wales, Australia
[7]Northwestern Breast Screen, The Royal Melbourne Hospital, Parkville, Victoria, Australia

Submitted: Dec 8, 2023; Revised: Feb 19, 2024; Accepted: Mar 3, 2024; Epub: 6 March 2024

Address for correspondence: Lesley Stafford, Genomic Medicine & Parkville Familial Cancer Centre, Level 2 Centre, 300 Grattan Street, Royal Melbourne Hospital, Victoria 3050, Australia.
E-mail contact: Lesley.Stafford@mh.org.au, Allison.rose@mh.org.au

1526-8209/$ - see front matter 
https://doi.org/10.1016/j.clbc.2024.03.002

## Introduction

Outcomes for treatment of early breast cancer (EBC) have improved due to a combination of early diagnosis and the near-routine use of effective adjuvant therapies. The prognosis of those diagnosed more recently are substantially better than those diagnosed over 25 years ago.[2] However, burdensome side effects, and additional costs and inconvenience of adjuvant therapies have prompted investigation of omission of some therapies, such as routine postsurgical breast radiotherapy (RT) in selected low risk EBC patients. While adjuvant RT does decrease the risk of local recurrence in EBC, which in turn may save lives, the absolute benefit in very low risk breast cancer is small.[3] RT prolongs treatment, is resource intensive and is associated with significant side effects[4,5] which in turn can lead to a deterioration in physical, psychological, and social wellbeing, ie, health-related quality of life (HRQoL).[6]

HRQoL is now regarded as a key component and endpoint in clinical trials, particularly where the treatment under investigation may offer limited advantages for recurrence or survival. Two published trials investigating de-escalation by RT omission[7,8] have included HRQoL outcomes. Whelan et al's[7] study of women treated with lumpectomy with or without axillary dissection and with or without RT but no systemic treatment found that RT was associated with increased physical symptoms, fatigue, and inconvenience at 2 months, and increased breast pain and irritation at 3 months but there were no differences at 2 years. The PRIME (Postoperative Radiotherapy In Minimum-risk Elderly) study[8] included 255 women older than 65 years with low-risk EBC treated with breast conserving surgery and endocrine therapy (ET), with or without RT. PRIME found that RT was associated with increased breast symptoms and fatigue in the short-term, and patients had significant concerns about the delivery of RT (eg, transport, travel costs), but there was no overall improvement in HRQoL with the omission of RT. More recent trials of different approaches to RT after breast conserving trials, involving 5 fractions either for whole-breast or partial-breast RT have shown substantially less toxicity than the approaches used in these trials of RT omission.[9,10]

There is ongoing work using varying approaches to define a group of women with EBC at sufficiently low risk in whom RT could be safely omitted.[11] Prospective studies using biomarker-based strategies to achieve this goal include EXPERT,[12] DEBRA,[13] LUMINA[14,15] and PRIMETIME.[16] In a move away from molecular markers, PROSPECT (Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial, ANZ-1002), a prospective nonrandomized cohort study, used magnetic resonance imaging (MRI) and pathological findings to identify a group of women for whom RT could be safely omitted. Women with favorable surgical pathology found to have unequivocally unifocal EBC on MRI (n = 201) were treated with breast conserving surgery and adjuvant systemic therapy, but without adjuvant RT. The primary analysis for PROSPECT showed a very low rate of local recurrence.[1] Patient-reported outcome measures, including HRQoL, were not included in PROSPECT.

To further understand the association between omission of RT and HRQoL, and to inform future prospective studies using the PROSPECT approach to treatment optimization, we conducted a large retrospective, exploratory study with women enrolled in PROSPECT as the reference group. We hypothesized that women who omitted RT would have better HRQoL. We also investigated functional and aesthetic outcomes, psychological morbidity, and decision regret regarding the decision to undergo preoperative MRI, and if appropriate, omit RT.

## Materials and Methods

### *Recruitment*

Three groups of patients were recruited from a large tertiary hospital in metropolitan Melbourne, Australia. Group A comprised women who underwent preoperative MRI as part of PROSPECT and were suitable for omission of RT. Group B underwent preoperative MRI as part of PROSPECT, were found to be unsuitable for de-escalation, and received RT. Group C comprised women approximately matched on age, tumor grade distribution, and tumor size to Groups A and B, but who were not approached for PROSPECT, did not undergo MRI, and did receive RT (ie, usual care). All participants had been diagnosed with EBC between 2011 and 2019, were at least 12 months postdiagnosis, had undergone breast conserving surgery with sentinel node biopsy and/or axillary dissection and could participate in English.

PROSPECT recruited 443 patients with clinical T1N0 non-TNBC who underwent preoperative MRI. All BIRADS 3 or above occult lesions were biopsied, identifying additional malignant lesions in 48/443 patients (11%). Patients without substantial background parenchymal enhancement on MRI, no occult malignant lesion and pT1N0 non-TNBC, without lymphovascular invasion or extensive DCIS and excised with a radial margin of at least 2 mm were eligible for treatment without adjuvant RT (Group A). Those not meeting the inclusion criteria were recommended to have RT and those treated with RT comprised Group B. Most RT was 16 fractions without a boost, and no partial-breast RT was used. The local recurrence rate when the median Group A patient reached 5 years was 1%.[1]

Eligible women were emailed or posted invitations to participate. Invitations included detailed study information including instructions for completing the questionnaire online, or how to request that a paper questionnaire be posted, and that in addition to the questionnaire, they could also opt in to be selected for a semi-structured interview. Where there was no response to the initial invite, follow-up calls were made after 2 weeks. A second and final invitation was sent if the 2 prior attempts to contact patients had been unsuccessful. Participants Institutional ethics approval was obtained [HREC approval number: 2020.002].

### *Measures*

*Questionnaire.* Quantitative data were collected using validated, psychometric measures: HRQoL was measured with the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30)[17] and its breast cancer-specific component, the BR23. The QLQ-C30 includes 5 subscales assessing functionality (physical, emotional, social, role, cognitive), 8 symptom subscales (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), an item assessing financial impact and a measure of global health/HRQoL. Responses are scored on a Likert scale. The BR23 comprises 23 items assessing

body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms, and hair loss. For both the QLQ-C30 and BR23 raw scores are linearly converted to a 0–100 scale with higher scores reflecting higher levels of function and higher levels of symptom burden, as appropriate.

Treatment-related aesthetic and functional outcomes were assessed with the Breast Cancer Treatment Outcomes Scale (BCTOS).[18] Participants are asked to record the extent to which they perceive a difference in appearance and functioning between treated and untreated breast/breast area using a Likert scale. The measure has 3 subscales (cosmetic status, functional status, breast specific pain) with higher scores indicating greater morbidity. An additional item about sensation was added due to investigator interest.

Symptoms of anxiety and depression were assessed with the Depression Anxiety Stress Scale Short Form-21 (DASS-21).[19,20] Participants rate the extent to which they have experienced symptoms of anxiety or depression over the past week on 4-point severity/frequency scales. Higher scores indicate greater symptom burden.

Responses to the first item of the Decision Regret Scale[21] "it was the right decision" were used to assess satisfaction with decisions to undergo MRI and to omit RT, respectively. Responses are scored on a Likert scale.

The 10-item Neuroticism subscale of the International Personality Item Pool[22] was included as negative affectivity is a well-known confounder of subjective perceptions of wellbeing.[23,24] Higher scores indicate greater levels of neuroticism.

Participant clinical data were collected from medical records including tumor characteristics, nodal stage, age, and time since diagnosis. Demographic data including level of education, relationship status, presence of any medical comorbidities, parity, language spoken at home, and current or past mental health treatment experience were self-reported in the questionnaire.

*Statistical Methods.* SPSS software version 28 was used for all analyses. Between group differences were assessed by ANOVA with Tukey-Kramer post-hoc tests, or appropriate nonparametric alternatives (Kruskal-Wallis tests with post-hoc pairwise comparisons, and Mann-Whitney U tests).

*Semistructured Interview.* The semi-structured interview guide was developed and refined by the multidisciplinary author group which included 2 expert psycho-oncologists, a specialist breast surgeon, breast care nurse, breast radiologist, and a consumer with lived experience of EBC. Telephonic interviews were conducted with a subset of participants intentionally selected from those who opted in, to include a range of scores on HRQoL scales. Participants were asked about experiences of RT, and which treatment had the biggest impact on their QoL. A psychologist with experience in interviewing oncology patients conducted the telephonic interviews which were recorded, transcribed, checked for accuracy and analyzed with NVivo 12 software. Analysis followed a qualitative descriptive approach[25] rooted in the principles of naturalistic enquiry.[26] Deductive codes were defined using a structured coding framework initially informed by interview questions (see Appendix for list of interview questions). A fifth of transcripts were independently coded by 2 authors, after which the coding matrix was expanded to include new codes, adjusted to achieve consensus, and applied to the remaining interviews. Themes were refined and checked against original data and codes for accuracy before illustrative quotes were selected. Interviews continued until saturation (no new themes emerging from 3 consecutive interviews) was achieved.

## Results

### *Study Participation*

Recruitment procedures have been previously described in greater detail.[27] Invitations to participate were sent to 808 women. Of those, 117 declined, and 306 were uncontactable or lost to follow-up. The final sample comprised 125 women in Group A, 102 in Group B and 173 in Group C. Fifteen women from each of Groups A and B participated in interviews and 14 women from Group C. See Figure 1, recruitment diagram.

### *Sample Characteristics*

Participants had a median age of 65 (range 51-84), a third of participants had received a tertiary education (29.6%) and most were partnered (68.5%). Median time since diagnosis for the whole sample was 4.4 years and was not significantly different between groups (Group A: 4.1, range 1.2-9.1; Group B: 4.3, range 1.1-9.8; Group C: 4.6, range 1-10). Similarly, there were no differences between the groups in age, level of education (tertiary vs. not), relationship status (partnered vs. not), parity, mental health treatment status, presence of medical comorbidities, or neuroticism. Group A had significantly smaller tumors, with more Grade 3 and node positive cancers than women in Groups B and C, but Groups B and C were not significantly different. See Table 1 for sample demographic and clinical characteristics.

### *Health-Related Quality of Life*

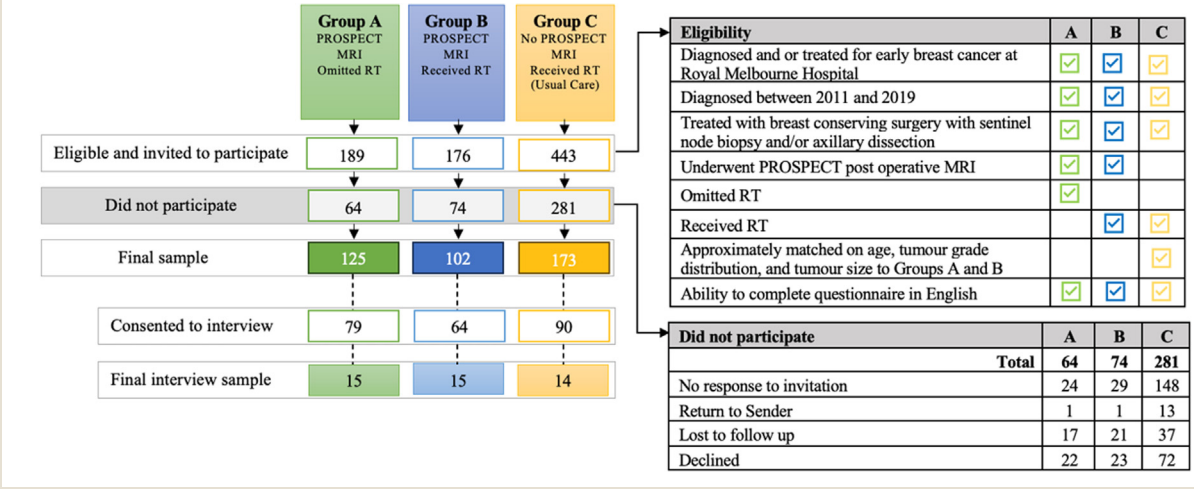
See Table 2 for means and standard deviations, medians and interquartile ranges, and between group *P*-values with MID estimates.

There were no significant differences between groups on any of the QLQ-C30 subscales. Scores on the body image, breast- and arm symptoms subscales of the BR23 favoured women who omitted RT: post-hoc tests showed that women in Group A had fewer breast symptoms than those in Group B ($P = .003$, 95%CI $= -10.32, -1.73$) and Group C ($P =< .001$, 95%CI $= -10.10, -2.55$), fewer arm symptoms than women in Group B ($P = .004$, 95%CI $= -12.02, -1.92$) and Group C ($P = .011$, 95%CI $= -9.90, -1.02$), and better body image than Group C ($P = .041$, 95%CI $= 0.19, 10.98$). There were no differences between women in Groups B and C.

### *Aesthetic and Functional Outcomes*

Between group differences were significant for all BCTOS subscales using non-parametric tests and post hoc pairwise comparisons. Group A was less likely than Group B or Group C to indicate there were differences in pain (A-B $P < .001$, $r = .305$. A-C $P < .001$, $r = .298$), sensation (A-B $P < .001$, $r = .253$. A-C $P < .001$,

**Figure 1** Study participation diagram.




| Eligibility | A | B | C |
|---|---|---|---|
| Diagnosed and or treated for early breast cancer at Royal Melbourne Hospital | ☑ | ☑ | ☑ |
| Diagnosed between 2011 and 2019 | ☑ | ☑ | ☑ |
| Treated with breast conserving surgery with sentinel node biopsy and/or axillary dissection | ☑ | ☑ | ☑ |
| Underwent PROSPECT post operative MRI | ☑ | ☑ | |
| Omitted RT | ☑ | | |
| Received RT | | ☑ | ☑ |
| Approximately matched on age, tumour grade distribution, and tumour size to Groups A and B | | | ☑ |
| Ability to complete questionnaire in English | ☑ | ☑ | ☑ |

| Did not participate | A | B | C |
|---|---|---|---|
| Total | 64 | 74 | 281 |
| No response to invitation | 24 | 29 | 148 |
| Return to Sender | 1 | 1 | 13 |
| Lost to follow up | 17 | 21 | 37 |
| Declined | 22 | 23 | 72 |

r = .279), or cosmetic appearance (A-B $P < .001$, r = .349. A-C $P < .001$, r = .395) between their treated and untreated beasts with small to medium effect sizes. Women in Group A were also less likely than those in Group C to indicate a functional difference ($P = .011$, r = .168) with medium effects. The functional differences between women in Groups B and C and women in Groups A and B were not statistically significant following Bonferroni correction for multiple tests.

To further examine the association between RT and these outcomes, we conducted exploratory comparisons between women who omitted RT (Group A) and those who did not (Groups B and C combined), as shown in Table 3. Women who omitted RT had less fatigue, insomnia and financial impact (small effects), fewer breast and arm symptoms (small to medium effects), and better body image (small effect) when compared to women who received RT. Women who omitted RT also reported fewer differences between their treated and untreated breasts across all subscales of the BCTOS with small to medium effects.

### *Psychological Morbidity*

There were no differences between the groups on the depression or anxiety subscales of the DASS-21.

### *Decision Regret*

Almost all of Group A (98%) and Group B (92%) agreed or strongly agreed that having the MRI was the right decision and 94% of Group A agreed that omitting RT was the right decision. No participants in either group disagreed with either item.

As those with tumors >20 mm in size, who had positive nodes or lymphovascular invasion were ineligible for RT omission in PROSPECT, the pathology of Group A patients was lower risk than those of Group B or C. We therefore conducted a secondary analysis to explore whether disease severity had any impact on outcomes (see Appendix). After excluding these cases (tumors larger than >20 mm, or presence of positive nodes, or lymphovascular invasion), 274 women remained. Findings were similar to the primary analysis. Women in Group A reported less financial impact, fewer breast, and arm symptoms, better overall cosmetic and functioning scores, fewer breast-specific pain symptoms, fewer differences in sensation between treated and untreated breasts, and lower depression than women in Group B. Women in Group A also perceived significantly fewer breast symptoms, less breast-specific pain, better cosmetic outcomes, and fewer differences in sensation between treated and untreated breasts than women in Group C.

### *Qualitative Outcomes*

Two deductive themes were found in response to questions about which aspects of treatment had the biggest impact on QoL and the specific nature of the impact of RT on QoL, if any. See Table 4 for Illustrative quotes.

*Treatment With the Biggest Impact on QoL.* In general, women who omitted RT (Group A), spoke less about the impact of breast cancer treatment and were more likely to indicate that treatment did not significantly affect their QoL. For most women, across groups, surgery had minimal impact on QoL. Some women indicated that surgery was a positive experience as having the cancer excised provided relief, while others noted that the effect of surgery was minimal compared to other treatments.

Five women noted that RT had the most pronounced impact on their QoL, however, endocrine therapy (ET) was the most highly cited treatment (n = 14) in terms of deleterious effect on QoL. ET was described as 'debilitating', 'disabling' and like 'premature ageing' by participants. Six women who underwent RT found it difficult to separate out the effects of individual treatments.

*Specific Impact of RT on QoL.* Women in Groups B and C recalled side-effects from RT such as burns, blisters, pain, discomfort, and associated emotional distress, and issues with RT delivery such as the inconvenience of attending appointments, appoint-

**Table 1** Demographic and Clinical Characteristics of the Sample

| | Group A (MRI, Omitted RT) n = 125 | Group B (MRI, Received RT) n = 102 | Group C (no MRI, Received RT) n = 173 | Total sample N = 400 |
|---|---|---|---|---|
| **Demographic characteristics** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** |
| Age (y)[a] | 66(61-72) | 65(60-71) | 63(60-69) | 65(60-70) |
| Neuroticism[a] | 22(16-29) | 23(17-30) | 23(18-30) | 23(17-29) |
| Number of children[a] | 2(2-3) | 2(2-3) | 2(2-3) | 2(2-3) |
| | **N(%)** | **N(%)** | **N(%)** | **N(%)** |
| University educated[a] | 22(26.4) | 28(27.5) | 57(32.9) | 118(29.6) |
| Partnered[a] | 84(67.2) | 74(72.5) | 116(67.1) | 274(68.5) |
| Currently receiving mental health treatment[a] | 21(16.8) | 20(19.6) | 46(26.6) | 87(21.8) |
| Previously received mental health treatment[a] | 47(37.6) | 40(39.2) | 80(46.2) | 167(41.8) |
| Presence of chronic medical conditions | 57(45.6) | 53(52) | 91(52.6) | 201(50.3) |
| **Clinical characteristics** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** |
| Tumor size (mm)[a]* | 10(8-12) | 13(10-16) | 14(9-19) | 12(12-16) |
| Mo since diagnosis[a] | 49(26-68) | 51(32-79) | 56(27-83) | 53(28-79) |
| | **N(%)** | **N(%)** | **N(%)** | **N(%)** |
| Tumor Stage | | | | |
| T1a or T1b | 73(58.4) | 31(30.4) | 53(30.6) | 157(39.3) |
| T1c | 52(41.6) | 60(58.8) | 82(47.4) | 194(48.5) |
| T2 | 0(0) | 11(10.8) | 38(22.0) | 49(12.3) |
| Nodal Stage | | | | |
| pN0 | 125(100.0) | 81(79.4) | 151(87.3) | 357(89.3) |
| pN1mi | 0(0.0) | 8(7.8) | 9(5.2) | 17(4.3) |
| pN1 | 0(0.0) | 13(12.7) | 13(7.5) | 26(6.5) |
| Nodal Status | | | | |
| Negative | 125(100.0) | 81(79.4) | 151(87.3) | 357(89.3) |
| Positive | 0(0.0) | 21(20.6) | 22(12.7) | 43(10.8) |
| Tumor Grade | | | | |
| 1 | 62(49.6) | 30(29.4) | 39(22.5) | 131(32.8) |
| 2 | 56(44.8) | 56(54.9) | 93(53.8) | 205(51.3) |
| 3 | 7(5.6) | 16(15.7) | 37(21.4) | 60(15.0) |
| Not Specified | 0(0.0) | 0(0.0) | 4(2.3) | 4(1.0) |
| Received endocrine therapy | 125(100.0) | 98(96.1) | 158(91.3) | 381(95.3) |

[a] Differences between groups were assessed using non-parametric tests.
[b] Difference between groups assessed as significant $P<.001$ as per independent samples Kruskal-Wallis test.

ment rescheduling, faulty RT equipment, and hospital parking. While these issues were challenging at the time of treatment, few women reported that RT had an ongoing negative impact on their QoL. Several women reported persistent memory difficulties and fatigue but could not definitively identify the source of these symptoms.

Some women who received RT reported feeling surprised by the severity of RT side-effects and would have liked more warning prior to treatment. Two women regretted having RT. Most women expressed the idea that RT is toxic and wanted to avoid it but endured the treatment as it was necessary to treat their disease. Many women minimized the experience of side-effects by expressing their gratitude for effective treatment or good fortune compared to others with worse disease.

## Discussion

Achieving optimal outcomes while minimizing toxicities is a key aim of modern treatment for EBC and several studies are seeking to define a sufficiently low-risk population in whom RT can be safely omitted.[11] Clearly, attempts to minimize physical morbidity and treatment burden should not inadvertently compromise psychosocial wellbeing. Previously we reported novel findings that the omission of RT in the context of PROSPECT is associated with lower fear of cancer recurrence.[27] Here we report on HRQoL outcomes in this setting. Our findings show a potential for superior HRQoL in this select sample of women in whom RT is omitted relative to their counterparts who received RT. Specifically, omission of RT was associated with fewer breast-, arm-, and breast-specific pain symptoms, and better cosmetic and sensation scores over 4

**Table 2** Health-Related Quality of Life, Psychological Morbidity, and Decision Regret

| | A (n = 125) | B (n = 102) | C (n = 173) | Total sample (N = 400) | |
|---|---|---|---|---|---|
| **EORTC QLQ-C30** | **Mean(SD)** | **Mean(SD)** | **Mean(SD)** | | |
| Summary score | 87.73(13.04) | 84.49(12.46) | 85.39(13.56) | 85.88(13.15) | |
| Global Health | 73.73(21.19) | 69.12(22.76) | 70.33(22.51) | 71.08(22.19) | |
| Functioning subscales | | | | | |
| Physical | 88.03(17.02) | 84.77(17.43) | 86.93(16.38) | 86.72(16.86) | |
| Emotional | 80.87(21.56) | 79.98(18.18) | 80.03(21.20) | 80.28(20.54) | |
| Cognitive | 83.2(22.75) | 83.01(19.34) | 82.27(19.37) | 82.75(20.43) | |
| Social | 91.2(21.02) | 88.56(20.97) | 91.04(19.15) | 90.46(20.20) | |
| Role | 88.13(23.74) | 84.8(26.13) | 87.86(22.17) | 87.17(23.70) | |
| Symptom subscales | | | | | |
| Fatigue | 19.38(21.26) | 26.36(22.16) | 23.31(22.44) | 22.86(22.11) | |
| Nausea/vomiting | 3.33(11.20) | 3.76(8.75) | 4.14(10.96) | 3.79(10.50) | |
| Pain | 18.8(25.92) | 23.69(26.58) | 18.79(25.01) | 20.04(25.73) | |
| Dyspnoea | 10.22(21.75) | 13.73(22.18) | 12.33(19.07) | 12.03(20.74) | |
| Insomnia | 28.27(29.04) | 35.29(32.44) | 35.07(33.00) | 33(31.75) | |
| Appetite loss | 6.93(16.56) | 4.90(13.59) | 6.36(16.22) | 6.17(15.68) | |
| Constipation | 6.99(18.17) | 9.15(21.06) | 10.6(20.26) | 9.11(19.86) | |
| Diarrhoea | 5.07(15.87) | 5.88(16.53) | 7.51(19.39) | 6.33(17.63) | |
| Financial impact | 3.2(13.00) | 8.17(19.02) | 7.51(19.39) | 6.33(17.63) | |
| **EORTC BR23** | **Mean(SD)** | **Mean(SD)** | **Mean(SD)** | **Mean(SD)** | ***P*, MID[#]** |
| Functioning subscales | | | | | |
| Body image | 89.73[a](15.16) | 85.62[ab](21.72) | 84.15[b](20.93) | 86.27(19.64) | .049, 11 |
| Future perspective | 73.6(22.52) | 69.28(26.40) | 67.63(28.63) | 69.92(26.34) | |
| Sexual functioning | 17.34(23.80) | 14.17(18.25) | 16.86(20.79) | 16.33(21.18) | |
| Sexual enjoyment | N = 41 | N = 34 | N = 69 | N = 144 | |
| | 52.85(27.86) | 50.98(28.70) | 52.17(26.49) | 52.08(27.23) | |
| Symptom subscales | | | | | |
| Breast symptoms | 4.98[a](9.72) | 11.00[b](13.13) | 11.30[b](16.18) | 9.25(13.94) | <.001, 6 |
| Systemic therapy side-effects | 14.86(13.85) | 16.81(14.13) | 16.27(13.38) | 15.96(13.71) | |
| Arm symptoms | 5.33[a](11.16) | 12.31[b](17.68) | 10.79[b](17.99) | 9.47(16.30) | .002, 11 |
| Hair loss | N = 36 | N = 38 | N = 49 | N = 123 | |
| | 31.48(28.67) | 29.82(29.8) | 37.42(33.77) | 33.33(31.07) | |
| **BCTOS** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** | | ***P*** |
| Cosmetic | 1.38[a](1.13-1.63) | 1.63[b](1.38-2.00) | 1.75[b](1.38-2.25) | 1.63(1.25-2.00) | <.001 |
| Functional | 1.00[a](1.00-1.29) | 1.00[ab](1.00-1.43) | 1.00[b](1.00-1.57) | 1.00(1.00-1.43) | .011 |
| Breast Specific Pain | 1.00[a](1.00-1.67) | 1.67[b](1.00-2.33) | 1.67[b](1.00-2.00) | 1.33(1.00-2.00) | <.001 |
| Sensation | 1.00[a](1.00-2.00) | 2.00[b](1.00-2.00) | 2.00[b](1.00-2.00) | 1.00(1.00-2.00) | <.001 |
| **DASS** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** | **Median(IQR)** | |
| Depression | 1.00(0.00-3.50) | 2.00(0.00-6.00) | 1.00(0.00-5.00) | 2.00(0.00-5.00) | |
| Anxiety | 1.00(0.00-3.00) | 2.00(0.00-5.00) | 2.00(0.00-4.00) | 2.00(0.00-4.00) | |
| Decision regret | | | | | |
| It was the right decision | | | | | |
| to have the MRI | **N(%)** | **N(%)** | | | |
| Neither agree nor disagree | 3(2.40) | 7(6.90) | | | |
| Agree or strongly agree | 122(97.60) | 94(92.20) | | | |
| to omit RT | | | | | |
| Neither agree nor disagree | 8(6.40) | | | | |
| Agree or strongly agree | 117(93.60) | | | | |

Abbreviation: EORTC QLQ- C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.
BR-23 = European Organization for Research and Treatment of Cancer breast cancer specific module.
BCTOS = Breast Cancer Treatment Outcomes Scale.
DASS = Depression Anxiety Stress Scale Short Form-21.
MID = Minimally important difference.
[ab] Each subscript letter denotes a subset of group whose proportions do not differ significantly from each other; different subscript letters indicate following a significant between groups test, the post hoc pairwise comparison between these groups was significant.
[#] MID point estimate as calculated by Ousmen et al.[28] NOTE: the sexual functioning and hair loss subscales of the BR23 were only answered if the participant indicated they were sexually active or had experienced hair loss resulting in smaller samples. *P* values only reported for significant results. MID scores only reported where available.

**Table 3** Differences in HRQoL Measures Between Women Who Omitted RT (Group A) and Women Who Received RT (Groups A+B)

| | A (n = 125) | B+C (n = 275) | | | | | |
|---|---|---|---|---|---|---|---|
| **QLQ-C30** | **Mean(SD)** | **Mean(SD)** | **t** | **Mean Difference (95%CI)** | **Std. Error** | ***P*, $\eta^2$** | **MID[#]** |
| Fatigue | 19.38(21.26) | 24.44(22.34) | −2.13 | −5.0(−9.73,−0.4) | 2.37 | .033, .01 | 20 |
| Insomnia | 28.27(29.04) | 35.15(32.73) | −2.02 | −6.88(−13.59,−0.18) | 3.41 | .044, .01 | 15 |
| Financial impact | 3.2(13.00) | 7.76(19.22) | −2.78 | −4.56(−7.79,−1.33) | 1.64 | .006, .02 | 5 |
| **BR23** | **Mean(SD)** | **Mean(SD)** | **t** | **Mean Difference (95%CI)** | **Std. Error** | ***P*, $\eta^2$** | **MID[#]** |
| Body image | 89.73(15.16) | 84.70(21.20) | 2.70 | 5.04(1.37,8.7) | 1.86 | .007, .02 | 11 |
| Breast symptoms | 4.98(9.72) | 11.19(15.10) | −4.94 | −6.21(−8.69,−3.74) | 1.26 | <.001, .06 | 6 |
| Arm symptoms | 5.33(11.16) | 11.35(17.86) | −4.10 | −6.02(−8.91,−3.13) | 1.47 | <.001, .04 | 11 |
| **BCTOS** | **Median(IQR)** | **Median(IQR)** | **MWU** | **Standard error** | **Standardized test statistic** | ***P*, r** | |
| Cosmetic | 1.38(1.13-1.63) | 1.75(1.38-2.25) | 24757.00 | 1068.21 | 7.086 | <.001, .35 | - |
| Functional | 1.00(1.00-1.29) | 1.00(1.00-1.43) | 20047.00 | 957.83 | 2.985 | .003, .15 | - |
| Breast Specific Pain | 1.00(1.00-1.67) | 1.67(1.00-2.33) | 23023.00 | 1034.88 | 5.629 | <.001, .28 | - |
| Sensation | 1.00(1.00-2.00) | 2.00(1.00-2.00) | 22086.50 | 971.50 | 5.043 | <.001, .25 | - |

EORTC QLQ- C30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.
BR-23: European Organization for Research and Treatment of Cancer breast cancer specific module.
BCTOS: Breast Cancer Treatment Outcomes Scale.
MID: Minimally important difference
$\eta^2$ = eta squared effect size, .010 = small, .060 = medium, .140 = large.
r = Cohen's r effect size, .1 = small, .3 = medium, .5 = large.
[#] MID point estimate as calculated by Ousmen et al.[28] MID scores only reported where available.

**Table 4** Illustrative Quotes for the Themes "Treatment With the Biggest Impact on QoL" and "Specific Impact of RT on QoL"

| Treatment with the biggest impact on QoL | Specific impact of RT on QoL |
|---|---|
| *"I think it was the best decision I made [omitting RT]… I've been able to forget that I even had breast cancer… I've just gone on living my life… [it's] just been good…there's been no side-effects as far as I'm concerned." A176* | *"…Listlessness… incredibly tired all the time with no reason why…as you're getting older, I don't know if I'm having… little memory things… not as quick to recall words... I don't know if that the lasting effect of [the RT], or it's just age, or medication"* C467 |
| *"[Surgery] hasn't affected the quality of my life at all… I've got one breast that's slightly smaller now than the other….[there was] a bit of pain for about five days. And that was very, very, very mild…. I'm feel totally normal [now]." C571* | *"I feel like I've been cooked…. like… when you're thawing a bit of meat in the microwave…I just have this feeling inside my mind that this is… what's happened to my breast….It's nothing compared to the fact that I'm alive. And I don't have cancer, and I'm not dying"* C9 |

years post-diagnosis when compared to women who received RT either following MRI staging or as a component of usual care. Further, the absence of significant differences between Groups B and C suggest that undergoing MRI in addition to RT did not impact HRQoL. Our qualitative findings suggest that women who omitted RT were grateful for this opportunity and identified less treatment-related adversity. Women who received RT tended to minimize their negative treatment experiences. The secondary analysis conducted to examine the potential impact of disease variables on HRQoL yielded similar findings to the primary analysis. While the effect sizes reported are not large, it is noted that even small effects may have a substantial impact on a patient's sense of wellbeing. Data from Ousmen et al.[28] further suggests that the difference between women in Group A and those in Groups B and C in breast symptom scores is clinically meaningful.

Our findings highlight that the impact on HRQoL from RT is more likely experienced as specific to breast- and arm functionality and cosmetic outcomes rather than affecting global social, emotional, physical, and role functioning. This suggests that broad measures of HRQoL, like the QLQ-C30, do not capture the impact of RT on HRQoL. Our findings are supported by the PRIME study which also found no between group differences on the QLQ-C30 core subscales but reported that RT was associated with more breast symptoms up to 5 years post study enrolment[8] on the BR23. While other studies (eg,[7,29]) have reported that RT has a limited and temporary impact on HRQoL, our findings suggest this is dependent on how HRQoL is conceptualized. Future studies using generic measures of HRQoL like the QLQ-C30 should include a breast-specific component (eg, the BR23 or the newer version, the BR45[30]) or consider using a breast-focused inventory like the BCTOS to best capture the effect of RT on subjective experience.

Further, we found that patients explicitly minimized the treatment burden associated with RT, suggesting that side effects from RT may be under-reported. Participants shared graphic memories

of side effects, and while these toxicities did not persist, it was evident that recalling the details was distressing. Many participants appeared reluctant to explicitly acknowledge the burden and impact of RT, as though doing so implied lack of gratitude for an improved prognosis or access to effective treatment. With shorter RT courses, reduction in irradiation breast tissue volume, and treatment techniques that reduce dose inhomogeneity, many of the same HRQoL outcomes studied here appear to be improved, especially with partial-breast irradiation as compared to whole-breast irradiation.[9,10] Recent ASTRO guideline KQ4 endorses short course partial-breast irradiation due to fewer late toxicities and improved cosmesis.[31] Still, it remains important that clinicians provide realistic expectations about short- and long-term effects of RT.[32]

An important finding was that side effects of ET were identified as a major source of morbidity in this cohort. Given that women were at least 12 months post diagnosis at the time of participation (with some women being up to 10 years post diagnosis), ET was the most recently experienced treatment which may have contributed to the prominence of this finding. Nonetheless, the prolonged toxicities associated with ET are well-established[33] and participants' identification of ET as being the treatment with the most negative impact on their HRQoL warrants further consideration. With previous trials suggesting that combining ET and RT in older women with EBC has less incremental benefit than expected and use of RT or ET alone results in excellent disease management (eg,[34]), the EUROPA trial is randomizing women >70 years after breast conserving surgery with T1N0 Luminal-A tumours to RT or ET alone, and HRQoL is the primary outcome.[35,36] Any future large-scale validation of PROSPECT might offer an opportunity for further investigation of whether ET can also be safely omitted in a subset of women with EBC and investigate associated differences in HRQoL.

While these data from a large study of women with EBC suggest superior HRQoL outcomes when post-operative RT is omitted in this context, the generalizability of these results needs to be considered within the methodological confines of the study design. Specifically, the sample was recruited from a single site, data was retrospective and cross-sectional in nature, and the groups were *a priori* clinically different to test the PROSPECT hypothesis. It is notable, however, that the groups did not differ on key characteristics (median age, time since diagnosis, or mental health treatment status) which may influence HRQoL reporting. The groups also did not differ on levels of neuroticism, a known predictor of subjective wellbeing,[37] which suggests the potential influence of trait anxiety can be ruled out as accounting for poorer outcomes among women who received RT. Further, the secondary analysis in which women with positive nodes, a Grade 3 tumor and/or tumors larger than 20 mm were excluded, also suggested preserved HRQoL associated with omission of RT. It is acknowledged that excluding women unable to participate due to language barriers is a limitation.

Future research investigating the association between treatment de-escalation via omission of RT and HRQoL needs to consider the specificity of measures used and prioritize inclusion of measures that target functional and cosmetic outcomes. Measures like the BCTOS and the updated breast-specific module of the EORTC, the BR45, are more likely to capture the specific treatment burden associated with RT than global measures of HRQoL (such as the EORTC-QLQC30). Similarly, future optimization studies should include analysis of the financial burden associated with RT, which was not examined here. The QLQ-30 includes only 1 item on the topic; however, estimates of financial toxicity in breast cancer patients are as high as 28% and this warrants closer scrutiny in a comprehensive assessment of HRQoL.[38,39] It will be critical that future studies of RT omission include the newer and less toxic RT schedules, with either 5-fraction whole or partial-breast RT, as the favorable HRQoL outcomes from these approaches may reduce the benefit of RT omission.

Within the limits of this study and for select women, omitting RT in this setting appears to be associated with better functional and cosmetic outcomes, and this should be taken to into account when discussing treatment options with patients. Undergoing pre-operative MRI prior to possible de-escalation by omission of RT is highly acceptable to patients even if ultimately, they are unsuitable for de-escalation. Clinicians should ensure that patients are well-informed regarding potential RT side-effects to minimise distress when they do occur.

## Conclusions

These findings provide preliminary evidence that de-escalation by omission of RT following pre-operative MRI and favorable pathology in this setting appears to be associated with superior HRQoL compared with standard care. Undergoing MRI and omitting RT in this context was highly acceptable to patients. The side effects of ET are a major source of morbidity for patients. HRQoL needs to be considered prospectively in de-escalation studies and future studies of treatment optimization should prioritise the inclusion of HRQoL measures that capture functional and cosmetic outcomes over measures of global functioning.

## Clinical Practice Points

### *What is Already Known About This Subject?*

- In select women with early breast cancer (EBC) it has been demonstrated that while adjuvant radiotherapy (RT) decreases the risk of local recurrence, surgery alone is sufficient for excellent clinical outcomes.[3] Consequently, identification of a group of women in whom adjuvant RT can be omitted is under investigation.[11-16] Little is known about the health-related quality of life (HRQoL) outcomes associated with omission of RT with extant literature suggesting minimal benefits to HRQoL.[7,8]

### *What are the New Findings?*

- Omission of RT following pre-operative MRI was associated with superior HRQoL outcomes when compared to women who received RT following pre-operative MRI, or who received RT as a component of usual care. This association was apparent across breast- and arm symptoms and functionality, and cosmetic outcomes. Women who omitted RT were less likely to discuss treatment-related adversity while women who received RT minimized RT- related treatment burden and experiences.

***How Might it Impact on Clinical Practice in the Foreseeable Future?***

- These findings provide compelling grounds to include HRQoL and other patient-reported outcome measures in future studies assessing patient outcomes in de-escalation; the impact of omission of RT on HRQoL needs to be studied prospectively.
- If recurrence rates are low and clinical outcomes are excellent in women suitable for omission of RT, patient-reported outcomes such as HRQoL may be relevant to treatment decisions regarding de-escalation of RT.

## Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval

Ethical approval was granted by The Royal Melbourne Hospital HREC approval number: 2020.002.

## Consent to Participate

Informed consent was obtained from all individual participants included in the study.

## Consent to Publish

The authors affirm that participants provided informed consent for publication of these data.

## Disclosure

The authors have no competing interests to declare.

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

## CRediT authorship contribution statement

**Lesley Stafford:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michelle Sinclair:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Phyllis Butow:** Writing – review & editing, Writing – original draft, Conceptualization. **Janemary Hughes:** Writing – review & editing, Data curation, Conceptualization. **Allan Park:** Writing – review & editing, Formal analysis, Data curation. **Leslie Gilham:** Writing – review & editing, Conceptualization. **Allison Rose:** Writing – review & editing, Conceptualization. **G. Bruce Mann:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Conceptualization.

## Acknowledgments

Michelle Sinclair is funded by a Fellowship from Breast Cancer Trials.

The authors acknowledge the Psycho-oncology Co-operative Research Group (PoCoG) who supported the development of this research. The Psycho-oncology Co-operative Research Group is funded by Cancer Australia through their Support for Clinical Trials Funding Scheme.

The authors acknowledge the contribution of Breast Cancer Trials in funding PROSPECT, without which the current work would not have been possible. Breast Cancer Trials receives funding from Cancer Australia.

## References

1. Mann GB, Skandarajah AR, Zdenkowski N, et al. Postoperative radiotherapy omission in selected patients with early breast cancer following preoperative breast MRI (PROSPECT): primary results of a prospective two-arm study. *Lancet North Am Ed*. 2023 Epub 2023 Dec 5. doi:10.1016/S0140-6736(23)02476-5.
2. Taylor C, McGale P, Probert J, et al. Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993-2015: population based observational cohort study. *Br Med J (Clin Res Ed)*. 2023;381:e074684. doi:10.1136/bmj-2022-074684.
3. Darby S, McGale P, Correa CEarly Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378:1717 1716.
4. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. *N Engl J Med*. 2001;344(26):1997.
5. Strobbe LJ, Peterse HL, van Tinteren H, et al. Angiosarcoma of the breast after conservation therapy for invasive cancer, the incidence and outcome. An unforseen sequela. *Breast Cancer Research and Treatment*. Netherlands: Kluwer Academic; 1998:101–109.
6. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *JAMA*. 1995;273(1):59–65. doi:10.1001/jama.1995.03520250075037.
7. Whelan TJ, Levine M, Julian J, et al. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. *Cancer*. 2000;88(10):2260–2266. doi:10.1002/(SICI)1097-0142(20000515)88:103.0.CO.
8. Williams LJ, Kunkler IH, King CC, et al. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. *Health Technol Assess (Rockv)*. 2011;15(12):1–57. doi:10.3310/hta15120.
9. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. *J Clin Oncol*. 2020;38(35):4175–4183. doi:10.1200/jco.20.00650.
10. Brunt MA, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet North Am Ed*. 2020;395(10237):1613–1626. doi:10.1016/S0140-6736(20)30932-6.
11. Franco P, De Rose F, De Santis MC, et al. Omission of postoperative radiation after breast conserving surgery: a progressive paradigm shift towards precision medicine. *Clin Transl Radiat Oncol*. 2020;21:112–119. doi:10.1016/j.ctro.2020.02.003.
12. Breast Cancer Trials, Australia and New Zealand. *Examining personalised radiation therapy for low-risk early breast cancer* https://classic.clinicaltrials.gov/show/NCT02889874.
13. White JR, Anderson SJ, Harris EE, et al. NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery (BCS) of stage 1, hormone receptor+, HER2-, RS ≤18 breast cancer. *J Clin Oncol*. 2022;40(16_suppl):TPS613. doi:10.1200/JCO.2022.40.16_suppl.TPS613.
14. Ontario Clinical Oncology Group and British Columbia Cancer Agency. *A prospective cohort study evaluating risk of local recurrence following breast conserving surgery and endocrine therapy in low risk luminal a breast cancer* https://classic.clinicaltrials.gov/show/NCT01791829.
15. Whelan TJ, Smith S, Parpia S, et al. Omitting radiotherapy after breast-conserving surgery in luminal a breast cancer. *N Engl J Med*. 2023;389(7):612–619. doi:10.1056/NEJMoa2302344.
16. Kirwan CC, Coles CE, Bliss J. It's Primetime. Postoperative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence. *Clin Oncol, Royal Coll Radiologists'*. 2016;28(9):594–596. doi:10.1016/j.clon.2016.06.007.
17. Sprangers M, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: First results from a three-country field study. *J Clin Oncol*. 1996;14(10):2756–2768.
18. Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. *Cancer*. 2001;91(12):2273–2281. doi:10.1002/1097-0142(20010615)91:12⟨2273::AID-CNCR1258⟩3.0.CO.
19. Lovibond SH, Lovibond PF. *Manual for the depression anxiety stress scales*. 2nd ed. Sydney, Australia: Psychology Foundation of Australia; 1996.
20. Henry J, Crawford J. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol*. 2005;44:227–239.

21. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making*. 2003;23(4):281–292. doi:10.1177/0272989X03256005.
22. Goldberg LR, et al. A broad-bandwidth, public domain, personality inventory measuring the lower-level facets of several five-factor models. In: Mervielde I, et al., eds. *Personality Psychology in Europe*. Tilburg, The Netherlands: Tilburg University Press; 1999:7–28.
23. Aarstad AK, Beisland E, Osthus AA, et al. Distress, quality of life, neuroticism and psychological coping are related in head and neck cancer patients during follow-up. *Acta Oncol (Madr)*. 2011;50(3):390–398. doi:10.3109/0284186x.2010.504227.
24. Husson O, Zebrack B, Block R, et al. Personality Traits and health-related quality of life among adolescent and young adult cancer patients: the role of psychological distress. *J Adolesc Young Adult Oncol*. 2017;6(2):358–362. doi:10.1089/jayao.2016.0083.
25. Sandelowski M. Whatever happened to qualitative description? *Res Nurs Health*. 2000;23(4):334–340.
26. Lincoln YS, Guba EG, Pilotta JJ. Naturalistic inquiry: Beverly Hills, CA: Sage Publications, 1985, 416 pp., $25.00 (Cloth). *Int J Intercultural Relations*. 1985;9(4):438–439. doi:10.1016/0147-1767(85)90062-8.
27. Stafford L, Sinclair M, Butow P, et al. Is de-escalation of treatment by omission of radiotherapy associated with fear of cancer recurrence in women with early breast cancer? An exploratory study. *Breast Cancer Res Treat*. 2023;201(3):367–376. doi:10.1007/s10549-023-07039-2.
28. Ousmen A, Conroy T, Guillemin F, et al. Impact of the occurrence of a response shift on the determination of the minimal important difference in a health-related quality of life score over time. *Health and Quality of Life Outcomes*. 2016;14(1):167. doi:10.1186/s12955-016-0569-5.
29. Battisti NML, Hatton MQ, Reed MWR, et al. Observational cohort study in older women with early breast cancer: Use of radiation therapy and impact on health-related quality of life and mortality. *Radiother Oncol*. 2021;161:166–176. doi:10.1016/j.radonc.2021.06.021.
30. Bjelic-Radisic V, Cardoso F, Cameron D, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45☆. *Ann Oncol*. 2020;31(2):283–288. doi:10.1016/j.annonc.2019.10.027.
31. Shaitelman SF, Anderson BM, Arthur DW, et al. Partial breast irradiation for patients with early-stage invasive breast cancer or ductal carcinoma in situ: an ASTRO clinical practice guideline. *Practic Radiat Oncol*. 2023;000:1–21. doi:10.1016/j.prro.2023.11.001.
32. Jagsi R, Griffith KA, Vicini F, et al. Identifying patients whose symptoms are underrecognized during treatment with breast radiotherapy. *JAMA Oncol*. 2022;8(6):887–894. doi:10.1001/jamaoncol.2022.0114.
33. Ferreira A, Di Meglio A, Pistilli B, et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. *Ann Oncol*. 2019;30(11):1784–1795.
34. Blamey RW, Bates T, Chetty U, et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer*. 2013;49(10):2294–2302. doi:10.1016/j.ejca.2013.02.031.
35. Careggi, A.O.-U. and U.o. Florence, Exclusive endocrine therapy or radiation therapy for women aged ≥70 years early stage breast cancer. 2021, https://classic.clinicaltrials.gov/show/NCT04134598.
36. Meattini I, Poortmans PMP, Marrazzo L, et al. Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598 - EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures. *J Geriatr Oncol*. 2021;12(2):182–189. doi:10.1016/j.jgo.2020.07.013.
37. Härtl K, Engel J, Herschbach P, et al. Personality traits and psychosocial stress: quality of life over 2 years following breast cancer diagnosis and psychological impact factors. *Psychooncology*. 2010;19(2):160–169. doi:10.1002/pon.1536.
38. Palmer JD, Patel TT, Eldredge-Hindy H, et al. Patients undergoing radiation therapy are at risk of financial toxicity: a patient-based prospective survey study. *Int J Radiat Oncol Biol Phys*. 2018;101(2):299–305. doi:10.1016/j.ijrobp.2018.03.014.
39. D'Rummo KA, Miller L, TenNapel MJ, et al. Assessing the financial toxicity of radiation oncology patients using the validated comprehensive score for financial toxicity as a patient-reported outcome. *Practic Radiat Oncol*. 2020;10(5):e322–e329. doi:10.1016/j.prro.2019.10.005.

## Appendix. Semi Structured Interview Questions

Supplementary Tables 1 and 2

- PROSPECT involvement
  - Were you approached for participation in a trial that involved the possibility of not having radiotherapy depending on the results of an MRI scan done soon after diagnosis (PROSPECT)?
    - If not approached: Would you have liked to have been considered? Why/why not?
    - If approached and consented: what motivated you to consent to PROSPECT?
    - If participant had been approached and had MRI but was not eligible: How did you feel about this outcome?
  - How did you feel/what did you think about having this MRI?
- Overall treatment experience
  - Can you tell me about your treatment for breast cancer?
  - Which aspects of your breast cancer treatment have had the most impact on your quality of life?
- Surgery
  - How, if at all, do you think breast cancer surgery affected or continues to affect your quality of life? Can you describe any side effects that you have from breast cancer surgery?
- Radiotherapy
  - Having had radiotherapy, can you describe how it affected you during treatment, afterwards and now? Can you describe any side effects that you have from radiotherapy? How, if at all, do you think radiotherapy affected or continues to affect your quality of life? Were there other aspects of radiotherapy that were difficult? If you had been given the opportunity to omit radiotherapy, do you think you would have chosen that path? Why/why not? How do you think your experience of cancer treatment might have been different (if at all) if you had not needed to have radiotherapy (i.e., if it had not been medically indicated)?

**Supplementary Table 1** Demographic and Clinical Characteristics of Secondary Analysis Sample

| Characteristic | Group A n = 118 | Group B n = 62 | Group C n = 94 | Total sample N = 274 |
|---|---|---|---|---|
| | Median(Range) | Median(Range) | Median(Range) | Median(Range) |
| Number of children[a] | 2(0-6) | 2(0-7) | 2(0-6) | 2(0-7) |
| Age (y)[a] | 66(51-83) | 65(54-77) | 63.5(51-79) | 65(51-83) |
| Neuroticism[a] | 21.5(10-48) | 22(10-49) | 24(10-43) | 23(10-49) |
| | N(%) | N(%) | N(%) | N(%) |
| University educated[a] | 33(28.0) | 14(22.6) | 25(26.5) | 72(26.3) |
| Partnered[a] | 79(66.9) | 44(71) | 70(74.5) | 193(70.4) |
| Current mental health treatment[a] | 19(16.1) | 13(21) | 25(26.6) | 57(20.8) |
| Previous mental health treatment[a] | 46(39) | 21(33.9) | 42(44.7) | 109(39.8) |
| Chronic medical conditions | 54(45.8) | 32(51.6) | 48(51) | 134(48.9) |
| | Median(Range) | Median(Range) | Median(Range) | Median(Range) |
| Tumor size[a,b] | 10[a](3-20) | 12[b](4-20) | 11[ab](1-20) | 11(1-20) |
| Mo since diagnosis[a] | 49(14-109) | 49(13-118) | 58(12-120) | 53(12-120) |
| | N(%) | N(%) | N(%) | N(%) |
| Tumor Stage | | | | |
| T1a or T1b | 69(58.5) | 22(35.5) | 40(42.6) | 131(47.8) |
| T1c | 49(41.5) | 40(64.5) | 54(57.4) | 143(52.2) |
| Nodal Stage | | | | |
| pN0 | 118(100.0) | 62(100.0) | 94(100.0) | 274(100.0) |
| Nodal Status | | | | |
| Negative | 118(100.0) | 62(100.0) | 94(100.0) | 274(100.0) |
| Tumor Grade | | | | |
| 1 | 62(52.5) | 23(37.1) | 30(31.9) | 115(42.0) |
| 2 | 56(47.5) | 39(62.9) | 61(64.9) | 156(56.9) |
| Not Specified | 0(0.0) | 0(0.0) | 3(3.2) | 3(1.1) |

Note: Where percentages do not equal 100, this is due to missing data.
[a] indicates differences between groups were assessed using nonparametric tests.
[b] Difference between groups assessed as significant $P<.05$ as per independent samples Kruskal-Wallis test.

**Supplementary Table 2** Health Related Quality of Life, Psychological Morbidity, and Decision Regret Outcomes Across Groups for Secondary Analysis Sample

| | A (n = 118) | B (n = 62) | C (n = 94) | Total sample (N = 274) | *P*, effect size |
|---|---|---|---|---|---|
| **QLQ-C30** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | |
| Summary score | 87.78 (13.24) | 83.40 (12.96) | 86.84 (11.59) | 86.45 (12.70) | |
| Global Health | 73.66 (21.74) | 67.61 (23.48) | 69.24 (22.33) | 70.77 (22.41) | |
| Functioning subscales | | | | | |
| Physical | 87.77 (17.28) | 84.30 (18.03) | 88.07 (14.27) | 87.09 (16.50) | |
| Emotional | 80.65 (21.92) | 79.44 (19.13) | 81.24 (20.29) | 80.58 (20.70) | |
| Cognitive | 83.05 (23.06) | 81.72 (20.85) | 82.62 (20.14) | 82.60 (21.53) | |
| Social | 91.24 (21.43) | 87.10 (23.26) | 92.55 (17.73) | 90.75 (20.71) | |
| Role | 88.28 (23.70) | 83.33 (26.82) | 92.02 (18.73) | 88.44 (23.05) | |
| Symptom subscales | | | | | |
| Fatigue | 19.30 (21.57) | 26.88 (23.16) | 22.46 (21.62) | 22.10 (22.07) | |
| Nausea/ vomiting | 3.25 (11.17) | 4.84 (9.73) | 3.55 (10.04) | 3.71 (10.45) | |
| Pain | 18.64 (25.89) | 24.19 (24.64) | 15.60 (21.97) | 18.86 (24.44) | |
| Dyspnea | 10.54 (22.17) | 15.59 (23.93) | 10.28 (16.95) | 11.60 (21.00) | |
| Insomnia | 27.12 (29.22) | 38.17 (33.52) | 33.33 (32.05) | 31.75 (31.41) | |
| Appetite loss | 7.06 (16.80) | 6.99 (16.12) | 6.74 (17.34) | 6.93 (16.78) | |
| Constipation | 7.12 (18.48) | 9.14 (21.06) | 9.93 (19.45) | 8.55 (19.39) | |
| Diarrhoea | 5.37 (16.29) | 5.91 (17.62) | 5.67 (13.51) | 5.60 (15.66) | |
| Financial impact | $2.82^{a}$ (12.00) | $9.14^{b}$ (18.28) | $6.38^{ab}$ (19.11) | 5.47 (16.34) | .030, $\eta^2 = .024$. |
| **BR-23** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | |
| Functioning subscales | | | | | |
| Body image | 89.69 (15.43) | 83.20 (25.54) | 86.17 (19.88) | 87.01 (19.73) | |
| Future perspective | 73.45 (22.88) | 68.82 (28.86) | 70.57 (27.15) | 71.41 (25.79) | |
| Sexual functioning | 18.23 (24.17) | 15.28 (19.48) | 18.28 (23.58) | 17.59 (22.95) | |
| Sexual enjoyment | N = 41 | N = 22 | N = 36 | N = 99 | |
| | 52.85 (27.86) | 48.48 (32.08) | 51.85 (26.96) | 51.52 (28.28) | |
| Symptom subscales | | | | | |
| Breast symptoms | $4.99^{a}$ (9.81) | $12.01^{b}$ (13.54) | $9.57^{b}$ (13.40) | 8.15 (12.32) | <.001, $\eta^2 = .055$ |
| Systemic therapy side-effects | 14.93 (14.07) | 17.67 (13.31) | 14.39 (11.87) | 15.36 (13.19) | |
| Arm symptoms | $5.37^{a}$ (11.41) | $13.80^{b}$ (19.26) | $9.81^{ab}$ (16.61) | 8.80 (15.61) | .003, $\eta^2 = .046$ |
| Hair loss | N = 35 | N = 22 | N = 26 | N = 83 | |
| | 31.43 (29.09) | 39.39 (31.93) | 37.18 (33.10) | 35.34 (30.95) | |
| **BCTOS** | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** | ***P*, effect size** |
| Cosmetic | $1.38^{a}$ (1.13-1.63) | $1.75^{b}$ (1.38-2.25) | $1.63^{b}$ (1.38-2.28) | 1.50 (1.00-1.29) | <.001, A-B r = .390, A-C r = .372 |
| Functional | $1.00^{a}$ (1.00-1.14) | $1.00^{b}$ (1.00-1.46) | $1.00^{ab}$ (1.00-1.43) | 1.00 (1.00-2.00) | .016, A-B r = .198 |
| Breast Specific Pain | $1.00^{a}$ (1.00-1.67) | $1.83^{b}$ (1.00-2.67) | $1.67^{b}$ (1.00-2.00) | 1.33 (1.00-2.00) | <.001, A-B r = .338, A-C r = .247 |
| Sensation | $1.00^{a}$ (1.00-2.00) | $2.00^{b}$ (1.00-3.00) | $2.00^{b}$ (1.00-2.00)$^{b}$ | 1.00 (1.00-1.25) | <.001, A-B r = .268, A-C r = .234 |
| DASS | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | |
| Depression | $1.00^{a}$ (0.00-4.00) | $3.00^{b}$ (0.00-6.25) | $1.00^{ab}$ (0.00-4.00) | 2.00 (0.00-4.00) | .035, A-B r = .186 |
| Anxiety | 1.00 (0.00-3.00) | 2.00 (0.00-5.00) | 1.50 (0.00-4.00) | 1.50 (81.71-95.30) | |

Abbreviation: QLQ- C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.
BR-23 = European Organization for Research and Treatment of Cancer breast cancer specific module.
BCTOS = Breast Cancer Treatment Outcomes Scale.
DASS = Depression Anxiety Stress Scale Short Form-21.
[ab]Each subscript letter denotes a subset of group whose proportions do not differ significantly from each other; different subscript letters indicate following a significant between groups test, the post hoc pairwise comparison between these groups was significant after Bonferroni correction.
$\eta^2$ = eta squared effect size calculated for between groups ANOVA, .010 = small, .060 = medium, .140 = large.
r= Cohen's r effect size calculated for non-parametric pairwise comparisons, .1 = small, .3 = medium, .5 = large
NOTE: the sexual functioning and hair loss subscales of the BR-23 were only answered if the participant indicated they were sexually active or had experienced hair loss resulting in smaller sample.