

# Individualising breast cancer treatment to improve survival and minimise complications in older women: a research programme including the PLACE RCT

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## Scientific summary

### The PLACE RCT

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# Scientific summary

## Individualising breast cancer treatment to improve survival and minimise complications

Over 44,000 breast cancers are diagnosed in the UK and 12,000 women die from the disease annually. Many older women do not receive appropriate management, and a disproportionate number of deaths (6500) occur among elderly patients. Many patients who are cured suffer complications of treatment, such as lymphoedema (gross swelling of the arm). Complications could be avoided by better identification of patients that takes account of variation in risk of recurrence and susceptibility to complications. We could then target preventative interventions to reduce complications. Such an approach will maximise survival while minimising complications, thus providing high-quality long-term survival.

### Maximising survival

We aimed to:

- 1a. identify the extent to which older women's receipt of suboptimal management is a result of surgeons' rather than patients' preference.

### Minimising complications

We aimed to:

- 1b. investigate the extent to which primary surgery for older women with early-stage breast cancer is effective, increases survival and health-related quality of life (HRQoL)
- 1c. investigate follow-up adjuvant treatment (radiotherapy and/or chemotherapy post surgery) for older breast cancer patients regarding:
  - i. the extent to which adjuvant treatment is effective, increases survival and HRQoL
  - ii. the extent to which lack of adjuvant treatment can be explained by patient health and choice
- 2a. prospectively assess the new health technology of multifrequency bioimpedance (BEA) with early ipsilateral arm-volume changes to identify women who are likely to develop lymphoedema after axillary node clearance (ANC) surgery
- 2b. identify a model to predict which women would develop lymphoedema
- 2c. develop a composite index to better define lymphoedema
3. determine whether, in women at high risk, applying external compression garments prevents the onset of chronic lymphoedema compared with standard management.

## Methods

### Workstream 1

Workstream 1 was a prospective cohort study of surgical consultations with women aged  $\geq 70$  years [mean age 77.01 years, 95% confidence interval (CI) 76.5 to 77.5 years] consecutively identified from newly diagnosed patients with operable cancer attending breast units. Data on surgeons' perceptions of responsibility for the surgical decision for individual consultations were collected using the Controlled

Preference Score (CPS) during brief post-consultation interviews. Women's preferences were collected using the CPS within 30 days of diagnosis.

### Workstream 1b

As part of the research funded by the Breast Cancer Campaign (BCC), National Institute for Health Research (NIHR) Fellowship and this programme, we planned to identify predictors of surgical risk using multivariate modelling and develop these predictors into a pre-treatment health assessment/screening tool to assess risk of adverse outcome (i.e. 'fitness for surgery'). Once we had developed the tool, we planned a feasibility trial following the Medical Research Council complex intervention framework and guidelines (Medical Research Council. *Developing and Evaluating Complex Interventions New Guidance*. London: Medical Research Council; 2008). However, our modelling revealed no significant strong predictors of surgical risk; therefore, we were not able to build a viable screening tool, and so could not proceed to conduct the planned feasibility RCT. We obtained approval from the programme board for further follow-up of our cohort of 910 women (IMPACT study) and several additional data analyses to investigate outcomes so that we could examine the impact of lack of treatments on older breast cancer patients in the UK. An analysis looking at the relationship between congruence (the patient getting the treatment decision-making style she preferred) and HRQoL at follow-up was undertaken, as was a qualitative study of women who did not receive surgery.

### Workstream 2

Women ( $n = 1100$ ) undergoing ANC for breast cancer in 21 centres across the UK underwent baseline (preoperative) and subsequent monitoring, including perometer arm measurements. The primary end point of lymphoedema was defined as a  $\geq 10\%$  relative arm-volume increase (RAVI) compared with the contralateral arm by perometry (Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women  $\geq 65$  years. *Br J Cancer* 2007;**96**:1197–203). Comparison of the diagnostic accuracy of BEA with perometer in the diagnosis of lymphoedema was assessed. Quality of life (QoL) and the effect of a diagnosis on QoL were studied prospectively. Demographic and treatment factors that predicted the subsequent development of lymphoedema were analysed to build a predictive model of the risk of developing lymphoedema.

### Workstream 3

Workstream 3 was a randomised controlled trial testing (1) standard management versus (2) an intervention comprising application of graduated compression garments to the affected arm, together with standard management, for 1 year in patients in WS2 with arm swelling of a 4–9% increase from baseline. With approval from the programme board, we conducted a nested qualitative study of recruitment to the trial.

## Workstream 1: older women's access to services – results

In our studies of preference, 800 women were included, of whom 83.0% (664) had surgery (95% CI 80.4% to 85.6%) and 48.0% had a Charlson comorbidity score of  $> 1$  (95% CI 44.5% to 51.5%); 34% were aged 70–74 years, 30% were aged 75–80 years, 19% were aged 80–84 years and 17% were aged  $> 85$  years. In total, 473 had a surgeon and patient CPS referring to the same index consultation and 249 cases both selected the same option regarding the patient's role in the surgical decision (52.6%:  $\kappa = 0.261$ ). In the univariable analyses, increasing age predicts not undergoing surgery from the age of 75 years, compared with 70- to 74-year-olds. Adjusting for health measures and choice, only women aged  $> 85$  years have reduced odds of surgery [odds ratio (OR) 0.18, 95% CI 0.07 to 0.44]. Each point increase in activities of daily living score (worsening functional status) reduced the odds of surgery (OR 0.23, 95% CI 0.15 to 0.35). Patient role in treatment decisions made no difference to whether or not they received surgery. Women who were active/collaborative were as likely to get surgery as those who left the decision to the surgeon. In our qualitative study of women who did not receive primary surgery for their operable breast cancer, we identified three approaches: 'patient declined', 'patient considered' and 'surgeon decided'.

Older age did not predict complications. Several health measures were associated with complications in univariable analysis, and were included in multivariable analyses, adjusting for type/extent of surgery and tumour characteristics. In the final models, pain predicted a higher count of complications [incidence rate ratio (IRR) 1.01, 95% CI 1.00 to 1.01;  $p = 0.004$ ]. Fatigue (OR 1.02, 95% CI 1.01 to 1.03;  $p = 0.004$ ), low platelet count (OR 4.19, 95% CI 1.03 to 17.12;  $p = 0.046$ ) and pulse rate (OR 0.96, 95% CI 0.93 to 0.99;  $p = 0.010$ ) predicted serious complications. We therefore conclude that the risk of serious complications from breast surgery is low for older patients. Surgical decisions should be based on patient fitness rather than on age. We were unable to build a pre-treatment risk screening tool on the basis of these results and had to rethink the second phase of the work to focus on further follow-up of our cohort.

Of the 759 women in the survival study (mean age 75.99 years, 95% CI 75.53 to 76.44 years), 48 died of breast cancer and 65 died of other causes. The number of observed cancer deaths exceeded those expected for participants whose tumours were of higher grade or stage and steroid receptor negative, and who did not undergo surgery and warranted chemotherapy. Adjusting for tumour stage, comorbidity and functional status, women undergoing surgery had one-third the hazard of dying of breast cancer.

Of the 225 patients in the subsample investigating the effect of surgery on HRQoL, 59 (26%) achieved congruence (i.e. they got the treatment decision-making style they preferred). Change in HRQoL was associated neither with congruence ( $p = 0.133$ ) nor with receipt of primary surgery ( $p = 0.841$ ) either in the univariate analyses ( $t$ -tests) or in a multiple linear regression analysis adjusting for the effects of each other ( $p = 0.135$  and  $p = 0.729$ , respectively).

We investigated if lack of chemotherapy and radiotherapy can be explained by patient choice or health in patients recruited from 22 English breast cancer units. The primary outcomes were curative adjuvant treatment, radiotherapy or chemotherapy, within 12 months of diagnosis. A univariable analysis of 688 women aged  $\geq 65$  years demonstrated that women aged  $\geq 75$  years have lower chemotherapy and radiotherapy rates than women aged 65–69 years. Adjusting for tumour characteristics, health measures and choice, women aged  $\geq 75$  years still had reduced odds of receiving chemotherapy (OR 0.06, 95% CI 0.02 to 0.16), but age did not alter the radiotherapy rates of older women. Lower chemotherapy rates in older women cannot be explained by either health or patient choice.

## Workstream 2: multifrequency bioimpedance study results

Overall, 1100 patients entered the study (minimum 24-month follow-up). Their mean age was 56 years (range 22–90 years), 47.0% had a mastectomy and ANC, 91% were node positive and the majority (80.6%) were estrogen receptor positive. Eighty-three per cent of patients received postoperative radiotherapy, 67.3% received chemotherapy and 82.4% were given endocrine treatment.

Using time to diagnosis of lymphoedema by a RAVI of  $\geq 10\%$ , Kaplan–Meier estimates of those developing lymphoedema by each time point, 14.6% were diagnosed by 12 months and 21.4% were diagnosed by 24 months. Lymphoedema by 24 months was detected in 39.4% by BEA. A correlation between perometer and BEA was found at 6 months ( $r = 0.61$ ). Using sleeve application as the clinical definition of lymphoedema meant that a RAVI of  $\geq 10\%$  had a specificity of 94% (95% CI 93% to 96%) with BEA of 80% (95% CI 79% to 83%), and a positive predictive value of 59% (95% CI 48% to 64%) with BEA of 34% (95% CI 28% to 40%). The negative predictive value was similar and sensitivity did not differ significantly. The sensitivity and specificity values for BEA fell below the percentage of 95% required according to the study protocol.

Among women developing a RAVI of  $> 5\%$  to  $< 10\%$  by 6 months, 35% required lymphoedema treatment by 24 months, whereas a RAVI of  $< 3\%$  was associated with an 8% lymphoedema rate at 24 months ( $p < 0.001$ ).

For a RAVI of  $\geq 10\%$ , univariate analysis that revealed body mass index (BMI) ( $p < 0.002$ ), number of nodes involved (median 2 nodes, range 0–41 nodes;  $p < 0.001$ ), and largest RAVI change by 6 months [ $p < 0.001$ ; hazard ratio (HR) 5.58 for  $\geq 5\%$  to  $< 10\%$  vs.  $< 3\%$ , 95% CI 3.61% to 8.62%] and a BIS of  $> 10\%$  ( $p < 0.001$ ) all predicted lymphoedema development after 6 months up to 2 years.

Multivariable analysis included RAVI change by 6 months ( $p < 0.001$ ; HR 5.22 for  $\geq 5\%$  to  $< 10\%$ , 95% CI 3.22 to 8.47), number of nodes involved (HR 1.05, 95% CI 1.02 to 1.07), adjuvant chemotherapy (HR 1.61, (95% CI 1.01 to 2.55), a BMI of  $> 30 \text{ kg/m}^2$  (HR 1.87, 95% CI 1.16 to 3.02) and a BIS of  $> 10\%$  ( $p = 0.069$ ) in the model for predicting lymphoedema development after 6 months up to 2 years.

Quality of life, as measured by Functional Assessment of Cancer Therapy – Breast Cancer, version 4 (FACT-B+4), declined in all patients over the first 6 months related to the effects of adjuvant chemotherapy, but increased above baseline values in patients who did not develop lymphoedema. QoL deficits [especially in the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B) Trial Outcome Index (TOI) and arm subscale] were significantly greater when lymphoedema developed and persisted to 24 months. Additionally, in a multivariate analysis QoL was reduced by smoking, high BMI and age. A general estimating equation analysis that included an interaction term between lymphoedema status by 6 months and time showed that TOI varied over the time period ( $p = 0.003$ ), those with lymphoedema by 6 months had significantly lower TOI overall ( $p = 0.028$ ) and the interaction between time and lymphoedema status was significant ( $p < 0.001$ ). There was a difference in the pattern of change over time between those with and those without lymphoedema. QoL, an important outcome for women, appears to be detrimentally affected by development of lymphoedema.

Predictive models for risk of lymphoedema from 1 and 6 months post surgery have been developed, with the 6-month model having a receiver operating characteristic (ROC) analysis area under the curve of 0.80, which comprises RAVI percentage, number of positive nodes, lymphoedema checklist heaviness score and FACT-B arm subscale. A composite definition of lymphoedema has also been developed.

Patients with a sleeve applied who had 'considerable' self-reported swelling had a higher RAVI, at  $> 9\%$ , and their QoL scores significantly improved after treatment, whereas in the absence of 'considerable' swelling, sleeve treatment did not improve QoL.

### Workstream 3: PLACE trial results

A total of 143 patients were randomised (74 to no sleeve and 69 to compression sleeves) between 1 October 2010 and November 2015. Because of slow recruitment, the number of centres were increased from 7 to 21 by November 2013 and a qualitative study commenced to understand the reasons behind the poor recruitment.

As well as identifying positive reasons why patients were motivated to take part in the trial, the qualitative study identified some potential reasons for slow recruitment. Key themes were identified from the focus group and interviews that reflected the main reasons why recruitment rates were low. Issues included patient motivators (altruism and potential personal advantages), patient barriers (focus on getting through treatment, stigma of compression garments) organisational barriers (staffing issues and turnover, network staff not being accountable to research team), procedural issues (staff failure to follow research protocol), lack of training/confidence (misunderstanding of trial and incorrect explanation to patients), and audit, trial management and staffing issues (despite audit, follow-through at site level was not always optimal; staff turnover).

From staff interviews it was clear that (1) wait and see culture, (2) conflicting roles, (3) misunderstanding the trial arms, and (4) paternalism/gatekeeping versus shared decision-making with patients all played important roles. These are all lessons for future trials.

Overall, lymphoedema rate in the trial is 40%. The final results from this trial will not be available until all patients have had a minimum 2-year follow-up (November 2018).

## Conclusions

### *Workstream 1*

Surgeons decide treatment options (with little patient input) in a great many elderly breast cancer patient consultations.

Surgery for older cancer patients reduces the hazard of breast cancer death by two-thirds, independent of age, comorbidity and tumour characteristics, and this needs to be explained clearly to elderly cancer patients.

The risk of serious complications from breast surgery is low for older patients. Surgical decisions are based on patient fitness, rather than on age.

Lower chemotherapy rates in older women cannot be explained by health or patient choice.

### *Workstream 2*

Perometer measurement of arm-volume changes from the pre-surgery baseline is the optimal diagnostic tool for lymphoedema, and an early increase in arm volume of > 5–9% by 9 months is associated with a 44% risk of lymphoedema by 24 months.

Lymphoedema is associated with significant and lasting QoL deficits.

Sleeve application without either a RAVI of > 9% or self-reported arm swelling is ineffective.

### *Workstream 3*

The PLACE (Prevention of Lymphoedema After Clearance by External compression) trial results await longer follow-up. Embedded qualitative substudies should be commenced in future RCTs from the start to provide insight and help rectify any issues in recruitment.

## Research recommendations

Trials of interventions to optimise elderly breast cancer treatment are required.

Investigation of factors influencing the application of compression sleeves in the absence of objective arm swelling are required.

Trials of weight loss and exercise after ANC surgery should investigate effects on lymphoedema.

## Trial registration

This trial is registered as ISRCTN48880939.

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