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Summary

Background Post-mastectomy chest-wall radiotherapy (PMRT) for 'intermediate' risk breast cancer is controversial. BIG2-04 MRC EORTC SUPREMO (ISRCTN61145589) is an international phase III randomised controlled trial assessing the role of PMRT in this patient group. The primary endpoint of SUPREMO is overall survival at 10 years, with quality of life (QOL) a secondary endpoint. The QOL sub-study examined the effects of PMRT on primary outcomes: global QOL, fatigue, physical function, chest-wall, arm symptoms, body image, anxiety/depression at 1, 2, 5 and 10 years. Here we report QOL results at 2 years.

Methods SUPREMO randomised women post mastectomy and axillary surgery to receive chest-wall radiotherapy or not (1:1 ratio). All UK centres participated in the QOL sub-study. Patients completed the EORTC QLQ-C30 and BR23 questionnaires, Body Image Scale, Hospital Anxiety and Depression Scale (HADS) and EQ-5D-3L pre-randomisation, 1 and 2 years. Repeated mixed-effects methods were employed, with baseline score, time and age as covariates. Exploratory analyses evaluated whether systemic treatments, axillary and reconstructive surgery influenced the QOL outcomes.

Findings

SUPREMO enrolled 1688 patients internationally between 2007-13. Of the 1258 UK patients 989 (79%) consented to participate in the QOL sub-study, 95·7% returned the baseline, 83·1% year 1 and 77·9% year 2 questionnaires. Patients receiving PMRT reported worse chest-wall symptoms (p=0·0161), with an improvement between years 1 and 2. Chemotherapy was associated with less improvement without interaction with radiotherapy. No significant between-group differences were observed for arm symptoms, body image, fatigue, pain, overall QOL, physical functioning or HADS scores. Younger patients reported worse body image problems (p=0·007) and anxiety (p=0·0001).

Interpretation PMRT led to more local symptoms up to 2 years post-randomisation, but the difference is small, and there was no impact on other pre-specified QOL domains.

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Research in Context

Evidence before this study

Adjuvant chest-wall irradiation after mastectomy remains a core effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practices vary. The Oxford overview in 2014 shows an advantage from PMRT in patients with 1-3 positive nodes. However, the generalisability of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain. Benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. The recent American Society of Clinical Oncology guidelines on the use of PMRT emphasizes the importance of evaluating the risk-benefit ratio, but the data is derived from patients treated several decades previously and only a limited number of small studies looked at patient-reported outcomes, such as symptoms and quality of life.

Added value of this study

Our study uniquely investigated the impact of adjuvant PMRT on quality of life in a randomised trial including a large, well characterised population of UK patients with 'intermediate-risk' breast cancer post-mastectomy. At 2 years PMRT was associated with worse self-reported local symptoms (pain, swelling, skin problems in the "area of the affected breast") in comparison with no radiotherapy, but the difference is small, unlikely to be of clinical significance and the symptoms improved over time. There were no differences in arm symptoms, body image, fatigue, pain, overall QOL, physical functioning anxiety or depression.

Implications of all the available evidence

The impact on PMRT on 10 year survival, the primary endpoint of the main SUPREMO trial, will not be known before 2023. In the meantime, both options of administering or omitting PMRT are legitimate for patients in the intermediate risk category (1-3 positive lymph nodes). Our data will inform shared decision-making (as recommended in the recent North American guidelines) and put patients in a better position to make an informed value judgment on what they consider relevant for their situation given the data on the patient-reported symptoms and QOL domains presented in this report. Both physicians and patients may be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and quality of life.

Introduction

Current multimodality treatment for breast cancer has improved survival rates. [1] Avoiding overtreatment and balancing the treatment burden against benefit has become an important research field. Examples of trials investigating selective omission of radiotherapy or chemotherapy have recently been reported. [2,3] While the impact of mastectomy and chemotherapy on quality of life has been well documented the additional effect of adjuvant radiotherapy following mastectomy is unclear. Chest wall pain, fatigue, anxiety about recurrence and depressive symptoms can all hold back recovery and return to normal activities of daily living. [4]

Adjuvant chest wall irradiation after mastectomy remains a core and highly effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practice and guidelines vary.[5] The Oxford overview in 2014 shows an advantage from PMRT which included at least the chest wall in the target volume in patients with both 1-3 and 4 or more positive nodes.[6] However, the generalisability of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain, especially as contemporary survival rates are much higher than in the studies included in the overview. Potential benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. A recent update by the American Society of Clinical Oncology on the use of post-mastectomy radiotherapy emphasizes the importance of evaluating the risk-benefit ratio, particularly in patients with a low risk of local failure.[7] The benefit of PMRT relies on estimates of recurrence risk, modulated by biological tumour characteristics, weighed against the negative impact of PMRT on the risks of late toxicity (e.g. cardiac toxicity from radiotherapy may be increased by the combination with systemic therapy).[8] The data currently available on these modulating effects is derived from patients treated several decades previously.

Selective use of post-mastectomy radiotherapy is being evaluated in the BIG 2.04 MRC/EORTC SUPREMO trial (ISRCTN61145589), which assesses the effects of adjuvant chest wall radiotherapy without axillary irradiation in patients with 'intermediate risk' early breast cancer who have undergone mastectomy and adequate systemic therapy following contemporary guidelines for all treatment modalities. This is the largest randomised trial to date to assess the role of PMRT in this subset of patients. The endpoints have been previously described. [9] In brief, the primary endpoint of the trial is overall survival at 10 years. Secondary end points include various breast cancer recurrence endpoints, toxicity, acute and late morbidity (cardiac morbidity and mortality) and quality of life. Sub-studies include the TRANS-SUPREMO seeking molecular markers of radiosensitivity, a cardiac sub-study, and for UK patients only Quality of Life (QOL) assessment and Health Economics evaluation. These sub-studies will provide an important high-quality evidence base on the balance of potential benefits and treatment burden, to support patients and health care professionals during shared decision-making.

The long-term impact of breast cancer and its treatment on everyday life has been identified as a critical knowledge gap and a key priority for breast cancer research [10]. For radiotherapy, there is a limited information on treatment impact. A small number of trials have investigated self-reported breast, arm, and shoulder symptoms, functional outcomes and quality of life after radiotherapy, predominantly in breast conserving therapy[11-13]. Patients usually report transient and short-term effects of radiotherapy, with relatively limited effect on overall quality of life [14,15] .

No comprehensive QOL data exists in patients having PMRT and only a few studies have compared patient-reported outcomes following breast-conserving surgery versus mastectomy with and without reconstruction. Recent introduction of oncoplastic surgical techniques is expected to have an impact on post-treatment morbidity and patient satisfaction with body image[16-19]. There is a

dearth of level 1 evidence assessing the impact of adjuvant post-mastectomy radiotherapy on QOL of patients who have undergone reconstruction.

The SUPREMO QOL sub-study aimed to examine the effects of PMRT on several primary QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) at 1, 2, 5, and 10 years post treatment. Here we report the 2-year results. To our knowledge, this is the first study looking at the impact of adjuvant radiotherapy on QOL in large randomised trial confined to patients treated by mastectomy for early breast cancer (including patients undergoing breast reconstruction).

Methods

Study design and Participants

SUPREMO was an open label parallel randomized trial. The full eligibility, exclusion criteria and trial procedures are described in the trial protocol provided in the supplementary web material. Briefly, patients were eligible if they had undergone mastectomy for unilateral breast cancer, and an axillary staging procedure with axillary lymph node dissection, if node positive. Patients with 'intermediate risk' breast cancer were eligible, defined as pT1-2N1, pT3N0 and pT2N0, if also grade III and/or with lympho-vascular invasion on histology. All patients had to receive adequate systemic therapy following contemporary guidelines depending on patient and tumour characteristics. If this included chemotherapy, treatment regimes containing at least 4 cycles of anthracyclines were recommended. Adjuvant trastuzumab was given according to local practice. In 2011 the eligibility criteria were widened, following a protocol amendment approved by the Ethics Committee, to include neo-adjuvant chemotherapy. For patients randomized to chest wall radiotherapy, radiation was given after the chemotherapy (when given). Radiotherapy treatment consisted of chest wall radiation to a total dose of 50 Gy in 25 daily fractions of 2 Gy over 5 weeks. Other permitted radiobiologically equivalent schedules included 45 Gy in 20 fractions over 4 weeks, and 40 Gy in 15 fractions over 3 weeks. Guidelines on treatment planning and set up were given, and there was a radiotherapy quality assurance programme in the trial. The use of bolus was permitted and had to be pre-specified per centre. Axillary irradiation was not permitted, but medial peri-clavicular and/or internal mammary chain irradiation was permitted according to local policy of the centres. Boost radiation was not permitted. Surgery, systemic therapy and pathology were also subject to pre-specified quality assurance. Additional recorded data included cardiovascular risk factors, radiotherapy cardiac and lung exposure parameters, systemic therapy (type, doses, dates) and any reconstructive surgery (type, immediate or delayed).

Randomisation and masking

Consenting patients were randomized post-operatively to either chest-wall radiotherapy or no chest-wall radiotherapy (1:1 ratio). Patients were randomised by permuted blocks with the block length being varied randomly to minimise the effect of entry bias. Stratification was by treatment centre due to possible between centre differences in the manner in which radiotherapy is given. Randomisation was performed via a telephone call to The Information and Statistical Division (ISD) at National Services Scotland.

Procedures

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QOL sub-study

All patients eligible for SUPREMO from UK centres were invited to participate in the QOL study. Patients who consented completed a questionnaire booklet in the clinic before randomisation. Completed booklets were sent to the trial's office and subsequent questionnaires were posted to

patients at 12 and 24 months by the trial's office. If the baseline questionnaire was not returned to the trial's office further questionnaires could not be sent, as patients' names and addresses were not available to the trial co-ordinator. Reminders were sent to the hospitals where baseline questionnaires were overdue. No reminders were sent to patients at 12 and 24 months.

QOL was assessed using several well-validated questionnaires.

EORTC QLQ-C30 (version 3·0) and the breast module QLQ-BR23 (version 1·0). The QLQ-C30 consists of 30 questions addressing 5 functional scales (cognitive, emotional, physical, social, and role), 9 symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, financial difficulties, insomnia, nausea and vomiting, and pain), and one Global Health Status/QOL scale[20]. The EORTC QLQ-BR23 focuses on breast cancer specific issues and includes 23 questions addressing 4 functional: body image, future perspective, sexual enjoyment, and sexual functioning and 4 symptom scales: arm symptoms (swelling in arm or hand, arm or shoulder pain, and difficulty raising the arm), breast/chest wall symptoms (pain, swelling, oversensitivity, and skin problems in the area of the affected breast), systemic therapy side-effects, and upset by hair loss[21]. All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100. Higher scores on the functional scales and Global QOL represent a superior level of functioning and better QOL, whereas higher scores in the symptom scales or items represent worse symptoms.

The Body Image Scale (BIS) is a 10-item scale designed specifically for use with cancer patients to assess aspects of attractiveness, sexual attractiveness and feelings or satisfaction with appearance. Scores were graded 0-3 and summed to produce a single score, where a higher score indicated more problems (score range from 0 to 30)[22].

Hospital Anxiety and Depression Scale (HADS) is a 14-item instrument with two sub-scales for anxiety and depression[23]. Scores range from 0 to 21 on each scale, with higher scores indicating more distress. Scores above 11 suggest probable cases of anxiety or depressive illness, and scores between 8 and 10 indicate borderline cases. A combined score of 19 or above is considered indicative of psychological distress.

EQ-5D-3L questionnaire measures health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents specify whether they have no problems, some problems or severe problems within each domain, on the day of response. These EQ-5D-3L health states descriptions are converted into a single summary index (range from 0 to 1) by attaching a value to each of the levels in each dimension. As is standard practice, these values were obtained from a large UK population study using a choice-based method of valuation. [24] The resulting summary score, or utility value, can then be used directly in the cost-utility analysis.

Outcomes

Statistical analysis

Sample size for the SUPREMO QOL study was considered as a problem of estimation rather than a significance testing. With 200 evaluable patients per group the proportion of patients exhibiting a particular side-effect or specified degree of morbidity in a QOL domain could be estimated with a standard error of 3·5% or less. The corresponding difference between the groups could be estimated with a standard error of 5% or less. However, as there is usually a significant attrition over time, in order to have sufficient numbers by 10 years a target of 800 patients was set. The total sample size of SUPREMO was reduced during the course of the trial, following a protocol amendment approved by the ethics committee, from 3500 to 1600 but this did not affect the QOL sub-study sample.

In order to maintain the Normality of the residuals, the difference from baseline to each subsequent questionnaire was calculated for each scale. Repeated analysis of covariance was conducted using PROC MIXED, to allow for observations that are missing at random. Time and treatment allocation interactions were tested for each scale but are to be reported where statistically significant. Baseline

scores are included in each model as a covariate. As the QOL study was not originally powered for hypothesis testing, p-values are only included for illustration. However, the treatment with radiotherapy was our primary outcome, and we will discuss any results that have a p-value of ≤0.05 with this variable. Due to the large number of models, clinical variables will only be discussed if they exceed the more conservative threshold value of 0.01.

The principal analysis modelled the change in score in the pre-specified QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) by time of follow up, age group (<45, 45-54, 55-69, ≥70), baseline score and treatment (± radiotherapy).

As almost all patients received some form of systemic therapy and some underwent breast reconstructive surgery, secondary exploratory analyses were performed to evaluate whether these treatments influenced the QOL outcome measures. The secondary analysis included clinical covariates also considered to have an impact on QOL (extent of axillary surgery, early breast reconstruction, adjuvant chemotherapy, adjuvant hormonal therapy and trastuzumab). This was performed by creating a basic model of age group, time and baseline score, then adding the clinical variables in turn to create a model of best fit. This process was then repeated until no variables added significantly to the model. The radiotherapy variable was then added to the best fit model. Only patients with complete data for all clinical variables were included in this modelling.

All analyses were on an intention to treat basis. The analysis was generated using version 9·4 of the SAS System for Windows (www.sas.com Copyright © 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.)

This study is registered [as an International Standard Randomised Controlled Trial, number ISRCTN61145589.

Role of Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and the joint senior authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 2007-May 2013 the trial recruited 1688 patients internationally, of which 1258 were from 111 UK centres and eligible for the QOL study. Ten UK centres did not include any of their 66 patients in the QOL study. A total of 989 (79%) UK patients consented to participate, of them 947 patients (95·7%) returned the baseline questionnaires (476/502 94·8% in the control and 471/487 96·7% in the radiotherapy arm). Due to the practical arrangements for the QOL data collection, questionnaires for years 1 and 2 could be sent only to patients who returned the baseline questionnaire. We have not formally recorded reasons for declining as according to the Ethics Committee approved patient information sheets, patients were not obliged to provide such reasons. The patients from UK who declined participation or did not return the baseline questionnaires were older (n=311 mean age 57.7 years, SD 11.9) than those who consented and returned the baseline questionnaire (n=947 mean age 56.1 years, SD=11.0; p=0.02). Comparing the age of QOL study participants with the rest of the main trial (UK patients not participating in QOL study and all patients from other countries) did not show an age difference (n=741 mean age 55.6 years SD 11.6, p=0.34). In order to check further for potential bias in patient selection for the QOL sub-study, we compared the clinical characteristics of the patients completing the QOL sub-study with those of the patients in the main trial in Table 1 (see below).

Good patient compliance was achieved with the completion of QOL measures: at year 1 388/466 83·3% in the control group and 388/467 83·1% in the radiotherapy group; at year 2 (350/463 75·6% and 367/457 80·3% respectively. A slightly better compliance was observed in the radiotherapy arm at baseline and year 2 (Figure 1).

Patient characteristics

Patients demographic, clinico-pathological characteristics and treatment details are shown in Table 1. Two-thirds of patients had T2 tumours, slightly over half were Grade 3, over 78% were ductal carcinomas, approximately 20% were Estrogen/Progesteron Receptor negative, and 30% Her2 positive. Only a small proportion of just over 10% had immediate reconstruction, and 10% late reconstruction (by 2 years). A further review of the type of breast reconstruction suggested more frequent autologous reconstructions in the radiotherapy group, whereas there were more reconstructions with an implant/expander in the control group (see supplementary file). This trend was observed for both the immediate and the late reconstructions. Over 80% of participants had adjuvant chemotherapy, 20% trastuzumab and over 70% endocrine therapy. No differences are observed between the QOL participants and the full trial.

The majority of patients in the radiotherapy group of the QOL study received 40 Gy in 15 fractions (69%), with the remaining patients equally divided between 50 Gy in 25 fractions (11%), 45 Gy in 20 fractions (10%) and other/unknown (10%). In the main trial, a smaller proportion of 52% received 40 Gy in 15 fractions, a larger proportion of 27% had 50 Gy in 25 fractions, 7% had 45 Gy in 20 fractions and 15% - other/unknown. The dose for all EORTC centres was 50 Gy in 25 fractions.

Baseline and follow-up QOL scores are shown in Table 2. Baseline scores were reported following surgery and prior to randomisation. Of note, patients reported relative impairment in global QOL with a mean score of 60 (100 is excellent), a high level of fatigue (mean of 40, where 100 is greatest degree of fatigue), insomnia (mean of 36-37; 100 is worse) and a degree of arm symptoms, chest wall symptoms and pain (in the range of 17 to 24; 100 is worst symptom).

Pre-specified primary QOL outcomes

Table 3 presents the results from mixed-effects models analysis of pre-specified primary QOL outcomes and pain (a pre-specified secondary QOL outcome). The tested clinical variables are included in Table 3 where they were found to have a significant effect ($p<0.01$) on either the radiotherapy treatment or on changes over time. Such effects were found for adjuvant chemotherapy and immediate breast reconstruction but not for extent of axillary surgery, adjuvant hormonotherapy or trastuzumab.

Chest wall symptoms were worse in the group receiving radiotherapy (estimate of effect 2·17; 95% Confidence Interval (CI) 0·40, 3·94; p=0·016). There was an improvement between years 1 and 2 (visit effect -1.34; 95% CI -2·36, -0·31; p=0·010), but the improvement was smaller in the radiotherapy group (Figure 2a). Of the clinical factors the use of chemotherapy was associated with less improvement in chest wall symptoms but there was no interaction with radiotherapy, suggesting an additive effect of chemotherapy (Figure 2a). There was a borderline age effect, with patients <45 years having worse chest wall symptoms than those ≥70 years (estimate of effect 4·49; 95% CI 0·59, 8·39; p=0·02).

Arm problems did not differ significantly according to radiotherapy treatment (Figure 2b), they improved in both group between years 1 and 2, with a greater improvement in older patients (data not shown). When clinical variables were included the effect of age was no longer apparent. However, chemotherapy had an effect with patients receiving chemotherapy showing less improvement of arm symptoms over time, suggesting that chemotherapy and age were confounders. Significantly more patients who received chemotherapy were in the younger age group (97% of patients <45 years, 97% in 45-54 years, 85% in 55-69 years, 37% in ≥70 years groups, P <

0·0001). Contrary to the clinical expectations, the extent of axillary surgery did not have an effect on arm/shoulder symptoms scores (models not shown).

Despite the observed differences in chest wall symptoms patients reported relatively few body image problems with improvement between years 1 and 2. Some age effect was observed with patients <45 years old reporting more concerns about their body image in comparison with patients ≥70 years old (estimate of effect 1·96; 95% CI 0·53, 3·39; p=0·007).

The overall QOL of patients was not affected by radiotherapy treatment. Furthermore, improvement in overall quality of life was observed between baseline and year 1 with further but smaller improvement by year 2 (Figure 2c).

Physical function was not affected by treatment and no change was observed over time (Figure 2d). As expected there was an age affect with the younger age group reporting better overall physical functioning (Table 3).

Patients reported high baseline level of fatigue, likely due to the preceding surgery. Significant improvement between year 1 and 2 was observed. Immediate reconstruction had a borderline impact on the change scores at year 1 (estimate of effect 5·32; 95% CI 0·94, 9·69; p=0·017), possibly related to slower recovery from the operation (Figure 2e), but without detectable differences in overall QOL or body image.

No group differences were seen in HADS-Anxiety and HADS-Depressions scores. Women younger than 70 reported higher levels of Anxiety with improvement from baseline to year 1 and to year 2 in both groups.

Pre-specified secondary QOL outcomes

An interesting pattern in self-reporting of general pain was observed. The mean score at baseline was just over 20 in both groups, but without any improvement from baseline to year 1 or year 2 independent of randomisation arm, which is at odds with some of the findings for the primary outcomes (global QOL, fatigue, chest-wall symptoms, body image and anxiety) where we observed an improvement from baseline. We investigated the potential impact of systemic treatments. Borderline effects were found for use of trastuzumab (P=0·06) and chemotherapy (P=0·08), possibly associated with the use of taxanes. No effect was found for endocrine therapy (none vs tamoxifen vs aromatase inhibitors).

No between-group differences were observed for nausea/vomiting, sexual, role and social functions. Gradual improvement over time was observed without any effect of treatments. Role function and social function showing the biggest numerical improvement over time, in year 1 with continued improvement in year 2. Patients having radiotherapy reported larger improvements in their social function in comparison with those who did not (details in online Appendix). Patients reported very low scores on sexual functioning (mean of 11 out of 100) suggesting that the vast majority of patients are not sexually active. This is supported by the fact that only about 25% responded to the optional question on sexual enjoyment (Table2).

The exploratory analysis of the other scales is in an online appendix. All remaining scales and items did not show any impact of radiotherapy treatment and all show improvement or stability over time.

Discussion

To our knowledge, this is the first study investigating the impact of adjuvant radiotherapy on quality of life after mastectomy in a large randomised trial including a large, well characterised population of UK patients with 'intermediate-risk' breast cancer. The key finding is that PMRT was associated with worse local self-reported symptoms (pain, swelling, oversensitivity and skin problems in the "area of the affected breast") in comparison with no radiotherapy, although these symptoms improved over time. The estimated effect is small, with a difference between the radiotherapy and

control group of 2·17 points; 95% CI 0·40, 3·94. To the best of our knowledge there is no available data on what difference in the sub-scale scores of EORTC-BR23 is clinically significant. Using a generic approach of 0.5 of the standard deviation to indicate minimally important difference, we calculated the standard deviation of the "change score' for chest wall symptoms from baseline to year 1 in the control group. [25] The standard deviation was 17.3 and a score 8.65 is likely to indicate a clinically meaningful difference. The observed difference of 2.17 is relatively small and unlikely to be of clinical significance, which is of course reassuring for patients and clinicians. Persistent pain following breast surgery (breast conserving or mastectomy) was also reported by Gartner et al and was commoner after adjuvant radiotherapy and in younger women. [26]

There was no impact of radiotherapy to the chest wall on arm symptoms (axillary radiotherapy was prohibited in the trial), body image, overall QOL, physical function, fatigue or symptoms of anxiety or depression. Exploratory analyses showed that systemic chemotherapy treatment had an additive borderline effect on patients' chest wall and arms symptoms but without an interaction with the radiotherapy treatment. This is consistent with other studies [27].

The use of sentinel node biopsy procedure is the current standard practice for axillary surgery. In SUPREMO about a quarter of patients (those with pN0 (sn) tumours) in the main and QoL sub-study underwent limited axillary surgery (sentinel node biopsy or nodal sampling). The extent of axillary surgery had no impact on any of the pre-specified QOL outcomes, including arm symptoms. This is perhaps an unexpected finding and could be due to lack of sensitivity of the EORTC BR23 scale (which has 3 items on 'pain in arm or shoulder', 'swollen arm or hand' and 'difficulty raising your arm'). The impact of radiotherapy to the axilla on arm symptoms cannot be evaluated in the SUPREMO trial, as this was prohibited, but this has been investigated in other trials.[28]

We observed a low rate of immediate breast reconstruction (only 111 patients), this procedure was associated with higher fatigue levels and slower recovery in comparison with no immediate reconstruction but no impact on body image or the other QOL outcomes. The estimated effect of immediate reconstruction on fatigue was 5.32, corresponding to a small clinically meaningful difference[29]. This was an exploratory analysis and we used a generic QOL and body image questionnaires rather than breast-reconstruction instruments (such as BREAST-Q), which is likely less sensitive to specific outcomes [17].

It should be noted that the observed levels of reconstructive surgery (either immediate or delayed to year 2) are low in the range of 10-13%. This likely reflects the pattern of care in the period of the SUPREMO trial recruitment (2006-2013) or may be due to concerns of entering patients who had reconstruction into a trial of radiotherapy. There appears to be a trend in using more autologous procedures in patients who had radiotherapy and more implants/expanders in those not receiving radiotherapy. Due to the small number of reconstructions, SUPREMO trial cannot provide useful information on the impact of radiotherapy on breast reconstruction, and further evidence is needed. We are collecting further information on delayed (beyond 2 years) reconstructions, which will be analysed at 5 and 10 years and provide valuable information on rates of breast reconstruction across the UK, as well as its impact on patients' experiences and satisfaction with body image.

Most of the published literature relating to the impact of adjuvant radiotherapy on QOL relates to non-randomised studies, often of small size, which may be subject to selection bias and neither surgery, radiotherapy or systemic treatments were subject to pre-specified quality assurance. Comparisons are often difficult because of differing types of surgery, stage of disease, QOL measure used and time-points of QOL assessment. The studies often included both patients treated by mastectomy and breast conserving surgery. The START trial looked at late effects of different schedules of radiotherapy at 5 years and found that up to a third of women reported moderate or marked pain in the arm and shoulder and more than 10% experienced arm/hand swelling[12]. The trial included a small number of mastectomy patients (about 20%) and although the QOL results are

consistent with ours, they are not directly comparable since only 10% had chemotherapy and 20% had regional nodal irradiation in addition to breast/chest wall radiotherapy. The experience of breast/arm symptoms over 5 years represents chronic morbidity that has stronger association than cosmesis with long-term quality of life, making these important outcomes in clinical trials[30].

A prospective study of 113 patients treated by mastectomy and 142 by breast conserving surgery using the EORTC QLQ-C30 and BR23 measures showed no overall difference in QOL between baseline and end of radiotherapy [31]. However, its period of evaluation was confined to the duration of radiotherapy. The Moving Beyond Cancer psychosocial intervention trial studied the QOL of 558 women with stage 1 and 2 breast cancer treated with surgery alone (breast conserving or mastectomy), surgery with radiation, or surgery followed by chemotherapy and radiation over 1 year, using SF-36 questionnaire. Similar to our study, physical and psychosocial function improved significantly over time. However, the measures of QOL differ from our study and details of chemotherapy regimes and staging were not available in the absence of case record review[27]. A similar pattern of improvement in a range of symptoms and QOL measures in the first year post diagnosis was observed in a cohort study of 285 women with early breast cancer, treated with surgery (just >20% had mastectomy), adjuvant radiotherapy (74%) and systemic therapy in (just >30% of the patients) [33].

Finally, we observed that younger women reported worse body image (if under 45) and anxiety problems (if under 70 years). This finding is supported by other breast cancer QOL studies, is concordant with clinical experience and emphasises the need for targeted psychological interventions in those women[11,19]. Younger women also reported higher general pain scores. The reasons for this are not clear. The same finding was also reported in a randomised trial of radiotherapy after breast conserving therapy and in a population-based prospective study of more than 3000 patients following breast cancer surgery[13,26]. In the latter study, half the patients experienced moderate to severe pain, consistent with the range of reported pain in the literature from 25%-60%. The wide variation, as the authors suggest, may relate to varying definitions of pain, different methods of pain assessment and mix of surgery and adjuvant therapy. There is insufficient evidence to draw conclusions on each of the treatment related risk factors for pain.

Reassuringly we observed no deterioration in symptoms and QOL scores over time. General pain did not improve with time, and this was not related to the use of aromatase inhibitors (data not shown). There is evidence of persistent pain in early breast cancer patients post-surgery, and our findings confirm these observations and call for better recognition of this problem in order to implement screening and patient support.

Several strengths of SUPREMO trial should be mentioned. It is the largest post-mastectomy study which investigated a well-defined large population of patients treated by mastectomy, which was representative of women with early 'intermediate-risk' breast cancer in the UK. Individuals in the QOL study were recruited from almost all UK sites (only 10 out of 111 sites did not recruit any patients). The QOL study was multi-centre from across UK , representing a wide geographical range, thus minimising participating centre bias. The pre-specified QOL sample size was achieved and exceeded, strengthening the confidence in the findings. The trial was sufficiently large to allow explorative evaluation of the effects of age and multi-modality treatments. High levels of adherence to questionnaire completion over time were attained (>70%). In addition, guidelines on surgery, radiotherapy and systemic therapy were standardised in the protocol, so any variations in these treatment modalities between treatment arms are unlikely to influence the results.

The main limitation of the QOL sub-study is not having a true pre-treatment baseline QOL assessment, as all patients were randomised following mastectomy. The relatively low QOL scores at the time of randomisation may be explained by the recent breast cancer diagnosis and the surgical procedure, and the subsequent improvement in almost all score, is to be expected. We did not record QOL scores during or shortly after the allocated radiotherapy treatment, so any differences in

acute symptoms between the groups, which may predict later toxicity, have not been captured. In addition, since the main trial is ongoing and the loco-regional control and survival status of the patients in the QoL sub-study are not known to us, it is possible patients who had relapsed or died may have had different patterns of QOL. A larger proportion of participants in the QOL study received the radiotherapy as 45 Gy in 15 fractions (69%) compared to 52% in the main trial, where a larger proportion of 27% received 50 Gy in 25 fractions. This difference reflects the variations between the standard practice in UK and EORTC centres at the time of the trial. At this 2-year analysis we have not evaluated any effect of fractionation on the QoL outcomes. However, as the clinical significance of the increased chest wall symptoms in the radiotherapy group at 2 years may be relatively limited, we do not expect a major clinical impact of fractionation at this early time point.

This paper presents a pre-planned analysis at 2 years post randomisation, with the main QOL analysis being planned at 5 years and QOL data to be collected for 10 years to capture late adverse events. Clearly our results are preliminary and we are therefore cautious in our interpretation. However, it is a reassuring that the loco-regional symptoms are minimal and do not impair global QOL and diminish over the initial 2 years of follow up. Further analyses will be reported at 5 and 10 years to determine if the trends at 2 years are sustained. It is possible that late radiotherapy toxicity not seen within the first two years (such as progressive chest wall fibrosis or increased cardiac toxicity due to the combination of radiotherapy and anthracycline-based chemotherapy) may be detected on longer term follow-up and should be captured in our 5 and 10 year analyses. However, we recognise that late cardiac toxicity from radiotherapy may occur beyond 10 years.

The impact on PMRT on 10 year survival, the primary end-point of the main SUPREMO trial, will not be known before 2023. In the meantime, the decision to administer or omit PMRT can be considered 'preference sensitive' for patients in the SUPREMO trial risk category of 1-3 positive lymph nodes, as both options are legitimate. The patients will be in a better position to make a value judgment on what they consider relevant for them, given the data on various QOL domains presented in this report. Both physicians and patients may thus be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and QOL endpoints. This will support the application of informed shared decision-making, as recommended by the recent North American guidelines, even before the main trial outcome becomes available [7].

In conclusion, chest wall radiotherapy led to more chest wall symptoms up to 2 years post-randomisation, but the difference is small and unlikely to be clinically significant. There was no impact on the other pre-specified QOL domains. However, the trend for worse QOL scores for anxiety, body image and chest wall symptoms in younger women irrespective of irradiation warrants further investigation. Longer term follow-up at 5 and 10 years will be needed to see if these early trends in quality of life are sustained.

Contributors

GV LW SW JMD IHK NSR were involved in the study design. IHK NSR oversaw the trial and GV LW SW JMD were members of the trial management group. JMD JL MH JC IHK NSR recruited patients. LW GV SW IHK NSR did the data analysis. GV SW JMD JL MH JC IHK NSR interpreted the data. GV LW SW IHK NSR wrote the paper. JMD JL MH JC reviewed the drafts. GV IHK NSR gave final approval of the manuscript.

Declarations of interest

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Tables

Table 1. Patients' demographic and clinical characteristics

Patient demographic and clinical characteristics	**QOL study**		**Full trial**	
	No RT	**RT**	**No RT**	**RT**
Demographic	476	471	835	853
Age (mean and SD)	56·3 (11·3)	55·8 (10·8)	55·9 (11·2)	55·8 (11·3)
Menopausal status (number, %)				
Pre-menopausal	126 (26·5)	135 (28·7)	246 (29·5)	243 (28·5)
Peri-menopausal	43 (9·0)	52 (11·0)	68 (8·1)	85 (10·0)
Post-menopausal	290 (60·9)	268 (56·9)	483 (57·8)	475 (55·7)
Not known	17 (3·6)	16 (3·4)	38 (4·6)	50 (5·9)
Tumour characteristics				
Side of primary tumour (number, %)				
Left	238 (51·2)	216 (47·8)	398 (50·1)	407 (51·3)
Right	227 (48·8)	236 (52·2)	396 (49·9)	387 (48·7)
Tumour size (number, %)				
≤2cm	132 (27·7)	138 (29·3)	249 (29·8)	261 (30·6)
2·1-5 cm	337 (70·8)	332 (70·5)	566 (67·8)	566 (66·4)
>5 cm	5 (1·1)	1 (0·2)	4 (0·5)	4 (0·5)
Unknown	2 (0·4)	0	16 (1·9)	22 (2·6)
Tumour grade (number, %)				
I	20 (4·2)	23 (4·9)	46 (5·5)	57 (6·7)
II	190 (39·9)	195 (41·4)	335 (40·1)	333 (39·0)
III	262 (55·0)	250 (53·1)	432 (51·7)	432 (50·6)
Not specified	4 (0·8)	3 (0·6)	22 (2·6)	31 (3·6)
Histological type (number, %)				
Ductal	372 (78·5)	374 (79·4)	641 (78·2)	661 (79·5)
Lobular	58 (12·2)	49 (10·4)	95 (11·6)	89 (10·7)
Mucinous	5 (1·1)	1 (0·2)	7 (0·9)	1 (0·1)
Tubular	1 (0·2)	3 (0·6)	4 (0·5)	4 (0·5)
Adenocarcinoma	3 (0·6)	5 (1·1)	16 (2·0)	13 (1·6)
Other	35 (7·4)	39 (8·3)	57 (7·0)	63 (7·6)
Molecular markers – (number, %)				
ER+/PR+	218 (46·8)	217 (46·7)	417 (51·5)	416 (50·6)
ER+/PR-	48 (10·3)	48 (10·3)	83 (10·3)	99 (12·0)
ER-/PR+	5 (1·1)	0 (0)	8 (1·0)	3 (0·4)
ER-/PR-	87 (18·7)	93 (20·0)	156 (19·3)	162 (19·7)
ER+/PR unknown	96 (20·6)	100 (21·5)	131 (16·2)	132 (16·0)
ER-/PR unknown	12 (2·6)	7 (1·5)	15 (1·9)	11 (1·3)
Her2 positive	140 (29·7)	145(31·1)	273 (33·5)	269 (32·5)
Her2 negative	286 (60·7)	281 (60·2)	475 (58·2)	469 (59·9)
Not measured	45 (9·6)	41 (8·8)	68 (8·3)	63 (7·6)

Patient demographic and clinical characteristics	**QOL study**		**Full trial**	
	No RT	**RT**	**No RT**	**RT**
Axillary Nodes (number, %)				
0 (negative)	130 (27·3)	113 (24·0)	219 (26·2)	212 (24·9)
1-	180 (37·8)	199 (42·3)	316 (37·8)	338 (39·6)
2-	101 (21·2)	111 (23·6)	178 (21·3)	194 (22·7)
3-	63(13·4)	48 (10·2)	107 (12·8)	88 (10·3)
Not known	2 (0·4)	0	15 (1·8)	21 (2·5)
Treatment				
Breast Surgery (number, %)				
Mastectomy only	371 (77·9)	359 (76·2)	653 (78·2)	669 (78·4)
Immediate breast reconstruction prior to RT	50 (10·5)	61 (13·0)	85 (10·2)	97 (11·4)
Late breast reconstruction	55 (11·6)	51 (10·8)	97 (11·6)	87 (10·2)
Axillary surgery (number, %)				
SLN / node sampling	131 (27·9)	108 (22·9)	207 (25·5)	189 (22·8)
SLN plus ANC (Axillary node clearance)	138 (29·4)	124 (26·3)	229 (28·2)	224 (27·0)
ANC (without SLN)	201 (42·8)	239 (50·7)	377 (46·4)	417 (50·2)
Systemic treatment (number Yes, %)				
Neo-adjuvant chemotherapy[1]	1/173 (0·58)	7/173 (4·1)	7/243 (2·9)	16/269 (6·0)
Adjuvant chemotherapy	395 (83·0)	401 (85·1)	682 (81·7)	709 (83·1)
Anthracyclines	372/395(94·2)	379/401(94·5)	636/682(93·3)	655/709(92·4)
Taxanes	197/395(49·9)	207/401(51·6)	392/682(57·5)	418/709(59·0)
Trastuzumab	91/454 (20·5)	92/460 (20·0)	150/782(19·2)	166/806(20·6)
Endocrine therapy (number Yes, %)				
Neo-adjuvant	2/200 (1·0)	8/206 (3·9)	10/288 (3·5)	17/316 (5·4)
Adjuvant	349 (73·3)	363 (77·1)	598 (71·6)	631 (73·9)
Aromatase inhibitor	173/349(49·6)	195/363(53·7)	275/598(46·0)	314/631(49·8)
Tamoxifen	174/349(49·9)	168/363(46·3)	319/598(53·3)	314/631(49·8)
Other	2/349 (0·6)	0/363 (0)	4/598 (0·8)	3/631 (0·5)

[1] Only recorded in protocol v29 onwards

ER- estrogen receptor; PR – progesteron receptor; SLN- sentinel lymph node(s) procedure; ANC – axillary node clearance

Table 2. Quality of Life (QOL) scores (Standard Deviations, SD) at baseline, year 1 and year 2 follow-up

QoL measure	**Baseline**		**Year 1**		**Year 2**	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Age at randomisation	56·3 (11·3)	55·8 (10·8)	56·5 (10·9)	56·1 (10·4)	56·8 (10·9)	56·1 (10·4)
Primary endpoints						
EORTC QLQ-C30						
Global Health/QoL*	60·9 (21·6)	60·4 (20·8)	70·0 (20·5)	70·0 (19·8)	70·2 (20·5)	71·8 (20·1)
Fatigue**	41·6 (25·2)	43·0 (26·1)	30·3 (23·2)	31·0 (24·1)	29·2 (24·2)	27·5 (23·8)
Physical Functioning*	79·6 (20·2)	80·1 (19·6)	81·9 (19·0)	81·1 (19·1)	82·0 (18·6)	82·1 (19·3)
EORTC QLQ-BR23						
Arm symptoms**	20·3 (20·5)	21·2 (21·7)	21·2 (21·7)	22·4 (22·0)	20·7 (21·4)	19·9 (20·3)
Chest wall/breast symptoms**	17·3 (17·0)	18·1 (18·3)	13·1 (16·3)	16·1 (16·7)	11·6 (14·6)	14·1 (15·8)
*Body Image Scale***	10·3 (7·9)	11·1 (8·2)	9·3 (7·6)	9·8 (7·7)	8·1 (6·7)	8·7 (7·4)
Hospital Anxiety and Depression Scale (HADS)						
Anxiety	6·2 (4·4)	6·1 (4·3)	6·8 (4·7)	6·5 (4·4)	6·3 (4·3)	6·5 (4·4)
Depression	4·5 (3·7)	4·6 (3·7)	4·2 (3·7)	4·2 (3·8)	4·0 (3·5)	4·2 (3·9)
Secondary endpoints						
EORTC QLQ-C30						
Role Functioning *	65·2 (30·9)	63·0 (30·5)	79·3 (27·1)	78·8 (25·8)	79·7 (27·6)	81·0 (26·9)
Social Functioning *	65·5 (28·7)	64·0 (29·1)	79·4 (25·6)	80·3 (24·7)	80·5 (26·1)	83·9 (25·2)
Pain**	22·6 (26·5)	24·8 (27·9)	21·7 (26·8)	23·7 (26·5)	23·4 (27·3)	21·6 (25·9)
Nausea Vomiting**	11·2 (17·6)	11·5 (20·1)	5·3 (13·1)	5·1 (12·1)	4·6 (12·2)	5·1 (13·6)
EORTC QLQ-BR23						
Sexual Functioning*	11·5 (18·1) n=455	12·5 (19·0) n=459	15·7 (20·5) n=372	17·6 (21·2) n=374	16·3 (21·7) n=325	18·1 (22·3) n=353
Exploratory variables						
EORTC QLQ-C30						
Emotional Functioning*	74·7 (22·6)	73·7 (24·4)	75·2 (23·6)	75·2 (22·3)	77·3 (22·5)	75·7 (23·3)
Cognitive Functioning*	77·1 (23·4)	75·0 (26·1)	78·2 (22·8)	78·2 (22·9)	78·6 (22·8)	78·2 (23·8)
Dyspnoea**	20·8 (26·4)	20·0 (26·1)	14·6 (23·5)	14·8 (23·0)	14·3 (23·2)	13·4 (22·5)

QoL measure	**Baseline**		**Year 1**		**Year 2**	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Insomnia**	36·3 (31·1)	37·2 (32·8)	36·4 (33·5)	38·5 (32·8)	33·9 (31·9)	35·0 (30·5)
Appetite loss**	20·7 (28·9)	19·2 (27·9)	9·5 (19·8)	8·7 (18·5)	9·1 (19·9)	9·0 (20·7)
Constipation**	18·2 (26·3)	17·0 (26·1)	14·9 (24·5)	14·5 (24·1)	17·6 (27·7)	14·5 (24·3)
Diarrhoea**	11·9 (20·7)	12·1 (23·8)	7·6 (17·5)	8·4 (18·7)	5·4 (15·1)	8·7 (19·1)
Financial difficulties**	23·9 (33·1)	23·2 (31·7)	15·8 (28·5)	17·1 (27·8)	14·1 (27·0)	13·8 (26·6)
EORTC QLQ-BR23						
Sexual enjoyment*	49·9 (26·9) n=121	53·0 (29·1) n=132	54·4 (28·3) n=136	56·5 (26·5) n=144	52·5 (26·1) n=115	56·6 (28·8) n=136
Future perspective**	45·8 (31·2)	46·4 (32·8)	49·8 (32·3)	50·9 (31·6)	54·4 (30·1)	54·1 (30·9)
Systemic therapy side-effects**	34·8 (23·1)	35·2 (22·7)	19·3 (15·2)	19·6 (15·6)	18·6 (14·9)	18·3 (15·0)
Hair loss**	29·6 (37·5)	31·7 (39·3)	6·2 (20·4)	6·4 (21·8)	3·8 (20·7)	4·9 (17·1)
EQ-5D-3L***	0·74 (0·22)	0·74 (0·22)	0·75 (0·25)	0·75 (0·24)	0·76 (0·24)	0·77 (0·22)

*EORTC QLQ-C30 Functional scores- range 0-100 (higher score = good functioning)
** EORTC QLQ-C30 Symptom scores – range 0-100 (higher score = worse symptoms)
*** EQ-5D-3L score-range 0-1.

Table 3. Mixed effects models (fixed effects) for the primary QOL outcomes

Outcome	Model variable	Estimate of effects	95% CI	p
Global QOL (C30)	Baseline score	-0·57	-0·63, -0·52	<0·0001
	Age- ref* >70	-	-	-
	- <45	1·12	-3·45, 5·78	0·64
	- 45-54	3·25	-0·62, 7·12	0·10
	- 55-69	3·54	-0·28, 7·36	0·07
	Visit-ref year1	0·75	-0·46, 1·97	0·23
	RT –ref no RT	1·39	-0·92, 3·71	0·24
		*Adjusted mean of 'change scores'***	*95% CI*	*p-value****
	RT	*8·63*	*6·86, 10·40*	*<0·0001*
	No RT	*7·23*	*5·46, 9·01*	*<0·0001*
Fatigue (C30)	Baseline score	-0·59	-0·65, -0·54	<0·0001
	Age- ref >70	-	-	-
	- <45	-2·41	-8·07, 3·26	0·40
	- 45-54	-4·14	-8·84, 0·56	0·08
	- 55-69	-3·13	-7·73, 1·47	0·18
	Visit-ref year1	-1·83	-3·20, -0·46	0·009
	Immediate reconstruction	5·32	0·94, 9·69	0·017
	Ref no recon			0·17
	RT –ref no RT	-1·93	-4·70, 0·84	
	RT	*-9·54*	*-12·19, -6·89*	*<0·0001*
	No RT	*-7·61*	*-10·35, -4·87*	*<0·0001*
Physical function (C30)	Baseline score	-0·41	-0·46, -0·35	<0·0001
	Age- ref >70	-	-	-
	- <45	7·91	3·94, 11·87	<0·0001
	- 45-54	7·06	3·80, 10·32	<0·0001
	- 55-69	4·29	1·06, 7·51	0·009
	Visit-ref year1	0·20	-0·68, 1·08	0·65
	RT –ref no RT	-0·17	-2·13, 1·79	0·87
	RT	*-0·02*	*-1·53, 1·48*	*0·97*
	No RT	*0·14*	*-1·36, 1·65*	*0·85*
Chest wall symptoms (BR23)	Baseline score	-0·57	-0·62, -0·52	<0·0001
	Age- ref >70	-	-	-
	- <45	4·49	0·59, 8·39	0·02
	- 45-54	1·88	-1·46, 5·22	0·26
	- 55-69	2·36	-0·79, 5·51	0·14
	Visit-ref year1	-1·34	-2·36, -0·31	0·010
	Chemo-ref no chemo	3·74	0·87, 6·61	0·011
	RT –ref no RT	2·17	0·40, 3·94	0·016
	RT	-3·13	-4·74, -1·51	0·0002

	No RT	-5·30	-6·88, -3·71	<0·0001
Arm and shoulder symptoms (BR23)	Baseline score	-0·51	-0·57, 0·45	<0·0001
	Age- ref >70	-	-	-
	- <45	0·86	-4·42, 6·14	0·74
	- 45-54	2·89	-1·64, 7·41	0·21
	- 55-69	2·76	-1·51, 7·03	0·20
	Visit-ref year1	-0·93	-2·22, 0·37	0·16
	Chemo-ref no chemo	6·15	2·26, 10·05	0·002
	RT –ref no RT	-0·53	-2·92, 1·86	0·66
	RT	-1·44	-3·63, 0·75	0·19
	No RT	-0·91	-3·06, 1·24	0·40
Body Image Scale	Baseline score	-0·39	-0·43, 0·34	<0·0001
	Age- ref >70	-	-	-
	<45	1·96	0·53, 3·39	0·007
	45-54	1·39	0·20, 2·58	0·022
	55-69	0·83	-0·33, 1·99	0·15
	Visit-ref year1	-0·91	-1·28, -0·55	<0·0001
	RT –ref no RT	-0·09	-0·79, 0·61	0·79
	RT	-1·36	-1·90, -0·83	<0·0001
	No RT	-1·27	-1·81, -0·73	<0·0001
HADS-Anxiety	Baseline score	-0·30	-0·35, -0·25	<0·0001
	Age- ref >70	-	-	-
	- <45	1·69	0·86, 2·53	<0·0001
	- 45-54	1·36	0·67, 2·06	0·0001
	- 55-69	1·21	0·53, 1·90	0·0005
	Visit-ref year1	-0·05	-0·29, 0·18	0·66
	RT –ref no RT	-0·16	-0·57, 0·25	0·44
	RT	0·44	0·13, 0·76	0·006
	No RT	0·60	0·29, 0·92	0·0002
HADS-Depression	Baseline score	-0·35	-0·41, 0·30	<0·0001
	Age- ref >70	-	-	-
	- <45	0·07	-0·73, 0·87	0·87
	- 45-54	-0·05	-0·72, 0·61	0·88
	- 55-69	-0·04	-0·69, 0·62	0·91
	Visit-ref year1	0·02	-0·16, 0·20	0·94
	RT –ref no RT	-0·14	0·54, 0·25	0·48
	RT	-0·19	-0·50, 0·11	0·21
	No RT	0·05	-0·35, 0·25	0·75
Pain (C30)	Baseline score	-0·51	-0·57, -0·46	<0·0001
	Age- ref >70	-	-	-
	- <45	-0·18	-6·16, 5·80	0·95
	- 45-54	2·76	-2·17, 7·69	0·27
	- 55-69	2·18	-2·70, 7·06	0·38
	Visit-ref year1	0·31	-1·29, 1·91	0·70
	RT –ref no RT	-0·65	-3·62, 2·33	0·67
	RT	0·28	-1·99, 2·56	0·81
	No RT	0·93	-1·35, 3·20	0·42

* ref =reference category in the mixed-effects models

** shaded cells - the adjusted mean for the individual arms is the mean of the 'change scores', (defined as change from baseline to year 1 and from baseline to year 2) in each of the treatment groups, adjusted for baseline score, visit, and age;

***p values - whether each of the means of the 'change scores' within each individual arm is significantly different from zero (i.e., improvement or deterioration in scores from baseline)