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TITLE

Observational cohort study in older women with early breast cancer: use of radiation therapy and impact on health-related quality of life and mortality.

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HIGHLIGHTS

- Radiotherapy use in older early-stage breast cancer patients is affected by age and relapse risk.
- Despite geographical variation, geriatric parameters do not influence radiotherapy decisions.
- Some fit older women with high-risk tumours do not receive radiotherapy.
- Some older patients with low-risk cancer receive radiotherapy after breast-conserving surgery.
- The impact of radiotherapy on quality-of-life is transient and mostly resolves by 18 months.

ABSTRACT

Background

Radiotherapy reduces in-breast recurrence risk in early breast cancer (EBC) in older women. This benefit may be small and should be balanced against treatment effect and holistic patient assessment. This study described treatment patterns according to fitness and impact on health-related quality-of-life (HRQoL).

Methods

A multicentre, observational study of EBC patients aged ≥70 years, undergoing breast-conserving surgery (BCS) or mastectomy, was undertaken. Associations between radiotherapy use, surgery, clinico-pathological parameters, fitness based on geriatric parameters and treatment centre were determined. HRQoL was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) questionnaires.

Results

In 2013-2018 2811 women in 56 UK study centres underwent surgery with a median follow-up of 52 months. On multivariable analysis, age and tumour risk predicted radiotherapy use. Among healthier patients (based on geriatric assessments) with high-risk tumours, 534/613 (87.1%) having BCS and 185/341 (54.2%) having mastectomy received radiotherapy. In less fit individuals with low-risk tumours undergoing BCS, 149/207 (72.0%) received radiotherapy. Radiotherapy effects on HRQoL domains, including breast symptoms and fatigue were seen, resolving by 18 months.

Conclusion

Radiotherapy use in EBC patients ≥70 years is affected by age and recurrence risk, whereas geriatric parameters have limited impact regardless of type of surgery. There was geographical variation in treatment, with some fit older women with high-risk tumours not receiving radiotherapy, and some older, low-risk, EBC patients receiving radiotherapy after BCS despite evidence of limited benefit. The impact on HRQoL is transient.

Keywords: Breast cancer, older, frailty, comorbidity, health-related quality of life, adjuvant radiotherapy.

Disclaimer

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Clinical Trial Registration: ISRCTN 46099296

MANUSCRIPT

INTRODUCTION

Half of breast cancer (BC) cases are diagnosed ≥65 years.[1] Nonetheless, outcomes are worse in older individuals[2, 3] who are underrepresented in trials.[4-6] In older patients outcomes may be influenced by competing risks, late presentation, and treatment variation:[7, 8] frailty data are crucial to aid decision-making.

Radiation therapy (RT) is generally well tolerated in older women after breast-conserving surgery (BCS) or mastectomy, although it may cause inconvenience.[9] Local recurrence rates after BCS are lower in older patients although RT benefits decline with age.[10, 11]

After BCS, the Cancer and Leukaemia Group B (CALGB) 9343 and PRIME-II trials showed that omitting RT in older women with small, node-negative, oestrogen receptor (ER)-positive tumours is associated with high loco-regional recurrence risk but no survival disadvantage.[12-14] An Early Breast Cancer Trialist's Collaborative Group (EBCTCG) meta-analysis found that whole breast RT reduced the 10-year absolute local recurrence risk and 15-year mortality, although the annual recurrence probability without RT inversely correlated with age.[15] However, survival effects may be less pronounced in older frail patients. RT omission may be appropriate in frail older women. Conversely, there is a risk of undertreating fit older patients at higher risk of recurrence and longer life expectancy.

Our study recruited older women with BC and included baseline geriatric assessments.[16-19] This analysis describes patients' characteristics undergoing RT and investigates the factors associated with RT use and impacts on health-related quality of life (HRQoL).

MATERIALS AND METHODS

Study design

The Bridging the Age Gap study was a multicentre, observational cohort study funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant reference number RP-PG-1209-10071). Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. Patients were recruited from 56 centres in England and Wales (Supplementary Table 1). Women ≥70 years with operable invasive BC (TNM stages: T1-3 and operable T4b, N0-1, M0) were eligible. Staging investigations were performed if clinically indicated. Those unsuitable for surgery or with previous EBC within 5 years were not eligible.

Baseline data collection

Consenting patients were recruited at EBC diagnosis and could participate at three levels: full, partial (no requirement to complete HRQoL questionnaires) or by proxy (third-party data collection for those with significant cognitive impairment). Baseline tumour, surgical, RT and systemic therapy data were collected.

At baseline, patients underwent geriatric assessments: comorbidities (Charlson Comorbidity Index),[20] nutrition (abridged Patient Generated Subjective Global Assessment),[21, 22], functional status (Activities of Daily Living),[23] advanced functional status (Instrumental Activities of Daily Living),[24] cognitive capacity (Mini Mental State Examination),[25] Eastern Cooperative Oncology Group Performance (ECOG) Status and medications.

HRQoL was assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) HRQoL Questionnaires: EORTC-QLQ-C30;[26] EORTC-QLQ-BR23;[27] EORTC-QLQ-ELD15;[28] EuroQol-5D-5L (EQ-5D-5L)[29] (Supplementary Table 2).

Follow-up and outcomes

Patients were followed up at 6 weeks, 6, 12, 18 and 24 months after enrolment (at the time of diagnosis) and assessed for recurrence and HRQoL. Complications were categorised using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Deaths were categorised as BC-related or other causes. Deaths were reviewed by the chief investigator blind to treatment decisions. Patients for whom the cause could not be established were excluded from cause-specific analyses.

Statistical methods

Analyses were performed in IBM SPSS version 24, R version 3.6.3[30] and Stata version 16.[31] A two-sided $p<0.05$ was considered statistically significant.

The relationships between RT use, tumour and patient characteristics were evaluated using univariate and multivariable logistic regression for patients undergoing BCS or mastectomy.

Patients undergoing BCS were considered at high risk of recurrence if the tumour was ≥3cm, ER-negative, human epidermal growth factor receptor 2 (HER2)-positive, node-positive, or grade 3 (Supplementary Table 3a).[13] Those undergoing mastectomy where considered high-risk if the tumour was T3, T4, or if ≥4 lymph nodes were involved (Supplementary Table 3a).[32, 33] Fitness was defined based on geriatric assessments in order to categorize women as fit, vulnerable or frail (Supplementary Table 3b). RT use was reported by recurrence risk and fitness.

Quality-of-life

The EORTC-QLQ questionnaires were scored according to the EORTC Scoring Manual (3rd Edition).[29] The pre-planned analysis was conducted separately for patients undergoing BCS or mastectomy. We also pre-planned to exclude from this analysis patients who received chemotherapy due to its significant effect on HRQoL.[18] The mean differences of the domain scores at each time point, adjusted for baseline, were calculated using linear regression models. The paper reports statistical significance. Clinically meaningful differences in global health status of 1, 7 and 13 for trivial, small and medium impacts respectively were inferred from the data.[34]

RESULTS

Between January 2013 and June 2018, 3456 women were recruited (Supplementary Table 1). This analysis included 2811 women undergoing surgery within 6 months of diagnosis (Figure 1).[35] Of these, 397 (14.1%) received chemotherapy. Overall, 2239/2354 (95.1%) ER-positive patients received endocrine therapy. Surgery was BCS in 1669 patients and mastectomy in 1087 patients (Table 1; Supplementary Tables 4-5).

Of the 1669 patients undergoing BCS, 1385 (83.0%) received RT within 12 months of surgery. Of 1383 patients undergoing BCS where the RT volume was known, 1372 (99.2%) received breast RT and 154 (11.2%) nodal RT (62 [4.5%] to axilla, 92 [6.7%] to supraclavicular fossa [SCF]). Internal mammary chain RT was not recorded. Of the 1087 patients undergoing a mastectomy, 341 (31.4%) received RT within 12 months. Of those 338 patients undergoing a mastectomy where the RT volume was known, 247 (73.1%) received chest wall RT and 221 (65.4%) nodal RT (68 [20.1%] to axilla, 153 [45.3%] to SCF) (Supplementary Table 4-6).

In the BCS cohort, younger patients with higher risk tumours (high grade, node positive) were more likely to receive RT (Table 2). In the mastectomy cohort, patients with larger tumours and higher nodal involvement were more likely to receive it.

In the BCS cohort, high-risk tumours were present in 820/1669 patients (49.1%); of these, 709/820 (86.5%) received RT compared with 676/849 (79.6%) of patients with low-risk tumours (Table 3a). Of those who were fit, 613 had high-risk tumours, and of these patients, 534/613 (87.1%) received RT (Table 3b). Of those 207 vulnerable individuals with low-risk tumours, 149/207 (72.0%) received RT.

In the mastectomy group, high-risk tumours were present in 479/1087 patients (44.1%) and 255/479 (53.2%) received RT compared with 86/608 (14.1%) of patients with non-high-risk tumours (Table 3c). Of those who were fit, 341 had high-risk tumours, and of these patients 185/341 (54.2%) received RT (Table 3d).

RT use varied from 17.6% to 90.9% between sites, although the number of patients recruited varied widely (Figure 3; Supplementary Table 7).

Among 2811 patients undergoing surgery, the HRQoL analysis was restricted to 1789/2811 (63.6%) who did not receive chemotherapy and who consented to full participation. Of the patients included, 1125/1789 (62.9%) underwent BCS and 628/1789 (35.1%) underwent a mastectomy. Out of those undergoing BCS, 927/1125 (82.4%) received RT; out of those undergoing a mastectomy, 177/628 (28.2%) received RT. Supplementary table 8 and figures 1-3 show HRQoL questionnaires completion rates.

Among those undergoing BCS, 1042/1125 patients (92.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary Table 8). No significant effects were observed at 6 weeks (after surgery but before RT). Patients undergoing RT reported worse breast symptoms at 6 months compared with those not receiving it (mean difference 6.27, 95% CI 3.34 to 9.19, p<0.001) which persisted at 12 months (mean difference 3.89, 95% CI 1.13 to 6.64, p=0.006) but not at 18 months or thereafter (Supplementary Table 9; Figure 2).

Among those undergoing a mastectomy, 588/628 patients (93.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary Table 8). No significant effects were seen at 6 weeks. At 6 months, a significant difference was observed in breast symptoms (5.52, 95% CI 2.67 to 8.37, p<0.001). At 12 months, the effect persisted in breast symptoms (7.12, 95% CI 4.07 to 10.17, p<0.001) and arm symptoms (6.34, 95% CI 2.99 to 9.70, p<0.001). No differences were found at 18 months; at 24 months these were observed in arm symptoms (6.19, 95% CI 1.21 to 11.17, p=0.015) (Supplementary Table 9; Figure 2).

1004/1125 patients (89.2%) undergoing BCS and 567/628 patients (90.3%) undergoing a mastectomy completed all questions included in the EORTC QLQ-C30 questionnaire at baseline (Supplementary Table 8). In the BCS cohort the RT effect on global health status was statistically (but not clinically) significant at 12 months (adjusted mean difference 3.19, 95% CI -0.08 to -6.29, p=0.044) but not afterwards (Supplementary Tables 10-11; Supplementary Figure 4).

Patients undergoing mastectomy and given RT experienced global health decline at 6 weeks (-3.18, 95% CI -6.32 to -0.04, p=0.047) which resolved subsequently (Supplementary Tables 10-11; Supplementary Figure 5). RT impacted fatigue at 6 months (adjusted mean difference 4.45, 95% CI 0.77 to 8.14, p=0.018), 12 months (7.26, 95% CI 3.07 to 11.46, p=0.001), 18 months (5.44, 95% CI 0.64 to 10.23, p=0.026) and 24 months (6.56, 95% CI 1.76 to 11.37, p=0.008), although this effect was clinically significant only at 12 months. No other effects were observed.

1002/1125 patients (89.1%) undergoing BCS and 559/628 patients (89.0%) undergoing a mastectomy completed all EORTC QLQ-ELD15 questions at baseline (Supplementary Table 8). In the BCS cohort, no significant impact was observed at 6 weeks in patients receiving RT compared with those not receiving it (usually predating RT). At 6 months, RT impacted on illness burden (5.49, 95% CI 1.33 to 9.64, p=0.010). At 12-18 months, no significant differences were observed; at 24 months, only on worries about others (-6.21, 95% CI -11.70 to -0.71, p=0.027) (Supplementary Table 12; Supplementary Figure 4).

In the mastectomy cohort, illness burden was impacted in patients receiving RT versus not at 6 weeks (5.54, 95% CI 0.84 to 10.24, p=0.021), 6 months (9.66, 95% CI 4.67 to 14.66, p<0.001), 12 months (5.70, 95% CI 0.34 to 11.06, p=0.037), 18 months (8.19, 95% CI 2.64 to 13.74, p=0.004) and 24 months (8.34, 95% CI 1.25 to 15.43, p=0.021) (Supplementary Table 12; Supplementary Figure 5).

Baseline EQ-5D-5L score was calculated in 1060/1125 patients undergoing BCS (94.2%) and in 593/628 patients (94.4%) undergoing mastectomy. No significant differences were observed in the BCS cohort (Supplementary Table 12; Supplementary Figure 4).

In the mastectomy cohort, RT impacted the visual analogue scale at 18 months (adjusted mean difference -0.04, 95% CI -0.07 to -0.01, p=0.029) and 24 months (-0.05, 95% CI -0.08 to -0.02, p=0.004) (Supplementary Table 13; Supplementary Figure 5).

Supplementary Table 15 reports adverse events.

At a median of 52 months of follow-up, mortality data were available for 2757/2811 patients (98.1% of cohort) and cause of death for 2738/2811 (97.4% of cohort). Of 464/2757 (16.8%) deaths due to all causes, 193/464 (41.6%) were due to BC (Supplementary Table 16).

In patients undergoing BCS, mortality data were available for 1631/1669 (97.7%) and death cause data for 1624/1669 (97.3%). Of those receiving RT with mortality data available, 149/1354 (11.0%) died from any cause; among those receiving RT for whom a death cause was known, 51/1348 (3.8%) died from BC. For those not receiving RT with mortality data available, 48/277 (17.3%) died from any cause; among those receiving RT for whom a death cause was known, 9/276 (3.3%) died from BC.

In patients undergoing a mastectomy, mortality data were available for 1073/1087 (98.7%) and cause of death data for 1062/1087 (97.7%). Of those receiving RT with mortality data available, 93/336 (27.7%) died from any cause; among those receiving RT for whom a death cause was known, 63/332 (19.0%) died from BC. For those not receiving RT with mortality data available, 163/737 (22.1%) died from any cause; among those receiving RT for whom a death cause was known, 65/730 (8.9%) died from BC.

DISCUSSION

This analysis is the largest prospective cohort study describing RT use patterns and its impact on HRQoL, adverse events and mortality in older EBC patients, which integrates tumour characteristics and geriatric assessments data.

Life expectancy is increasing in Western countries[36] and older patients may experience disease relapse within their lifetime. Recurrence has symptomatic, adverse psychological and cost implications even without influencing survival.[11] Therefore, ensuring that older patients are adequately treated is a priority.

RT following BCS is standard-of-care for all EBC patients not at low risk. However, the definition of recurrence risk differs among national[32] and international guidelines[37, 38] and might explain RT uptake variations. Guidelines support omitting RT in low-risk patients ≥70 years assuming that they remain on endocrine therapy. However, compliance cannot be guaranteed when RT is omitted.[39] A meta-analysis did not document any differential benefit of post-mastectomy RT (PMRT) on locoregional recurrence in patients ≥60 years.[40]. The SUPREMO study excluded patients defined as high-risk in this analysis.[41] RT use after BCS or mastectomy declines with age[42] although it might relate to age, comorbidities, frailty, patient reluctance, or HRQoL impact.

In our analysis almost 13% of fit, high-risk patients undergoing BCS and more than 45% of fit, high-risk patients undergoing mastectomy did not receive RT. This may relate to patient, clinician and geographical factors. Recently 5 RT fractions over one week were found non-inferior to the previous standard for local control in patients with pT1-3 N0-1 tumours after BCS or mastectomy.[43] This may facilitate compliance with RT scehdules.

In low-risk older patients, there is a low additional ipsilateral recurrence risk and no survival or breast preservation benefits without RT.[12, 13, 44, 45] In the PRIME II study, at 10 years 93.4% of mortality was not due to BC,[14] despite the rate of ipsilateral breast recurrence (1.3% with RT versus 4.1% with no RT) observed also in this specific age group. In our analysis, in the BCS cohort only one third of mortality was due to BC and RT might be safely omitted in low-risk older patients with a shorter life expectancy.[46] In our study, despite 849/1669 patients (50.9%) having a low risk of recurrence after BCS (some of whom were vulnerable/frail), 82.1% received RT. This suggests a degree of over-treatment which reflects the lack of concordance between national and international guidelines for the omission of RT after BCS and underlines the importance of considering risk profile and health status in decision-making.

Previous trials did not include fitness data which may impact life expectancy and mitigate local recurrence benefits. This study overcomes these limitations, by defining risk of recurrence and fitness, and still demonstrates a low impact of fitness considerations on RT uptake. Some clinicians overestimate the benefits of RT[47] although this does not always correspond with patients' perceived risks, lack of benefit and inconvenience.[48] Geriatric assessments are standard-of-care to evaluate fitness and guide anticancer treatment decisions in older adults with cancer based on international consensus.[49-51] This may also prove valuable for to radiotherapy decision-making and reduce treatment variation. Our findings demonstrate significant RT use variation as previously confirmed,[42, 52, 53] although caution is required in view of case-mix and geography bias.

This analysis demonstrates that RT has limited and temporary impact on toxicities and HRQoL, a meaningful endpoint due to the lack of survival benefits and increased toxicity risk on standard treatments in this population. The most significant impact occurred on breast symptoms, although this resolved by 18 months. Our findings are consistent with the PRIME study documenting no effect of RT on overall HRQoL in patients ≥65 years at low risk of recurrence after BCS[54] and with the SUPREMO trial showing an effect of PMRT on chest wall symptoms up to 2 years in patients undergoing a mastectomy.[34] The recent UK IMPORT LOW study demonstrated that partial breast RT could be employed with a reduction in breast effects and a non-inferior impact on local recurrence.[55] Trials investigating the role of biomarkers to select patients at low recurrence risk who may be spared RT, such as PRIMETIME (ISRCTN41579286), PRECISION (NCT02653755), LUMINA (NCT01791829), NATURAL (NCT03646955) and EUROPA (NCT04134598) will be highly relevant to older BC patients.

This analysis also has some limitations. The study criteria to define high-risk EBC did not include data on lymphovascular invasion, which is considered for radiotherapy decision-making after a mastectomy and an eligibility criterion for the adjuvant RT trials.[56, 57] The definitions of recurrence risk, whilst based on published data and justifiable, would no doubt be debated between clinicians. Similarly, the definitions of fitness could be challenged. Nonetheless, there are no universally agreed definitions in the published literature, these definitions were predefined and have been used consistently across our analyses.[17, 18] Despite broad eligibility criteria and a pragmatic design selection bias was possible due to clinician issues, staffing resources, patients' lack of interest and trial burden.[58] Missing data on longitudinal HRQoL assessments may have influenced our findings. The impact of endocrine therapy was not factored in the HRQoL analysis although this can be prolonged.[59] We could not investigate the impact of RT dose and nodal RT on HRQoL as those data were not routinely collected within the study and only 13.7% of patients received it to the regional

nodes. Our findings may not be applicable to other countries, although previous data appear comparable.[60] Some statistically significant effects of RT on HRQoL might not be clinically relevant, whereas small effects may still substantially influence patients' perceived well-being. Finally, we have not evaluated the impact of RT on ipsilateral recurrence risk as data on relapse laterality were not captured.

In summary, this study demonstrates that fitness is not a major determinant of RT decisions for older EBC patients undergoing BCS or mastectomy and a significant number of vulnerable older women with both high-risk and low-risk EBC receive adjuvant RT. Some may derive little benefit from RT. There was also a low PMRT rate of in women at high-risk suggesting some undertreatment. Potential risks and benefits require discussion in view of the toxicity risk and the transient negative impact on breast symptoms. Nonetheless, individualised treatment decisions and discussions should be made to ensure the best outcomes. These findings argue for the routine measurement of fitness in older patients to be included in radiotherapy practice guidelines for older patients with operable breast cancer.

ADDITIONAL INFORMATION

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Authors' contributions

All the authors conceived and designed the work that led to the submission, drafted and revised the manuscript and approved the final version.

Ethics approval and consent to participate

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

Consent for publication

Not applicable.

Data availability

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

Competing interests

The authors declare no conflict of interest. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators, Jenna Morgan is a NIHR Clinical Lecturer and Kate Lifford was funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

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FIGURE AND TABLE CAPTIONS

FIGURE CAPTIONS

- Figure 1 - STROBE flow diagram for the radiotherapy vs no radiotherapy analyses.
- Table 1 - Postoperative tumour, patient and treatment characteristics by surgery type.
- Table 2 - Relationship between radiotherapy use and patient characteristics: univariate (Table 2a) and multivariable (Table 2b) analyses.
    - Table 2a - Results for univariate logistic regression models.
    - Table 2b - Results from the multivariable logistic regression model.
- Table 3 - Radiotherapy use according to risk of recurrence and fitness.
    - Table 3a - Use of radiotherapy after breast-conserving surgery by risk of recurrence and fitness.
    - Table 3b - Use of radiotherapy after breast-conserving surgery by combined risk of recurrence and fitness.
    - Table 3c - Use of radiotherapy after mastectomy by risk of recurrence and fitness.
    - Table 3d - Use of radiotherapy after mastectomy by combined risk of recurrence and fitness.
- Figure 2 – Mean (95% CI) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-BR23 in patients undergoing breast-conserving surgery (A) and a mastectomy (B).
- Figure 3 – Funnel plot of radiotherapy use by site (N=56). Proportion of patients enrolled in cohort study receiving radiotherapy against number of patients enrolled.

Figure 1.

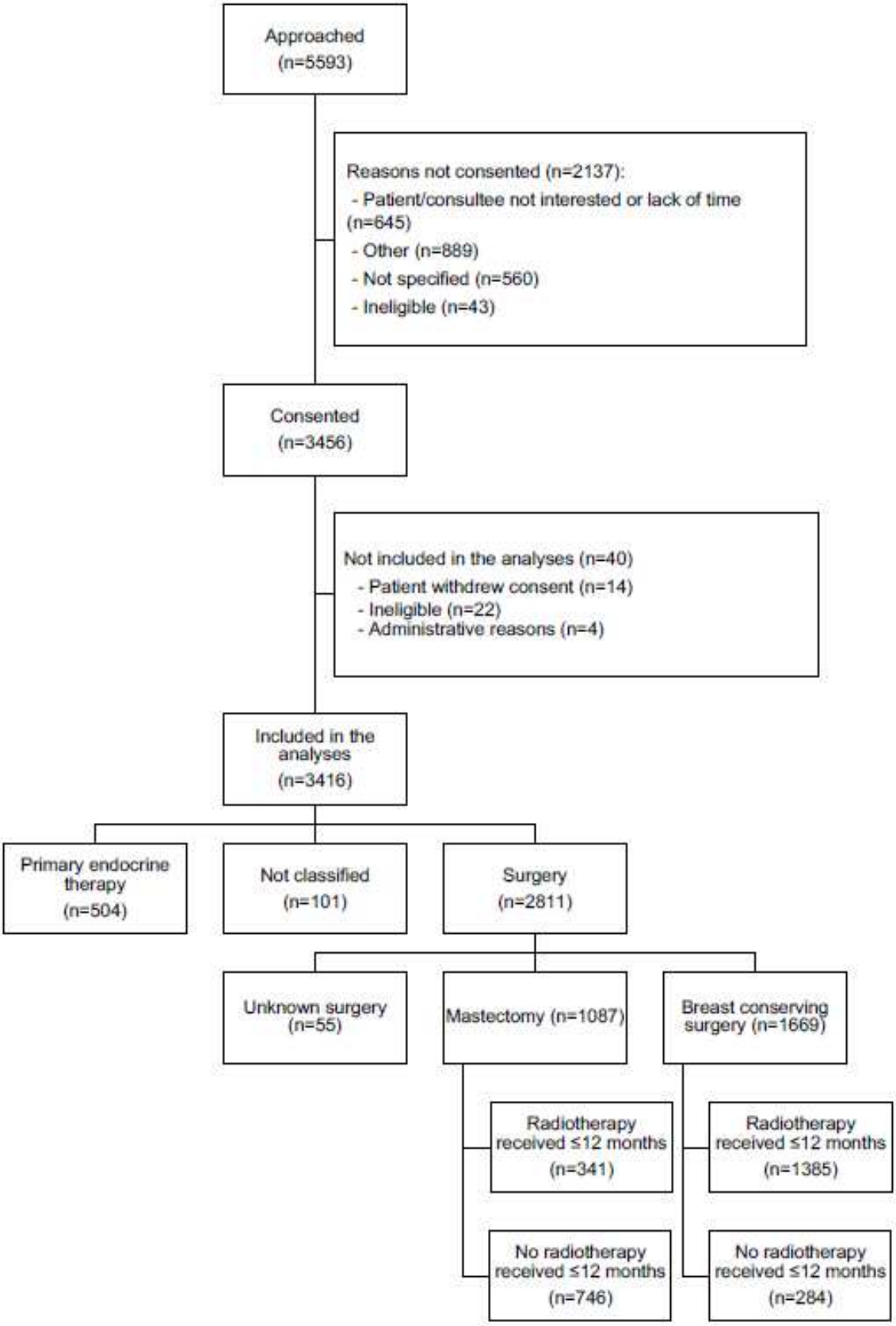
Approached
(n=5593)
Reasons not consented (n=2137):
- Patient/consultee not interested or lack of time (n=645)
- Other (n=889)
- Not specified (n=560)
- Ineligible (n=43)
Consented
(n=3456)
Not included in the analyses (n=40)
- Patient withdrew consent (n=14)
- Ineligible (n=22)
- Administrative reasons (n=4)
Included in the analyses
(n=3416)
Primary endocrine therapy
(n=504)
Not classified
(n=101)
Surgery
(n=2811)
Unknown surgery
(n=55)
Mastectomy (n=1087)
Breast conserving surgery (n=1669)
Radiotherapy received ≤12 months
(n=341)
Radiotherapy received ≤12 months
(n=1385)
No radiotherapy received ≤12 months
(n=746)
No radiotherapy received ≤12 months
(n=284)

Figure 2. Panel A

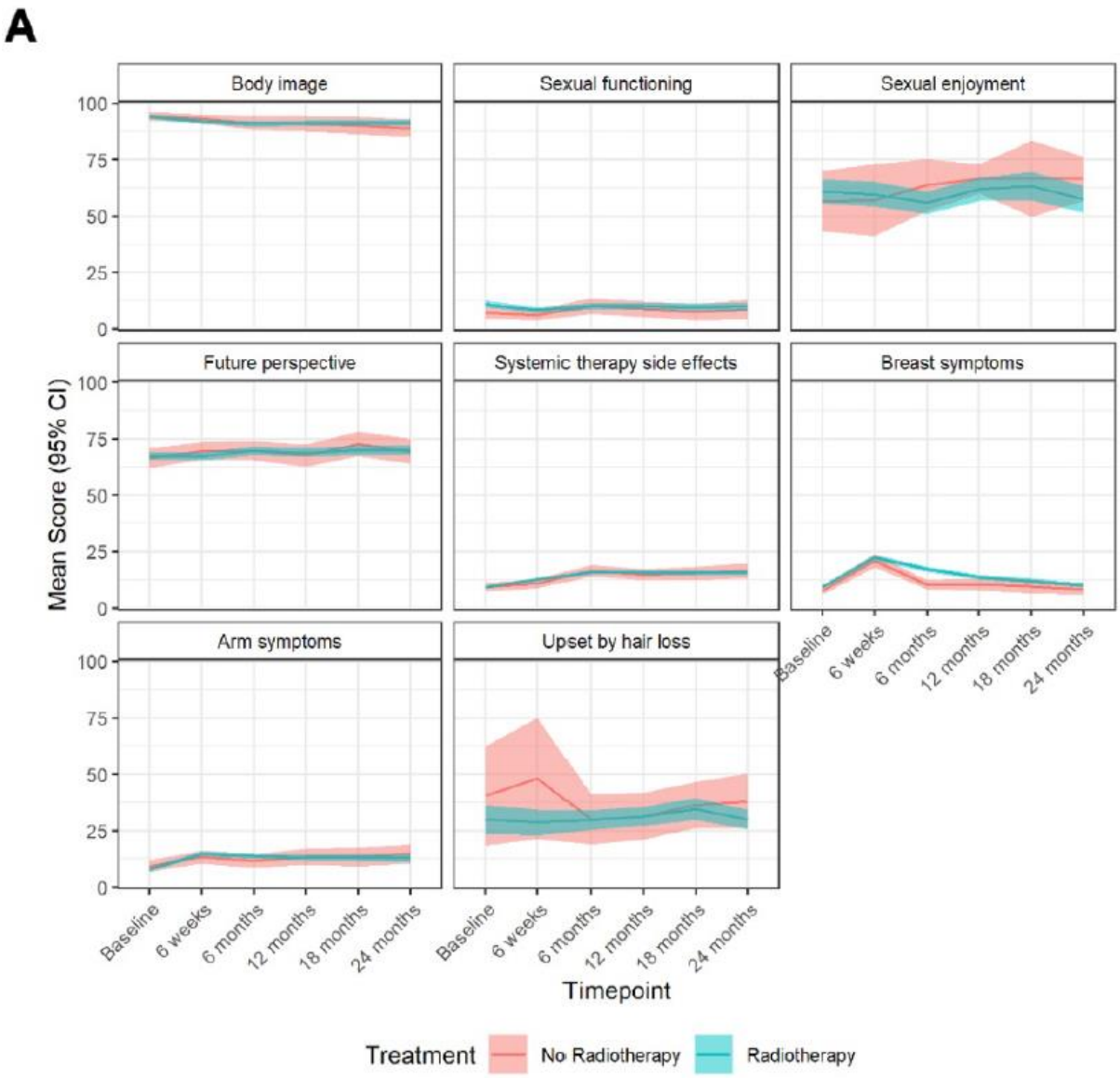

Figure 2. Panel B

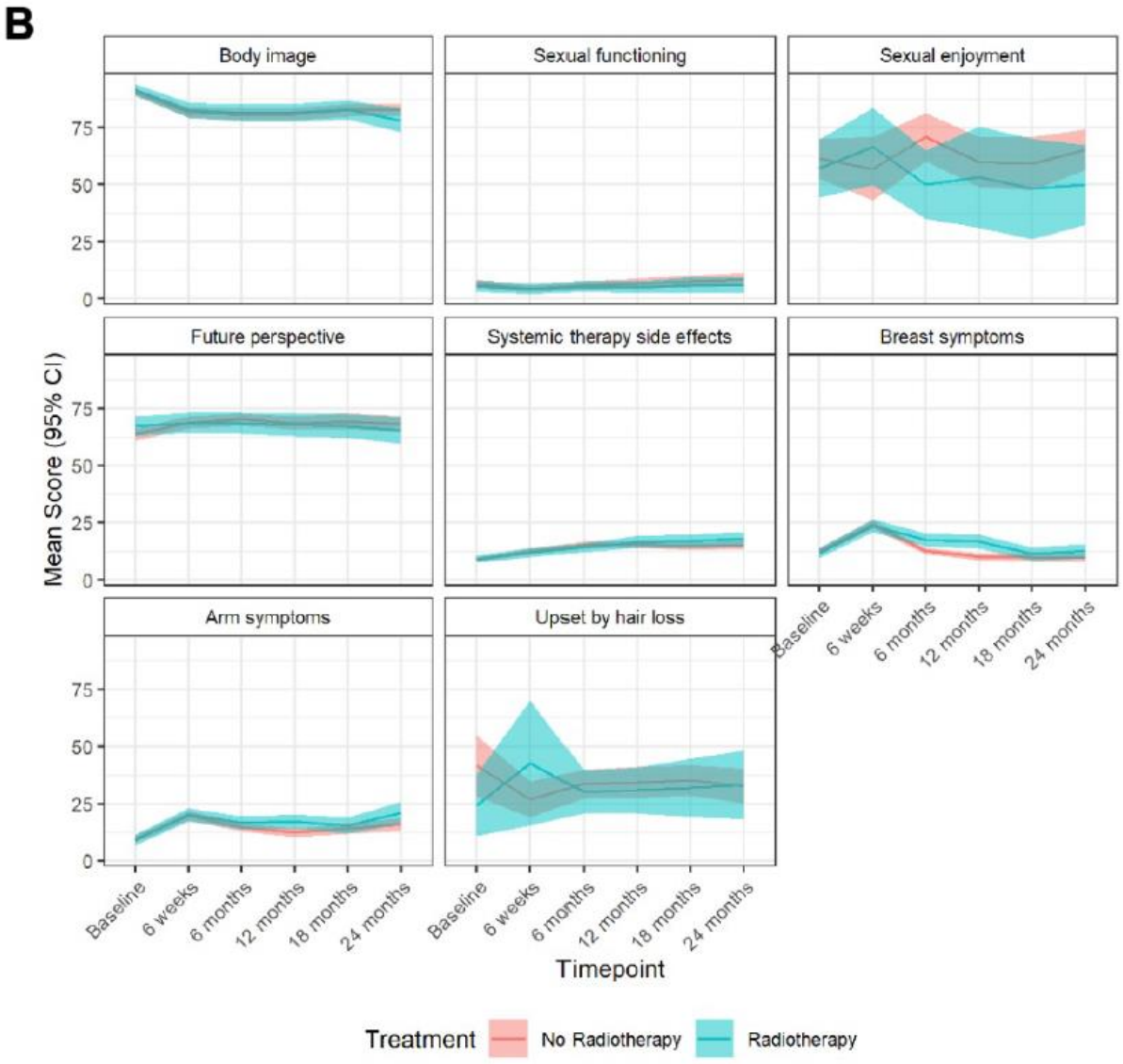

Figure 3.

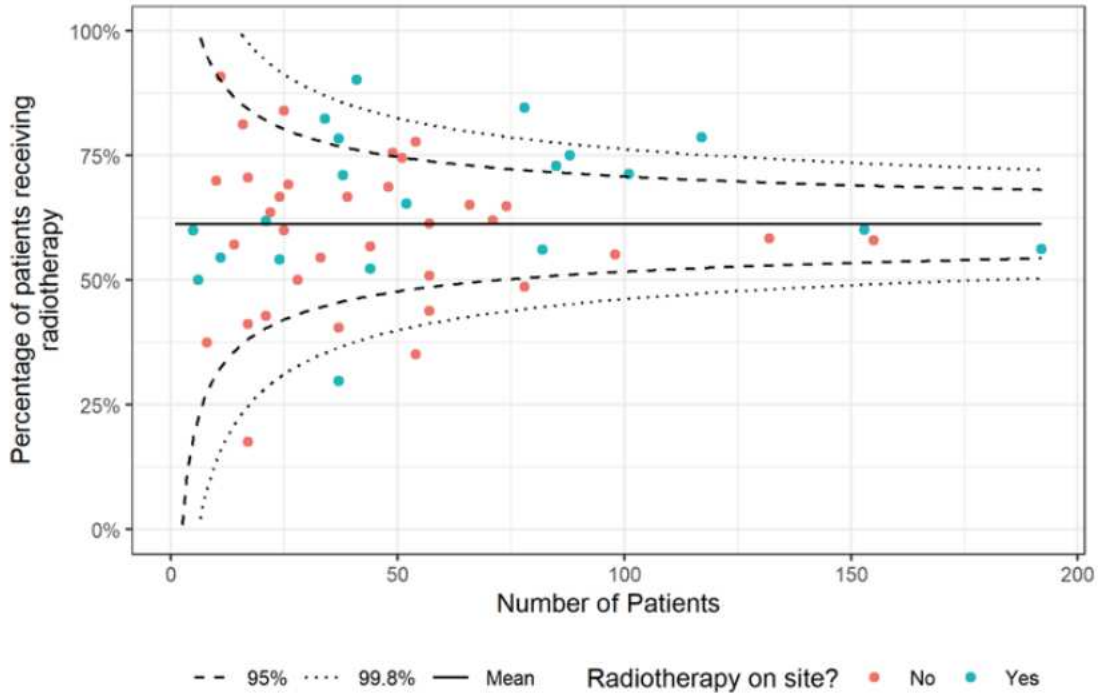
100%
75%
50%
25%
0%
Percentage of patients receiving radiotherapy
0
50
100
150
200
Number of Patients
95%
99.8%
Mean
Radiotherapy on site?
No
Yes

Table 1 - Postoperative tumour, patient and treatment characteristics by surgery type.

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	N = 2811
Age (years)	**70-74**	813 (48.7%)	342 (31.5%)	18 (32.7%)	1173 (41.7%)
	75-79	521 (31.2%)	356 (32.7%)	22 (40.0%)	899 (32.0%)
	80-84	243 (14.5%)	253 (23.3%)	10 (18.2%)	506 (18.0%)
	≥85	92 (5.6%)	136 (12.5%)	5 (9.1%)	233 (8.3%)
Participation level	**Full**	1277 (76.5%)	792 (72.9%)	42 (76.4%)	2111 (75.1%)
	Partial	356 (21.3%)	253 (23.3%)	12 (21.8%)	621 (22.1%)
	Consultee	36 (2.2%)	42 (3.9%)	1 (1.8%)	79 (2.8%)
Laterality	**Right**	776 (46.5%)	501 (46.1%)	28 (50.9%)	1305 (46.4%)
	Left	893 (53.5%)	586 (53.9%)	27 (49.1%)	1506 (53.6%)
Tumour size (mm)	**≤ 20**	1001 (60.0%)	278 (25.6%)	0 (0.0%)	1279 (45.5%)
	21-50	641 (38.4%)	644 (59.2%)	0 (0.0%)	1285 (45.7%)
	> 50	24 (1.4%)	163 (15.0%)	1 (1.8%)	188 (6.7%)
	Unknown	3 (0.2%)	2 (0.2%)	54 (98.2%)	59 (2.1%)
Nodal status	**pN0**	1302 (78.0%)	610 (56.1%)	1 (1.8%)	1913 (68.1%)
	pN1	302 (18.1%)	310 (28.5%)	0 (0.0%)	612 (21.8%)
	pN2	48 (2.9%)	99 (9.1%)	0 (0.0%)	147 (5.2%)
	pN3	13 (0.8%)	64 (5.9%)	0 (0.0%)	77 (2.7%)
	Unknown	4 (0.2%)	4 (0.4%)	54 (98.2%)	62 (2.2%)
Grade	**1**	306 (18.3%)	75 (6.9%)	0 (0.0%)	381 (13.6%)
	2	920 (55.1%)	565 (52.0%)	0 (0.0%)	1485 (52.8%)
	3	427 (25.6%)	437 (40.2%)	1 (1.8%)	865 (30.8%)
	Unknown	16 (1.0%)	10 (0.9%)	54 (98.2%)	80 (2.8%)
Histology	**Ductal carcinoma**	1133 (67.9%)	658 (60.5%)	24 (43.6%)	1815 (64.6%)
	Lobular carcinoma	163 (9.8%)	202 (18.6%)	10 (18.2%)	375 (13.3%)
	Tubular carcinoma	27 (1.6%)	2 (0.2%)	0 (0.0%)	29 (1.0%)

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	N = 2811
	Mucinous carcinoma	47 (2.8%)	23 (2.1%)	1 (1.8%)	71 (2.5%)
	Other	162 (9.7%)	103 (9.5%)	1 (1.8%)	266 (9.5%)
	Unknown	137 (8.2%)	99 (9.1%)	19 (34.5%)	255 (9.1%)
ER status	**Negative**	167 (10.0%)	205 (18.9%)	0 (0.0%)	372 (13.2%)
	Positive	1487 (89.1%)	866 (79.7%)	1 (1.8%)	2354 (83.7%)
	Unknown	15 (0.9%)	16 (1.5%)	54 (98.2%)	85 (3.0%)
HER2 status	**Negative**	1424 (85.3%)	847 (77.9%)	1 (1.8%)	2272 (80.8%)
	Positive	146 (8.7%)	186 (17.1%)	0 (0.0%)	332 (11.8%)
	Inconclusive	16 (1.0%)	6 (0.6%)	0 (0.0%)	22 (0.8%)
	Unknown	83 (5.0%)	48 (4.4%)	54 (98.2%)	185 (6.6%)
ADL category	**No dependency**	1203 (72.1%)	759 (69.8%)	42 (76.4%)	2004 (71.3%)
	Mild dependency	184 (11.0%)	122 (11.2%)	2 (3.6%)	308 (11.0%)
	Moderate/severe dependency	152 (9.1%)	123 (11.3%)	3 (5.5%)	278 (9.9%)
	Unknown	130 (7.8%)	83 (7.6%)	8 (14.5%)	221 (7.9%)
IADL category	**No dependency**	1269 (76.0%)	767 (70.6%)	33 (60.0%)	2069 (73.6%)
	Mild dependency	134 (8.0%)	108 (9.9%)	7 (12.7%)	249 (8.9%)
	Moderate/severe dependency	128 (7.7%)	122 (11.2%)	8 (14.5%)	258 (9.2%)
	Unknown	138 (8.3%)	90 (8.3%)	7 (12.7%)	235 (8.4%)
MMSE category	**Normal function**	1498 (89.8%)	945 (86.9%)	51 (92.7%)	2494 (88.7%)
	Mild impairment	135 (8.1%)	111 (10.2%)	2 (3.6%)	248 (8.8%)
	Moderate impairment	19 (1.1%)	16 (1.5%)	1 (1.8%)	36 (1.3%)
	Severe impairment	17 (1.0%)	15 (1.4%)	1 (1.8%)	33 (1.2%)
AGP SGA category	**Low**	1310 (78.5%)	834 (76.7%)	36 (65.5%)	2180 (77.6%)
	Moderate	159 (9.5%)	122 (11.2%)	7 (12.7%)	288 (10.2%)
	High	27 (1.6%)	13 (1.2%)	0 (0.0%)	40 (1.4%)
	Unknown	173 (10.4%)	118 (10.9%)	12 (21.8%)	303 (10.8%)
ECOG performance status	**0**	1197 (71.7%)	717 (66.0%)	30 (54.5%)	1944 (69.2%)

		BCS N = 1669	Mastectomy N = 1087	Unknown N = 55	Total N = 2811
	1	332 (19.9%)	259 (23.8%)	16 (29.1%)	607 (21.6%)
	2	39 (2.3%)	38 (3.5%)	3 (5.5%)	80 (2.8%)
	3	15 (0.9%)	21 (1.9%)	0 (0.0%)	36 (1.3%)
	4	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	86 (5.2%)	51 (4.7%)	6 (10.9%)	143 (5.1%)
Charlson comorbidity index (no age)	**n**	1607	1052	48	2707
	Mean (SD)	1.00 (1.26)	1.05 (1.36)	1.58 (1.32)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	2.00 (1.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	**n**	1447	961	38	2446
	Mean (SD)	4.02 (2.63)	4.11 (2.66)	4.37 (2.55)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (3.00, 5.75)	4.00 (2.00, 5.75)
	Min, Max	0, 15	0, 18	1, 13	0, 18
Axillary surgery	**Axillary sampling**	49 (2.9%)	37 (3.4%)	2 (3.6%)	88 (3.1%)
	Axillary clearance	113 (6.8%)	292 (26.9%)	9 (16.4%)	414 (14.7%)
	Sentinel lymph node biopsy	1329 (79.6%)	628 (57.8%)	23 (41.8%)	1980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	44 (2.6%)	34 (3.1%)	2 (3.6%)	80 (2.8%)
	Unknown	134 (8.0%)	95 (8.7%)	19 (34.5%)	248 (8.8%)
Chemotherapy use	**Yes**	186 (11.1%)	202 (18.6%)	9 (16.4%)	397 (14.1%)
	No	1483 (88.9%)	885 (81.4%)	46 (83.6%)	2414 (85.9%)
Radiotherapy use	**Yes**	1385 (83.0%)	341 (31.4%)	27 (49.1%)	1753 (62.4%)
	No	284 (17.0%)	746 (68.6%)	28 (50.9%)	1058 (37.6%)

Table 2 - Relationship between radiotherapy use and patient characteristics: univariate (Table 2a) and multivariable (Table 2b) analyses.

Table 2a - Results for univariate logistic regression models.

Variable	Level	OR (95% CI)	P-value
	Breast conserving surgery cohort		
Increasing age		0.94 (0.92, 0.97)	<0.001
Increasing ADL score		1.02 (1.00, 1.05)	0.070
Increasing IADL score		1.34 (1.17, 1.53)	<0.001
Increasing CCI (not age-adjusted)		0.93 (0.84, 1.03)	0.163
Increasing APG SGA score		0.94 (0.89, 1.00)	0.051
MMSE category	**Normal function**	-	-
	Mild impairment	0.64 (0.42, 0.99)	0.039
	Moderate impairment	0.72 (0.26, 2.53)	0.555
	Severe impairment	0.17 (0.06, 0.45)	<0.001
Tumour grade	**Grade 1**	-	-
	Grade 2	1.97 (1.44, 2.69)	<0.001
	Grade 3	2.49 (1.70, 3.66)	<0.001
ER-positive status		1.10 (0.71, 1.65)	0.657
HER2 status*	**Negative**	-	-
	Positive	0.87 (0.57, 1.38)	0.539
Nodal status**	**pN0**	-	-
	pN1	2.50 (1.66, 3.95)	<0.001
	pN2	0.86 (0.44, 1.84)	0.674
	pN3	0.26 (0.09, 0.83)	0.017
	Mastectomy cohort		
Increasing age		0.99 (0.97, 1.02)	0.519
Increasing ADL score		1.00 (0.98, 1.02)	0.906
Increasing IADL score		1.01 (0.90, 1.15)	0.831
Increasing CCI (not age-adjusted)		1.07 (0.97, 1.17)	0.184
Increasing APG SGA score		1.01 (0.93, 1.09)	0.800
MMSE category	**Normal function**	-	-
	Mild impairment	0.82 (0.52, 1.25)	0.364
	Moderate impairment	0.96 (0.30, 2.66)	0.938
	Severe	0.15 (0.01, 0.75)	0.068
Tumour grade	**Grade 1**	-	-
	Grade 2	3.08 (1.58, 6.75)	0.002
	Grade 3	4.24 (2.16, 9.33)	<0.001
ER-positive status		0.89 (0.64, 1.23)	0.472
HER2 status*	**Negative**	-	-
	Positive	1.04 (0.74, 1.46)	0.821
T stage	**T1**	-	-
	T2	3.38 (2.30, 5.08)	<0.001
	T3	11.39 (7.14, 18.58)	<0.001

Variable	Level	OR (95% CI)	P-value
Nodal status**	**pN0**	-	-
	pN1	4.46 (3.24, 6.16)	<0.001
	pN2	17.11 (10.48, 28.71)	<0.001
	pN3	19.90 (10.94, 38.21)	<0.001

* Tests marked as 'Inconclusive' were removed from this analysis.
** Those with nodal status pNx were removed from this analysis

Table 2b - Results from the multivariable logistic regression model.

Variable	Level	OR (95% CI)	P-value
	Breast conserving surgery cohort		
Increasing age		0.95 (0.92, 0.99)	0.008
Increasing IADL score		1.14 (0.93, 1.38)	0.208
Increasing APG SGA score		0.96 (0.90, 1.03)	0.212
Tumour grade	**Grade 1**	-	-
	Grade 2	1.87 (1.23, 2.83)	0.003
	Grade 3	3.68 (2.14, 6.46)	<0.001
MMSE category	**Normal function**	-	-
	Mild impairment	0.64 (0.37, 1.11)	0.103
	Moderate/severe impairment*	1.14 (0.34, 5.30)	0.851
Nodal status**	**pN0**	-	-
	pN1	2.55 (1.45, 4.87)	0.002
	pN2	0.90 (0.38, 2.50)	0.825
	pN3	1.03 (0.16, 20.43)	0.976
	Mastectomy cohort		
Tumour grade	**Grade 1**	-	-
	Grade 2	1.55 (0.74, 3.58)	0.269
	Grade 3	1.73 (0.82, 4.02)	0.172
T stage	**T1**	-	-
	T2	2.27 (1.47, 3.58)	<0.001
	T3	7.52 (4.42, 13.06)	<0.001
Nodal status*	**pN0**	-	-
	pN1	4.37 (3.12, 6.16)	<0.001
	pN2	14.19 (8.48, 24.38)	<0.001
	pN3	14.22 (7.59, 27.98)	<0.001

** Moderate and severe categories have been combined due to small numbers in the severe category.*
*** Those with nodal status pNx were removed from this analysis*

Table 3 - Radiotherapy use according to risk of recurrence and fitness.*

Table 3a - Use of radiotherapy after breast-conserving surgery by risk of recurrence and fitness.

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	709 (86.5%)	111 (13.5%)	**820 (100.0%)**
Lower risk	676 (79.6%)	173 (20.4%)	**849 (100.0%)**
Total	**1385 (14.1%)**	**284 (85.9%)**	**1669 (100.0%)**
Fitness			
Fit	**1061 (84.5%)**	**194 (15.4%)**	**1255 (100.0%)**
Vulnerable	**323 (78.2%)**	**90 (21.8%)**	**413 (100.0%)**
Frail	**1 (100.0%)**	**0 (0.0%)**	**1 (100.0%)**
Total	**1385 (83.0%)**	**284 (17.0%)**	**1669 (100.0%)**

Table 3b - Use of radiotherapy after breast-conserving surgery by combined risk of recurrence and fitness.

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy	
Fit	534 (42.55%)	79 (6.29%)	527 (41.99%)	115 (9.16%)	**1255 (100.00%)**
Vulnerable	174 (42.1%)	32 (7.7%)	149 (36.1%)	58 (14.0%)	**413 (100.0%)**
Frail	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1 (100%)**
Total	**709 (42.5%)**	**111 (6.7%)**	**676 (40.5%)**	**173 (10.4%)**	**1669 (100.0%)**

Table 3c - Use of radiotherapy after mastectomy by risk of recurrence and fitness.

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	255 (53.2%)	224 (46.8%)	**479 (100.0%)**
Lower risk	86 (14.1%)	522 (85.9%)	**608 (100.0%)**
Total	**341 (31.4%)**	**746 (68.6%)**	**1087 (100.0%)**
Fitness			
Fit	**242 (31.6%)**	**524 (68.4%)**	**766 (100.0%)**
Vulnerable	**98 (30.6%)**	**222 (69.4%)**	**320 (100.0%)**
Frail	**1 (100.0%)**	**0 (0.0%)**	**1 (100.0%)**
Total	**341 (31.4%)**	**746 (68.6%)**	**1087 (100.0%)**

Table 3d - Use of radiotherapy after mastectomy by combined risk of recurrence and fitness.

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No Radiotherapy	Radiotherapy	No Radiotherapy	
Fit	185 (24.2%)	156 (20.4%)	57 (7.4%)	368 (48.0%)	766 (100.0%)
Vulnerable	70 (21.88%)	68 (21.25%)	28 (8.75%)	154 (48.12%)	320 (100.00%)
Frail	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)	1 (100%)
Total	255 (23.5%)	224 (20.6%)	86 (7.9%)	522 (48.0%)	1087 (100.0%)

**Risk of recurrence and fitness defined as shown in Supplementary Table 3.*